

Practical Approaches to Managing Hypertension: Reducing Global Cardiovascular Risk

What We Know About Hypertension

- More than 50 million Americans have high blood pressure
- If hypertension is present, peripheral artery disease (PAD), coronary artery disease (CAD), and/or cerebrovascular disease probably are also
- The optimal therapeutic approach treats hypertension within the context of cardiovascular (CV) risk

Learning Objectives

After completing this activity, participants should be better able to:

- State the prevalence of hypertension and its role in the CV disease continuum
- Formulate hypertension management according to risk stratification
- Describe the importance of targeting improvement in vascular function in patients with hypertension

Looking Beyond Blood Vessels

Hypertension is prevalent in developed societies and is estimated to affect more than 50 million Americans,¹ with consequences that extend beyond the blood vessels. Hypertension often coexists with other CV risk factors as part of the CV continuum (Figure 1).² Risk factors, including hypertension, contribute to endothelial dysfunction, which leads to atherosclerosis and acute coronary syndromes. The outcome can be myocardial infarction (MI), congestive heart failure (CHF), and death.² Cardiovascular symptoms are interrelated: if hypertension is present, PAD (see *Stepping Up Awareness of Peripheral Arterial Disease*, pages 64-65),

Hypertension should be treated in the context of individual CV risk profiles.

What can be done for patients who deny having hypertension? What tools can clinicians use to educate patients about blood pressure management? See page 81

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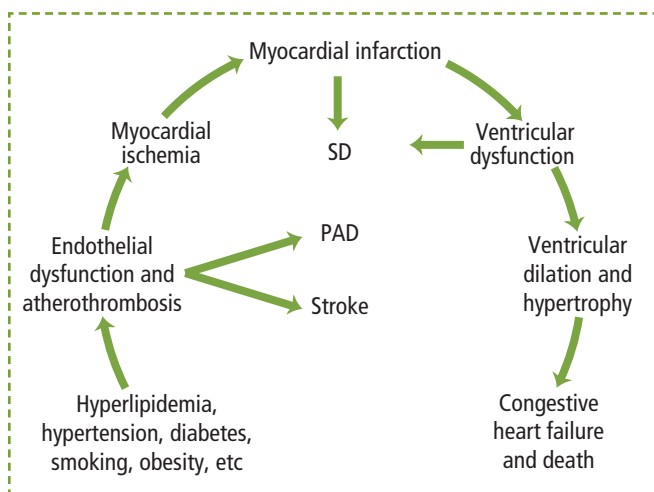


Figure 1. Progression of CV disease: the CV continuum. The CV continuum illustrates the pathway from risk factors, such as hypertension and diabetes, through various stages of dysfunction to congestive heart failure and death. The continuum can be interrupted; the most effective way to prevent CV death is to modify or prevent risk factors as early as possible. SD = sudden death. Adapted from Dzau V et al.²

CAD, and/or cerebrovascular disease also may be present. The continuum can be interrupted at any point to prevent progression of CV disease. Because the system is interrelated, it is important to intervene as early as possible to prevent or alter risk factors.²

Hypertension also acts as an independent risk factor. It can cause heart failure through left ventricular hypertrophy (LVH) and acute coronary syndromes even in the absence of other risk factors.³ LVH begins as adaptive remodeling in response to chronic pressure overload and is subject to neurohormonal influences such as angiotensin II (AII).² This condition contributes to diastolic heart failure, which occurs when the heart muscle cannot relax after contraction.³ Structural and functional changes associated with hypertension evolve over decades, but can be prevented with antihypertensive treatment. This underscores the importance of early, effective intervention.

Vascular disease occurs early in the continuum and is a key factor in the cascade that leads to all forms of coronary syndromes and disease. Hypertension is a key risk factor for oxidative stress, which occurs in early-stage vascular disease (Figure 2).² Oxidative stress results from the production of reactive oxygen species, which are toxic in tissue. The presence of excessive reactive oxygen species in tissue leads to endothelial dysfunction through vasoconstriction due to nitric oxide (NO) effects and inflammation and has downstream effects on thrombosis and remodeling.^{2,4} Crucial to this cascade is the renin-angiotensin-aldosterone system (RAAS) and, in particular, AII and angiotensin-converting enzyme (ACE), which are important therapeutic targets in blood pressure management.

Cardiovascular Risk: A Complex Picture

Hypertension is one element in a complex web of factors that help define a person's global CV risk. Clinicians recognize that treating hypertension in isolation is not the optimal approach. Hypertension should be treated in the context of each person's CV risk factor profile, using interventions that achieve target blood pressure levels, help mediate other CV risk factors, and avoid CV and renal morbidity and mortality. Risk factors for CV disease are listed in Table 1.

Few people have only 1 CV risk factor. Data from the Framingham Study show that more than half of all men and women with hypertension have at least 2 additional risk factors. The number and type of risk factors determine the likelihood of developing coronary heart disease (CHD) (Figure 3).⁵ Irrespective of severity or intensity, each additional CHD risk factor or risk equivalent can intensify the overall 10-year risk of coronary death in men and women. Risk factors include obesity, dyslipidemia (see the *Dyslipidemia* section, page 23), diabetes (see the *Diabetes* section, page 1), cigarette smoking, and LVH.⁴ The Framingham risk score offers a simple way for clinicians to calculate patients' 10-year risk

JNC 7 Cardiovascular Risk Factors

- Hypertension
- Cigarette smoking
- Obesity (BMI ≥ 30 kg/m²)
- Physical inactivity
- Dyslipidemia
- Diabetes mellitus
- Microalbuminuria or estimated GFR <60 mL/min
- Age (men >55 yr; women >65 yr)
- Family history of premature CV disease

BMI = body mass index; GFR = glomerular filtration rate; JNC 7 = Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. From Chobanian AV et al.¹

TABLE 1

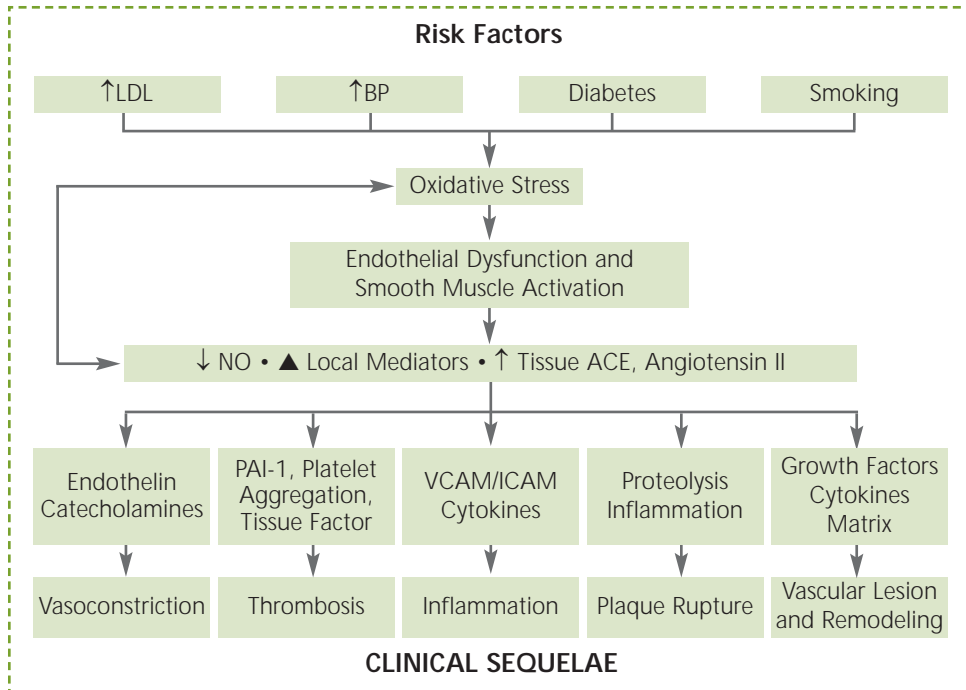


Figure 2. Development and progression of vascular disease. In this cascade, a common mechanism by which CV risk factors initiate the disease process is oxidative stress, leading to endothelial dysfunction and vascular inflammation. The figure illustrates the complex interrelationship of tissue ACE and angiotensin II with various biologically active mediators, CV risk factors, and pathobiologic mechanisms that contribute to the vascular disease process. Angiotensin II acts as a direct mediator as well as an amplifier in vascular pathology, thereby activating various pathobiologic processes that lead to vascular complications. BP = blood pressure; ICAM = intercellular adhesion molecule; LDL = low-density lipoprotein; PAI = plasminogen activator inhibitor; VCAM = vascular cell adhesion molecule. Dzau V.⁴

Hypertension

Stepping Up Awareness of Peripheral Arterial Disease

WHAT is peripheral arterial disease?

