



# HYPERTENSION: CLINICAL PRACTICE UPDATES

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## LEARNING OBJECTIVES

1. Discuss differences in existing hypertension (HTN) treatment recommendations and apply these recommendations to clinical practice.
2. Apply evidence from recently published landmark clinical studies in formulating evidence-based treatment plans for the care of patients with HTN.
3. Assess changes in the treatment of antihypertensive disease and consider the impact of new literature on future treatment recommendations.
4. Evaluate the role of new agents in HTN treatment.
5. Assess the role of the pharmacist and quality improvement programs for treatment of HTN.

## INTRODUCTION

The treatment of essential hypertension (HTN) in the United States is complicated by disease prevalence and presentation. Uncontrolled HTN places patients at significant risk of complications including coronary artery disease (CAD), cerebrovascular disease, hypertensive retinopathy, chronic kidney disease (CKD), and cardiovascular death. These vascular events challenge the U.S. health care system, and it is projected that the direct and indirect costs of essential HTN will exceed \$73.4 billion in 2009. As the cost of health care continues to outpace inflation, and the gap in health care coverage widens (about 47 million Americans are uninsured), the role of the pharmacist in providing evidence-based care to patients becomes more important. This

chapter provides an update of the evidence for managing essential HTN and reviews the controversies surrounding treatment of this disease.

## OVERVIEW

Since the late 1990s, the American Heart Association (AHA) has worked to improve the treatment of HTN and the control of risk factors for cardiovascular complications associated with uncontrolled HTN. Despite this, an estimated 22.7 million patients with HTN remain untreated, and more than half of patients being actively treated require additional clinical interventions to achieve recommended blood pressure targets. According to the most recent AHA information (2005–2006), 29% of adults 20 years and older have uncontrolled HTN. Of these, 78% are aware of their condition, and 68% are receiving treatment. However, of those treated, only 64% receive therapies that achieve the recommended evidence-based blood pressure goals.

The treatment of HTN is often challenged by the combination of clinical inertia and rapid availability of new medical literature. Clinical inertia is defined as a combination of patient- and prescriber-related factors that prevent the achievement of evidence-based treatment goals. These factors include the lack of treatment initiation, poor adherence to prescribed therapy, failure to modify or intensify therapy based on patient response, and incomplete or inappropriate patient monitoring or follow-up. Many clinicians overestimate of the quality of care they provide and do

## BASELINE REVIEW RESOURCES

The goal of PSAP is to provide only the most recent (past 3–5 years) information or topics. Chapters do not provide an overall review. Suggested resources for background information on this topic include:

- Saseen JJ, MacLaughlin EJ. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 7th ed. Boston: McGraw-Hill, 2008:chaps 15–17, 22.
- Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560–72.

## ABBREVIATIONS IN THIS CHAPTER

ACE	Angiotensin-converting enzyme
AHA	American Heart Association
ARB	Angiotensin receptor blocker
CAD	Coronary artery disease
CCB	Calcium channel blocker
CHEP	Canadian Hypertension Education Program
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HBPM	Home blood pressure monitoring
HTN	Hypertension
JNC 7	Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
LVD	Left ventricular dysfunction
MI	Myocardial infarction
SBP	Systolic blood pressure

not fully appreciate the impact of not achieving evidence-based treatment goals. Others are not educated regarding current treatment recommendations or do not remain current with new medical literature. Patients commonly do not seek therapy for their condition, nor do they adhere to their treatment plans because of the asymptomatic nature of HTN. In fact, the U.S. health care system has historically been driven by disease management rather than disease prevention; thus, asymptomatic conditions such as HTN are often inadequately addressed. Pharmacists can play a pivotal role in changing the culture of clinical inertia and promoting incremental treatment of HTN. By actively promoting implementation of evidence-based treatment guidelines, keeping abreast of current literature, and discussing how new data should be incorporated into clinical practice, pharmacists can facilitate appropriate interventions to improve patient care.

## EVIDENCE-BASED TREATMENT

Published clinical practice guidelines include the seventh edition of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), the Joint Scientific Statements from the AHA and the American Society of Hypertension, the Canadian Hypertension Education Program (CHEP), and the European Society of Cardiology (ESC) and European Society of Hypertension (ESH) practice guidelines.

Collectively, these references provide a standardized framework for best evidence-based patient care.

### JNC 7 Guidelines 2003

Although the JNC 7 is now dated compared with other HTN treatment recommendations, it is noteworthy that the JNC 7 simplified the classification structure for patients and provided staged goals for treatment. The JNC 7 also established more aggressive blood pressure targets for patients with diabetes mellitus or CKD and encouraged clinicians to more aggressively manage severe HTN with multidrug treatment. Unlike more recent recommendations, the drug therapy algorithm promoted by the JNC 7 included five drug classes for patients without compelling comorbidities: thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs),  $\beta$ -blockers, and calcium channel blockers (CCBs). The JNC 7 recommended thiazide diuretics as the preferred first-line therapy over other agents such as ACE inhibitors. Table 1-1 compares the JNC 7 recommendations with other national treatment guidelines.

### AHA Scientific Statement 2007

In 2007, the AHA released a scientific statement regarding the treatment of HTN in the prevention and management of ischemic heart disease. The AHA recommendations modified the goals set by the JNC 7 for specific patients. No changes were made to the blood pressure goals for the primary prevention of CAD (goal less than 140/90 mm Hg) or for high-risk patients with diabetes or CKD (goal less than 130/80 mm Hg). However, it was recommended to treat patients with left ventricular dysfunction (LVD) to a blood pressure target of less than 120/80 mm Hg. In addition, the high-risk category was expanded to include patients with CAD risk equivalents (e.g., carotid artery disease, peripheral arterial disease, abdominal aortic aneurysm) and patients with documented CAD (i.e., stable angina, unstable angina, and after myocardial infarction [MI]) given their high risk of cardiovascular events and mortality. Patients with a 10-year Framingham risk assessment score of 10% or greater were included in the high-risk population.

The recommendations for primary CAD prevention were also modified by the AHA to include four drug classes as first-line treatment: thiazide diuretics, ACE inhibitors, ARBs, and CCBs.  $\beta$ -Blockers were removed as first-line therapy for patients who do not have existing CAD.  $\beta$ -Blockers remain the drugs of choice for patients with stable angina or previous MI, as well as for patients with congestive heart failure.  $\beta$ -Blockers may also be considered after ACE inhibitors and thiazide diuretics for treatment of HTN in patients with diabetes mellitus. The AHA does not promote any single agent as preferred first-line therapy, and thiazide diuretics are not considered the gold standard as suggested by the JNC 7. The AHA goes so far as to state that there is no best agent and that the selection of a first-line drug can

