Review

Reducing Global Risk for Cardiovascular Disease: Using Lifestyle Changes and Pharmacotherapy

ALAN CHENG, M.D., JOEL B. BRAUNSTEIN, M.D., CHERYL DENNISON, M.S.N., C.R.N.P., CAITLIN NASS, M.S.N., N.P.,
ROGER S. BLUMENTHAL, M.D., FACC, FCCP

The Ciccarone Center for Prevention of Heart Disease, The Johns Hopkins Hospital, Baltimore, Maryland, USA

Summary: Cardiovascular disease (CVD) is the leading cause of death and disability in industrialized societies, due in large part to the lack of a comprehensive approach to control the risk factors for atherosclerosis. One strategy for reducing an individual's global CVD risk relies on a targeted approach that modifies each of the major independent risk factors prevalent in both symptomatic (secondary prevention) and asymptomatic (primary prevention) patients. These interventions include lipid lowering, smoking cessation, blood pressure control, glycemic control, regular exercise, and the use of various medications. This review offers an evidence-based strategy toward reducing an individual's global risk for CVD by addressing the modifiable, major independent risk factors.

Key words: prevention, risk factors, lipids, hypertension, lifestyle

Introduction

Cardiovascular disease (CVD) is a global epidemic and is the primary cause of death in nearly 60% of all American adults.^{1,2} For substantial reduction of CVD events, we need improved identification and modification of the major risk factors known for atherosclerosis. Large epidemiologic surveys³ have led to the identification of several major risk factors for CVD, which include cigarette smoking, hypertension, hyper-

lipidemia, diabetes, obesity, physical inactivity, advancing age, male gender, postmenopausal state, and a family history of premature CVD (Tables I, II). A number of other CVD risk factors have also been identified, but their importance is not as well defined (Table III). Risk factor modification traditionally focuses on preventing recurrent events in persons with known CVD (secondary prevention); however, increasing focus has been directed to risk factor modification in those without CVD (primary prevention).^{4,5}

Modifiable Major Independent Risk Factors

Cigarette Smoking

An estimated 25 to 30% of all Americans actively smoke. Clinical studies show that within 3 years of smoking cessation, an individual's risk of developing CVD dramatically declines to nearly that of a nonsmoker.^{6,7} Patients who participated in the Coronary Artery Surgery Study (CASS) reduced their risk of a second coronary event by 50% if they stopped smoking.⁸ Cigarette smoking was the most powerful risk factor for recurrent cardiovascular events.⁹

Unfortunately, the success of long-term smoking cessation remains poor. Large randomized trials on the use of bupropion demonstrated that smokers who took the drug experienced less craving for cigarettes.¹⁰ Furthermore, a study comparing the use of bupropion and nicotine patches suggested that combination therapy was superior to using either one alone.¹¹

Bupropion should be used with caution in persons with a seizure disorder or bulimia since it lowers the seizure threshold. Clinicians often advocate administering the second dose early in the evening to minimize complaints of sleeplessness. When bupropion is contraindicated, an alternative strategy of nicotine replacement and behavioral modification has achieved long-term efficacy rates of 20%.¹² Cessation efforts are more effective after a major coronary event than as a primary preventive strategy.¹³

Hypertension

An estimated 50 million Americans have hypertension. Hypertension has a direct role in CVD¹⁴ by impairing en-

Address for reprints:

Dr. Roger Blumenthal
600 North Wolfe Street, Carnegie 538
Baltimore, MD 21205, USA
e-mail: rblument@jhmi.edu

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TABLE I Modifiable major independent risk factors for cardiovascular disease^a

Factor	Increased risk states
Cigarette smoking	Smoking to any degree increases risk of CVD. Exposure to passive smoke increases risk as well. ⁷⁶
Hypertension	Blood pressures > 140/90 mmHg
LDL cholesterol	LDL-C > 130 mg/dl for patients with established CVD or type 2 diabetes and LDL-C > 160 mg/dl for others.
HDL cholesterol	HDL-C < 40 mg/dl
Diabetes mellitus	Fasting or random blood sugar level > 126 mg/dl or > 200 mg/dl, respectively
Obesity	Body mass index > 30 kg/m ² ; waist circumference > 40" in men or > 35" in women
Physical inactivity	Sedentary lifestyle before and after initial MI

^a Adapted from the National Cholesterol Education Program Report and the American Heart Association.

