

A white paper on modifiable risk factors in cardiovascular disease

This supplement to *The Journal of Family Practice* is supported by a grant from Pfizer Inc and was submitted by The Primary Care Education Consortium. It was edited and peer reviewed by *The Journal of Family Practice*.

SUPPLEMENT TO

THE JOURNAL OF FAMILY PRACTICE

Available at jfponline.com  March 2008

Managing multiple cardiovascular risk factors

Key Points and Recommendations

- When determining a treatment plan to reduce CVD risk, treat risk factors concomitantly rather than sequentially, thereby providing the greatest impact on overall CVD risk. This is particularly important because risk factors for CVD tend to cluster and interact in individuals, which exerts a greater combined risk.
- Simplify treatment plans to increase patient compliance.
- Individualize risk assessment and the subsequent treatment plan for each patient, targeting the lower end of treatment goal ranges. This is important because even if the number of individual risk factors is only moderate, the collective impact of multiple risk factors is intensified.
- Treatment of CVD risk factors should include such lifestyle changes as smoking cessation, dietary modification, and increased physical activity, as well as pharmacotherapy, when indicated.

Disclosures

Editorial support for the development of this supplement was provided by The Primary Care Education Consortium (PCEC) and funded by Pfizer Inc. Dr Blank and Dr Brunton each received an honorarium from PCEC in connection with the development of this supplement. Dr Brunton is on advisory boards for Amylin Pharmaceuticals, Inc., Novo Nordisk, and Pfizer Inc. Dr Blank reports that he has received grant or research support from Takeda Pharmaceuticals, Merck & Co., Inc, and Pfizer Inc.

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This article focuses on modifiable risk factors for which strong evidence supports the link to cardiovascular disease (CVD) and which can be addressed in a primary care practice. For best patient outcomes in such patients, clinicians should provide aggressive treatment for all modifiable risk factors—tobacco smoke, high blood cholesterol, high blood pressure, physical inactivity, obesity and overweight, and diabetes mellitus. Although controversy exists about which risk factors are most important, patients with diabetes should be treated as if they have known coronary heart disease. They should also receive aggressive and concurrent treatment for blood glucose, blood pressure, and lipids.

The Comparative Risk Assessment Collaborating Group module of the global burden of disease 2000 study (a World Health Organization initiative) systematically assessed the changes in population health that would result from modifying the population distribution of exposure to a risk factor or a group of risk factors. The group identified tobacco, high blood pressure (BP), and high cholesterol as being among the most significant contributors to lost years of healthy life.¹ Disease management strategies should consider simultaneous treatment of all of these risk factors to reduce the risk of CVD.²

Multiple risk factors and escalating CVD risk

Multiple risk factors compound a patient's overall CVD risk; the effects of the major risk factors for CVD are multiplicative



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(ie, if one factor doubles risk and another triples it, their joint effects increase risk 6-fold). For example, diabetes alone is a coronary heart disease (CHD) risk equivalent and is, therefore, an important risk factor for intervention; however, the likelihood of cardiovascular events increases substantially in patients with concomitant diabetes and hypertension. The most common clustering of risk factors includes hypertension, dyslipidemia, and impaired glucose tolerance or type 2 diabetes.²

Diabetes as a CHD risk equivalent was originally demonstrated in a 1998 study (7 year follow-up) in which patients with diabetes but no history of myocardial infarction (MI) were found to have the same risk of CHD death as did nondiabetic patients with a prior MI history.³ After 18 years of follow-up, the investigators stated that if the definition of CHD is expanded from MI alone to include ischemic electrocardiogram changes or angina pectoris, patients with type 2 diabetes (especially women) have an even higher risk of CHD death than do nondiabetic patients with prior CHD.⁴

It is beyond the scope of this article to discuss the current controversy of metabolic syndrome as a discrete diagnosis. What we must keep in mind, however, is that each risk factor is important, risk factors have synergistic detrimental effects, and modifiable risk factors should, in fact, be modified.

Cardiovascular risk assessment

The Framingham risk score is a commonly used tool to predict cardiovascular risk.⁵ The algorithm assigns points according to risk factor exposure and severity, starting with age and including total cholesterol, high-density lipoprotein cholesterol (HDL-C), BP, and whether or not the patient smokes tobacco (available at <http://hp2010.nhlbi.nih.net/atp/iii/calculator.asp?usertype=prof#moreinfo>).