**Table 1-1.** Comparison of Hypertension Treatment Recommendations and Blood Pressure Targets

Sponsoring Organization (year)	Patient Assessment	Target SBP/DBP (mm Hg)	Initial Drug Choices	
JNC 7 (2003)	No compelling indication	Stage 1 hypertension (SBP 140–159 or DBP 90–99)	Thiazide diuretic (for most patients), ACE inhibitor, ARB, $\beta$ -blocker, CCB, or combination	
		Stage 2 hypertension (SBP $\geq$ 160 or DBP $\geq$ 100)	Two-drug combination for most patients (thiazide diuretics plus ACE inhibitor, ARB, $\beta$ -blocker, or CCB)	
	Compelling disease indication <sup>a</sup>	Diabetes mellitus	< 130/80	1st – ACE inhibitor or ARB 2nd – Thiazide diuretic 3rd – $\beta$ -Blocker or CCB
		Chronic kidney disease	< 130/80	1st – ACE inhibitor or ARB
AHA and ACC (2007 & 2008)	Primary prevention	Framingham risk score < 10%	< 140/90	ACE inhibitor (or ARB), CCB, thiazide diuretic, or combination if needed
		Framingham risk score $\geq$ 10%	< 130/80	ACE inhibitor (or ARB), CCB, thiazide diuretic, or combination if needed
	High CAD risk	Diabetes mellitus	< 130/80	1st – ACE inhibitor (or ARB) 2nd – Thiazide diuretic 3rd – $\beta$ -Blocker or CCB
		Chronic kidney disease	< 130/80	1st – ACE inhibitor or ARB
	CAD	Chronic stable angina Unstable angina Prior/acute MI (NSTEMI or STEMI)	< 130/80	1st – $\beta$ -Blocker, ACE inhibitor, or ARB 2nd – Thiazide diuretic 3rd – CCB
		CAD risk equivalent <sup>b</sup> – Carotid artery disease (prior stroke or TIA)	< 130/80	1st – ACE inhibitor (or ARB) or thiazide diuretic 2nd – CCB
	LVD	ACC/AHA HF classification: Stage B – Structural heart disease without history of HF symptoms Stage C – Structural heart disease with prior or current HF symptoms Stage D – Refractory disease requiring specialized interventions	< 120/80	Stage B – ACE inhibitor (or ARB) and $\beta$ -blocker Stage C/D – ACE inhibitor (or ARB), $\beta$ -blocker, diuretic (thiazide or loop), aldosterone antagonist and hydralazine, plus isosorbide dinitrate
	Home blood pressure monitoring	Primary CAD prevention	< 135/85	Thiazide diuretic (for most patients), ACE inhibitor, ARB, $\beta$ -blocker, CCB, or combination
		High-risk patients <sup>a,b</sup>	< 130/80	As above based on comorbidity

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**Table 1-1.** Comparison of Hypertension Treatment Recommendations and Blood Pressure Targets (*continued*)

Sponsoring Organization (year)	Patient Assessment	Target SBP/DBP (mm Hg)	Initial Drug Choices	
European Society of Cardiology and European Society of Hypertension (2007)	No compelling indication	Grade 1 hypertension (SBP 140–159 or DBP 90–99)	< 140/90 Thiazide diuretic, CCB, ACE inhibitor, or ARB	
		Grade 2 hypertension (SBP 160–179 or DBP 100–109)	< 140/90 Thiazide diuretic, CCB, ACE inhibitor, ARB, or combination therapy	
		Grade 3 hypertension (SBP ≥ 180 or DBP ≥ 110)	< 140/90 Combination therapy with thiazide or CCB plus ACE inhibitor, ARB, or CCB	
	Compelling disease indication	Diabetes mellitus	< 130/80	1st – ACE inhibitor (or ARB) 2nd – Thiazide diuretic or CCB Avoid β-blockers alone or in combination with thiazide diuretics
High-risk conditions <sup>c</sup>		< 130/80	ACE inhibitor, ARB, or β-blocker	
Canadian Hypertension Education Program (2009)	No compelling indication	Age ≤ 60 years	< 140/90 1st – Thiazide diuretic, β-blocker, ACE inhibitor, ARB, or long-acting CCB 2nd – Combination therapy	
		Age > 60 years	< 140/90 1st – Thiazide diuretic, ACE inhibitor, ARB, or long-acting CCB 2nd – Combination therapy Avoid β-blockers	
	Diabetes mellitus	With nephropathy (albumin-to-creatinine ratio ≥ 2.0 mg/mmol in men and ≥ 2.8 mg/mmol in women)	< 130/80	1st – ACE inhibitor or ARB 2nd – Add thiazide diuretic, β <sub>1</sub> -selective blocker, long-acting CCB
		Without nephropathy (albumin-to-creatinine ratio < 2.0 mg/mmol in men and < 2.8 mg/mmol in women)	< 130/80	1st – ACE inhibitor, ARB, dihydropyridine CCB, or thiazide diuretics 2nd – Combination therapy
	CAD	Angina or MI	< 140/90	1st – β-Blocker, ACE inhibitor, or ARB 2nd – Long-acting CCB
	LVD	NYHA functional class: Class II – mild symptoms and slight limitation during ordinary activity Class III – marked limitation in activity owing to symptoms, even during less-than-ordinary activity Class IV – severe limitations owing to symptoms at rest	< 140/90	1st – β-Blocker, ACE inhibitor, or ARB 2nd – ACE inhibitor plus ARB, hydralazine plus isosorbide dinitrate, loop diuretics as additive to all therapies NYHA class III or IV – add spironolactone
	Other conditions	Stroke or TIA	< 140/90	ACE inhibitor plus thiazide diuretic
Chronic kidney disease		< 130/80	ACE inhibitor or ARB	

<sup>a</sup>Compelling disease indication may include a variety of other comorbidities. However, the JNC 7 does not differentiate blood pressure targets for these diseases.

<sup>b</sup>CAD risk equivalent also includes peripheral arterial disease and abdominal aortic aneurysm, which have the same blood pressure target as carotid artery disease. Treatment options, however, include ACE inhibitor (ARB), CCB, thiazide diuretic, or combination if needed.

<sup>c</sup>High-risk conditions include stroke, MI, renal dysfunction, and proteinuria.

ACC = American College of Cardiology; ACE = angiotensin-converting enzyme; AHA = American Heart Association; ARB = angiotensin receptor blocker; CAD = coronary artery disease; CCB = calcium channel blocker; DBP = diastolic blood pressure; HF = heart failure; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LVD = left ventricular dysfunction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; NYHA = New York Heart Association; SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack.

be controversial. All treatment decisions should be based on patient-specific guidelines; if no compelling indications exist, the AHA suggests that it does not matter which drug is selected as long as the blood pressure is appropriately lowered to goal.

### ***Removal of $\beta$ -Blockers for Primary CAD Prevention***

The restriction of  $\beta$ -blockers by the AHA to patients with prior CAD and the removal of these agents from first-line therapy for primary prevention of CAD are not surprising. Older data suggest that  $\beta$ -blockers likely have a limited role in the treatment of essential HTN. In the Losartan Intervention for Endpoint (LIFE) trial, losartan was statistically better than atenolol at lowering the rate of death, stroke, and MI combined (23.8% vs. 27.9%, respectively) in patients with isolated systolic HTN and left ventricular hypertrophy. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), there was no difference in the primary end point of nonfatal MI or fatal CAD between atenolol and amlodipine for patients with HTN and three other cardiovascular risk factors. However, the secondary end points of all coronary events or stroke favored amlodipine. Based on this literature,  $\beta$ -blockers slipped in favor in the JNC 7 guidelines, yet the drugs were still included as an option for patients with stage 1 and stage 2 HTN.

