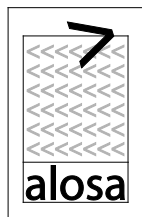


*Don't let the pressure get to you:*

*Evidence-based management of  
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August 2010

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## Table of Contents

Introduction .....	4
Epidemiology, classification, and initial management .....	5
Managing hypertension: the clinical evidence .....	10
Treatment recommendations .....	13
Choosing a specific regimen .....	17
Appendix 1: Glossary of abbreviations .....	28
References .....	29

# Introduction

Hypertension is the most common chronic illness in the United States, and the success or failure of its management has profound public health consequences. Currently 75 million people in the US and 1 billion worldwide have hypertension.<sup>1</sup> The World Health Organization reports that suboptimal blood pressure control is responsible for 49% of all ischemic heart disease and 62% of cerebrovascular disease worldwide.<sup>2</sup> While there are many medications to treat this condition, only about two thirds of Americans with hypertension are receiving treatment, and only about half have their blood pressure appropriately controlled.<sup>3,4</sup> Although these rates are inadequate, they have improved somewhat since 2000.<sup>3</sup>

These shortfalls have many causes. One key barrier is “clinical inertia” – a term used to describe the challenge of initiating or intensifying treatment and the counseling time it requires.<sup>5</sup> Patient factors also play a role, as fully 30-50% of patients stop taking their antihypertensive medications.<sup>6,7</sup>

This evidence document provides a synthesis of the current evidence about hypertension management, including the following issues:

1. rationale for controlling blood pressure;
2. summary of key evidence for drug treatment;
3. review of the current national guidelines; and
4. synthesis of additional studies, with a focus on selecting specific agents to reach treatment goals.

The Independent Drug Information Service (iDiS) also provides educational materials to enhance patients' participation in their own hypertension management, at [www.RxFacts.org](http://www.RxFacts.org).

**Bottom line: Hypertension is common and, if untreated, is the single most important cause of cardiovascular and cerebrovascular disease. Only two thirds of hypertensive Americans are receiving treatment, and only half are adequately controlled.**

# Epidemiology, classification, and initial management

## Prevalence of hypertension and cardiovascular risk

The National Health and Nutrition Survey found that 31% of Americans over age 18 have hypertension, defined as blood pressure >140/90 mmHg or use of an antihypertensive medication.<sup>3</sup> The prevalence increases dramatically with age, ranging from 9% in those under 39 to 77% in those over 70.<sup>3</sup> In the Framingham Heart Study, people who were normotensive at age 55 and survived to age 80 had a lifetime risk of hypertension of 90%.<sup>8</sup>

The association between elevated blood pressure and ischemic heart disease and cerebrovascular disease is well known. Each blood pressure increment of 20/10 mmHg doubles the risk of CAD.<sup>9</sup> Similarly, improving blood pressure dramatically reduces adverse health outcomes. **In hypertensive patients, achieving a 12 mmHg reduction in systolic blood pressure (SBP) over 10 years will prevent 1 death for every 11 patients treated, making this one of the most powerful tools a physician has for preventing devastating illness and disability.**<sup>10</sup> A meta-analysis of clinical trials for various antihypertensive medications found that effective antihypertensive therapy reduces other CV outcomes as shown below.<sup>11</sup>

**Table 1: Impact of effective antihypertensive therapy in reducing clinical outcomes.**

Outcome	Average percent reduction
Stroke	35-40%
Myocardial infarction	20-25%
Heart failure	50%

**Bottom line: Hypertension affects about a third of all Americans and its prevalence increases with age. Controlling blood pressure markedly reduces the risk of stroke, MI, and CHF, as well as all-cause mortality.**

## Classification of blood pressure: JNC 7 guidelines

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), sponsored by the National Institutes of Health, performed a systematic review of the available evidence and convened an expert panel to develop hypertension treatment guidelines. A coordinating committee of

representatives from professional societies, physician groups, and federal agencies participated in the process.<sup>4</sup>

JNC analyzed data describing the lifetime risk of hypertension and the “impressive increase in the risk of cardiovascular complications associated with levels of blood pressure previously considered to be normal” to introduce the following blood pressure classification system, used to set goals for hypertension control.

**Table 2: JNC-7 blood pressure classifications.**

BP classification	Systolic (SBP), mmHg		Diastolic (DBP), mmHg
Normal	<120	and	<80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥160	or	≥100

“Prehypertension” is not a disease category, but a designation to identify patients at high risk of developing hypertension.

### Evaluating the patient

The JNC guidelines suggest that a clinician perform two readings five minutes apart, with the patient sitting relaxed in a chair. Elevated pressure should be confirmed in the contralateral arm. Patients should avoid caffeine, tobacco, and exercise in the 30 minutes prior to measurement. Ambulatory blood pressure monitoring is indicated for evaluation of “white-coat” hypertension, which is present in 20-35% of patients found to be hypertensive in the office.<sup>12</sup> This can provide information about blood pressure during daily activities and sleep, and offers a more accurate measurement of blood pressure for patients in whom there is suspicion of white-coat hypertension, drug resistance, or episodic hypertension. Self-measurement of blood pressure at home, work, or in a pharmacy can provide useful information on response to therapy, and may also be helpful in assessing suspected white-coat hypertension. Except for extremely high levels, at least two elevated measurements on separate days are needed before making the diagnosis of hypertension.

Once a patient has been identified as hypertensive, the clinician has four key objectives:

1. address potential lifestyle factors that may be elevating blood pressure, including diet, alcohol, and weight;

2. identify other cardiovascular risk factors or concomitant disorders that will affect prognosis and guide treatment;
3. search for identifiable secondary causes of high blood pressure;
4. assess target organ damage.

Specific comorbidities are evaluated because they must also be treated, and because their presence may influence target blood pressure and therapeutic choices. These include:

- diabetes
- renal insufficiency
- hyperlipidemia
- family history of heart disease
- microalbuminuria
- physical inactivity
- obesity
- tobacco use

Causes of secondary hypertension may indicate an alternative treatment strategy; they should be particularly sought in patients with an abdominal bruit, accelerated or resistant hypertension, recurrent flash pulmonary edema, renal failure, or onset of hypertension under age 30 without a family history. Potential causes of secondary hypertension include:

- sleep apnea
- drug-induced hypertension
- chronic kidney disease
- primary aldosteronism
- renovascular disease
- chronic steroid therapy or Cushing's syndrome
- pheochromocytoma
- coarctation of the aorta
- thyroid or parathyroid disease.

