Fixed-Dose Triple-Combination Treatments In the Management of Hypertension

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ABSTRACT
Hypertension remains uncontrolled in approximately 50% of patients with hypertension, which increases the risk of cardiovascular morbidity and mortality in these individuals. A key factor contributing to poor blood pressure (BP) control is nonadherence to prescribed antihypertensive medications. Improving patient adherence to antihypertensive therapy is the key to improving BP goal attainment. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommend a stepwise treatment algorithm for patients with stage 1 hypertension, with initial treatment consisting of a single antihypertensive drug. For most patients, however, combinations of 2 or more antihypertensive agents are necessary for adequate BP control. Antihypertensive regimens that combine agents from different antihypertensive drug classes can facilitate attainment of BP goals and improve cardiovascular outcomes at lower drug doses compared with monotherapy. Patient adherence to antihypertensive therapy decreases with increasing number of pills in multiple pill regimens, but fixed-dose triple-combination treatments for hypertension provide a tool for addressing patient nonadherence associated with pill burden. For patients whose antihypertensive therapy includes multiple medications, the use of a single-pill, fixed-dose combination therapy can significantly improve compliance and thereby help patients achieve BP goals. In addition, single-pill combinations may reduce health care utilization and medical costs compared with multiple single-pill therapies. The purpose of this article is to review the role of novel single-pill, fixed-dose, triple-combination treatments for modern hypertension management.

Keywords: Hypertension, Drug Combinations, Medication Adherence, Treatment Outcome, Cost Savings

INTRODUCTION
The prevalence of hypertension (defined as systolic blood pressure [SBP] ≥140 mm Hg or diastolic BP [DBP ≥ 90 mm Hg]) has increased over the past 2 decades, such that nearly one third of U.S. adults – about 78 million people ≥20 years of age – have high BP (Go 2013). The National Health and Nutrition Examination Survey (NHANES) 2007-2010 collected data showing that, among US adults with hypertension, 82% were aware of their condition, 75% were under treatment, and 53% had their hypertension under control (Go 2013).

The prevalence of hypertension in the elderly is even higher: According to data from NHANES 2007-2010, 64% and 71% of males and females, respectively, aged 65 to 74 years and 72% and 80% aged ≥75 years had hypertension (Go 2013). The increasing prevalence of hypertension can be attributed to 2 factors: 1) newer definitions and BP thresholds; and 2) increased survival of elderly patients with hypertension.

The economic impact of hypertension is substantial. In a retrospective study of health care costs using a database of about 2.8 million Medicaid patients, annual disease-related costs for hypertension were estimated to be $587 per patient, including medical care and prescription costs (Priest 2011). The costs associated with secondary medical outcomes in patients with hypertension are even higher: poor BP control is associated with an increased risk of cerebrovascular disease, ischemic cardiovascular disease, renal damage, and vascular dementia (Chobanian 2003, Law 2009, Lu 2009, Sharp 2011, WHO 2002). Coronary artery disease and heart failure (HF) were the costliest conditions studied in the Medicaid population, with per-patient medical and prescription expenses estimated at approximately $5,000 and $6,000 per year, respectively (Priest 2011). The American Heart Association projects that direct medical costs of treating hypertension in the U.S. will increase from $70 billion in 2010 (in 2008$) to over $200 billion in 2030, while the cost of hypertension as a risk factor for cardiovascular disease (a portion of the costs of complications associated with hypertension, including HF, coronary heart disease [CHD], stroke, and other cardiovascular disease) will increase from $131 billion in 2010 to $389 billion in 2030 (Heidenreich 2011).

Treatments that effectively lower BP can reduce the risk of cardiovascular and cerebrovascular events and
cardiovascular morbidity and mortality across a wide range of patient populations (Neal 2000, Ogden 2000, Verdecchia 2010). Most patients with hypertension can achieve BP goals (Cushman 2002), but clinicians must determine which antihypertensive drug or drug combination is appropriate for the individual patient.

Several classes of antihypertensive agents with different mechanisms of action — including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), and thiazide-type diuretics — have demonstrated efficacy for lowering BP (Chobanian 2003). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines recommend a stepwise treatment algorithm, generally initiating therapy with thiazide-type diuretics for patients with stage 1 hypertension (SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg) (Chobanian 2003).

