Cardiovascular Prevention in High-Risk Patients: Evaluating Current Evidence to Improve Outcomes in Managed Care

An overview of evidence-based strategies to prevent cardiovascular events in high-risk patients through pharmacologic interventions and lifestyle modifications

Sponsored by the University of Kentucky College of Medicine

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June 2008
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Release date: June 16, 2008; Expiration date: June 16, 2009

Estimated time to complete: 1 hour

There is no fee associated with this activity.

**TARGET AUDIENCE**

This activity is designed for managed markets physicians and pharmacists.

**LEARNING OBJECTIVES**

After completing this activity, participants should be able to:

- Describe the clinical and cost burden of cardiovascular disease (CVD) in the United States and frequent barriers to cardiovascular prevention
- Summarize nonpharmacologic and pharmacologic interventions for secondary prevention of CVD
- Outline emerging data on pharmacologic approaches to cardiovascular prevention
- Put into practice current guidelines and evidence to assist providers in improving outcomes in cardiovascular prevention for high-risk patients

**STATEMENT OF NEED**

CVD affects approximately 80 million Americans and is responsible for roughly one third of US mortality, with nearly 2400 CVD-associated deaths occurring each day—more than cancer, chronic lower respiratory diseases, accidents, and diabetes mellitus combined. Among the identified modifiable risk factors for CVD are smoking, high cholesterol, hypertension, physical inactivity, obesity, and diabetes mellitus; in addition, the aging of the US population also contributes to the incidence of CVD, as more than 80% of individuals who die from coronary heart disease are 65 years of age or older. Practice guidelines such as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the Clinical Practice Guidelines for Cholesterol Management in Adults, and the American Heart Association Guidelines for Primary Prevention of Cardiovascular Disease and Stroke are available to guide clinicians and managed markets professionals in cardiovascular prevention and treatment, addressing the use of both nonpharmacologic and pharmacologic modalities. Nonpharmacologic interventions include smoking cessation, exercise, and dietary changes. Among the pharmacotherapeutic interventions available for cardiovascular prevention are diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers for the management of hypertension, and statins for the management of high cholesterol. As data continue to emerge regarding the effectiveness of traditional and new pharmacologic interventions in cardiovascular prevention, evidence suggests the importance of an individualized approach to patient care. To implement personalized treatment strategies and achieve optimal patient outcomes, managed markets physicians and pharmacists require education on patient-specific screening methods and current evidence for preventive cardiovascular measures.

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Cardiovascular disease (CVD) encompasses a set of potentially disabling conditions characterized by compromised function of the heart and arteries. CVD is the leading cause of death in the United States; nearly 2400 Americans die of CVD each day, with an average of 1 death every 37 seconds. CVD-associated mortality is linked with common clinical manifestations of the disease—52% is attributable to coronary heart disease (CHD), 17% to a cerebrovascular accident (CVA), 7% to heart failure, 6% to high blood pressure, 4% to arterial disease, and 14% to other unspecified underlying disease processes—many of which share common risk factors.

A single cardiovascular event of any type signifies heightened risk of experiencing another incident, and the initial episode may impair return to normal functional status. Approximately two thirds of myocardial infarction (MI) survivors do not make a complete recovery, and 16% of men and 22% of women between 40 and 69 years of age are at risk for a recurrent MI or CHD-associated death within a 5-year period following the initial event. The American Heart Association (AHA) estimates that each year an additional 175,000 individuals will have a silent MI and approximately 780,000 people will experience a new or recurring CVA, with 1 event occurring every 40 seconds. Any elevation in individual risk status attributable to established disease necessitates a targeted management approach to minimize recurrent events and to avoid the need for interventional cardiac procedures. Focused secondary prevention strategies need to be tailored to the expanding at-risk CVD patient population with existing comorbidities that increase with age; two thirds of stroke survivors 65 years of age and older have at least 3 comorbid conditions, whereas less than 3% lack comorbidities and physical impairments.

US trends in blood pressure lowering, reduction of high cholesterol levels, and minimization of other risk factors for heart disease have driven CHD-associated cost savings in previous decades; however, the estimated direct and indirect cost of CVD for 2008 is projected to escalate to $448.5 billion, with more than $100 billion anticipated to be spent on CHD alone. Despite recognition of CVD as an epidemic, preventive methods and medical therapies for secondary cardiovascular prevention are underutilized, and consistency among the treatment of patients with a history of CVD remains deficient. The average hospital stay (approximately 72 hours) for a patient who suffers an acute coronary event has been shortened in an attempt to control costs, a measure that reduces the opportunity to initiate key health-related interventions such as cardioprotective lifestyle modifications, which have demonstrated efficacy in complementing pharmacotherapy for high-risk patients with nonmodifiable risk factors.

