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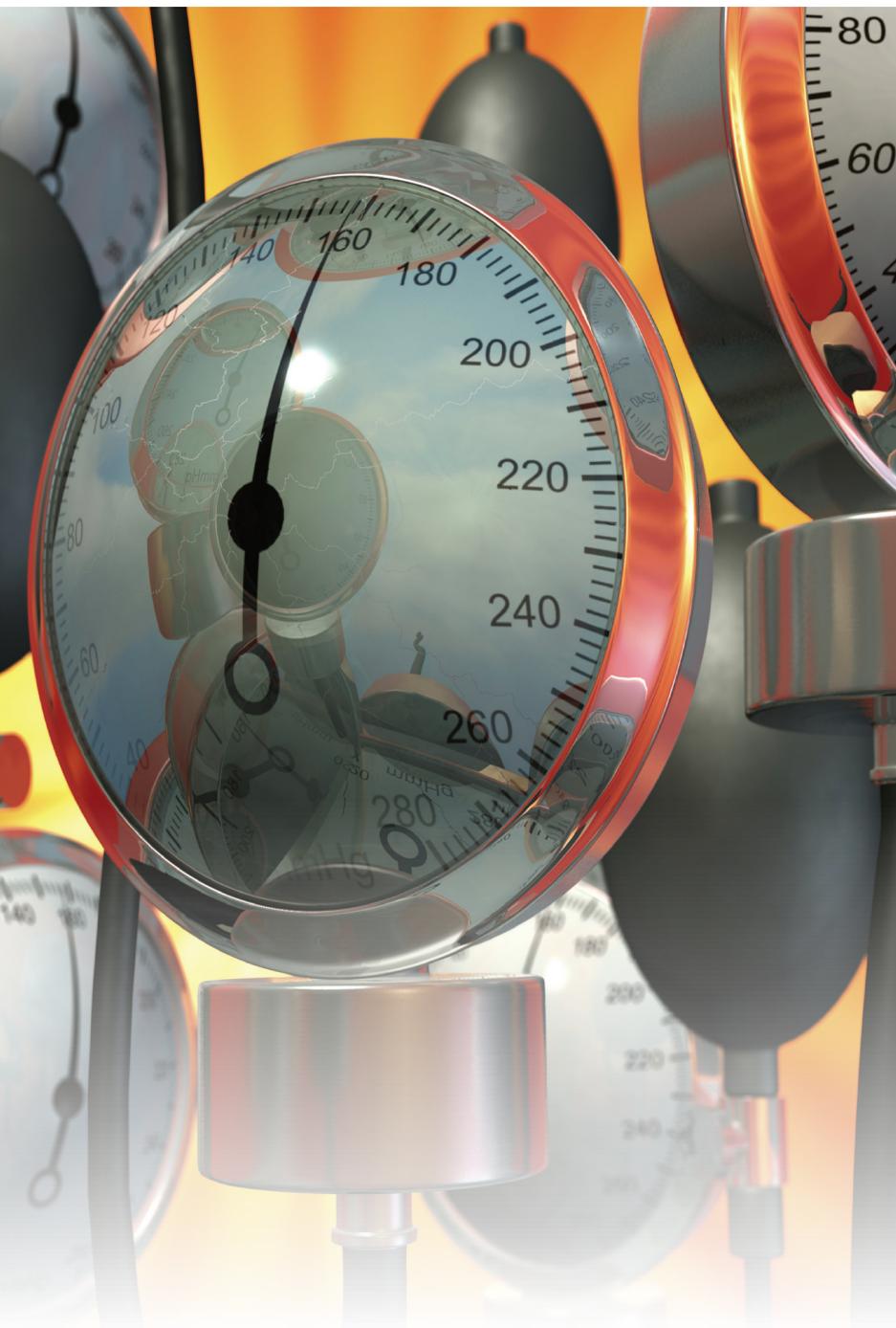
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## Getting to Goal:

How Thiazide-Type Diuretics,  
Following the Guidelines, and  
Improving Patient Adherence  
Can Help

**S5** **MODULE 1:**  
**Historical Review of  
Evidence-Based Treatment  
of Hypertension**  
William B. White, MD, FASH

**S15** **MODULE 2:**  
**Rethinking the Role of  
Thiazide-Type Diuretics in the  
Management of Hypertension:  
Which Diuretic Is Best?**  
William C. Cushman, MD

**S20** **MODULE 3:**  
**Using Thiazide-Type Diuretics  
in African Americans with  
Hypertension**  
Jackson T. Wright, Jr, MD, PhD

**S23** **MODULE 4:**  
**Enhancing Adherence with  
Antihypertensives: The Role  
of Fixed-Dose Combinations  
and Home Blood Pressure  
Monitoring**  
Louis Kuritzky, MD

**S27** **Post-Tests and Evaluations**

## Getting to Goal: How Thiazide-Type Diuretics, Following the Guidelines, and Improving Patient Adherence Can Help

Release date: August 1, 2012

Expiration date: July 31, 2013

Estimated time to complete all activities: 3.25 hours

### TARGET AUDIENCE

This activity has been designed to meet the educational needs of cardiologists, primary care physicians, and other health care professionals involved in the management of patients with hypertension.

### STATEMENT OF NEED

An estimated 1 of every 3 Americans has hypertension, and approximately 8% of them are unaware of their condition. Hypertension is even more prevalent among African Americans, affecting 41.4% of blacks overall and 44% of black women. By 2030, because of the coexisting epidemics of obesity and diabetes, coupled with an aging population, another 27 million people (a nearly 10% increase in prevalence) will be diagnosed with hypertension.

Hypertension is often called the “silent killer” because it rarely manifests with symptoms. Yet it significantly increases the risk of cardiovascular disease, heart failure, stroke, and kidney disease and is often comorbid with other cardiometabolic conditions, including diabetes and hyperlipidemia.

Despite the availability of numerous effective medications to control high blood pressure, just half of those with hypertension who are under treatment meet their blood pressure goal. This represents a significant gap in the quality of care patients receive. This gap is not only clinically relevant but may be financially relevant for your organization and physicians because more health plans and accrediting organizations base reimbursement and accreditation on the quality of blood pressure management provided.

Clearly, there is a need for continuing medical education (CME) for physicians, nurses, and other patient-facing professionals to ensure that they adhere to evidence-based approaches that help patients meet their blood pressure goal.

### LEARNING OBJECTIVES

1. Discuss key clinical trials on the role of medication in hypertension and their influence on current sequencing algorithms for the pharmacologic treatment of hypertension
2. Improve adherence to current sequencing algorithms for the management of hypertension
3. Describe pharmacokinetic/pharmacodynamic differ-

ences between the thiazide-type diuretics chlorthalidone and hydrochlorothiazide, outcomes of clinical trials with the two drugs, and the relevance of these two drugs in the contemporary management of hypertension

4. Describe the outcomes of ALLHAT in African Americans and the implications of this trial for clinical practice
5. Discuss the potential benefits of fixed-dose combination antihypertensive therapy and home blood pressure monitoring to improve patient adherence to antihypertensive therapy

### FACULTY

#### Module 1: Historical Review of Evidence-Based Treatment of Hypertension

**William B. White, MD, FASH**

Professor, Department of Medicine

Chief, Division of Hypertension and Clinical Pharmacology

Calhoun Cardiology Center

University of Connecticut Health Center

Farmington, CT

#### Module 2: Rethinking the Role of Thiazide-Type Diuretics in the Management of Hypertension: Which Diuretic Is Best?

**William C. Cushman, MD**

Professor of Preventive Medicine, Medicine, and Physiology

University of Tennessee College of Medicine

Chief, Preventive Medicine Section

Veterans Affairs Medical Center

Memphis, TN

#### Module 3: Using Thiazide-Type Diuretics in African Americans with Hypertension

**Jackson T. Wright, Jr, MD, PhD**

Professor of Medicine

Program Director, William T. Dahms M.D. Clinical Research Unit

Director of Clinical Hypertension Program

University Hospitals Case Medical Center

Case Western Reserve University

Cleveland, OH

#### Module 4: Enhancing Adherence with Antihypertensives: The Role of Fixed-Dose Combinations and Home Blood Pressure Monitoring

**Louis Kuritzky, MD**

Clinical Assistant Professor

Department of Community Health and Family Medicine

University of Florida

Gainesville, FL

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- Module 1 – 1.0 CME hours
- Module 2 – 0.75 CME hours
- Module 3 – 0.75 CME hours
- Module 4 – 0.75 CME hours

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Contracted Research: Merck & Co, Inc

Louis Kuritzky, MD

Consulting fees: Takeda Pharmaceuticals International, Inc

William B. White, MD, FASH

Consulting fees: Abbott Immunology; Ardea Biosciences, Inc; AstraZeneca; BioSante Pharmaceuticals, Inc; Forest Research Institute, Inc; Novartis Corporation; Roche Laboratories, Inc; Takeda Global Research & Development Center, Inc

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Jeanne Prater

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Laura Chase and Jaime Symowicz, PhD

Nothing to disclose with regard to commercial support

Debra Gordon, MS

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# Historical Review of Evidence-Based Treatment of Hypertension

William B. White, MD, FASH

## Introduction

Hypertension is a transformative condition in modern medicine due to the various numeric definitions of the disease, the decision of when to initiate therapy and to what level to treat, and the evolution of our understanding of the long-term complications of the hypertensive disease process. Hypertension is notable as 1 of the first conditions that only rarely manifested symptoms and whose eventual sequelae could take years, if not decades, to become known. In addition, hypertension was the first condition in which clinicians initiated therapy for patients who were otherwise healthy. Hypertension also led to 1 of the first screening programs for any disease as well as the first robust preventive effort for a chronic medical condition.<sup>1</sup>

Clinical trials have been performed for 5 decades to evaluate the potential benefits of lowering blood pressure (BP) in patients with hypertension and its comorbid conditions (**FIGURE 1**).<sup>2-37</sup> The first clinical trial to identify the increased risk of cardiovascular (CV) mortality related to hypertension was published in the mid-1960s.<sup>2,38</sup> In fact, the Veterans Administration (VA) Cooperative trial was the first randomized, placebo-controlled, double-blind, multi-institutional drug efficacy trial ever conducted in CV medicine.<sup>38</sup> It involved 143 men who met the 1964 definition of hypertension (ie, diastolic BP [DBP]  $\geq 115$  mm Hg) and who were randomized to either triple therapy with low doses of hydrochlorothiazide (HCTZ), reserpine, and hydralazine, or to placebo. The trial was terminated early when, after 18 months of treatment, rates of morbidity and mortality were substantially lower in the treated group than in the pla-

cebo group.<sup>2</sup> The trial was the first to confirm that antihypertensive treatment, even in patients with existing CV damage and significant hypertension, could dramatically reduce the incidence of stroke, congestive heart failure (CHF), and progressive kidney damage.<sup>38</sup>

Although the Framingham Study ([www.framinghamheartstudy.org](http://www.framinghamheartstudy.org)) was, of course, one of the seminal studies in the field of CV medicine, it was observational in nature, rather than interventional like most of the studies highlighted in this article.

The Medical Research Council trial of the treatment of mild hypertension (MRC-1) (ie, defined as DBP 90-109 mm Hg) demonstrated that a significant reduction in DBP among individuals receiving the diuretic bendroflumethiazide or the beta-blocker propranolol significantly reduced the rate of stroke compared with placebo, with a rate of 1.4 per 1000 patient-years of observation in the treatment group vs 2.6 per 1000 patient-years in the placebo group ( $P < .01$ ).<sup>5</sup> The treatment group also had significantly lower rates of all CV events than the placebo group, and this difference was statistically significant ( $P < .05$ ). However, the treatment groups experienced significantly increased rates of adverse effects compared with placebo.<sup>5</sup>