Evidence of target organ damage is a key measure of the extent of disease. Examples include:

- **Heart:** left ventricular hypertrophy or CHF, as well as angina, MI, or a history of coronary revascularization
- **Brain:** stroke or transient ischemic attack
- **Kidneys:** renal insufficiency
- **Arteries:** peripheral arterial disease
- **Eyes:** retinopathy.

Bottom line: JNC 7 recommends hypertensive patients be evaluated for:

- Lifestyle factors that elevate blood pressure
- Other diseases/factors that affect prognosis and treatment choices
- Secondary causes of high blood pressure
- Evidence of target organ damage

## Goals of hypertension treatment

The main goal of hypertension treatment is to reduce cardiovascular, cerebrovascular, renal, and ocular disease. Since most patients with hypertension will reach their diastolic BP goal once the systolic BP goal is met (especially those over age 50), the systolic level remains the primary focus of management. **The current JNC 7 goal is to achieve blood pressure <140/90 mmHg, with a lower goal of <130/80 mmHg in patients with diabetes or chronic kidney disease.** Recent literature also indicates that a lower goal (SBP <130) in non-diabetics is both safe and effective in reducing cardiovascular endpoints, but this has not yet been incorporated into treatment guidelines.<sup>13</sup> Lowering SBP<120mmHg does not appear to be beneficial and may be harmful. In the ACCORD-BP trial, 4733 high risk diabetics were randomized to SBP goals of <140mmHg or <120mmHg. The attained mean SBP in the 2 groups were 134mmHg and 119mmHg respectively. There was no significant difference between the groups for the primary outcome (cardiovascular death, MI, or stroke), but the intensive lowering group had significantly higher rates of medication-related adverse events (including hypotension, hyperkalemia, and bradycardia).<sup>14</sup>

Bottom line: The current JNC 7 goal is to achieve blood pressure <140/90 mmHg, for patients with diabetes or chronic kidney disease the goal is <130/80 mmHg. Lowering SBP<120mmHg in diabetics does not appear to be beneficial and may be harmful.

## Lifestyle modification

All patients with prehypertension or hypertension should attempt to modify their lifestyle. The JNC 7 guidelines for this approach are summarized in Table 3.<sup>4</sup>

**Table 3: Lifestyle modifications for reducing hypertension.**

<b>Modification</b>	<b>Recommendation</b>	<b>Approximate SBP reduction</b>
Reduce weight	Maintain normal body mass index	5–20 mmHg per 10 kg of weight loss
Adopt “DASH” diet	Low-fat diet rich in fruits and vegetables	8–14 mmHg
Restrict dietary sodium	Less than 100 mmol/day (2.3 g/day)	2–8 mmHg
Physical activity	Aerobic physical activity 30 minutes a day, most days	4–9 mmHg
Moderate alcohol consumption	Men < 2 ounces a day Women < 1 ounce a day	2–4 mmHg

Smoking cessation is another important component of management, both for improved blood pressure control and to reduce cardiovascular risk.

### **Pharmacologic treatment**

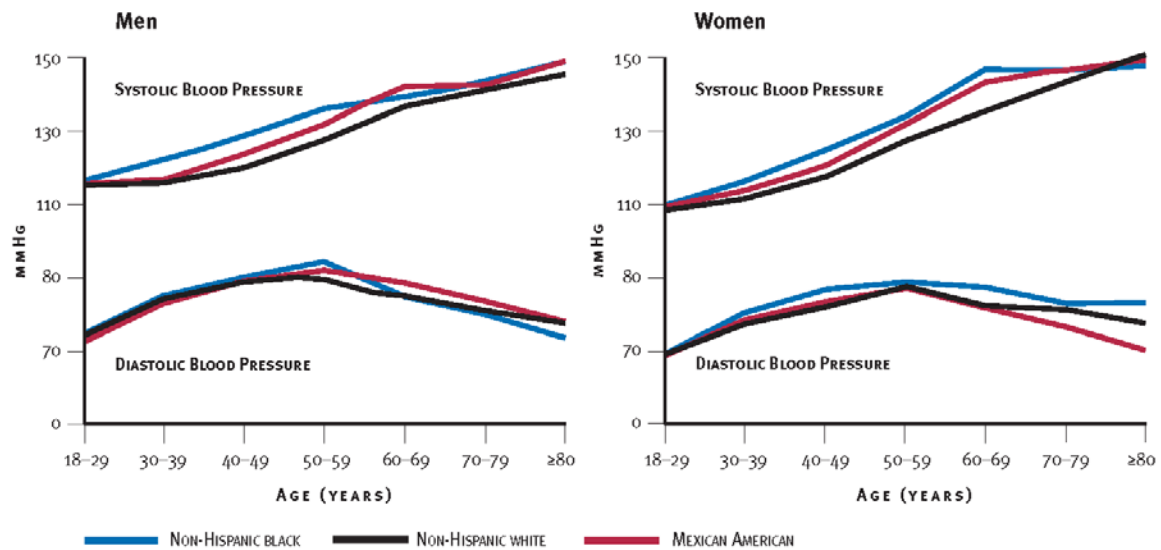
Patients who do not respond to an adequate trial of lifestyle modifications will require drug therapy. Stage 1 hypertension should be treated with one agent or combination therapy, and patients with Stage 2 hypertension should be started on two agents simultaneously. Over two-thirds of hypertensive patients will eventually require more than one medication.<sup>15</sup> Randomized trial findings provide guidance on which drugs should be chosen for best clinical outcomes.

**Bottom line: In patients who do not respond to lifestyle modifications, at least one agent should be initiated in Stage 1 hypertension, and two agents should be initiated in Stage 2 hypertension**

### **Systolic blood pressure: the primary target of therapy**

As people age, SBP increases steadily, while DBP peaks in the fifth and sixth decades of life and then slowly declines. This is true in both men and women and across ethnic groups. As the figure below demonstrates, isolated systolic hypertension with a relatively normal DBP is common in older patients.

Figure 1. Changes in systolic and diastolic blood pressure with age.<sup>16</sup>



SBP and DBP by age and race or ethnicity for men and women over 18 years of age in the U.S. population. Data from NHANES III, 1988-1991.