Although the understanding of atherosclerosis and effective treatment of acute complications of the disease have progressed, the implementation of life-saving risk-reduction practices for both inpatients and outpatients remains inadequate. Scarce community resources, limited government-sponsored initiatives, and lack of healthcare system rewards for preventive efforts exemplify current barriers to improving patient outcomes. A more concentrated focus on cardiovascular prevention is required to effectively contend with the CVD epidemic. Current guidelines promulgated for secondary cardiovascular prevention—including the AHA/American College of Cardiology (ACC) guidelines most recently updated in 2006—are supported by clinical data classifying optimal pharmacologic classes and nonpharmacologic strategies for the prevention of cardiovascular events in high-risk patients. Evidence-based recommendations require integration into practice to promote effective disease management and to assist clinicians in reducing the impact of CVD.

SECONDARY CARDIOVASCULAR PREVENTION WITH ANTIPLATELET THERAPY

Aspirin and clopidogrel bisulfate are the 2 most widely used antiplatelet agents for the prevention of recurrent CVD events. The cardioprotective effects of aspirin are generated by a decrease in the production of thromboxane—a factor that promotes platelet aggregation, by irreversibly inhibiting the cyclooxygenase enzyme—whereas clopidogrel inhibits platelet activation by blocking the binding of adenosine diphosphate to its receptor on the platelet surface. Aspirin use has most frequently been associated with dose-dependent bleeding (depending on age and individual risk factors), gastrointestinal symp-
Combination antiplatelet therapy with aspirin and clopidogrel for high-risk patients following percutaneous coronary intervention (PCI) has been examined in 2 key studies. The Percutaneous Coronary Intervention–Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) trial and the Clopidogrel for High Atherothrombotic Risk and Vascular Events (CHARISMA) trial did not establish a benefit associated with dual antiplatelet therapy in primary prevention, but did demonstrate a modest 1.5% absolute risk reduction in stable secondary prevention subjects.

Several studies have compared the relative efficacy of aspirin with that of clopidogrel for secondary prevention of CVD. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study included 19,185 patients with a history of MI, CVA, or symptomatic peripheral arterial disease. Participants were randomized to receive either aspirin (325 mg/day) or clopidogrel (75 mg/day) for up to 3 years. The results demonstrated a 9% relative reduction in CVD events associated with clopidogrel compared with aspirin (5.3% vs 5.8%; P=.04), with a similar incidence of medication-related adverse effects in both groups. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial studied 12,562 patients presenting with an acute coronary syndrome (ACS) randomized to immediate and long-term therapy with aspirin (75-325 mg) or aspirin plus clopidogrel (300 mg/day initially, followed by 75 mg/day). A 20% relative reduction in the composite end point of CVD events was exhibited by the clopidogrel group at 12 months (9.3% vs 7.5%; P=.002), along with a higher incidence of major bleeding (3.7% vs 2.7%; P=.003). No significant difference in life-threatening bleeding episodes was evident (2.2% vs 1.8%; P=.13). As demonstrated by a post-hoc analysis, the risk of bleeding could be reduced while maintaining therapy efficacy if lower aspirin doses (75-81 mg) were used in combination with clopidogrel.

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ANTIHYPERTENSIVE THERAPY FOR HIGH-RISK PATIENTS

Another major cause of CVD-associated morbidity and mortality, the overall annual death rate from hypertension increased 27% over the 10-year period from 1994 to 2004. More than 70 million US individuals 20 years of age and older suffer from high blood pressure—with African Americans at greatest risk—and 61% of hypertensive individuals are currently undergoing treatment. Only 35% of affected individuals have blood pressure under control, whereas 65% have uncontrolled hypertension. Pharmacologic management of this condition mitigates arterial damage to reduce the CVD risk conferred by high blood pressure. Several antihypertensive drug classes—including beta-blockers, diuretics, calcium channel blockers, and agents interacting with the renin-angiotensin system—act through various mechanisms to facilitate reaching and maintaining guideline-based target measurements. The AHA/ACC recommend a blood pressure goal of 140/90 mm Hg—or 130/80 mm Hg in diabetics or patients with chronic kidney disease—and defines high blood pressure in these individuals as any readings that exceed these targets. According to the Seventh Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, in individuals older than 55 years of age, systolic blood pressure (SBP) greater than 140 mm Hg is a more important CVD risk factor than diastolic blood pressure (DBP), which declines as the arteries get stiffer and less compliant with age. In addition, beginning at blood pressure readings of 115/75 mm Hg, CVD risk doubles for all patients with each increment of 20/10 mm Hg.

The JNC 7 also highlights several treatment considerations for high-risk patients. For uncomplicated hypertension cases, thiazide diuretics should be selected, either alone or in combination with other antihypertensive drug classes. Two or more blood pressure medications—including an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB)—are generally required to achieve goal blood pressure in patients with diabetes and chronic kidney disease. Antihypertensive treatment of lower risk patients without CVD or diabetes should be initiated if SBP is 140 mm Hg or higher, or if DBP is 90 mm Hg or higher.