Abbreviations: CVD = cardiovascular disease, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, MI = myocardial infarction.

TABLE II Nonmodifiable major independent risk factors for cardiovascular disease

Factor	Risk
Age	Increased age (men > 45 years old, women > 55 years old)
Gender	Men have more CVD events than do women. This gender discrepancy diminishes after menopause. Data on the use of HRT in primary prevention remain unclear. Data on secondary prevention demonstrated no benefit for estrogen/medroxyprogesterone acetate replacement therapy. Studies aimed at better defining the role of HRT are expected in 2005 (Women's Health Initiative)
Postmenopausal	See description in "Gender" section.

Abbreviations: CVD = cardiovascular disease, HRT = hormone replacement therapy.

TABLE III Other risk factors for cardiovascular disease^a

Factor	Risk
Hypertriglyceridemia	Based on NCEP guidelines, triglyceride levels are classified into four categories: < 150 mg/dl; (desirable), 150–199 (borderline), 200–499 (high), ≥ 500 (very high). Individuals with CVD and/or diabetes should be treated to a goal of < 150 mg/dl
Hyperhomocysteinemia	Homocysteine levels > 24 μM have been demonstrated to be a risk factor for CVD development. ⁷⁷ Folic acid supplementation can reduce homocysteine levels, ⁷⁸ but no interventional trials to date demonstrate a mortality benefit
Elevated lipoprotein(a)	Lp(a) is LDL-C with the addition of an apolipoprotein(a) moiety. Elevated levels > 30 mg/dl are associated with increased CVD risk. ⁷⁹ Some recommend that with elevated Lp(a) levels, a target LDL-C should be < 90 mg/dl ⁸⁰
Family history of CVD	First-degree relatives (< 55 years old for men and < 65 years old for women) with CVD ⁸¹
Ethnic predisposition	South Asians have a 2-time greater risk of CVD (compared with Caucasians) even when major risk factors are matched. ⁸² Hispanic-Americans have a risk comparable with Caucasians, ⁸³ while Asian-Americans have a lower risk ⁸⁴
Psychosocial factors	Studies have shown some association of increased CVD risk with depression, social isolation, passive-submissive personalities, and hostility ⁸⁵
Prothrombotic states	Elevated levels of fibrinogen, ⁸⁶ PAI-1, Factor VIII, and von Willebrand factor ⁸⁷ have been associated with increased CVD risk
Inflammatory states	Elevated C-reactive protein levels, ⁸⁸ leukocyte counts, and pro-oxidant states have been associated with increased CVD risk. These findings may in part explain the cardiovascular benefits of aspirin beyond its ability to inhibit platelet aggregation.

^a Whether or not these factors have an independent effect on CVD risk is unclear but all have been demonstrated to impart some risk.

Abbreviations: Lp(a) = lipoprotein(a) cholesterol, PAI-1 = plasminogen activator inhibitor-1. Other abbreviations as in Table I.

endothelial cell function, increasing the risk of plaque rupture, and promoting left ventricular (LV) hypertrophy.¹⁵ Hypertension management is effective as both a primary and secondary preventive strategy.

Despite an overall decline in the prevalence of hypertension from the 1950s to the 1980s, the Framingham investigators demonstrated a direct relationship between isolated systolic hypertension and a 50–60% increased risk of CVD-related

death.¹⁶ Among the primary prevention trials, the Metoprolol Atherosclerosis Prevention in Hypertension (MAPHY)¹⁷ and the Systolic Hypertension in the Elderly Program (SHEP)¹⁸ trials were instrumental in establishing a role for lowering blood pressure to prevent CVD. In the MAPHY trial, all individuals with lower blood pressures had a lower incidence of cardiovascular mortality. The SHEP trial demonstrated similar findings and extended them to individuals with systolic hypertension. Lower systolic blood pressure conferred not only a 36% reduction in strokes (primary endpoint), but also a 27% reduction in nonfatal myocardial infarction and CVD-related death. Many other studies utilizing various antihypertensive medications and lifestyle therapies have since validated the benefits of lowering blood pressure on CVD risk.