Switching to a drug in a different class or to a combination of 2 or more drugs is considered for patients who do not achieve adequate BP control with first-line therapy and for patients with stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) (Chobanian 2003). The American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention, and the Canadian Hypertension Education Program Recommendations Task Force also recommend the use of thiazide diuretics, ACE inhibitors, ARBs, or CCBs as first-line treatment, and a drug combination when target BP is not achieved with a single medication (Rabi 2011, Rosendorff 2007).

For most patients, combinations of 2 or more antihypertensive agents are necessary for adequate BP control (i.e., <140/90 mm Hg). The investigators of the Antihypertensive and Lипid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported that by treatment year 5, 62.5% of patients were using 2 or more drugs and 27.3% were using 3 or more (Cushman 2002). The ALLHAT investigators found that participating clinicians did not consistently intensify therapy when SBP remained >140 mm Hg, suggesting that an even greater percentage of patients in clinical practice will require multiple antihypertensive medications to achieve adequate SBP control (Cushman 2002).

The percentage of US patients with hypertension whose BP is controlled has increased over the past 2 decades as both awareness of the risks of hypertension and the number of treatment options have increased (Egan 2010). However, NHANES data indicate that BP still remains uncontrolled in approximately 50% of patients with hypertension (Egan 2010). Among the factors accounting for high rates of patients with inadequate control are clinical inertia, or the failure to increase antihypertensive drug dosage or prescribe additional medications, and nonadherence to the therapy prescribed (Chobanian 2003). Finding ways to improve patient adherence to antihypertensive therapies is a critical step in bringing more patients to BP goals. The aim of this article is to review the role, benefits, and clinical trial data of 3 single-pill, fixed-dose, triple-combination treatments for hypertension management.

**Combination therapy for hypertension**

**Clinical benefits of combination therapy**

Extensive data from randomized controlled trials and population-based studies have demonstrated that combination therapy regimens can reduce BP, facilitate attainment of BP goals, and improve cardiovascular outcomes compared with a mono-therapy approach (Corrao 2011, Feldman 2009, Lv 2010, Wald 2009). Combining BP-lowering medications from drug classes that act on different physiological pathways involved in BP regulation can yield additional reductions by blocking complementary pressor mechanisms and preventing compensatory response to any single drug class (Elijovich 2009, Escobar 2010, Gradman 2010b).

JNC 7 and guidelines from the American College of Cardiology/American Heart Association (ACC/AHA), the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (KDOQI), and the American Diabetes Association (ADA) recommend combination antihypertensive drug therapies as first-line treatment for patients with stage 2 hypertension (SBP ≥160 mm Hg or DBP ≥100 mm Hg) (Chobanian 2003) and for patients with complicating comorbidities including HF, CHD, diabetes, and chronic kidney disease (Wright 2011).

These recommendations are based on the fact that combination therapies are associated with quick and safe achievement of BP goals. Compared with monotherapy, drug combinations can bring patients to BP goals more rapidly than single-drug therapies (Weir 2007, Weir 2011). In the large, double-blind, placebo-controlled Combination of Olmesartan Medoxomil and Amlodipine Besylate in Controlling High Blood Pressure (COACH) trial, patients with mild to severe hypertension (N=1490) randomly assigned to receive olmesartan/amldodipine combination therapies achieved greater reductions in SBP and DBP at week 8 compared with patients administered olmesartan or amlodipine monotherapy (Chrysant 2008a). Differences between the combination vs. monotherapy groups were evident by week 2, and response plateaued by week 4 (Chrysant 2008a, Chrysant 2008b).
Lowering BP rapidly can reduce the risk of cardiac events and stroke. In clinical trials, treatment groups that achieved a lower BP earlier in treatment had lower risk of myocardial infarction, HF hospitalizations, stroke, composite cardiac mortality and morbidity, and all-cause death (Julius 2004, Staessen 2004), and risks were lower particularly during the early time period when BP differences between the groups were greatest (Julius 2004).

The recommendations also take into account that specific antihypertensive drug classes offer increased target organ protection and reduce morbidity and mortality beyond that accounted for by BP reduction alone (Lindholm 2002, Okin 2003, Parving 2008). Table 1 lists the classes of antihypertensive drugs recommended for patients with compelling conditions according to JNC 7. Table 2 summarizes guidelines and expert consensus statements on combination therapy in patients with hypertension.

