

A Practical and Evidence-Based Approach to Cardiovascular Disease Risk Reduction

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Implementation of the numerous lifestyle and medical management options for secondary prevention of cardiovascular disease remains a daunting goal for primary care physicians and cardiologists alike. Despite the existence of expert consensus guidelines on cardiovascular prevention by the American College of Cardiology and the American Heart Association, therapies known to improve patient care and decrease morbidity and mortality remain underutilized. This review attempts to simplify cardiovascular risk reduction by summarizing key clinical trials in an “ABC” format. We believe that if health care providers and patients use such a format, important lifestyle and pharmacologic options will more likely be addressed.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States.¹ In 2000, acute myocardial infarction (MI) was diagnosed in 1.1 million Americans and approximately 850 000 patients underwent coronary revascularization.¹ In spite of this, studies have documented that medical therapies for secondary cardiovascular (CV) prevention are underutilized and that a wide variation in practice patterns exists for management of patients with coronary artery disease (CAD).²⁻⁵ In addition, the average hospital stay for an acute coronary syndrome has been shortened, limiting the opportunity to counsel patients about risk-reducing strategies such as improved diet, increased exercise, and smoking cessation.⁶ Thus, while advances in risk factor modification and a better understanding of the atherosclerotic process have led to a decline in CVD mortality, implementation of risk-reducing practices for both inpatients and outpatients remains suboptimal.⁷

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The treatment gap in secondary prevention of CVD has become a major challenge in health care. Recognizing that clinical trials remain the cornerstone for defining target treatment goals, our review article

uses an “ABC” format^{8,9} to summarize the key studies that guide an evidence-based approach to secondary prevention of CVD (**Table**). This approach is useful not only in the development of inpatient critical pathways, but also in the outpatient management of individuals with vascular disease and/or type 2 diabetes mellitus (DM). A simplified version of this approach is also helpful in allowing patients to better understand their risk factors.

ANTIPLATELET AGENTS

Aspirin

Aspirin irreversibly inhibits the cyclooxygenase enzyme involved in the production of thromboxane, a factor that promotes platelet aggregation. All patients with a history of CVD and/or DM should take 75 to 325 mg of aspirin daily.^{10,11} Major adverse effects include dose-dependent bleeding, gastrointestinal symptoms (in 2%-10% of individuals), tinnitus and hearing loss (in 0.3% with higher doses), and sensitivity reactions including bronchospasm, urticaria, and angioedema (in 0.3%).¹²

Evidence: Two large-scale meta-analyses by the Antiplatelet Trialists Collaboration have demonstrated the importance of aspirin therapy in secondary prevention of CVD. The first meta-analysis reviewed 25 trials and demonstrated that aspirin reduced vascular mortality by 15% (SD±4%) and CVD events by 30% (SD±4%).¹³ A follow-

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ABCs of Cardiovascular Disease Risk Management

A	B	C	D	E
Antiplatelet agents Aspirin Clopidogrel	Blood pressure control First-line therapy Angiotensin-converting enzyme inhibitors	Cholesterol management Statins Fibrates Nicotinic acid	Diet and weight management ≥500 kcal/d caloric reduction	Exercise Aerobic Weight training
Anticoagulant therapy Warfarin	β-Blockers Thiazide diuretics Second-line therapy	Cigarette smoking cessation Counseling Medical therapy	Diabetes mellitus Prevention Impaired glucose tolerance Impaired fasting glucose	Ejection fraction Assessment Therapy Angiotensin-converting enzyme inhibitors β-Blockers Aldosterone inhibitors Spironolactone Eplerenone Digitalis Implantable cardioverter defibrillator
Angiotensin-converting enzyme inhibitors	Aldosterone antagonists Angiotensin receptor blockers	Bupropion Nicotine patch	Management Hemoglobin A _{1c} <7%	
Angiotensin receptor blockers	Calcium channel blockers β-Blockers			

up meta-analysis of about 70 000 patients with CVD found that 75 to 325 mg of aspirin daily resulted in an approximately 33% relative reduction (RR) in CVD events ($P < .0001$).¹⁴

Clopidogrel Bisulfate

Clopidogrel inhibits platelet activation by blocking the binding of adenosine diphosphate to its receptor on the platelet surface. Clopidogrel should be used in place of aspirin in patients who are intolerant of or resistant to the effects of aspirin.¹⁵ Clopidogrel (75 mg/d) should also be taken in addition to aspirin (75-325 mg/d) for at least 8 to 12 months by patients with an acute coronary syndrome,¹⁶ especially after undergoing percutaneous coronary intervention (PCI).^{17,18} Major adverse effects include rash (in 4.2% of patients) and gastrointestinal bleeding (in 2.0%).¹⁹ The long-term use of clopidogrel is currently limited largely by its cost.²⁰

Evidence: The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study randomized 19 185 patients with a history of a MI, stroke, or symptomatic peripheral arterial disease to receive either aspirin (325 mg/d) or clopidogrel (75 mg/d) for up to 3 years.²¹ There was an 8.7% RR in CVD events in the clopidogrel group compared with the group receiving aspirin (5.3% vs 5.8%; $P = .04$). There was no significant difference in adverse effects between patients taking aspirin or clopidogrel.