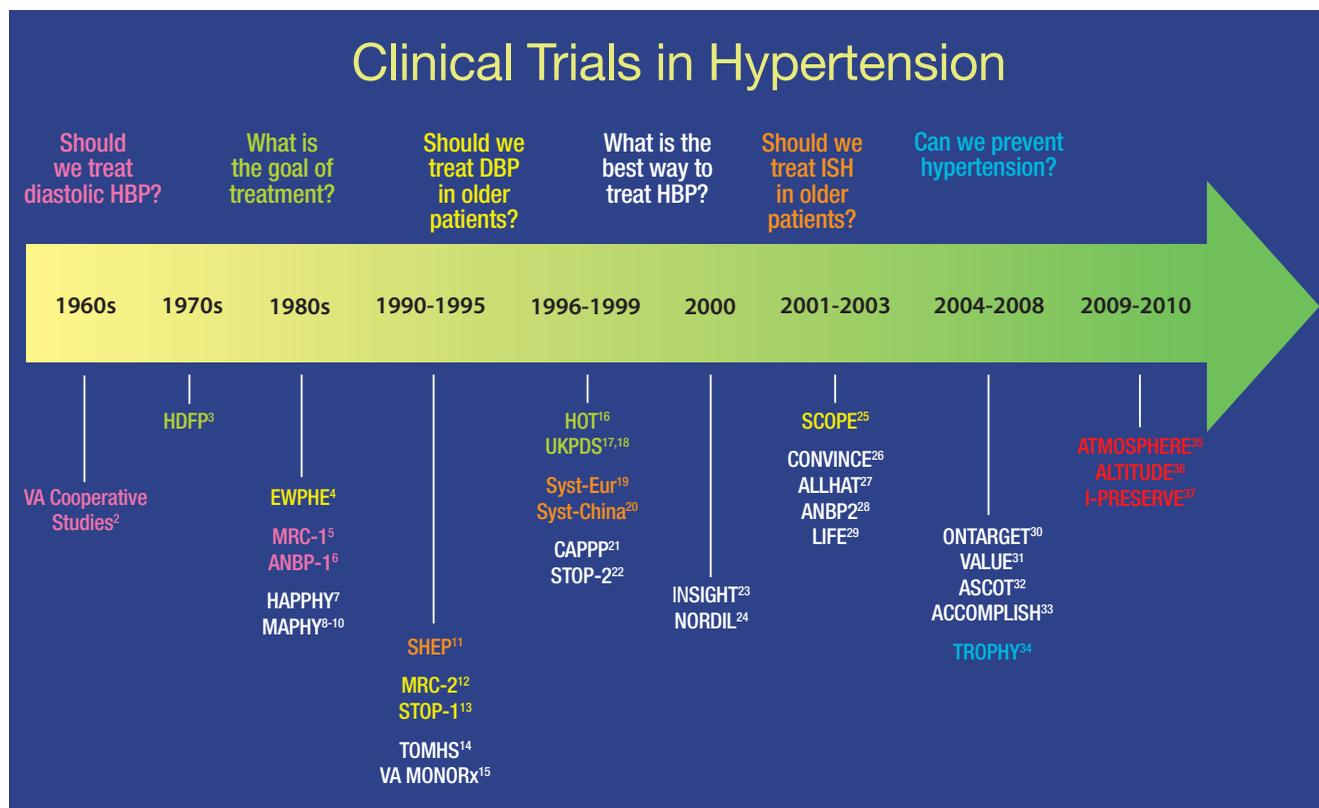
Other early notable clinical trials that evaluated treatment options for hypertension in the general public include the Hypertension Detection and Follow-up Program (HDFP),<sup>3</sup> the Hypertension Optimal Treatment (HOT) study,<sup>16</sup> and the United Kingdom Prospective Diabetes Study/Hypertension in Diabetes (UKPDS/HDS).<sup>17,18</sup> The key outcomes of these trials are shown in **TABLE 1**.<sup>3,4,11,12,16-20,22,25,39,40</sup>

Given that hypertension is far more common in older people who have increased rates of hypertensive target organ damage or CV disease (CVD), researchers have focused on the effects of antihypertensive therapy in this population for some time.<sup>41</sup> Sentinel studies in this population include the European Working Party on High Blood Pressure in the Elderly (EWPHE) study,<sup>4</sup> the Medical Research Council trial of treatment of hypertension in older adults (MRC-2),<sup>12</sup> the Swedish Trial in Old Patients with Hypertension-2 (STOP-2),<sup>22</sup> the Study on Cognition and Prognosis in the Elderly (SCOPE),<sup>25</sup> the Systolic Hypertension in the Elderly

**William B. White, MD, FASH**, Professor, Department of Medicine, Chief, Division of Hypertension and Clinical Pharmacology, Calhoun Cardiology Center, University of Connecticut Health Center, Farmington, CT

## DISCLOSURE

*Dr White is President of the American Society of Hypertension (voluntary unpaid position) and is a paid cardiovascular safety consultant to Abbott Immunology; Ardea Biosciences, Inc; AstraZeneca; BioSante Pharmaceuticals, Inc; Forest Research Institute, Inc; Novartis Corporation; Roche Laboratories, Inc; and Takeda Global Research & Development Center, Inc. He holds no stocks in pharmaceutical companies and is not a member of any speakers' bureaus.*

**FIGURE 1** Clinical trials in hypertension during the past 5 decades

ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension trial; ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints; ANBP1, Australian National Blood Pressure Study 1; ANBP2, Australian National Blood Pressure Study 2; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ATMOSPHERE, Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbi-mortality in Patients With Chronic Heart Failure study; CAPPP, Captopril Prevention Project; CONVINCE, Controlled Onset Verapamil Investigation of Cardiovascular End Points trial; DBP, diastolic blood pressure; EWPHE, European Working Party on High Blood Pressure in the Elderly study; HAPPHY, Heart Attack Primary Prevention in Hypertension trial; HBP, high blood pressure; HDFP, Hypertension Detection and Follow-up Program; HOT, Hypertension Optimal Treatment study; INSIGHT, International Nifedipine GITS Study of Intervention as a Goal in Hypertension Treatment; I-PRESERVE, Irbesartan in Heart Failure with Preserved Systolic Function study; ISH, isolated systolic hypertension; LIFE, Losartan Intervention For Endpoint Reduction in Hypertension trial; MAPHY, Metoprolol Atherosclerosis Prevention in Hypertensives study; MRC-1, Medical Research Council trial of treatment of mild hypertension; MRC-2, Medical Research Council trial of treatment of hypertension in older adults; NORDIL, Nordic Diltiazem study; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP-1, Swedish Trial in Old Patients with Hypertension-1; STOP-2, Swedish Trial in Old Patients with Hypertension-2; Syst-China, Systolic Hypertension in China trial; Syst-Eur, Systolic Hypertension in Europe trial; TOMHS, Treatment of Mild Hypertension Study; TROPHY, Trial of Preventing Hypertension; UKPDS, United Kingdom Prospective Diabetes Study; VA, Veterans Administration; VA MONORx, VA Monotherapy of Hypertension study; VALUE, Valsartan Antihypertensive Long-term Use Evaluation trial.

Program (SHEP) study,<sup>11</sup> the Systolic Hypertension in Europe (Syst-Eur) study,<sup>19</sup> and the Systolic Hypertension in China (Syst-China) study.<sup>20</sup> The key outcomes of these trials are shown in **TABLE 1**. In general, these trials have shown that antihypertensive therapy has a marked benefit in a shorter period of time in older patients than in younger patients, particularly in terms of reduced stroke and CHF rates.

The Hypertension in the Very Elderly Trial (HYVET), which enrolled participants 80 years of age and older, demonstrated that reducing systolic BP (SBP) from 170 mm Hg to 145 mm Hg with indapamide sustained release 1.5 mg and perindopril 2 to 4 mg as needed reduced all-cause deaths 21% ( $P = .02$ ), stroke-related deaths 39% ( $P = .05$ ), and fatal

and nonfatal heart failure (HF) 64% ( $P < .001$ ), compared with placebo.<sup>42</sup> The intervention group also experienced a 34% reduction in all CV events ( $P < .001$ ) and a 30% reduction in stroke ( $P = .055$ ).<sup>42</sup> However, there is still no good evidence that reducing BP further in this population provides additional benefits over the concomitant risks.

In the 1980s, numerous trials were developed to address the question: "What is the best way to treat high BP?" These included the Heart Attack Primary Prevention in Hypertension (HAPPHY) trial,<sup>7</sup> the Metoprolol Atherosclerosis Prevention in Hypertensives (MAPHY) study,<sup>8-10</sup> the Treatment of Mild Hypertension Study (TOMHS),<sup>14</sup> and the VA Cooperative Study on single drug therapy.<sup>15</sup>

**TABLE 1** Findings from the early clinical trials in hypertension

Clinical Trial	Intervention	Primary Outcome	Result
HDFP <sup>3,39</sup>	Patients randomized to systemic antihypertensive treatment or community medical therapy (referral)	5-year mortality	5-year mortality reduced by 17% in treatment group ( $P < 0.01$ ); after 12 years, BP still higher in treatment than in stepped-care treatment group
HOT <sup>16</sup>	Patients all began on felodipine, with an ACEI or a BB added as necessary If BP goal was still not reached, HCTZ could be added Patients in each group also randomized to low-dose aspirin or placebo Subjects were randomly assigned to reach 1 of 3 DBP goals: $\leq 90$ mm Hg; $\leq 85$ mm Hg; or $\leq 80$ mm Hg	Major CV events with 3 target DBPs reached during therapy and with low-dose aspirin therapy	Lowest incidence of major CV events achieved at mean BP of 138.5/82.6 mm Hg; lowest risk of CV mortality achieved at mean BP of 138.8/86.5 mm Hg Low-dose aspirin reduced major CV events by 15% and all MI by 36%, although nonfatal major bleeding was twice as common with low-dose aspirin than with placebo
UKPDS/HDS <sup>17,18</sup>	Patients with T2DM randomized to atenolol or captopril, with additional antihypertensive agents (other than ACEIs or BBs) allowed	Effect of tight BP control on diabetes-related complications, morbidity, and mortality	Tight BP control ( $< 150/85$ mm Hg) with either atenolol or captopril significantly reduced the risk of all endpoints, including risk of diabetes-related death or complication, stroke, MI, and heart failure
EWPHE <sup>4</sup>	Patients $\geq 60$ years of age randomized to HCTZ + triamterene + methyldopa or placebo	CV and MI mortality; nonfatal CV events	Significant reduction in CV and MI mortality ( $P < .05$ ) but not nonfatal CV events in treatment group vs placebo Found U-shaped relationship between mortality and SBP in treated group vs mortality and DBP in placebo group
MRC-2 <sup>12</sup>	Patients 65-74 years of age randomized to atenolol + HCTZ or amiloride	Reduction in mortality and morbidity due to stroke and CHD and reduction in mortality due to all causes	Only the HCTZ group demonstrated a significant reduction in stroke, coronary events, and all CV events ( $P = .4$ , $P = .0009$ , and $P = .0005$ , respectively)
STOP-2 <sup>22</sup>	Patients 70-84 years of age randomized to atenolol + HCTZ or amiloride; or to metoprolol or prindolol	Incidence of fatal stroke, MI, or other CVD mortality	Similar reductions in BP, mortality, and major events in all treatment groups
SCOPE <sup>25</sup>	Patients 70-89 years of age randomized to candesartan or placebo (open-label antihypertensive therapy added as needed and extensively used in control group)	Major CV events; secondary measures included CV death, nonfatal and fatal stroke and MI, cognitive function	Greater BP decreases in candesartan group but no significant risk reduction in major CV events between the 2 groups Significant reduction in nonfatal stroke ( $P = .04$ ) and all stroke ( $P = .06$ ) in the treatment group No other significant differences between the groups, although a post-hoc analysis found less cognitive decline among those with only mild cognitive impairment at baseline in the candesartan-treated group ( $P = .04$ ) <sup>40</sup>

CONTINUED

**TABLE 1** Findings from the early clinical trials in hypertension (continued)

Clinical Trial	Intervention	Primary Outcome	Result
SHEP <sup>11</sup>	Patients ≥60 years of age randomized to chlorthalidone with or without atenolol or reserpine, with nifedipine as third-line therapy, or to placebo	Stroke; nonfatal MI, coronary death, major CV events, death due to all causes	Significant reduction in 5-year incidence of total stroke in active treatment group ( $P = .0003$ ) and significant reduction in all secondary endpoints
Syst-Eur <sup>19</sup>	Patients >60 years of age randomized to nitrendipine with possible addition of enalapril, HCTZ, or both, or to placebo	Fatal and nonfatal stroke, fatal and nonfatal cardiac events including sudden death, all-cause mortality	Significant reductions in all endpoints except all-cause mortality in treatment group; study halted early because of the 42% total stroke reduction in treatment arm ( $P < .003$ )
Syst-China <sup>20</sup>	Patients ≥60 years of age randomized to nitrendipine with captopril or HCTZ, or both if needed; or matching placebo	Nonfatal stroke; all-cause, CV, and stroke mortality; and all fatal and nonfatal CV events	Significant reductions in all endpoints

ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blocker; BP, blood pressure; CV, cardiovascular; CHD, coronary heart disease; CVD, CV disease; DBP, diastolic BP; EWPHE, European Working Party on High Blood Pressure in the Elderly study; HDFP, Hypertension Detection and Follow-up Program; HCTZ, hydrochlorothiazide; HOT, Hypertension Optimal Treatment study; MI, myocardial infarction; MRC-2, Medical Research Council trial of treatment of hypertension in older adults; SBP, systolic BP; SCOPE, Study on Cognition and Prognosis in the Elderly; SHEP, Systolic Hypertension in the Elderly Program; STOP-2, Swedish Trial in Old Patients with Hypertension-2; Syst-Eur, Systolic Hypertension in Europe trial; Syst-China, Systolic Hypertension in China trial; T2DM, type 2 diabetes mellitus; UKPDS/HDS, United Kingdom Prospective Diabetes Study/Hypertension in Diabetes.