The ACC/AHA guidelines mention that most patients will require more than 1 antihypertensive agent to achieve BP control and that pharmacotherapy should begin with known outcome-improving agents. These guidelines recommend addition of a β-blocker, ACE inhibitor, ARB, and/or long-acting CCBs to a thiazide diuretic for treating hypertension in patients with unstable angina and non-ST-segment elevation myocardial infarction (Wright 2011). The ADA and American Association of Clinical Endocrinologists state that multiple-drug therapy (2 or more agents) is generally required to achieve BP targets in patients with hypertension and diabetes (Arauz-Pacheco 2004; Handelsman 2011). The ADA recommends initial drug therapy with ACE inhibitors, ARBs, β-blockers, CCBs, or diuretics for treating patients with BP >140/90 mm Hg (Arauz-Pacheco 2004). All patients with diabetes and hypertension should be treated with either an ACE inhibitor or an ARB (Arauz-Pacheco 2004, Handelsman 2011). ACE inhibitors are recommended to delay progression of diabetic nephropathy and ACE inhibitors and ARBs to delay progression of macroalbuminuria. If BP targets are not being met, a thiazide diuretic should be added (Arauz-Pacheco 2004).

The KDOQI guidelines include the use of ACE inhibitors or ARBs in combination with a diuretic for treating hypertension in patients with diabetes (NKF 2007); CCBs and β-blockers also are considered effective therapies. A position paper from the American Society of Hypertension states that single-pill combinations may be used as initial treatment in a patient in whom multidrug therapy is likely to be needed, in a patient partially controlled on monotherapy, or as a substitute for independently titrated doses of individual components. It also is acknowledged that it is easier for a patient to comply with an antihypertensive treatment regimen that includes fewer pills (Gradman 2010b).

Combining medications from different classes can provide added protective effects on the cardiovascular system, reducing the risk of cardiovascular and cerebrovascular events (Aronow 2011). In a meta-analysis of SBP reductions in 42 trials (N=10,698), each of 4 classes of antihypertensive drugs (thiazide diuretics, ACE inhibitors, β-blockers, and CCBs) was compared with pairwise combinations among the classes (Wald 2009). The reductions in SBP for each class were additive when drugs from 2 classes were combined, and the combination of any 2 medications from different BP-lowering drug classes was approximately 5 times more effective than doubling the dose of a single drug.

Finally, antihypertensive drug combinations can improve tolerability compared with monotherapy. Similar or greater BP reduction achieved with antihypertensive drug combinations means that lower drug doses are required to reach BP goals compared with a single, higher-dose drug (Aronow 2011; Neutel 1999). Furthermore, one component of an antihypertensive combination therapy can reduce the occurrence of adverse events caused by a second component. Patients with uncomplicated hypertension treated with the CCB

### Table 1

**Target organ protection: benefits of antihypertensive drug classes**

<table>
<thead>
<tr>
<th>Condition</th>
<th>JNC 7-recommended Classes of Antihypertensive Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Diuretics, β-blockers, ACE inhibitors, ARBs, aldosterone antagonists</td>
</tr>
<tr>
<td>Post–myocardial infarction</td>
<td>β-blockers, ACE inhibitors, aldosterone antagonists</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>Diuretics, β-blockers, ACE inhibitors, CCBs</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diuretics, β-blockers, ACE inhibitors, ARBs, CCBs</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACE inhibitors, ARBs</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>Diuretics, ACE inhibitors</td>
</tr>
</tbody>
</table>

ACE=angiotensin-converting enzyme; ARBs=angiotensin receptor blockers; CCBs=calcium channel blockers.

Adapted with permission from Chobanian et al (Chobanian 2003).
amlodipine 10 mg/d experienced statistically significant increases in 2 objective measures of ankle edema, ankle foot volume (AFV), and pretibial subcutaneous tissue pressure (PSTP) (Fogari 2007). Patients who were administered valsartan 160 mg/d in addition to amlodipine, however, experienced no changes in edema from baseline and had significantly lower AFV and PSTP compared with the amlodipine monotherapy group.

