

PREVENTION OF CARDIOVASCULAR DISEASE



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Learning Objectives

1. Distinguish among those preventive strategies that are primordial, primary, or secondary in the prevention of cardiovascular disease.
2. Develop a plan for a specific patient using primordial, primary, or secondary prevention strategies based upon published literature.
3. Given patient-specific information, develop and justify your treatment plan for the prevention of cardiovascular disease.
4. Give your opinion regarding the “cost-effectiveness” of a particular strategy in the prevention of cardiovascular disease.
5. Given a specific type of pharmacological therapy, evaluate the risk versus benefit in the prevention of cardiovascular disease for an individual patient.
6. Assess the appropriateness of the application of the Framingham risk prediction score in a variety of patient populations.

Introduction

Cardiovascular disease is the leading cause of death and disability in the United States, as well as the entire industrialized world. It is rapidly becoming a major threat in the developing parts of the world. Cardiovascular disease includes coronary heart disease (CHD), stroke, hypertension, heart failure (HF), and peripheral arterial disease (PAD). Although age-adjusted rates of mortality have declined throughout past 4 decades, the absolute mortality has changed little in the past 20 years. Cardiovascular disease is increasing in prevalence on a worldwide basis. This is due to increases in lifespan as a result of reduction in death from infectious disease and

malnutrition. The increasing prevalence of obesity and diabetes also has a profound effect on the development of cardiovascular disease, including CHD, HF, stroke, and PAD.

Cardiovascular disease needs to be examined in light of abnormal neurohormonal, metabolic, inflammatory and immunologic findings. In the past, clinicians have examined and treated each risk factor somewhat independently, and developed practice guidelines without considering the entire spectrum of the cardiometabolic syndrome.

The prevention of cardiovascular disease is a complex subject. There are well-known risk factors, such as smoking, hypertension, dyslipidemia, and diabetes, that contribute to the development of cardiovascular disease. However, understanding the relationships among these and other emerging risk factors, such as elevated concentrations of C-reactive protein (CRP) and hyperhomocystinemia, is an evolving science.

Epidemiology

Risk factors for the development of cardiovascular disease are common in the United States. Hypertension affects 25%, dyslipidemia affects 20–50%, and cigarette smoking affects 25% of the adult population.

In 2000, cardiovascular disease accounted for 39.4% of mortality in the United States, and was listed as a primary or contributing cause on 1.4 million death certificates. A major cause of cardiovascular disease is CHD. Sudden cardiac death comprises an increasing proportion of the mortality burden, and often is associated with acute myocardial infarction (MI). Even if a patient survives an acute MI, the patient may go on to develop HF. Heart failure is considered the most common hospital discharge diagnosis in patients over age 65. Hypertension also is a major contributor to HF.

Significant progress has been made in the past 40 years in reducing CHD mortality. Unfortunately, the rate of

Abbreviations in this Chapter

ACE	Angiotensin-converting enzyme	HF	Heart failure
ADP	Adenosine diphosphate	HOPE	Heart Outcomes Prevention Evaluation
ALLHAT	Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial	HPS	Heart Protection Study
ALLHAT-LLT	Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial-Lipid Lowering Trial	HT	Hormone therapy
Ang II	Angiotensin II	IL	Interleukin
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm	JNC	Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension
AT ₁	Angiotensin II type 1 receptor	LDL	Low-density lipoprotein
ATP	Adult Treatment Panel	LIFE	Losartan Intervention for Endpoint Reduction
BMI	Body mass index	LVH	Left ventricular hypertrophy
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events	MI	Myocardial infarction
CHD	Coronary heart disease	MRFIT	Multiple Risk Factor Interventions Trial
CLASS	Celecoxib Long-term Arthritis Safety Study	MMP	Matrix metalloproteinase enzyme
COX	Cyclooxygenase	NCEP	National Cholesterol Education Program
CRP	C-reactive protein	NSAID	Nonsteroidal anti-inflammatory drug
DHA	Docosahexaenoic acid	PAD	Peripheral arterial disease
ECG	Electrocardiogram	RAAS	Renin-angiotensin-aldosterone system
EPA	Eicosapentaenoic acid	TZD	Thiazolidinedione
HATS	HDL Atherosclerosis Treatment Study	VIGOR	Vioxx Gastrointestinal Clinical Outcomes Research
Hb A1C	Hemoglobin A1C	VLDL	Very-low-density lipoprotein
HDL	High-density lipoprotein	WHI	Women's Health Initiative
HERS	Hormone Replacement Study	WHO	World Health Organization

decrease does not affect all populations equally. Economically disadvantaged groups and certain regions of the country (Appalachia and the South) experience higher rates of cardiovascular disease and CHD.

Initially, better detection and treatment of hypertension contributed to the reduction in CHD, stroke, and HF mortality. Similarly, decreases in smoking and cholesterol concentrations have positive effects. However, since 1990, risk factors have not declined at the same rate. In fact obesity, lack of exercise, and diabetes have emerged as prominent risk factors.

It is estimated that 40 million people in the United States have impaired glucose tolerance and have a 10% annualized risk for developing type 2 diabetes mellitus mellitus. Unfortunately, cardiovascular disease accounts for 70% of the deaths in patients with diabetes, and diabetes is considered equivalent to having a cardiovascular disease (CHD equivalent) when considering secondary prevention goals.

A study looking at various races in the United Kingdom showed that people of African origin had less CHD but more hypertension, diabetes, strokes, and renal failure compared with whites. South Asians had more CHD,

hypertension, diabetes, and central obesity compared to whites. The estimated 10-year risk of CHD adjusted for age and sex varied significantly by ethnic group. South Asians had the greatest risk of CHD and combined cardiovascular disease, whereas people of African origin had the lowest. However, people of African origin had the highest risk of stroke. For any calculated 10-year risk score for CHD, the estimated risk of combined cardiovascular disease is higher in people of African and South Asian origin than whites.

The risks for CHD, stroke, and cardiovascular disease attributable to systolic blood pressure were higher in people of African origin, followed by South Asians, and whites. For cardiovascular disease, the risks were 1.11 (0.88–1.34), 0.92 (0.68–1.15), and 0.67 (0.49–0.85) per 1000 population per year for each ethnic group, respectively. These differences suggest that adequate treatment of high blood pressure might prevent a proportionally greater number of cardiovascular events in people of African origin and South Asians than whites.

In the Atherosclerosis Risk in Communities Study, over 14,000 black and white men and women were followed 10 years. The traditional risk factors of hypertension, smoking, elevated low-density lipoprotein (LDL), and

Cappuccio FP, Oakeshott P, Strazzullo P, Kerry SM. Application of Framingham risk estimates to ethnic minorities in United Kingdom and implications for primary prevention of heart disease in general practice: cross sectional population based study. *BMJ* 2002;325:1271–77.

Table 1-1. Tools to Assess Cardiovascular Risk on the Internet

<http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm>

- Free Web site that contains links to the full text and executive summary of the ATP III guidelines
- Link to an online 10-year risk assessment tool
- Download 10-year risk assessment calculator (uses excel spreadsheet)
- Patient information materials

<http://www.nhlbi.nih.gov/about/framingham/riskabs.htm>

- Free Web site that contains links to four files to help calculate a Framingham coronary disease risk prediction score for men or women based on total cholesterol concentration or LDL cholesterol concentration

www.intmed.mcw.edu/clincalc/heartrisk.html

- Free Web site from the Medical College of Wisconsin that contains an online risk assessment tool based on the Framingham coronary disease risk prediction score

<http://www.hyp.ac.uk/bhs/resources/guidelines.htm>

- Free Web site of the British Hypertension Society that contains guidelines for treating hypertension as well as CHD prediction charts from the University of Manchester. The predictions charts are difficult to read due to their size

<http://www.med-decisions.com/>

- Free online risk assessment tool that calculates how the risk is reduced with certain interventions (aspirin, lipid lowering, and blood pressure control)

ATP III = Third Adult Treatment Panel; CHD = coronary heart disease; LDL = low-density lipoprotein.

diabetes were associated with CHD for all race-gender groups, but there are some interesting differences. In particular, hypertension is a more powerful predictor in black women than in other race and gender groups. Left ventricular hypertrophy (LVH) also is a known independent risk factor. Rates of disease were substantially higher in black women with LVH on their electrocardiogram (ECG) compared with those without LVH on the ECG. Diabetes was a weaker predictor in black women compared to white women.

Historically, the Framingham study has provided invaluable data regarding risk factors for CHD; however, it may not accurately reflect the probability of risk for ethnic minorities. The Framingham risk assessment is not validated in blacks and other nonwhite groups.

In addition, the risk of CHD is not the same as the risk for cardiovascular disease in the minority population. A lower threshold for risk is needed for some groups. Clinicians have difficulty accurately estimating risk in individual patients without assessment aids. There are several risk factor assessment tools available on the Internet (See Table 1-1). Using the Framingham risk prediction score, a nonsmoking 52-year-old woman with LDL between 100 and 129 mg/dl and high-density lipoprotein (HDL) cholesterol between 50 and 59 mg/dl would receive six points for her age. If her systolic blood is between 120 and 129 mm Hg and she does not have diabetes, then she receives no additional points. This puts her 10-year CHD risk at 6%, which is below the average for a woman of her age.

Pathogenesis

By early adulthood, most individuals in developed countries have some degree of atherosclerotic disease. Atherosclerotic plaques consist of extracellular lipid, foam cells, and collagen. Low-density lipoprotein cholesterol plays a major role in the development of these plaques. The sequence of reactions—from associated cardiovascular disease risk factors causing oxidative stress, leading to endothelial dysfunction, imbalance of vasoactive substances, vascular inflammation, and remodeling—can result in cardiac events, such as angina, MI, and HF.

The endothelium is a complex and dynamic organ that activates vasoactive substances in response to environmental stimuli. These vasoactive substances mediate vascular tone, structure, and function by influencing vascular smooth muscle cell growth, apoptosis, platelet aggregation, monocyte and leukocyte adhesion, and thrombosis. Hypertension and other cardiovascular risk factors are associated with endothelial dysfunction.

Elevated concentrations of angiotensin-converting enzyme (ACE) and angiotensin II (Ang II) further enhance oxidative stress, which leads to more endothelial dysfunction, cell growth, and inflammation. These changes lead to an upregulation in endothelin-1, adhesion molecules and other mediators of inflammation. One of the major mediators of Ang II is the angiotensin II type 1 receptor (AT₁). Stimulation of the AT₁ receptor promotes vasoconstriction, extracellular matrix molecule deposition, inflammation, and cell migration. This cell growth and collagen deposition leads to vascular remodeling and a narrowed vascular lumen.

Jones DW, Chambless LE, Folsom AR, et al. Risk factors for coronary heart disease in blacks. *Arch Intern Med* 2002;162:2565–71.

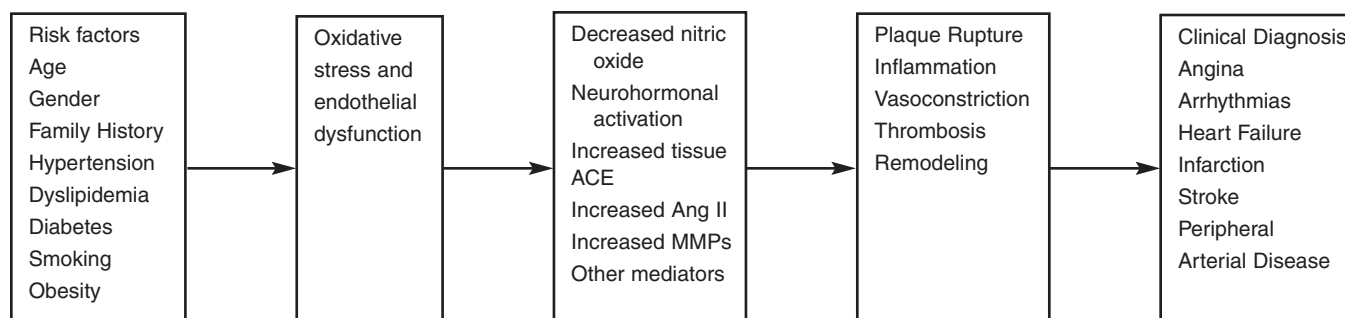


Figure 1-1. Relationship of clinical diagnosis to cardiovascular risk factors.