Meta-analyses in 2004, 2005, and 2006 provided further information to suggest that  $\beta$ -blockers do not exhibit as much cardiovascular event reduction as other agents and prompted reconsideration of the role of  $\beta$ -blockers in the treatment of primary HTN. A 2007 review of 13 randomized trials in 91,561 patients added further to the discussions of  $\beta$ -blocker utility. This review evaluated the relative risk of patients developing cardiovascular disease (CVD), stroke, and all-cause mortality with  $\beta$ -blockers compared with placebo, diuretics, ACE inhibitors or ARBs, and CCBs.  $\beta$ -Blockers were found to statistically reduce the risk of CVD and stroke versus placebo, but no statistical difference was noted in all-cause mortality. There was no difference in any of the three end points for  $\beta$ -blockers compared with diuretics. Compared with ACE inhibitors or ARBs, there was no difference in CVD and all-cause mortality with  $\beta$ -blockers; however, ACE inhibitors and ARBs showed a lower incidence of stroke versus  $\beta$ -blockers. Compared with CCBs,  $\beta$ -blockers had a higher incidence of all three end points. Although these data have contributed to the differences in the AHA and JNC 7 recommendations, they also highlight the need to better study other  $\beta$ -blockers.

Debate over class effect in the treatment of HTN continues, but it is reasonable to assume that agents within drug classes with a high degree of homogeneity in pharmacokinetic and pharmacodynamic elements are interchangeable if dosed appropriately. This applies to thiazide diuretics, ACE inhibitors, and ARBs. Alternatively, for classes that have significant differences in mechanism of action and adverse effects (e.g.,  $\beta$ -blockers, CCBs), drugs should be

evaluated individually and with patient-specific guidelines in mind. Most essential HTN studies comparing a  $\beta$ -blocker for primary CAD prevention have used atenolol. In contrast, studies assessing patients with existing CAD have used other  $\beta$ -blockers such as carvedilol and metoprolol succinate.

Dosing discrepancies may also contribute to differences in the study outcomes with  $\beta$ -blockers. Based on its serum half-life (6–7 hours), atenolol appears to require twice-daily dosing. However, most HTN studies using atenolol have employed single daily doses. Failure of atenolol to show significant improvements in targeted cardiovascular end points in long-term HTN studies may be related to dosing strategies that do not appropriately correspond with adequate target daily dosing. Target daily drug dosing is not a new concept in the cardiovascular literature; however, HTN studies typically have emphasized achieving a blood pressure goal rather than targeting a specific drug dose, which is consistent with AHA philosophy. Although it is unclear whether pleiotropic drug effects play a role in HTN, it is logical to assume that dosing inconsistent with a drug's pharmacokinetic and pharmacodynamic properties may confound long-term clinical outcomes. Despite the controversy of  $\beta$ -blocker dose versus mechanism of action in primary CAD prevention, the value of  $\beta$ -blockers in the treatment of HTN with existing CAD is not in question (Class I, level of evidence A).

### ***Removal of Thiazide Diuretics as Preferred First-Line Therapy***

Much of the weight surrounding the role of thiazide diuretics as preferred first-line therapy for primary CAD prevention in the JNC 7 was provided by secondary end points in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Debate ensued among clinicians regarding the role of thiazide diuretics, and when the entire body of outcomes literature was considered by the AHA, thiazide diuretics were not preferred over alternative first-line agents.

In addition, the incidence of adverse events with thiazide diuretics has challenged the first-line role of these agents. A 2007 meta-analysis of 22 long-term antihypertensive clinical trials found long-term diuretics to have the greatest risk of inducing new-onset diabetes in patients compared with alternative agents (e.g., ACE inhibitors, ARBs, CCBs,  $\beta$ -blockers) or placebo. The mechanism of action for this effect is thought to be related to potassium depletion. Patients with serum potassium concentrations lower than 3.9 mEq/L (i.e., subclinical hypokalemia) have compromised ability to use endogenous insulin. This leads to increases in blood glucose concentrations, an adverse event that is not a new concept. In ALLHAT, hypokalemia, hyperglycemia, and new diagnoses of diabetes mellitus were higher with chlorthalidone than other agents. The ALLHAT authors proposed that these adverse events, and new-onset diabetes in particular, should not influence

coronary events, and clinicians have accepted the common rhetoric that this adverse drug reaction is clinically insignificant. However, the impact of these adverse events may be clouded by the duration of follow-up, and long-term adverse events may not be readily apparent. Therefore, over time, drug-induced hyperglycemia may mimic the microvascular and macrovascular complications of diabetes.

Despite this adverse event, thiazide diuretics may be considered an effective and affordable treatment option for HTN. Clinicians should not, however, overlook this adverse event and should closely monitor the patient's serum potassium concentrations. Recent literature has suggested that thiazide diuretics can be used to treat HTN provided that clinicians appropriately maintain the patient's serum potassium concentrations in the range of 4–5 mEq/L. Administering potassium supplements is one way to do this. Clinicians may also consider initiating the combination of a thiazide diuretic with a potassium-sparing diuretic (e.g., triamterene), ACE inhibitor, or ARB. Using low-dose thiazide diuretics (e.g., chlorthalidone 6.25–12.5 mg/day or hydrochlorothiazide 12.5–25 mg/day) and adding more agents for more pronounced blood pressure reduction are also important interventions.

#### ESC and ESH Guidelines 2007

In 2007, the ESC and ESH jointly published the second version of the European guidelines for the treatment of arterial HTN. This new document is largely based on the same principles as the 2003 version, with the aim of focusing on patient education. As with the previous ESC and ESH guidelines, the European panel does not advocate the use of the term *prehypertension*. They propose that this type of classification raises anxiety among patients and leads to unnecessary physician visits. The panel also argues that the population in a prehypertension category is too diverse to standardize treatment recommendations.

Unlike the AHA recommendations, the European recommendations are not classified by level or by the strength of the evidence on which they are based. Drug therapy recommendations also differ because the European guidelines still include  $\beta$ -blockers in the list of initial agents together with thiazide diuretics, CCBs, ACE inhibitors, and ARBs. The European guidelines do not identify a preferred first-line agent and acknowledge that most patients require combination therapy. However, the ESC and ESH emphasize that thiazide diuretics and CCBs be used in combination with other products. The only two-drug combinations recommended are a thiazide diuretic and ACE inhibitor; a thiazide diuretic and ARB; a thiazide diuretic and CCB; CCB and ACE inhibitor; CCB and ARB; or CCB and  $\beta$ -blocker.

The 2007 ESC and ESH treatment recommendations use the same blood pressure classification as the 2003 version, which was based on the 1999 World Health Organization/International Society of Hypertension classification. Because this classification system is similar to the JNC 6 and is

considered dated compared with the recent AHA classification system, European recommendations are not discussed in detail in this chapter. However, Table 1-1 compares the ESC and ESH recommendations with those of other organizations.

#### CHEP 2008 and 2009

The CHEP annually provides updated recommendations for the treatment of HTN, and the 2009 version marks the 10th consecutive year of these revisions. Overall, the 2009 CHEP recommendations are similar to those provided by the AHA in 2007, including the same blood pressure targets for primary CAD prevention and aggressive treatment of patients with diabetes. However, there are a few noteworthy differences. For patients with CVD and cerebrovascular disease, the CHEP recommends a blood pressure goal of less than 140/90 mm Hg versus the goal of less than 130/80 mm Hg recommended by the AHA. Drug recommendations differ slightly from the AHA because the CHEP maintains  $\beta$ -blockers as first-line therapy for patients younger than 60 years. In addition, thiazide diuretics are preferred agents for patients without compelling risk factors. Furthermore, the CHEP recommends this class of drugs be used before other agents. The 2009 version of the CHEP no longer recommends a dihydropyridine CCB as first-line therapy for patients with LVD. Similar to its European counterparts, the CHEP promotes two-drug therapy with a thiazide diuretic or CCB in combination with an ACE inhibitor, ARB, or  $\beta$ -blocker.