**TABLE 2**
Recommendations for antihypertensive combination therapy in patients with hypertension

<table>
<thead>
<tr>
<th>Guidelines/expert consensus statement</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report (Chobanian 2003)</td>
<td>Thiazide-type diuretics should be used as initial therapy for most patients with hypertension, either alone or in combination with a drug from another class (ACE inhibitors, ARBs, β-blockers, CCBs) also demonstrated to be beneficial in randomized controlled outcome trials. Adding a second drug from a different class should be initiated when use of a single drug in adequate doses fails to achieve BP goal. When BP is &gt;20/10 mm Hg above goal, consider initiating therapy with 2 drugs. If BP goal is not reached, additional drugs can be added until goal is achieved.</td>
</tr>
<tr>
<td>ACCF/AHA 2011 Expert Consensus Document on Hypertension in the Elderly (Aronow 2011)</td>
<td>Thiazide diuretics are recommended for initiating therapy. If BP response is inadequate after reaching “full dose” (not necessarily maximum recommended dose), a second drug from another class (β-blockers, CCBs, ACE inhibitors, ARBs) should be added. If a diuretic is not the initial drug, it is usually indicated as the second drug. If the antihypertensive response is inadequate after reaching full doses of 2 classes of drugs, a third drug from another class should be added. When BP is &gt;20/10 mm Hg above goal, therapy should be initiated with 2 antihypertensive drugs.</td>
</tr>
<tr>
<td>2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Wright 2011)</td>
<td>Pharmacotherapy should begin with known outcome-improving medications (primarily thiazide diuretics as first choice, with the addition of β-blockers, ACE inhibitors, ARBs, and/or long-acting CCBs). (Primary prevention patients with high BP should be treated according to JNC 7 recommendations.)</td>
</tr>
<tr>
<td>Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease: KDOQI (NKF 2007)</td>
<td>Hypertensive patients with diabetes and CKD stages 1–4 should be treated with an ACE inhibitor or an ARB, usually in combination with a diuretic.</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for Developing a Diabetes Mellitus Comprehensive Care Plan (Handelsman 2011)</td>
<td>Initially, antihypertensive agents are selected on the basis of their ability to reduce BP and to prevent or slow progression of nephropathy and retinopathy; ACE inhibitors or ARBs are the preferred choice in patients with diabetes mellitus. The use of combination therapy is likely required, including CCBs, diuretics, combined α/β-adrenergic blockers, and newer-generation β-adrenergic blockers in addition to agents that block the renin-angiotensin system.</td>
</tr>
<tr>
<td>Hypertension Management in Adults With Diabetes: American Diabetes Association (Arauz-Pacheco 2004)</td>
<td>Initial drug therapy should be with a drug class demonstrated to reduce CVD events in patients with diabetes (ACE inhibitors, ARBs, β-blockers, diuretics, CCBs). All patients with diabetes and hypertension should be treated with a regimen including either an ACE inhibitor or ARB. If BP targets are not achieved, a thiazide diuretic should be added.</td>
</tr>
</tbody>
</table>

**Antihypertensive treatment adherence**
Persistence with antihypertensive medications has been estimated to be approximately 60% to 75% after 1 year, declining to approximately 55%
after 3 years and 40% after 10 years (Perreault 2005, van Wijk 2005). Nonadherence is associated with reduced BP goal achievement (Bramley 2006, Fung 2007, Ho 2008, Yiannakopoulou 2005) and a higher risk of CHD, cerebrovascular disease, HF, and death (Bailey 2010, Cherry 2009, Dragomir 2010, Kettani 2009, Perreault 2009). Patient nonadherence to antihypertensive medication was significantly associated with uncontrolled BP in several retrospective studies of pharmacy and BP records from U.S. managed care databases (Bramley 2006, Fung 2007, Ho 2008). In a prospective assessment of long-term adherence to antihypertensive treatment and its effect on BP outcomes, decreases in SBP and DBP were proportional to rates of persistence with treatment (Veronesi 2007). Improving adherence to hypertension treatment regimens thus is likely to increase the number of patients with hypertension who meet the recommended BP goals.