The Sixth Report of the Joint National Committee (JNC VI) on high blood pressure defines hypertension as a systolic blood pressure (SBP) > 140 mmHg and/or a diastolic blood pressure (DBP) > 90 mmHg.¹⁹ The JNC VI report recommends risk stratifying individuals based on evidence of CVD, diabetes, or end-organ damage in order to determine the optimal time for initiation of pharmacologic therapy. Risk group A includes individuals with no clinical evidence of CVD; risk group B includes those with other CVD risk factors excluding diabetes; and risk group C includes those with CVD, end-organ disease, or diabetes. All individuals with hypertension warrant encouragement of weight loss, increased physical activity, and dietary modification. Individuals in risk groups A and B warrant pharmacotherapy if their SBP is > 160 mmHg or their DBP > 100 mmHg with target blood pressures < 140/90 mmHg. Prompt initiation of antihypertensive medications in risk group C is recommended to target blood pressures < 130/85 mmHg. However, in the presence of diabetes or overt nephropathy (> 1 gm/day of proteinuria), more aggressive reductions should target blood pressures < 130/80 and < 125/75 mmHg, respectively.

Diuretics and/or beta blockers are appropriate first line-agents regardless of risk group status. In light of evidence from other clinical studies, adding angiotensin-converting enzyme (ACE) inhibitors²⁰ or possibly an angiotensin receptor blocker²¹ for individuals in risk group C and those with decreased LV systolic function²² are indicated. The use of calcium-channel blockers²³ as a first-line agent remains controversial.

Once an individual's blood pressure is controlled, initiating aspirin therapy in all patients without contraindications to antiplatelet therapy is recommended.^{24, 25} Elderly patients with isolated systolic hypertension may be good candidates for long-acting calcium-channel blockers or low-dose thiazide diuretics.²⁶ One approach is to treat individuals with either ECG criteria for LV hypertrophy or persistently elevated systolic blood pressures from ambulatory blood pressure monitoring.²⁷ The use of other medications such as alpha blockers is not recommended for first-line use.²⁸

Hyperlipidemia

An estimated 40 million Americans have total cholesterol levels > 240 mg/dl. The role of hyperlipidemia in CVD was

established in many clinical trials,^{29, 30} which demonstrated that a 10% decrease in an individual's total cholesterol results in a 10–15% reduction in CVD-related mortality and a 20% reduction in myocardial infarction risk. High low-density lipoprotein cholesterol (LDL-C) is more directly related than total cholesterol (TC) to the development of CVD. Conversely, elevated high-density lipoprotein cholesterol (HDL-C) is recognized to be a cardioprotective factor.³¹

Primary prevention: The benefits of treating hypercholesterolemia in individuals without known CVD stem from three landmark, prospective randomized trials: the Lipid Research Clinics-Coronary Primary Prevention Trial^{32, 33} (LRC-CPPT), the West of Scotland Coronary Prevention Trial Study (WOSCOPS),³⁴ and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).³⁵ The LRC-CPPT trial demonstrated a 19% CVD risk reduction in men with primary hypercholesterolemia who were treated with cholestyramine and followed for 7 years. The WOSCOPS and AFCAPS/TexCAPS trials used statins to demonstrate a significant reduction in CVD-related endpoints with the lowering of LDL-C.

In the WOSCOPS trial, men with hypercholesterolemia (mean TC = 272mg/dl) and no CVD were randomized to dietary modification plus either placebo or pravastatin. Individuals were followed for 5 years and treatment with pravastatin led to a 20% reduction in TC, 26% reduction in LDL-C, 12% reduction in triglycerides, and 5% elevation in HDL-C. Among these individuals, CVD-related events and mortality were reduced by 31 and 22%, respectively. The WOSCOPS trial did not evaluate whether men and women with mild or moderate hypercholesterolemia also benefit from lipid lowering.

The AFCAPS/TexCAPS study addressed this question by evaluating men and women with an average TC and LDL-C of 221 and 150 mg/dl, respectively. Participants were randomly assigned to diet and placebo versus lovastatin. After 5 years of therapy, there was a 37% risk reduction in acute coronary events irrespective of gender, age, history of diabetes, or cigarette use.