The Clopidogrel in Unstable Angina to Prevent Recurrent Events

(CURE) trial randomized 12 562 patients presenting with an acute coronary syndrome to immediate and long-term therapy with aspirin (75-325 mg/d) or aspirin plus clopidogrel (300 mg/d initially, followed by 75 mg/d).¹⁶ The clopidogrel group demonstrated a 20% RR in the composite end point of CVD events at 12 months (9.3% vs 11.4%; $P < .001$). This benefit was seen within a few hours of randomization and persisted throughout the trial. The clopidogrel group experienced a higher incidence of major bleeding (3.7% vs 2.7%; $P = .001$), but there was no difference in life-threatening bleeding events (2.2% vs 1.8%; $P = .13$). Post hoc analysis found a lower risk of bleeding but similar efficacy when a lower dose of aspirin (75-81 mg/d) was used in combination with clopidogrel.²²

The Percutaneous Coronary Intervention–Clopidogrel in Unstable Angina to Prevent Recurrent Events (PCI-CURE) trial¹⁷ and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial¹⁸ evaluated combination antiplatelet therapy of aspirin and clopidogrel with PCI. These studies enrolled 4774 patients who were scheduled to undergo PCI. Randomization to aspirin (75-325 mg/d) or aspirin plus clopidogrel (300 mg/d initially, followed by 75 mg/d) occurred prior to PCI and was continued for 8 to 12 months. Most patients, however, received open-label clopidogrel for up to 4 weeks following PCI. Patients receiving combination antiplatelet therapy had

a 28% RR in end points that included all-cause mortality, CV death, MI, and/or stroke ($P = .02$). There were no significant differences in major bleeding between the 2 groups. Thus, patients who present with an acute coronary syndrome and undergo PCI should be given strong consideration for combination antiplatelet therapy for 1 year.

ANTICOAGULATION

Warfarin Sodium

Warfarin exerts its anticoagulant effect primarily by antagonizing the vitamin K–dependent carboxylation of several procoagulant proteins (factors II, VII, IX, and X and proteins C and S). Anticoagulation with warfarin is indicated in patients with atrial fibrillation and/or a left ventricular thrombus, as well as in those unable to take aspirin following an MI.²³ Warfarin should also be considered primary therapy in some patients following an acute MI.²⁴ Major adverse effects include dose-dependent bleeding and the potential for drug-drug interaction, especially among medications metabolized by the hepatic cytochrome CYP2C9 and CYP3A4 isoenzymes.²⁵

Whether low-dose aspirin should routinely be added to warfarin remains controversial. Recent analyses suggest a trend toward improved outcomes when combination therapy is used in patients with known CVD.^{24,26} However, patients receiving long-term warfarin treatment have a small increased

risk of major bleeding compared with patients treated with aspirin alone.^{24,26}

Evidence: A meta-analysis of 31 trials compared warfarin therapy with or without aspirin with aspirin or placebo alone.²⁶ When compared with placebo, warfarin at moderate (international normalized ratio [INR], 2-3) and high (INR, 2.8-4.8) doses was associated with a 52% and 42% RR in MI, respectively ($P < .001$). However, patients treated with moderate- or high-dose warfarin and those treated with aspirin had no difference in MI incidence (5.0% vs 5.3%; $P = .10$). Finally, patients treated with moderate- or high-dose warfarin plus aspirin rather than aspirin alone showed a trend toward a reduction in MI incidence (4.2% vs 7.5%; $P = .32$). This trend did not reach statistical significance, possibly because of the relatively small numbers of patients included. There was a statistically significant increased risk of major bleeding in patients receiving moderate- or high-dose warfarin.

The Warfarin, Aspirin or Both After MI (WARIS II) study attempted to determine whether treatments with warfarin or warfarin plus aspirin were superior to aspirin therapy alone.²⁴ This open-label trial randomized 3630 hospitalized patients with an acute MI to receive daily warfarin (INR, 2.8-4.2), aspirin (160 mg/d), or warfarin (INR, 2.0-2.5) plus aspirin (75 mg/d) for 4 years. Patients receiving aspirin plus warfarin or warfarin alone had a 29% ($P = .001$) and 19% ($P = .03$) RR in CVD events, respectively, compared with those receiving aspirin alone. There was no statistical difference between the 2 groups receiving warfarin; however, patients in these groups were at an increased risk for major, nonfatal bleeding compared with those receiving aspirin alone (0.62/y vs 0.17%/y; $P < .001$).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors (ACEIs) interfere with the conversion of angiotensin I to angiotensin II. This treatment blocks the renin-angiotensin system and inhibits the breakdown of bradykinin. Angiotensin-converting enzyme inhibi-

tors are indicated in patients with CVD in association with heart failure (HF),²⁷ left ventricular systolic dysfunction (LVSD),²⁷ and/or a recent MI,²⁸ and they are also indicated in patients with CVD and/or DM irrespective of left ventricular systolic function²⁹ as long as the systolic blood pressure (BP) is greater than 120 mm Hg (current American College of Cardiology/American Heart Association [ACC/AHA] class IIa indication⁸). Major adverse effects include renal insufficiency (in up to 50% of patients with bilateral renal artery stenosis),³⁰ cough (in up to 20% of all patients),³¹ hyperkalemia (in up to 10%),³² and angioedema (in 0.1%-0.2%).³¹