Source: Burt VL, et al. Prevalence of hypertension in the U.S. adult population. Results from the Third National Health and Nutrition Examination Survey, 1988-1991. *Hypertension* 1995;25(3):305-13.

Traditionally, physicians focused on DBP as the more important component of hypertension, and for years isolated elevation of SBP with normal DBP was thought to be a “normal” part of aging. Treatment to lower SBP was incorrectly thought to carry an unacceptable risk of adverse effects in older patients. But multiple clinical trials have demonstrated that isolated systolic hypertension is associated with bad outcomes in a linear fashion: the higher the SBP, the worse for the patient.<sup>17-19</sup>

Bottom line: Elevated SBP, even with a normal DBP, represents a significant risk factor for cardiovascular outcomes and is a strong indication for treatment.

## Managing hypertension: the clinical evidence

### The impact of treating SBP

Two key trials published in the 1990s studied the impact of drug treatment for isolated systolic hypertension in the elderly: *The Systolic Hypertension in the Elderly Program (SHEP)* and *The Systolic Hypertension in Europe Trial (Syst-Eur)*.<sup>20,21</sup> Both included populations of over 4,500 older patients with near-normal DBP and SBP > 160. Patients in SHEP were treated with chlorthalidone (a thiazide-type diuretic), and patients in Syst-Eur were treated with nitrendipine (a calcium-channel blocker). In both

studies, treated patients had significantly lower rates of stroke and cardiovascular outcomes. A recent meta-analysis confirmed these benefits, showing a significant reduction in total mortality and cardiovascular morbidity and mortality, in patients over age 60 treated for hypertension.<sup>22</sup>

**Table 4: Reduction in stroke and CV disease (per 1,000 patients) in SHEP and Syst-Eur trials.**

Impact of treating elevated systolic blood pressure: Trial results		
Results	SHEP	Syst-Eur
SBP reduction	12 mmHg	10 mmHg
Reduced strokes (%)	30	29
Reduced CV events (%)	55	53

After these early studies were published, scores of additional clinical trials have compared individual antihypertensive medications to placebo, using blood pressure lowering as the main outcome. Meta-analyses have combined these data to calculate the average effect on blood pressure of each of the major classes of antihypertensive medication. The pressure-lowering effects of standard-dose antihypertensives in each major drug class are very similar.<sup>16,23,24</sup> In addition, most of the blood pressure-lowering effect for each drug class can be achieved with only half of the standard dose, with only small increases in efficacy as doses are increased.

**Table 5: Effect of standard doses of anti-hypertensive drug classes on SBP.**

Effect of standard dose antihypertensive on SBP	
Drug class	SBP reduction
Thiazide	8.8
Beta-blocker	9.2
ACEI	8.5
ARB	10.3
CCB	8.8
Renin Inhibitor	8.7

This table demonstrates that **all major antihypertensive medication classes can lower blood pressure compared to placebo**, but these data do not provide clear guidance for choosing among drug classes. Based on many clinical trials, manufacturers of individual drugs have been able to promote their medications as having an advantage relative to

placebo. However, more information is needed to choose not just an effective antihypertensive, but the **most** effective antihypertensive for a given patient. Determining the best choice requires comparative efficacy data, based on randomized clinical trials, with large enough study samples to measure clinical endpoints such as CAD, CHF, and mortality -- not just blood pressure lowering. These data were provided by the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial.<sup>25</sup>

**Bottom line: Lowering isolated systolic hypertension is beneficial. All major classes of hypertension medications lower SBP by a similar degree (9-10 mmHg).**

### **Comparative efficacy data: ALLHAT**

The ALLHAT trial was a large controlled clinical trial funded by the National Institutes of Health that compared thiazide-type diuretics with calcium channel blockers (CCBs), ACE inhibitors (ACEIs) and alpha-blockers. It randomized more than 40,000 hypertensive patients to one of these regimens. The alpha-blocker arm was stopped early because patient outcomes were substantially worse compared to thiazides.<sup>25</sup> The major findings:

- Thiazides were more effective than CCBs and ACEIs in controlling SBP.
- Thiazides were as well tolerated as other classes of medications, and were better tolerated in African-Americans.
- Thiazides were equivalent to CCBs and ACEIs in preventing major coronary events and mortality.
- Thiazides were superior to CCBs in preventing CHF, both overall and for hospitalized / fatal cases.
- Thiazides were superior to ACEIs in preventing cardiovascular events, principally stroke, CHF, and angina.

**Bottom line: ALLHAT trial provided comprehensive evidence that thiazides are tolerable, safe, and effective in reducing blood pressure and clinical outcomes, and often superior to ACEIs and CCBs.**

### **What about thiazide side effects?**

Some clinicians have been reluctant to prescribe thiazides because of concern over metabolic side effects such as hypokalemia, hyperglycemia, hyperuricemia, or hyponatremia. Perceptions about these problems were based primarily on early studies and practice, in

which unnecessarily high doses of thiazides were used (e.g., 50–100 mg/d of HCTZ). The dose response relationship for the antihypertensive effect of thiazides is relatively flat, with **little blood pressure benefit gained above 12.5 to 25mg/d of HCTZ**. [26] However, larger doses seriously increase the incidence of side effects, particularly metabolic derangements. At lower doses, thiazides provide very effective blood pressure control and side effects rates that are indistinguishable from other classes of antihypertensives (and only 2% more than placebo).<sup>23, 27, 28</sup> In ALLHAT, chlorthalidone (12.5 mg/d) reduced serum potassium by only 0.3-0.5 meq/L (compared to CCBs and ACEIs respectively), increased fasting glucose by only 5-7 mg/dL (compared to CCBs and ACEIs respectively), and increased cholesterol by only 3 mg/dL (compared to either CCBs or ACEIs). These differences were clinically trivial and did not lead to any negative clinical outcomes.<sup>25</sup>

Bottom line: Low dose thiazides cause only minor metabolic derangements, similar to those seen with ACEIs and CCBs.