ACE = angiotensin-converting enzyme; Ang II = angiotensin II; MMPs = matrix metalloproteinase enzymes.

Matrix metalloproteinase enzymes (MMPs) also are activated with oxidative stress, leading to the breakdown of collagen and other vascular tissue. Enhanced activity of MMPs is shown to be associated with atherosclerotic plaque instability and rupture.

Endothelial dysfunction also is associated with a decrease in the amount of nitric oxide, a vasodilator that is secreted in response to hemodynamic stress. Therefore, the balance of vasoconstriction and vasodilation is interrupted and leads to vascular remodeling and injury. Preventive strategies that target cardiovascular risk factors known to cause oxidative stress and endothelial dysfunction can result in decreased cardiac disorders, such as angina, MI, and HF (see Figure 1-1).

Modifiable Cardiovascular Risk Factors

Trends in Established Risk Factors

Hypertension

For more than 100 years, the relationship between high blood pressure and cardiovascular morbidity and mortality has been recognized. However, effective drug treatment has only been available for the past 3 decades. Beginning in 1977, the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension (JNC) periodically issues practice guidelines to help clinicians manage patients with hypertension. In addition to JNC, the World Health Organization (WHO) and the International Society of Hypertension also issue recommendations. Consider which guideline is the most recent. Older guidelines lack the most recent clinical trial data. Other considerations the strength of the evidence, such as the number, size, and type of trials considered by the experts writing the guidelines.

One of the most significant trends recognized throughout the years is the importance of systolic blood pressure. Much of earlier research in patients with hypertension focused on diastolic blood pressure, although it is now recognized that

systolic blood pressure is a more powerful predictor of mortality due to cardiovascular disease and stroke. The relative importance of systolic blood pressure increases with advancing age.

Data from the Framingham Heart Study show that in patients younger than 50 years old, diastolic blood pressure was the strongest predictor of CHD. In patients 50–59 years old, diastolic blood pressure, systolic blood pressure, and pulse pressure, which is the difference between systolic and diastolic pressure, also predicted risk of CHD. In patients older than 60 years old, diastolic blood pressure is inversely related to CHD risk and systolic blood pressure became an important component of pulse pressure, which emerged as the strongest risk factor.

In another study using data from the Multiple Risk Factor Interventions Trial (MRFIT), the relative predictive powers of diastolic blood pressure, systolic blood pressure, and pulse pressure were evaluated. The study found that systolic blood pressure, compared to diastolic blood pressure, was an increasingly important risk factor in men 45 years old and older.

Another changing target is the definition of “optimal blood pressure”. Again, a study using data from the Framingham study, a stepwise increase in the rate of cardiovascular events is noted to correlate with a higher baseline blood pressure across three ranges (optimal less than 120/80 mm Hg, normal 120–129/80–84 mm Hg, and high-normal 130–139/85–89 mm Hg). Compared with optimal blood pressure, high-normal blood pressure was associated with a risk-factor-adjusted hazard ratio of 2.5 in women and 1.6 in men. These results demonstrate that even small changes in blood pressure within the normal range are associated with increased risk for cardiovascular disease.

Throughout the years, the reports from the JNC evolved into a sophisticated tool for the definition of hypertension. In 1977, hypertension was defined as a diastolic blood pressure of greater than or equal to 105 mm Hg with no recommendations for systolic blood pressure. With JNC-VI, there are six risk stratification categories, with lower blood pressure goals for patients already at high risk for cardiovascular disease (e.g., patients with diabetes,

Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease change with aging? *Circulation* 2001;103:1245–49.

Domanski M, Mitchell G, Pfeiffer M, et al. Pulse pressure and cardiovascular disease-related mortality. *JAMA* 2002;287:2677–83.

Vasan RS, Larson MG, Leip EP, et al. Impact of high normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291–97.

patients with target organ damage). The WHO and the International Society of Hypertension have taken similar approaches. Their guidelines also stress using other risk factors for cardiovascular disease when evaluating blood pressure.

Despite the progress made in identifying blood pressure as a risk for cardiovascular disease, the aggressive goals for controlling blood pressure, and the large number of drugs available to treat blood pressure, major challenges remain. It is estimated that about 34% of patients with hypertension in the United States have their blood pressure controlled to the level of 140/90 mm Hg. Globally, the rates for control of blood pressure are worse.

The JNC-7 report continued the downward shift in the definition of hypertension. The JNC-7 recommends individuals with a systolic blood pressure of 120–139 mm Hg or a diastolic blood pressure of 80–89 mm Hg be defined as prehypertensive and begin lifestyle modifications. If blood pressure is greater than 20/10 mm Hg above goal blood pressure, consideration should be given to initiating drug therapy with two agents, one of which is usually a thiazide diuretic.

Smoking

Cigarette smoking is the single most preventable cause of premature death in the United States, and a major cause of cardiovascular disease and death. In fact, nearly 20% of deaths in the United States are smoking related. It has been estimated that the number of cardiovascular deaths attributable to smoking exceeds 118,000 in men and 61,000 in women each year. On average, smokers die almost 7 years earlier than nonsmokers.

Cigarette smoking is common in society. According to government estimates in the United States, 29% of the general population smokes, including 4.5 million adolescents. There are important regional differences in smoking trends in the United States. These regional differences in smoking prevalence parallel regional differences in cardiovascular disease prevalence: lower in the West compared with the Northeast and South.

Smoking rates also are associated with educational level: 37% of adults who did not complete high school smoke cigarettes, whereas only 17% of college graduates smoke. A similar association exists between educational level and cardiovascular disease.

Smoking is common among racial and ethnic minorities, the fastest growing segments of the American population. Among all four major United States racial and ethnic minority groups (black, American Indian/Alaskan Native, Asian American/Pacific Islander, and Hispanic), cigarette smoking is a major cause of death and disease.

Differences in the magnitude of disease risk are directly related to differences in patterns of smoking. Of the four major ethnic groups, black men bear one of the greatest health burdens. Among women smokers from minority groups, Asian-American and Hispanic women have the lowest prevalence of smoking. The patterns of tobacco use result from multiple factors, including socioeconomic status, cultural characteristics, psychological stress, targeted advertising, price of tobacco products, and ability of communities to mount effective tobacco control initiatives.

There is an increase in the number of women smokers. The largest growing group of new smokers is young girls and female teenagers. Compared with men, women also have lower smoking cessation rates despite the fact that women comprise a larger percentage of adult smokers who would like to stop smoking. Smoking may cause a greater relative risk for cardiovascular disease in women than men. Although the risk for smoking-related vascular complications increases in a stepwise fashion with the number of cigarettes smoked, even smoking one to four cigarettes per day doubles or triples the risk of CHD.

Smoking enhances thrombogenesis. In female smokers older than 35 years old who are receiving oral contraceptives, there is a well-established increased risk of MI and stroke. Current users of oral contraceptives who are younger than 50 years old and smoke heavily (more than 25 cigarettes/day) have a relative risk of MI that is 20-fold greater than past users or women who have never used oral contraceptives. The primary mechanism by which oral contraceptives are associated with cardiovascular disease in smokers is believed to be thromboembolic, as opposed to worsened atherosclerotic plaque development, given that both smoking and oral contraceptive use effect coagulation and platelet activity.

Women who smoke undergo natural menopause at a younger age—on average, 1–2 years earlier—than nonsmokers. A longer time in menopausal status for female smokers may further enhance coronary risk because earlier menopause is associated with an increased risk of CHD.

Cigarette smoking may be associated with an antiestrogenic effect increasing estradiol 2-hydroxylation due to increased hepatic metabolism. This irreversible metabolic pathway yields 2-hydroxyestrogens, which possess minimal peripheral estrogenic activity. A significant increase in estradiol 2-hydroxylation is reported in premenopausal women who smoked at least 15 cigarettes/day.

Mainstream tobacco smoke, or smoke that is directly inhaled into the smoker's upper airway and lower respiratory tract, is known to have deleterious cardiovascular effects and to be linked with fatal and nonfatal cardiovascular disease. Mainstream cigarette smoke stimulates a significant increase in monocytes and a dose-dependent increase in monocyte adherence to the endothelium. Adherence and migration of monocytes into the subendothelial space, their phenotypic transformation into macrophages, and their uptake of cholesterol are among the primary events in the development of an atheroma in the vascular system. Data also indicate that tobacco smoke exposure activates platelets through a variety of mechanisms, including production of platelet-activating factor, increased concentrations of circulating Von Willebrand factor, increased concentrations of circulating catecholamines, inhibition of cyclooxygenase, inhibition of prostaglandin I_2 , increased thromboxane synthesis, and release of platelet-derived growth factor. The release of platelet-derived growth factor stimulates smooth muscle cell proliferation, which is one of the initial steps in the development of atherosclerosis. The net result of these changes is that it is predisposed to thrombus formation,

which can lead to MI in patients with and without coronary atherosclerosis.

In addition to the effect that cigarette smoking has on platelets, there are data to support an adverse effect on lipid metabolism. It is suggested that smoking increases very-low-density lipoprotein (VLDL), LDL, and plasma free fatty acids while causing a decrease in HDL in a dose-dependent manner. Oxidation of lipids and fatty acids is known to be a major cause of morbidity and mortality in cardiovascular disease. Cigarette smoking initiates lipid oxidation by generating an abundance of free radicals when inhaled.

Exposure to tobacco smoke leads to changes in heart function and structure. Tobacco smoke adversely alters the myocardial oxygen supply-demand relationship, which can predispose the myocardium to ischemia, and can alter myocardial performance. Increases in carboxyhemoglobin as a result of tobacco smoke leads to decreased oxygen-carrying capacity, whereas nicotine activation of the alpha-adrenergic sympathetic nervous system leads to coronary vasoconstriction and decreased blood flow to the myocardium. These two effects predispose the myocardium to ischemia and/or cardiomyopathy.

Dyslipidemia

The Adult Treatment Panel (ATP) guidelines of the National Cholesterol Education Program (NCEP) evolved in much the same way as the JNC guidelines for hypertension. Throughout the years, guidelines have become increasingly specific and aggressive for patients considered at the highest risk for coronary events.

Since the ATP-III guidelines were last published, the Heart Protection Study (HPS) supplied additional support for the use of statin therapy in patients at high risk for coronary events even in the face of LDL at concentrations of 130 mg/dl or lower. In fact, there is a benefit from simvastatin even in patients who were “at goal” in this group of high-risk patients. Of equal importance is the finding that antioxidant vitamins, specifically vitamins E, C, and beta-carotene, were not effective in reducing coronary events.

What the ideal or target lipid goals should be is debated. Ongoing trials attempt to answer the question whether maximal versus conventional doses are best for patients at high risk for coronary disease. It also is important to assess combination therapy with niacin given the impressive reduction in coronary events in the HDL Atherosclerosis Treatment Study (HATS).