The 2009 CHEP recommendations continue to focus on the health care professional's role in encouraging appropriate patients to properly measure their blood pressure at home. The CHEP also weighs in on the controversy regarding drug therapy for the elderly and use of dual renin-angiotensin-aldosterone system therapy. In short, the program bases blood pressure treatment goals for elderly patients on the same criteria as for younger adults, but it urges caution in elderly patients who are frail or who have postural hypotension. The 2009 CHEP also cautions against the use of combination ACE inhibitor and ARB therapy and suggests that dual therapy be considered only in select and closely monitored patients with advanced heart failure or proteinuric nephropathy.

#### Changes Expected with the JNC 8

The eighth report of the JNC is expected to be released in the spring of 2010. This report will be a comprehensive, integrated set of recommendations for the treatment of HTN (JNC 8), cholesterol (National Cholesterol Education Program [Adult Treatment Panel IV]), and obesity. The document will also include innovative tools to improve adoption of the guidelines by clinicians and adherence to goals by patients. It is logical to expect that many of the recent changes outlined by the AHA 2007 Scientific Statement will be included in the forthcoming JNC 8 guidelines, particularly a more aggressive disease-based treatment

approach and streamlined choices for initial drug therapy. Many studies have been published since the AHA 2007 Scientific Statement, and these trials may play a role in the new JNC 8 recommendations for the evidence-based use of combination therapy, treatment of very elderly patients, and treatment of patients with various comorbidities.

## **NEW LITERATURE AND CLINICAL CONSIDERATIONS**

### **Special Patient Populations** ***Secondary Stroke Prevention***

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study evaluated the effect of ARBs on recurrent stroke. Previous trials examined the effect of renin-angiotensin system blockade on recurrent stroke with mixed results. The PROFESS investigators hypothesized that early initiation (within 4 months of the initial ischemic stroke) of telmisartan would reduce the risk of stroke regardless of blood pressure before treatment. After 2.5 years of follow-up, telmisartan did not reduce recurrent stroke or other major cardiovascular events such as MI, vascular death, or worsening heart failure. The fairly low mean blood pressure on entry in the study (144/84 mm Hg) may have contributed to the lack of benefit of therapy. Consequently, it is still unclear whether ARB therapy has pleiotropic effects for patients with a history of ischemic stroke, and clinicians are reminded to focus on blood pressure targets for these patients.

### ***African Americans with CKD***

A cohort study of the African American Study of Kidney Disease (AASK) and Hypertension Collaborative Research group assessed patients with hypertensive renal disease. The original AASK, completed in 2001, showed a slower rate of decline in glomerular filtration rate among patients treated with ramipril compared with those treated with amlodipine or metoprolol, regardless of blood pressure goals. Participants of the original AASK study without end-stage renal disease were enrolled in the cohort study in 2002 and treated with renin-angiotensin blocking agents to a blood pressure goal of less than 130/80 mm Hg. Patients intolerant of ramipril were changed to an ARB. Despite treatment, there was continued progression of CKD as defined by the composite end point of the doubling of serum creatinine, end-stage renal disease, or death. This study is not expected to change the recommendations for use of ACE inhibitors or ARBs in these patients.

### ***Patients with Diabetes***

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial focused on benefits of blood pressure reduction on micro- and macrovascular events in patients

with type 2 diabetes mellitus. The study had two arms, a glucose control arm and a blood pressure–lowering arm. In the blood pressure–lowering arm, the combination of perindopril and indapamide was compared with placebo. Patients in this study were 55 years and older with type 2 diabetes and one or more CVD risk factors. The active treatment arm achieved a mean 5.6/2.2-mm Hg greater reduction than the placebo arm, translating into a 9% reduction in relative risk of a major macro- or microvascular event. When analyzed separately, the reductions in micro- and macrovascular events were not significant. These benefits were observed in patients with HTN and with normal blood pressure. Renal protection was noted with lower systolic blood pressure (SBP), the lowest of which was 106 mm Hg. This finding is of interest given that the current recommendations set a target of only 130/80 mm Hg. These data contribute to the debate regarding the use of thiazide diuretics and the proposed class effect associated with these agents.

### ***Elderly Patients***

Historically, the approach to and value of blood pressure treatment in very elderly patients (older than 70–80 years) has been debated among clinicians because previous studies have not had a sufficient cohort of elderly patients. Studies and meta-analyses that assessed these patients found lower blood pressure to be associated with increased adverse events and possibly mortality. The Hypertension in the Very Elderly Trial (HYVET) evaluated the impact of treating elderly patients to conventional blood pressure targets with indapamide-based therapy. Study results showed no increase in adverse events and a significant decrease in mortality (all-cause death decreased by 21%) with therapy. The trial was discontinued early because of 30% decreases in stroke, death from stroke, cardiovascular events, and any cardiovascular event. The results of HYVET have added new perspective to HTN treatment in the very elderly and have dramatically shaped CHEP recommendations.

## **Clinical Controversies**

### ***Combination Therapy with ACE Inhibitors and ARBs***

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) was a non-inferiority study comparing telmisartan alone, ramipril alone, and the combination of both drugs. The study was also designed to evaluate the superiority of the combination versus ramipril monotherapy. The patients enrolled were age 55 years or older, had evidence of vascular disease or diabetes with end-organ damage, and had a mean blood pressure of about 142/82 mm Hg at baseline. The groups randomized to telmisartan and combination therapy had lower blood pressure readings throughout the study compared with the ramipril group. The primary outcome of cardiovascular death, MI, stroke, or hospitalization for heart failure was not significantly different between the groups. Of note, combination therapy resulted in significantly

higher discontinuation rates of study drugs. Compared with telmisartan or ramipril alone, more patients in the combination therapy group experienced renal impairment and renal failure requiring dialysis. Data from this study are expected to strengthen recommendations against dual renin-angiotensin blockade.

### **Early Combination Therapy for Cardiovascular Event Prevention**

Perhaps one of the most significant trials published in 2008 was the Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, which compared benazepril with either hydrochlorothiazide or amlodipine in patients 60 years or older with at least two cardiovascular-related diseases or target organ damage. Both high-risk groups had a mean baseline blood pressure of 145/80 mm Hg despite previous therapy for HTN in most patients. A significant reduction in the composite end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, need for resuscitation after sudden cardiac arrest, and coronary revascularization was observed in the benazepril and amlodipine group. Thiazide diuretics have been the recommended drug class for initial HTN therapy without compelling indications. The results of this study, combined with the previous literature about thiazide-induced diabetes mellitus, are expected to have an effect on the JNC 8 recommendations regarding the role of thiazide diuretics. The results also add to the debates on the selection of combination therapy and on the treatment of older patients.

### **Aggressive Blood Pressure–Lowering Targets**

Current recommendations to reduce blood pressure to less than 130/80 mm Hg have not been well supported by randomized, controlled trials. The best data regarding optimal blood pressure targets in patients with diabetes come from the previously mentioned ADVANCE trial. The continuing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial is not a trial of a specific drug regimen but rather a test of the hypothesis that an SBP of less than 120 mm Hg will reduce the rate of CVD compared with treatment to a blood pressure of less than 140 mm Hg in patients with diabetes and good glycemic control. Data from this trial are expected to provide more solid evidence regarding the legitimacy of aggressive treatment of blood pressure in patients with diabetes. The recently announced Systolic Blood Pressure Intervention Trial is designed to compare aggressive blood pressure reduction with target SBP goals of less than 120 mm Hg versus less than 140 mm Hg. The three high-risk populations targeted in this study are patients with CVD, those with stage 3 CKD, and those without CVD but with other risk factors for CVD. This study is complementary to the ACCORD trial because it will include patients at high risk because of CAD but will not include patients with diabetes or previous stroke.