Subsequently, several trials were conducted that focused on the safety of calcium antagonists for the primary or background treatment of hypertension. These included the International Nifedipine GITS Study of Intervention as a Goal in Hypertension Treatment (INSIGHT),<sup>23</sup> the Nordic Diltiazem (NORDIL) study,<sup>24</sup> the Australian National Blood Pressure Study 2 (ANBP2),<sup>28</sup> the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) trial,<sup>26</sup> the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial,<sup>29</sup> and the Irbesartan in Heart Failure with Preserved Systolic Function (I-PRESERVE) study.<sup>37</sup>

These studies, conducted from the mid 1990s to the present, have shown that calcium antagonists, including amlodipine, diltiazem, nifedipine, and verapamil, are as effective as thiazide-type diuretics or beta-blockers in preventing CV events in patients with hypertension. Further, the LIFE trial demonstrated that the angiotensin II receptor blocker (ARB) losartan was more effective than the beta-blocker atenolol in reducing stroke events and that blockade of the renin-angiotensin system did not seem to affect CV outcomes in patients with HF with preserved systolic function, a common problem in patients with prolonged hypertension and left ventricular hypertrophy.<sup>29</sup>

The largest randomized, double-blind, antihypertensive trial performed to date is the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). It involved 33,357 participants 55 years of age and older with hypertension and at least 1 other coronary heart

disease (CHD) risk factor.<sup>27</sup> Participants were randomized to chlorthalidone, amlodipine, doxazosin, or lisinopril. The doxazosin arm was discontinued early because an increase in CV events was observed after 2 years, relative to the other treatment arms. At follow-up (mean, 4.9 years), there was no difference between the 3 groups in terms of the primary outcome (combined fatal CHD or nonfatal myocardial infarction [MI], analyzed by intent-to-treat) or all-cause mortality.<sup>27</sup> Of note, 5-year SBP levels were higher in the amlodipine (0.8 mm Hg,  $P = .03$ ) and lisinopril (2 mm Hg,  $P < .001$ ) groups than in the chlorthalidone group, whereas the 5-year DBP levels were significantly lower in the amlodipine group (0.8 mm Hg,  $P < .001$ ).<sup>27</sup>

Secondary analyses showed a higher 6-year rate of HF development in the amlodipine group than in the chlorthalidone group (10.2% vs 7.7%; relative risk [RR], 1.38; 95% confidence interval [CI], 1.25-1.52), whereas the lisinopril group had a higher 6-year rate of combined CVD (33.3% vs 30.9%; RR, 1.10; 95% CI, 1.05-1.16), stroke (6.3% vs 5.6%; RR, 1.15; 95% CI, 1.02-1.30), and HF (8.7% vs 7.7%; RR, 1.19; 95% CI, 1.07-1.31) than the chlorthalidone group. The design of ALLHAT led to worsened control of BP in African Americans relative to white patients who were receiving lisinopril, which may have been an important factor in the subsequent increased rate of stroke in African American patients who were receiving lisinopril rather than chlorthalidone.<sup>27</sup>

Subsequent to ALLHAT, the benefits and safety of calcium antagonists vs a thiazide diuretic combined with an

angiotensin-converting enzyme inhibitor (ACEI) were addressed by the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) trial.<sup>33</sup> This study randomized 11,506 patients with a mean BP of 145/80 mm Hg to combination therapy with benazepril (40 mg/d) and amlodipine (5-10 mg/d) or benazepril and HCTZ (12.5-25 mg/d). Other antihypertensive medications could be added to reach a target BP < 140/90 mm Hg (130/80 mm Hg in patients with diabetes or renal insufficiency).<sup>33</sup> The study was stopped early at 3 years because the primary outcome of CV death, nonfatal MI or stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization occurred in 552 patients in the benazepril-amlodipine group compared with 679 patients in the benazepril-HCTZ group (9.6% vs 11.8%; RR ratio, 19.6%; hazard ratio [HR], 0.80;  $P < .001$ ). The mechanism for the benefit observed in the benazepril-amlodipine group may relate in part to improved coronary blood flow that occurs with a calcium antagonist (compared with a diuretic) since BP control was virtually the same in both groups.

Another major hypertension study during the same era was the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT).<sup>32</sup> This study enrolled 19,257 patients in northern Europe with a mean age of 63 years, an untreated baseline BP  $\geq 160/100$  mm Hg or a treated mean BP  $\geq 140/90$  mm Hg, and 3 or more of 11 prespecified risk factors for CV. Patients were randomized to amlodipine, with or without perindopril, or atenolol, with or without a thiazide diuretic, and were titrated to reach a BP goal < 140/90 mm Hg. The study was halted early after a mean follow up of 5.5 years. Although there was no statistically significant difference in the primary events of nonfatal MI plus fatal CHF between the 2 arms, fewer patients randomized to the amlodipine-based regimen experienced a fatal or nonfatal stroke (327 vs 422; HR, 0.77; 95% CI, 0.66-0.89;  $P = .0003$ ) and total CV events and procedures were lower in patients taking the amlodipine-based regimen than in those taking the atenolol-based regimen (1362 vs 1602; HR, 0.84; 95% CI, 0.78-0.90;  $P < .0001$ ).<sup>32</sup> All-cause mortality was also lower in the amlodipine-based group (738 vs 820; HR, 0.89; 95% CI, 0.81-0.99;  $P = .025$ ), and significantly fewer patients in this arm developed diabetes (567 vs 799; HR, 0.70; 95% CI, 0.63-0.78;  $P < .0001$ ).<sup>32</sup>

Patients with diabetes in ASCOT who were titrated to achieve a target BP < 130/80 mm Hg experienced significantly lower mortality and stroke when taking the amlodipine-based regimen than when taking the atenolol-based regimen (HR, 0.86; 95% CI, 0.76-0.98;  $P = .026$ ).<sup>32</sup> In the group taking the atenolol-based regimen, fatal and nonfatal strokes were reduced by 25% ( $P = .017$ ), peripheral arterial disease by 48% ( $P = .004$ ), and peripheral revascularization procedures by

57% ( $P < .001$ ). There were no statistically significant differences in the endpoints of CHD deaths and nonfatal MI in the diabetes subgroup.

### Combination therapy and guideline recommendations

By the 1970s, it became clear that combinations of antihypertensive drugs increased BP lowering efficacy through both additive and synergistic mechanisms. These combinations also reduced adverse events because lower doses of each drug could be used, whereas drugs from different classes might offset each other's adverse effects. In addition, combining antihypertensive drugs could prolong duration of action, possibly providing additional target organ protection.<sup>43</sup> Combining drugs from complementary classes has also been shown to increase the likelihood of BP lowering compared with increasing the dose of a single drug, thus reducing the time required to reach BP goal.<sup>31,44-46</sup>

The 2010 American Society of Hypertension (ASH) position statement on combination therapy in hypertension therapy notes that at least 75% of patients will require combination therapy to reach goal.<sup>47</sup> In addition, a meta-analysis of 9 randomized clinical trials found that combination treatment using a thiazide or thiazide-like diuretic as one of the components could provide a significantly greater effect than monotherapy lacking the diuretic, with similar discontinuation rates.<sup>48</sup>

Government guidelines in the United States, now nearly 10 years old, do not recommend combination therapy as a first-line approach unless patients have stage 2 hypertension (SBP  $\geq 160$  mm Hg or DBP  $\geq 100$  mm Hg). At that point, the guidelines recommend combination therapy with a thiazide or thiazide-type diuretic plus either an ACEI, ARB, beta-blocker, or calcium antagonist.<sup>49</sup> More-specific recommendations are provided for patients with compelling indications (eg, HF, ischemic heart disease, chronic kidney disease, recurrent stroke, diabetes, and high coronary disease risk), as shown in **TABLE 2**.<sup>41,49</sup> New recommendations from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) are expected later this year.

Recent guidelines from ASH describe combination therapies of hypertension in categories of preferred, acceptable, and less effective, based on efficacy in lowering BP, safety and tolerability, and certain known outcomes from longer-term trials (**TABLE 3**).<sup>47</sup>

In 2010, the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) published an expert consensus document on hypertension in the elderly. It recommends single therapy or combination therapy with an ACEI, ARB, calcium antagonist, or diuretic for patients

**TABLE 2** Antihypertensive treatment in patients with compelling indications<sup>41,49</sup>

Indication	Diuretic	BB	ACEI	ARB	Calcium antagonist	Aldosterone antagonist
Heart failure	X ✓	X ✓	X ✓	✓	X	X ✓
Post MI		X ✓	X ✓		X	X ✓
CVD or high CVD risk	X ✓	X ✓	X ✓		X ✓	
Angina <sup>a</sup>		X			X	
Aortopathy/aortic aneurysm <sup>a</sup>	X	X	X	X	X	
Diabetes	X ✓	X ✓	X ✓	X ✓	X ✓	
Recurrent stroke prevention	X ✓		X ✓	X	X	
CKD <sup>b</sup>			✓	✓		
Early dementia <sup>a</sup>	Blood pressure control/no medication (X)					

X = ACCF/AHA recommendation; ✓ = JNC-7 Express recommendation.

ACCF, American College of Cardiology Foundation; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin-receptor blocker; BB, beta-blocker; CVD, cardiovascular disease; CKD, chronic kidney disease; MI, myocardial infarction.

<sup>a</sup>Not considered "compelling" indication in JNC-7 Express guidelines.

<sup>b</sup>Not considered "compelling" recommendation in ACCF/AHA recommendations.

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**TABLE 3** Drug combinations in hypertension: Recommendations from the American Society of Hypertension<sup>47</sup>

Preferred	Acceptable	Less Effective
ACEI + diuretic <sup>a</sup>	BB + diuretic <sup>a</sup>	ACEI + ARB
ARB + diuretic <sup>a</sup>	Calcium antagonist + diuretic	ACEI + BB
ACEI + CCB <sup>a</sup>	Renin inhibitor + diuretic	ARB + BB
ARB + CCB <sup>a</sup>	Renin inhibitor + ARB <sup>a,b</sup>	CCB (non-dihydropyridine) + BB
	Thiazide diuretic + potassium-sparing diuretic <sup>a</sup>	Centrally acting agent + BB

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; BB, beta-blocker; CCB, calcium channel blocker.

<sup>a</sup>Available as single-pill combination.

<sup>b</sup>This may be medically inappropriate in patients with diabetes and chronic diabetic nephropathy.

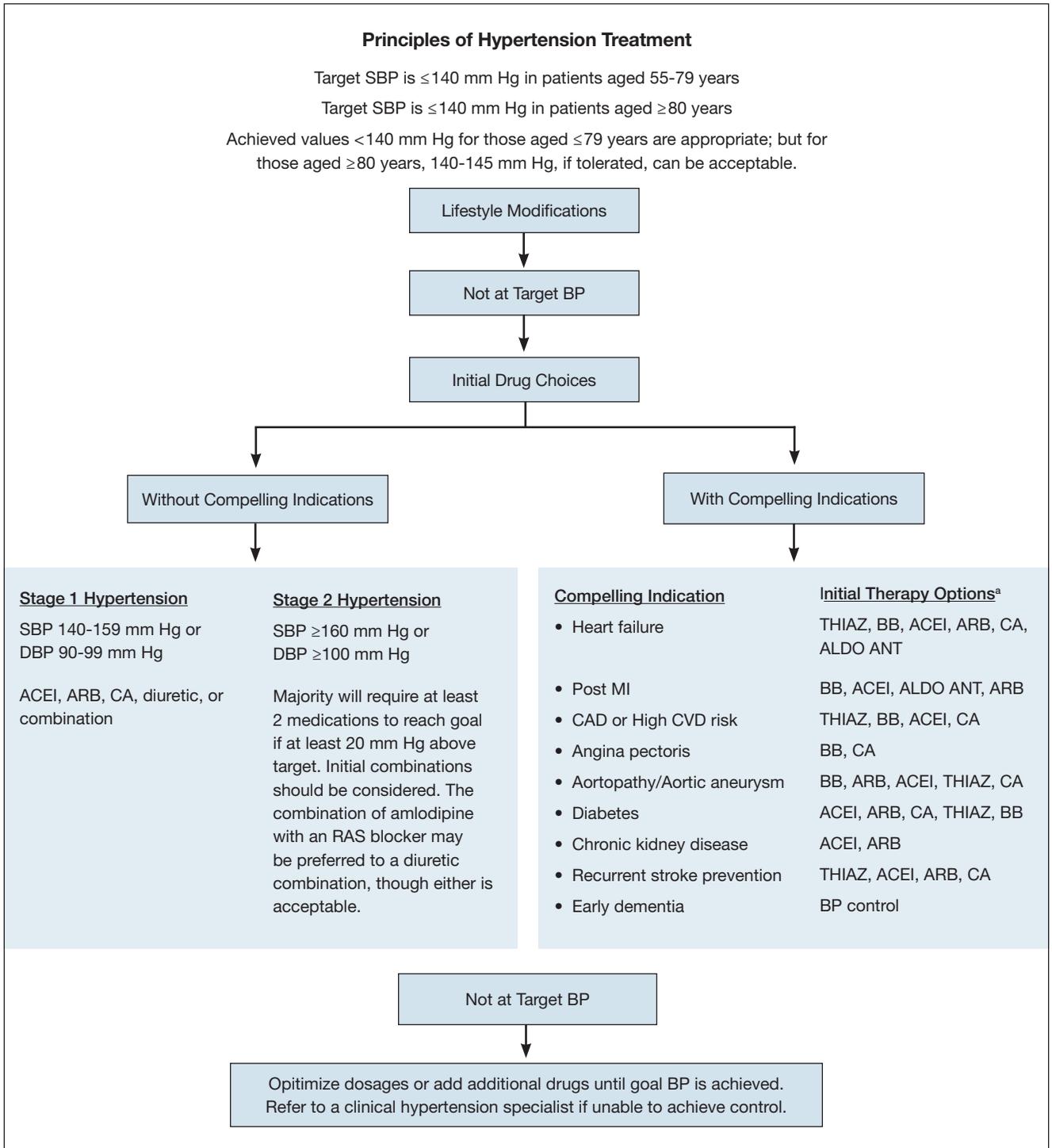
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65 years of age and older with stage 1 hypertension and no "compelling" indications (eg, HF, post-MI, known coronary disease, angina, aortopathy/aortic aneurysm, diabetes, recurrent stroke prevention, chronic kidney disease, and early vascular dementia), but combination therapy for those with stage 2 hypertension and no compelling indica-

tions. For the former group, the panel notes that the combination of amlodipine with a renin-angiotensin aldosterone system blocker may be preferable to a diuretic combination, although either is acceptable.<sup>41</sup>