## Treatment recommendations

### Thiazide-type diuretics are the preferred initial agent for most patients

The findings of the ALLHAT trial, along with a wealth of data indicating that thiazide diuretics are both safe and effective in managing hypertension, led JNC 7 to recommend thiazide diuretics as the first line treatment for hypertension, either alone in combination with another medication, in patients without a “compelling indication” for other treatment (see below for a discussion of compelling indications).<sup>25,29</sup>

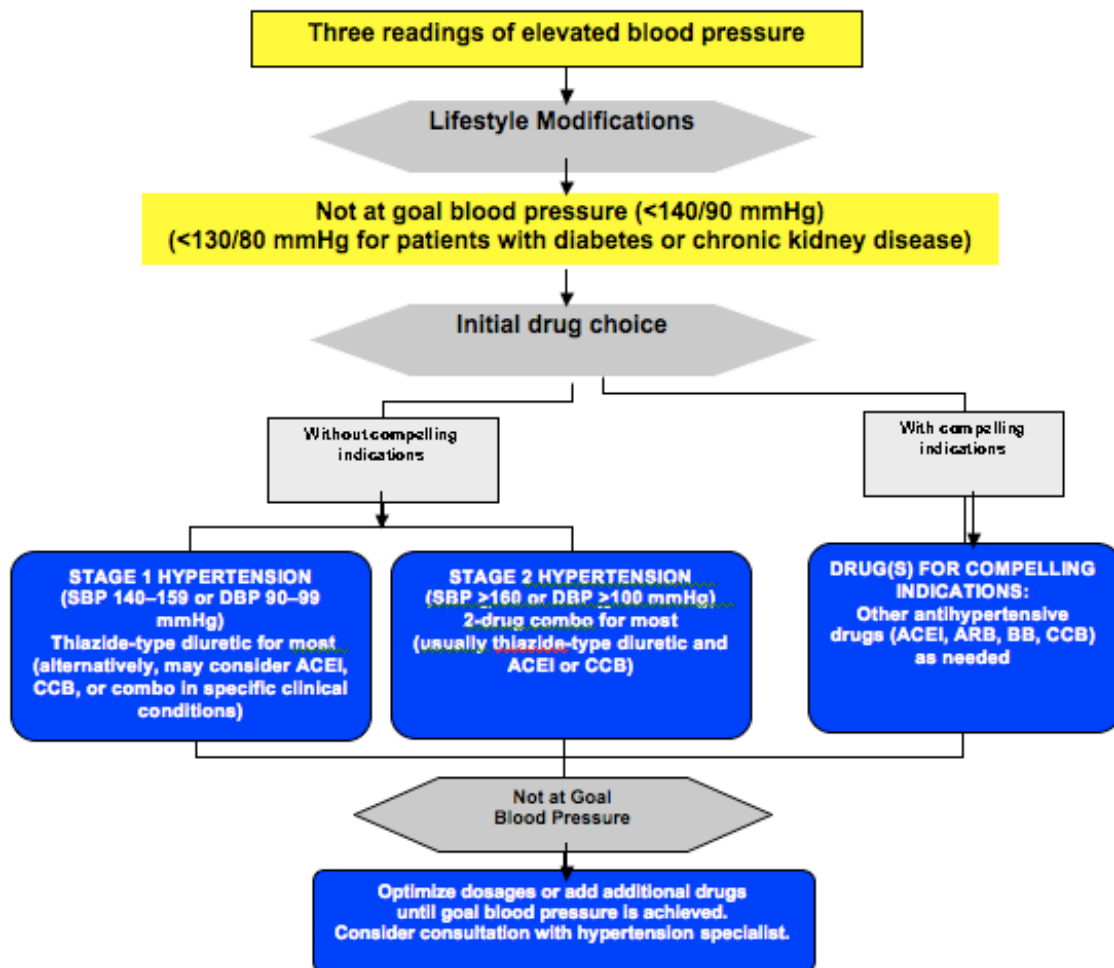
In addition to being safe and effective, thiazide diuretics are also associated with higher quality of life and lower cost than other antihypertensive medications. In the [Treatment of Mild Hypertension Study \(TOMHS\)](#), mildly hypertensive patients randomized to one of six antihypertensive drugs had similar blood pressure lowering effects from all the medication classes, but quality of life measures were most favorable for thiazides and beta-blockers.<sup>30</sup> A cost-effectiveness analysis comparing chlorthalidone, amlodipine, and lisinopril found chlorthalidone was significantly less expensive over the course of a lifetime compared to the other agents.<sup>31</sup>

The blood pressure lowering effect of thiazides is not immediate. Most patients will respond with a reduction in blood pressure within 4 weeks, although a minority of patients will not achieve maximum

reduction for up to 12 weeks.<sup>32</sup> If blood pressure control is inadequate after a reasonable time period, rather than increase the dose of the diuretic, it is better to add another drug from a different class, and to re-emphasize the importance of lifestyle changes. For patients who require more than one drug to control their hypertension, thiazides should generally be part of the regimen.

Bottom line: Thiazides are the preferred initial agent for patients without a “compelling indication” for another treatment.

The JNC 7 guidelines for the management of hypertension are presented below.



## Compelling indications

The JNC 7 report evaluated the clinical trial evidence about patients with specific co-morbidities and highlighted six “compelling indications” which warrant tailoring hypertension therapy as noted in the table below.

Compelling indication	Drug Class	Target Subgroups
<b>Congestive heart failure</b>	ACEI (ARB if intolerant) Beta blocker Aldosterone blocker	All EF<40% EF<40% and symptoms
<b>MI/ischemic heart disease</b>	Beta blocker ACEI	All All
<b>High risk of coronary artery disease, angina, silent ischemia</b>	Beta blocker (CCB if intolerant)	All
<b>Diabetes</b>	ACEI (ARB if intolerant)	All
<b>Chronic kidney disease</b>	ACEI (ARB if intolerant)	All
<b>Cerebrovascular disease</b>	No clear agent preference	

- Congestive heart failure:** Hypertension precedes CHF in 90% of cases and increases the risk of CHF by 2-3 times. In general, CHF is a compelling condition for the use of an ACEI; these drugs have consistently been shown to improve morbidity and mortality in CHF.<sup>33,34</sup> In patients intolerant of ACEIs (e.g., because of cough or angioedema), ARBs can be used.<sup>35</sup> Further drug selection is related to the stage of CHF. In patients with CHF and reduced ejection fraction (< 40%), beta-blockers should also be used.<sup>36,37</sup> In patients with low ejection fraction CHF and symptoms, an aldosterone antagonist (e.g., spironolactone) is indicated, in addition to an ACEI or ARB and a beta-blocker.<sup>38</sup> Loop diuretics are often needed as well for fluid management.
- Ischemic heart disease:** Hypertensive patients are at increased risk of MI and ischemic heart disease. Both are a compelling indication for treatment with a beta-blocker and an ACEI to reduce morbidity and mortality.<sup>39</sup>
- Stable angina and silent ischemia:** In patients at high risk of CAD, therapy is directed toward preventing MI and death, and reducing anginal symptoms. In such patients, a beta-blocker is appropriate initial therapy.<sup>40</sup> If this is ineffective or contraindicated (e.g., because of reactive airway disease, AV nodal block, or sick sinus), then a CCB can be used. If combining a BB and CCB, a dihydropyridine CCB is

preferred (e.g., amlodipine [Norvasc and generics], nifedipine [Procardia and generics]), to avoid severe bradycardia or high degree heart block.