Evidence: Three major studies have assessed ACE inhibition in patients with CVD along with clinical HF and/or LVSD (with an ejection fraction $\leq 35\%$ or $\leq 40\%$, depending on the study): the Acute Infarction Ramipril Efficacy (AIRE) study,³³ the Trandolapril Cardiac Evaluation (TRACE) study,³⁴ and the Survival and Ventricular Enlargement (SAVE) study.³⁵ Each trial randomized patients diagnosed with HF or LVSD to ACE inhibition or placebo within 2 to 16 days of an acute MI. A total of 6843 patients were followed up for a mean of 42 to 59 months. Patients randomized to an ACEI had a 17% to 28% RR in the primary end point of all-cause mortality ($P = .019$ to $P = .001$, depending on the study).³⁶

The Fourth International Study of Infarct Survival (ISIS-4),³⁷ the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) study,³⁸ and the Survival of Myocardial Infarction Long-term Evaluation (SMILE) study³⁹ assessed ACE inhibition immediately following an MI. Each trial randomized patients to an ACEI or placebo within 24 hours of an MI. A total of 78600 patients were followed up for 6 to 12 months. Patients randomized to an ACEI had a 5% to 29% RR in the primary end point of death ($P = .03$ to $P = .011$).⁴⁰

In the Heart Outcomes Prevention Evaluation (HOPE) study, 9297 patients were randomized to ramipril (10 mg/d) or placebo to assess the occurrence of vascular events in high-risk patients without LVSD.⁴¹ High-risk patients were defined as

having a history of vascular disease or DM plus 1 additional CV risk factor. Ramipril reduced the risk of CV death, MI, and stroke by 22% over 5 years (14.0% vs 17.8%; $P < .001$).

ANGIOTENSIN RECEPTOR BLOCKERS

Angiotensin receptor blockers (ARBs) inhibit the effects of angiotensin II at the receptor level and are indicated in patients with diabetic nephropathy,⁴² hypertension,⁴³ or HF.⁴⁴ Angiotensin receptor blockers, however, have not been shown to provide greater CVD protection than ACEIs in patients with HF, and therefore should only be used as primary therapy in patients who are intolerant of ACEIs.⁴⁴ Combination therapy with an ARB and an ACEI in patients with HF appears to provide greater benefit through more complete renin-angiotensin system blockade.⁴⁵ Major adverse effects are similar to those seen with ACEIs, except for the effects related to bradykinins (eg, cough).⁴⁶

Evidence: The renoprotective effects of ARBs in patients with nephropathy and DM were evaluated in the Reduction of Endpoints in NIDDM (type 2 non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL) study⁴⁷ and the Irbesartan Diabetic Nephropathy Trial.⁴⁸ These studies randomized 3228 patients to either losartan (up to 100 mg/d), or irbesartan (up to 300 mg/d) vs placebo for 2.6 to 3.4 years. There was a 16% to 20% RR in the composite end point of a doubling of the baseline serum creatinine concentration, end-stage renal disease, or death ($P = .02$). Among secondary CVD end points, there were no significant differences in fatal or nonfatal events; however, there was a 23% to 29% RR in first hospitalizations for HF ($P = .005$).

In the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) trial, 9193 patients with essential hypertension (systolic BP > 160 mm Hg) and left ventricular hypertrophy detected by electrocardiogram were randomized to losartan (up to 100 mg/d) or atenolol (up to 100 mg/d) over 4 years.⁴⁹ Treatment with losartan resulted in a 25% RR in both stroke and the development of DM ($P = .001$), but no statistically signifi-

cant reduction in MI ($P = .50$). Among patients with isolated systolic hypertension, however, treatment with losartan resulted in a 46% RR in CV mortality (8.7% vs 16.9%; $P = .01$).⁵⁰

The effect of ARBs on cardiovascular outcomes was assessed in a large meta-analysis that evaluated 12469 patients from 17 randomized, double-blind, placebo-controlled trials.⁵¹ There was no significant reduction in all-cause mortality among patients treated with an ARB (RR, 1.09; 95% confidence interval [CI], 0.92-1.29) or an ARB plus an ACEI (RR, 1.04; 95% CI, 0.91-1.20). Patients treated with an ARB plus an ACEI, however, had an RR of 26% in rates of hospitalization for HF compared with patients treated with an ACEI alone (95% CI, 0.60-0.84). Of note, within a more recent trial not included in the meta-analysis, the Candesartan in Heart Failure—Assessment of Reduction in Mortality and Morbidity (CHARM) program, there was a 15% RR in the incidence of CV death or hospitalization for HF among patients receiving an ARB plus an ACEI compared with those treated with an ACEI alone ($P = .011$).⁴⁵

BP CONTROL

The Seventh Joint National Committee (JNC 7) on prevention, detection, evaluation, and treatment of high BP recommends that patients with DM and/or chronic kidney disease be treated to achieve a BP lower than 130/80 mm Hg.⁵² The prior JNC 6 guidelines recommended that in diabetic patients with more than 1 g/dL of proteinuria, a BP lower than 125/75 mm Hg should be the target.⁵³ Although the JNC 7 guidelines do not define a goal BP for patients with HF and/or CVD, fastidious control is recommended.⁵² Finally, the treatment of patients without CVD or DM should be initiated if their systolic BP is 140 mm Hg or higher or their diastolic BP is 90 mm Hg or higher.⁵²