## **NEW ANTIHYPERTENSIVE THERAPIES**

### **Aliskiren**

Aliskiren, the first marketed direct renin inhibitor, targets the enzyme responsible for the conversion of angiotensinogen to angiotensin I, which is the rate-limiting step in the production of angiotensin II. Unlike ACE inhibitors and ARBs, aliskiren is not limited by angiotensin II production through non-ACE-dependent pathways or indirect activation of angiotensin II type 2 or type 4 receptors. Aliskiren is approved for use alone or in combination with other agents. Nine monotherapy studies have compared aliskiren with hydrochlorothiazide, ACE inhibitors, or ARBs. Aliskiren has shown modest dose-dependent decreases in blood pressure similar to ACE inhibitors or ARBs (SBP, 5.7–15.8 mm Hg; diastolic blood pressure [DBP], 4.0–12.9 mm Hg). The peak plasma renin inhibitory effects of aliskiren are observed 2 hours after a single dose, and the maximal blood pressure effects are noted after 2 weeks of therapy.

Nine studies of combination therapy have evaluated aliskiren as an add-on to hydrochlorothiazide, ACE inhibitors, ARBs, and CCBs for 8 weeks to 1 year. Reductions in SBP and DBP, as well as response rates to goal (less than 140/90 mm Hg), were similar to other agents. Unlike hydrochlorothiazide, ACE inhibitors, and ARBs, which increase plasma renin activity, aliskiren reduces renin activity by 80% and, when given in combination, appears to blunt the iatrogenic renin activity increases induced by these other agents. The clinical utility of this effect is unclear at this point.

The impact of this new product on long-term morbidity and mortality has yet to be clarified. Several trials have used surrogate markers of end-organ damage (e.g., urinary albumin-to-creatinine ratio, left ventricular mass, neurohormonal concentrations such as B-type natriuretic peptide) to assess the beneficial effects of aliskiren. However, few data are available to define the role of this agent in preventing disease progression and cardiovascular death. Studies are under way to directly assess the impact of aliskiren on the development of CKD related to diabetes as well as morbidity and mortality after MI. Aliskiren's place in therapy is limited by a lack of long-term outcomes data as well as by the cost of the product. Clinicians may consider this agent for add-on therapy to achieve modest, additive blood pressure–lowering effects and mild proteinuria reduction. More data are needed to define the role of this agent for patients with other comorbid disease states such as CAD, heart failure, and stroke.

### **Nebivolol**

Nebivolol is a highly cardioselective, third-generation  $\beta$ -blocker with nitric oxide–potentiating vasodilatory effects. The net hemodynamic effect of nebivolol occurs from a combination of reduced peripheral vascular resistance and increased stroke volume with preservation of cardiac output. Nebivolol has no  $\alpha$ -blocking effects and

is 3.5 times more  $\beta_1$ -receptor selective than bisoprolol, making it the most  $\beta_1$ -selective agent available. The blood pressure-lowering effects of nebivolol are observed 3 hours after a single dose, and daily doses may be increased at 2-week intervals.

Nebivolol has been evaluated in three placebo and eight active comparator trials and was approved by the U.S. Food and Drug Administration (FDA) in 2007 for the treatment of HTN alone or in combination with other antihypertensive agents. Direct comparisons have shown blood pressure reductions similar to atenolol, bisoprolol, ACE inhibitors, ARBs, and CCBs (SBP, 3.7–17 mm Hg; DBP, 6.6–13 mm Hg). Compared with placebo, no quality-of-life changes were noted regarding adverse events such as fatigue and exercise intolerance. Compared with atenolol, nebivolol showed less fatigue and sexual dysfunction. No data comparing nebivolol with carvedilol or metoprolol are available.

A limited amount of clinical outcomes data are available for nebivolol. A randomized trial, the Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors (SENIORS), examined the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure. Trial results showed nebivolol to be effective at reducing cardiovascular death or hospitalization caused by heart failure. Nebivolol added to standard treatments (i.e., ACE inhibitors, ARBs, diuretics, digoxin, and/or aldosterone antagonists) reduced all-cause death or first occurrence of cardiovascular-related hospital admission, similar to other  $\beta$ -blocker studies. However, unlike previous  $\beta$ -blocker trials, SENIORS included patients 70 years or older and patients with preserved or mildly depressed left ventricular systolic function. The data from this study are consequently more reflective of patient care seen in community practice settings. Despite these clinical data, the role of nebivolol in the treatment of HTN or stable heart failure remains debatable. The effect of nebivolol on reducing SBP is modest and similar to other, less expensive agents. Future evaluations of nebivolol should include comparisons with other agents such as metoprolol succinate or carvedilol for heart failure, CAD after MI, and angina.

## Pipeline Agents

### *Endothelin Type A Receptor Antagonist*

Darusentan is a new endothelin type A receptor antagonist that blocks the vasoconstrictor effects as well as the local autocrine and paracrine effects of endothelin 1. Darusentan is related to bosentan but has higher specificity to antagonize endothelin type A versus type B receptors. Consequently, darusentan has a greater effect on arterial blood pressure than pulmonary blood pressure. Although better tolerated than bosentan, darusentan still causes more peripheral edema, headache, flushing, and nasal symptoms than placebo. Hematologic adverse events or hepatotoxicity, which are common with bosentan, do not appear to be a problem with darusentan; however, darusentan is FDA

pregnancy risk category X. Darusentan has been evaluated as monotherapy in phase II trials, and clinically significant reductions in blood pressure versus placebo (11.3/6.3 mm Hg) were noted in patients with untreated stage 2 HTN. These reductions are larger than the effects seen with other agents used as monotherapy. Darusentan is also beneficial as part of combination therapy. Further evaluations of the efficacy and safety of darusentan in patients with resistant HTN are under way in additional phase II trials. The place of darusentan in therapy will remain unclear until the completion of phase III trials; however, data appear to support future use in combination therapy for patients with resistant HTN.

### *Dual-Acting Angiotensin and Endothelin Type A Receptor Antagonist*

A dual-acting angiotensin II type 1 and endothelin type A receptor antagonist, PS433540, is under evaluation in phase II clinical trials. Reductions of up to 15 mm Hg in 24-hour ambulatory SBP were observed with PS433540 compared with placebo. In comparison with irbesartan, PS433540 significantly reduced SBP after 12 weeks of therapy. Although the effect of only the highest dose of PS433540 was significantly greater compared with irbesartan, the effects of all doses on SBP are clinically promising. Current data support the safety of PS433540; however, edema was described in 11% of patients. This novel compound remains intriguing, not only for HTN but also for its potential use in heart failure, diabetic nephropathy, and pulmonary arterial HTN.

### *Angiotensin II Vaccine*

CYT006-AngQb is a conjugate vaccine containing virus particles covalently coupled to angiotensin II. This investigational vaccine has been designed to stimulate the development of antibodies targeting angiotensin II. A phase IIb study evaluated the effect of the vaccine on adults with untreated mild to moderate HTN (140–179/90–109 mm Hg). Patients were given subcutaneous injections of 100 mcg, 300 mcg, or placebo at weeks 0, 4, and 12. In general, the vaccine promoted antibody titers to angiotensin II, but this translated to only minor effects on blood pressure. Acute adverse events included injection site reactions and flulike symptoms; however, the long-term impact of angiotensin II inhibition is unknown. Although this novel treatment approach is intriguing because of the possible lifelong impact on blood pressure and the typically poor adherence to antihypertensive therapy, the benefits of CYT006-AngQb vaccine appear to be limited.