Diabetes

About 17 million Americans have diabetes, 90% of whom have type 2 diabetes mellitus. The prevalence of diabetes is dramatically increasing. The number of Americans with some degree of abnormal glucose tolerance (those at risk for developing diabetes) is nearing 35 million.

The growing epidemic of obesity (now estimated at 44 million) and lack of physical activity may ensure that diabetes continues to be a major contributor to cardiovascular disease in the decades to come.

People with diabetes should undergo a thorough risk assessment for cardiovascular disease. People with type 2 diabetes mellitus have 2–5 times the risk of cardiovascular disease compared to those without type 2 diabetes mellitus. People with diabetes often have additional modifiable risk factors such as hypertension, dyslipidemia, and obesity. All of these risk factors must be managed in order to successfully reduce the risk of cardiovascular disease.

Diabetes is considered a CHD equivalent, meaning the risk for a cardiovascular event, such as MI, is the same as for an individual who has documented coronary artery disease. Glucose control should be maintained in order to achieve a hemoglobin A1C (Hb A1C) of less than 7%. According to the American Diabetes Association, LDL should be less than 100 mg/dl and HDL should be 45 mg/dl or greater.

Hypertension should be aggressively treated in patients with diabetes. The association between age and pulse pressure is enhanced by the presence of type 2 diabetes mellitus and by the magnitude of the mean arterial pressure. In type 2 diabetes mellitus, elevated pulse pressure is positively associated with cardiovascular mortality. These findings support the concept of accelerated vascular aging in type 2 diabetes mellitus.

Patients with diabetes should have a blood pressure of 130/80 mm Hg or less. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers should be used in patients with microalbuminuria (30–299 mg/24 hours) or proteinuria (greater than or equal to 300 mg/24 hours), and in patients more than 55 years old with another risk factor for cardiovascular disease. The subset of patients with diabetes from the Heart Outcomes Prevention Evaluation (HOPE) trial, received a substantial benefit when ramipril was added to their medical regimen, irrespective of blood pressure lowering. Ramipril lowered the risk of the combined end point (MI, stroke, or cardiovascular death) by 25% compared to placebo. When the outcomes were individually analyzed, there was a 22% reduction in MI, 33% reduction in stroke, and a 37% reduction in cardiovascular death. It is not clear whether ACE inhibitors are better than angiotensin receptor blockers in this patient population because are not any “head-to-head” trials.

Aspirin (81–325 mg/day) should be considered in all patients with diabetes older than 30 years old, especially if they smoke, have hypertension, dyslipidemia, microalbuminuria, or are obese. The use of aspirin is not recommended in patients less than 21 years old due to the incidence of Reye’s syndrome. Clopidogrel may be used as an alternative to aspirin for primary or secondary prevention.

Smoking increases the microvascular and macrovascular complications of diabetes. Smoking cessation is advised in

Brown BG, Zhao X, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;345:1583–92.

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000;355:253–59.

all patients with diabetes due to the heightened risk of morbidity and mortality.

Intensive control of diabetes, hypertension, and dyslipidemia is needed to modify the risk and progression of cardiovascular disease. The “single best regimen” for all patients is elusive; however, it is clear that aggressive pharmacotherapy, designed to reach individual therapeutic goals as soon as possible, in combination with lifestyle changes is warranted.

Emerging Risk Factors

The number of risk factors for CHD is substantial and continues to grow. It is likely that in addition to the traditional risk factors mentioned, emerging risk factors will become increasingly important in helping clinicians tailor treatment strategies to specific patients. Risk stratification is important because it can help direct specific therapy and financial resources to those patients most likely to benefit.

C-Reactive Protein

There is increasing interest in CRP as a predictor of cardiovascular disease. It is known that atherothrombosis occurs in the absence of elevated LDL. It also is noted that CRP, a marker of inflammation, is associated with an increased risk of MI. The CRP also is associated with central adiposity and insulin resistance. Highly sensitive assays for CRP that detect low-grade inflammation are available and used with increasing frequency to recognize patients at risk for cardiovascular disease. The definitions of low risk (less than 1.0 mg/L), average risk (1.0–3.0 mg/L), and high risk (more than 3.0 mg/L), which correspond to approximate tertiles of high sensitivity-CRP in the adult population. The high-risk tertile has a 2-fold increase in relative risk compared with the low-risk tertile. These tertiles are based on distributions of hs-CRP samples from more than 15 populations involving more than 40,000 people.

One possible use for CRP measurement is to motivate people at moderate to high risk for cardiovascular disease to improve their lifestyles (e.g., smoking cessation, dietary modification, exercise, and weight loss) or to comply with drug therapies. At this time, routine measurement in the general population is not indicated.

Some studies suggest that CRP directly contributes to vascular damage. The CRP is frequently detected in atherosclerotic plaques, has the ability to stimulate tissue factor production by macrophages, increases red blood cell adhesiveness, and enhances complement activation after binding partly degraded, non-oxidized LDL. This is consistent with the recent finding of widespread neutrophil activation across the coronary vascular bed in patients with unstable angina but not found in control patients or those with chronic stable angina. A significant correlation was found between systemic concentrations of CRP and laboratory assessment of neutrophil activation.

Recently, the CRP and LDL concentrations were assessed before randomization in almost 28,000 women participating in the Women’s Health Study, a trial evaluating aspirin and vitamin E as primary prevention for CHD. After adjusting for age, smoking, hypertension, diabetes, and the use of hormone therapy (HT), strong positive correlations were observed for both CRP and LDL. However, in this trial, CRP proved to be superior compared to LDL in predicting risk for a first cardiovascular event (CHD, stroke, and death from cardiovascular causes). The CRP and LDL concentrations were minimally correlated, suggesting that each marker was detecting a different high-risk group.

Another finding from this large trial was that CRP added to the 10-year risk assessment calculated using the Framingham risk score. Women with high CRP and low LDL were at greater risk for cardiovascular events compared to women with low CRP and high LDL. The age-adjusted rates of events per 1000 person-years were 1.3 (low CRP and low LDL), 2.0 (low CRP and high LDL), 2.6 (high CRP and low LDL), and 3.9 (high CRP and high LDL).

The CRP may be a marker, a causative agent, or a consequence of CHD. Additional studies are needed to determine the relevance of apparently sustained falls in CRP concentrations after the use of lipid-lowering statin drugs, as well as apparently sustained increases in CRP concentrations after initiation of postmenopausal HT. It is conceivable that inflammation-guided therapy by the monitoring of CRP may become standard practice in the future.

Cytokines

Interleukin-6 (IL-6), like CRP, also is being evaluated as a potential marker for cardiovascular disease. Increases in body mass index (BMI), blood pressure and smoking are associated with IL-6 and CRP elevations. The IL-6 concentrations are noted to be inversely related to exercise frequency and the use of HT. Data from the Women’s Health Study revealed that IL-6 concentrations were highest among women who never used HT, whereas CRP concentrations were highest among women who currently used HT. There was minimal association among IL-6, CRP, and lipid concentrations. Based on these data, IL-6 and CRP are independently related to several clinical cardiovascular risk factors among apparently healthy women.

Fibrinogen

Fibrinogen also is identified as an independent risk factor for CHD in several prospective epidemiologic studies. In a meta-analysis of six studies, there was a more than 2-fold increase of MI or stroke in patients with high fibrinogen concentrations. Unfortunately, no long-term

Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557–65.

Bermudez EA, Rifai N, Buring J, et al. Interrelationships among circulating interleukin-6, C-reactive protein, and traditional cardiovascular risk factors in women. *Arterioscler Thromb Vasc Biol* 2002;22(10):1668–73.

pharmacological interventions can significantly reduce fibrinogen concentrations.

Infection

Some studies show an increased risk of CHD in individuals who have been exposed to certain infectious agents. The data for *Chlamydia pneumoniae* is the most compelling. The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia study treated 302 patients with CAD and elevated titers to *C. pneumoniae* with azithromycin in a prospective randomized trial. Patients received azithromycin for 3 months. There were no significant differences between the placebo and azithromycin groups in the incidence of the 3-month composite end point of four inflammatory markers (CRP, IL-1, IL-6, and tumor necrosis factor). At the end of 6 months, CRP and IL-6 concentrations were lower in the azithromycin group but antibody titers were not changed and there was no difference in the incidence of cardiovascular events.

Metabolic Syndrome

The constellation of hypertension, dyslipidemia, insulin resistance, and obesity is labeled as Syndrome X or the metabolic syndrome. Both NCEP and WHO have similar definitions of the metabolic syndrome (see Table 1-2) that incorporate objective quantification of the risk factors to assign the diagnosis of metabolic syndrome. Almost 35 million Americans have some degree of abnormal glucose tolerance. Many of these individuals also have the metabolic syndrome. The risk factors associated with the

Table 1-2. Definitions of Metabolic Syndrome

NCEP

Three of the following:

- Fasting glucose of > 110 mg/dl
- Abdominal obesity; waist circumference > 102 cm for men and > 99 cm for women
- Serum triglycerides > 150 mg/dl,
- Serum HDL cholesterol < 40 mg/dl for men and < 50 mg/dl for women and
- Blood pressure > 130/85 mm Hg or taking antihypertensive drug

Modified WHO

Hyperinsulinemia or a fasting glucose of > 110 mg/dl

Plus at least two of the following:

- Abdominal obesity (waist-to-hip ratio > 0.90 or body mass index > 30 or waist girth > 94 cm),

Dyslipidemia (serum triglycerides > 150 mg/dl or HDL cholesterol < 35 mg/dl),

Hypertension (blood pressure > 140/90 mm Hg or taking medication)

HDL = high-density lipoprotein; NCEP = National Cholesterol Education Program; WHO = World Health Organization.

metabolic syndrome contribute to oxidative stress, which impairs endothelial function. One of the abnormalities associated with the metabolic syndrome (insulin resistance) predisposes the patient to the development of type 2 diabetes mellitus. The metabolic syndrome is becoming increasingly common due to the growing problem of obesity and physical inactivity.

The pathophysiological basis behind the metabolic syndrome is a complex interplay of many factors and may be different among different patients. Many observations have been made regarding these patients.

Visceral fat is an important source of inflammatory cytokines and CRP is noted to be elevated in patients dealing with obesity. Obesity is associated with enhanced lipid peroxidation and persistent platelet activation especially in women with android obesity (hip-to-waist ratio of 0.86 or more). The highest rates of both lipid peroxidation and platelet activation occur in women in the upper third and fourth quartiles of CRP and with android obesity. Conversely, normal rates of platelet activation occur in women in the two lower quartiles of CRP. Following weight loss in women in this same study, CRP levels declined and platelet activation rates returned to normal. The CRP levels also are observed to fall in parallel to weight loss-associated improvements in insulin resistance.

Obesity and hypertension play major roles in the metabolic syndrome. Hemodynamically, the expanded plasma volume caused by obesity leads to left ventricular overload, thereby increasing cardiac output. At the same time, hypertension compounds this ventricular stress by causing an associated pressure overload resulting in LVH.

Associated with obesity is an increased burden of neurohormonal activation resulting in increases in catecholamines, angiotensin II, endothelin, insulin, leptin, growth hormone, steroids, and thyroid hormone. Behavioral modification and pharmacotherapy of obesity is woefully inadequate. Many drugs used to treat obesity raise arterial pressure or have other adverse effects. Fortunately, there are no contraindications imparted by obesity that complicate the drug treatment of the associated hypertension.

Many studies show a relationship between socioeconomic status and cardiovascular disease. It has been suggested that belonging to a poor socioeconomic class in childhood (and adulthood) is related to insulin resistance, reduced HDL, increased triglycerides, and obesity.