The optimal agent for lowering BP in patients with CVD has yet to be clearly defined. While several medications, including ACEIs, β -blockers, and thiazide diuretics remain first-line agents, ARBs, aldosterone antagonists, and long-acting calcium channel blockers

should also be strongly considered, especially for patients with HF and/or stable angina pectoris.⁵² Most hypertensive patients will require at least 2 antihypertensive medications to achieve their target BP.⁵⁴

Evidence: A large meta-analysis, the Individual Data Analysis of Antihypertensive intervention trials (INDANA), evaluated more than 40000 hypertensive patients randomized to treatment with thiazide diuretics, β -blockers, or placebo.⁵⁵ Among patients randomized to a study drug, there were significant reductions in the incidence of stroke and major coronary events ($P < .001$).

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), 33357 patients who were 55 years or older and had at least 1 coronary heart disease risk factor were randomized to chlorthalidone (up to 25 mg/d), amlodipine (up to 10 mg/d), or lisinopril (up to 40 mg/d) for a mean of 5 years.⁵⁶ There was no observed difference in the primary combined outcome of fatal coronary heart disease or nonfatal MI between patients taking any of the 3 antihypertensive drugs (95% CI, 0.90-1.08). Because of their lower cost, thiazide diuretics were considered the preferred first-line antihypertensive agents.

The data reviewed in the ACEI, ARB, β -blocker, and aldosterone antagonist sections of this review provide strong support for the use of these medications in hypertensive patients with a history of CVD, HF, and/or DM.

β -BLOCKERS

β -Blockers competitively inhibit the effects of catecholamines on β -adrenergic receptors. They impart antiarrhythmic, antianginal, and sympatholytic effects by reducing myocardial ionotropic and chronotropic stimulation. β -Blockers should be used in the secondary prevention of CVD in patients with an MI,⁵⁷ HF/LVSD,²⁷ and/or hypertension.⁵⁸ Major adverse effects include potential short-term exacerbations of HF symptoms,⁵⁹ fatigue (1.8%),⁶⁰ and sexual dysfunction (0.5%).⁶⁰

Evidence: Two major studies, the Norwegian Multicenter Study Group

trial⁶¹ and the Beta-blocker Heart Attack Trial (BHAT),⁶² were among the first to assess β -blockade following an MI. A total of 5766 patients were randomized to treatment with timolol (up to 20 mg/d) or propranolol (up to 240 mg/d) vs placebo within 5 to 28 days following an acute MI. Among patients taking a β -blocker, there was a 26% to 39% RR in death ($P = .005$ to $P = .0005$).

The Cardiovascular Cooperative Project, a retrospective review of 201752 unselected Medicare patients diagnosed with an acute MI,⁶³ tracked differences in mortality among those taking β -blockers after discharge. Overall, mortality was decreased by 40% over 2 years in all patients receiving β -blockers and by 32% to 40% among the subset of patients previously excluded from some studies because of coexisting chronic obstructive pulmonary disease, DM, and/or severe LVSD.

A large meta-analysis of 54234 patients from 82 randomized trials attempted to further determine whether CV outcomes differed according to β -blockade duration after an MI.⁵⁷ Long-term (6-48 months)—but not short-term (<6 weeks)— β -blockade was associated with a significant reduction in mortality (odds ratio, 0.77; 95% CI, 0.69-0.85).

The effect of β -blockade in ischemic LVSD was prospectively evaluated in the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial,⁶⁴ which randomized 1959 patients with known LVSD (ejection fraction $\leq 40\%$) following a MI to carvedilol (up to 25 mg twice daily) or placebo for a mean of 1.3 years. Patients receiving carvedilol had a significant reduction in all-cause mortality (hazard ratio, 0.77; $P = .03$) and nonfatal MI (hazard ratio, 0.59; $P = .01$).

The INDANA meta-analysis⁵⁵ (reviewed above in the “BP Control” section) supports the use of a β -blocker as a first-line antihypertensive agent among patients with CVD.

CHOLESTEROL MANAGEMENT

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in

Adults (Adult Treatment Panel [ATP] III) recommends a target low-density lipoprotein cholesterol (LDL-C) level less than 100 mg/dL (2.6 mmol/L) in patients with CVD, DM, or, based on the Framingham Risk Score, a 10-year risk of death by MI or coronary heart disease higher than 20%.⁶⁵ The guidelines classify normal triglyceride (TG) levels as less than 150 mg/dL (3.8 mmol/L) and normal high-density lipoprotein cholesterol (HDL-C) levels as 40 mg/dL (1.0 mmol/L) or greater. In women, HDL-C values less than 50 mg/dL (1.3 mmol/L) are 1 criterion for the metabolic syndrome.

Recent data from the Heart Protection Study (HPS),⁶⁶ however, challenge the cut point set forth by ATP III and suggest that further LDL-C reduction in patients with a LDL-C of 90 to 100 mg/dL (2.3 to 2.6 mmol/L) results in reduced CV events in subjects with known DM or CVD. Trials are being carried out to better determine the desired threshold for LDL-C in secondary prevention. At any rate, lifestyle changes, including diet and exercise, and pharmacotherapy should be implemented to bring LDL-C levels below 100 mg/dL (2.6 mmol/L).