## Additional Targets

### *Aminopeptidase A Inhibitors*

The renin-angiotensin system continues to be a focus for researchers interested in the treatment of HTN. Recently, the brain renin-angiotensin system was implicated in the development and maintenance of HTN; it is

being evaluated independently of systemic pathways. The research focus on the central renin-angiotensin system involves the conversion of angiotensin II to angiotensin III in the brain by aminopeptidase A. Both neurohormones have similar affinities for the angiotensin II type 1 receptor; thus, aminopeptidase A theoretically represents a central nervous system target for the treatment of HTN. Specific and selective aminopeptidase A inhibitors are currently being evaluated in animal studies.

### **ACE2 Activators**

Angiotensin-converting enzyme 2 is a key component of the counter-regulatory mechanisms that balance the vasoconstrictive and vasodilator activities of the renin-angiotensin system. Angiotensin-converting enzyme 2 is responsible for the degradation of angiotensin II to angiotensin I, and use of ACE inhibitors and ARBs increases cardiac ACE2 expression. Animal studies evaluating the activity of ACE2 have shown that activation of this enzyme leads to decreases in blood pressure, suggesting that ACE2 activators can be considered a valid concept for antihypertensive drug development. Thus, development of a new class of antihypertensive drugs specific for ACE2 may serve as a complementary strategy in the treatment of HTN.

## **QUALITY IMPROVEMENT PROGRAMS**

### **Home Blood Pressure Monitoring**

The traditional approach for measuring blood pressure has been by auscultatory assessment performed by a physician or nurse in the clinic or office setting. This has been the cornerstone for the diagnosis and treatment of HTN and is the approach most often used in HTN clinical trials. However, home blood pressure monitoring (HBPM) has shown a stronger association with cardiovascular prognosis than office-based readings. In particular, home measurements in patients with HTN and diabetes correlate better with both microvascular complications (nephropathy and retinopathy) and macrovascular complications (CAD and cerebral vascular disease).

In the past decade, self-assessment of blood pressure by patients has increased. About 55% of patients used HBPM in 2005 (up from 38% in 2000), and that number is projected to increase to almost 70% in 2009. Oscillometric devices specifically designed for patient use are now more available, increasing the popularity of HBPM. These devices provide the same therapeutic benefit as home glucose monitoring, which has become a standard element of diabetes treatment. Despite this, HBPM has had limited exposure in HTN treatment guidelines and, unlike home blood glucose monitoring, has not been incorporated in standard clinical practice. Fortunately, the AHA, ESH, and CHEP have increased clinician awareness by initiating a call to action for the use of HBPM and encouraging its use as a basic element of HTN treatment.

### **AHA HBPM Recommendations 2008**

Home blood pressure readings are usually lower than clinic or office readings. Consequently, the AHA defined HTN treatment goals with home assessments as less than 135/85 mm Hg for primary CAD prevention and less than 130/80 mm Hg for patients at high risk. In general, HBPM is recommended as a routine component of care for patients with documented HTN or patients with prehypertension who are thought to be at risk of developing HTN. Specifically, HBPM is useful to assess newly diagnosed HTN and to differentiate between sustained essential HTN and white-coat HTN. It is of particular benefit in elderly patients in whom blood pressure variability and the white-coat effect are problematic.

One benefit of HBPM is assessing the response to drug therapy and the impact of drug therapy changes. Thus, HBPM is recommended to provide close assessment of patients at high risk such as those with diabetes, CKD, or CAD. These patients benefit from tight blood pressure control, and HBPM provides a venue for close assessment and more aggressive therapy titration to target goals. Furthermore, HBPM provides a strategy to increase patient adherence to drug therapy and may be helpful in assessing patients with resistant HTN who are refractory to in-office blood pressure evaluations. In addition, HBPM is recommended for patients identified as having prehypertension but thought to have masked HTN; this occurs when the patient's in-office blood pressure readings are less than 140/90 mm Hg but ambulatory or home readings are greater than 135/85 mm Hg (greater than 130/80 mm Hg for patients at high risk). The prevalence of masked (or reverse white coat) HTN in the general untreated population is estimated to be 10%. In addition, masked HTN may be common among patients receiving drug therapy for HTN whose blood pressure is otherwise classified by office assessment as well controlled. Although no standardized approach for identifying these patients exists, HBPM provides a strategy for identifying and monitoring these patients.

### **Patient Education and Diagnosis of HTN**

Patients should be counseled to purchase oscillometric monitors that assess blood pressure in the upper arm. Wrist monitors are not recommended by the AHA for routine use or for diagnosis of HTN. Appropriate arm cuff size is important for accurate readings; patients should be informed that large adult cuffs are not standard with most monitoring kits and must be purchased separately. Before purchasing a blood pressure monitor, patients should be encouraged to review the updated list of validated monitors on the Dabl Educational Web site ([www.dableducational.org](http://www.dableducational.org)) and the British Hypertension Society Web site ([www.bhsoc.org](http://www.bhsoc.org)). Patients should only purchase products that have been validated for accuracy and reliability according to standard international testing protocols.

Patients should also be educated about the appropriate use of home monitors. Specifically, readings should be taken after resting for 5 minutes; the patient should be sitting with the arm supported on a flat surface at the level of the heart. A cuff size appropriate for the patient's arm should be positioned so that the midportion lies over the brachial artery. Typically, two or three readings (separated by about 1 minute) should be taken during a single morning (and evening) assessment before routine physical activity or the intake of antihypertensive drugs. Readings should also be taken before having coffee or other stimulant products. The ESH and ASH recommend disregarding the initial blood pressure assessments from the first day and collecting at least 12 readings during a single week for use in clinical decisions about HTN assessment or treatment.

### **HBPM and Pharmacist Care**

The HBPM provides a variety of benefits for both the patient and physician; also, it provides another venue for pharmacists to affect HTN treatment. This was shown by the results of the Electronic Communications and Home Blood Pressure Monitoring (e-BP) study, in which pharmacist care was added to HBPM and Web-based teaching. The HBPM treatment alone resulted in small benefits in blood pressure control compared with usual care. However, the combination of HBPM and pharmacist treatment resulted in significant reductions in both adjusted SBP and DBP (14.2 mm Hg and 7.0 mm Hg, respectively). Patients with stage 2 HTN experienced even greater benefit in adjusted SBP and DBP from this combination (27.6 mm Hg and 10.2 mm Hg, respectively). These data exemplify the importance of pharmacist involvement and provide an innovative practice model for HTN treatment.

### **The Pharmacist's Role in Preventing Clinical Inertia**

Because of their availability to the public, pharmacists should interact with patients to improve disease awareness, identify cardiovascular risk factors that complicate treatment, and educate patients regarding drug adherence. Patients who receive this interaction are more likely to seek therapy for disease treatment and remain committed to target blood pressure goals and lifestyle modifications. Pharmacists can also work with medical providers to promote aggressive clinical treatment of HTN. Optimization of drug doses is an initial step, particularly if the current blood pressure is close to goal or the drug has documented benefits at target daily doses (specifically, patients with heart failure or after MI). However, 80% of the typical blood pressure reduction is achieved at half-standard doses of conventional agents. Consequently, pharmacists should promote early combination therapy, remind prescribers that the average number of drugs required to achieve goal blood pressure targets is three agents, and use combination dosage forms when possible. Through these roles, pharmacists play integral roles in HTN treatment and challenge traditional paradigms that promote clinical inertia.