Peripheral arterial disease (PAD) is an atherosclerotic obstruction of blood flow in the legs, usually in the femoral-iliac artery system.¹ The typical symptom of PAD is transient leg pain (due to intermittent claudication) with exertion, such as during a walk. The pain persists with walking and is relieved by rest. However, most patients with PAD are asymptomatic or present with atypical symptoms.¹ PAD is estimated to affect 8 to 12 million Americans.² The incidence of PAD increases with age,^{3,4} affecting 15% to 20% of people aged ≥ 70 years.⁴ PAD affects men and women equally.¹ By 2050, 19 million people in the United States are expected to have PAD.²

WHY should clinicians be aware of peripheral arterial disease?

PAD is associated with significant morbidity and mortality due to stroke and myocardial infarction (MI).¹ Identification of PAD is the clinician's signal to evaluate the patient for other cardiovascular (CV) risk factors. Patients with PAD are likely to have coronary artery disease, cerebral artery disease, or a combination.⁴

PAD presents a special challenge because, although the condition is common, relatively few clinicians are alert to it, and the rates of PAD recorded in various studies underestimate its frequency.⁷⁻¹² Clinicians who rely on the cardinal symptom of intermittent claudication to identify PAD are overlooking patients who are asymptomatic or present with atypical symptoms. The American Heart Association estimates that as many as 40% of patients with PAD are asymptomatic, 50% have atypical symptoms, and only 10% have the classic presentation.² Another study found that 40% of patients had atypical symptoms.¹³

Up to 90% of PAD would be missed if a history of claudication were the sole criterion for diagnosis.⁷

WHO is at risk and should be evaluated for peripheral arterial disease?

Evaluate for PAD if any of the following are present:

- CV disease^{4,5}
- Diabetes¹
- Current smoking¹
- Hypertension⁶
- Erectile dysfunction
- Elevated total cholesterol⁶
- Non-Hispanic black race⁴
- Age >40 years⁴
- Male sex⁴

HOW can clinicians use a simple test to detect peripheral arterial disease?

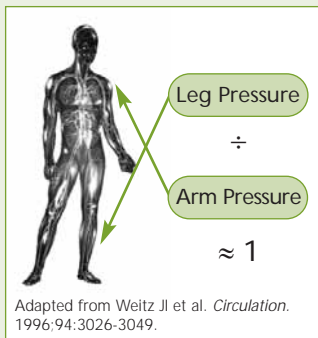
A number of physical examination findings suggest the presence of PAD.¹⁴ The examination should be performed with the patient's pants and shoes removed. The limbs are compared for differences in skin tone and color, nail growth, or hair loss, and for the presence of arterial bruits, tissue ulceration, or diminished pulses.¹²

The ankle-brachial index (ABI), a simple test that can be performed in the office, is a key tool for detecting PAD. The test is based on the concept of segmental blood pressure (BP) measurement. With arterial narrowing, systolic BP measurements drop progressively as the distance from the site of the blockage increases.¹⁵ The ABI is the ratio of the BP recorded in

the leg to the highest BP recorded in the left and right arms.

The American Diabetes Association recommends the following steps for measuring the ABI.^{6,16}

- Gather equipment (pressure cuff and handheld Doppler probe)



- Have patient rest in supine position for 5 minutes
- Measure BP in both arms; use higher value as reference
- Position cuff above ankle
- Measure pressure in dorsalis pedis artery
- Measure pressure in posterior tibial artery
- Repeat process in opposite leg

In a healthy person, systolic BP at the ankle is higher than at the upper arm¹³; when the ankle pressure is compared with the higher of the right and left brachial pressures, the index should be ≥ 1 . An ABI score $< .9$ is suggestive of PAD, with progressively lower ABI scores indicating more severe occlusion.¹³ The lower the ABI, the higher the risk of CV disease and death.¹

In the PAD Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) program, the ABI was calculated for all patients aged >70 years (or >50 if they had diabetes or were smokers) at each clinic visit. The results revealed a PAD incidence of 29%, compared with 4.3% to 18% in other studies.⁸ The PARTNERS findings underscore the frequency of hidden PAD among typical primary care patients, which leaves such patients vulnerable to illness and death from cardiovascular disease. PARTNERS participants increased their weekly use of the ABI from 12% before the program to 43% afterwards, and their monthly use from 13% before the program to 39% afterwards.¹⁷

References

1. Hiatt WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med*. 2001;344:1608-1621.
2. American Heart Association. *Heart Disease and Stroke Statistics—2005 Update*. Dallas, Tex: American Heart Association; 2005.
3. Creager M, ed. *Management of Peripheral Arterial Disease: Medical, Surgical, and Interventional Aspects*. London, England: ReMEDICA Publishing Limited; 2000.
4. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, on behalf of the TASC II Working Group. Inter-society consensus for the management of peripheral arterial disease (TASC II). *J Vasc Surg*. 2007;45(suppl S):S5-S67.
5. Bhatt DL, Steg PG, Ohman EM, Rother J, Wilson PWF, on Behalf of the REACH Registry Investigators. Risk profile and undertreatment of peripheral arterial disease: 7,013 patients from the International REACH Registry. Presented at: American College of Cardiology Scientific Session; March 6-9, 2005; Orlando, Fla.
6. Newman AB, Siscovick DS, Manolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Health Study Collaborative Research Group. *Circulation*. 1993;88:837-845.
7. Criqui MH. Peripheral arterial disease—epidemiological aspects. *Vasc Med*. 2001;6(3 suppl):3-7.
8. Hirsch AT, Criqui MH, Treat-Jacobson D, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA*. 2001;286:1317-1324.
9. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. *Circulation*. 2004;110:738-743.
10. Diehm C, Schuster A, Allenberg JR, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. *Atherosclerosis*. 2004;172:95-105.
11. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: The Rotterdam Study. *Arterioscler Thromb Vasc Biol*. 1998;18:185-192.
12. Criqui MH, Fronek A, Barrett-Connor E, Klauber MR, Gabriel S, Goodman D. The prevalence of peripheral arterial disease in a defined population. *Circulation*. 1985;71:510-515.
13. Criqui MH, Denenberg JO, Bird CE, Fronek A, Klauber MR, Langer RD. The correlation between symptoms and noninvasive test results in patients referred for peripheral arterial disease testing. *Vasc Med*. 1996;1:65-71.
14. Gey DC, Lesho EP, Manngold J. Management of peripheral arterial disease. *Am Fam Physician*. 2004;69:525-532.
15. Weitz JI, Byrne J, Clagett GP, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation*. 1996;94:3026-3049.
16. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). *J Vasc Surg*. 2000;31:S1-S296.
17. Mohler ER, Treat-Jacobson D, Reilly MP, et al. Utility and barriers to performance of the ankle-brachial index in primary care practice. *Vasc Med*. 2004;9:253-260.

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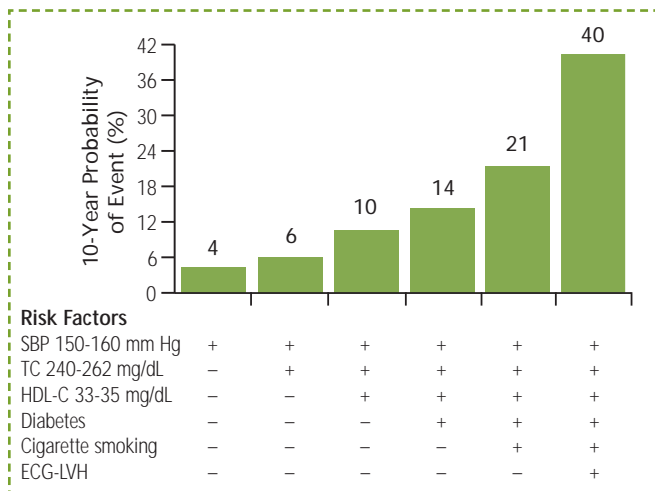


Figure 3. Risk of CHD in patients with mild hypertension by intensity of associated risk factors. ECG = electrocardiogram; HDL-C = high-density lipoprotein; TC = total cholesterol. Kannel WB.⁵

of developing CV disease on the basis of their risk factor profiles (Figure 4).⁶ Its use in risk assessment is illustrated in the *Case Study* on page 78. To choose the most effective therapy, clinicians must consider the total burden of risk factors.⁴

Prehypertension: Setting the Stage

Rigorous blood pressure control is necessary to reduce CV events. Guidelines issued by *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)* classify blood pressure into 4 categories: normal, prehypertension, stage 1 hypertension, and stage 2 hypertension (Figure 5).¹

Age (y)	20-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Points	-9	-4	0	3	6	8	10	11	12	13

	Points				
	Age (y)				
TC (mg/dL)					
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

Age (y)	20-39	40-49	50-59	60-69	70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

Point total	<0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	>17
10-y risk (%)	<1	1	1	1	1	1	2	2	3	4	5	6	8	10	12	16	20	25	≥30

HDL-C (mg/dL)	Points
	≥60
50-59	0
40-49	1
<40	2

SBP (mm Hg)	Points	
	Untreated	Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Figure 4. The National Cholesterol Education Program (NCEP) and Framingham risk scores for the case study patient. National Cholesterol Education Program.⁶

Prehypertension, an important addition to earlier classifications, is defined as systolic blood pressure (SBP) 120 to 139 mm Hg and diastolic blood pressure (DBP) 80 to 89 mm Hg.¹ Treatment should be considered for patients with prehypertension with comorbidities, starting with intensive lifestyle modification. If target blood pressure cannot be achieved, then antihypertensives should be added to the treatment strategy. Antihypertensive treatment is recommended for all patients with stages 1 and 2 hypertension.