HMG-CoA Reductase Inhibitors (Statins)

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, an enzyme involved in the rate-limiting step of cholesterol synthesis. They are the most powerful class of drugs for lowering LDL-C, but also help to raise HDL-C and lower TG. Statins should be considered the first-line lipid lowering medication for most patients with CVD and/or DM. Major adverse effects include myalgias (1%-6%), significant dose-dependent elevations of serum aminotransferases (0.1%-3.0%), myopathy (0.7%), and fatal rhabdomyolysis (<.00002%).⁶⁷

Evidence: Four major studies have assessed the role of statins in the secondary prevention of CVD. These include the Scandinavian Simvastatin Survival Study (4S),⁶⁸ the Cholesterol Recurrent Events (CARE) trial,⁶⁹ the Long-Term Intervention With Pravastatin in Is-

chaemic Disease (LIPID) trial,⁷⁰ and the Heart Protection Study (HPS).⁶⁶

The 4S Study assessed 4444 patients with angina or a history of a MI and elevations in total cholesterol and LDL-C (mean of 261 mg/dL and 188 mg/dL, respectively). Patients were randomized to receive dietary modification plus simvastatin (up to 40 mg/d) or placebo with a goal total cholesterol less than 200 mg/dL (5.2 mmol/dL). Over 5.4 years, patients receiving simvastatin had a 30% RR in mortality (8.2% vs 11.5%; $P = .0003$).

The benefit of lowering mildly elevated cholesterol levels was assessed in the CARE trial, in which 4159 patients with a mean LDL-C of 139 mg/dL and a history of MI were randomized to receive pravastatin (40 mg/d) or placebo. The pravastatin group experienced a 24% RR (10.2% vs 13.2%; $P = .003$) in the primary end point of a fatal coronary event or non-fatal MI over 5 years. The LIPID study group randomized 9014 patients with a history of MI or unstable angina and an elevated total cholesterol level (155-271 mg/dL) to pravastatin (40 mg/d) or placebo over 6.1 years. There was a 22% RR in total mortality (11.0% vs 14.1%; $P < .001$) in the pravastatin arm.

The HPS study randomized 20536 patients with CVD and/or DM to simvastatin (40 mg/d) or placebo over 5 years. All-cause mortality was significantly reduced (12.9% vs 14.7%; $P = .0003$) and there was an RR of 25% to 30% in major CVD events independent of the LDL-C level.

Fibrates

Fibrates activate peroxisome proliferator-activated receptors to stimulate lipoprotein lipase, resulting in lower TG and higher HDL-C levels.⁶⁵ They are appropriate first-line agents in patients with isolated hypertriglyceridemia. Combination therapy with a statin can be considered in high-risk patients with elevated LDL-C and either low HDL-C or high TG levels. The major adverse effect is myopathy, which is potentiated by coadministration with statins.⁷¹

Evidence: Currently, there are no studies that have independently evaluated the effect of solely lower-

ing TG since fibrates also raise HDL-C. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) randomized 2531 men with CAD to gemfibrozil (1200 mg/d) or placebo over 5 years and found a 22% RR in the primary outcome of nonfatal MI or coronary heart disease death in the patients treated with gemfibrozil (17.3% vs 21.7%; $P = .006$).⁷²

Nicotinic Acid

Nicotinic acid (niacin) raises HDL-C and inhibits hepatic production of very low-density lipoprotein cholesterol and LDL-C. It can be used in combination therapy with statins in the treatment of hyperlipidemia in patients with normal or low levels of HDL-C.⁶⁵ Major adverse effects include flushing (in up to 80% of individuals with the crystalline preparation),⁷³ pruritus (in 20%),⁷³ paresthesias (in 20%),⁷³ nausea (in 20%),⁷³ hepatotoxicity, hyperglycemia from insulin resistance,⁷⁴ hyperuricemia, hypotension,⁷⁵ and elevation of serum homocysteine levels.⁷⁶

Evidence: The HDL-Atherosclerosis Treatment Study (HATS) evaluated the effect of niacin in combination with a statin.⁷⁷ This study randomized 160 patients to simvastatin and niacin or to placebo to evaluate the occurrence of a first CV event and assess the effects on coronary artery stenoses angiographically. The mean \pm SD simvastatin and niacin doses were 13 \pm 6 mg and 2.4 \pm 2.0 g daily, respectively, and resulted in a 42% RR in LDL-C and a 26% relative rise in HDL-C. Treatment with simvastatin and niacin resulted in slight regression rather than progression of angiographic stenoses ($P < .001$) and a 60% RR in the CV event rate ($P = .02$).

CIGARETTE SMOKING CESSATION

An estimated 23.5% of adult Americans smoke tobacco.⁷⁸ Smoking has been shown to promote the development and progression of CVD⁷⁹ and, in persons with established CAD, smoking is an important predictor of future CV events.⁸⁰ A combination of long-term behavioral support⁸¹ and pharmacologic

therapy with bupropion, with or without nicotine replacement,⁸² should be offered to all patients with CVD.

Evidence: A systematic review sought to determine the effects of individual counseling on smoking cessation.⁸³ Patients receiving individual counseling for 6 months or longer had an odds ratio of 1.62 for successful smoking cessation (95% CI, 1.35-1.94).