Because diabetes is considered a CHD risk equivalent, it is not included in the Framingham scoring algorithm. The resulting score provides a 10-year *absolute* risk assessment of CHD. A 10-year absolute risk of $\geq 20\%$ defines patients for whom intensified risk reduction should be implemented; these patients are considered to have a cardiovascular event risk equivalent to that of individuals who have CHD.⁶

The Framingham scoring algorithm was developed for people *without* known heart disease and is based on a primarily white, middle-class, male population. Still, the risk factor exposure has been shown to be reasonably accurate when measured in other populations.⁷ The INTERHEART study identified 9 risk factors for acute MI: Dyslipidemia, smoking, diabetes, hypertension, and abdominal obesity, in that order, were the top 5 strongest modifiable risk factors for CHD, accounting for approximately 80% of the risk for an acute MI.⁸ These risk factors are easily identifiable in patients seen in the primary care setting. Newer methods of detection (eg, carotid intima-media thickness, coronary calcium scoring) are not necessarily advocated but are being increasingly used by some physicians as a component of risk assessment.

Assessing risk

Because family physicians need to identify patients at risk, some method of risk assessment is necessary. There are many ways to assess risk; however, the key is to find a method that is practical in your clinical setting and apply it in a consistent fashion. Avoid choosing an overly complex approach that you will not use consistently. As stated, the modifiable risk factors in most patients—dyslipidemia, smoking, diabetes, hypertension, and abdominal obesity—will be readily identifiable. Once the assessment is completed and risks are identified, it is important to move on to modifying risk and providing ongoing monitoring of patients' progress. The importance of addressing all identified risks concomitantly cannot be overstated.

Recommendations for modification of cardiovascular risk factors

Physical activity

Ask all patients about their level of physical activity.⁸ In those who are physically able, encourage 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, 5 to 7 days per week, as well as an increase in their daily lifestyle activities (eg, walking, gardening, household work). Encourage resistance training 2 days a week. Advise high-risk patients to participate

in medically supervised programs. For patient-oriented information on increasing physical activity, go online to <http://www.cdc.gov/nccdphp/dnpa/physical/index.htm>.

Weight control

At each visit, assess a patient's body mass index (BMI) and/or waist circumference, and consistently encourage weight reduction or maintenance through an appropriate balance of physical activity, reduced caloric intake, and formal behavior modification programs, when indicated. The American Heart Association (AHA) Council on Nutrition, Physical Activity, and Metabolism recommends that weight loss and physical activity be considered a primary therapy for obese patients with CVD.⁸ The goals recommended by the AHA and the American College of Cardiology include a reduction in body weight of ~10% from baseline, a BMI between 18.5 and 24.9 kg/m², and a waist circumference of <40 inches for men and <35 inches for women.⁹ The ways in which family physicians can facilitate

weight loss remain a challenge. For example, a recent meta-analysis of 30 controlled studies of currently available weight loss drugs showed that, compared with placebo, mean weight reduction achieved with weight loss agents was <5 kg, or <5% of mean total body weight.¹⁰

Lifestyle modification, however, including increased physical activity, is effective and is an integral part of an effective management plan. Another meta-analysis showed that a program of regular brisk walking can significantly increase aerobic fitness and decrease BMI, percentage of body fat, and resting diastolic BP in previously sedentary adults.¹¹

Due to time and space constraints, we will not be discussing the patient whose BMI may be >35 kg/m² and for whom bariatric surgery may be an option. The National Institutes of Health guidelines on the role of bariatric surgery for patients with morbid obesity who are unable to lose weight by more conservative measures are available online at http://www.nhlbi.nih.gov/guidelines/obesity/sum_clin.htm.