- **Diabetes:** More than half of patients with type 2 diabetes also have hypertension, which further increases the risk of micro- and macrovascular complications.<sup>41</sup> Patients with diabetes have a 70% chance of premature death from CAD or stroke. However, a 10% decrease in SBP in these patients can reduce mortality by 15%.<sup>42</sup> Microalbuminuria predicts worse outcomes in diabetics, and renal function declines progressively at SBP > 125 mmHg.<sup>43,44</sup> According to both the American Diabetes Association and JNC 7, the blood pressure goal for patients with diabetes is 130/80. In diabetics, ACEIs and ARBs reduce the risk of MI, stroke, and renal dysfunction.<sup>45-47</sup> Targeting SBP further, to below 120mmHg, does not appear to be beneficial and may be harmful.<sup>14</sup> ACEIs also significantly reduce the risk of developing microalbuminuria, compared to placebo or CCBs, regardless of baseline blood pressure. Contrary to earlier misconceptions, results from ALLHAT indicate that thiazide-type diuretics are beneficial in diabetes and should be included if combination therapy is needed.<sup>25,48</sup>
- **Chronic kidney disease:** Renal function declines by 4-8 ml/min/year when SBP is not controlled.<sup>48</sup> In addition, microalbuminuria predicts a 50% increase in the risk of CAD, and macroalbuminuria a 350% increase. There is good evidence that maintaining SBP <130 mmHg slows progression to end-stage renal disease.<sup>49</sup> As a result, the American Society of Nephrology, the National Kidney Foundation, and JNC 7 have established a blood pressure goal of 130/80 in patients with chronic kidney disease. Most such patients should receive an ACEI or ARB and a diuretic; some will also require a loop diuretic such as furosemide for fluid management. Most such patients will need two or more medications to reach their goal blood pressure.
- **Cerebrovascular disease:** The risk of cerebrovascular disease increases with increasing levels of blood pressure, but that risk can be similarly reduced by adequate hypertension control. JNC 7 concluded that “no specific agent has been proven to be clearly superior to others for stroke prevention.” In ALLHAT, stroke incidence was 15% lower in patients who received thiazides or CCBs compared to those who received ACEIs, and blood pressure was better controlled in the thiazide and CCB arms than in the ACEI arm of the trial.<sup>50</sup> However, the LIFE trial found fewer strokes in patients randomized to losartan than to atenolol.<sup>51</sup> The PROGRESS trial demonstrated that the addition of a

thiazide to an ACEI led to a 43% reduction in stroke, which appears to have been related to better blood pressure control.<sup>52,53</sup> Recommendations for the selection of specific drug classes to treat hypertension in patients with a history of cerebrovascular disease remain unclear, but an aggressive approach to lowering blood pressure seems to be the best means available of preventing stroke in these patients.

**Bottom line: JNC 7 recommends 6 “compelling indications” to consider non-thiazide agents for initial hypertension therapy (see Table).**

### **Patient follow-up and monitoring**

JNC 7 recommends that patients return for follow-up and adjustment of medications approximately monthly until the blood pressure goal is reached. More frequent visits may be needed for Stage 2 hypertension or with comorbid conditions. Serum potassium and creatinine should be monitored 1–2 times per year, and more frequently when therapy is first initiated. After blood pressure is at goal and stable, follow-up visits can be scheduled at 3- to 6-month intervals.

Patient adherence to antihypertensive medications is disturbingly low, and represents one of the most important causes of inadequate blood pressure control. Many patients do not fill their first prescription, and within a few months almost half of patients have stopped taking their medications.<sup>6</sup> Research has shown that adherence to medication improves when drug regimens are simple and affordable.<sup>54</sup>

**Bottom line: See patients monthly until BP is controlled, then at least 2-4 times a year, and more often with other comorbid conditions. Make the regimen as simple and affordable as possible to enhance adherence.**

## **Choosing a specific regimen**

While guidelines can provide evidence on which drug class to prescribe, many products are available within each class. Based on several head-to-head trials of blood pressure lowering effectiveness and safety, and other trials assessing the comparability of these agents in other conditions, we summarize the comparative efficacy, safety, and cost of the different agents within each class below.

## Thiazides

No head-to-head trials have compared different thiazides with one another in terms of clinical outcomes, although both chlorthalidone and HCTZ lower blood pressure effectively.<sup>55</sup> Indirect comparisons of thiazides suggest that both agents have equal effects on reducing rates of serious cardiovascular events, and both appear equally safe.<sup>56</sup> Increasing the dose achieves little additional gain in blood pressure control, but does increase the rate of adverse effects. Nearly all thiazides are available generically and are very – and equally – affordable.

**Bottom line: Hydrochlorothiazide and chlorthalidone have similar efficacy, safety, and cost.**

## ACE Inhibitors (ACEIs)

While there have been no randomized head-to-head trials comparing different ACEIs in patients with hypertension that measured clinically important outcomes, many studies compared specific ACEIs with placebo, or with drugs from other antihypertensive classes. These trials have not found any consistent advantage of any one ACEI over another.<sup>57,58</sup> Similarly, evidence from head-to-head trials of ACEIs for the treatment of CHF and other conditions suggests that ACEIs seem to be similar in their short-term effectiveness.<sup>57</sup> Several head-to-head trials compared the rates of adverse events from ACEIs in patients with hypertension. These trials found no important differences among ACEIs in rates of cough, angioedema, hyperkalemia or acute renal insufficiency.<sup>57</sup> However, there are substantial differences in the cost of different ACEIs.