In an attempt to resolve the debate regarding the optimal class of antihypertensive medications for blood pressure lowering, a meta-analysis known as the Individual Data Analysis of Antihypertensive Intervention (INDANA) trial evaluated more than 40,000 hypertensive patients randomized to treatment with thiazide diuretics, beta-blockers, or placebo. Subjects randomized to a study drug experienced a significant reduction in the risk of stroke and major coronary events (P<.001). To compare diuretics with other antihypertensive agents, another major large-scale trial—the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial—randomized a total of 33,357 subjects 55 years of age or older with at least 1 CHD risk factor to the diuretic chlorthalidone (up to 25 mg/day), the calcium channel blocker amlodipine (up to 10 mg/day), or the ACEI lisinopril (up to 40 mg/day) for a mean of 5 years. There was no significant difference in the primary combined end point of fatal CHD or nonfatal MI between patients taking any of the 3 drugs (95% CI, 0.90-1.08); however, due to lower cost of the drug class, thiazide diuretics were considered the preferred first-line agents.

The results of 2 recent antihypertensive trials have demonstrated the role of combination therapy in secondary cardiovascular prevention. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial randomized 10,704 high-risk patients with hypertension to ACEI combination therapy with the diuretic hydrochlorothiazide (HCTZ) plus benazepril or the calcium channel blocker amlodipine plus benazepril. Individuals were followed for a period of 3 years with a primary composite end point of cardiovascular events. Results showed that the incidence of cardiovascular events was significantly lower in the amlodipine/benazepril-treated group (11.4% vs 9.2%; P<.0002), suggesting that amlodipine is preferable to HCTZ when added to an ACEI.

The Hypertension in the Very Elderly Trial (HYVET) has provided insight into the treatment of high blood pressure in the older population. The study randomly assigned 3845 patients older than 80 years of age with sustained SBP of 160 mm Hg or higher to receive the diuretic indapamide (sustained release 1.5 mg) or matching placebo. The ACEI perindopril (2 or 4 mg) or matching placebo was added, if necessary, to achieve the target blood pressure of 150/80 mm Hg, and the primary end point was fatal or nonfatal stroke. After 2 years, active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (P<.06), a 39% reduction in the rate of death from stroke (P<.05), a 21% reduction in the rate of death from any cause (P<.02), a 23% reduction in the rate of death from cardiovascular causes (P<.06), and a 64% reduction in the heart failure rate (P<.001). Based on study results, control of SBP is an important consideration in individuals of all ages.

THE ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN SECONDARY CARDIOVASCULAR PREVENTION

ACEIs and ARBs influence the renin-angiotensin system to promote cardiovascular protection. ACEIs block the conversion of angiotensin I to angiotensin II, primarily affecting the renin-angiotensin system and inhibiting the breakdown of the vasodilator bradykinin. However, ACEIs—indicated in individuals with concomitant CVD and heart failure—and concomitant left ventricular systolic dysfunction (LVSD) have been associated with the development of renal insufficiency (up to 50% of patients with bilateral renal artery stenosis), cough (up to 20% of patients), hyperkalemia (up to 10%), and angioedema (0.1%-0.2%). ARBs antagonize the effects of angiotensin II at the receptor level and are usually prescribed for patients with diabetic nephropathy, hypertension, or heart failure. Major adverse effects observed with ARBs are similar to those seen with ACEIs, with the exception of the bradykinin-related effects of a cough.

ACEI Evidence. The effects of ACE inhibition on mortality in post-MI patients were assessed in the Acute Infarction Ramipril Efficacy (aire), the Trandolapril Cardiac Evaluation (TRACE), and the Survival and Ventricular Enlargement (SAVE) studies, which collectively randomized patients diagnosed with heart failure or LVSD to ACE inhibition or placebo within 2 to 16 days of an acute MI. A total of 6843 patients were followed for a mean of 42 to 59 months, and the reduction in all-cause mortality associated with the use of an ACEI ranged from 17% to 28% (P=.019 to P=.001, depending on the study).

The influence of ACE inhibition immediately following a coronary event has also been investigated by the Fourth International Study of Infarct Survival (ISIS-4), the Gruppo Italiano per lo Studio della
Sopravvivenza nell’Infarto Miocardico (GISSI-3), and the Survival of Myocardial Infarction Long-Term Evaluation (SMILE) study, each of which randomized patients to an ACEI or placebo within 24 hours of an MI.\textsuperscript{12-51} A total of 78,600 subjects were followed for 6 to 12 months, and the results demonstrated that individuals randomized to an ACEI had a 5% to 29% relative reduction in the primary end point of death ($P=0.03$ to $P=0.01$).\textsuperscript{12-51}

To examine the role of ACEIs in another population at increased risk for CVD events, the Heart Outcomes Prevention Evaluation (HOPE) study randomized 9297 high-risk individuals with a history of vascular disease—including coronary artery disease (CAD) or stroke—or diabetes mellitus (DM) plus 1 additional CVD risk factor, but no LVSD, to 10 mg/day of the ACEI ramipril or placebo.\textsuperscript{55} Ramipril treatment was associated with a 22% risk reduction in cardiovascular events over a 5-year period.\textsuperscript{55}