TABLE 1
JNC 7 classification and management of blood pressure

Category	SBP ^a (mm Hg)	DBP ^a (mm Hg)	Lifestyle Modification	Considerations for Initial Therapy	
				Without Compelling Indications	With Compelling Indications
Normal	<120	and <80	Encourage	No antihypertensive drugs indicated	Drug(s) for compelling indications ^c
Prehypertension	120–139	or 80–89	Yes		
Stage 1 Hypertension	140–159	or 90–99	Yes	Thiazide-type diuretics for most. May consider ACEI, ARB, BB, CCB, or combination	Drug(s) for compelling indications ^c
Stage 2 Hypertension	≥160	or ≥100	Yes	2-drug combination for most (usually thiazide- type diuretic and ACEI or ARB or BB or CCB) ^b	Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta-blocker; BP, blood pressure; CCB, calcium channel blocker. DBP, diastolic blood pressure; SBP, systolic blood pressure.

^aTreatment determined by highest BP category.

^bInitial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

^cTreat patients with chronic kidney disease or diabetes to BP goal of <130/80 mm Hg.

Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572.

TABLE 2
JNC 7 compelling indications for specific antihypertensive agents based on favorable outcomes data from clinical trials

	Diuretic	Beta-Blocker	Angiotensin-Converting Enzyme Inhibitor	Angiotensin Receptor Blocker	Calcium Channel Blocker	Aldosterone Antagonist
CHF	✓	✓	✓	✓		✓
Post-MI		✓	✓			✓
CAD Risk	✓	✓	✓		✓	
Diabetes Mellitus	✓	✓	✓	✓	✓	
Renal Disease			✓	✓		
Recurrent Stroke Prevention	✓		✓			

CAD, coronary artery disease; CHF, congestive heart failure; MI, myocardial infarction.

Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572.

Blood Pressure Control

Minimum BP goals are <140/90 mm Hg, or <130/80 mm Hg if the patient has diabetes or chronic kidney disease.¹² Prehypertension describes people with systolic BP between 120 and 139 mm Hg, or diastolic BP between 80 and 89 mm Hg. Lifestyle changes can help patients with prehypertension, and physicians should motivate these patients to adopt health-promoting lifestyles. All patients with elevated BP should be encouraged to control their weight, engage in regular physical activity, moderate alcohol and sodium consumption, and increase the amounts of fresh fruits, vegetables, and low-fat dairy products they consume. Patients can be referred to the Dietary Approaches to Stop Hypertension (DASH) diet, available online at http://www.nhlbi.nih.gov/health/public/heart/hbp/dash/new_dash.pdf.

Often, lifestyle changes alone are not sufficient to control BP, and the addition of antihypertensive medications may be needed. Treatment can be initiated with any of the major classes of antihypertensive agents. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) provides compelling indications for the use of the different classes of antihypertensive drugs in the various categories of hypertension,

as summarized in **TABLES 1** and **2**.¹² The JNC 7 treatment algorithm is summarized in the **FIGURE**.¹²

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study demonstrated that goal-oriented treatment titration in patients with elevated BP—many of whom also had other cardiovascular risk factors (half had CHD, one third had diabetes, one third had dyslipidemia, and one quarter were smokers)—results in treatment benefits and achievement of BP goals.¹³ In this study, treatment was based on valsartan, 80 mg, or amlodipine, 5 mg. More than 90% of patients were able to achieve the diastolic BP goal, and the systolic BP goal was achieved in more than half of the patients at 1 year.¹³ The VALUE trial demonstrated that early (within 6 months) control of BP improves outcomes.¹⁴

If BP levels are >20/10 mm Hg above the desired goal, treatment with 2 agents of different classes should be initiated. The necessity of combination therapy to achieve BP goals has been confirmed in several trials. After 5 years of follow-up, BP was controlled at <140/90 mm Hg in 66% of patients in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial.¹⁵ To achieve this level of control, 62% of patients were taking ≥2 antihypertensive drugs. In the International Verapamil-Trandolapril Study

(INVEST), nearly half of the patients needed ≥ 3 antihypertensive agents to achieve BP goals.¹⁶ The choice of agents used to treat hypertension may also affect cardiovascular outcomes.