The modulation of insulin resistance is possible with metformin and the thiazolidinediones (TZDs). Thiazolidinediones only lower the Hg A1C by about 1%, but they have additional potentially beneficial effects. Thiazolidinediones favorably impact lipoprotein metabolism, fibrinolysis, endothelial function, and inflammation. Thiazolidinediones may raise HDL by 20% and decrease elevated triglycerides. They also facilitate the

Anderson JL, Muhlestein JG, Carlquist J, et al. Randomized secondary prevention trial of azithromycin in patients with coronary artery disease and serological evidence for *Chlamydia pneumoniae* infection. *Circulation* 1999;99:1540–47.

Marso SP. Optimizing the diabetic formulary: beyond aspirin and insulin. *J Am Coll Card* 2002;40:652–61.

transition of small, dense LDL particles into larger, more buoyant and less atherogenic particles.

Thiazolidinediones must be used with caution in patients with HF because their use is associated with fluid retention. These agents are contraindicated in patients with New York Heart Association class III and IV failure. Other disadvantages of TZDs include weight gain and may potentiate the formation of colonic polyps.

Metformin has the advantage of reducing hepatic glucose production while enhancing glucose utilization in the periphery. It minimizes weight gain or promotes weight loss. Metformin has favorable effects on lipoproteins, reducing triglycerides and LDL while increasing HDL slightly.

Homocysteine

Throughout the past 10 years, increased levels of homocysteine have been recognized to be associated with cardiovascular disease. Numerous case-controlled and observational studies have confirmed that elevated homocysteine concentrations are present in people with cardiovascular disease or who are at highest risk of cardiovascular disease. However, it is unclear if elevated homocysteine is a cause of cardiovascular disease or merely a marker of the presence of cardiovascular disease.

Homocysteine is an amino acid that builds and maintains tissue. A normal fasting serum concentration is less than 12–15 $\mu\text{mol/L}$. Some observational studies report that for every 5 $\mu\text{mol/L}$ increase in plasma homocysteine, the odds ratio of cardiovascular disease increases by 1.6 in males, and 1.8 in females. Increased homocysteine concentrations are associated with endothelial dysfunction and platelet aggregation. If there is a causal relationship between homocysteine concentrations and cardiovascular disease, the hypothesis is that the autooxidation of homocysteine and subsequent generation of reactive oxygen species may accelerate LDL oxidation. Support for a causal role of homocysteine in the development of cardiovascular disease, is provided by children with inborn errors of metabolism that cause extremely increased homocysteine concentrations. These children exhibit early vascular thrombosis and death.

Alternative theories suggest elevated homocysteine is merely a marker of the presence of atherosclerotic disease, whether or not the patient has experienced an actual cardiovascular disease-defining event. This viewpoint is supported by the body of evidence that indicates homocysteine concentrations are increased in proportion to disease severity, and that the risk of cardiovascular events is continuous and graded with increasing homocysteine concentrations. It is suggested that moderately elevated homocysteine concentrations are a marker of tissue damage and repair and do not contribute to new vascular damage or thrombosis.

Vitamins B₁₂ and B₆ and folic acid are each essential co-factors to metabolic pathways that degrade homocysteine. Daily consumption of these three vitamins

decrease plasma homocysteine by an average of 40%. Current research is focusing on the impact of vitamin supplementation on cardiovascular disease events and progression. At this time, the American Heart Association recommends screening for hyperhomocystinemia in high-risk patients with either a personal or family history of cardiovascular disease. However, what to do with the results is not clear. Some practitioners advocate empiric administration of a daily vitamin “cocktail” consisting of vitamin B₁₂ (0.4–1 mg), vitamin B₆ (10–50 mg), and folic acid (1–2.5 mg) to lower plasma homocysteine concentrations, citing the potential benefits are not outweighed by any significant side effects or prohibitive costs. Others feel increased emphasis on the currently underutilized agents proven to decrease cardiovascular disease morbidity and mortality, such as lipid-lowering agents, should take priority over the promotion of unproven therapies.

Cardiovascular Prevention Strategies

Prevention and Risk Assessment

Cardiovascular prevention is defined as a reduction in the absolute risk for cardiovascular disease. Absolute risk is the probability of developing cardiovascular disease in a finite period, such as within the next 10 years. Absolute risk is used to calculate the number of patients needed to treat (with a drug or a procedure) to prevent one event. The number needed to treat to prevent one event is calculated by dividing the difference of the absolute risk (the absolute risk of group A vs. group B) into one (1/absolute risk difference). Relative risk is the ratio of the likelihood of CHD developing in people with and without a given risk factor, or at a given intensity of a risk factor. Relative risk can be thought of as the rate at which an individual is accruing absolute risk. Serum cholesterol data provide a good example of the difference between relative and absolute risk. A young adult with a high-serum cholesterol concentration carries a low absolute risk for cardiovascular disease, but has a high relative risk compared with a young adult with a low-serum cholesterol concentration. The young adult with high-serum cholesterol is unlikely to have a cardiac event within the next 10 years, but the risk of experiencing premature heart disease is higher than a similar individual with a normal lipid profile. The goal for reducing elevated serum cholesterol in young adults is to retard atherogenesis throughout life, not to simply prevent MI in the next decade.

Some experts have suggested having three distinct strategies (primordial, primary, and secondary) for prevention of cardiovascular disease. Primordial prevention is the prevention of developing risk factors. Primordial preventive strategies are aimed at lifestyle and behaviors. Primary prevention is generally aimed at modifying risk

Christen WG, Ajani UA, Glynn RJ, Hennekens CH. Blood levels of homocysteine and increased risks of cardiovascular disease. *Arch Int Med* 2000;160:422–34.

factors in hope of delaying or preventing cardiovascular disease. Secondary prevention is aimed at controlling risk factors, as well as direct therapeutic intervention in patients with clinically detectable cardiovascular disease. Patients with clinical manifestations of atherosclerotic disease (angina pectoris, MI, history of cardiac revascularization, PAD, and cerebrovascular disease) are at high risk for numerous types of cardiovascular events and aggressive preventive measures are needed (see Table 1-3).

The ultimate goal of cardiovascular disease prevention relies on the reduction of the overall absolute risk of disease rather than the immediate end point of individual risk factor management. The strategy for primary prevention in individuals with no history of cardiovascular disease is to estimate the absolute risk of a vascular event and to take appropriate action according to that level of risk.

Primordial prevention strategies require a different approach than current strategies of focusing on patients at high risk for cardiovascular disease. Primordial prevention strategies need to focus on children and teens, and foster healthy lifestyle behaviors with an emphasis on appropriate exercise, diet, and abstention from tobacco products.

Primary prevention strategies are aimed at preventing clinical events in patients with risk factors that require drug treatment (e.g., hypertension and dyslipidemia). Effective primordial strategies are more cost-effective than life-long drug treatment for primary prevention.

Secondary preventive strategies are aimed at patients with established cardiovascular disease who are at the highest risk for cardiovascular events. When evaluating the cost-effectiveness of drug therapy, the number of patients needed to treat to prevent one clinical event is lowest for secondary prevention. Despite well-established benefits for certain drugs (e.g., ACE inhibitor use in HF and β -blockers post-MI), the data suggest that practitioners are slowly adopting their use. There are several reasons that could explain the slow rate of adoption of practice guidelines, including lack of awareness by some physicians, overemphasis on relative contraindications of drugs, and lack of sufficient time during outpatient visits to adequately assess the need for and discuss preventive treatments. Health care providers can direct patients lacking financial resources to pharmaceutical industry programs designed to help them secure medication. The Web site <http://www.needymeds.com> contains links describing available programs.

Peripheral arterial disease can result from vasospasm or occlusive disease. It is estimated that 20% of individuals older than 70 years old have PAD. Individuals with PAD are identified using the ankle-brachial index, which is the ratio of the arterial pressures in the ankle and the arm, as a noninvasive and simple-to-perform screening tool. Patients with PAD are at increased risk for cardiovascular mortality, but these patients often are treated less intensively with lipid-lowering agents, antiplatelet therapy, and antihypertensives. Cigarette smoking is one of the most important risk factors for PAD and the sequelae of claudication, limb-threatening ischemia, and amputation.

Table 1-3. Levels of Cardiovascular Prevention and Strategies

Primordial	Physical activity Healthy eating Maintaining ideal weight Psycho-social factors Familial predisposition
Primary	Treatment of dyslipidemia, hypertension, or diabetes Smoking cessation Use of aspirin in appropriate patients in addition to primordial strategies
Secondary	Aspirin Angiotensin-converting enzyme inhibitors β -Blockers Rehabilitation in addition to primordial/primary strategies

Smoking cessation should be recommended for all patients with PAD who currently smoke, and any pharmacological or behavioral therapies that provide benefit should be used to assist in attaining this goal.

Issues Surrounding the Effectiveness of Preventive Strategies

The observed effect of drugs in clinical trials is typically more than what is seen in actual clinical practice. This phenomenon was recently demonstrated with statin therapy and its effect on LDL lowering. Results from a study of more than 350 patients found that the observed:expected ratio for the overall sample was 0.79, thus, on average, LDL reductions were about 80% of expected (based on data presented in the package insert). The results from this study were not normally distributed. Twenty-five percent of patients had less than 50% of the expected response to the prescribed dose. The below expected response to therapy is due to less than optimal patient adherence to the prescribed medical regimen and diet. It is possible that some patients may be “poor responders” to certain types of drug therapy due to differences in metabolism or other unidentified mechanisms. It is important for future research to identify potential genetic factors that help optimize this aspect of cardiovascular therapy.

Increasing adherence to a medical regimen is difficult. Most studies have evaluated behavioral or a combination of behavioral and educational interventions. Behavioral interventions, such as telephone or postal reminders, may increase compliance with drug therapy, but only to a limited extent. One research group analyzed adherence patterns with lipid-lowering therapy among 5600 Medicaid or indigent patients to lipid-lowering therapy. The group found that patients with no co-payment were less likely to adhere to a drug regimen than patients with a \$2 co-pay. This

Frolkix JP, Pearce GL, Nambi V, Minor S, Sprecher DL. Statins do not meet expectations for lowering low-density lipoprotein cholesterol levels when used in clinical practice. *Am J Med* 2002;113:625–9.

finding reinforces the concept that patients must have “buy-in” to the concept of preventive health measures and they must value necessary measures taken to achieve the long-term goal.

Specific intervention programs may be effective. Using the American Diabetes Association guidelines, patients with diabetes, in a primary care clinic, were screened for daily prophylactic aspirin use by pharmacists. At baseline, 33% of patients were receiving aspirin. After either a telephone intervention or clinic intervention, 82% of patients were receiving aspirin or had accepted the recommendation to take aspirin on a daily basis. This is an example where community pharmacists have an impact as aspirin does not require a prescription.

Barriers and Challenges to Cardioprotection

Social and economic factors play a large role in lifestyle, as well as healthy behaviors and health outcomes. The prevalence of obesity has risen from 22.9% in 1994 to 30.5% in 2000, in part due to lower food prices and higher paying, yet more sedentary work. In addition, more women are working, resulting in more families eating prepared meals (e.g., “fast food”).

Both type 2 diabetes mellitus and obesity are preventable by adapting appropriate lifestyle behaviors. Increasing physical activity and reducing caloric intake are fundamental steps in achieving ideal body weight. Yet it is estimated that 25% of adults do not engage in any leisure time physical activity. Incentives from employers (memberships in health clubs) and/or the government (tax-deductible memberships) may be needed to help motivate some people to increase exercise activity.

Delivering the highest quality of care for patients is necessary to achieve the best possible outcomes. How to determine whether clinicians are delivering the highest quality of care can be difficult. Measuring performance is limited by the data available in the medical record. Legitimate reasons for not prescribing a specific agent are lacking when doing retrospective reviews.