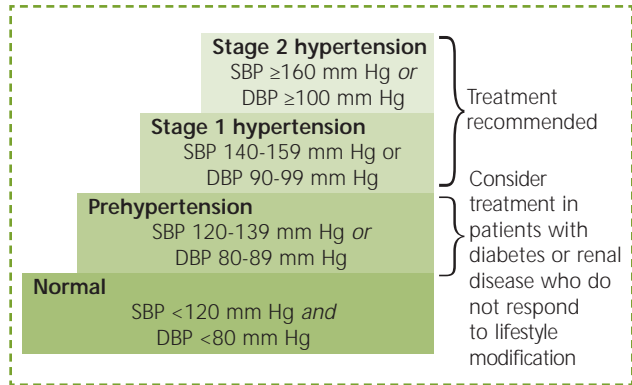


Figure 5. JNC 7 classification of blood pressure. The category of *prehypertension* was added as a hypertension classification in the 2004 JNC 7 report. Although not a disease category, the classification of prehypertension is used to identify persons at risk of developing hypertension to encourage lifestyle changes to prevent or delay the disease. Those with prehypertension require intensive lifestyle modification and should be considered for antihypertensive therapy if comorbidities are present. Chobanian AV et al.¹

As with glycemic control in diabetes, there appears to be no lower threshold for benefit with blood pressure reduction; the only limit is the development of hypotension. Whereas an

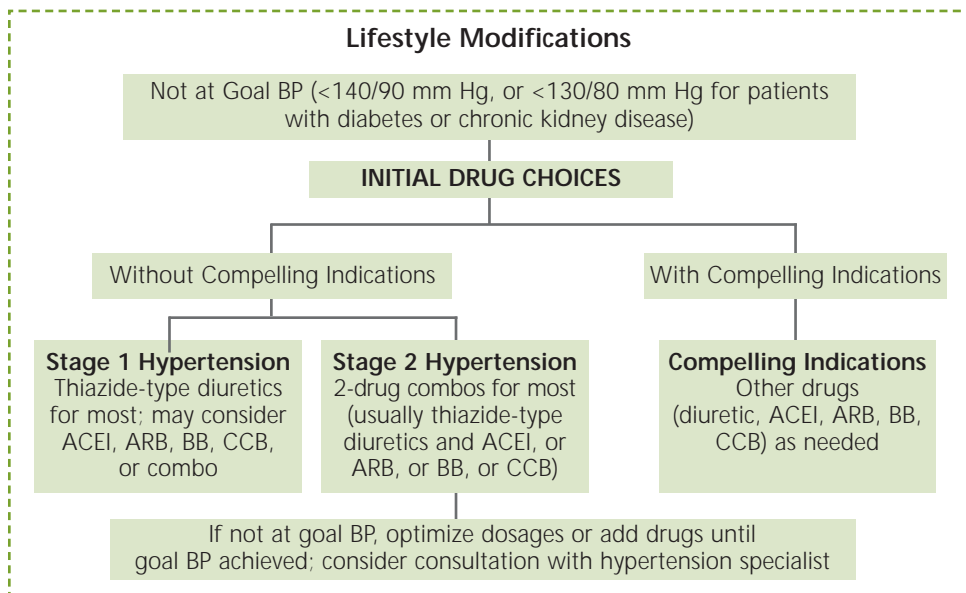


Figure 6. JNC 7 algorithm for treatment of hypertension. Pharmacologic therapy usually is needed to treat high blood pressure. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta-blocker; CCB = calcium channel blocker. Chobanian AV et al.¹

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SBP of 140 mm Hg traditionally was considered a treatment target, clinical experience has shown that any SBP level >115 mm Hg confers additional CV risk.¹ In addition, poorly controlled SBP alone is a major contributor to CV disease and death. Therefore, antihypertensive treatment should aggressively target the lowest possible SBP for each patient and be applied with the goal of modifying all risk factors and fostering a healthy heart.

Treating Patients With Hypertension: The JNC 7 Approach

JNC 7 included a comprehensive review of the evidence delineating the risks of hypertension and supporting the benefits associated with therapy to control high blood pressure. The JNC 7 algorithm (Figure 6) offers a treatment approach based on a patient's

individual risk factors and compelling indications, such as comorbidities. Blood pressure control can be achieved in most patients with hypertension. However, the majority of patients require at least 2 antihypertensive agents to achieve the accepted blood pressure goals of <140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease.^{1,7-9} In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial

(ALLHAT), more than 33,000 patients with hypertension and at least 1 other CV risk factor were followed for a mean of 5 years. In the study, 26% of patients required 2 or more drugs to achieve the target blood pressure of <140/90 mm Hg at 6-month follow-up and that number increased to 62% at 5 years.¹⁰ As with diabetes and other chronic illnesses, hypertension should be considered a progressive condition. Clinicians must be vigilant to ensure that treatment is intensified as needed to maintain blood pressure levels at or below goals.

Lifestyle Modifications

As a first step toward heart health, all patients should be counseled on lifestyle modifications (Table 2). Although it can be difficult to adhere consistently to lifestyle changes, a healthful change in diet and activity level leads to improvement in general health for most patients. Therapeutic lifestyle changes that have been shown to lower SBP include weight loss (blood pressure decreases on average ~7 mm Hg with a >4.4-kg loss),¹¹ reduced sodium intake (reduction of ~5 mm Hg with consistently lower salt consumption),¹² increased aerobic exercise (decrease of ~4 mm Hg with regular exercise),¹³ dietary potassium supplementation (decrease of ~3 mm Hg),¹⁴ and reduced alcohol consumption (decrease of ~3 mm Hg).¹⁴

Lifestyle Changes Help Lower Blood Pressure

Lifestyle Change	Amount	Effect on SBP/DBP
Weight loss ¹¹	>4.4 kg	-5.0/-7.0 mm Hg
Reduced sodium intake ¹²	100 mmol/d	-5.75/-2.54 mm Hg
Aerobic exercise ¹³	Any intensity helpful Greatest benefit at >150 min/wk	-3.84/-2.58 mm Hg
Potassium supplement ¹⁴	75 mmol/d	-4.4/-2.4 mm Hg
Decreased alcohol use ¹⁴	Median 76%	-3.31/-2.04 mm Hg

TABLE 2

Hypertension

Pharmacologic Therapy

Patients whose SBP is >20 mm Hg or DBP >10 mm Hg above goal should receive pharmacologic therapy, which may be monotherapy, combined therapy, or a fixed-dose combination.¹

The presence of comorbid conditions strongly influences the choice of treatment. Evidence from clinical trials supports the use of certain treatments for conditions that result from hypertension, such as heart failure, renal disease, or MI; or are associated with hypertension, such as diabetes (Table 3).¹

Compelling Indications for Antihypertensive Drug Classes From JNC 7

Compelling Indication	Recommended Drugs					
	Diuretic	ACEI	BB	ARB	CCB	Aldo ANT
Heart failure	•	•	•	•		•
Post-MI		•	•			•
High coronary disease risk	•	•	•		•	
Diabetes	•	•	•	•	•	
Chronic kidney disease		•		•		
Recurrent stroke prevention	•	•				

Aldo ANT = aldosterone antagonist.
Chobanian AV et al.¹

Wider Implications: Hypertension and Diabetes

A comprehensive review of diabetes goals and treatment appears in the *Diabetes* section of this workbook, but it is worthwhile to note the relationship linking hypertension, diabetes, and CV morbidity. Patients with hypertension and diabetes have approximately double the risk for CV events compared with patients who have high blood pressure but not diabetes.¹⁵ Results of clinical trials show that comprehensive management of CV risk factors in patients with diabetes can reduce their risk for major CV events and mortality.