**Bottom line: While all ACEIs have similar efficacy and safety, there are substantial differences in cost. Since patients are more likely to adhere to medications that are taken less frequently and are affordable, choose a once-daily ACEI that is available generically (e.g., lisinopril or benazepril).**

## Angiotensin receptor blockers (ARBs)

As with ACEIs, there have been no head-to-head trials of ARBs that have measured clinically important outcomes or safety.<sup>59</sup> The existing data do not suggest any meaningful differences among different ARBs.<sup>60</sup>

Bottom line: All ARBs have similar efficacy, safety, and cost.

### **ACEI or ARB?**

In treating hypertensive patients with a compelling indication for a renin-angiotensin-aldosterone (RAA) blocker, clinicians must decide whether to use an ACEI or an ARB. ACEIs have been extensively studied and widely used for decades. ARBs were introduced into routine practice more recently and have gained favor primarily because of the lower incidence of cough with their use.

Many trials have directly compared different RAA blockers and have found that ACEIs and ARBs are equally effective at lowering blood pressure.<sup>61</sup> A systematic review also found that ACEIs and ARBs had similar effects on quality of life, progression to diabetes, progression of renal disease, left ventricular function, cardiovascular events, and mortality. Another randomized controlled trial found ACEIs and ARBs were similar in the combined outcome of cardiovascular death, MI, stroke, and CHF hospitalizations.<sup>62,63</sup>

Both ACEIs and ARBs are well tolerated, with low rates of side effects, although the incidence of cough is higher with ACEIs than ARBs (approximately 10% vs. 3%). Serious adverse reactions such as hypotension, hyperkalemia and acute renal failure are equally likely with both classes of drugs.<sup>60,62</sup> Because most ARBs are still protected by patents, there are significant differences between ACEIs and ARBs with respect to cost.

Bottom line: ACEIs and ARBs have similar efficacy and safety; ACEIs more commonly cause cough, and ARBs are significantly more expensive. When prescribing an RAA blocker, use an ACEI for initial therapy. If the patient develops cough, switch to an ARB.

### **Is there any benefit to combining an ACEI and an ARB?**

Numerous small trials have assessed whether combining an ACEI and an ARB provides additional benefit compared to either agent alone for patients with hypertension. While these trials demonstrate greater reductions in blood pressure from combined therapy, many of the trials had significant methodological flaws (such as the use of sub-maximal doses and inappropriate dosing frequencies), so their results may simply reflect higher total medication doses, rather than a synergistic effect between the two drug classes.<sup>64</sup> Independent of blood pressure lowering,

combined therapy does appear to reduce proteinuria in patients with nephropathy to a greater extent than ACEI or ARB monotherapy.<sup>64,65</sup>

However, a recent large randomized controlled trial in high risk patients (vascular and diabetic patients) found that combination therapy did not reduce rates of a composite outcome (cardiovascular death, MI, stroke, or CHF hospitalization). However, the combination did produce significantly higher rates of adverse events than did either single agent, including hypotension, syncope, and renal dysfunction.<sup>63</sup>

Several trials have also assessed the value of combination ACEI-ARB therapy for conditions other than hypertension. The CHARM-ADDED trial found a survival advantage from an ARB added to an ACEI (compared with ACEI alone) for patients with chronic CHF.<sup>66</sup> In contrast, the VALIANT trial of patients with acute MI and left ventricular systolic dysfunction/CHF did not find an added benefit from combining an ACEI and ARB, compared to either drug alone.<sup>67</sup> Both trials also found higher rates of adverse events with combined therapy.<sup>66,67</sup>

**Bottom line: While combining an ACEI and an ARB may reduce blood pressure and proteinuria more than using either drug alone, the benefit of combination therapy for other clinical outcomes is unclear in patients with hypertension, and increases adverse events.**

## **Beta-blockers**

No head-to-head randomized trials of beta-blockers in hypertension have measured clinically important outcomes, and all beta-blockers appear equally effective at lowering blood pressure.<sup>68</sup> Studies of beta-blockers to treat angina, MI and CHF also fail to show meaningful differences among the various beta-blockers, with the exception of the superiority of carvedilol vs. metoprolol for patients with advanced CHF.<sup>68</sup> Many head-to-head trials have compared safety outcomes, and have included patients with hypertension. Overall, these have shown no consistent safety differences among beta-blockers.<sup>68</sup> Most of the commonly used beta-blockers are available generically and are equally affordable.

In prior versions of the JNC guidelines, beta-blockers were recommended as first-line agents for treating uncomplicated hypertension. But since 2005, several reviews have highlighted problems with beta-blockers.<sup>69-71</sup> These analyses found that while beta-blockers were superior to placebo, they were inferior to the other major antihypertensive drug classes in preventing stroke, and were borderline

inferior in preventing other cardiovascular outcomes such as MI. This appears to be a particular problem for older patients, and less of a concern in the young.<sup>69</sup> Beta-blockers will continue to play a very important role in treating hypertensive patients with compelling indications such as CAD and CHF, but they are no longer considered a first choice agent for uncomplicated hypertension.

**Bottom line: With the exception of carvedilol for patients with advanced CHF, all beta blockers have similar efficacy, safety, and cost. Beta-blockers should be used for patients with hypertension and CAD or CHF, but are no longer first-line treatment for uncomplicated hypertension.**

### **Calcium channel blockers (CCBs)**

As with other drug classes, there are no reported head-to-head trials of CCBs that measure clinical outcomes or safety. Many trials do demonstrate that most CCBs are equally effective at lowering blood pressure. Trials of CCBs to treat other conditions do not suggest any important differences in efficacy.<sup>72</sup> Indirect comparisons of CCBs suggest they are all equally safe when used to treat hypertension.<sup>72</sup> Similarly, short-term head-to-head trials of patients with angina do not suggest any safety differences among members of this class.<sup>72</sup>

There are significant differences in the average cost of different calcium channel blockers, as some are still protected by patents.