There are several studies evaluating the economic consequences of cardiovascular disease preventive strategies. These studies generally focus on the incremental cost of an intervention per incremental unit of health outcome. Absolute reductions rather than relative differences determine cost-effectiveness. Because patients with diabetes are at a high risk for CHD and concomitant risk factors in this patient population such as hypertension and dyslipidemia, aggressive treatment of diabetes is economically attractive.

There are not many studies evaluating the long-term effects of exercise. However, if it is assumed that sedentary behavior increases the risk of heart disease almost 2-fold, more than \$6 billion could be saved if the entire population began a simple but regular exercise program consisting of walking 30 minutes/day at least 3 times/week. The cost per year of life gained is below \$20,000.

Another problem in assessing the cost benefit of a particular strategy includes the concept of “discounting”. People prefer to receive a benefit immediately and to delay the cost indefinitely. Discounting incorporates this concept

into an economic analysis by weighing costs and benefits less heavily the farther into the future they occur. The fact that people and society value the present more highly than the future adversely affects decisions regarding prevention strategies.

Although primary prevention is more attractive on an emotional level, economic analyses usually find secondary prevention to be more cost efficient. The number needed to treat is much smaller for secondary prevention and the cost to save a life is also smaller. The decision to implement a preventive strategy for a lower risk group may take money away from other important social needs such as housing or education. Finally, health policy is influenced by many other factors (e.g., political, social, human, or scientific) and not necessarily solely by an economic analysis.

Pharmacological Therapy and Other Strategies for Cardioprevention

Antithrombotic Agents

Aspirin

Aspirin, an inhibitor of the enzyme cyclooxygenase, has both antiplatelet and anti-inflammatory properties making it an important agent in the prevention and treatment of atherothrombotic disease. Aspirin is inexpensive and well tolerated, especially at low doses, in the majority of individuals, which makes it an ideal preventive agent.

The use of aspirin as a primary preventive strategy was recently reviewed. There are five randomized trials evaluating the use of aspirin for primary prevention. With the exception of one trial (British Doctors’ Trial), all showed a benefit of using aspirin, primarily due to a reduction in the occurrence of MI. The absolute risk reduction ranged from 0.03 to 0.31% per year. A meta-analysis found a relative risk reduction of 15%.

The beneficial effect of aspirin depends on the absolute risk of MI at baseline. For example, when the 5-year absolute risk of a coronary event was estimated to be 5%, aspirin reduced the absolute risk by 0.3% per year. When the 5-year absolute risk of a coronary event was estimated to be 1%, aspirin reduced the absolute risk by 0.06% per year. In one subgroup analysis, the beneficial effect of aspirin was most notable in men with elevated concentrations of CRP. One suggested algorithm recommends aspirin use for primary prevention for all patients (without a contraindication) with an absolute risk for CHD of 1.5% or more per year. For patients with an absolute risk of 0.6% or less per year, the risk of aspirin outweighs the benefit. For a patient with a risk between 0.7 and 1.4% per year, aspirin should be considered if the patient has diabetes, has target organ damage due to hypertension, poor physical fitness, or the patient has a strong desire to take aspirin.

Chronic aspirin use is associated with an increased risk of hemorrhage. The most common site of major bleeding (leading to death, transfusion, or surgery) is from the gastrointestinal tract. Minor bleeding manifests as epistaxis

and easy bruising. Aspirin use is estimated to increase the absolute risk of cerebral hemorrhage by 12 events per 30,000 person-years of follow-up. Because aspirin use is associated with an increase in cerebral hemorrhages, systolic blood pressure should be well controlled in patients taking aspirin.

The ideal aspirin dose is unknown. In primary prevention trials, the aspirin doses varied from 75 to 500 mg/day. There are no head-to-head trials comparing different aspirin doses for primary prevention. Studies looking at aspirin and platelet function show that low doses (less than 100 mg/day) are effective.

Most of the patients in the randomized primary prevention trials were men. Observational data from the Nurses' Health Study, which was conducted in women, suggested that aspirin use reduced the combined rate of nonfatal MI and fatal coronary disease by 25%; however, no benefit was seen in women younger than 50 years old. There is currently an ongoing, randomized trial in women evaluating the use of aspirin for primary prevention.

In the American Heart Association / American College of Cardiology guidelines for secondary prevention of MI and death in patients with atherosclerotic cardiovascular disease, the recommended aspirin dose is 75–325 mg/day. This dose should be continued indefinitely. Some patients, perhaps as many as 10% of those with stable coronary disease, are observed to have “aspirin resistance”, meaning they do not exhibit a reduction in platelet function when receiving aspirin. It is unclear whether these patients have a worse prognosis or derive no benefit from aspirin. It also is not known whether these patients should receive an alternative antiplatelet agent or whether they should receive combination therapy with another antiplatelet agent such as clopidogrel.

Other Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit platelet function by their effects on the cyclooxygenase-1 and -2 (COX-1 and COX-2) enzymes. Through inhibition of COX-1, the production of thromboxane A₂ is reduced, rendering a reduction in platelet activation and aggregation. Inhibition of COX-1 also compromises the intestinal mucosa, predisposing the patient to gastrointestinal bleeding. The COX-2 inhibitors have analgesic and anti-inflammatory effects; however, they do not inhibit platelet function. Recently, the proposed advantage of less gastrointestinal bleeding with the COX-2 inhibitors has come into question because the use of a conventional NSAID with a proton pump inhibitor may be as effective. In addition, there is some concern that use of COX-2 inhibitors is associated with an increase occurrence of acute MI.

The relative safety of the COX-2 inhibitors and other non-aspirin anti-inflammatory agents were recently examined. Concerns regarding the safety of COX-2 inhibitors began with the publication of the Vioxx Gastrointestinal Clinical Outcomes Research (VIGOR) study in November 2000. In VIGOR, rofecoxib 50 mg/day was compared to naproxen 500 mg 2 times/day in more than 8000 patients with rheumatoid arthritis. The drugs were similar in efficacy; however, there were more

gastrointestinal events in the naproxen group. The overall mortality rates were similar, but there were fewer MIs in patients receiving naproxen compared to rofecoxib (0.4% vs. 0.1%; relative risk = 0.2; 95% confidence interval = 0.1–0.7). It was unclear whether the increased number of MIs was a result of an adverse effect of rofecoxib or a protective effect of naproxen.

In August 2001, a review article examined VIGOR, Celecoxib Long-term Arthritis Safety Study (CLASS), and two other trials. The authors reported the annualized rate of MI in patients treated with COX-2 inhibitors and compared it to placebo patients from primary prevention trials. In this review, an increase in cardiovascular events among the patients taking the COX-2 inhibitor was found.

Another review of data from studies involving 28,000 patients treated with rofecoxib, showed no excess of thrombotic effects (as defined by the Antiplatelet Trialists Collaboration) when compared to placebo or NSAIDs other than naproxen. Rofecoxib patients did have a higher incidence of events compared to patients receiving naproxen. Additional case control studies show a cardioprotective effect of naproxen compared to other NSAIDs or no NSAID use.

Because many patients who require drugs for arthritis are in the age group at risk for cardiovascular disease, it is reasonable to recommend concomitant use of low-dose aspirin in those patients taking a COX-2 inhibitor or a NSAID. A large controlled trial directly investigating the use of COX-2 inhibitors and their effects on cardiovascular disease is warranted.

Clopidogrel

Clopidogrel is an adenosine diphosphate (ADP) antagonist that is currently approved as an antiplatelet agent. By preventing the binding of ADP to the platelet receptor, clopidogrel inhibits platelet activation and aggregation. The antiplatelet effect of clopidogrel is irreversible and the major adverse effect is bleeding. Because the mechanisms of aspirin and clopidogrel differ, a potential exists for additive benefit with the combination. There have been several trials evaluating the addition of clopidogrel to aspirin in patients with acute coronary syndrome or in those patients undergoing percutaneous coronary intervention. The addition of clopidogrel to aspirin reduced the composite end point of cardiovascular death, MI, and urgent revascularization. The most recent version of the American College of Cardiology/American Heart Association Guideline Update for the Management of Patients with Unstable Angina and Non-ST Segment Elevation MI recommends, in patients with acute coronary syndrome, clopidogrel and aspirin therapy should be initiated at admission to the hospital and continued for at least 1 month and up to 9 months. In those clopidogrel-treated patients who need coronary artery bypass grafting, clopidogrel should be withheld for 5–7 days before surgery to minimize the risk of bleeding.

There was one large trial that directly compared aspirin to clopidogrel as a preventive therapy. In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, more than 19,000 patients with a recent MI, ischemic stroke, or PAD were randomized to either

clopidogrel or aspirin in a prospective, randomized design. The primary end point was ischemic stroke, MI, or vascular death. The clopidogrel group had an 8.7% relative risk reduction in the composite end point (5.32% vs. 5.83% per year). Of interest, the patients in the PAD subgroup had a significant 23.8% reduction in the primary end point, whereas the stroke and MI patients had reductions that were not statistically significant. Clopidogrel is recommended as a substitute for patients who are unable to take aspirin as a result of hypersensitivity or gastrointestinal intolerance.

Neurohormonal Blockade

While traditional risk factors such as age, hypertension, dyslipidemia, diabetes, and smoking go a long way to identify patients at high risk of cardiovascular disease, these risk factors do not identify everyone. Subgroup analyses of therapies that mediate Ang II suggested that cardiovascular ischemic events were decreased with such therapies beyond that which could be explained by blood pressure reduction alone. In addition, ACE inhibitor use after coronary angioplasty is associated with decreased restenosis. Prospective trials to assess the unique cardiovascular protective effects of ACE inhibitors and Ang II blockers were initiated, and appropriately excluded patients with systolic HF for which ACE inhibitors are known to be extremely beneficial and are the cornerstone of therapy.

In the HOPE study, ramipril was added to usual care in patients with established cardiovascular disease or diabetes plus one other risk factor. Over a 4-year period, there was a striking 22% risk reduction in MI, stroke, or death from cardiovascular causes, that was consistently present in all subgroups and for all three individual end points. The magnitude of reduction in events with ramipril cannot be explained entirely by better blood pressure control, which was only improved 3 and 1 mm Hg systolic and diastolic, respectively. Similarly, in the Losartan Intervention For Endpoint Reduction (LIFE) study, despite equal blood pressure reduction in patients with hypertension and LVH compared to atenolol, losartan reduced the incidence of stroke an additional 25% throughout a 4-year period. This study result suggests Ang II blockers extend additional cardiovascular protection compared to atenolol, another neurohormonal blocking agent. While catecholamine blockade by β -adrenergic blockers such as atenolol is extremely beneficial for blood pressure control and cardiovascular end point reduction, there does not appear to be equal cardiovascular benefit when compared to an Ang II blocker. While the mechanism of additional benefit conferred by agents that mediate the renin-angiotensin-aldosterone system (RAAS) remains unclear, these findings do support the hypothesis that these agents provide benefit independent of their blood pressure effects.

In contrast, the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT) demonstrated that the thiazide diuretic chlorthalidone, with no direct neurohormonal effects, was equal to lisinopril as

the initial agent in the management of hypertension in patients at high risk of cardiovascular events on the composite end point of fatal CHD and nonfatal MI. This result is intriguing and confusing. There were about 32% black participants in ALLHAT. It was established that this population has less renin-dependent hypertension, and responds more favorably to thiazide diuretics compared to whites. The secondary end point of stroke reduction was significantly decreased by 15% in the total population, yet by 40% in the black subgroup. While this subgroup did experience slightly greater blood pressure reduction with the diuretic compared to the ACE inhibitor, the substantially increased stroke benefit exceeds that explained by blood pressure reduction alone.