In a post hoc analysis of data from the Systolic Hypertension in Europe (Syst-Eur) trial, patients with diabetes derived more benefit from improved blood pressure control in terms of reduced CV risk than patients without diabetes.¹⁶ In this trial, patients >60 years of age with SBP of 160 to 219 mm Hg and DBP <95 mm Hg (N = 4695; n = 492 with diabetes) were randomly assigned to treatment with 1 or more antihypertensive drugs to attain the study's SBP goal or to placebo. In patients with diabetes, active treatment reduced overall mortality by 41%, CV disease mortality by 70%, all CV events combined by 62%, fatal and nonfatal stroke by 69%, and all cardiac events combined by 57%. The reductions in CV disease mortality, all CV events, fatal and nonfatal stroke, and fatal and nonfatal cardiac events were significantly greater among patients with diabetes than those without diabetes.¹⁶

In the Hypertension Optimal Treatment (HOT) study of patients with hypertension and diabetes, aggressive lowering of DBP was associated with significantly reduced risk for CV end points compared with less aggressive DBP targets.¹⁷ The HOT researchers randomly assigned subjects to achieve 1 of 3 DBP targets: ≤80, ≤85, or ≤90 mm Hg in a 3.8-year study. All subjects initially received a dihydropyridine calcium channel antagonist; approximately 70% also received other antihypertensives as necessary to achieve DBP goal. Active lowering of blood pressure was particularly beneficial in the subgroup

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of 1501 patients with diabetes. In the group randomized to the DBP target ≤ 80 mm Hg, the risk of a major CV event (MI, stroke, or CV death) was 51% lower than in the group randomized to the DBP target of ≤ 90 mm Hg, with 11.9 events and 24.4 events per 1000 patient-years, respectively ($P < .005$).¹⁷

The results of other clinical trials in patients with diabetes support the importance of aggressive blood pressure management (target: 130/80 mm Hg), usually achieved with more than 3 antihypertensive medications, in reducing the risk of CV and renal disease.⁵ Data from the United Kingdom Prospective Diabetes Study Group (UKPDS) suggest that tight blood pressure control is more effective than tight glycemic control in reducing the risk of stroke, microvascular complications, diabetes-related death, and all diabetes-related end points.^{7,18} For patients with hypertension and type 2 diabetes, the JNC 7 guidelines recommend ACE inhibitors or angiotensin receptor blockers (ARBs) as preferred agents.

Focus on the RAAS

The RAAS is a key factor in the development of hypertension. Many of the risk factors for vascular disease are mediated by the RAAS. Therefore, interventions that interrupt stages in the RAAS potentially have the greatest effect on the vascular system and other risk factors.

The RAAS is a sequence of metabolic pathways that regulate blood pressure and endothelial function. Renin secreted from the kidney converts the prohormone angiotensinogen, which is produced in the liver, to angiotensin I (AI). Biologically inactive AI is converted by ACE to the powerful AII (Figure 7).¹⁹ ACE also plays a role in the degradation of bradykinin, a substance that promotes vasodilation by stimulating the production of NO and other vasodilating chemicals in the vascular endothelium and causes natriuresis through direct tubular effects in the kidney.¹⁹ ACE regulates the balance between the vasodilatory and natriuretic properties of bradykinin. It also regulates the balance between the vasoconstrictive and salt-retentive properties of AII.¹⁹ NO plays a leading role in vascular health by acting as a vasodilator and inhibiting inflammation

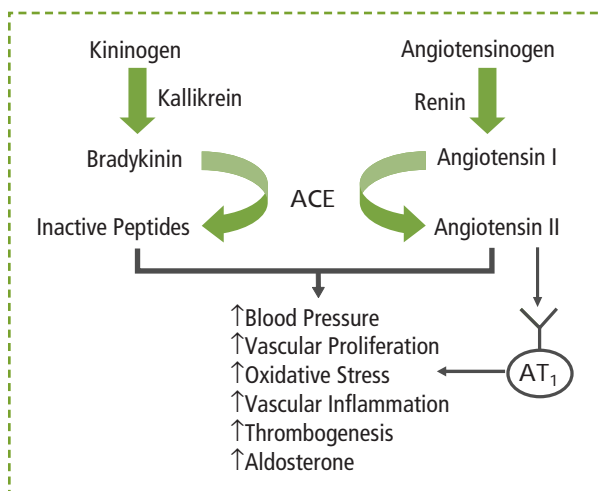


Figure 7.

The RAAS regulates blood pressure and endothelial function through its actions on NO release and the balance of vasodilatory and vasoconstrictive factors. ACE degrades bradykinin to inactive peptides, preventing NO production (left). Renin mediates the production of angiotensin I (right), which ACE converts to vasoconstrictive angiotensin II, the actions of which are mediated through the AT₁ receptor. Together, these pathways lead to increases in blood pressure, oxidative stress, thrombogenesis, and other deleterious effects. Brown NJ et al¹⁹; Endemann DH et al.²⁰

and platelet aggregation²⁰; thus, the loss of bradykinin-induced NO has a deleterious effect on the vasculature.

A potent vasoconstrictor, AII acts directly on vascular smooth muscle cells, increases vascular tone through sympathetic nervous system action, and leads to volume expansion by promoting retention of sodium (through the hormone aldosterone) and fluid (by release of anti-diuretic hormone).¹⁹ AII promotes cellular proliferation, migration, and hypertrophy.^{2,19} The actions of AII are mediated largely through the AT₁ receptor.¹⁹

The concentration of aldosterone is increased by AII, which leads to increased sodium retention and accelerated potassium excretion. Aldosterone is produced locally in the CV system as well as in the renal system and has proinflammatory and prothrombotic effects.²¹ It has been associated with the development of hypertrophy and arterial stiffness.²¹

Blocking the RAAS Pathway

There are several different classes of medication for hypertension (Table 4) that target different points along the RAAS pathway (Figure 8). Blocking the actions of ACE can reduce AII levels and increase bradykinin levels. Angiotensin-converting enzyme mediates the effects of AII upstream by converting AI to AII. Blocking the AT₁ receptor interferes with the vasoconstricting actions of AII. Further up the pathway, a new class of renin inhibitors recently entered clinical use with a newly released agent, aliskiren. This class blocks RAAS early in the cascade by preventing renin from stimulating the conversion of angiotensinogen into AI, with downstream effects on the release of AII. Further down the pathway, the aldosterone receptor blockers prevent the action of aldosterone on mineralocorticoid receptors.

Clinical Effects of ACE Inhibitors

Several studies have evaluated the long-term use of ACE inhibitors in patients with CV disease.²²⁻²⁶ Among these studies were the Survival and Ventricular Enlargement (SAVE) trial, Prevention of Events with ACE (PEACE) and Quinapril Ischemic Event Trial (QUIET), European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery disease (EUROPA), and Heart Outcomes Prevention

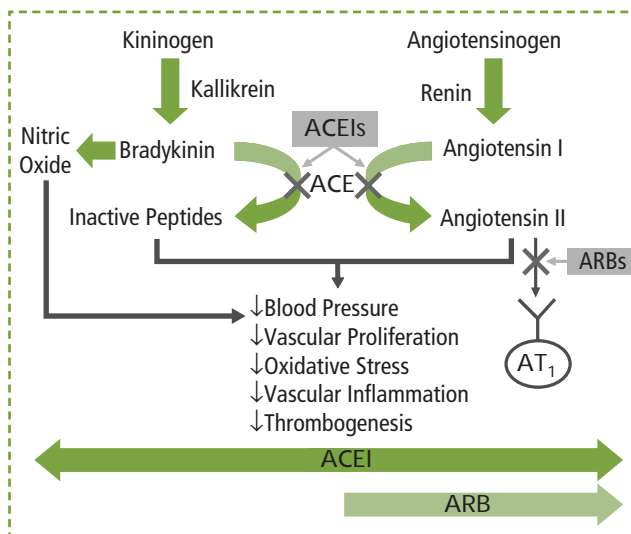
Mechanism of Action of Antihypertensive Medications

Drug Class	Mechanism of Action
Diuretics	<ul style="list-style-type: none"> ➤ Rid body of excess fluids and sodium ➤ May enhance effect of other BP medications
ACEIs	<ul style="list-style-type: none"> ➤ Lower levels of angiotensin II ➤ Dilate blood vessels
ARBs	<ul style="list-style-type: none"> ➤ Block angiotensin II receptors ➤ Dilate blood vessels
BBs	<ul style="list-style-type: none"> ➤ Decrease heart rate and cardiac output
CCBs	<ul style="list-style-type: none"> ➤ Interrupt movement of calcium into heart and vessel cells
Aldosterone receptor blockers	<ul style="list-style-type: none"> ➤ Decrease salt and water retention
Renin inhibitors	<ul style="list-style-type: none"> ➤ Block action of renin, decreasing formation of angiotensin I

American Heart Association. December 11, 2006. Available at: <http://www.americanheart.org>. Accessed July 10, 2007.