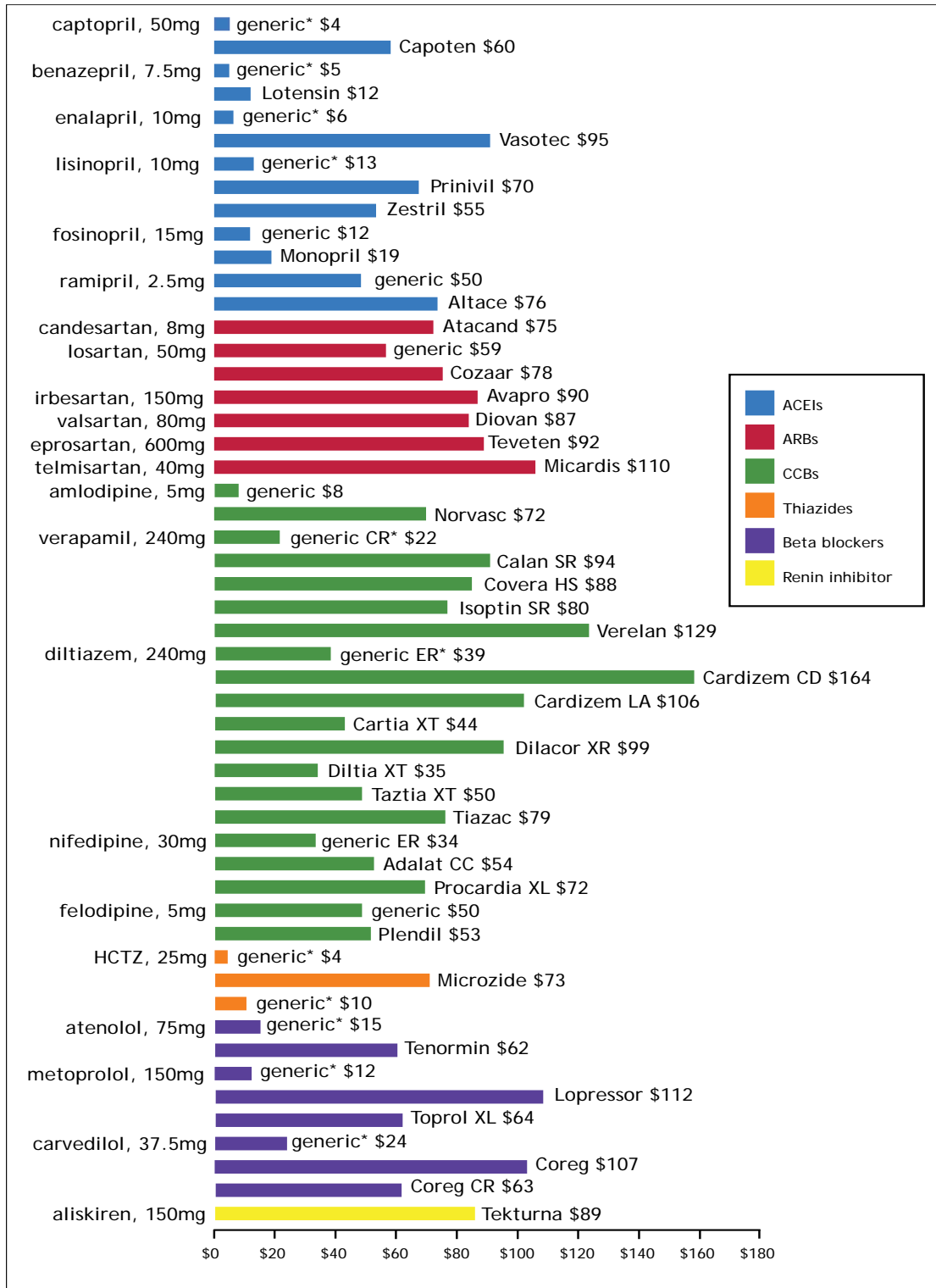
**Bottom line: All CCBs have similar efficacy and safety, but do differ in cost.**

### **Renin Inhibitors:**

Direct renin inhibitors are a new class of medications which block the conversion of angiotensinogen to angiotensin I. Aliskiren (Tekturna) is the first available direct renin inhibitor and was approved by the FDA in 2007 for treatment of primary hypertension. Direct renin inhibitors have the purported advantage of not affecting kinin metabolism, and therefore a lower incidence of cough or angioedema. However, **there have been no head-to-head comparisons of aliskiren with ACEIs or ARBs for efficacy or safety.** A recent meta-analysis found that standard doses of aliskiren lower SBP to an extent similar to other anti-hypertensive classes.<sup>24</sup> Aliskiren reduces the albumin-to-creatinine ratio in diabetics when added to an ARB, indicating it could have reno-protective effects independent of blood pressure control.<sup>73</sup> Other clinical outcomes (such as death, MI, stroke, and cardiovascular outcomes) have not been evaluated.

Bottom line: Aliskiren, a direct renin inhibitor, lowers BP to the same extent as other drug classes. It reduces proteinuria when added to an ARB, but other clinically important outcomes have not been documented. Aliskiren's high cost is similar to that of ARBs, and it is much more expensive than ACEIs.

Figure 2. Monthly costs of antihypertensive medications.



The defined daily dose is based on the World Health Organization's average daily maintenance dose of a drug, based on the primary indication of use in adults (available at [http://www.whocc.no/atc\\_ddd\\_index](http://www.whocc.no/atc_ddd_index)). The lowest available drug cost was obtained from drugstore.com (available at <http://www.drugstore.com>)

## Choosing drugs: combination therapy

Since most antihypertensive medications at standard doses will lower SBP by 9-10 mmHg, combination therapy is often required for patients with Stage 1 hypertension, and almost always for patients with Stage 2 hypertension. In the ALLHAT trial, only about a quarter of patients were controlled on monotherapy.<sup>50</sup> To choose the best combination of drugs, consider the impact of the combination on efficacy, adverse events, and adherence.

One notable large trial (ACCOMPLISH) of add-on therapy compared patients at high risk for cardiovascular disease (pre-existing ischemic heart disease, peripheral vascular disease, stroke, LVH, or diabetes), who were randomized to an ACEI-CCB or an ACEI-thiazide combination. The ACEI-CCB group had a 20% reduction in the primary endpoint (cardiovascular morbidity/mortality) compared to the ACEI-thiazide group, and a 46% reduction in progression of chronic kidney disease.<sup>74,75</sup> There may be an advantage of CCB over thiazides for add-on therapy in high-risk patients already on an ACEI.