The National Cholesterol Education Program (NCEP) recently published its third report on recommendations for initiating dietary modification and drug treatment in adults with elevated LDL-C.³⁶ Dietary modification for individuals without CVD is recommended for LDL-C > 160 mg/dl if 0–1 additional CVD risk factors are present, and LDL-C > 130 mg/dl for individuals with ≥ 2 additional risk factors. This includes adopting a regimen low in saturated fat and high in fruits and vegetables. Drug therapy is advised with LDL-C > 190 and > 160 mg/dl, respectively. Increasing HDL-C and lowering triglycerides may have a role in primary prevention as well.^{37, 38}

One exception to the current guidelines exists for individuals with diabetes who have no CVD. Patients with diabetes should be aggressively managed; the recommended LDL-C level for initiation of dietary therapy is > 100 mg/dl and for initiation of drug therapy is > 130 mg/dl.³⁹ The LDL-C levels should be lowered < 100 mg/dl. This approach stems from recently published data demonstrating that patients with type 2

diabetes and no established CVD carry the same mortality risk as nondiabetic patients with established CVD.⁴⁰

The present issue raising debate in lipid-lowering strategies for primary CVD prevention is not if, but when clinicians should implement drug interventions for their hyperlipidemic patients. Recent data suggest that even younger adults with hypercholesterolemia should receive aggressive treatment.⁴¹

Secondary prevention: There are five major prospective, randomized, controlled trials of cholesterol lowering in secondary prevention: the Scandinavian Simvastatin Survival Study (4S), the Cholesterol and Recurrent Events Trial (CARE), the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial, and the Veterans' Affairs HDL Cholesterol Intervention Trial (VA-HIT). The 4S Study⁴² randomized 4,444 patients with CVD and a TC between 212 and 309 mg/dl to simvastatin or placebo. The dose was titrated to reduce TC < 200 mg/dl. After a 5.4-year period, the simvastatin-treated group had a 42% relative risk reduction of CVD-related death. However, 4S did not answer whether individuals with established CVD and mild elevations in their cholesterol would also benefit from pharmacologic intervention.

In the CARE⁴³ study, men and women with a prior history of myocardial infarction (mean LDL-C = 139) were randomized to receive placebo versus pravastatin 40 mg daily. Individuals treated with pravastatin had lower LDL-C levels (mean = 97 mg/dl), resulting in a 20% decrease for men and a 46% decrease for women in CVD-related events after 5 years of therapy. The LIPID⁴⁴ trial confirmed the findings from CARE. The LIPID investigators randomized individuals with CVD and normal or mildly elevated TC levels (155–271 mg/dl) to pravastatin or dietary therapy. After 6 years, men and women in the statin group demonstrated a 26 and 11% respective reduction in CVD-related events. Taken together, these data recommend targeting LDL-C < 100 mg/dl in individuals with CVD. A more aggressive LDL-C target (< 85 mg/dl) may be warranted for patients who have undergone coronary artery bypass graft (CABG) utilizing saphenous veins.⁴⁵

Few studies have evaluated the effects of increasing HDL-C or lowering triglycerides on secondary prevention of CVD. One such study was VA-HIT,⁴⁶ which evaluated the use of gemfibrozil for secondary prevention in patients with mean LDL-C of 111 mg/dl, mean triglycerides of 161 mg/dl, and mean HDL-C of 32 mg/dl. Individuals treated with 1200 mg of gemfibrozil daily for 5 years demonstrated a 22% reduction in CVD deaths. This reduction occurred in the presence of a 6% mean increase in HDL-C and 31% mean fall in triglycerides; LDL-C remained unchanged. The current recommendations for those with CVD target LDL-C < 100 mg/dl, and normal triglyceride levels are classified as < 150 mg/dl.³⁶

First-line therapy for treating hypercholesterolemia involves the use of statins. Individuals with isolated hypertriglyceridemia should receive fibrates as first-line therapy. Bile acid resins (except for colestevlam) should be avoided in these individuals since they may exacerbate hypertriglyceridemia. Individuals with isolated decreased levels of HDL-C should be initiated on niacin or a fibrate. Niacin should be

used with caution in patients with diabetes or the metabolic syndrome since in high doses it may worsen hyperglycemia and promote insulin resistance. Finally, in postmenopausal women, utilizing hormone replacement therapy (HRT) to treat mild hyperlipidemia may be reasonable in women without CVD, but data from a recent study suggest that use of combination estrogen/progesterone replacement provides no improved clinical outcomes for those with CVD.⁴⁷ Statins remain first-line therapy in women with known atherosclerotic vascular disease.