Lipid Management

Guidelines published in 2004 recommend a low-density lipoprotein cholesterol (LDL-C) level <100 mg/dL for patients with at least 2 cardiovascular risk factors.¹⁷ Because diabetes is regarded as a CHD risk equivalent, a lower LDL goal is justified. Other major risk factors (exclusive of LDL-C) that modify LDL goals are cigarette smoking, hypertension (BP $\geq 140/90$ mm Hg or taking antihypertensive medication), low HDL-C (<40 mg/dL), family history of premature CHD (male first-degree relative, age <55 years; female first-degree relative, age <65 years), and age (men, ≥ 45 years; women, ≥ 55 years). An HDL-C level ≥ 60 mg/dL counts as a “negative” risk factor, in that its presence removes 1 risk factor from the total count. Based on studies published after these guidelines, an LDL-C level <100 mg/dL should now be considered the goal of therapy, with an optional goal of <70 mg/dL in high-risk patients.

Achieving an LDL-C level <70 mg/dL can be challenging; however, a number of lipid-lowering agents are available. Statins are the preferred initial agent for LDL-C management, based on their efficacy, outcome data, and tolerability. The use of high-dose statins or combination therapy with a statin and ezetimibe (now controversial due to the ENHANCE study) or colesvelam may be necessary to achieve aggressive LDL-C goals. Fibrates, omega-3 agents, or niacin may be needed for patients with mixed lipid disorders, including reduced levels of HDL-C or elevated levels of triglycerides and non-HDL-C.

Glycemic Control

In patients with diabetes, a glycosylated hemoglobin (HbA1c) goal of $<7\%$, or as close to normal ($<6\%$) as possible without hypoglycemic events, should be the target.¹⁸ According to recommendations from the American Diabetes Association and the European Association for the Study of Diabetes, initial treatment for these patients should include therapeutic lifestyle management and, in the absence of contraindications, the use of metformin.¹⁹ If HbA1c goals are not achieved within 1

TABLE 3
Summary of treatment goals for blood pressure, lipids, and blood glucose

	Goal
Blood Pressure	$<140/90$ mm Hg ($<130/80$ mm Hg in patients with diabetes or chronic kidney disease)
LDL-C	<100 mg/dL (<70 mg/dL optional in high-risk patients)
Blood Glucose, HbA1c	$<7\%$ in general (as close to 6% as possible without significant hypoglycemia for individual patients)

HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol.

Chobanian AV, et al, for the National High Blood Pressure Education Program Coordinating Committee. *JAMA*. 2003;289:2560-2572.

Grundy SM, et al, for the Coordinating Committee of the National Cholesterol Education Program. *Circulation*. 2004;110:227-239.

American Diabetes Association. *Diabetes Care*. 2007; 30(suppl 1):S4-S41.