The costs of nonadherence, in terms of patient outcomes and health care utilization, are high. Because better antihypertensive medication adherence is associated with higher levels of BP goal attainment (Bramley 2006, Fung 2007), improving adherence can save lives and substantially reduce health care utilization in patients with hypertension. In a retrospective cohort study in which 61% of patients were nonadherent to antihypertensive medication (ie, took <80% of prescribed drugs based on Medication Refill Adherence), it was estimated that approximately 200,000 lives could be saved over a 5-year period by increasing adherence for patients with hypertension to ≥80% (Bailey 2010). Patients adherent to prescribed antihypertensive medications have fewer emergency department visits, hospitalizations, inpatient hospital days, and consequently lower health care costs (Dragomir 2010, Pittman 2010). Estimated excess hospitalization costs associated with nonadherence in approximately 19,000 Canadian patients with hypertension were $25.2 million from 1999 to 2002 (Dragomir 2010).

The advantages of single-pill combination therapies for hypertension may be offset by the negative effect on adherence of a regimen composed of multiple single pills. Patients may find that managing multiple pills daily is cumbersome and confusing. Indeed, adherence to hypertension therapy is reduced as the number of pills in a regimen increases (Fung 2007): in a historical cohort study of 84,929 Medicare beneficiaries aged ≥65 years who were prescribed antihypertensive medications, Fung and colleagues assessed patient adherence to at least 1 hypertension medication and to the full prescribed hypertension treatment regimen by number of drugs prescribed. They observed that the percentage of patients who were adherent to the full treatment regimen decreased with increasing number of prescribed antihypertensive medications (Figure 1). Notably, among patients who were not fully adherent to the multiple-medication regimen, partial compliance increased with the number of medications prescribed— that is, the more medications in the regimen, the more likely patients were to take at least 1 of their pills (Figure 1) (Fung 2007). Findings from this study suggest that, even in patients motivated to adhere to the hypertension treatment plan, multiple medication regimens can be a barrier to full compliance. In an effort to reduce pill burden and increase compliance, single-pill, fixed-dose combination therapies for hypertension have been introduced.

**Single-pill, fixed-dose combination therapy for hypertension**

An extensive range of antihypertensive drug combinations are available as single-pill, fixed-dose medications, most including a diuretic plus a second antihypertensive drug from a different class. Fixed-dose, single-pill combination therapies reduce pill counts and thereby improve adherence to hypertension treatment regimens (Gradman 2010). Several retrospective studies of pharmacy
records from large medical administrative databases have demonstrated that prescribing fixed-dose combination pills can lead to increased adherence to antihypertensive medications compared with the use of multiple individual-component pills (Brixner 2008, Dezii 2000, Dickson 2008, Panjabi 2013, Yang 2010, Zeng 2010). Adherence or compliance rates ranged from approximately 63% to 73% for single-pill combination drugs and 28% to 61% for patients prescribed the individual components (Brixner 2008, Dezii 2000, Dickson 2008, Yang 2010).

A meta-analysis of 6 studies, including 30,295 patients prescribed antihypertensive medications, reported a statistically significant 29% increase in compliance with fixed-dose combination pills compared with free-drug combinations (Gupta 2010). A second meta-analysis of 12 retrospective database studies published between 2000 and 2010 found that, in the 7 studies reporting medication possession ratios and in the overall meta-analysis, patients prescribed single-pill, fixed-dose antihypertensive combination therapy had significantly higher treatment adherence compared with patients prescribed free-drug combinations (Sherrill 2011). The pooled risk ratio for persistence in the meta-analysis was 2.1 (95% confidence interval [CI], 1.1-4.1), favoring the single-pill combination therapy. Persistence with single-pill compared with free-drug combinations is shown in Figure 2 (Sherrill 2011).

Although the use of fixed-dose combination therapies offers several advantages, some disadvantages are associated with them: branded fixed-dose combinations may be more expensive than equivalent free-dose combinations; the duration of action of individual components may not be equivalent, and this may not justify a single daily dosing of the combination; the use of fixed-dose combinations results in less flexibility in modifying the doses of individual components; and patients may be exposed to unnecessary therapy (Angeli 2012).

**FIGURE 2**

**Persistence with antihypertensive therapy regimens; single-pill combination therapy vs free-drug combinations.**

Persistence was defined as the percentage of patients meeting a predefined threshold (depending on the study) during a 12-month follow-up period (Sherrill 2011).