A later trial did not find an additive benefit of ACE inhibition in a population of patients that had largely undergone previous revascularization.\textsuperscript{64} The Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial was designed to test the hypothesis that patients with stable CAD and normal or slightly reduced left ventricular function derive therapeutic benefit from the addition of ACEIs to modern conventional therapy.\textsuperscript{64} The incidence of the primary end point (death from cardiovascular causes, MI, or coronary revascularization) was 22% in thetrandolapril group, as compared with 22.5% in the placebo group (HR in the trandolapril group, 0.96; 95% CI, 0.88-1.06; $P=.43$) over a median follow-up period of 5 years.\textsuperscript{56}

**ARB Clinical Data.** The impact of ARBs, as well as combination therapy with an ARB and an ACEI, on cardiovascular outcomes has been examined in numerous trials. The Reduction of Endpoints in NIDDM (Non-Insulin-Dependent Diabetes Mellitus) with the Angiotensin II Antagonist Losartan (RENAAL) study\textsuperscript{57} and the Irbesartan Diabetic Nephropathy Trial (IDNT)\textsuperscript{58} randomized 3228 patients with type 2 diabetes and nephropathy to losartan (up to 100 mg/day) or irbesartan (up to 300 mg/day) versus placebo for 2.6 to 3.4 years.\textsuperscript{57,58} Both trials demonstrated a slowing of the rate of renal disease progression; among secondary CVD end points, there were no significant differences in fatal or nonfatal events between the ARB-treated groups.\textsuperscript{57,58}

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial randomized 9193 patients with essential hypertension (SBP $>$160 mm Hg) and electrocardiogram-detected left ventricular hypertrophy to losartan (up to 100 mg/day) or the beta-blocker atenolol (up to 100 mg/day) with a follow-up period of 4 years.\textsuperscript{59} Therapy with losartan resulted in a 25% relative reduction in both stroke and the development of diabetes ($P=.001$), and no difference was observed in the reduction of MBs.\textsuperscript{60} Kjeldsen and colleagues found that, among individuals with isolated systolic hypertension, treatment with losartan resulted in a 46% relative reduction in cardiovascular mortality (8.7% vs 16.9%; $P=.01$).\textsuperscript{60} A significantly large reduction in CVD events with losartan was also seen in the subgroup of patients with diabetes.\textsuperscript{60} Forty-four diabetic patients died of sudden cardiac death, with significantly fewer deaths in the losartan group than in the atenolol group (30; $P=.027$).\textsuperscript{60} In the losartan group, 5 (6%) of 86 diabetic patients with atrial fibrillation and 9 (2%) of 500 diabetic patients without atrial fibrillation died of sudden cardiac death; the respective figures for the atenolol group were 14 (13%) of 105 and 16 (3%) of 504.\textsuperscript{60}

A 2002 meta-analysis of 17 randomized trials and 12,469 patients by Jong and colleagues evaluated the effect of ARBs on mortality.\textsuperscript{61} Results showed no significant mortality benefit among individuals treated with an ARB or an ARB plus an ACEI.\textsuperscript{61} However, patients treated with combination therapy experienced a 26% relative reduction in heart failure hospitalizations compared with patients treated with an ACEI alone.\textsuperscript{61} A more recent trial, the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program, demonstrated a 15% relative reduction in cardiovascular death or hospitalization for heart failure in patients who were treated with an ARB and an ACEI compared with an ACEI alone ($P=.011$).\textsuperscript{62}

The Valsartan in Acute Myocardial Infarction (VALIANT) trial, published in 2003 by Pfeffer and colleagues, compared the effects of the ARB valsartan, the ACEI captopril, and combination therapy on mortality among patients with MI complicated by LVSD.\textsuperscript{63} Patients receiving traditional therapy were randomized 0.5 to 10 days post-MI to additional treatment with valsartan (4909 subjects), valsartan plus captopril (4885 subjects), or captopril (4909 subjects) with a median follow-up of 25 months.\textsuperscript{63} There was no significant difference in mortality between the 3 groups; however, the valsartan and captopril group had the most drug-related adverse effects, including hypotension.\textsuperscript{63}

More recently, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared the ACEI ramipril, the ARB telmisartan, and the combination of the 2 drugs in patients with vascular disease or high-risk diabetes.\textsuperscript{64} Following a 3-week, single-blind, run-in period, patients underwent double-blind randomization, with 8576 administered to receive 10 mg of ramipril per day, 8542 administered 80 mg of telmisartan daily, and 8502 assigned to combination therapy.\textsuperscript{65} There was no significant difference in the primary composite end point of death from any cause, MI, CVA, or hospitalization for heart failure between the 3 groups.\textsuperscript{65} A higher rate of drug-related adverse effects was observed in the combination therapy group.\textsuperscript{65} Generally, ARBs are considered to provide equivalent benefits to ACEI drugs, but at a higher cost.