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Figure 8. Antihypertensives and the RAAS. ACEIs prevent the degradation of bradykinin (left) by ACE, resulting in increased NO production, improved vasodilation, and reduced inflammation. ACEIs also block the conversion of inactive angiotensin I to active angiotensin II (right), preventing the latter's vasoconstrictive actions. ARBs prevent angiotensin II from docking with the AT₁ receptor, which again blocks the deleterious effects of angiotensin II on the vasculature. ARBs limit the biologic effects of aldosterone by competing for receptors. The renin inhibitors block the RAAS early in the cascade. Brown NJ et al¹⁹; Endemann DH et al.²⁰



Evaluation (HOPE). The results for the primary outcomes of 4 of these studies are shown in Figure 9. In the EUROPA and HOPE trials, ACE inhibitor treatment was associated with significantly lower risk in a combined end point of CV events, including MI and CV death,^{23,24} but the other 2 trials (PEACE and QUIET) showed no significant benefit with ACE inhibitor therapy on combined CV end points that included CV death, MI, coronary revascularization,²⁵ or all CV events.²⁶ It is important to note that these studies looked at different populations; those patients enrolled in the PEACE and QUIET studies were at lower CV risk than those in the EUROPA and HOPE trials.²⁵

The landmark HOPE trial, published in 2000, randomly assigned 9297 patients at high risk for CV events but without LV dysfunction or heart failure to receive treatment with ramipril 10 mg/d or placebo for a mean of 5 years.²⁴ Mean blood pressure at baseline was 139/79 mm Hg.²⁴ The primary end point of this study was a composite of MI, stroke, or death from CV causes.²⁴ Patients treated with ramipril to lower blood pressure had significantly ($P < .001$) fewer events over the 5-year study period than those who received placebo (Figure 9, upper right).²⁴

The EUROPA trial randomly assigned 12,218 patients to treatment with perindopril 8 mg or placebo.²³ Patients had a history of MI (64%), angiography with significant stenoses (61%), previous revascularization (55%), and diabetes (12%).²³ Mean blood pressure at baseline was 137/82 mm Hg.²³ At 5 years of follow-up, ACE inhibitor treatment was associated with a significantly ($P < .003$) lower rate of CV events (composite end point of CV mortality, nonfatal MI, and resuscitated cardiac arrest) compared with placebo (Figure 9, upper left).²³

The PEACE trial enrolled 8290 patients with stable CAD and preserved LV function; they were randomly assigned to treatment with trandolapril 4 mg/d or placebo. At mean follow-up of 4.8 years, no significant difference was seen between the 2

groups (Figure 9, lower left). Patients in PEACE had better blood pressure at baseline (134/78 mm Hg) and received more intensive risk factor management than those in HOPE and EUROPA, which may explain why treatment failed to improve outcomes.²⁵ In QUIET, 1750 patients were randomly assigned to quinapril 20 mg/d or placebo. At mean follow-up of 27 months, 37.7% in the quinapril group and 38.5% in the placebo group had experienced a CV event; the difference was not significant (Figure 9, lower right).²⁶ The researchers concluded that the study might have been underpowered to detect a difference in these relatively healthy patients.²⁶

Treatment with ACE inhibitors compared with placebo provided reductions in CV events in subsets of patients with diabetes in the HOPE (MICRO-HOPE; n = 3577) and EUROPA (PERSUADE; n = 1502) trials. There was a significant ($P = .0004$) 25% reduction in risk for CV events with ramipril compared with placebo,^{24,27} whereas patients treated with perindopril compared with placebo had a lower, although not

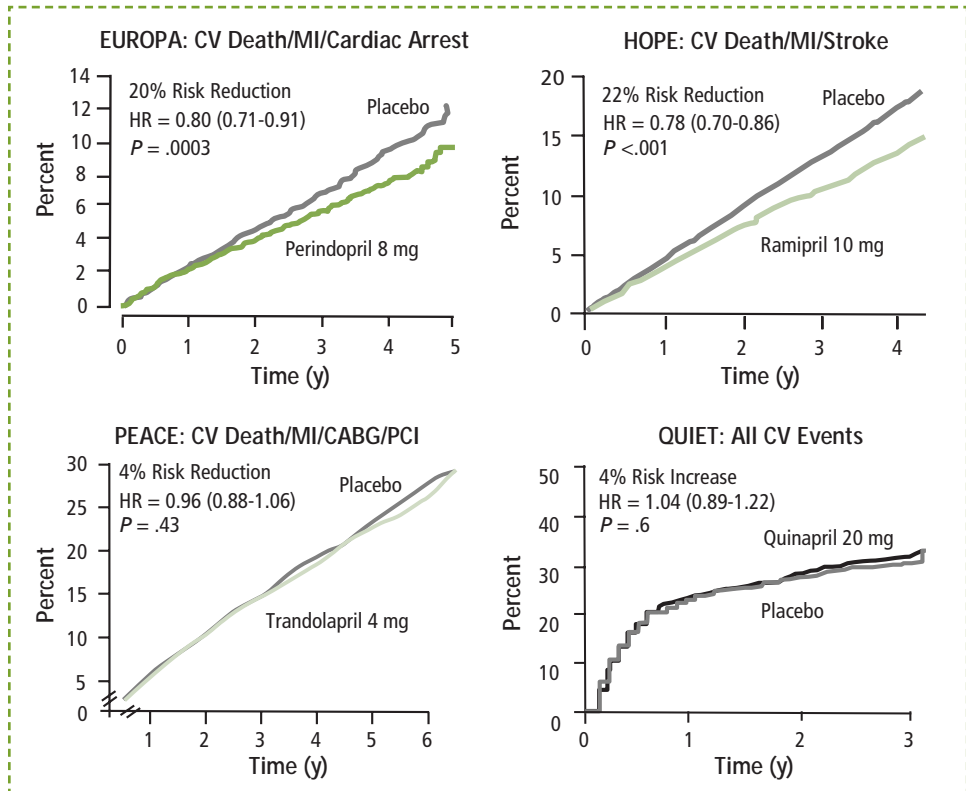


Figure 9. Primary outcomes in 4 long-term ACE inhibitor trials in CAD without heart failure. ACE inhibitors with placebo were compared with the composite primary outcome end points of CV events, MI, stroke, or revascularization in 4 studies. EUROPA and HOPE (upper panels) found significant benefit to treatment with ACE inhibitors. Results in PEACE and QUIET were neutral. CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention. Fox KM et al²³; Yusuf S et al²⁴; Braunwald E et al²⁵; Pitt B et al.²⁶

statistically significant incidence of CV events (13.1% vs 17.9%, respectively; $P = .13$).²⁸ Treatment with ramipril also reduced the rates of complications related to diabetes compared with placebo (RR = 0.84; $P = .03$).²⁴ The presence of microalbuminuria in patients with or without diabetes is a powerful risk factor for endothelial dysfunction. In MICRO-HOPE, ramipril decreased albuminuria and the risk for developing overt nephropathy.²⁷

ACE inhibitors interrupt the AII and the bradykinin pathways (Figure 7). Reduction of blood pressure, although a key benefit of ACE inhibitors, does not fully explain the many clinical benefits of these agents. A decrease in atherosclerosis, improvement in vascular function, reductions in LVH, and lowered blood glucose levels were observed with ramipril (10 mg/d) treatment in the HOPE and associated studies.²⁹

Clinical Effects of Angiotensin Receptor Blockers

ARBs block the action of AII at the AT₁ receptor while allowing the action of AII on the AT₂ receptor, which benefits the CV system. They have no effect on bradykinin degradation. Clinical trials suggest that ARBs are equivalent to older antihypertensives in terms of blood pressure control.¹ The evidence for additional cardio- or cerebro-protection independent of blood pressure-lowering effects is mixed. Studies have shown a 13% reduction in CV events with losartan use compared with atenolol³⁰ and a reduction in sudden death and death from worsening heart failure in patients with left ventricular ejection fraction (LVEF) $\leq 40\%$ treated with candesartan.³¹ However, treatment with valsartan was shown to confer no additional benefit in terms of diastolic function³² or reduced incidence of CV events.³³ There is a debate over whether ARBs increase the risk for MI,³⁴ and whether losartan poses a higher risk for mortality than other ARBs.³⁵ There is good evidence to suggest that ARBs confer renal protection independent of blood pressure lowering in patients with type 2 diabetes and hypertension.^{8,9} Compelling indications for ARB therapy as cited by JNC 7 are heart failure, diabetes, and chronic kidney failure.¹