For patients with compelling indications, the ACCF/AHA panel recommends condition-based combination

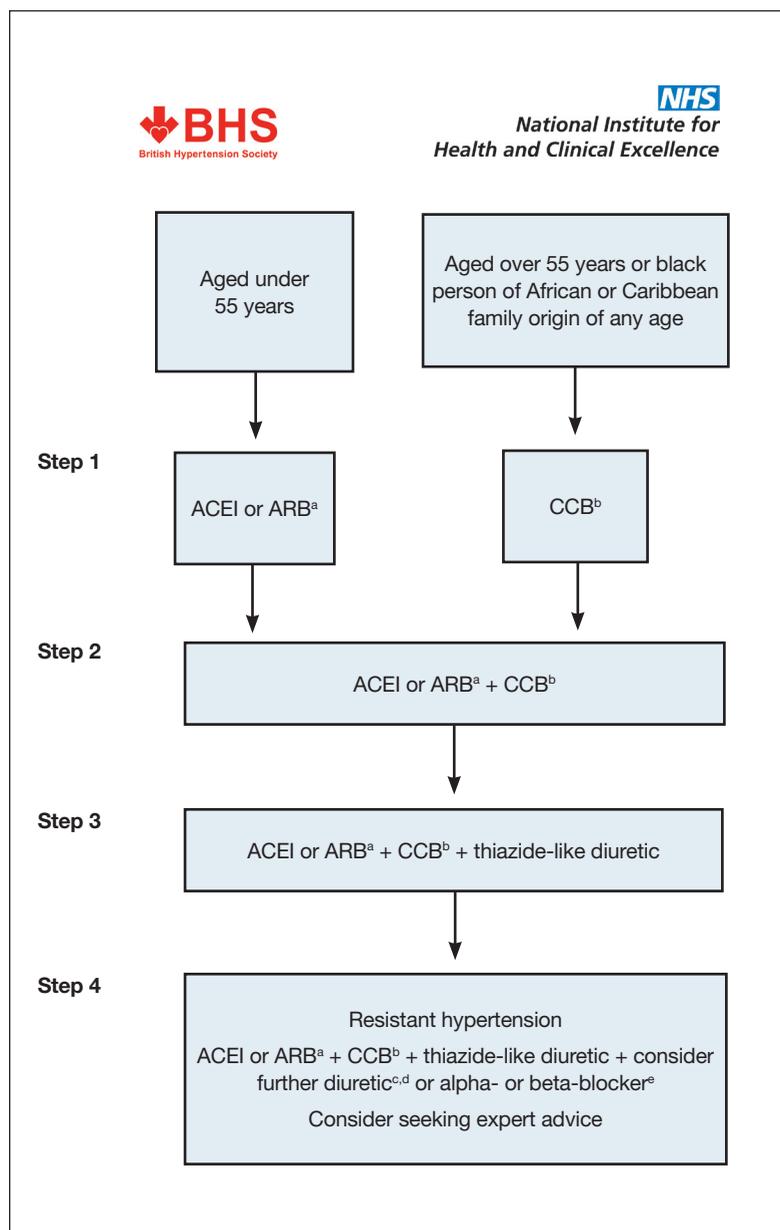
**FIGURE 2 ACCF/AHA algorithm for the management of hypertension in the elderly<sup>41</sup>**



ACCF, American College of Cardiology Foundation; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ALDO ANT, aldosterone antagonist; ARB, angiotensin II receptor blocker; BB, beta-blocker; BP, blood pressure; CA, calcium antagonist; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic BP; MI, myocardial infarction; RAS, renin-angiotensin system; SBP, systolic BP; THIAZ, thiazide diuretic.

<sup>a</sup>Combination therapy.

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**FIGURE 3** NICE algorithm for treatment of hypertension<sup>50</sup>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; NICE, National Institute for Health and Clinical Excellence.

<sup>a</sup>Choose a low-cost ARB.

<sup>b</sup>A CCB is preferred but consider a thiazide-like diuretic if a CCB is not tolerated or the person has edema, evidence of heart failure, or a high risk of heart failure.

<sup>c</sup>Consider a low dose of spironolactone<sup>d</sup> or higher doses of thiazide-like diuretic

<sup>d</sup>At the time of publication (August 2011), spironolactone did not have a UK marketing authorization for this indication. Informed consent should be obtained and documented.

<sup>e</sup>Consider an alpha- or beta-blocker if further diuretic therapy is not tolerated or is contraindicated or ineffective.

**Source:** National Institute for Health and Clinical Excellence (2011) CG 127 Hypertension: clinical management of primary hypertension in adults. London: NICE. Available from [www.nice.org.uk/guidance/CG127](http://www.nice.org.uk/guidance/CG127). Reproduced with permission. The NICE guidance that this algorithm relates to was prepared for the National Health Service in England and Wales. NICE guidance does not apply to the United States and NICE has not been involved in the development or adaptation of any guidance for use in the United States.

therapy with 2 or more of the therapies summarized in **TABLE 2**.<sup>41,49</sup> The panel's algorithm for the management of hypertension in the elderly is depicted in **FIGURE 2**.<sup>41</sup>

The National Institute for Health and Clinical Excellence (NICE), the United Kingdom-based clinical guideline development organization, recommends in its 2011 guidelines for the clinical management of primary hypertension in adults that patients less than 55 years of age, not of black African or Caribbean heritage, begin treatment with an ACEI or ARB.<sup>50</sup> The guidelines do not recommend beta-blockers for initial therapy, noting that they should be considered only in younger patients with intolerance or contraindications to ACEIs and ARBs, reproductive-aged women, and those with clinical evidence of increased sympathetic drive.<sup>50</sup>

In contrast, patients 55 years and older, or blacks of African or Caribbean origin of any age, should begin treatment with a calcium channel blocker (CCB).<sup>50</sup> If they cannot tolerate a CCB, or for those with HF (or at high risk of HF), the guidelines recommend beginning therapy with a diuretic (preferably chlorthalidone or indapamide unless the patient's hypertension is already controlled with bendroflumethiazide or HCTZ).

If initial treatment fails to lower BP adequately, step 2 of the NICE guidelines for all populations is treatment with an ACEI or ARB in combination with a calcium antagonist.<sup>50</sup> If further therapy is necessary (step 3), a thiazide diuretic (or thiazide-like) should be added to that combination. It is also recommended that patients with drug-resistant hypertension (ie, taking 3 agents at maximally tolerated doses, 1 of which should be a diuretic) should receive additional treatment with low-dose spironolactone (if their serum potassium level is  $\leq 4.5$  mmol/L) and higher-dose thiazide-type diuretics (if their serum potassium level is  $> 4.5$  mmol/L). If the diuretic is not tolerated or is ineffective, an alpha- or beta-blocker may be added. If patients continue to exhibit continued resistance, NICE recommends referral to a hypertension specialist. The NICE algorithm for the treatment of hypertension is shown in **FIGURE 3**.<sup>50</sup>

The ACCF/AHA and NICE guidelines also recommend that clinicians monitor electrolyte

levels of patients on ACEIs/ARBs, with the frequency depending on each patient's medical condition.<sup>41,50</sup>

## Conclusion

With 7 major classes of antihypertensive drugs and several drugs within each class, there are numerous combinations available to clinicians to manage hypertension. Existing clinical trials cannot possibly evaluate all possible combinations. Yet, as noted in the ASH statement on combination therapy, the importance of achieving goal BP in individual patients cannot be overemphasized because small differences in on-treatment BP translate into major differences in the rates of CV events.<sup>47</sup> When considering appropriate and effective antihypertensive therapies, clinicians should assess the evidence presented in this article and from the various clinical guidelines cited. Each patient is unique and it is important for clinicians to identify the most-effective treatment regimen for each individual patient. ■

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## MODULE 2:

# Rethinking the Role of Thiazide-Type Diuretics in the Management of Hypertension: Which Diuretic Is Best?

William C. Cushman, MD

## Background

Despite the availability of 7 major classes of effective and safe antihypertensive medications and numerous combination drugs designed to reduce pill burden and improve adherence, just 50.1% of the estimated 76.4 million US adults with hypertension (33.5% of the population) have their condition under control.<sup>1</sup>

One of the greatest challenges for clinicians who manage patients with hypertension is choosing the most appropriate drug, whether as initial treatment or add-on therapy. Clinicians may be guided in this decision, however, by guidelines and algorithms that are provided for hypertension management. These algorithms are reviewed in the first article in this supplement by Dr William B. White.

National guidelines recommend thiazide-type diuretics as initial therapy for most patients with hypertension, regardless of the severity of the condition, either alone or in combination with 1 of the other classes of hypertension medications that have also been shown to reduce 1 or more hypertensive complications in randomized controlled outcome trials.<sup>2,3</sup> These recommendations are based primarily on more than 50 years of data on the safety and efficacy of thiazide-type diuretics.

The first evidence of the benefits of thiazide-type diuretics came from publications of the VA (Veterans Administration) Cooperative Study in 1967 and 1970. It was the first trial to demonstrate reduced stroke, heart failure (HF), and progressive kidney damage in patients receiving antihypertensive treatment, including the then-newly released hydrochlorothiazide (HCTZ), a thiazide diuretic.<sup>4</sup>

Since then, hundreds of clinical trials have demonstrated the efficacy of thiazide-type diuretics. During that

time, however, numerous other classes of antihypertensive medications were introduced, leading to the question of the appropriate place of thiazides within the antihypertensive arsenal. The seminal trial to answer this question was the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). This randomized, double-blind, multicenter, clinical trial was designed to determine whether the occurrence of fatal coronary heart disease (CHD) or nonfatal myocardial infarction (MI) was lower for high-risk hypertensive patients 55 years of age and older who were treated with the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor (ACEI) lisinopril, or the alpha-blocker doxazosin compared with the thiazide-type diuretic chlorthalidone (CTD).<sup>5</sup> Investigators could add atenolol, clonidine, reserpine, and/or hydralazine as necessary to achieve blood pressure (BP) goal. The trial randomized 42,418 patients, 90% of whom had been previously treated.

At a mean follow-up of 4.9 years, there was no significant difference in the primary outcome or mortality between the 4 drugs.<sup>5</sup> There was a 38% higher rate of HF with amlodipine, and a 10%, 15%, and 19% higher rate of cardiovascular disease (CVD), stroke, and HF, respectively, with lisinopril compared with CTD. For stroke, there was a statistically significant race-by-treatment interaction (40% higher stroke rate with lisinopril vs CTD in black participants). Participants in the doxazosin treatment group (n = 9061) were followed for a mean of 3.2 years. This arm was terminated early because of a 25% higher incidence of CVD events, including a nearly 2-fold higher risk of HF, accompanied by a low probability of reaching a statistically significant difference in the primary endpoint.<sup>5</sup>

Additional rationale for the use of diuretics in elderly populations came from the Systolic Hypertension in the Elderly Program (SHEP), a multicenter, randomized, double-blind, placebo-controlled trial of patients aged 60 years and older.<sup>6</sup> Participants were randomized to either CTD 12.5 to 25 mg once daily ± atenolol 25 to 50 mg once daily, or reserpine 0.05 mg once daily, or placebo. Treatment reduced

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William C. Cushman, MD, Professor of Preventive Medicine, Medicine, and Physiology, University of Tennessee College of Medicine, Chief, Preventive Medicine Section, Veterans Affairs Medical Center, Memphis, TN

## DISCLOSURE

Dr Cushman is a paid consultant to Daiichi-Sankyo, Inc; Merck & Co, Inc; Omron Healthcare, Inc; and Takeda Pharmaceuticals International, Inc. He has performed contracted research for Merck & Co, Inc.

the incidence of all fatal and nonfatal strokes by 36%, MI by 27%, all CHD by 27%, and all CVD by 32%.<sup>6</sup>

### Underuse of diuretics

Despite trials such as SHEP and ALLHAT, and despite the long record of safety and efficacy in numerous patient populations, thiazide-type diuretics remain significantly underused in clinical practice.<sup>7-10</sup>

Even intensive academic detailing designed to increase the use of thiazide-type diuretics found that the prescribing rates of 37.1% immediately before the intervention only increased to 39.6% overall after the intervention (46.5% in areas that received the most intensive intervention), reflecting what appears to be clinical resistance to this class of drugs (FIGURE 1).<sup>11</sup> Even 4 years after the ALLHAT results were published, national use of thiazide-type drugs had not increased significantly.<sup>12</sup>

### Hydrochlorothiazide and chlorthalidone: Similarities and differences

Underuse of thiazide-type diuretics is just 1 challenge. Others include which diuretic to use (HCTZ or CTD) and at what dosage.<sup>13-17</sup> These 2 diuretics were approved at about the same time and, until recently, were considered equivalent and interchangeable despite differences in structure, pharmacokinetics, and pharmacodynamics.<sup>16,17</sup>

The publication of the VA Cooperative Morbidity Trial, the successful marketing and popularity of HCTZ and low-dose HCTZ/triamterene, the fear of hypokalemia (which