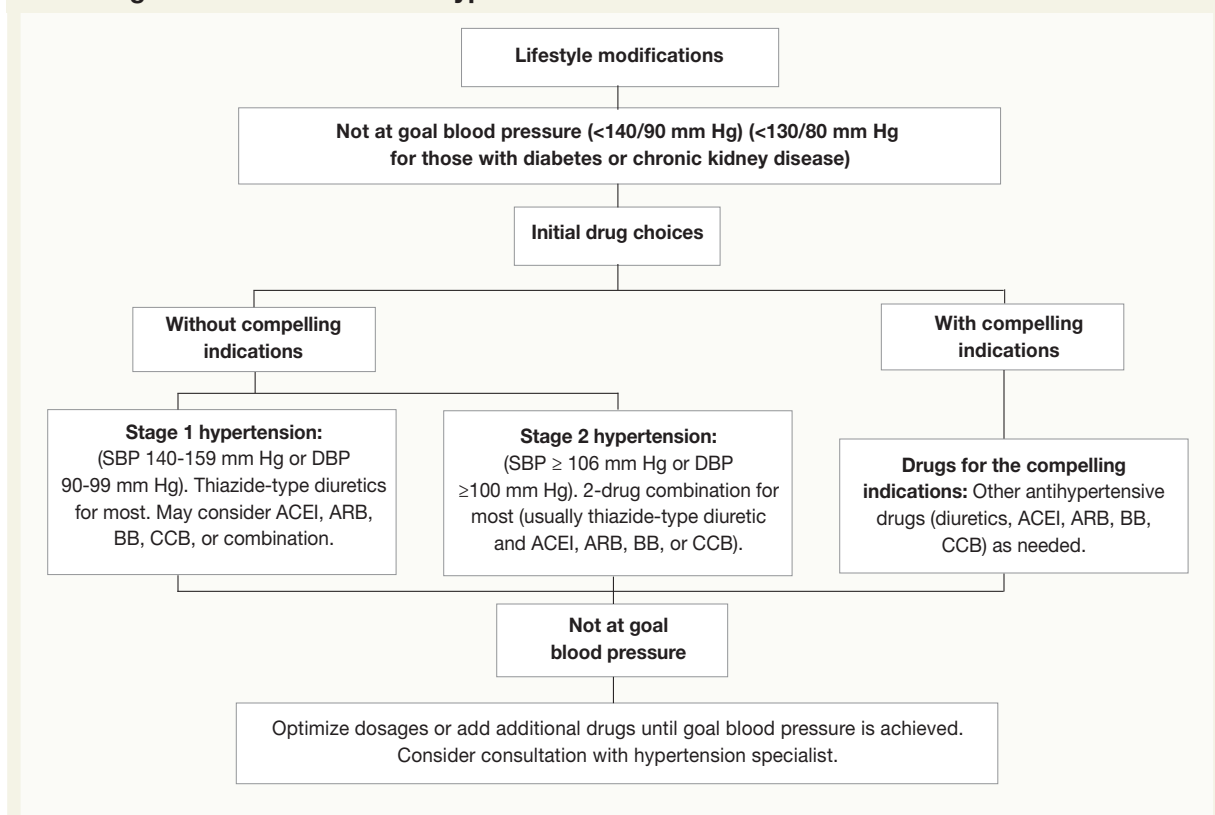
to 2 months, rapid addition of other therapies (eg, a sulfonylurea, thiazolidinedione [TZD], long-acting insulin, or incretin therapy) is indicated. The agent(s) chosen depends on a thorough evaluation of the patient and his or her comorbid conditions. Because this decision is potentially quite complex, it is important to consider the severity of glucose imbalance, the presence of obesity, knowledge of the patient’s left ventricular function, as well as the status of his or her renal function. Note that TZDs are relatively contraindicated in patients with congestive heart failure (CHF), and rosiglitazone has received a black box warning for patients with previous MI.

Treatment goals for BP, LDL-C, and glucose levels are summarized in **TABLE 3**.^{12,17,18}

Smoking

Complete cessation of smoking and avoidance of environmental exposure to tobacco smoke is an obvious goal for all individuals.⁷ At every office visit, ask patients about their tobacco use and advise every tobacco user to quit. All patients should avoid exposure to environmental tobacco smoke. For those who use tobacco, assess their

FIGURE
JNC-7 algorithm for treatment of hypertension



ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, calcium channel blocker.

Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2006;289:2560-2572.

willingness to quit and provide assistance in developing a plan for quitting. Arrange for follow-up, referral to special programs, or pharmacotherapy, including nicotine replacement, bupropion, or varenicline. Several online resources are available, including www.Anti-Smoking.org and www.cdc.gov/tobacco/how2quit.htm.

Value of treatment on CVD outcomes

Modification of risk factors can significantly improve CVD outcomes. Data now suggest that risk reduction can be achieved in otherwise asymptomatic patients and in younger patients. For example, the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) was the first study to show the benefits of

lowering lipids in patients with hypertension and 3 additional cardiovascular risk factors but without lipid levels previously considered to represent dyslipidemia.²⁰ In the Collaborative Atorvastatin Diabetes Study (CARDS), treatment with atorvastatin in patients with diabetes but without high LDL-C levels reduced the risk of first CVD events, including stroke.²¹ Although these patients had LDL levels not previously considered elevated, they did have other identified risk factors (≥1 of the following: retinopathy, albuminuria, current smoking, or hypertension). The CARDS trial was stopped 2 years early because the prespecified end point—reduction of first occurrence of acute CHD events, coronary revascularization, or stroke—had been met. Assessed separately, the relative risk of acute CHD events was reduced by 36%, coronary revascularizations by 31%, and stroke

by 48%. These data indicate that lipid-lowering therapy should be considered in patients at high risk of CVD. The findings of the CARDS study confirmed those of the Heart Protection Study, which demonstrated the benefit of treating patients at high risk of a coronary event with simvastatin, 40 mg daily, regardless of baseline LDL levels.²² These studies show that the decision to treat lipids should be based on a patient's cardiovascular risk rather than absolute lipid results. Lipid measurements (eg, LDL-C levels) represent a continuum, with the optimal value being approximately 70 mg/dL.^{12,17,18}