## **ANNOTATED BIBLIOGRAPHY**

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This study randomized more than 20,000 patients 50 years or older with prior ischemic stroke to telmisartan or placebo in a  $2 \times 2$  factorial design. Blood pressure was 3.8/2 mm Hg lower in the telmisartan arm compared with the placebo arm after a mean follow-up of 2.5 years. Telmisartan did not reduce the primary end point of recurrent stroke (hazard ratio [HR] = 0.95; 95% confidence interval [CI], 0.86–1.04). There was no difference between groups in the secondary end point of major cardiovascular events including stroke, MI, and new or worsening heart failure (HR = 0.94; 95% CI, 0.87–1.01). There was a small increase in the absolute risk of adverse events (3.2%), mainly driven by hypotension in the telmisartan group. Patients in this study had a relatively low blood pressure at entry (144/84 mm Hg), which could have contributed to the lack of benefit of therapy given the small reduction required to reach goal blood pressure. Adjustment for differences in blood pressure after randomization did not alter the effects of telmisartan for stroke overall (HR = 0.96; 95% CI, 0.87–1.05). Prior trials that showed benefit from renin-angiotensin blockade enrolled patients with higher blood pressure measurements at entry and observed patients for more than 2.5 years, raising the question of whether follow-up was long enough to show a benefit in this study.

2. Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease (TRANSCEND) Investigators. Yusuf S, Teo K, Anderson C, Pogue J, Dyal L, Copland I, et al. Effects of the angiotensin-receptor blocker telmisartan on cardiovascular events in high-risk patients intolerant to angiotensin-converting enzyme inhibitors: a randomised controlled trial. *Lancet* 2008;372:1174–83.

In this study, 5926 people with established CAD, stroke, peripheral vascular disease, or diabetes with end-organ damage and prior intolerance of ACE inhibitors were randomized to telmisartan 80 mg/day or placebo. The mean baseline blood pressure was 141/69 mm Hg. After a median follow-up of 2.5 years, the mean blood pressure was 3.2/1.3 mm Hg lower in the telmisartan group compared with the placebo group. There was no difference between groups in the primary outcome of cardiovascular death, MI, stroke, or hospitalization for heart failure (HR = 0.92; 95% CI, 0.81–1.05). The short duration of follow-up may have been a reason for lack of benefit with telmisartan. The use of nonstudy antihypertensives, including diuretics, was higher in the placebo group, likely contributing to the minimal difference in blood pressure between groups. There were fewer strokes and MIs in the telmisartan group, but the differences were not significant.

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chronic kidney disease in African Americans. *Arch Intern Med* 2008;168:832–9.

This 15-year follow-up study was designed to evaluate the long-term effects of the currently recommended blood pressure goals in patients with CKD. The multicenter cohort study observed the original randomized group of 1094 African Americans with hypertensive CKD. The original trial was a 3 × 2 factorial trial from 1995 to 2001 testing ACE inhibitors, CCBs, and β-blockers with two levels of blood pressure control. The cohort observed was the ACE inhibitor–treated group, treated to the blood pressure goal of lower than 130/80 mm Hg. The primary composite outcome was the doubling of serum creatinine, end-stage renal disease, or death. The mean blood pressure throughout the study was 133/78 mm Hg. Despite the use of recommended therapy and well-controlled blood pressure, the cumulative 10-year incidence of the composite outcome was 53.9%. The rate of renal decline was predicted to be slower in treated patients than in untreated patients; however, the prevention of kidney disease was not observed.

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In the ONTARGET trial, ramipril, telmisartan, and the combination of both drugs were assessed in patients 55 years or older with vascular disease or diabetes with end-organ damage. The telmisartan and combination therapy groups had lower blood pressure readings (–0.9/–0.6 mm Hg and –2.4/–1.4 mm Hg, respectively) than the ramipril group. No significant difference was seen in the primary composite outcome of death from cardiovascular cause, MI, stroke, or hospitalization for heart failure between the ramipril and telmisartan groups or between the combination therapy and ramipril groups. Combination therapy was associated with an increased rate of dialysis and a doubling of serum creatinine compared with ramipril alone (HR = 1.09; 95% CI, 1.01–1.18). Combination therapy was also associated with higher rates of study drug discontinuation because of syncope and renal impairment compared with ramipril alone. This study provided support for recommendations to avoid dual renin-angiotensin blockade for the treatment of HTN.

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This landmark study randomized 11,506 patients at high risk of HTN to receive either benazepril and amlodipine or benazepril and hydrochlorothiazide. The primary end point was a composite of death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization. The study was terminated at 36 months when the prespecified boundary for discontinuing was exceeded. The mean blood pressure in the benazepril and amlodipine group was 141.6/73.3 mm Hg; in the benazepril and hydrochlorothiazide group, it was 132.5/74.4 mm Hg. Event rates for the primary outcome were lower in the

ACE inhibitor and CCB group than the ACE inhibitor and thiazide diuretic group (HR = 0.80; 95% CI, 0.72–0.9). The results of this trial suggest that combination therapy including thiazide diuretics is not warranted in all patients.

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The ADVANCE trial is unique as the first clinical trial to show the benefits of blood pressure reduction on micro- and macrovascular events in patients with type 2 diabetes mellitus with or without HTN. This large trial had two study arms, a blood pressure–lowering arm and a glucose control arm. The blood pressure–lowering arm assessed the effect of fixed doses of perindopril 2 mg/day and indapamide 0.625 mg/day versus placebo in patients 55 years or older with one or more cardiovascular risk factors in addition to diabetes. Blood pressure was reduced 5.6/2.2 mm Hg in the treatment group compared with placebo after a mean follow-up of 4.3 years. Of the patients in the active treatment group, 15.5% experienced microvascular or macrovascular events compared with 16.8% in the placebo group (relative risk reduction, 9%; 95% CI, 0–17). The benefits appeared to be independent of the initial blood pressure on study entry. Treatment also proved beneficial for renal protection, resulting in a 21% reduction in all renal events.

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This prospective, randomized, double-blind, placebo-controlled trial evaluated the effect of indapamide-based therapy on the incidence of fatal and nonfatal stroke in patients 80 years or older. This trial, the largest to date studying the effects of blood pressure lowering in this age group, enrolled 3845 patients with a sustained SBP of 160 mm Hg or greater. The trial included patients with elevated SBP and DBP as well as those with isolated systolic HTN. After 2 years, the active treatment group had a mean sitting blood pressure 15/6.1 mm Hg lower than the placebo group. This translated to a 30% reduction in the primary outcome of stroke but did not reach statistical significance (95% CI, 1–51, p=0.06). It was determined that 11 strokes could be prevented for every 1000 patients treated for 2 years. The target blood pressure of 150/80 mm Hg was reached in 48% of patients in the active treatment group and 19.9% of patients in the placebo group. The addition of the ACE inhibitor perindopril was required to reach the goal blood pressure in 73.4% of the patients in the active treatment group. A 39% reduction in death from stroke, a 21% reduction in death from any cause, and a 23% reduction in death rate from CVD were also seen, which differs from previous trials in elderly patients. These results have been incorporated into the most recent Canadian guidelines for treatment of HTN and are expected to affect recommendations in the new U.S. guidelines as well.