While mechanistically unclear, these new data suggest if clinicians accept that mediators of the RAAS decrease ischemic events above and beyond those derived by blood pressure reduction, then it must be accepted that thiazide diuretics appear to be just as efficacious, and perhaps slightly better in some of the predefined secondary end points, as initial therapy for hypertension, especially in black patients at high risk of cardiovascular events. Understanding the specific effects of neurohormonal blockade in the prevention of cardiovascular events in patients without systolic dysfunction is in its infancy. Future studies will hopefully clarify the role of these neurohormones and their attenuation on the occurrence of cardiovascular events such as stroke and MI.

Statins

The effect of statin therapy on lipid lowering and reducing cardiovascular events in patients with dyslipidemia is well documented, and is an important aspect of practice guidelines and standard of care. Lowering LDL is a major focus of primary and secondary preventive strategies; however, secondary goals aimed at lowering triglycerides and raising HDL are receiving more attention recently. In addition to lipid-lowering effects, statins are thought to benefit cardiac patients through so called pleiotropic effects, which include improving endothelial function, decreasing vascular inflammation, and stabilizing ruptured plaques.

In primary prevention, lowering LDL focuses on good dietary habits and exercise. A meta-analysis of the Lipid Research Clinic (evaluating cholestyramine), the Helsinki Heart Study (evaluating gemfibrozil), West of Scotland Coronary Prevention Study (evaluating pravastatin), and Air Force/Texas Coronary Prevention Study (evaluating lovastatin) was published in October 2000. The effect of treatment reduced CHD events by 30%, CHD mortality by 29%, and demonstrated a slight benefit on all cause mortality. When the authors analyzed three trials using only statin therapy (West of Scotland Coronary Prevention Study, Air Force/Texas Coronary Prevention Study, and one additional small trial), the beneficial effects were slightly greater. Primary prevention trials do not reduce all cause mortality because the mortality risk over a 5-year period for

CAPRIE Steering Committee. A randomized, blinded trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE.) *Lancet* 1996;348:1329–39.

Dahlöf B, Devereux RB, Kjeldsen S, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint Reduction in hypertension study (LIFE): a randomized trial against atenolol. *Lancet* 2002;359:995–1003.

this patient population is low. It is possible that preventing nonfatal events will eventually lead to an improvement in survival curves if these patients in primary prevention trials were followed for a longer time period. Unfortunately, the trials used in this meta-analysis had an under-representation of women and minorities. The trials also did not control for the use of aspirin.

The Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial-Lipid Lowering Trial (ALLHAT-LLT) compared pravastatin to usual care in about 10,000 patients with hypertension plus one additional risk factor. About 50% of patients had cardiovascular disease at the time of enrollment. The number of deaths did not differ between the groups. Some unique features of ALLHAT-LLT are that the patients also were participating in a hypertension study at the time, and there were large numbers of diabetic and nonwhite patients included. Unfortunately, there was a significant crossover effect that occurred during the trial, rendering the results less useful than anticipated. This crossover partially explains the rather modest difference in total cholesterol lowering seen between the two groups (only 9.6%). By the end of the study, only 70% of the pravastatin patients were taking a statin, whereas 28.5% of the usual care group had started taking a lipid-lowering drug (with 26% taking a statin).

The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) is similar to ALLHAT-LLT in study design. In ASCOT-LLA the population consisted of hypertensive patients with at least three other risk factors for cardiovascular disease. The majority of patients were White (95%) and male (81%). Patients with a serum cholesterol concentration less than 250 mg/dl were randomized to atorvastatin 10 mg/day or placebo. The antihypertensive arm of the study is ongoing; however, the lipid-lowering arm of the ASCOT was stopped after 3.3 years due to a 36% reduction in MI/fatal CHD events and 27% reduction in fatal/nonfatal stroke in the atorvastatin arm.

Although the relationship between dyslipidemia and coronary disease is clear, total cholesterol concentrations have not correlated well with the incidence of stroke. Yet, the observed incidence of stroke was reduced from 2.38% to 1.67% in a meta-analysis of more than 19,000 patients receiving statin therapy in primary and secondary prevention studies. It is suggested that the neuroprotection seen with statins is due to the prevention of LDL oxidation resulting in plaque stabilization, a reduction in thrombogenesis due to reduced platelet aggregation, or inhibition of activation of clotting factors II, V, and XIII. Statins also are anti-inflammatory and are shown to decrease CRP concentrations.

According to the current NCEP guidelines, patients with established cardiovascular disease and/or diabetes should achieve a LDL less than 100 mg/dl, and those with one and two risk factors for cardiovascular disease should have LDL less than 160 and 130 mg/dl, respectively. However, recent

data suggests that patients at risk for cardiovascular disease may benefit from further lowering of LDL concentrations. The ideal LDL concentration is unknown, although the results from aggressive lipid-lowering studies are forthcoming. Current trials are ongoing that will evaluate the use of statins in patients with normal lipid concentrations but high CRP values. These additional studies help identify patients who will benefit from the nonlipid-lowering effects of statin therapy.

Vitamin Supplementation

During the 1990s, vitamin supplementation for the prevention and treatment of cardiovascular disease was a topic of research and hoped to be a simple solution to a complex problem. The vitamins under investigation were largely categorized as antioxidants, specifically vitamin C, vitamin E, and beta-carotene. In vitro, these vitamins demonstrated the ability to decrease LDL oxidation, which could lead to decreased production of highly atherogenic foam cells, and retard the aggressive formation of unstable plaques. Observational studies of dietary antioxidant consumption reported a decreased risk of cardiovascular disease associated with the diets highest in antioxidant vitamins, although the decreased risk appeared most consistent and pronounced with vitamins E and beta-carotene compared with vitamin C. Furthermore, similarly designed studies assessing vitamin E consumption reported a decreased cardiovascular disease risk associated with its use. Theoretically, a lipid-soluble antioxidant such as vitamin E is expected to provide greater LDL oxidative resistance compared to water-soluble antioxidants.

In prospective primary prevention trials, beta-carotene resulted in either no effect, or a small increase in cardiovascular disease and lung cancer. Some of these studies were performed in smokers, so the negative effects may be most pronounced in this population; however, there are no prospective data available suggesting supplementation with beta-carotene provides any cardiovascular protection. Similarly, vitamin E demonstrated no benefit when administered for the primary prevention of cardiovascular disease.

In terms of secondary prevention of cardiovascular disease, three large prospective trials failed to demonstrate any mortality benefit. One early study suggested a decreased incidence of MI with vitamin E consumption in this patient population, although this was not confirmed in subsequent, larger studies. Similarly, a combination of vitamins C, E, and beta-carotene demonstrated no cardiovascular benefit in patients with established CHD.

Despite observational data suggesting benefit, and a logical mechanism of benefit, antioxidant vitamin supplementation is not proven to be of benefit in cardiovascular disease prevention or treatment. It is plausible that the benefit consistently seen in the

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin versus usual care. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 2002;288:2298-3007.

Tribble DL. Antioxidant consumption and risk of coronary heart disease: emphasis on vitamin C, vitamin E, and β -carotene. *Circulation* 1999;99:591-5.

observational studies was due to an overall healthier lifestyle in antioxidant consumers, and the decreased saturated fat and cholesterol and increased fiber and micronutrients present in foods, which also were high in antioxidants.

Folic acid and vitamins B₁₂ and B₆ for the lowering of homocysteine concentrations only recently began to be rigorously studied. Although it is clear that both folic acid alone, and folic acid plus vitamins B₁₂ and B₆, significantly decrease plasma homocysteine concentrations (by about 25% and 40%, respectively), their effect on the primary and secondary prevention of cardiovascular disease is still unknown. Conflicting data are available regarding the impact of the vitamins on endothelial function, and few prospective objective data are available regarding their effect on cardiovascular disease. The most compelling data published suggest that in patients with established CHD, folic acid 1 mg, vitamin B₁₂ 0.4 mg, and vitamin B₆ 10 mg orally for 6 months decrease the rate of restenosis following successful angioplasty.

There are no compelling data at this time to support the routine use of any other natural product pharmaceuticals for either primary or secondary prevention. In fact some natural products such as ephedra are suspected of being harmful.

Hormone Therapy

The Women's Health Initiative (WHI) was the first large-scale randomized trial of HT for primary prevention conducted in the United States. The unexpected negative results of the WHI were distressing for millions of women receiving or contemplating the use of HT in their postmenopausal years. The continuous, combined estrogen plus progestin arm of the WHI study was stopped by the data and safety monitoring board because the test statistic for invasive breast cancer had exceeded the pre-established boundary. However, the estrogen-only arm of the WHI study is continuing.

Results from the continuous combined estrogen plus progestin arm of the trial showed a hazard ratio of 1.29 for CHD, 1.26 for breast cancer, 1.41 for stroke, 2.13 for pulmonary embolus, 0.63 for colon cancer, 0.83 for endometrial cancer, 0.66 for hip fracture and 0.92 for death due to other causes. This means that for 10,000 people-years of treatment with combined estrogen plus progestin, there would be seven additional CHD events, eight additional strokes, eight additional pulmonary embolic events, eight additional breast cancers, six fewer colorectal cancers, and five fewer hip fractures. These results are similar to those published by the Hormone Replacement Study (HERS) which was a secondary prevention trial showing no benefit of HT.

Whether the results of the WHI study can be extrapolated to all forms of HT, or lower doses of the same formulation, remains speculative. The administration of estrogen can

increase CRP concentrations; however, the administration route is shown to be an important factor. Compared with women not receiving HT, median CRP concentrations were 40% higher among women taking oral estrogen ($p < 0.05$) and 35% lower among women using transdermal estradiol ($p < 0.05$). Median CRP concentrations were more than twice as high among women taking oral estrogen than among women receiving transdermal estradiol (2.75 mg/L vs. 1.27 mg/L; $p < 0.001$). It is suggested that the higher concentration of estrogen reaching the liver after oral administration influence the hepatic synthesis of lipoproteins, thyroid hormone-binding globulin, angiotensinogen, and some coagulation factors. Similarly, estrogen may induce the synthesis of CRP by the liver.

A different effect of estrogen occurs with the slow absorption of transdermal formulations. The decrease in CRP concentrations following transdermal estradiol administration may be due to a reduction in circulating proinflammatory cytokines. Whether this difference compared to oral formulations has any impact on clinical outcomes is unknown. A clinical trial is needed to explore this hypothesis.

Hormone therapy with estrogen and progestin is not recommended for primary or secondary prevention of CHD. Proven alternate cardioprotective regimens should be considered. The effect of estrogen monotherapy on CHD is not yet clear. Until confirming data are available, estrogen monotherapy should not be used for primary or secondary prevention of CHD.

Smoking Cessation

The relationship between smoking and cardiovascular disease results from multiple mechanisms that interact to contribute to atherosclerosis, vascular injury, thrombosis, and vascular dysfunction. Health care providers, educators, and policy makers must recognize the changing patterns of smoking and the impact of smoking on cardiovascular disease. Campaigns aimed at enhancing smoking cessation should be continued in the general population and in teenagers.

Efforts also should be made to limit smoke exposure to the general public. In an analysis of 18 studies, nonsmokers exposed to second-hand smoke had a relative risk of CHD of 1.25 compared to nonsmokers not exposed. A significant dose-relationship was demonstrated such that the relative risk was 1.23 if exposed to less than 20 cigarettes/day versus a relative risk of 1.31 if exposed to 20 cigarettes or more.