**AHA/ACC Guidelines on ACEIs and ARBs.** The AHA/ACC recommend initiating ACEI therapy with indefinite continuation in all patients with a left ventricular ejection fraction (LVEF) less than or equal to 40% and in individuals with hypertension, diabetes, or chronic kidney disease, unless contraindicated (IA).\textsuperscript{8} Use of ACEIs is also indicated for consideration in all patients with coronary and/or vascular disease (IB), whereas use of ACEIs is optional and may be beneficial for lower-risk patients with normal LVEF and well-controlled cardiovascular risk fac-
tors and previous revascularization (IIa B).10 ARBs are effective for patients intolerant to ACEIs with heart failure or previous MI, and LVEF less than or equal to 40% (IA).11 ARBs may also be considered for other patients who are ACEI intolerant (IB) or for use in combination with ACEIs in systolic-dysfunction heart failure (IIb B).11

EFFICACY OF BETA-BLOCKERS IN SECONDARY PREVENTION OF CVD
Beta-blockers bind to adrenergic receptors, inhibiting the effects of circulating catecholamines and exerting an antiarrhythmic, antianginal, and sympatholitic effect by reducing myocardial chronotropic and ionotropic stimulation. Beta-blockers have been proven efficacious for secondary prevention of CVD in patients who have experienced an MI,26 heart failure or LVSD,44 and/or hypertension64 with associated major adverse effects including exacerbations of heart failure symptoms,67 fatigue (1.8%),68 and sexual dysfunction (0.5%).68

Two of the initial studies to assess the effects of beta-blockade following MI are the Norwegian Study Group trial and the Beta-Blocker Heart Attack Trial (BHAT), in which a total of 5766 subjects were randomized to treatment with the beta-blockers timolol (up to 20 mg/day) or propranolol (up to 240 mg/day) versus placebo within 5 to 28 days following an MI.65,66 Individuals randomized to a beta-blocker experienced a 26% to 39% relative reduction in mortality (P=.005 to P=.0005).65,66 A retrospective review of 201,752 unselected Medicare patients diagnosed with an acute MI tracked differences in mortality among individuals taking beta-blockers following discharge.69 Overall, the use of beta-blockers resulted in a 40% decrease in mortality over 2 years.70

FREEMANTLE and colleagues conducted a meta-analysis, which included 54,234 patients from 82 randomized trials, to investigate variations in cardiovascular outcomes according to post-MI beta-blockade duration; long-term beta-blockade (6-48 months), but not short-term use (<6 weeks), of these medications was associated with a mortality benefit (odds ratio [OR], 0.77; 95% CI, 0.69-0.85).69 The Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) study assessed the effect of beta-blockade in ischemic LVSD and randomized 1959 subjects with LVSD (ejection fraction ≤40%) following an MI to carvedilol (up to 25 mg twice daily) or placebo for a mean of 1.3 years.71 Subjects randomized to carvedilol experienced a significant reduction in mortality (HR, 0.77; P=.03) and nonfatal MI (HR, 0.59; P=.01).72

AHA/ACC Guidelines for Beta-Blockers. Initiation and indefinite continuation of beta-blockers in individuals who have experienced an MI, ACS, LVSD with or without failure symptoms, is recommended by the AHA/ACC for secondary cardiovascular prevention, unless contraindicated (IA).9 Beta-blockers are reasonable for chronic treatment of all other patients with coronary or other vascular disease or diabetes, unless contraindicated (IIa C).9

LIPID MANAGEMENT IN HIGH-RISK PATIENTS
Blood levels of fatty substances including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) are major contributors to cardiovascular risk level.73 The National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) changed its risk stratification and treatment guidelines in 2001 to recommend that individuals with DM, peripheral arterial disease, CVD, and those with a Framingham Risk Score (FRS) greater than 20% achieve and maintain an LDL-C plasma level less than 100 mg/dL.74 The guidelines also classified normal TG levels as less than 150 mg/dL and normal HDL-C levels as 40 mg/dL or greater in men and 50 mg/dL or greater in women.75 According to the AHA/ACC guidelines for secondary cardiovascular prevention, individuals should achieve a goal LDL-C of less than 100 mg/dL, whereas further reduction to less than 70 mg/dL represents a reasonable target for high-risk patients.81 If TG levels are greater than 200, non-HDL-C should be less than 130 mg/dL.82

Nonpharmacologic approaches for lipid management should include reduction of saturated fat (to less than 7% of total calories), trans-fatty acids, and cholesterol (to less than 200 mg/dL) (IB).83 To complement daily physical activity and weight management strategies (IB), the AHA/ACC recommend adding plant stanols/sterols (2 grams/day) and viscous fiber (≥10 grams/day) to a diet to further lower LDL-C (IB) in addition to increasing intake of omega-3 fatty acids through consumption of fish or in capsule form (1 gram/day) for