<table>
<thead>
<tr>
<th>Study</th>
<th>Single-pill combination (%)</th>
<th>Free-drug combination (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>54.0</td>
<td>19.1</td>
</tr>
<tr>
<td>Study 2</td>
<td>68.7</td>
<td>35.6</td>
</tr>
<tr>
<td>Study 3</td>
<td>70.0</td>
<td>36.4</td>
</tr>
<tr>
<td>Study 4</td>
<td>57.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Study 5</td>
<td>58.3</td>
<td>14.9</td>
</tr>
<tr>
<td>Overall</td>
<td>59.3</td>
<td>20.9</td>
</tr>
</tbody>
</table>

**Potential economic benefits of single-pill combinations**

Single-pill combinations increase adherence to antihypertensive therapy and, as expected, reduce health care costs compared with multiple-pill therapies (Dickson 2008, Panjabi 2013, Yang 2010). Prescription drug costs sometimes (but not always) are higher for single-pill combination therapies compared with the component drugs (Brixner 2008), yet reduced health care utilization in patients prescribed single-pill combinations results in lower overall medical service expenditures. In a retrospective study using data from a large, nationwide medical administrative database, the reduction in medical services expenditures for patients with hypertension receiving single-pill combination therapy over 6 months of treatment (compared with a 6-month pre-treatment baseline) was $208 (95% CI, $114-$302) greater per patient compared with the reduction in medical services expenditures for patients receiving the individual component drugs (Figure 3) (Yang 2010). In the meta-analysis of 12 retrospective database studies, single-pill, fixed-dose combination therapy was associated with lower overall and hypertension-related medical costs compared with free-drug combinations (Sherrill 2011).

**FDA-APPROVED TRIPLE-COMBINATION TREATMENTS FOR HYPERTENSION**

A triple combination treatment (reserpine, hydralazine, and hydrochlorothiazide) was first utilized in the 1960s (VACS 1967), but sequential monotherapy was recommended over drug combinations in practice at that time (Black 2009). The use of multiple-drug treatments is now common for patients who do not achieve BP goals with a single antihypertensive medication, have stage 2 hypertension, or have target organ damage.
Fixed-dose Triple-Combination Hypertension Treatments

Changes in health care costs were calculated as the costs incurred during the 6-month post-index period minus those incurred during the 6-month baseline period. Reproduced with permission from Yang et al (Yang 2010). CI=confidence interval; CV=cardiovascular.

FIGURE 3
Change from baseline in health care costs in patients with hypertension using either a single-pill combination or free-drug combination.

Changes in health care costs were calculated as the costs incurred during the 6-month post-index period minus those incurred during the 6-month baseline period. Reproduced with permission from Yang et al (Yang 2010). CI=confidence interval; CV=cardiovascular.

TABLE 3
U.S. FDA-approved triple-combination antihypertensive treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Exforge HCT</th>
<th>Tribenzor</th>
<th>Amturnide</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA approval date</td>
<td>April 30, 2009</td>
<td>July 23, 2010</td>
<td>December 21, 2010</td>
</tr>
<tr>
<td>Components</td>
<td>Valsartan (ARB&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>Olmesartan (ARB&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>Aliskiren (direct renin inhibitor)</td>
</tr>
<tr>
<td></td>
<td>Amlodipine (CCB&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>Amlodipine (CCB&lt;sup&gt;+&lt;/sup&gt;)</td>
<td>Amlodipine (CCB&lt;sup&gt;+&lt;/sup&gt;)</td>
</tr>
<tr>
<td></td>
<td>Hydrochlorothiazide (thiazide diuretic)</td>
<td>Hydrochlorothiazide (thiazide diuretic)</td>
<td>Hydrochlorothiazide (thiazide diuretic)</td>
</tr>
<tr>
<td>Pivotal trial</td>
<td>Calhoun 2009a</td>
<td>Oparil 2010</td>
<td>Lacourciere 2012</td>
</tr>
</tbody>
</table>

*AT<sub>1</sub> receptor subtype; †Dihydropyridine class.
Fixed-dose Triple-Combination Hypertension Treatments

Gradman 2010a, Gradman 2010b), with the choice of triple-combination pill based on the currently prescribed components and patient comorbidities. No head-to-head trials among the 3 triple combinations have been published to date.