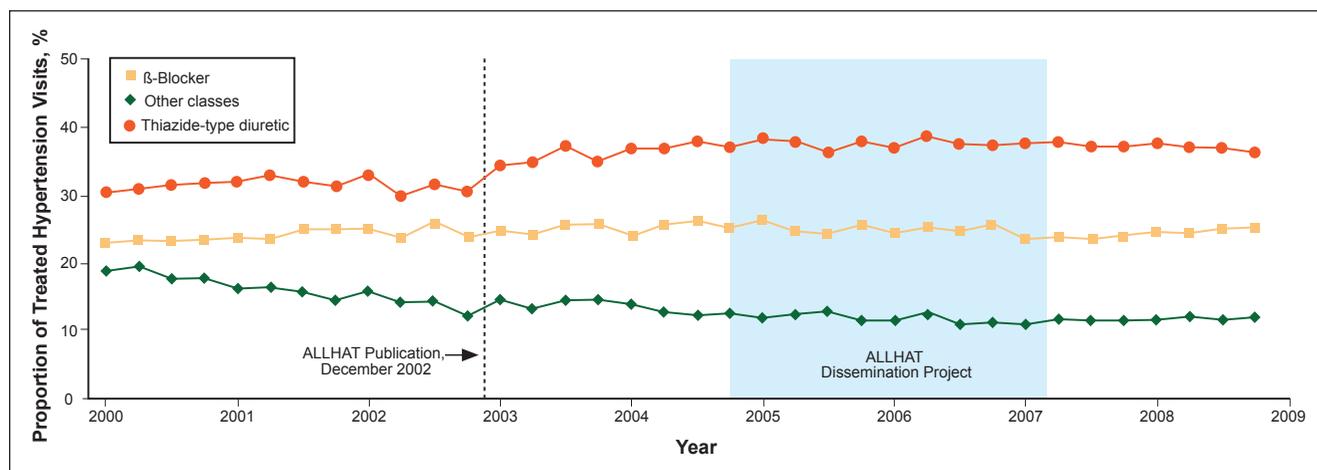
was seen more often in the high doses of CTD initially used), and the subsequent inclusion of HCTZ as the primary diuretic in single-pill combination antihypertensives with ACEIs and angiotensin II receptor blockers (ARBs) led to HCTZ becoming the market leader for this class. Nonetheless, CTD was the diuretic chosen for many major randomized clinical trials, especially those sponsored by the National Heart, Lung, and Blood Institute (NHLBI).<sup>5,6,18-20</sup>

One reason for CTD's relegation as a second-tier option to HCTZ could be the higher risk of hypokalemia observed at the higher dosages typically used in early studies.<sup>21-23</sup> However, later studies found that substantially lower dosages of CTD could provide similar BP reductions with a significantly lower risk of hypokalemia.<sup>24</sup> Materson et al,<sup>25</sup> for instance, demonstrated that the 25-mg dosage of CTD was at least as effective for hypertension as the 50-mg and 75-mg dosages, while the 25-mg dosage was associated with less hypokalemia.

Increasingly, however, hypertension specialists, particularly those involved in research, have come to appreciate that CTD and HCTZ are, indeed, not interchangeable and do not have dosing equivalency. This understanding, together with the results of clinical trials like ALLHAT, has led to a resurgence of interest in the use of CTD.<sup>17,19,26</sup>

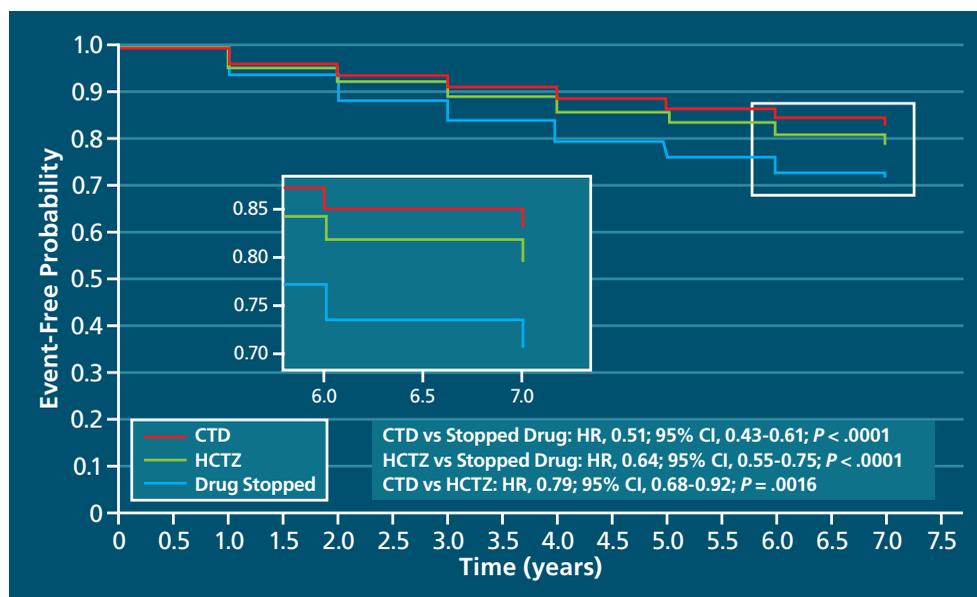
One assessment of outpatient prescription data from the VA from 2003 to 2008 found that although the proportion of patients receiving HCTZ during the period remained stable, the number of new users dropped 30% even as the proportion of thiazide users receiving CTD prescriptions

**FIGURE 1** Proportion of visits by drug class among patients with drug-treated hypertension<sup>11</sup>



Data are from the IMS Health National Disease and Therapeutic Index, 2000 through 2008. "Other classes" indicates  $\alpha$ -adrenergic receptor blockers, potassium-sparing diuretics, loop diuretics, and centrally acting agents.

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**FIGURE 2** Adjusted event-free probability of cardiovascular events<sup>30</sup>

CI, confidence interval; CTD, chlorthalidone; HCTZ, hydrochlorothiazide; HR, hazard ratio.

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doubled from 1.1% to 2.4% and the number of new prescriptions for CTD increased 40%.<sup>19</sup>

### Chlorthalidone or hydrochlorothiazide: Study outcomes

The resurgence of interest in CTD has come with the publication of trials demonstrating its benefits in reducing CVD risk.<sup>5,6,27,28</sup>

The Multiple Risk Factor Intervention Trial (MRFIT) is the only large, long-term, randomized trial to directly compare HCTZ and CTD, although not in a randomized assignment. The primary endpoint was cardiovascular (CV) outcomes. The study launched in 1973 and enrolled 12,866 males aged 35 to 57 years who were in the upper 15% risk of death from chronic heart disease.<sup>29</sup> Participants in the special care group were given HCTZ or CTD (investigator's choice) at either 50 or 100 mg daily, depending on weight and sodium levels, and were given additional drugs as needed. The control group received usual care at that time from their health care provider. A 44% higher rate of CHD mortality in the HCTZ group observed towards the latter part of the trial led its Policy Advisory Board to change the option between the 2 diuretics and require CTD only. Following the change, the rate of CHD mortality decreased by 28% ( $P = .04$  for comparison between the 2 time frames).<sup>29</sup>

A recent retrospective analysis of MRFIT found significantly lower CV event rates in participants who received either CTD or HCTZ than in those receiving neither (CTD: adjusted hazard ratio [aHR], 0.51; 95% confidence interval [CI], 0.43-0.61;  $P < .0001$ ; HCTZ: aHR, 0.65; 95% CI, 0.55-0.75;  $P < .0001$ ), but rates of non-fatal CV events were significantly lower in participants who received CTD than those who received HCTZ (aHR, 0.79; 95% CI, 0.68-0.92;  $P < .0016$ ).<sup>30</sup> The results are depicted in **FIGURE 2**.<sup>30</sup>

A recent meta-analysis of 108 trials with HCTZ and 29 with CTD found that the 2 drugs did not provide equivalent reductions in systolic BP (SBP) within equivalent dosages. The study found that the median change in SBP with the median dose of HCTZ was  $-17$  mm Hg, compared with  $-26$  mm Hg for CTD. The slightly greater potassium loss observed with CTD was still nearly equivalent to that observed with HCTZ.<sup>31</sup>

### Considerations for greater chlorthalidone efficacy

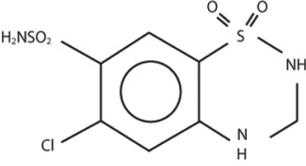
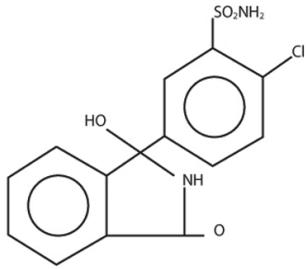
The differences between CTD and HCTZ, despite similar molecular structures, is a topic of much discussion.<sup>23</sup> It is likely that these 2 drugs have different pharmacokinetic and pharmacodynamic properties, as shown in **TABLE 1**.<sup>17</sup>

There is also evidence from an in vitro study that, compared with HCTZ, CTD has additional pleiotropic effects: reducing carbonic anhydrase activity, platelet aggregation, and vascular permeability while promoting angiogenesis.<sup>32</sup>

Another reason for the differences in efficacy between CTD and HCTZ could be the dosages of HCTZ used. Worldwide, nearly all prescriptions for HCTZ are for 12.5 to 25 mg/d, while most modern combination pills containing HCTZ incorporate these lower dosages.<sup>33</sup> However, there is little evidence that such dosages lead to significantly improved outcomes.<sup>14,19,34-36</sup>

This was an issue in the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. This study was

**TABLE 1** Pharmacokinetic/pharmacodynamic comparison of hydrochlorothiazide and chlorthalidone<sup>17</sup>

	Onset (h)	Peak (h)	Half-life (h)	Duration (h)
Hydrochlorothiazide 	2	4-6	6-9 (single dose) 8-15 (long-term dosing)	12 (single dose) 16-24 (long-term dosing)
Chlorthalidone 	2-3	2-6	40 (single dose) 45-60 (long-term dosing)	24-48 (single dose) 48-72 (long-term dosing)

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designed to compare first-step therapy with benazepril/HCTZ 20/12.5 mg.<sup>37</sup> Benazepril was force-titrated to 40 mg in each arm, whereas HCTZ and amlodipine were titrated to 25 mg and 10 mg, respectively, only if needed for BP control. The study was conducted in 11,506 high-risk patients 55 years of age and older. Other antihypertensive drugs could be added as needed for BP control. The study was stopped early after a mean follow-up of 36 months when the benazepril/amlodipine group demonstrated an HR of 0.8 (95% CI, 0.72-0.90) for the composite outcome of death from CV events, nonfatal MI or stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization compared with the benazepril/HCTZ group.<sup>37</sup>

The ACCOMPLISH trial has been controversial for many reasons, with editorials suggesting that its design led to a “stacked deck” that favored amlodipine/benazepril over benazepril/HCTZ. Questions were raised as to why HCTZ was the diuretic of choice because CTD has been used in most thiazide-type trials. The dosages chosen were also questioned because outcome trials demonstrating reduced CV events with HCTZ used target doses of 50 mg/d or higher.<sup>14,21,22,38</sup>

Indeed, a meta-analysis published in 2011 found that despite the extensive use of HCTZ worldwide, the 12.5 to

25 mg dosage was inferior in reducing BP compared with standard doses of other antihypertensive agents (ACEIs, ARBs, beta blockers, and calcium channel blockers) in studies using 24-hour ambulatory BP monitoring.<sup>33</sup> The efficacy of HCTZ closely mirrors that of the other drug classes at the 50-mg level, although that dose results in somewhat higher rates of hypokalemia. As the dose of HCTZ is increased to 100 mg, there is little or no further increase in antihypertensive efficacy, but hypokalemia becomes much more common.<sup>39</sup>

Thus, it can be clinically challenging to prescribe the optimum BP medication if practitioners prefer to use single-pill combinations that include HCTZ. Although the use of such single-pill combinations is warranted, particularly given the improved adherence with taking single-pill combinations compared with taking 2 or 3 pills, as noted in **TABLE 1**, most combinations include HCTZ dosages of 12.5 to 25 mg, which will often be less effective than full doses of 2 other medications.

## Conclusion

Although thiazide-type diuretics are recommended as first-line therapy for most patients with hypertension, either alone or in combination with other classes of antihyperten-

sives, they remain underused in clinical practice. In addition, HCTZ, which is the most commonly used diuretic (indeed, the most commonly prescribed antihypertensive) is prescribed at dosages too low to provide sufficient clinical efficacy in BP reduction and lower than what was proven to reduce CV events in clinical trials.

Chlorthalidone, a diuretic often considered a thiazide-type diuretic, has demonstrated superiority to HCTZ in reducing BP as evidenced in the MRFIT study and has been shown in numerous clinical trials to provide similar if not greater efficacy than other classes of antihypertensives in reducing BP, stroke, and CV events, with a good safety profile.