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<thead>
<tr>
<th>Mechanism</th>
<th>Indication</th>
<th>Major Adverse Effects</th>
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<tr>
<td>Statins</td>
<td>Inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase</td>
<td>Should be considered first-line lipid-lowering medication for most patients with CVD and/or diabetes</td>
</tr>
<tr>
<td></td>
<td>Lower LDL-C and increase HDL-C</td>
<td>Myalgias (1%-6%); Elevation LFTs (0.1%-3.0%); Myopathy (0.7%)</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Activate peroxisome proliferator-activated receptors to stimulate lipoprotein lipase, resulting in lower TG and increased HDL-C</td>
<td>First-line agents for patients with isolated hypertriglyceridemia; Fenofibrate can be used in combination with a statin for high-risk patients with elevated LDL-C and either high levels of TG or low levels of HDL-C</td>
</tr>
<tr>
<td></td>
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<td>Myopathy (could be potentiated by coadministration of statins)</td>
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<tr>
<td>Niacin</td>
<td>Raises HDL-C and inhibits hepatic production of VLDL-C and LDL-C</td>
<td>Can be used in combination therapy with statins in the treatment of hyperlipidemia in patients with normal or low levels of HDL-C</td>
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<td>Flushing (up to 80% of individuals with the crystalline preparation); Pruritus (20%); Paresthesias (20%); Nausea (20%); Hepatotoxicity; Hyperglycemia; Hyperuricemia</td>
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</tbody>
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LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; LFTs = liver function tests; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol.
risk reduction. Higher doses might be necessary for elevated TG to achieve risk reduction (IIb B). The Table illustrates the principal drugs used in the treatment of hyperlipidemia, their mechanisms, indications, and major adverse effects.  

Results of several influential secondary prevention trials have become available since the most recent NCEP/ATP III guidelines. The Heart Protection Study (HPS) randomized 20,536 subjects with known CAD, peripheral arterial disease, or diabetes to receive 40 mg of the statin simvastatin or placebo. The use of simvastatin was associated with a decrease in all-cause mortality, major vascular events, coronary death rate, CVA, and number of revascularization procedures. HPS demonstrated that lowering LDL-C was beneficial, irrespective of the baseline level.  

The Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22 (PROVE-IT/TIMI 22) trial randomized 4162 subjects diagnosed with an ACS within the preceding 10 days to statin therapy using 80 mg of atorvastatin or 40 mg of pravastatin. Individuals in the atorvastatin arm of the study achieved an LDL-C of 62 mg/dL, whereas the pravastatin group achieved an LDL-C of 95 mg/dL. The study results revealed a 16% reduction associated with the atorvastatin group in the composite end point of all-cause mortality, occurrence of MI, unstable angina requiring rehospitalization, the need for revascularization, or the occurrence of a CVA.  

PROVE-IT established that among patients who have suffered a recent ACS, lower LDL-C is associated with better outcomes. The Treating to New Targets (TNT) study expanded this concept to individuals with stable CAD, and randomized 10,003 subjects with stable CAD to 10 or 80 mg of atorvastatin, following study participants for 4.9 years, with a primary end point of occurrence of a major coronary event. Subjects in the 80-mg atorvastatin arm of the study experienced a 2.2% absolute risk reduction in the primary end point and a 22% relative risk reduction, demonstrating that intensive statin therapy is more beneficial than moderate therapy.  

Although HPS, PROVE-IT, and TNT all support the use of higher statin doses, there is still debate regarding the pathophysiologic mechanism(s) by which statins produce beneficial effects. Both a decrease in LDL-C causing atherosclerosis regression and an anti-inflammatory effect leading to plaque stabilization have been proposed as conceivable mechanisms. The results of the discussed trials have provided the foundation for NCEP/ATP III to add to their guidelines the reason-able LDL-C goal of less than 70 mg/dL for high-risk patients.  

### LIFESTYLE MODIFICATION FOR CARDIOVASCULAR PREVENTION: SMOKING, DIET AND WEIGHT, AND EXERCISE  

As a fundamental component of comprehensive CVD management plans, nonpharmacologic interventions—with and without concurrent pharmacotherapy—are relatively effective in reducing risk conferred by modifiable factors. Patients are encouraged to take an active role in the disease management process by reducing or eliminating tobacco use, altering body weight through dietary improvements, and increasing levels of physical activity.  

**Cigarette Smoking.** Smoking promotes the development and progression of CVD and, in individuals with CAD, smoking is an important predictor of cardiovascular events. Two agents recently used for facilitating smoking cessation are bupropion, a nonnicotine agent previously used as an antidepressant and currently approved to treat nicotine dependence, and varenicline, a nicotinic receptor partial agonist. A combination of behavioral support and pharmacotherapy with bupropion—with or without nicotine replacement—or with varenicline alone should be offered to all CVD patients as a risk-reduction tactic.  

Gonzales and colleagues published the results of a randomized controlled trial of varenicline versus bupropion versus placebo. The study was conducted at 19 US centers and included 1025 generally healthy smokers (>10 cigarettes/day) with fewer than 3 months of abstinence within the past year. The study drug was given for 12 weeks, and subjects were followed for 40 weeks following drug discontinuation. The results showed that for weeks 9 to 12, the 4-week continuous abstinence rates were 44% for varenicline versus 17.7% for placebo (OR, 3.85; 95% CI, 2.7-5.5) and versus 29.5% for bupropion (OR, 1.93; 95% CI, 1.4-2.69). Bupropion was significantly more efficacious than placebo (OR, 2.0; 95% CI, 1.38-2.89) in managing nicotine addiction. For weeks 9 to 52, the continuous abstinence rates were 22% for varenicline versus 8% for placebo (OR, 3.09; 95% CI, 1.95-4.91) and versus 16% for bupropion (OR, 1.46; 95% CI, 0.99-2.17).  