In a double-blind, placebo-controlled study, 893 smokers were randomized to receive bupropion (150 mg/d for 3 days, then 150 mg twice daily) with or without a nicotine patch (21 mg, tapered to 7 mg), a nicotine patch alone, or placebo over 9 weeks.⁸⁴ At 12 months, the relative abstinence rates in the bupropion groups, with or without a nicotine patch, were significantly higher (36% and 30%, respectively; $P < .001$) than in the nicotine patch only (16%) and placebo groups (16%).

DIET AND WEIGHT MANAGEMENT

Excessive body weight has become a major public health problem, as fewer than half of all Americans are at or below a healthy weight.⁸⁵ The body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) categorizes patients as healthy (BMI, 19-25), overweight (BMI, 25-30), or obese (BMI >30), and correlates with CV risk.⁸⁶ The waist circumference, which is considered increased if greater than 40 in (102 cm) in men or 35 in (89 cm) in women, is an indirect measure of visceral or central obesity that has also been shown to correlate with CV risk.^{87,88}

Overweight states are associated with increased rates of CV events and death, as well as the development of comorbid conditions (ie, DM, hypertension, and hypercholesterolemia).⁸⁹ Caloric reductions of 500 kcal/d or more should be instituted in most patients at an unhealthy weight until they reach their ideal body weight.⁹⁰ A diet containing protein, complex carbohydrates, omega-3 fatty acids, fruits, vegetables, nuts, and whole grains and restricted in satu-

rated fat and cholesterol should be adopted by all patients with CVD.^{67,91,92}

Evidence: Most of the evidence on the CV benefits of weight reduction has been obtained from observational studies where weight loss was a secondary end point. The Lyon Diet Heart Study randomized 605 patients following an MI to a Mediterranean diet rich in fiber and polyunsaturated fat or a typical western diet low in fiber and high in saturated fats.⁹³ Although there was no significant difference in BMI between the 2 groups, patients consuming the Mediterranean diet showed a trend toward a reduction in BMI, as well as a 68% RR in the outcome of cardiac death and nonfatal MI ($P = .0001$), over 46 months.

DIABETES PREVENTION AND MANAGEMENT

Diabetes Prevention

Diabetes mellitus is a comprehensive term used to describe several conditions associated with altered carbohydrate metabolism and resultant hyperglycemia. It is defined by fasting plasma glucose levels of 126 mg/dL (7.0 mmol/L) or greater and/or 200 mg/dL (11.1 mmol/L) or greater after an oral glucose load.⁹⁴ The type 2 form, which is the most common, accounts for 90% or more of all cases of DM.⁹⁵

During the transition from normoglycemia to overt DM, many patients develop intermediate states of altered carbohydrate metabolism. Impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) occur in most of the patients who go on to develop DM.⁹⁶ Defined by an oral glucose tolerance test finding of 140 to 199 mg/dL (7.8-11 mmol/dL) and a fasting plasma glucose level of 110 to 125 mg/dL (6.1-6.9 mmol/dL),⁹⁶ respectively, IGT and IFG probably result from the same state of relative insulin resistance and/or insulin deficiency that develops in patients with DM.⁹⁷ All patients with CVD who have coexisting IGT and/or IFG should initiate lifestyle changes to reduce weight and intake of dietary saturated fat and increase regular physical activity.

Evidence: In the Finnish Diabetes Prevention Trial, 522 men and women, aged between 40 and 65 years and with IGT and a BMI greater than 25, were randomized to a control or intervention group.⁹⁸ The control group was given general oral and written instructions about diet and exercise. The intervention group was given detailed advice about how to achieve a weight reduction of 5%, with an intake of saturated fat less than 10% of the total energy consumed, an increase in fiber intake to at least 15 g per 1000 kcal, and moderate exercise for 30 minutes per day. The cumulative incidence of DM after 4 years was 11% in the intervention group and 23% in the control group, with an RR of 58% ($P < .001$).

In the Diabetes Prevention Program, 3234 nondiabetic patients with a fasting plasma glucose level of 95 to 125 mg/dL (5.3-6.9 mmol/L) and IGT were randomized to metformin (850 mg twice daily), a lifestyle program (goals of a 7% weight loss and 150 minutes of physical activity per week), or placebo for 2.8 years.⁹⁹ The lifestyle intervention and metformin arms reduced the incidence of DM by 58% (95% CI, 0.48-0.66) and 31% (95% CI, 0.17-0.43), respectively.

Diabetes Management

Type 2 DM is a potent risk factor for CVD and is associated with accelerated rates of atherosclerosis.¹⁰⁰ Coronary artery disease accounts for more than 65% of all deaths in persons with DM.¹⁰¹ Patients with CVD and DM should concentrate on good glycemic control with a target glycosylated hemoglobin (HbA_{1c}) value of less than 7%.¹⁰²

Evidence: The United Kingdom Prospective Diabetes Study (UKPDS-35), an observational study of 4585 patients with DM, found that for each 1% reduction in mean HbA_{1c} there was a 21% RR ($P < .0001$) in any end point related to diabetes.¹⁰³ There was a 14% RR for nonfatal MI ($P < .0001$) and a 37% RR for microvascular complications ($P < .0001$) with each 1% reduction in HbA_{1c}. Patients with HbA_{1c} levels in the normal range (<6.0%) carried the lowest risk.