Clinicians need to manage patients with hypertension on an individual basis, selecting drugs and antihypertensive medication classes with the best outcomes in trials and then determining the most efficacious therapies with the lowest risk of adverse events for each patient. However, when prescribing a diuretic, they should also ensure that the drug used is prescribed at the appropriate therapeutic dosage level to enable patients to prevent the CV, thrombotic, and renal events that occur with long-term hypertension. ■

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# Using Thiazide-Type Diuretics in African Americans with Hypertension

Jackson T. Wright, Jr, MD, PhD

## Introduction

Hypertension and hypertensive target organ damage are more prevalent and more severe in certain minority populations, especially African Americans. Hypertension is more common, more severe, develops at an earlier age, and leads to greater morbidity and mortality in African Americans than in age-matched non-Hispanic whites.<sup>1</sup> African Americans have among the highest rates of hypertension in the world (41% overall, 44% among black women) and develop the condition an average of 5 years earlier than whites.<sup>1</sup>

A recent report found that although treatment rates between whites and African Americans overall are similar, a smaller percentage of African Americans with hypertension are controlled to <140/90 mm Hg compared with whites.<sup>2</sup> This may at least partly explain the 4 to 5 times higher hypertension-related mortality, 2 to 4 times increased risk of left ventricular hypertrophy (LVH), coronary heart disease (CHD), congestive heart failure, and stroke, and the 4 times higher rate of end-stage renal disease (ESRD) in African Americans compared with whites.<sup>1,3</sup> The higher prevalence of diabetes mellitus, cigarette smoking, obesity, lipid disorders, and LVH in blacks exacerbates the existing risk posed by hypertension, making the need for aggressive blood pressure (BP) control even more critical.<sup>1</sup>

## Antihypertensive treatment in African Americans

Lifestyle modification is recommended for all hypertensive patients but is especially important for African Americans. This population has a greater prevalence of obesity than whites, so weight loss is critical.<sup>4</sup> Further, African Americans tend to have a greater sensitivity to salt because of a combination of obesity, abnormalities in renal salt handling, and a tendency to consume a high salt/low potassium diet.<sup>3</sup> Afri-

can Americans have been shown to benefit at least as much as other subgroups with hypertension from reductions in dietary salt and improvements in diet quality, such as the Dietary Approaches to Stop Hypertension (DASH) diet.<sup>5-7</sup>

Several studies have documented the efficacy of diuretics in lowering BP in African Americans.<sup>3,8-10</sup> In the Anti-hypertensive and Lipid-Lowering to Prevent Heart Attack Trial (ALLHAT), treatment initiated with the thiazide-type diuretic (THZD) chlorthalidone (CTD) reduced systolic BP (SBP) by 4 mm Hg more than treatment based on the angiotensin-converting enzyme inhibitor (ACEI) lisinopril or the alpha-blocker doxazosin in black ALLHAT participants who were receiving similar background antihypertensive drug treatment.<sup>9,10</sup> The greater BP lowering in the THZD arm was associated with a significantly reduced rate in 1 or more cardiovascular disease (CVD) outcomes. Other inhibitors of the renin-angiotensin system (eg, angiotensin-receptor blockers [ARBs], direct renin inhibitors, and beta-blockers) are similarly less effective in lowering BP in African Americans.<sup>3</sup> In contrast, when the calcium channel blocker (CCB) amlodipine was compared with CTD in blacks or when CTD was compared with lisinopril or doxazosin in nonblacks, SBP reductions were only ~1 mm Hg.<sup>8,10</sup>

As a class, diuretics have been shown to decrease hypertension-related morbidity and mortality in both African Americans and whites.<sup>10-15</sup> In fact, much of the evidence for the benefits of antihypertensive therapy in preventing hypertension-related morbidity and mortality was conducted with THZDs, with several of the relevant trials containing significant numbers of African American participants (**TABLE 1**).<sup>8,10,13-16</sup>

In the Veterans Administration (VA) Cooperative Trial, African American men comprised 42% of participants, all of whom were randomized to a combination of hydrochlorothiazide, reserpine, and hydralazine, or to placebo.<sup>13</sup> In the Hypertension Detection and Follow-Up Program (HDFP) trial, 44% of participants were African American. All participants were randomized to stepped therapy with CTD, reserpine, methyldopa, and hydralazine, or to usual community care.<sup>14</sup> Both of these pioneering trials documented the benefit of a THZD-based regimen in lowering BP and

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Jackson T. Wright, Jr, MD, PhD, Professor of Medicine, Program Director, William T. Dahms M.D. Clinical Research Unit, Director of Clinical Hypertension Program, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH

## DISCLOSURE

Dr Wright is a paid consultant to The Medical Letter, Inc, and Takeda Pharmaceuticals International, Inc. He is on an advisory board of Medtronic, Inc.

**TABLE 1** Outcomes of major clinical trials of diuretics in African Americans

Clinical trial	Relative risk reduction (RRR) or hazard ratio (HR) by endpoint					
	Mortality	CVD	CHD	Stroke	HF	ESRD
<b>VA Cooperative:</b> HCTZ + RES + HYD vs placebo (RRR) <sup>13</sup>		0.46				
<b>HDFP:</b> stepped therapy with CTD vs usual care (HR) <sup>14</sup>	0.76 <sup>a</sup>					
<b>SHEP:</b> CTD + atenolol vs placebo (HR) <sup>15</sup>				0.68 <sup>a</sup>		
<b>ALLHAT:</b> All African Americans (RRR) <sup>8,10</sup>						
AML vs CTD	0.97	1.06	1.03	0.93	1.46 <sup>a</sup>	1.15
DOX vs CTD	N/A	1.28 <sup>a</sup>	1.11	1.38 <sup>a</sup>	1.84 <sup>a</sup>	0.99
LIS vs CTD	1.06	1.19 <sup>a</sup>	1.15 <sup>a</sup>	1.40 <sup>a</sup>	1.30 <sup>a</sup>	1.29
<b>ALLHAT:</b> African Americans with diabetes and metabolic syndrome (RRR) <sup>16</sup>						
AML vs CTD	1.02	1.14 <sup>a</sup>	1.09	1.01	1.50	1.50
DOX vs CTD	1.18	1.37 <sup>a</sup>	1.15	1.49 <sup>a</sup>	1.88 <sup>a</sup>	1.17
LIS vs CTD	0.96	1.24 <sup>a</sup>	1.19 <sup>a</sup>	1.37 <sup>a</sup>	1.49 <sup>a</sup>	1.70 <sup>a</sup>

ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; AML, amlodipine; CHD, coronary heart disease; CTD, chlorthalidone; CVD, cardiovascular disease; DOX, doxazosin; ESRD, end-stage renal disease; HCTZ, hydrochlorothiazide; HDFP, Hypertension Detection and Follow-up Program; HF, heart failure; HYD, hydralazine; LIS, lisinopril; RES, reserpine; SHEP, Systolic Hypertension in the Elderly Program; VA, Veterans Administration

<sup>a</sup>P ≤ 0.05

improving clinical outcomes in African Americans with hypertension. The Systolic Hypertension in the Elderly Program (SHEP) trial, in which 14% of participants were African American, extended earlier results from the VA Cooperative and HDFP trials by demonstrating that, compared with placebo, active treatment with CTD and the beta-blocker atenolol produced clinical outcome reductions in African Americans and whites with isolated systolic hypertension as well as in those with elevated diastolic BP.<sup>15</sup>

In comparative trials with newer classes of antihypertensives, THZDs have remained unsurpassed in preventing complications of hypertension, including in African Americans (TABLE 1). ALLHAT was the first outcome study to evaluate the relative benefit of antihypertensive treatment initiated with newer classes of antihypertensive agents vs treatment initiated with a THZD in blacks. ALLHAT included more than 15,000 African Americans and Afro-Caribbeans and confirmed the findings of studies in other populations that neither an ACEI, a CCB, or alpha-blocker-initiated therapy surpassed therapy initiated with a THZD (CTD) in lowering BP or in preventing CVD or renal outcomes.<sup>8,10</sup> Overall, the THZD-based therapy was superior to the alpha-blocker, ACEI, and CCB-based therapies in preventing 1 or more major forms of CVD, including stroke and heart failure (HF). In blacks, THZD-based therapy was superior to alpha-blocker-based therapy in lowering BP and in preventing overall CVD (especially HF and stroke), and was superior to

the ACEI-based regimen in preventing stroke, HF, and overall CVD (a composite of CHD, stroke, and HF endpoints). Compared with CCB-based therapy (ie, amlodipine), THZD (CTD)-based therapy was similar in overall CVD protection but superior in preventing HF.

These results in ALLHAT were even more impressive in blacks with diabetes or the metabolic syndrome (TABLE 1).<sup>16</sup> In addition to the above-mentioned CVD outcomes in black hypertensive patients, neither the CCB-based nor the ACEI-based regimens were superior to the THZD-based regimen in preventing ESRD overall or when stratified by diabetes or baseline estimated glomerular filtration rate.<sup>10,16,17</sup> In black ALLHAT participants with diabetes or the metabolic syndrome, CTD was associated with substantially reduced rates of ESRD compared with those randomized to doxazosin, amlodipine, or the ACEI lisinopril.<sup>16</sup> It should also be noted that nearly all previous renal outcome trials with renin-angiotensin system inhibitors included background therapy with a diuretic.<sup>17</sup>

## Recommendations

Most national and international guidelines recommend THZDs as first-line therapy in African Americans.<sup>18-21</sup> Calcium channel blockers are a reasonable alternate first-line choice in African Americans who are unable to tolerate a diuretic.

In addition, the Joint National Committee (JNC-7) guidelines recommend the use of ACEIs and ARBs as first-

line therapy in all patients with hypertension comorbid with chronic kidney disease (CKD) or HF, including African Americans.<sup>18</sup> These drugs, along with alpha-blockers and all other agents in the antihypertensive armamentarium, should be used as add-on therapy, as needed, to achieve BP goals in African Americans already receiving a THZD or CCB.

Importantly, multiple drug therapy should be considered for initial treatment in all individuals whose BP is more than 20/10 mm Hg above target.<sup>18</sup> In addition, multiple antihypertensive agents are usually required to achieve long-term control in most patients, particularly in African Americans who, as noted earlier, tend to have more-severe hypertension.<sup>19</sup>

## Conclusion

Treatment of hypertension in African Americans should include both lifestyle modifications and pharmacologic intervention, usually with multiple agents. In the absence of compelling indications for alternative therapies, THZD-based regimens should be considered first-line treatment given significant evidence from large randomized studies that document their ability to reduce both BP and hypertensive complications in this population.

Monotherapy with ACEIs, ARBs, direct renin inhibitors, or beta-blockers is less effective in lowering BP in African Americans than in other populations. ACEIs and ARBs should be included in antihypertensive regimens prescribed for African Americans with concomitant CKD or HF. They can also be considered as add-on therapy to regimens containing a THZD or CCB in the absence of these conditions. ■

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# Enhancing Adherence with Antihypertensives: The Role of Fixed-Dose Combinations and Home Blood Pressure Monitoring

Louis Kuritzky, MD

**A**lthough an estimated 1 out of 3 people in the United States has been diagnosed with hypertension, data from the 2007-2008 National Health and Nutrition Examination Survey found that just 72% are currently being treated and, of those, just half have their blood pressure (BP) controlled with lifestyle changes and/or medication.<sup>1</sup>

The failure of so many people with hypertension to obtain BP control, despite the availability of numerous effective medications, is partially due to a lack of adherence to recommended treatments (eg, taking medication, following a diet, and executing lifestyle changes). Adherence is a significant problem in hypertension and evidence shows that just half of patients who initiate drug therapy are persistent with treatment after 1 year.<sup>2</sup>

Although few studies link nonadherence with long-term outcomes, 1 study found that patients who “forgot” to take their antihypertensive medication were nearly one-third more likely to experience a cardiovascular event or death (hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.04-1.57).<sup>3</sup> Adherence is important not only for the health of the patient, but also to provide overall cost savings from the reductions of hospitalizations for complications from an untreated disease.<sup>4</sup>

## Barriers to adherence

A significant contributor to nonadherence is treatment complexity, which manifests in hypertension as pill burden. Up to 75% of patients will require more than 1 medication to control their BP; those with resistant hypertension will require 4 or more.<sup>5,6</sup> These medications must often be taken at different times of the day, with varying frequency.<sup>6-9</sup>

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Louis Kuritzky, MD, Clinical Assistant Professor, Department of Community Health and Family Medicine, University of Florida, Gainesville, FL

## DISCLOSURE

Dr Kuritzky is a paid consultant to Takeda Pharmaceuticals International, Inc.

Reducing the number of daily doses has been consistently found to enhance adherence, and should be considered routinely as a first-line strategy. Complex strategies (eg, group visits, designated office staff to assist hypertensive patients, pharmacist consultation and comanagement, exercise counseling, dietary counseling, multidisciplinary hypertension team care, specific interviewing techniques such as motivational interviewing) are promising, but individual clinicians may not have the resources to take advantage of such labor-intensive intervention. Further, when multimodal intervention is employed, it is often difficult to discern which component(s) of the intervention were most impactful, unless multifactorial study design is employed, which it rarely is. We await further randomized controlled trials in this regard.