The greatest risk of CHD occurs in smokers with other risk factors. Data from the Nurses Health Study demonstrated a relative risk of 22.2 for smoking plus hypertension, 18.9 for smoking plus dyslipidemia, and 22.3 for smoking plus diabetes.

Among individuals who quit smoking, the risk for cardiovascular disease gradually returns to baseline after

Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med* 2001;345:1593-600.

Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women. *JAMA* 2002;288:321-33.

Modena MG, Bursi F, Fantini G, et al. Effects of hormone replacement therapy on C-reactive protein levels in healthy postmenopausal women: comparison between oral and transdermal administration of estrogen. *Am J Med* 2002;113:331-4.

10–14 years. Smoking trends today greatly influence the burden of cardiovascular disease in the future. Programs that aim at early intervention and reflect cultural diversity are key in the battle against tobacco use.

The National Committee for Quality Assurance has identified five quality of care performance measures related to preventing and treating cardiovascular disease. Advising patients to stop smoking is one of the performance measures being evaluated. In 1999, only 65.3% of patients were advised to quit smoking by a health care professional. All health care professionals should make an effort to advise patients to stop smoking.

Physical Activity, Diet, and Weight Management

Physical activity and diet are two inseparable components that together determine individual body weight. Both independently and combined, they have a significant impact on cardiovascular health. The American Heart Association has developed comprehensive, evidence-based dietary guidelines to assist with the attainment of optimal body weight by employing foods proven to have cardiovascular benefit. These guidelines are readily available on the American Heart Association's Web site at <http://www.americanheart.org>. Even if weight loss is not desired, these guidelines contain diet recommendations that improve the cardiovascular health of individuals who follow them.

In broad terms, there are several key points in regard to a diet that has cardiovascular benefit. The first point is that foods from all groups should be included (e.g., fruits and vegetables, grains, low-fat dairy, fish, legumes, poultry, and lean meats) to provide not only complete macronutrients (e.g., carbohydrates, protein, and fat), but also to ensure complete micronutrient consumption (e.g., vitamins and minerals), as different micronutrients concentrate in different food groups.

The second point is to attain and maintain an appropriate body weight. This goal should be achieved by focusing on energy consumption not exceeding energy expenditures. Exercise also improves this ratio, in addition to improving cardiovascular fitness and improving blood pressure. Meta-analyses suggest that for each kilogram of weight lost, the systolic and diastolic blood pressures decrease by 1.6 and 1.1 mm Hg, respectively. In men, the amount of and intensity of exercise are inversely related to CHD risk. Walking is associated with a decreased cardiovascular risk; however, brisk walking is more beneficial than slower walking, even if a shorter distance is covered when walking briskly.

The third principle of a cardiovascular healthy diet is progress toward a desirable cholesterol concentration through diet modifications. Specifically, a desirable cholesterol concentration is achieved by decreasing consumption of saturated fatty acids, which are found in full-fat dairy products, fatty meats and tropical oils, and *trans*-unsaturated fatty acids from hydrogenated vegetable oils that may then be used to fry foods or prepare baked products. Dietary components shown to decrease LDL include mono- and polyunsaturated fatty acids and fiber. For patients with elevated triglycerides, consumption of

foods high in omega-3 fatty acids, such as fatty fish, help lower these concentrations.

The last principle is following a diet that does not adversely affect blood pressure, and uses food choices that actually decrease blood pressure. The avoidance of salt is paramount to this goal. A salt intake reduced to 6 g (2.4 g sodium) reduces the incidence of hypertension by 20% in patients at a high risk of developing hypertension. In patients with established hypertension, decreasing sodium intake by 1.8 g/day decreases systolic and diastolic blood pressures by an average of 4 and 2 mm Hg, respectively. Restricting sodium intake is difficult for people to achieve without education about the prevalence of sodium in processed foods, strategies to avoid “hidden salt,” and instruction regarding how to read nutrition labels for sodium content. Limiting alcohol consumption to no greater than two alcoholic drinks (about 2 ounces of alcohol) per day for males and one drink (about 1 ounce of alcohol) per day for females also minimizes the development of hypertension. Weight loss and increased physical activity also are beneficial for blood pressure lowering, as is a diet that consists of 5–9 servings of fruits and vegetables per day and 2–4 servings of nonfat or low-fat dairy products per day. This amount of fruit, vegetable, and dairy intake is shown to decrease systolic and diastolic blood pressure by 3.5 and 2.1 mm Hg, respectively, in individuals who are normotensive, and by 11.4 and 5.5 mm Hg, respectively, in patients with hypertension.

In addition to blood pressure benefits, diets high in fruits and vegetables (more than five servings per day) are associated with decreased cardiovascular disease. This beneficial effect is at least partially due to the high nutrient/low calorie content of these foods and their contribution to a healthy weight maintenance. Diets high in grains (more than six servings per day) and fiber also are associated with a decreased risk of cardiovascular disease. Grains (e.g., bread, pasta, and cereal) are a preferred carbohydrate source compared to mono- and disaccharides (sugars). In addition to lowering LDL, fiber promotes a feeling of satiety and aids in overall decreased calorie consumption.

Omega-3 fatty acid consumption is associated with decreased cardiovascular risk in numerous epidemiological studies. Although there is some evidence to the contrary, as a whole, prospective studies for secondary prevention support the benefit of omega-3 fatty acids by decreasing sudden death and arrhythmias and decreased morbidity and mortality in patients with CHD. The highest amounts of omega-3 fatty acids are found in fatty fish such as salmon, herring, and mackerel. Possible mechanisms for protection include decreased triglycerides, a small hypotensive effect, myocardial stabilization, as well as decreased platelet aggregation. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are two omega-3 fatty acids found primarily in fish oils and alpha-linolenic acid is found in nuts, flaxseed, canola, soybean, and flaxseed oils. Eicosapentaenoic acid and DHA are present in all fish, but in varying amounts. The current dietary guidelines recommend the consumption of fish 2 times/week, in part to obtain increased omega-3 fatty acids. It is important to remember that processed or fried fish may not be as

beneficial because they may be high in *trans*-unsaturated fatty acids. Individuals with CHD unable to consistently consume this much fish may use fish oil supplements containing EPA and DHA that also show benefit in this patient population.

The cardiovascular healthy diet guidelines emphasize avoidance of excess energy (calorie) consumption, maintenance of a healthy weight, and regular physical activity. Guidelines also recommend fat intake of 30% or less of total calories, salt intake less than 6 g/day, alcohol intake limited, fish is consumed at least 2 times/week, as well as 4–6 servings of fruits and vegetables and 2–4 servings of nonfat or low-fat dairy products are consumed on a daily basis. Patients with concomitant disease states such as diabetes, HF, or renal disease may require diet modifications that preclude some of these recommendations. However, for the general population, adherence to these recommendations decrease blood pressure, lower cholesterol, work to achieve and maintain a healthy weight, and decrease individual risk of cardiovascular events.

Conclusion

Prevention of cardiovascular disease should be thought of as a continuum, and not necessarily as primary or secondary prevention. Evaluation tools can help clinicians estimate the absolute risk for a cardiovascular event in individuals. A comprehensive risk reduction program emphasizes healthy lifestyle choices beginning in childhood.

From a purely economic standpoint, the most cost-effective medical therapies are those that emphasize secondary prevention in individuals at the highest risk for cardiovascular events. However, even small changes in blood pressure and cholesterol have a beneficial impact when looking at the population as a whole. Community programs focusing on healthy lifestyles, screening for risk factors and treating patients at risk have a positive effect on cardiovascular health outcomes. Additional research on adherence to lifestyle and medical recommendations for the prevention of cardiovascular disease is needed.

Annotated Bibliography

1. Whelton PK, He J, Appel LJ, et al. Primary prevention of hypertension. JAMA 2002;288:1882–8.

These are the most recent guidelines (updated from 1993) from the National High Blood Pressure Education Program Coordinating Committee. The work was funded by the National Heart, Lung, and Blood Institute. This report debunks the theory that there is a “J curve” regarding the relationship between high blood pressure and cardiovascular/renal disease. It further emphasizes the importance of systolic blood pressure as a risk factor for cardiovascular disease. The report recommends a two-pronged approach; one aimed at the general population and one aimed at individuals at high risk for developing hypertension. It reviews the well-known life style

modifications, and provides a summary of the data supporting these recommendations. The report continues to promote better diets and exercise. The report is clear, concise, and evidence-based.

2. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002;347:1557–65.

This analysis sheds light on the importance of C-reactive protein (CRP) as a predictor for cardiovascular events. In this study of almost 28,000 healthy women, CRP proved to be superior to low-density lipoprotein (LDL) cholesterol as a measure for cardiovascular risk. Forty-six percent of the cardiovascular events occurred in women whose LDL cholesterol was below 130 mg/dl (the current National Cholesterol Education Program threshold for intervention). In this trial, women in the high CRP/low LDL group were at higher risk than the high LDL/low CRP group. These findings have important implications for identification and treatment of people with high CRP/low LDL levels and support the need for a large-scale trial targeted at this population.

3. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care 2002;25:S33–S49.

Due to the increasing number of patients with diabetes and their increased risk for cardiovascular disease pharmacists and other clinicians should become familiar with standards of care for this important group of patients. These standards review not only treatment goals and present them in simplified tables, but also review criteria for diagnosis and screening. There are sections on preconception care, immunizations, and special considerations for children and older adults with diabetes. Recommendations are presented according to levels of evidence. There are additional papers in this supplement that elaborate on the treatment of patients with diabetes who have hypertension or hyperlipidemia, and the use of aspirin in patients with diabetes.

4. Krauss RM, Eckel RH, Howard B, et al. AHA dietary guidelines—Revision 2000: a statement for healthcare professionals from the nutrition committee of the American Heart Association. Circulation 2000;102:2284–99.

This reference contains comprehensive, evidence-based, dietary guidelines that promote cardiovascular health in all individuals, not only those with cardiovascular disease. The main goals of a heart healthy diet are presented, and each section describes the magnitude of effect each recommendation has on individual cardiovascular risk factors, such as blood pressure, cholesterol, and weight loss. These guidelines provide concrete numbers that clinicians can share with their patients in order to enhance adherence. The issues surrounding the various fat sources are clearly delineated making this a reference for this often-confusing issue. Guidance on alcohol consumption and the recommended intake of various food groups also is provided, in addition to modifications that may be necessary in specific populations such as patients with diabetes, renal disease, and congestive heart failure. High-protein diets also are addressed.

5. Schnyder G, Roffi M, Pin R, et al. Decreased rate of coronary restenosis after lowering of plasma homocysteine levels. *N Engl J Med* 2001;345:1593–600.

This secondary prevention trial of folic acid and vitamins B₆ and B₁₂ supports the role of these vitamins in the treatment of cardiovascular disease. Six months of vitamin therapy after successful angioplasty decreased the rate of restenosis by 52%, the degree of stenosis was less severe with vitamin therapy, and the need for revascularization also was decreased significantly. The benefit did not reach statistical significance when subgroup analysis was performed on patients with stented lesions; however, the magnitude of benefit was similar and this may be a function of statistical power. While the benefits can only be stated as modest at this point, and the effect on more clinically relevant end points, such as myocardial infarction and death, are not known. This is evidence about an inexpensive and safe therapy for coronary heart disease. However, the results from the Folate after Coronary Intervention Trial presented at the 2003 American College of Cardiology meeting were contradictory. The Folate after Coronary Intervention Trial evaluated patients undergoing coronary stenting. Despite a reduction in homocysteine levels, there was an increase in restenosis and major clinical events in patients receiving the vitamin therapy. This is an area requiring further investigation.