EXERCISE

As many as 75% of adult Americans have an inadequate level of activity or exercise,¹⁰⁴ resulting in about a 2-fold higher risk of CV events.¹⁰⁵ Among patients with known CVD, regular exercise has been shown to reduce the rates of CV and all-cause mortality.¹⁰⁶ All patients with a history of CVD should engage in moderate levels of aerobic and weight-training exercise for 30 minutes or more on most days of the week.^{107,108} For patients with chronic stable angina pectoris, a recent MI, recent coronary artery bypass surgery, and/or LVSD, supervised exercise in a cardiovascular rehabilitation program should be strongly considered.¹⁰⁹

Evidence: To assess the effect of regular exercise on atherosclerosis, 62 patients with angiographically proven CAD were randomized to regular physical exercise or usual care.¹¹⁰ After 1 year, patients underwent a second coronary angiogram. Among patients who exercised the least (mean energy expended, 1000 kcal/wk) atherosclerosis progressed, whereas in those who exercised the most (mean, 2200 kcal/wk), atherosclerosis modestly regressed ($P < .005$).

In a prospective observational study, 773 men with known CAD were followed up for 5 years.¹⁰⁶ Based on self-reported levels of exertion, they were classified into groups according to their level of activity (light, moderate, or vigorous). Compared with the men who engaged in minimal or no activity, those who engaged in light and moderate levels of activity had RRs in all-cause mortality of 58% (CI, 0.25-0.71) and 53% (95% CI, 0.24-0.92), respectively.

Prospective data from an ethnically diverse cohort of postmenopausal women enrolled in the Women's Health Initiative Observational Study found that walking and vigorous exercise were associated with a significant reduction in relative risk for CV events.¹¹¹ Women in increasing quintiles of energy expenditure (means of metabolic equivalents, 0, 4.2, 10, 17.5, and 32.8) had a significant inverse correlation with age-adjusted relative risk for coronary events (1.0, 0.73, 0.69, 0.68, and 0.47; $P < .001$ for trend). Walking and vigorous exercise were associ-

ated with similar risk reductions and were independent of race or ethnic group, age, and BMI.

EJECTION FRACTION

For any patient with known CVD, an assessment of left ventricular function through ejection fraction measurement is important. A depressed ejection fraction is associated with an increased risk of life-threatening arrhythmias, HF, and death.¹¹² The ejection fraction also helps to determine whether patients should be considered for adjunctive therapies. These include treatment with ACEIs, β -blockers, aldosterone inhibitors, digoxin, and an implantable cardioverter defibrillator.

ACEIs

Angiotensin-converting enzyme inhibitors are strongly indicated in patients with a depressed ejection fraction, especially following an MI.²⁷

Evidence: In addition to findings previously described, 3 major studies have prospectively evaluated the use of ACEIs in patients with HF and/or LVSD: the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS),¹¹³ the Study of Left Ventricular Dysfunction (SOLVD),¹¹⁴ and the Vasolidator Heart Failure Trial (V-HeFT).¹¹⁵ Most patients had an LVSD & ischemic etiology. In total, 3626 patients with HF were randomized to enalapril (up to 40 mg/d) or placebo for a mean of 6 to 41 months. Among patients on an ACEI, mortality was significantly reduced by 16% to 40% ($P = .016$ to $P = .002$, depending on the study).

A meta-analysis of 5 randomized controlled trials of long-term ACE inhibition assessed 12 763 patients with HF and/or LVSD.¹¹⁶ Patients receiving an ACEI had a lower mortality rate (23.0% vs 26.8%; 95% CI, 0.74-0.87), reinfarction rate (8.9% vs 11.0%; 95% CI, 0.70-0.89), and rate of hospital readmission for HF (13.7% vs 18.9%; 95% CI, 0.61-0.74).

β -Blockers

β -Blockers are strongly indicated in patients with a depressed ejection fraction, especially following an MI.²⁷

Evidence: In addition to data previously described, 4 major studies have prospectively evaluated β -blockade in patients with HF and/or LVSD: the Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure (MERIT-HF),¹¹⁷ the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II),¹¹⁸ the Carvedilol Prospective Randomized Cumulative Survival Study,¹¹⁹ and the Beta-Blocker Evaluation of Survival Trial.¹²⁰ Most patients had LVSD of an ischemic etiology. In total, 11 635 patients with LVSD (with an ejection fraction between $\leq 25\%$ and $\leq 40\%$, depending on the study) were randomized to β -blockade with metoprolol, bisoprolol, carvedilol, or bucindolol vs placebo for a mean of 10 to 24 months. A significant RR in all-cause mortality was noted in patients taking each of the β -blockers, (hazard ratio, 0.65-0.75; $P = .0014$ to $P = .00009$), except bucindolol ($P = .13$). In addition, 2 meta-analyses have evaluated a total of 15 984 patients with stable HF and demonstrated that β -blockers significantly reduce morbidity and mortality.^{121,122}

Aldosterone Inhibitors

Spirolactone and eplerenone antagonize the effects of aldosterone on the heart and result in increased sodium excretion and reduced potassium excretion through their actions on the kidney. Patients with advanced New York Heart Association (NYHA) class III or IV HF and/or LVSD (ejection fraction $\leq 40\%$) following a MI should be treated with spironolactone (up to 25 mg/d)¹²³ or eplerenone (up to 50 mg/d),¹²⁴ unless contraindicated. Major adverse effects include serious gynecomastia or breast pain (with spironolactone, in 10% of patients)¹²³ and serious hyperkalemia of 6.0 mEq/L (6.0 mmol/L) or greater (with eplerenone, in 5.5%).¹²⁴