Diabetes

Patients with diabetes have long been recognized to carry a substantially increased risk of CVD.⁴⁸ Individuals with either type 1 or type 2 diabetes have 2 to 4 times the risk of CVD of nondiabetics matched for the same level of cholesterol.⁴⁹ Once patients with diabetes develop clinical CVD, cardiac complications occur with increased frequency, resulting in higher postmyocardial infarction mortality rates than those in their nondiabetic counterparts.⁵⁰ The mechanism by which diabetes imparts a poor overall clinical outcome is unclear but may be due in part to elevated serum glucose levels;⁵¹ however, the severity of hyperglycemia is not linearly related to an increased risk of CVD development.⁵² Nevertheless, many clinical studies have attempted to assess whether improved glycemic control reduces a patient's risk for developing CVD. The United Kingdom Prospective Diabetes Study evaluated patients with type 2 diabetes and the clinical outcomes associated with improved blood glucose control. Despite improvements in glycosylated hemoglobin (HgbA_{1c}) levels and reductions in microangiopathy, it had no significant effect on CVD event rates.⁵³

The American Diabetes Association (ADA) recommends tight glucose control with a target HgbA_{1c} < 7%; more recent studies suggest an even lower goal.^{54, 55} While these recommendations do not aim at preventing CVD development, they are strongly encouraged since strict glycemic control mitigates microangiopathy and other diabetic comorbidities. The ADA also recommends tight lipid control to achieve LDL-C < 100 mg/dl and triglycerides < 200 mg/dl.

Individuals who have diabetes and hypercholesterolemia should be initiated more promptly on drug therapy than their nondiabetic counterparts. In addition to controlling lipid levels, aggressive blood pressure control is also important. Current data⁵⁶ support targeting blood pressures in diabetic patients < 130/80 mmHg. Checking for proteinuria⁵⁷ on a yearly basis is similarly important and may prompt more aggressive blood pressure control < 125/75 mmHg in individuals with > 1 gm/day of proteinuria.

Angiotensin-converting enzyme inhibitors are highly effective in patients with diabetes. The Heart Outcomes Prevention Evaluation⁵⁸ (HOPE) examined men and women ≥ 55 years old with established vascular disease or diabetes with one additional CVD risk factor. Individuals with congestive heart failure or LV systolic dysfunction were excluded. The study was terminated early because of the highly significant benefits

observed in patients randomized to ramipril. All ramipril-treated individuals, particularly those with diabetes, showed a marked reduction in the composite endpoints of death, heart attacks, and strokes. Furthermore, ramipril reduced the incidence of diabetic complications by 16%. The number of new cases of type 2 diabetes was also lower. Based upon these recent observations, a strong argument can be made to treat virtually all diabetic patients with ACE inhibition.

Obesity

It is estimated that one of every two Americans is considered obese or overweight, based on recent guidelines⁵⁹ recommending an ideal body mass index (BMI) of $< 25 \text{ kg/m}^2$. Individuals with a BMI between 25 and 30 kg/m^2 are considered overweight while a BMI $> 30 \text{ kg/m}^2$ is considered obese. Whether or not obesity has a direct, independent effect on CVD is controversial since obesity is strongly associated with other known CVD risk factors such as hypertension, hyperlipidemia, and diabetes. The Nurses' Health Study has perhaps made the most compelling observations between obesity and CVD risk.⁶⁰ The study's cohort included 115,000 nurses with no CVD. Modest weight gains of 5–8 kg over an 18-year period conferred an increased CVD risk of ≥ 1.25 . Although there are currently no prospective studies showing a decreased risk of CVD with intentional weight loss, long-term modification of lifestyle and diet can be effective as a primary preventive strategy against CVD.⁶¹ Even modest weight losses of 5–10% have been shown to be beneficial in diabetes, hypertension, dyslipidemia, and CVD.⁶²