A study of approximately 85,000 members of a large managed care organization found that the greater the number of antihypertensive medications prescribed, the lower the rate of patient adherence. Just 63% of those receiving 3-drug regimens and 55% of those receiving 4-drug regimens were completely adherent.<sup>10</sup>

In addition, many patients with hypertension, particularly older patients, have comorbid conditions (eg, dyslipidemia or diabetes) that also require treatment, leading to increased treatment complexity and pill burden.<sup>11,12</sup>

One option for reducing pill burden is the use of fixed-dose therapies (**TABLE**). Since 2000, many new fixed-dose combinations, including at least 3 triple therapies, have entered the market.<sup>13</sup> In addition, a so-called “poly-pill” that combines aspirin, 3 antihypertensives, and a statin is under investigation and demonstrating good results in reducing BP and cholesterol levels.<sup>14</sup>

Studies have found that patients receiving fixed-dose combination pills are more likely to reach their target BP, physicians are more satisfied with their ability to manage hypertension, and adverse effects are either similar or less with the fixed-dose therapies compared with monotherapies.<sup>15,16</sup>

Studies of adherence patterns among patients treated with fixed-dose combinations of antihypertensive agents

**TABLE** Currently available combination therapies

Fixed-Dose Combination	Brand Name	Dose Range, Total, mg/d <sup>a</sup>
<b>Angiotensin II Receptor Blocker + Thiazide Diuretic</b>		
Azilsartan/chlorthalidone	Edarbyclor	40/12.5; 40/25
Candesartan/HCTZ	Atacand HCT	16/12.5; 32/12.5; 32/25
Eprosartan/HCTZ	Teveten HCT	600/12.5; 600/25
Irbesartan/HCTZ	Avalide	150/12.5; 300/25
Losartan/HCTZ	Hyzaar	50/12.5; 100/12.5; 100/25
Olmesartan/HCTZ	Benicar HCT	20/12.5; 30/12.5
Telmisartan/HCTZ	Micardis HCT	40/12.5; 80/12.5; 80/25
Valsartan/HCTZ	Diovan HCT	80/12.5; 160/12.5; 160/25; 320/12.5
<b>β-Blocker + Thiazide Diuretic</b>		
Atenolol/chlorthalidone	Tenoretic	50/25; 100/25
Bisoprolol/HCTZ	Ziac	2.5/6.25; 5/6.25; 10/6.25
Metoprolol tartrate/HCTZ	Lopressor HCT	50/25; 100/25; 100/50
Metoprolol succinate extended/release + HCTZ	Dutoprol	25/12.5; 50/12.5; 100/12.5
Nadolol + bendroflumethiazide	Corzide	40/5; 80/5
Propranolol + HCTZ	Inderide	40/25; 80/25
<b>Calcium Channel Blocker + ACEI</b>		
Amlodipine/benazepril	Lotrel	2.5/10; 5/10; 5/20; 5/40; 10/20; 10/40
<b>ACEI + Thiazide Diuretic</b>		
Benazepril/HCTZ	Lotensin HCT	5/6.25; 10/12.5; 20/12.5; 20/25
Captopril/HCTZ	Capozide	25/15; 25/25; 50/15; 50/25
Enalapril/HCTZ	Vaseretic	10/25 (1-2)
Fosinopril/HCTZ	Monopril HCT	10/12.5; 20/12.5
Lisinopril/HCTZ	Prinzide Zestoretic	10/12.5; 20/12.5 20/25
Moexipril/HCTZ	Uniretic	7.5/12.5; 15/12.5; 15/25
Quinapril + HCTZ	Accuretic	10/12.5; 20/12.5; 20/25
<b>ACEI + Calcium Channel Blocker</b>		
Trandolapril/verapamil	Tarka	2/180; 2/240; 4/240
Enalapril/felodipine	Lexxel	5/5
<b>Angiotensin II Receptor Blocker + Calcium Channel Blocker</b>		
Telmisartan/amlodipine	Twynsta	40/5; 40/10; 80/5; 80/10
<b>Angiotensin II Receptor Blocker + Calcium Channel Blocker + Thiazide Diuretic</b>		
Olmesartan/amlodipine/HCTZ	Tribenzor	40/10/25
<b>Calcium Channel Blocker + Angiotensin II Receptor Blocker</b>		
Amlodipine/olmesartan	Azor	5/20; 5/40; 10/20; 10/40
Amlodipine/valsartan	Exforge	5/160; 10/160; 5/320; 10/320

CONTINUED

**TABLE** Currently available combination therapies (continued)

<b>Calcium Channel Blocker + Angiotensin II Receptor Blocker + Thiazide Diuretic</b>		
Amlodipine/valsartan/HCTZ	Exforge HCT	5/160/12.5; 10/160/12.5; 5/160/25; 10/160/25; 10/320/25
<b>Central <math>\alpha</math>-Agonist + Thiazide Diuretic</b>		
Methyldopa/HCTZ	Aldoril Aldoril D	250/15; 250/25 500/30; 500/50
<b>Direct Renin Inhibitor + Angiotensin II Receptor Blocker</b>		
Aliskiren/valsartan	Valturna	150/160; 300/320
<b>Direct Renin Inhibitor + Calcium Channel Blocker</b>		
Aliskiren + amlodipine	Tekamlo	150/5; 150/10; 300/5; 300/10
<b>Direct Renin Inhibitor + Thiazide Diuretic</b>		
Aliskiren/HCTZ	Tekturna HCT	150/12.5; 150/25; 300/12.5; 300/25
<b>Direct Renin Inhibitor + Calcium Channel Blocker + Thiazide Diuretic</b>		
Aliskiren/amlodipine/HCTZ	Amturnide	150/5/12.5; 300/5/12.5; 300/5/25; 300/10/12.5; 300/10/25
<b>Diuretic Combination (K<sup>+</sup> Sparing + Thiazide)</b>		
Amiloride/HCTZ	Several generics	5/50 (1-2)
Spirolactone/HCTZ	Aldactazide	25/25 (1/2-1)
Triamterene/HCTZ	Dyazide Maxide	37.5/25 (1/2-1) 37.5/25; 75/50

ACEI, angiotensin-converting enzyme inhibitor; HCTZ, hydrochlorothiazide.

\*All 1 dose/d unless otherwise noted.

**Source:** Available at: <http://www.RxList.com>; <http://www.Drugs.com>; <http://www.empr.com/combination-treatments-for-hypertension-chart/article/191718/>. Accessed June 27-28, 2012.

vs separate antihypertensive agents demonstrate increased adherence among patients treated with fixed-dose combinations.<sup>17-21</sup> In a clinical trial involving 4146 participants who were treated with a fixed dose of amlodipine and atorvastatin or separate pills, 33% of patients in the fixed-dose cohort had ceased treatment by 12 months compared with 59% of patients who were taking the 2-pill regimen (HR, 2.17; 95% CI, 2.05-2.13;  $P < .0001$ ), resulting in a 117% higher rate of nonadherence in the 2-pill regimen. The median persistence time (ie, time to discontinuation with medication) was 8 months with the 2-pill regimen, but 37 months or longer with the fixed-dose combination.<sup>21</sup>

A meta-analysis of 9 studies found that fixed-dose combinations reduced the risk of nonadherence by 26% compared with single-pill combination therapy.<sup>22</sup>

One downside to fixed-dose therapy is cost. Out-of-pocket costs are a significant barrier to medication adherence and most fixed-dose options are branded drugs that generally require higher copayments or coinsurance vs generic single-pill drugs that may have copayments as low as \$4.<sup>6</sup>

### Other opportunities to improve adherence to antihypertensive medications

Other evidence-based opportunities to improve adherence to antihypertensive medications include improved relationships with, and communication from, health care providers, given that patients often do not understand their disease and recommended treatments.<sup>23,24</sup>

Interviews with 826 patients with hypertension found that although 90% knew that lowering their BP would improve their health and 91% reported that a health care provider had told them that they had hypertension or high BP, 41% did not know their BP level. In addition, just 34% of patients with hypertension identified systolic BP (SBP) as the “top” number of their reading and only 32% identified diastolic BP (DBP) as the “bottom” number. Finally, only one-third of patients were able to identify both SBP and DBP, and one-quarter of them did not know the optimal level for either.<sup>25</sup>

Other provider interventions that have resulted in improved adherence include changing medication to reduce or avoid adverse effects, simplifying dosing (as described ear-

lier), and switching to less-expensive drugs if cost is an issue. Nurses and pharmacists are also important members of the team when it comes to improving adherence and reinforcing education.<sup>24</sup>

### Home blood pressure monitoring

Another reason for nonadherence is that patients may not believe they need treatment since hypertension rarely manifests with symptoms. Furthermore, patients may not perceive that the medication they take has any effect because they did not have symptoms to begin with. Home BP monitoring (HBPM), or self BP monitoring, is one tool for improving adherence, possibly by providing immediate feedback to patients on how well their BP is controlled.<sup>26</sup> Many major medical societies recommend HBPM as part of any hypertension management strategy.<sup>27-30</sup>

Patients who use HBPM can avoid many limitations associated with office BP monitoring (OBPM), including poor measurement techniques, infrequent measurement, white coat hypertension, and masked hypertension. Patients can also avoid reverse white coat hypertension, where OBPM is normal although out-of-office BP is high.<sup>28</sup> Patients should take 3 readings at 1-minute intervals, usually in the morning and evening. The weekly average of these readings is their home BP (normotension is defined as an average BP <135/85 mm Hg).<sup>31</sup> Typically, the HBPM monitoring is more accurate in identifying risk than OBPM when there are discrepancies between them.<sup>28</sup> It is good practice to instruct patients utilizing HBPM to bring their home BP device to the office for a comparison.

There is some evidence that HBPM may contribute to improved adherence. A systematic review of 11 randomized controlled trials found that in 6 trials the use of HBPM resulted in improved medication adherence, although in 5 of those studies additional interventions were used. These interventions included patient counseling about adverse effects of the medication, timepiece caps that reminded patients to take their medication, tips to enhance adherence, and reinforcement of positive behavior by nurses, pharmacists, lay health workers, or a telephonic system.<sup>32</sup> This illustrates an important point in adherence interventions: more is better, and it usually takes a combination of approaches to improve adherence.<sup>33,34</sup>

The only trial in the review that demonstrated that HBPM alone improved adherence randomized 628 patients to either HBPM or usual care for 6 weeks. The groups had similar compliance rates at baseline, and both demonstrated less adherence at the end of the 6-week trial. However, patients who measured their BP at home still demonstrated greater compliance than those receiving usual care ( $P < .05$ ).<sup>35</sup>

A more recent trial in 57 patients, 38 of whom measured their BP at home and 19 of whom received usual care, found greater medication adherence in the HBPM group than in the control group (100% vs 88%,  $P < .031$ ). The HBPM group also reached their treatment goals significantly faster than the control group ( $P = .02$ ).<sup>36</sup>

### Conclusion

Approximately 50% of individuals with hypertension who receive antihypertensive medication still do not reach their BP goal. One reason is nonadherence to medication, which is often related to treatment complexity, or pill burden. Given that most patients with hypertension will require more than 1 drug to manage their blood pressure, it is important that clinicians identify opportunities to simplify treatment. This may include fixed-dose combination therapy, which can improve adherence, as well as additional education regarding the efficacy and adverse effects of therapy.

The use of HBPM may also improve adherence by providing frequent feedback on treatment effectiveness.

It is important, however, that clinicians understand that no single approach to adherence will work for every patient. The greatest success comes with combining several approaches based on the barriers that affect each individual patient. ■

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(CONTINUED ON PAGE S35)



## Module 1: Post-Test *Historical Review of Evidence-Based Treatment of Hypertension*

Project ID: 8450-EJ-37

# POST-TEST QUESTIONS

In order to obtain credit, you may either complete the post-test and evaluation form online or you may fax it in.

To complete this activity online and receive an immediate certificate, please go to [www.cmeuniversity.com](http://www.cmeuniversity.com). In the box at the top of the page marked "Find Post-Test/Evaluation by Course," type in **8450** and click on the activity title. Please register or log in and complete the post-test and the activity evaluation. Upon successful completion of the post-

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To complete this activity by FAX, please send the completed post-test AND evaluation form to **303-790-4876**. You must fax in both sides of the form to receive credit. Upon successful completion of the post-test, with a passing score of 70% or better, your certificate will be mailed within three (3) weeks.