Evidence: The Randomized Aldactone Evaluation Study (RALES) randomized 1663 patients with severe HF (NYHA class III or IV) with an ejection fraction of 35% or less to spironolactone (up to 25 mg/d) or placebo for 24 months.¹²³ Only 11% of patients were taking β -blockers. Patients randomized to spironolactone had a 30% RR in total mortality

($P < .001$). There was an additional 35% RR in hospitalization for HF ($P < .001$) and a significant improvement in HF symptoms and NYHA class ($P < .001$).

The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) randomized 6642 patients with LVSD (ejection fraction $\leq 40\%$) 3 to 14 days following MI to eplerenone (up to 50 mg/d) or placebo for a mean of 16 months.¹²⁴ Patients randomized to eplerenone had significant reductions in hospitalization and death from CV causes (relative risk, 0.87; $P = .002$), sudden cardiac death (relative risk, 0.79; $P = .03$), and all-cause mortality (relative risk, 0.85; $P = .008$).

Digitalis

Digitalis is a cardiac glycoside that has been shown to reduce hospitalization rates among patients with LVSD. Therapy with digitalis should be considered for any patient with HF to reduce symptoms.²⁷ Major adverse effects include dose-dependent dysrhythmias and conduction block that are potentiated by hypokalemia and hypomagnesemia, dizziness (in 5% of patients), headache (in 3%), yellow or blurred vision, gastrointestinal symptoms (in 2%-3%), rash (in 2%), and the possibility of drug-drug interaction.¹²⁵

Evidence: The Digitalis Investigation Group (DIG) study randomized 6800 patients with an ejection fraction of or higher than 45% to digoxin or placebo for 37 months to assess the effect on mortality and rate of hospitalization for HF.¹²⁶ There was no significant reduction in mortality, but there was a 28% RR in hospitalization for HF (26.8% vs 34.7%; $P < .001$).

Implantable Cardioverter Defibrillator

Because patients with an MI and marked LVSD are at significantly increased risk for arrhythmogenic sudden cardiac death,¹²⁷ they should be strongly considered for prophylactic implantation of an implantable cardioverter defibrillator.

Evidence: The Multicenter Automatic Defibrillator Implantation

Trial (MADIT II) randomized 1232 patients with an ischemic cardiomyopathy (ejection fraction $\leq 30\%$) to the prophylactic implantation of a cardioverter defibrillator 1 month after MI or later.¹²⁸ Invasive electrophysiological testing for risk stratification was not required. There was a 31% RR in all-cause mortality (95% CI, 0.51-0.93; $P = .016$) among patients randomized to the implantable cardioverter defibrillator.

CONCLUSIONS

Effective secondary prevention of CVD is an attainable and necessary step in the reduction of CV risk. Without effective preventive strategies, CV mortality rates can be as high as 10% per year.¹²⁹ To address this, specialized programs dedicated to simplifying multifactor CV risk reduction have been developed, resulting in significant improvements in clinical outcomes.¹³⁰⁻¹³³

In spite of this a patient diagnosed with CVD today can be expected to take as many as 5 or more medications to achieve optimal risk reduction. Limited by cost, concerns about compliance, and the potential for drug-drug interaction, some physicians remain skeptical of the benefits derived from this form of CV polypharmacy. This concern is further fueled by the fact that many of the aforementioned trials demonstrating CV benefit enrolled patients who were not fully receiving therapies known to reduce CV risk.

Nonetheless, most CV risk-reducing strategies have been found to be both medically justified and cost-effective.^{134,135} In fact, through the institution of many of these therapies over the last decade, we have seen improvements in the quality of care provided to patients with CVD^{136,137} resulting in reduced CVD mortality.¹ Newly available poly-pills combining different classes of medications into a single pill¹³⁸⁻¹⁴⁰ may represent a creative solution to the limitations of CV polypharmacy and provide the hope that improvement in CVD risk reduction will continue for years to come.

As the list of medications and interventions for CVD continues to grow, clinicians and patients must remain informed of these thera-

pies. An "ABC" approach, as we have used in this review, can help by providing evidence for current therapies as well as a framework on which to build an individual therapeutic course of action. The use of this approach can help to increase adherence to guidelines, thereby further helping to reduce morbidity and mortality from CVD.

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Correction

Errors in Text. There were 2 errors in the article by Gluckman et al titled "A Practical and Evidence-Based Approach to Cardiovascular Disease Risk Reduction" published in the July 26 issue of the ARCHIVES (2004;164:1490-1500). Under the "ACEIs" subheading on page 1496, the sentence "Most patients had an LVSD & ischemic etiology" should read "Most patients had an ischemic etiology for their LVSD." Under the "Digitalis" subheading on page 1497, the sentence "The Digitalis Investigation Group (DIG) randomized 6800 patients with an ejection fraction of or higher than 45% to digoxin or placebo for 37 months" should read "The Digitalis Investigation Group (DIG) randomized 6800 patients with an ejection fraction of 45% or less to digoxin or placebo for 37 months."