**Bottom line: Most patients with Stage 1, and all patients with Stage 2 hypertension will require more than one agent. Combination therapy choices should consider efficacy, safety, cost, and adherence.**

## Efficacy of combination therapy

Most clinical trials in hypertension allowed for the addition of a second medication to reach target blood pressure levels. The combined data from these trials provide estimated effects of such combination therapy. Large reviews and meta-analysis have demonstrated that for the vast majority of antihypertensive combinations, the effect of combining two drug different classes equals the additive impact of each individual agent.<sup>23,76</sup>

**Bottom line: The blood pressure lowering effect of combination therapy using drugs from multiple classes is the sum of the impact of each agent.**

## Combination therapy and adverse events

Combination therapy requires a careful evaluation of each drug's dose-response relationship and dose-side effect relationship. For example, a half standard dose of HCTZ (12.5mg) results in an adverse event rate of only 2% more than placebo, which is indistinguishable from other major drug classes (such as CCBs, ARBs, or beta-blockers).<sup>23</sup> On the other hand, at twice the standard dose (50mg), the rate of adverse effects with

thiazides is 18% more than placebo, and higher than all other drug classes. Combining information on the dose-response relationship with information on the dose-side effect relationship reveals a critical lesson for using thiazides: While a low-dose thiazide provides excellent SBP reduction with minimal side effects, moving to high doses offers on average only 3 mmHg of additional SBP reduction, in exchange for an extra 16% risk of adverse effects.

As with thiazide diuretics, escalating doses of CCBs and beta-blockers also provides only small increases in blood pressure control, while adding markedly higher risks of adverse events. Fortunately, most side effects are not additive across drug classes. The important exceptions to this include the increased risk of bradycardia with beta-blocker/CCB combinations, and the risk of hyperkalemia, hypotension, syncope, and renal dysfunction with ACEI/ARB combinations.

**Bottom line:** Combination therapy with low to moderate doses of agents from different classes can deliver additive blood pressure control while minimizing the risk of adverse events. Notable exceptions include beta blocker/CCB combinations, and ACEI/ARB combinations.

### **Combination medications and adherence**

Patient non-adherence to prescribed medications is common, especially for chronic medications such as antihypertensives that are taken for a lifetime. While patient education and physician interventions are appealing means to improve adherence, there is only limited data supporting their impact on adherence. One of the most effective ways of improving adherence is to simplify medication regimens, ensure that the most affordable regimen is used, and prescribe the most patient-friendly options, such as single-pill combinations of multiple medications, once the appropriate doses of the constituent drugs have been established.<sup>51,54</sup>

**Bottom line:** Simple and affordable medication regimens are vital to ensure compliance. Prescribing single-pill combinations of multiple medications can be useful in patients taking more than one medication.

### **Special populations**

**African-Americans:** The prevalence and severity of hypertension are both higher in African-Americans, and their response to therapy is somewhat different than that of non-Hispanic whites. African-Americans often have less blood pressure response to beta-blockers, ACEIs, and ARBs compared to thiazide diuretics or CCBs. In ALLHAT, the benefits of

thiazides were increased in African-Americans. Compared to black patients randomized to thiazides, black patients given ACEIs had a 40% higher risk of stroke, a 32% increase in CHF, and a 19% increase in CAD.<sup>25</sup> In addition, the DASH study found that blood pressure in African-Americans is more responsive to modifications in diet.<sup>77</sup>

**Bottom line:** African Americans with hypertension are especially responsive to dietary modification, thiazides, and CCBs.

**Elderly:** Hypertension management is of particular importance in the elderly. More than two-thirds of people over 65 have hypertension, but this age group has the lowest rate of blood pressure control. Numerous studies have documented improvements in CAD, stroke and mortality in the elderly treated for this condition, especially those over age 60-65, and even those over 80.<sup>22</sup> A RCT of patients over age 80 with SBP > 160 who were randomized to a diuretic or placebo found a 30% reduction in stroke and 21% reduction in mortality.<sup>78</sup> Before starting a medication, weight loss and sodium restriction can be especially effective in the elderly. Drug treatment, including for patients with isolated systolic hypertension, generally follows the same principles outlined for all patients. However, lower initial drug doses are usually appropriate, following the main guideline of geriatric pharmacology: "Start low and go slow."

**Bottom line:** Elderly patients have the highest prevalence of hypertension and the lowest prevalence of being adequately controlled. Patients over age 80 continue to benefit from hypertension treatment. Lower initial doses are usually appropriate in the elderly, following the dictum "start low and go slow."

**Dementia:** Cognitive impairment occurs more commonly in people with hypertension, often because high blood pressure is a risk for multi-infarct ("vascular") dementia. Reduced progression of cognitive impairment occurs with effective antihypertensive therapy.<sup>79</sup> CCBs have been shown to slow the decline in dementia,<sup>80</sup> though other drug classes have not been well tested. While vascular dementia itself is not reversible, better hypertension control can slow its progression; hypertension should therefore be carefully managed in this population.

**Bottom line:** Adequate control of hypertension can reduce progression of cognitive impairment in patients with vascular dementia.

## Future advances in hypertension management

The JNC 7 guideline is scheduled to be updated in 2011 and will likely contain more nuanced treatment targets for specialized conditions and patient populations. Treatment targets may be slightly lower, as treatment regimes targeting modestly lower blood pressure goals in non-diabetics appear to be safe and effective at reducing important clinical outcomes.

There will likely be more information in the future on the pharmacogenomics of hypertension treatments. For example, an ongoing clinical trial (PEAR study) aims to identify the genetic determinants of efficacy and safety of thiazides and beta blockers.<sup>81</sup> Eventually, this and similar trials may help determine how to predict a specific patient's blood pressure response and adverse event profile before initiation of an agent. Such tailored treatment may help improve efficacy, cost, and compliance in the future. For now, use of the best available evidence, tailored toward individual patient characteristics (such as age, race, and co-morbid conditions) is the best approach to anti-hypertensive management.

## Appendix 1: Glossary of abbreviations

**ACEI:** Angiotensin converting enzyme inhibitor

**ARB:** Angiotensin receptor blocker

**CAD:** Coronary artery disease

**CCB:** Calcium channel blocker

**CHD:** Coronary heart disease

**CHF:** Congestive heart failure

**DBP:** Diastolic blood pressure

**HCTZ:** Hydrochlorothiazide

**JNC 7:** Seventh Report of the Joint National Committee on Prevention,  
Detection, Evaluation, and Treatment of High Blood Pressure

**MI:** Myocardial infarction

**RAA:** Renin-angiotension-aldosterone blocker

**SBP:** Systolic blood pressure

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