- The first clinical trial to confirm that treating hypertension could reduce the rate of stroke, congestive heart failure, and kidney damage was:**

  - MRC-1
  - VA Cooperative
  - HDFP
  - UKPDS/HDS
- The SHEP study, Syst-Eur study, STOP, and SCOPE were notable because they investigated antihypertensives in which population?**

  - African Americans
  - Hispanics
  - Elderly
  - Adolescents
- A key finding from antihypertensive trials in the elderly is that:**

  - Antihypertensive therapy demonstrates benefits faster in the elderly than in younger populations
  - Antihypertensive therapy demonstrates benefits slower in the elderly than in younger populations
  - Angiotensin-converting enzyme inhibitors are not recommended for an older population
  - HCTZ is less effective in an elderly population than in a younger population
- Which type of antihypertensive medication for the primary or background treatment of hypertension was investigated by The Australian National Blood Pressure Study 2?**

  - Thiazide-type diuretic
  - Calcium antagonists
  - Angiotensin-converting enzyme inhibitor
  - Angiotensin-receptor blocker
- Which 4 drugs were initially evaluated in the ALLHAT trial?**

  - HCTZ, amlodipine, doxazosin, lisinopril
  - HCTZ, nifedipine, doxazosin, lisinopril
  - Chlorthalidone, HCTZ, amlodipine, doxazosin
  - Chlorthalidone, amlodipine, doxazosin, lisinopril
- The ACCOMPLISH trial demonstrated:**

  - A significantly lower risk of the primary outcome with a combination of benazepril/amlodipine than with benazepril/HCTZ even though both groups of patients achieved similar blood pressure goals
  - A significantly lower risk of the primary outcome with a combination of benazepril/HCTZ than with benazepril/amlodipine even though both groups of patients achieved similar blood pressure goals
  - Benazepril/HCTZ is more effective than benazepril/amlodipine at reducing blood pressure
  - Benazepril/amlodipine is more effective than benazepril/HCTZ at reducing blood pressure
- Which of the following does the American Society of Hypertension consider "less effective" in terms of reducing blood pressure and with regard to safety and tolerability?**

  - ACEI + ARB
  - ARB + diuretic
  - Renin inhibitor + diuretic
  - ARB + CCB

## Module 1: Evaluation Form

### Historical Review of Evidence-Based Treatment of Hypertension

Project ID: 8450-EJ-37

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. **You must complete this evaluation form to receive acknowledgment for completing this activity.**

*Please rate your level of agreement by circling the appropriate rating:*  
 1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objectives	After participating in this activity, I am now better able to:
Discuss key clinical trials on the role of medication in hypertension and their influence on current sequencing algorithms for the pharmacologic treatment of hypertension	1 2 3 4 5
Improve adherence to current sequencing algorithms for the management of hypertension in my patients	1 2 3 4 5

*Based upon your participation in this activity, choose the statement(s) that apply:*

- I gained new strategies/skills/information that I can apply to my area of practice.
- I plan to implement new strategies/skills/information into my practice.
- I need more information before I can implement new strategies/skills/information into my practice.
- This activity will not change my practice because my current practice is consistent with the information presented.
- This activity will not change my practice because I do not agree with the information presented.

*What strategies/changes do you plan to implement into your practice?*

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

*How confident are you that you will be able to make this change?*

Very confident    Somewhat confident    Unsure    Not very confident

*What barriers do you see to making a change in your practice?*

\_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

*Please rate your level of agreement by circling the appropriate rating:*  
 1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

*The content presentation:*

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence (Provide details of any perceived bias in the comments section below.)	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (eg, case studies, discussion, Q & A)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

*Handout materials were useful:*  Yes  No  No handouts for this activity

*May we contact you via email regarding future CME activities?*  Yes  No

*If yes, please provide your preferred email address if different than the one you provided below:*

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*Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:*

\_\_\_\_\_

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I participated in only part of the activity/module and claim \_\_\_\_ credit.





## Module 2: Post-Test

### *Rethinking the Role of Thiazide-Type Diuretics in the Management of Hypertension: Which Diuretic Is Best?*

Project ID: 8451-EJ-37

## POST-TEST QUESTIONS

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the post-test, with a passing score of 70% or better, your certificate will be made available immediately.

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1. **Which class of antihypertensive drugs do national guidelines recommend as first-line therapy for most patients with hypertension?**
  - a. Thiazide-type diuretic
  - b. ACE inhibitor
  - c. Beta blocker
  - d. Calcium antagonist
2. **Chlorthalidone and HCTZ have similar molecular structures and pharmacokinetic/pharmacodynamic properties, and thus both drugs may be used interchangeably.**
  - a. True
  - b. False
3. **Which of the following appears to be the most effective dose of HCTZ?**
  - a. 6.25-12.5 mg
  - b. 12.5-25 mg
  - c. 25-50 mg
  - d. 50-100 mg
4. **Which of the following aspects of the ACCOMPLISH trial were questioned by some critics?**
  - a. The choice of HCTZ over chlorthalidone as a thiazide-type diuretic
  - b. Including heart failure as a primary outcome
  - c. The choice of chlorthalidone over HCTZ as a thiazide-type diuretic
  - d. The dosages used for benazepril

## Module 2: Evaluation Form

### *Rethinking the Role of Thiazide-Type Diuretics in the Management of Hypertension: Which Diuretic Is Best?*

Project ID: 8451-EJ-37

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. **You must complete this evaluation form to receive acknowledgment for completing this activity.**

*Please rate your level of agreement by circling the appropriate rating:*  
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objective	After participating in this activity, I am now better able to:
Describe pharmacokinetic/pharmacodynamic differences between the thiazide-type diuretics chlorthalidone and hydrochlorothiazide, outcomes of clinical trials with the two drugs, and the role of these two drugs in the contemporary management of hypertension	1 2 3 4 5

*Based upon your participation in this activity, choose the statement(s) that apply:*

- I gained new strategies/skills/information that I can apply to my area of practice.
- I plan to implement new strategies/skills/information into my practice.
- I need more information before I can implement new strategies/skills/information into my practice.
- This activity will not change my practice because my current practice is consistent with the information presented.
- This activity will not change my practice because I do not agree with the information presented.

*What strategies/changes do you plan to implement into your practice?*

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*How confident are you that you will be able to make this change?*

Very confident    Somewhat confident    Unsure    Not very confident

*What barriers do you see to making a change in your practice?*

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*Please rate your level of agreement by circling the appropriate rating:*  
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

*The content presentation:*

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
Promoted improvements or quality in health care	1 2 3 4 5
Was scientifically rigorous and evidence-based	1 2 3 4 5
Avoided commercial bias or influence (Provide details of any perceived bias in the comments section below.)	1 2 3 4 5
Provided appropriate and effective opportunities for active learning (eg, case studies, discussion, Q & A)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

*Handout materials were useful:*  Yes  No  No handouts for this activity

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*I certify my actual time spent to complete this activity to be:*

- I participated in the entire activity/module and claim 0.75 credit.
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## Module 3: Post-Test

### *Using Thiazide-Type Diuretics in African Americans with Hypertension*

Project ID: 8452-EJ-37

## POST-TEST QUESTIONS

In order to obtain credit, you may either complete the post-test and evaluation form online or you may fax it in.

To complete this activity online and receive an immediate certificate, please go to [www.cmeuniversity.com](http://www.cmeuniversity.com). In the box at the top of the page marked "Find Post-Test/Evaluation by Course," type in **8452** and click on the activity title. Please register or log in and complete the post-test and the activity evaluation. Upon successful completion of

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To complete this activity by FAX, please send the completed post-test AND evaluation form to **303-790-4876**. You must fax in both sides of the form to receive credit. Upon successful completion of the post-test, with a passing score of 70% or better, your certificate will be mailed within three (3) weeks.

1. **Which of the following is NOT a key difference between blacks and whites when it comes to hypertension?**
  - a. Blacks tend to develop hypertension, on average, 5 years earlier than whites
  - b. Blacks tend to experience greater morbidity/mortality from hypertension than whites
  - c. Blacks are less likely than whites to receive treatment for their hypertension
  - d. Blacks are less likely than whites to have their hypertension controlled
2. **Which of the following is NOT a unique consideration that must be taken into account when treating African Americans versus whites with hypertension?**
  - a. Greater salt sensitivity
  - b. Higher rate of obesity
  - c. Higher prevalence of diabetes
  - d. Higher rate of atrial fibrillation
3. **One challenge in choosing the most appropriate antihypertensive therapy for blacks is that there were a small number of blacks enrolled in most of the major trials evaluating the various compounds.**
  - a. True
  - b. False
4. **Which of the following outcomes of ALLHAT did NOT occur in the black cohort?**
  - a. A significantly lower risk of the primary outcome (fatal coronary heart disease and nonfatal myocardial infarction) in patients receiving chlorthalidone versus lisinopril
  - b. No significant differences between chlorthalidone, lisinopril, and amlodipine in the primary outcome
  - c. An increased risk of heart failure in the amlodipine cohort
  - d. A greater reduction in systolic blood pressure in the chlorthalidone cohort compared with the lisinopril cohort
5. **Compared with those who received lisinopril, black participants in ALLHAT with the metabolic syndrome who received chlorthalidone had a significantly reduced risk of:**
  - a. Myocardial infarction
  - b. Stroke
  - c. End-stage renal disease
  - d. Heart failure

## Module 3: Evaluation Form

### Using Thiazide-Type Diuretics in African Americans with Hypertension

Project ID: 8452-EJ-37

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 1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objective	After participating in this activity, I am now better able to:
Describe the outcomes of ALLHAT in African Americans and the implications of this trial for clinical practice	1   2   3   4   5

*Based upon your participation in this activity, choose the statement(s) that apply:*

- I gained new strategies/skills/information that I can apply to my area of practice.
- I plan to implement new strategies/skills/information into my practice.
- I need more information before I can implement new strategies/skills/information into my practice.
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- This activity will not change my practice because I do not agree with the information presented.

*What strategies/changes do you plan to implement into your practice?*

\_\_\_\_\_

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*How confident are you that you will be able to make this change?*

Very confident    Somewhat confident    Unsure    Not very confident

*What barriers do you see to making a change in your practice?*

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*Please rate your level of agreement by circling the appropriate rating:*  
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*The content presentation:*

Enhanced my current knowledge base	1   2   3   4   5
Addressed my most pressing questions	1   2   3   4   5
Promoted improvements or quality in health care	1   2   3   4   5
Was scientifically rigorous and evidence-based	1   2   3   4   5
Avoided commercial bias or influence (Provide details of any perceived bias in the comments section below.)	1   2   3   4   5
Provided appropriate and effective opportunities for active learning (eg, case studies, discussion, Q & A)	1   2   3   4   5
My opportunity for learning assessment was appropriate to the activity	1   2   3   4   5

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## Module 4: Post-Test

### *Enhancing Adherence with Antihypertensives: The Role of Fixed-Dose Combinations and Home Blood Pressure Monitoring*

Project ID: 8453-EJ-37

## POST-TEST QUESTIONS

In order to obtain credit, you may either complete the post-test and evaluation form online or you may fax it in.

To complete this activity online and receive an immediate certificate, please go to [www.cmeuniversity.com](http://www.cmeuniversity.com). In the box at the top of the page marked "Find Post-Test/Evaluation by Course," type in **8453** and click on the activity title. Please register or log in and complete the post-test and the activity evaluation. Upon successful completion of

the post-test, with a passing score of 70% or better, your certificate will be made available immediately.

To complete this activity by FAX, please send the completed post-test AND evaluation form to **303-790-4876**. You must fax in both sides of the form to receive credit. Upon successful completion of the post-test, with a passing score of 70% or better, your certificate will be mailed within three (3) weeks.

1. **What percentage of patients with hypertension who are prescribed antihypertensive medications are persistent with their treatment at 1 year?**
  - a. 15%
  - b. 25%
  - c. 50%
  - d. 75%
2. **According to one study, patients who forget to take their antihypertensive medications may have a nearly one-third increased risk of:**
  - a. Stroke
  - b. Cardiovascular event or death
  - c. Heart failure
  - d. Developing end-stage renal disease
3. **What percentage of patients with hypertension will likely require more than 1 medication to obtain their blood pressure goal?**
  - a. 25%
  - b. 50%
  - c. 60%
  - d. 75%
4. **Which of the following has NOT been demonstrated to improve adherence to antihypertensive medication?**
  - a. Fixed-dose combinations
  - b. Improving patient understanding of their disease
  - c. Home blood pressure monitoring
  - d. Warning the patient of dire consequences
5. **Which of the following will likely NOT improve patient adherence to hypertensive medication?**
  - a. Choosing only 1 intervention
  - b. Identifying opportunities to reduce out-of-pocket costs
  - c. Providing nurse- or pharmacist-based counseling
  - d. Developing strategies to ensure refills

## Module 4: Evaluation Form

### *Enhancing Adherence with Antihypertensives: The Role of Fixed-Dose Combinations and Home Blood Pressure Monitoring*

Project ID: 8453-EJ-37

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. **You must complete this evaluation form to receive acknowledgment for completing this activity.**

*Please rate your level of agreement by circling the appropriate rating:*  
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

Learning Objective	After participating in this activity, I am now better able to:
Discuss the potential benefits of fixed-dose combination antihypertensive therapy and home blood pressure monitoring to improve patient adherence to antihypertensive therapy	1 2 3 4 5

*Based upon your participation in this activity, choose the statement(s) that apply:*

- I gained new strategies/skills/information that I can apply to my area of practice.
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- I need more information before I can implement new strategies/skills/information into my practice.
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- This activity will not change my practice because I do not agree with the information presented.

*What strategies/changes do you plan to implement into your practice?*

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*How confident are you that you will be able to make this change?*  
 Very confident    Somewhat confident    Unsure    Not very confident

*What barriers do you see to making a change in your practice?*

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*Please rate your level of agreement by circling the appropriate rating:*  
1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5 = Strongly Agree

*The content presentation:*

Enhanced my current knowledge base	1 2 3 4 5
Addressed my most pressing questions	1 2 3 4 5
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Provided appropriate and effective opportunities for active learning (eg, case studies, discussion, Q & A)	1 2 3 4 5
My opportunity for learning assessment was appropriate to the activity	1 2 3 4 5

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*Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:*

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(CONTINUED FROM PAGE S26)

- effects. theHeart.org Web site. [http://www.theheart.org/article/1387105.do?utm\\_campaign=newsletter&utm\\_medium=email&utm\\_source=20120419\\_EN\\_Heartwire](http://www.theheart.org/article/1387105.do?utm_campaign=newsletter&utm_medium=email&utm_source=20120419_EN_Heartwire). Published April 19, 2012. Accessed April 20, 2012.
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# Getting to Goal:

*How Thiazide-Type Diuretics, Following the Guidelines, and Improving Patient Adherence Can Help*



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Program Chair, President,  
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