A prespecified objective of ASCOT was to assess whether any synergistic effects were apparent between lipid-lowering and blood-pressure-lowering treatments for preventing cardiovascular events.²³ In this 2 × 2 analysis, atorvastatin reduced the relative risk of the primary end point of nonfatal MI and fatal CHD events by 36%, total cardiovascular events by 21%, and stroke by 27%, compared with placebo. The Steno-2 study demonstrated a 50% relative risk reduction in cardiovascular and microvascular events with use of stepwise lifestyle modification and pharmacotherapy aimed at hyperglycemia, hypertension, dyslipidemia, and microalbuminuria, along with secondary prevention of CVD with aspirin.²⁴ The results of the Steno-2 study also provide convincing evidence of the significant benefits of treating all risk factors concomitantly.

A prospective meta-analysis of data from >90,000 participants in 14 randomized trials showed that statin therapy can safely reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by one fifth per each mmol/L (39 mg/dL) reduction in LDL-C.²⁵ Risk reductions were independent of the baseline LDL-C level and were proportional to the absolute LDL-C reductions.

The Treating to New Targets (TNT) trial demonstrated a highly significant reduction in coronary events and the benefit of more intensive statin therapy in patients with stable coronary artery disease.²⁶ In this study, the use of high-dose atorvastatin (80 mg) versus starting-dose atorvastatin (10 mg) resulted in a relative risk reduction of 22% for cardiovascular events ($P < .001$). Furthermore, a post hoc analysis of TNT showed that the best results in terms of risk reduction were achieved

in patients who not only received intensive LDL-lowering therapy but who also had their BP levels managed (systolic BP <140 mm Hg).²⁷ Patients with a mean LDL-C level of 60 mg/dL and a mean systolic BP of 122 mm Hg had an event rate of 7.2%, whereas those with an LDL-C level of 132 mg/dL and a systolic BP of 122 mm Hg had an event rate of 11% ($P < .0001$).

These data confirm that reducing multiple risks simultaneously is beneficial in reducing cardiovascular risk.

The importance of adherence

The above data show the common need for more than one pharmacologic agent to achieve therapeutic goals for a given risk factor. Acknowledging that risk factors tend to cluster brings us to the conclusion that patients may be faced with a significant pill burden, which can create a barrier to patient adherence to the treatment plan.

Chapman et al showed only 45% and 36% of patients are adherent to treatment with anti-hypertensive and lipid-lowering medications, respectively. Patients were more likely to adhere to treatment if antihypertensive and lipid-lowering therapies were initiated together, if they had a history of CHD or CHF, or if they took fewer other medications.²⁸ Follow-up physician visits and lipid tests are associated with improved adherence to statin therapy.²⁹

Family physicians can improve adherence to therapy through regular patient monitoring and patient education. Potential interventions include one-on-one discussions, written materials, telephone follow-up, and group sessions.³⁰ In addition, the use of combination products can reduce pill burden and improve adherence. Bangalore et al found that, compared with free-drug combination regimens, fixed-dose combinations resulted in a 26% decrease in the risk of patient noncompliance.³¹ Other suggestions include prescribing medications with limited potential for side effects, prescribing drugs that can be taken once daily, and improving patient access to support staff to report or discuss concerns.³⁰

The family physician and the patient must work together to reduce the patient's risk of CVD. Asking simple questions routinely about CVD

risk factors can promote patient awareness and adherence to lifestyle choices. Office staff can aid in CVD risk reduction efforts by administering simple risk questionnaires. The use of such risk assessment questionnaires as well as patient flow sheets can allow a primary care practice to improve CVD risk reduction strategies. Patient support resources are also available on the Internet and in your community.