**Approaching Ideal Weight via Healthy Diet.** As determined by body mass index (BMI), approximately 142 million Americans are currently either overweight or obese. BMI categorizes individuals as being an ideal body weight (BMI 19 to <25), overweight (BMI 25-30), or obese (BMI >30) and has been shown to correlate with cardiovascular event risk. A waist circumference greater than 40 inches in men and greater than 35 inches in women is also associated with an increased cardiovascular risk that varies with age.  

In addition to its association with cardiovascular events, obesity is also related to other comorbid conditions such as diabetes, hypertension, and hypercholesterolemia. The implementation of caloric reduction strategies until ideal body weight is reached (reductions of 500 kcal/day) is an important element of the treatment of obese individuals. Every individual with a history of CVD or at high risk for the development of cardiovascular events should follow a diet containing proteins, complex carbohydrates, omega-3 fatty acids, fruits, vegetables, nuts, whole grains, and restricted in saturated fat and cholesterol to minimize CVD risk level regardless of concurrent pharmacologic therapy. Despite the awareness among the general population of weight as a contributing CVD risk factor, approximately 24% of Americans older than 18 years of age choose to remain inactive and as many as 75% have a suboptimal level of activity or exercise, resulting in a 2-fold higher risk of cardiovascular events. Regular aerobic exercise has been shown to reduce the rates of events in individuals with CVD, and patients at high risk for a cardiovascular event are encouraged to engage in moderate aerobic exercise for 30 minutes or more on most days of the week as a risk-reduction strategy.  

**Physical Activity.** Many studies have assessed the relationship between exercise and CVD. Hambrecht and colleagues randomized 62 subjects with angiographically-proven CAD to regular physical exercise or usual care, requiring each study participant to undergo a second cardiac
Cardiovascular Prevention in High-Risk Patients

HIGH-RISK PATIENTS WITH DIABETES MELLITUS

Individuals with diabetes mellitus type 2 (DM2) are at increased risk of developing vascular disease and cardiovascular complications; in fact, DM2 plus an FRS higher than 20% are considered CAD equivalents. Patients with DM2 tend to have a high TG level, a low HDL-C level, and small dense LDL-C particles, which are more prone to oxidation and, thus, play an important role in atherosclerosis development. The lipid profile of individuals with DM2 would suggest that therapies reducing TG and increasing HDL-C (eg, fibrates) produce a beneficial cardiovascular effect.

Several studies have examined the cardiovascular benefit of fibrates in individuals with DM2 with conflicting results. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial did not show a significant reduction in cardiovascular events in subjects taking 200 mg of fenofibrate daily versus placebo; the results were probably confounded by the high background use of statins in the placebo group. Although the results of the FIELD study were not promising, previous studies had shown a modest benefit. Currently, statins remain the first-line lipid-lowering therapy for individuals with DM2.

Traditionally, hyperglycemia control has been the cornerstone of DM2 treatment. Clinical trials in patients with DM1 and DM2 confirm the benefit of good glycemic control in preventing macrovascular complications; however, the efficacy of tight glucose control in preventing microvascular complications is an issue of current debate. According to public results recently released, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was stopped early due to an increased mortality rate in subjects randomized to intensive glucose control (hemoglobin A1C below recommended levels), and the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial results showed no such increased risk associated with intensive therapy. In addition to hyperglycemia control and lipid management, individuals with DM2 need to take other therapies into consideration including blood pressure control, smoking cessation, physical activity, and following the appropriate diet to effectively manage their risk for CVD.

CONCLUSION

CVD includes a number of prevalent conditions that are associated with a considerable clinical and economic burden. Patients at high risk for developing any type of CVD—or for experiencing a recurrent cardiovascular event—are in a strategic position to minimize their risk level through lifestyle modifications and compliance with cost-effective pharmacologic therapies determined by their cardiovascular history and current health status. Regardless of potential adverse effects, evidence-based treatment recommendations, including combination therapies, have been proven effective for secondary cardiovascular prevention, and early control of risk factors through any intervention presents a valuable opportunity to avoid unnecessary hospitalizations, avert additional healthcare consumption for disease complications, and improve patient outcomes.

48. Tilkkanen JJ, Omvik P, Jensen HA. Comparison of the angiotensin II antagon-


Clinical Commentary

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Many obstacles prevent patients from achieving recommended cardiovascular prevention goals, including inaccurate cardiac risk assessment and ineffective risk reduction therapy. A thorough cardiac assessment evaluates an individual's risk level by screening for cardiovascular risk factors and the presence or absence of clinical cardiovascular disease (CVD) to stratify patients into low-, moderate-, and high-risk categories. Goals for the modification of CVD risk factors are determined according to risk classification and guideline-based risk minimization strategies, which offer best practice recommendations derived from expert panel consensus following thorough review of medical literature.