Physical Inactivity

Many clinical trials have established reductions in CVD with physical activity.⁶³ Two well-known meta-analyses demonstrated an overall 25% decrease in CVD-related mortality after initiation of a cardiac rehabilitation program.^{64, 65} These initial observations led others to demonstrate an inverse relationship between peak exercise capacity and CVD mortality.⁶⁶ Current recommendations on physical activity for individuals with CVD include enrollment in a moderate-intensity exercise program. This should be preceded by a symptom-limited exercise stress test 3–6 weeks after a patient's CVD event. In the absence of ischemia or arrhythmia, exercise intensity should approximate 50–80% of VO_2max .⁶⁷ Without stress test results, individuals should exercise to initially target their heart rate approximately 20–30 beats/min above their resting rate. The duration of exercise should be symptom limiting and subsequently increased by 5-min increments per week.⁶⁸ In the presence of ischemic symptoms or arrhythmia, exercise should be medically supervised and targeted to a goal of 10 beats/min below the heart rate associated with the abnormal event.⁶⁹

Sedentary lifestyles correlate with increased risk of CVD.⁷⁰ The role of increasing physical activity in primary prevention of CVD was unclear until more recent clinical trial data. Two such studies include the Honolulu Heart Pro-

gram⁷¹ and the Nurses' Health Study,⁷² which demonstrated a protective effect of exercise on primary prevention of CVD. In the Nurses' Health Study, brisk walking was found to be as cardioprotective as vigorous exercise, suggesting that individuals without CVD gain beneficial effects from even low to moderate intensity physical activity. Current recommendations regarding physical activity for primary prevention of CVD include moderately intense aerobic exercise for 30 min on most days of the week.⁷³ Resistive exercises such as weight lifting and lifestyle modifications such as walking up stairs should also be encouraged.

Conclusion

Secondary Prevention

Over the past two decades, several clinical trials have demonstrated the efficacy of medical intervention on reducing the incidence of CVD. Optimizing blood pressure control, stopping smoking, controlling dyslipidemia, tightening blood glucose regulation, and increasing physical activity are proven ways to reduce CVD-related mortality. Men and women with CVD should target blood pressures $< 130/85 \text{ mmHg}$. Patients with diabetes should aim for blood pressures $< 130/80 \text{ mmHg}$. Diuretics and beta blockers are appropriate first-line agents. Strong consideration should be made to include an ACE inhibitor in all patients in JNC VI risk group C. An aspirin per day should be initiated and continued indefinitely. If aspirin is not advised, consideration should be made on utilizing other agents such as clopidogrel.⁷⁴ Lipid profiles also require optimization, utilizing statins as first-line drugs to target LDL-C $< 100 \text{ mg/dl}$. Targets for HDL-C and triglycerides are less well defined but currently are $> 40 \text{ mg/dl}$ and $< 150 \text{ mg/dl}$ according to the 2001 NCEP guidelines. In diabetic patients, one should target $\text{HgbA}_{1\text{C}} < 7\%$ or as low as tolerable.

Primary Prevention

Patients with no prior history of CVD also benefit from risk factor modification. Blood pressures should be optimized $< 130/85 \text{ mmHg}$. Patients with controlled hypertension should initiate daily aspirin therapy. First-line agents include a diuretic or beta blocker. Elderly individuals with isolated systolic hypertension benefit from initiation of a long-acting calcium-channel blocker or a diuretic. Patients with diabetes should also start aspirin therapy⁷⁵ and an ACE inhibitor with the addition of a diuretic or other antihypertensive agent as needed to target blood pressures $< 130/80 \text{ mmHg}$. First-line lipid-lowering therapy includes the use of statins to achieve target LDL-C $< 130 \text{ mg/dl}$ in individuals with ≥ 2 additional CVD risk factors and $< 160 \text{ mg/dl}$ in individuals with 0–1 additional CVD risk factor. Recommendations for lipid lowering in diabetic patients without CVD target LDL-C $< 100 \text{ mg/dl}$. Most of these recommendations on blood pressure, lipid levels and glucose control are based on trials that evaluated middle-aged and elderly individuals.

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