Conclusion

The importance of risk factor assessment cannot be overestimated. Addressing all modifiable risk factors that are identified in a given patient

is vitally important. Monitoring the patient and modifying therapy, as required, to achieve and maintain treatment goals must be done on an ongoing basis and must take into account the impact of treatment choices on patient adherence. The unique relationship between the primary care physician and the patient provides an opportunity for the physician to have a positive impact on the patient's CV outcome. ■

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References

- Ezzati M, Lopez AD, Rodgers A, et al; Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. *Lancet*. 2002;360:1347-1360.
- Selby JV, Peng T, Karter AJ, et al. High rates of co-occurrence of hypertension, elevated low-density lipoprotein cholesterol, and diabetes mellitus in a large managed care population. *Am J Manag Care*. 2004;10:163-170.
- Haffner SM, Lehto S, Ronnema T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229-234.
- Juutilainen A, Lehto S, Ronnema T, et al. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care*. 2005;28:2901-2907.
- American Heart Association. Risk Factors and Coronary Heart Disease. <http://www.americanheart.org/presenter.jhtml?identifier=500>. Accessed Jan 10, 2008.
- Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update; Endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363-2372.
- Padwal R, Straus SE, McAlister FA. Evidence based management of hypertension. Cardiovascular risk factors and their effects on the decision to treat hypertension: evidence based review. *BMJ*. 2001;322:977-980.
- Yusuf S, Hawken S, Ounpuu S, et al, on behalf of the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-952.
- Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism. Endorsed by the American College of Cardiology Foundation. *Circulation*. 2004;110:2952-2967.
- Rucker D, Padwal R, Li SK, et al. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. *BMJ*. 2007; doi: 10.1136/bmj.39385.413113.25 (published online Nov. 15 2007).
- Murphy MH, Nevill AM, Murtagh EM, et al. The effect of walking on fitness, fatness and resting blood pressure: a meta-analysis of randomised, controlled trials. *Prev Med*. 2007;44:377-385.
- Chobanian AV, Bakris GL, Black HR, et al, for the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560-2572.
- Julius S, Kjeldsen SE, Brunner H, et al. VALUE Trial: Long-term blood pressure trends in 13,449 patients with hypertension and high cardiovascular risk. *Am J Hypertens*. 2003;16:544-548.
- Julius S, Kjeldsen SE, Weber M, for the VALUE trial group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022-2031.
- Cushman WC, Ford CE, Cutler JA, et al, for the ALLHAT Collaborative Research Group. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). *J Clin Hypertens*. 2002;4:393-404.
- Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al, for the INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003;290:2805-2816.
- Grundy SM, Cleeman JI, Merz CN, et al, for the Coordinating Committee of the National Cholesterol Education Program. Endorsed by the National Heart, Lung, and Blood Institute, American College of Cardiology Foundation, and American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227-239.
- American Diabetes Association. Standards of medical care in diabetes—2007. *Diabetes Care*. 2007;30(suppl 1):S4-S41.
- Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy. A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2006;29:1963-1972.
- Sever PS, Dahlöf B, Poulter NR, et al, for the ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet*. 2003;361:1149-1158.
- Colhoun HM, Betteridge DJ, Durrington PN, et al, for the CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet*. 2004;364:685-696.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
- Sever P, Dahlöf B, Poulter N, et al, for the ASCOT Steering Committee Members. Potential synergy between lipid-lowering and blood-pressure-lowering in the Anglo-Scandinavian Cardiac Outcomes Trial. *Eur Heart J*. 2006;27:2982-2988.
- Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.
- Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267-1278.
- LaRosa JC, Grundy SM, Waters DD, et al, for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425-1435.
- Kostis JB, Breazno A, LaRosa JC, et al. The benefits of intensive lipid lowering in patients with stable CHD and systolic blood pressure above or below 140 mm Hg: a post-hoc analysis of the TNT study. *J Clin Hypertens*. 2006;8:455 (abstract).
- Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive an lipid-lowering therapy. *Arch Intern Med*. 2005;165:1147-1152.
- Brookhart MA, Patrick AR, Schneeweiss S, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. *Arch Intern Med*. 2007;167:847-852.
- Munger MA, Van Tassel BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. *Med Gen Med*. 2007;9:58.
- Bangalore S, Kamalakkannan G, Pankar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120:713-719.