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The effect of HBPM, Web communication, and pharmacist care was assessed in 778 patients with uncontrolled HTN. Patients were randomly assigned to one of three treatment arms: (1) usual care; (2) HBPM and Web site training; and (3) HBPM, Web site training, and pharmacist-assisted care through Web communication. The primary study outcomes were percentage of patients reaching a target blood pressure of less than 140/90 mm Hg and the change in SBP and DBP at 12 months from baseline. The HBPM and Web site training group experienced a small increase in the percentage of patients with controlled blood pressure compared with usual care (36% vs. 31%). However, adding pharmacist-assisted treatment to HBPM resulted in a statistically significant increase in the percentage of patients with controlled blood pressure (56%; 95% CI, 49–62) compared with usual care. Mean SBP values were also significantly improved in the pharmacist-managed group compared with the usual care and HBPM-only groups (mean SBP = 137.9 mm Hg, 146.3 mm Hg, and 143.8 mm Hg, respectively). Blood pressure effects were most pronounced for patients with stage 2 HTN in the pharmacist-managed group compared with the usual care and HBPM-only groups (mean SBPs of 139.8 mm Hg, 151.0 mm Hg, and 152.4 mm Hg, respectively). Pharmacist-managed care also resulted in statistically significant changes in DBP in the overall population and in patients with stage 2 HTN. Overall, patients who received HBPM and Web training plus pharmacist care experienced greater reductions in blood pressure compared with usual care (RR = 3.32; 95% CI, 1.86–5.94). This study exemplifies the role of a pharmacist in blood pressure treatment and provides an innovative practice model for HTN management.

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This review article provides a discussion of the renin-angiotensin system and an overview of the literature regarding the development of the renin inhibitors as a drug class. The article begins with a detailed presentation of the biochemical and physiologic properties associated with the neurohormone renin and the pathology related to its direct intracellular effects. Discussion of the history behind renin as a pharmacologic target provides insight on the development of aliskiren, and the authors provide a review of the preclinical pharmacodynamic and clinical pharmacokinetic studies. The article also provides details regarding the relevant clinical trials evaluating aliskiren versus placebo as well as active agents used for the treatment of HTN. Data comparing aliskiren with hydrochlorothiazide, ramipril, and several ARBs (e.g., losartan, irbesartan, valsartan) provide insight on active comparator monotherapy studies. Safety and efficacy data from studies combining aliskiren with thiazide diuretics, CCBs, ACE inhibitors, and ARBs provide information relevant to contemporary treatment of HTN.

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The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study evaluated the potential renoprotective benefit of dual blockade of the renin-angiotensin system. A total of 599 patients with HTN and type 2 diabetes mellitus were randomized to receive aliskiren and losartan versus losartan monotherapy. Patients treated with dual therapy showed a 20% reduction in the primary outcome of the albumin-to-creatinine ratio (18% adjusted for blood pressure) versus patients treated with losartan monotherapy ( $p < 0.001$ ). A 50% reduction in albumin-to-creatinine ratio was observed in one-fourth of the study participants receiving aliskiren therapy. No difference in blood pressure reduction was noted between the combination therapy and the losartan monotherapy groups. Adverse drug event rates were similar in both treatment arms. These results suggest a potential renal-protective effect provided by aliskiren compared with ARB monotherapy. Clinical trials evaluating outcomes related to progression of renal disease, the need for patients to undergo dialysis, and CKD-related death still are needed.

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In the recent Aliskiren Observation of Heart Failure Treatment (ALOFT) study, aliskiren was assessed as add-on therapy to standard heart failure drug regimens (which included either an ACE inhibitor or an ARB, if tolerated). This study used plasma brain natriuretic peptide (BNP) concentrations as a surrogate marker of disease in patients with New York Heart Association class II–IV heart failure. Patients with current HTN or a history of HTN, BNP concentrations greater than 100 pg/mL, and current therapy with an ACE inhibitor (or ARB) and  $\beta$ -blocker were randomized to 3 months of add-on treatment with placebo or aliskiren 150 mg/day. The primary efficacy outcome was the between-treatment difference in N-terminal pro-BNP. Significant reductions in the plasma N-terminal pro-BNP concentrations were observed in patients receiving aliskiren compared with standard therapy alone. Plasma N-terminal pro-BNP increased by 762 pg/mL with placebo and decreased by 244 pg/mL with aliskiren ( $p = 0.0106$ ). Aliskiren also reduced BNP and urinary aldosterone concentrations. Although this study suggests that the addition of aliskiren to conventional heart failure treatment strategies is beneficial, the relationship of these surrogate markers with long-term clinical outcomes remains unknown.

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The SENIORS trial showed that nebivolol is effective at reducing cardiovascular death or hospitalization in

patients with heart failure. This placebo-controlled study was designed to address clinical inertia-related failure of physicians to prescribe  $\beta$ -blockers to patients with heart failure, specifically elderly patients and patients with relatively preserved left ventricular systolic function. Patients 70 years or older with stable heart failure (ejection fraction less than 35%) not receiving a  $\beta$ -blocker at baseline were considered for enrollment in the trial. Nebivolol or placebo was added to existing treatments of ACE inhibitors, ARBs, diuretics, digoxin, and/or aldosterone antagonists. The combination of nebivolol with standard therapies reduced the first occurrence of all-cause death or cardiovascular-related hospital admission (about 3% absolute risk reduction, number needed to treat = 33), which is similar to previous studies evaluating the effect of  $\beta$ -blockers on heart failure outcomes. However, SENIORS provides data more applicable to community patient care than other trials (i.e., the U.S. Carvedilol Heart Failure Program, Metoprolol CR/XL Randomised Intervention Trial in Heart Failure [MERIT-HF], Cardiac Insufficiency Bisoprolol Trial II [CIBIS-II], and Carvedilol Prospective Randomized Cumulative Survival [COPERNICUS]). Evidence-based patient care in the community is challenged by a high prevalence of mildly reduced or normal left ventricular systolic function among elderly patients, particularly women. The results of SENIORS may be used to promote the use of and reduce clinical inertia regarding  $\beta$ -blockers. However, it also raises questions regarding the potential benefits of  $\beta$ -blockers in patients with heart failure and normal ejection fraction.

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This study evaluated the benefit of pharmacist-initiated drug therapy management services on patients in the BlueCross BlueShield of Minnesota member network. The purpose of the study was to assess the effect of pharmacist-initiated drug therapy management services on patients achieving treatment goals for HTN and hyperlipidemia. The control group was a cohort of similar patients without these services. The authors also evaluated total health expenditures for the intervention cohort by comparing mean patient expenses the year before drug therapy management services with the year after. The three primary clinical end points were the percentage of patients meeting goals of therapy achieved, the number of drug therapy problems resolved, and percentage of patients achieving Healthcare Effectiveness Data and Information Set (HEDIS) goals. Economic outcomes were calculated from the medical claims database and pharmacy claims database. Throughout the study, drug therapy management services increased the patients at treatment goal from 76% to 90%. Regarding achieving HEDIS goals, 71% of patients receiving drug therapy management services met HEDIS criteria versus only 59% of patients in the control group. The annual total health expenditures of patients receiving drug therapy management services went from \$11,965/person-year to \$8197/person-year. Drug therapy management services were also used to resolve drug therapy

problems, most of which (78%) were resolved between the pharmacist and the patient without direct involvement of a physician. This study provides evidence that having pharmacists directly involved in drug therapy management benefits not only achievement of therapy goals by patients but also that of third-party payers.