Expanding the Antihypertensive Armamentarium

Eplerenone, a new aldosterone receptor blocker, is more selective for the mineralocorticoid receptor and has fewer endocrine side effects³⁶ than other drugs in this class (eg, spironolactone).^{20,37} Decreases of 6 to 13 mm Hg in SBP were observed in clinical trials of eplerenone.³⁸

The first direct renin inhibitor, aliskiren, is now available. The data suggest that it lowers blood pressure to a degree similar to existing agents. Long-term outcomes data are expected later in 2007. At the recommended dose of 150 mg, aliskiren lowered SBP by 2.1 to 9.3 mm Hg more than placebo and DBP by 1.7 to 5.4 mm Hg in clinical trials.³⁹ Aliskiren has been shown to be safe in combination with other antihypertensive drugs^{40,41} and in the elderly.⁴²

Hypertension and Metabolic Syndrome

The increase in obesity in our society has led to a surge in the metabolic syndrome, a term that covers a cluster of atherosclerotic CV risk factors. Metabolic syndrome is characterized by visceral adiposity, insulin resistance, dyslipidemia, and proinflammatory

and prothrombotic states throughout the body.^{6,43} Persons with metabolic syndrome are at risk for developing diabetes and dyslipidemia, as well as hypertension. It is estimated that 25% of Americans >20 years of age and as many as 45% of those >50 years of age may be affected by metabolic syndrome.⁴⁴

Key to the development of metabolic syndrome is the presence of central obesity, or excess fat in the abdomen.⁴⁵ The visceral adipose tissue present in central obesity is associated with detrimental biologic effects, including insulin resistance. Visceral adipose tissue is an active organ that produces cytokines and chemokines such as angiotensinogen, which give rise to AII, and other elements of the RAAS,⁴⁵ many of which increase the risk for coronary events.

Metabolic syndrome is characterized by elevated triglycerides (>150 mg/dL), low levels of high-density lipoprotein cholesterol (HDL-C) (<40 mg/dL in men and <50 mg/dL in women), elevated blood pressure (\geq 130/85 mm Hg), and raised fasting plasma glucose (>100 mg/dL) or diagnosed type 2 diabetes.⁴⁶ Metabolic syndrome is identified in men or women with large waist circumference (men, >40 in; women, >35 in) or body mass index (BMI) >30 kg/m² plus 2 risk factors; ongoing or previous treatment for risk factors is also considered a risk factor.⁴⁵

Metabolic syndrome is the central point at which diabetes, dyslipidemia, and CV disease meet and define an individual's global CV risk. Hypertension is a pivotal factor in that risk.

Hypertension: The Standard of Care

Table 5 presents the standard of care issued by the American College of Cardiology and the American Heart Association on the basis of evidence from clinical trials and population registries.^{44,45,47,48} For patients with CV disease, primary or secondary prevention should address dyslipidemia, blood pressure, atherothrombosis, and blood glucose levels. Patients certainly need to adopt therapeutic lifestyle changes, including a healthful diet and weight loss program. For treating hypertension, the results of several clinical trials suggest that ACE inhibitors effectively lower blood pressure^{39,40} and may confer additional CV benefits, including reduced risk of serious CV events,^{39,40} atherosclerosis and atherothrombosis,⁴⁶ and nephropathy in patients with diabetes,⁶ making ACE inhibitor treatment an attractive choice. Treatment with ACE inhibitors or ARBs

AHA/ACC Guidelines Update in Patients With Atherosclerotic CV Disease

Lifestyle Modification

(DASH, weight loss, exercise, smoking cessation)

Supplemental Medication Recommendations*

- Lipid-lowering therapy to achieve
 - LDL-C: <100 mg/dL (optional: <70 mg/dL)
 - Non-HDL-C: <130 mg/dL (optional: <100 mg/dL)
- Antiplatelet therapy: aspirin and/or clopidogrel
- Antihypertensive therapy to achieve BP <140/90 mm Hg
 - <130/80 mm Hg in the patient with diabetes
 - Ideal BP \leq 120/80 mm Hg (JNC 7)
- Oral/insulin therapy to achieve glycemic control:
 - A1C <7% (ADA)
- ACE inhibitor
- Beta-blocker
- Influenza vaccine

*In the absence of specific contraindications.

ADA = American Diabetes Association; DASH = Dietary Approaches to Stop Hypertension.

Smith SC Jr et al^{45,49}; Krumholz HM et al⁴⁶; Braunwald E et al.⁴⁸

Practical Tips to Improve Adherence

Talk to your patient

- Explain the condition and why specific therapy is important
- Ask about adherence
- Involve the patient as a partner in treatment
- Provide clear written and oral instructions
- Tailor the regimen to the patient's lifestyle and needs
- Use motivational interviewing techniques

Look for

- Different ways to approach patients based on individual patient attitudes
- Allies in patient care—family, friends
- Ways to simplify the regimen
- Refill dates (if the patient has not refilled the prescription, the medication is not being taken)

Use systematic approaches

- Disease management programs
- Periodic review of electronic medical records or manual chart audits
- Group/shared medical appointments blend care, education, social support

Other techniques

- Follow-up (telephone/mail/e-mail) and reminder cards
- Signed agreements/contracts
- Self-monitoring tools (eg, tape measure, pedometer, home testing devices)
- Patient assistance programs
- Support patients where medication costs are a barrier to adherence

Fonarow GC et al. *Am J Cardiol.* 2001;87:819-822; Grundy SM et al. *Circulation.* 2004;110:227-239; Ockene IS et al.⁵³

has been effective in reducing the rate of progression of chronic kidney disease in type 1 and type 2 diabetes.

Motivating Patients to Adhere to Long-term Therapies

Adherence to antihypertensive therapy is an ever-present clinical challenge, complicated by the fact that patients take multiple medications. In a study comparing data from 1988 to 1994 and 1999 to 2000 on glycemic control, blood pressure control, and lipid management in patients with diabetes, only 7.3% achieved target goals for all 3 risk factors.⁴⁹

Many factors contribute to poor adherence to a treatment regimen, including side effects,

cost, lack of understanding of the treatment's purpose or importance, poor communication between practitioner and patient, complex regimens, senility or other cognitive issues, poor mobility, lack of social support, and lack of discharge planning.⁵⁰ Patients also discontinue therapy if they perceive a lack of benefit or necessity for taking the medication.⁵¹ Because patients do not “feel” their high blood pressure, they may assume after a few weeks of therapy that they are “cured.” In a study of patients taking antihypertensives in the New York area, compliance decreased from 85% during the first 3 months of the study to 64% 1 year later.⁵¹ Practitioners have to do more to help patients improve their adherence to treatments.

Table 6 lists 6 steps developed by an American College of Cardiology task force to help clinicians achieve patient adherence to prevention or treatment regimens.⁵² A study showed that after treatment for MI, patients given a systematized approach to CV management in the hospital setting are more likely to comply postdischarge with recommended measures, including antiplatelet and antihypertensive medications. Results showed that a higher percentage of patients achieved low-density lipoprotein cholesterol (LDL-C) targets, as well as lower MI recurrence and 1-year mortality after the system was used.⁵³

Summary

Cardiovascular disease is still the leading cause of death in the United States. Risk factors for CV disease most often occur in clusters. Patients with hypertension often have multiple CV risk factors, such as diabetes, obesity, and dyslipidemia and should be evaluated for these other risk factors. Disease management must address all risk factors if the goal is to reduce patients' global CV risk. Clinicians and patients must work together to develop creative approaches to achieve adherence, trying different approaches as necessary. Different patients respond to different incentives. Importantly, clinicians and patients must realize that controlling hypertension produces concrete, long-term benefits in the form of reduced morbidity and mortality. When it comes to blood pressure control, "near enough" is not good enough: aggressive therapy to get to goal should be the rule. Treatments that offer multiple cardioprotective benefits are always preferable.

CASE STUDY

A 55-Year-Old Man With Hypertension and Diabetes

Presentation

The patient is a 55-year-old man who has recently moved to the United States from India. He has a history of asymptomatic hypertension and type 2 diabetes. He does not smoke. Physical examination and laboratory values show that the patient is not at target levels for blood pressure or blood glucose.