The success rate in achieving optimal risk reduction targets has been variable. Only 38% of individuals have achieved the National Cholesterol Education Program/Adult Treatment Panel III lipid goals specific to their risk category, with highest-risk patients proving to be least likely to achieve the set goals. 1 Institution of quality measures, such as hospital-based systems focusing on the initiation of antiplatelet therapy, beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, and statin therapy in the Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP) has increased the number of at-goal individuals to more than 80%. 2 The American Heart Association Get With The Guidelines program, a collaborative model designed to improve patient management through a multidisciplinary hospital-based approach to systems change, has shown improvement in a number of quality measures such as aspirin, beta-blocker, ACE inhibitor, and statin use for acute myocardial infarction. 3 The attainment of other goals has been less successful—only about 54% of Americans treated for hypertension have reached minimal blood pressure goals, 4 and data indicate less than 8% of patients with diabetes are able to reach the American Diabetes Association–recommended lipid, blood pressure, and glucose goals. 5

Methods to increase the number of patients reaching CVD risk reduction goals include the provision of quality patient education and widespread insurance coverage of cardioprotective services and therapies. In the clinical setting, electronic medical record prompts to alert a physician if a patient is not at goal can be useful, and healthcare provider incentives linked to patient goal achievement may also prove valuable. 6

Residual risk presents another challenge to favorable cardiovascular outcomes—although lipid treatment and blood pressure lowering have decreased relative and absolute risk, 7,8 patients receiving optimal treatment have still experienced CVD events, possibly due to limitations of current therapies to achieve select levels of risk reduction or comorbidities that contribute to ongoing risk, but are often not addressed in specific clinical trials. Because risk factors tend to cluster within an individual, further risk reduction may require multiple treatment modalities to maximize advantages.

Although further studies are needed to establish best practices for residual risk reduction, healthy lifestyle habits, including diet and exercise, should be fervently encouraged to augment prescribed pharmacologic therapy. In addition, pharmacologic strategies targeting multiple risk factors and utilizing newer agents that engage high-density lipoprotein cholesterol, further lower blood pressure, enable superior diabetic control, and have potential for enduring residual risk reductions should be staples in each clinician’s treatment armamentarium. Finally, guidance from expert panels is needed via updated cardiovascular prevention guidelines with optimal and achievable patient treatment goals.

References

A wide array of clinical and environmental causes contributes to the development of cardiovascular disease (CVD), the burden of which has an enormous impact on societal well-being and healthcare resource use. For managed care companies, encouraging the health and wellness of its members is critically important from both a societal and financial perspective. Managed care organizations employ a variety of programs designed to positively affect the cardiovascular health of their membership, usually offering a cardiac disease management portal on their webpage with links to resources promoting regular cholesterol testing, blood pressure and diabetes monitoring, and the adoption of healthy lifestyle habits, including diet and exercise modifications. Additionally, smoking cessation techniques and support require integration as essential elements of patient education portals.

To bolster clinician responsibilities to the CVD patient population, managed care organizations endorse treatment algorithms using the latest published cardioprevention guidelines. In addition, physicians are incentivized with pay-for-performance programs, which assess performance using nationally recognized agency metrics from organizations such as the National Committee for Quality Assurance (NCQA). NCQA publishes the Healthcare Effectiveness Data and Information Set® measures, which include specific targets for the treatment of CVD and its comorbidities. Many companies publish physician honor rolls to cultivate the clinical expertise of their network. These efforts support managed care’s objectives of quality improvements in the care of its members and alleviation of the CVD economic burden on the healthcare system.

The identification of major modifiable risk factors for CVD is a precondition to the implementation of cardiovascular prevention strategies. Managed care companies possess the claims data necessary to support outreach, which must include disease and treatment information, to their clinician network and patients impacted by CVD if clinical outcomes are to improve.

The central component of both primary and secondary cardiopreventive patient management regimens is risk factor modification; patients at high risk for CVD require aggressive reduction of lipid levels using both dietary modification and pharmacologic therapy as necessary. Managed care formulary committees make decisions regarding the inclusion of these therapies based on guidelines, peer-reviewed efficacy, safety, and relative costs of agents within treatment classes.

Managed care companies are well aware of the challenges associated with CVD management, particularly considering the frequency with which multiple interrelated CVD factors must be addressed in a single patient. The most difficult task for managed care is to provide adequate support to the clinical community treating this disease. Success can be achieved through identification and reduction of the administrative burden on the physician network by confronting administrative hurdles such as prior authorization, step editing to assess treatment value, and reducing managed care organization expenses. Managed care companies should take an active role in the assessment and distribution of evidence-based guidelines, the delivery of utilization information to physicians in a standardized manner to facilitate data pooling, and the encouragement of electronic medical record utilization with data that can be analyzed to advance CVD patient care.

References