SELF-ASSESSMENT QUESTIONS

- Which one of the following is an example of a primordial prevention strategy for the avoidance of coronary heart disease?
 - Maintaining ideal body weight.
 - Controlling hypertension.
 - Controlling dyslipidemia.
 - Aspirin use after a positive stress test.
- F.C. is a 19-year-old woman with type 2 diabetes mellitus and gastroesophageal reflux. Her physical examination reveals weight 172 pounds (body mass index [BMI] 27 kg/m^2), blood pressure (BP) = 135/88 mm Hg, and heart rate 75 beats/minute. On her last clinic visit, laboratory tests showed a fasting lipid profile of total cholesterol = 189 mg/dl, triglycerides = 173 mg/dl, high-density lipoprotein (HDL) cholesterol = 30 mg/dl, low-density lipoprotein (LDL) cholesterol = 120 mg/dl, and hemoglobin A1C (Hb A1C) of 7.0%. Her current drug regimen includes ramipril 10 mg/day, simvastatin 20 mg/day at bedtime, lansoprazole 30 mg/day at bedtime, and glyburide 10 mg 2 times/day. In addition to encouraging weight reduction and physical activity, which one of the following strategies should be implemented?
 - Add vitamin E.
 - Increase ramipril.
 - Add aspirin.
 - Increase both simvastatin and ramipril.
- You are one of the financial administrators for a large health maintenance organization that provides acute care, ambulatory care, and full prescription coverage for lives covered. Which one of the following interventions are you most likely to support?
 - An intervention that reduces cardiovascular death, but no change on overall mortality.
 - An intervention shown to reduce a major coronary event within the next 20 years.
 - An intervention shown to reduce hospital length of stay.
 - An intervention that reduces indirect costs through improving quality of life.
- Discussion of a 71-year-old woman with diabetes with newly diagnosed isolated systolic hypertension (BP = 164/82 mm Hg and heart rate 70 = beats/minute) is taking place among a group of family medicine residents. Although this is a new diagnosis, she is noted to have left ventricle hypertrophy (LVH) on her electrocardiogram. Her urinalysis shows microalbuminuria. In your opinion, which one of the following treatment strategies should be used initially because it has the least risk and greatest benefit?
 - Atenolol.
 - Losartan.
 - Hydrochlorothiazide.
 - Nifedipine (extended release).
- A 49-year-old woman comes to your community pharmacy for a free cholesterol screening program. Her only medication is estrogen therapy, which she has taken for the past 18 months for control of her perimenopausal symptoms. She had a hysterectomy 3 years ago. Her BP is 118/70 mm Hg. She is about 20 pounds above her ideal body weight, but has no other risk factors for cardiovascular disease. Her cholesterol panel reveals a total cholesterol = 223 mg/dl, LDL = 137 mg/dl, HDL = 71 mg/dl, and

- triglycerides = 73 mg/dl. Which one of the following preventive strategies should you recommend?
- Initiate weight loss.
 - Initiate aspirin therapy.
 - Initiate atorvastatin.
 - Discontinue hormone therapy.
- A 45-year-old man with a 10-year history of type 2 diabetes mellitus comes to the clinic after hospitalization for an inferior wall myocardial infarction 2 weeks ago. His current drug regimen includes aspirin, metoprolol, simvastatin, and rosiglitazone. His last Hb A1C was measured at 6.9%. Which one of the following medication changes should be made to this patient's regimen?

 - Switch aspirin to clopidogrel.
 - Discontinue metoprolol.
 - Add ramipril.
 - Add vitamin E.
 - A 57-year-old woman came to her physician's office complaining of exertional chest tightness. She has a history of rheumatoid arthritis, hypertension, and dyslipidemia. Her drugs include rofecoxib, atorvastatin, and hydrochlorothiazide. To further assess the cause of her chest tightness, she underwent an exercise stress thallium study the next day, which was within normal limits. Which one of the following would you recommend?

 - No changes, continue present regimen.
 - Switch from rofecoxib to celecoxib.
 - Switch from rofecoxib to acetaminophen.
 - Switch from rofecoxib to naproxen.
 - A 68-year-old woman with a history of intermittent claudication comes to your clinic for an initial visit. She has a history of smoking but quit 3 years ago. She has hypertension (BP = 138/90 mm Hg), which is treated with hydrochlorothiazide. Her LDL cholesterol is 120 mg/dl. Which one of the following would you add to her current drug regimen?

 - Atenolol.
 - Doxazosin.
 - Simvastatin.
 - Simvastatin and aspirin.
 - A 57-year-old man with a history of hypertension, non-ST segment elevation myocardial infarction, and dyslipidemia returns to the clinic for a follow-up appointment. His BP is under control with valsartan/hydrochlorothiazide. He was started on simvastatin 20 mg/day 3 months ago (at the time of his infarction) because his LDL cholesterol was noted to be elevated (145 mg/dl). His laboratory results from today's visit reveal a decrease in his LDL (now 114 mg/dl) with normal triglycerides (110 mg/dl) and HDL (45 mg/dl). His liver function tests have increased to 2 times the upper limit of normal. Which one of the following should you recommend?

 - Continue with the present regimen.
 - Increase the simvastatin dose to 40 mg/day.
 - Continue simvastatin 20 mg and add gemfibrozil.
 - Discontinue simvastatin and initiate ezetimibe.
 - A 52-year-old woman comes to the clinic for a routine yearly physical examination. She has no complaints but tells her physician she would like to be screened for cardiovascular disease because her mother had a heart attack when she was 55 years old. The patient stopped her oral estrogen/progestin hormone therapy 3 months ago, but has not had any annoying menopausal symptoms. Her BP = 125/70 mm Hg, total cholesterol = 227 mg/dl, HDL = 76 mg/dl, and her CRP is elevated at 3.3 mg/L. Which one of the following would you recommend to her physician?

 - Restart the hormone therapy.
 - Initiate pravastatin and aspirin.
 - Initiate a β -blocker.
 - Initiate thiamine and vitamin E.
 - Your neighbor has just returned from the pharmacy with a variety of vitamins and herbal medications. He is interested in reducing his risk for cardiovascular disease because he has a homocysteine level of 18 μ mol/L. Which one of the following is most likely to safely provide the stated benefit for your neighbor?

 - Folic acid for homocysteine lowering.
 - Ma huang (ephedra) for weight loss.
 - Garlic for atherosclerosis prevention.
 - Beta-carotene for antioxidant effect.
 - A 75-year-old black man with isolated systolic hypertension and dyslipidemia comes to the clinic for an early afternoon follow-up appointment. He is currently treated with isradipine 10 mg/day and lovastatin 20 mg/day at bedtime. He has no complaints. His BP on this visit is 150/80 mm Hg. His laboratory tests drawn on arrival reveal a serum creatinine of 1.5 mg/dl, and his total cholesterol = 195 mg/dl, triglycerides = 341 mg/dl, HDL = 27 mg/dl, and LDL = 100 mg/dl. Refill records suggest he is compliant with his medications as prescribed. Which one of the choices represents the best strategy for this patient?

 - Make no changes, and have him return in 1 year.
 - Increase lovastatin.
 - Add chlorthalidone.
 - Increase isradipine.
 - A 36-year-old woman with diabetes with hypertension presents to your clinic for a routine visit. She tells you

she missed her last two periods, which are usually regular. A home pregnancy test performed last week indicates she is pregnant. Her BP = 145/90 mm Hg, and heart rate = 82 beats/minute. She currently is taking enalapril 5 mg/day and aspirin. Which one of the following should you recommend?

- A. Increase enalapril to 10 mg/day.
- B. No change to therapy is necessary.
- C. Discontinue enalapril, and add valsartan 80 mg twice daily.
- D. Discontinue enalapril and add labetalol.

Questions 14 and 15 pertain to the following case.

You work for an health maintenance organization that has recently acquired an account to provide medical services to the employees of a large Fortune 500 company's headquarters in Chicago. A 5-year contract has been negotiated, with the option to renew at the end of that period. To aid in the initiation of appropriate cardiovascular prevention strategies and to educate individuals about their cardiac risk, the Framingham Coronary Heart Disease Risk Prediction Score (<http://www.nhlbi.nih.gov/about/framingham/riskabs.htm>) is being used. J.L. is a 51-year-old white man with no significant past medical history who takes no medications other than the occasional ibuprofen or cold preparation. He does not smoke. His fasting lipid profile is total cholesterol = 185 mg/dl, LDL = 145 mg/dl, HDL = 26 mg/dl, and triglycerides = 75 mg/dl. His BP today = 156/82 mm Hg.

14. Which one of the following is the correct interpretation of his Framingham risk score?
 - A. He is at low risk of a stroke overall, and compared to his peers, is especially low.
 - B. His 14% risk of coronary heart disease (CHD) in his lifetime is about average for a man his age.
 - C. His 7% risk of developing CHD is below average for a man his age.
 - D. He has a 14% chance of a CHD event in the next 10 years.
15. What is the best intervention to decrease his cardiovascular risk, in addition to diet, exercise, and aspirin 325 mg/day?
 - A. Simvastatin.
 - B. Ramipril.
 - C. Doxazosin.
 - D. Fish oil supplement.
16. Assume patient population A, consisting of women 50–55 years old with hypertension and diabetes, has an absolute risk of a cardiovascular event of 10% throughout the next 5 years. Population B, consisting of women 45–50 years old with hypertension and dyslipidemia, has an absolute risk of a cardiovascular event of 5% throughout the next 5 years. Which one of the following is group B's relative risk of a cardiovascular event compared to group A's risk throughout the next 5 years?
 - A. 5%.
 - B. 10%.
 - C. 50%.
 - D. 200%.
17. Assume there are 18 studies of the relationship between homocysteine and CHD. In each of the studies, individuals with the highest levels of homocysteine have the greatest prevalence of CHD. In addition, in several of the studies, adding daily folic acid and B vitamins lowered homocysteine levels by an average of 32%. Based on these data, which one of the following statements is correct?
 - A. High homocysteine levels are associated with CHD.
 - B. Elevated homocysteine causes vascular damage, resulting in increased CHD.
 - C. Homocysteine degradation is inhibited in patients with CHD.
 - D. Patients with CHD need supplementation with folic acid and B vitamins.
18. Your patient is a 63-year-old black man with newly diagnosed hypertension with two systolic BP readings of more than 150 mm Hg. His only significant medical history is a motor vehicle accident 3 years ago, from which he has sciatic nerve pain that is aggravated with movement of his left hip. His family history is significant in that his mother had a stroke at 68 and his father died of a myocardial infarction at 77. All siblings are alive and well, and three of the four also have hypertension. In addition to appropriate pharmacological therapy, which one of the following is the best recommendation for this patient at this time?
 - A. Initiate daily folic acid and vitamins B₁₂ and B₆.
 - B. Decrease sodium intake to 2.4 g/day.
 - C. Encourage brisk walking for at least 3 days/week.
 - D. Counsel him to avoid exposure to second-hand smoke.
19. You are out to dinner at the local cafeteria, and trying to follow a healthy cardiovascular diet. Which is the best selection for you to make?
 - A. Fried chicken with steamed broccoli and fried potatoes.
 - B. Grilled salmon over risotto pasta with steamed broccoli and squash.
 - C. Fried chicken with mashed potatoes and gravy and a dinner roll.
 - D. Grilled salmon over rice with a cream sauce and steamed broccoli.
20. The Framingham risk score underestimated CHD risk in which one of the following patients?

- A. A 55-year-old white man with hypertension.
- B. A 60-year-old black man with metabolic syndrome.
- C. A 70-year-old white woman with systolic hypertension.
- D. A 30-year-old white man with no risk factors.