Physical Examination

- Blood pressure: 148/96 mm Hg
- Height: 64 in
- Weight: 178 lb
- BMI: 30 kg/m²
- Waist circumference: 38 in
- Normal ventricular function (LVEF = 68%)

Laboratory Values

- Fasting plasma glucose: 148 mg/dL
- A1C: 8.8%
- Creatinine: 1.5 mg/dL
- Urinalysis: 1+ proteinuria
- Lipid profile
 - TC: 268 mg/dL
 - LDL-C: 168 mg/dL
 - HDL-C: 42 mg/dL
 - Triglyceride: 296 mg/dL

Medications

- Hydrochlorothiazide 25 mg/d
- Glyburide 5 mg/d

Comment

The patient's Framingham risk score is 15, which gives a 10-year risk for CHD of 20%, on the borderline of very high risk (Figure 4).⁵¹

Clinical Decision Point

What is the JNC 7 goal for this patient who has hypertension, diabetes, and renal disease?

- <120/80 mm Hg
- <130/80 mm Hg
- <140/80 mm Hg
- <140/90 mm Hg

Comment

Patients with diabetes or renal disease should be considered for antihypertensive

therapy if lifestyle modifications do not reduce their blood pressure to below 130/80 mm Hg.¹ Blood pressure of 120 to 139/80 to 90 mm Hg in patients without diabetes is considered prehypertension. High-risk patients with concurrent diabetes or renal disease benefit from aggressive lowering of blood pressure, even to levels of 120/80 mm Hg.

Clinical Decision Point

The patient's blood pressure is 148/96 mm Hg on current medications. Which medication would be a good choice to lower his blood pressure to <130/80 mm Hg?

Comment

According to the patient's other CV risk factors and comorbidities, an ACE inhibitor or ARB could be a sound choice. Both diabetes and renal disease are compelling indications for early use of antihypertensive therapy, with evidence supporting the use of ACE inhibitors and ARBs for both conditions (Table 3, page 69).¹ Several studies have found that ACE inhibitors confer renal protection and reduce the risk of nephropathy in patients with diabetes,³⁶ and there is evidence that ACE inhibitors may help mediate glucose metabolism.³⁸ This patient could benefit from the spectrum of benefits associated with ACE inhibitors.

An ACE inhibitor is added to his antihypertensive regimen and insulin therapy is initiated to better control his glucose levels. He is referred to a diabetes educator for help with nutrition, diet, and exercise. At his 6-month follow-up examination, his blood pressure is 135/90 mm Hg and his A1C is 7.2%.

QUESTIONS FROM SYMPOSIUM PARTICIPANTS

➔ **Q:** When is an ACE inhibitor contraindicated?

A: ACE inhibitor therapy is usually tolerated, but a history of angioedema indicates a need for caution. If there is an allergic response after starting ACE inhibitor therapy, angioedema should be suspected. Some patients develop a cough with ACE inhibitor therapy. If clinicians counsel their patients to expect the cough, patients are more likely to accept it and continue the medication. If the cough is debilitating, an alternative is to prescribe an ARB.

➔ **Q:** Is hyperkalemia an issue with the renin inhibitor aliskiren?

A: Yes. In a recent clinical trial⁴¹ the hyperkalemia incidence was 6% with placebo and 9% with aliskiren. Hyperkalemia may be a concern in patients with diabetes who have renal insufficiency or are taking an ACE inhibitor.

➔ **Q:** Are there any over-the-counter (OTC) supplements that can have an immediate antihypertensive effect when blood pressure spikes?

A: Most OTC products, such as dietary calcium or potassium, and foods (low-fat yogurt, tomatoes, and green vegetables) have a long-term effect and aren't useful for spikes in blood pressure. Some patients have success with meditation and breathing techniques, but a prescribed drug that can acutely lower blood pressure is usually needed. Still, it doesn't hurt to recommend relaxation. All beneficial lifestyle strategies are important in reducing the number of pills a patient has to take.

➔ **Q:** Is the Dietary Approaches to Stop Hypertension (DASH) diet really defensible as equivalent to 1-drug therapy?

A: It is, but it is also true that DASH is sometimes difficult or expensive to follow. The DASH investigators had all the food prepared in a metabolic kitchen, so they knew exactly what the food contained and that subjects ate that food and didn't substitute.¹ DASH provided proof of the concept that if people eat adequate fruits and vegetables, they can expect a blood pressure decrease equivalent to an antihypertensive. If patients reduce their daily salt consumption to 2 g or no added salt, it is the equivalent of adding a second antihypertensive. Patients can avoid 2 drugs by following DASH and not adding salt. To determine whether internet-based messaging is enough to encourage patients to stay on the diet or whether they need to be brought in for extended visits and other strategies to help adherence, investigators are studying the diet without the benefit of a metabolic kitchen.

➔ **Q:** Does borderline hypertension of 130/80 mm Hg in a healthy person with low CV risk factors still cause damage? Should it be treated?

A: In theory, the onset of hypertension could be delayed by pretreatment with a drug that blocks the renin-angiotensin system. Pretreatment prevents high blood pressure. But because it is a minimal effect and people are exposed to actual therapy, it is not being adopted as a practical strategy.

➔ **Q:** What is a good antihypertensive choice for women who are pregnant or may become pregnant?

A: This is an important question. If antihypertensives are required during pregnancy, diuretics and beta-blockers are used. Obstetricians often prefer labetalol. Diuretics can be used during pregnancy to control the edema associated with pregnancy. ARBs and renin inhibitors are contraindicated during pregnancy. The emphasis should be on therapeutic lifestyle changes so that pregnant women don't need any drug.

➔ **Q:** What class of medication can be added to the treatment regimen of patients with diabetes who are taking ACE inhibitors and diuretics?

A: Without question, a calcium channel blocker (CCB) is a good choice. CCBs are among the most effective drugs for lowering blood pressure across gender, age, and ethnicity, without adding a lot of side effects.

➔ **Q:** Is monitoring for microalbuminuria indicated, other than in patients with diabetes? With diuretics, what should be monitored with regard to potassium? Are there other lab studies that should be monitored, particularly with ACE inhibitors?

A: Every patient should be tested for microalbuminuria, because it is a sign of glomerular dysfunction. Microalbuminuria is as important as lipid profiles and blood pressure. Monitoring potassium, blood urea nitrogen (BUN), and creatinine is important with high-dose diuretics as well as ACE inhibitors, ARBs, and direct renin inhibitors.

➔ **Q:** Is there a creatinine level above which ACE inhibitor therapy should not be used?

A: A patient with serum creatinine <2 mg/dL can be given an ACE inhibitor or an ARB if renal function and blood pressure are monitored closely. Patients with mildly elevated creatinine should be cautioned against becoming dehydrated, which often results in a precipitous drop in blood pressure and subsequent nephropathy. Patients who have higher creatinine values still benefit, but need to be cautious about medication dose and titration. One suggestion for patients with renal dysfunction is to use an ACE inhibitor metabolized by the kidneys and the liver, such as fosinopril.

➔ **Q:** At what point should a patient with persistent hypertension who is unresponsive to several medications be referred for renal imaging?

A: There are 2 patient populations in whom renal imaging is particularly important. Young women (<20 years) who present with high blood pressure in the absence of oral contraceptives, regardless of response to antihypertensive drug therapy, should be evaluated for fibromuscular hyperplasia. Patients >65 years with no history of hypertension who present with severe hypertension or well-controlled hypertension that develops into uncontrolled hypertension are also candidates for atherosclerotic renovascular disease and renal artery stenosis. Any patient who is resistant to 4-drug therapy is likely to have a secondary cause of hypertension and should be evaluated.

➔ **Q:** Is “white-coat hypertension” clinically significant?

A: Patients who experience white-coat hypertension have a greater risk for hypertension than patients who have consistently normal values, but a lower risk than those with consistently elevated values. However, if a person’s blood pressure rises in the relatively unthreatening conditions of the clinician’s office, one has to wonder what other daily circumstances are going to elevate the blood pressure. In addition, epidemiologic data are based on blood pressure measured in an office setting. At the very least, patients with white-coat hypertension should receive education about lifestyle changes.

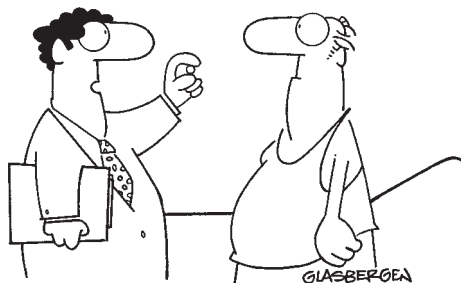
➔ **Q:** Why is starting therapy with a diuretic possibly less beneficial than starting with an ACE inhibitor or ARB?