Valsartan/amlodipine/hydrochlorothiazide

The first triple combination approved by the FDA, valsartan/amlodipine/hydrochlorothiazide (10/320/25 mg), was associated with greater SBP and DBP reductions (last observation carried forward) compared with the component dual-combination therapies (amlodipine/valsartan, amlodipine/hydrochlorothiazide, valsartan/hydrochlorothiazide) in an 8-week, randomized, double-blind, parallel-group trial (N=2271) (Calhoun 2009a). The study included a single-blind, placebo run-in period followed by double-blind treatment for 8 weeks; patients were randomly assigned to 1 of 4 groups titrated to valsartan/amlodipine/hydrochlorothiazide 320/10/25 mg, valsartan/hydrochlorothiazide 320/25 mg, amlodipine/valsartan 10/320 mg, or amlodipine/hydrochlorothiazide 10/25 mg once daily (Calhoun 2009a).

Beginning at screening and continuing throughout the study, each patient took 2 tablets and 2 capsules except on days when clinic visits were scheduled. Placebo was administered as either a tablet or capsule to maintain blinding. Greater BP reductions were observed for the triple combination compared with the dual combinations regardless of age, sex, race, or ethnicity. In addition, the proportion of patients achieving BP control (<140/90 mm Hg) at study end point was significantly greater with the triple combination (70.8%) compared with the dual combinations (44.8–54.1%).

In a secondary analysis of data from that study, significant differences between the triple combination and all dual combinations were observed by week 3, after patients in the triple-dose arm had received all 3 components for 1 week (Calhoun 2009b). Valsartan/amlodipine/hydrochlorothiazide efficacy also was assessed in a subset of patients who received 24-hour ambulatory BP monitoring at baseline and after 8 weeks of therapy (Lacourciere 2011). In this subset, the triple combination was significantly more effective than any of the dual combinations, reflecting the results of the total study population.

The percentages of patients reporting at least 1 adverse event ranged from 45% to 48% in the total study population, with no differences observed between treatment groups (Calhoun 2009a). An adverse event was the most common reason for discontinuation from the double-blind treatment phase. The most common adverse events (≥2%) reported by patients administered the triple combination were dizziness (7.7%), ankle edema (4.5%), and headache (4.3%) (Calhoun 2009a). In a 52-week, open-label safety and tolerability study enrolling patients with mild to moderate hypertension, 17% of patients reported peripheral edema at the 10/160/12.5 mg dose (Domenech 2010).

Olmesartan/amlodipine/hydrochlorothiazide

The triple-combination treatment olmesartan/amlodipine/hydrochlorothiazide (40/10/25 mg) was compared with the component dual combinations (olmesartan/amlodipine, amlodipine/hydrochlorothiazide, and olmesartan/hydrochlorothiazide) in a phase 3, 12-week, randomized, double-blind, parallel-group efficacy and safety trial (TRINITY, the Triple Therapy with Olmesartan Medoxomil, Amlodipine, and Hydrochlorothiazide in Hypertensive Patients Study) that enrolled 2492 patients with BP ≥140/100 mm Hg or ≥160/90 mm Hg off antihypertensive treatment (Oparil 2010). Participants were randomized (stratified by age, race, and diabetes status) at the start of the study to a treatment sequence that led to their final treatment assignment: either 1 of the 3 component dual-combination treatments or the triple-combination treatment (olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg, olmesartan/amlodipine 40/10 mg, olmesartan/hydrochlorothiazide 40/25 mg, or amlodipine/hydrochlorothiazide 10/25 mg). Patients could be newly diagnosed with hypertension; not be receiving current antihypertensive therapy (ie, no antihypertensive medication for at least 3 weeks); or be undergoing a washout of current antihypertensive therapy.

The study consisted of a 3-week washout period with no study medication and a 12-week double-blind treatment period. Patients received a total of 5 tablets per day, each of which looked different, corresponding to either the active treatment or placebo image. Adherence to study medication was similar across treatment groups, ranging from 98.0% to 98.5%.