A: Most of the evidence for diuretic and beta-blocker therapy came from the ALLHAT trial. ALLHAT had a unique design and didn’t include modern therapies. In addition, patients treated with diuretics responded better than the other treatment group because the trial included a very high percentage of elderly patients and African American patients, 2 populations that tend to be volume-dependent. Thus ALLHAT was skewed in favor of diuretic therapy. The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in Europe compared diuretic plus beta-blocker therapy to ACE inhibitor plus CCB therapy and found that the latter was much more effective in terms of reducing CV events. For that reason and because the principal mechanism of hypertension is vasoconstriction, the use of vasodilating drugs alone or in combination and especially the use of drugs that disrupt the renin-angiotensin system is favored because of the multiple benefits in the initial treatment of patients who are newly diagnosed.

➔ **Q:** What can be done for patients who deny having hypertension? What tools can clinicians use to educate patients about blood pressure management?

A: Unfortunately, blood pressure has dropped off the radar screen as a national health priority. The reason patients are in denial is that they have no symptoms. Clinicians have to emphasize that in contrast to arthritis with its physical symptoms, the effects of hypertension may remain “silent” until they cause a heart attack or stroke. Many patients don’t realize that hypertension is the biggest risk factor for stroke. Self-monitoring blood pressure at home is one way to educate patients. If they are clearly hypertensive at the outset, they will get the reinforcement of the benefit of antihypertensive drug therapy, which will help promote adherence to the regimen.

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“To prevent a heart attack, take one aspirin every day.
Take it out for a jog, then take it to the gym,
then take it for a bike ride...”

References

1. 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*. Bethesda, Md: National Heart, Lung, and Blood Institute; August 2002. NIH publication no. 04-5230. Available at: www.nhlbi.nih.gov/guidelines/hypertension/jnc7full.pdf. Accessed July 18, 2007.
2. Dzau V, Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. *Am Heart J*. 1991;121:1244-1263.
3. Vasan RS, Levy D. The role of hypertension in the pathogenesis of heart failure. A clinical mechanistic overview. *Arch Intern Med*. 1996;156:1789-1796.
4. Dzau V. Tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. *Hypertension*. 2001;37:1047-1052.
5. Kannel WB. Risk stratification in hypertension: new insights from the Framingham Study. *Am J Hypertens*. 2000;13:3S-10S.
6. National Cholesterol Education Program. Third Report of NCEP Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Bethesda, Md: National Heart, Lung, and Blood Institute; September 2002. NIH publication no. 02-5215.
7. Bakris GL, Williams M, Dworkin L, et al. Preserving renal function in adults with hypertension and diabetes: a consensus approach. *Am J Kidney Dis*. 2000;36:646-661.
8. Brenner BM, Cooper ME, de Zeeuw D, et al, for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
9. Lewis EJ, Hunsicker LG, Clarke WR, et al, for the Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-860.
10. Cushman WC, Ford CE, Cutler JA, et al. 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.
11. Stevens VJ, Obarzanek E, Cook NR, et al. Long-term weight loss and changes in blood pressure: results of the Trials of Hypertension Prevention, Phase II. *Ann Intern Med*. 2001;134:1-11.
12. Cutler JA, Follman D, Allender PS. Randomized trials of sodium reduction: an overview. *Am J Clin Nutr*. 1997;65(suppl):643S-651S.
13. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 2002;136:493-503.
14. Xin X, He J, Frontini MG, Ogden LG, Motsamai OI, Whelton PK. Effects of alcohol reduction on blood pressure: a meta-analysis of randomized controlled trials. *Hypertension*. 2001;38:1112-1117.
15. Curb JD, Pressel SL, Cutler JA, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA*. 1996;276:1886-1892.
16. Tuomilehto J, Rastenyte D, Birkenhager WH, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N Engl J Med*. 1999;340:677-684.
17. Hansson L, Zanchetti A, Carruthers SG, et al, for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351:1755-1762.
18. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317:703-713.

19. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. *Circulation*. 1998;97:1411-1420.
20. Endemann DH, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol*. 2004;15:1983-1992.
21. Grandi AM. Antihypertensive therapy: role of aldosterone antagonists. *Curr Pharm Des*. 2005;11:2235-2242.
22. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on morbidity and mortality in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. *N Engl J Med*. 1992;327:669-677.
23. Fox KM; EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788.
24. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145-153.
25. Braunwald E, Domanski MJ, Fowler SE, et al, PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058-2068.
26. Pitt B, O'Neill B, Feldman R, et al. The Quinapril Ischemic Event Trial: evaluation of chronic ACE inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. *Am J Cardiol*. 2001;87:1058-1062.
27. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet*. 2000;355:253-259.
28. Daly CA, Fox KM, Remme WJ, Bertrand ME, Ferrari R, Simoons ML, on behalf of the EUROPA Investigators. The effect of perindopril on cardiovascular morbidity and mortality in patients with diabetes in the EUROPA study: results from the PERSUADE substudy. *Eur Heart J*. 2005;26:1369-1378.
29. Lonn E, Gerstein HC, Smieja M, Mann JFE, Yusuf S. Mechanisms of cardiovascular risk reduction with ramipril: insights from HOPE and HOPE substudies. *Eur Heart J*. 2003;5(suppl A):A43-A48.
30. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint Reduction in Hypertension Study (LIFE): a randomized trial against atenolol. *Lancet*. 2002;359:995-1003.
31. Solomon SD, Janardhanan R, Verma A, et al. Effect of angiotensin receptor blockade and antihypertensive drugs on diastolic function in patients with hypertension and diastolic dysfunction: a randomized trial. *Lancet*. 2007;369:2079-2087.
32. Solomon SD, Wang D, Finn P. Effect of candesartan on cause-specific mortality in heart failure patients: the Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity program. *Circulation*. 2004;110:2180-2183.
33. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with valsartan- or amlodipine-based regimens: VALUE, a randomised trial. *Lancet*. 2004;363:2022-2031.
34. Brady AJ. Perindopril versus angiotensin II receptor blockade in hypertension and coronary artery disease: implications of clinical trials. *Clin Drug Investig*. 2007;27:149-161.
35. Hudson M, Humphries K, Tu JV, et al. Angiotensin II receptor blockers for the treatment of heart failure: a class effect? *Pharmacotherapy*. 2007;27:526-534.
36. Magni P, Motta M. Aldosterone receptor antagonists: biology and novel therapeutic applications. *Curr Hypertens Rep*. 2005;7:206-211.
37. Davis KL, Nappi JM. The cardiovascular effects of eplerenone, a selective aldos-

- terone-receptor antagonist. *Clin Ther.* 2003;25:2647-2668.
38. Inspra® (eplerenone). Prescribing information. New York, NY: GD Searle LLC subsidiary of Pfizer Inc; 2005.
39. Tekturna® (aliskiren). Prescribing information. East Hanover, NJ: Novartis Pharmaceuticals, Inc; 2007.
40. Oh BH, Mitchell J, Herron JR, Chung J, Khan M, Keefe DL. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. *J Am Coll Cardiol.* 2007;49:1157-1163.
41. Gradman AH, Traub D. The efficacy of aliskiren, a direct renin inhibitor, in the treatment of hypertension. *Rev Cardiovasc Med.* 2007;8(suppl 2):S22-S30.
42. Vaidyanathan S, Reynolds C, Yeh CM, et al. Pharmacokinetics, safety, and tolerability of the novel oral direct renin inhibitor aliskiren in elderly healthy subjects. *J Clin Pharmacol.* 2007;47:453-460.
43. Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? *Circulation.* 2003;108:1546-1551.
44. Grundy SM, Brewer HB, Cleeman JI, Smith SC Jr, Lenfant C, for the Conference Participants. Definition of metabolic syndrome. Report of the National Heart, Lung, and Blood Institute/AHA Conference on Scientific Issues Related to Definition. *Circulation.* 2004;109:433-438.
45. Smith SC Jr, Blair SN, Bonow RO, et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 Update. *Circulation.* 2001;104:1577-1579.
46. Krumholz HM, Anderson JL, Brooks NH, et al. ACC/AHA clinical performance measures for adults with ST-elevation and non-ST-elevation myocardial infarction. *Circulation.* 2006;113:732-761.
47. International Diabetes Foundation. *The IDF Worldwide Consensus Definition of Metabolic Syndrome.* Brussels, Belgium: IDF Communications; 2006.
48. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: summary article. *J Am Coll Cardiol.* 2002;40:1366-1374.
49. 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. *J Am Coll Cardiol.* 2006;47:2130-2139.
50. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA.* 2004;291:335-342.
51. Vermeire E, Hearnshaw H, Van Royen P, Denekens J. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001;26:331-342.
52. Cheng JWM, Kalis MM, Feifer S. Patient-reported adherence to guidelines of the Sixth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Pharmacotherapy.* 2001;21:828-841.
53. Ockene IS, Hayman LL, Pasternak RC, Schron E, Dunbar-Jacob J. Task Force #4: adherence issues and behavior changes: achieving a long-term solution. *J Am Coll Cardiol.* 2002;40:630-640.