Patients administered olmesartan/amlodipine/hydrochlorothiazide achieved significantly greater mean reductions in SBP and DBP at week 12 compared with each of the dual combinations. A greater percentage of patients in the olmesartan/amlodipine/hydrochlorothiazide group reached BP goal (<140/90 mm Hg or <130/80 mm Hg for patients with diabetes, chronic kidney disease, or chronic cardiovascular disease) compared with each dual combination at weeks 6, 8, 10, and 12 (week 6 represented the treatment effect 2 weeks after patients received the triple-combination treatment). At week 12, 70% of patients administered olmesartan/amlodipine/hydrochlorothiazide achieved a BP target of <140/90 mm Hg com-
pared with 41% to 53% of patients receiving the dual combinations.

The percentages of patients reporting at least 1 treatment-emergent adverse event ranged from 52% to 59%, with no differences observed between treatment groups. The most common treatment-emergent adverse events (≥3%) reported by patients administering the triple combination were dizziness (9.9%), ankle edema (7.7%), headache (6.4%), fatigue (4.2%), nasopharyngitis (3.5%), muscle spasms (3.1%), and nausea (3.0%) (Oparil 2010). In an open-label, long-term extension of an efficacy study for aliskiren/olmesartan, 56% of 440 patients who received olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg reported adverse events; the drug-related treatment-emergent adverse event of edema occurred in 10.7% of patients receiving olmesartan/amlodipine/hydrochlorothiazide 40/10/25 mg (Chrysant 2009).

Aliskiren/amlodipine/hydrochlorothiazide

The triple combination of aliskiren/amlodipine/hydrochlorothiazide (300/10/25 mg) was compared with the component dual combinations (aliskiren/amlodipine, amlodipine/hydrochlorothiazide, aliskiren/hydrochlorothiazide) in a randomized, double-blind, 8-week trial enrolling patients with moderate to severe hypertension (Lacourciere 2012). Eligible patients entered a 1–4-week single-blind placebo run-in period to establish baseline BP and eligibility for randomization based on the entry criteria, followed by an 8-week double-blind treatment period (Lacourciere 2012). Patients administered aliskiren/amlodipine/hydrochlorothiazide had significantly greater reductions in SBP and DBP compared with patients receiving the dual combinations. BP control (<140/90 mm Hg) was achieved by 62.3% of patients receiving triple-combination treatment compared with 33.1% to 41.3% receiving dual-combination treatments.

Most adverse events were mild or moderate, with the overall incidence comparable in the 4 treatment groups: 33.4% (aliskiren/amlodipine), 32.3% (aliskiren/hydrochlorothiazide), 33.6% (amlodipine/hydrochlorothiazide), and 36.2% (aliskiren/amlodipine/hydrochlorothiazide). Peripheral edema was the most frequently reported adverse event (Lacourciere 2012).

The Aliskiren Amlodipine HCTZ in Minority Patients with Stage 2 Hypertension (ASCENT) study evaluated the efficacy of aliskiren/amlodipine/hydrochlorothiazide vs. the dual combination of aliskiren/amlodipine in 412 self-identified minority patients (black, Hispanic/Latino) (Ferdinand 2011). In this study, the triple combination also resulted in greater mean BP reductions and goal achievement (<140/90 mm Hg) compared with aliskiren/amlodipine.

SUMMARY

There is a clinically desirable role for single-pill, fixed-dose triple combination therapies in bringing patients with hypertension to BP goals and reducing cardiovascular and cerebrovascular events. Nonadherence to antihypertensive therapy is a substantial barrier to effective BP control (Bramley 2006, Fung 2007) and has been associated with poor cardiovascular outcomes and increased medical costs (Bailey 2010, Dragomir 2010). Reducing pill-count burden is one step clinicians can take to improve adherence in patients prescribed multiple medications for hypertension and related comorbidities. Patients prescribed single-pill combination therapies have higher rates of treatment compliance and are more likely to achieve BP goals compared with patients taking the individual component drugs (Fung 2007). Further, overall and hypertension-related medical costs are significantly lower for patients taking single-pill combinations (Dragomir 2010). Improving patient adherence with the use of triple-combination therapy has the potential to save lives and reduce health care costs in patients with uncontrolled BP (Bailey 2010, Dragomir 2010).

Acknowledgments

Research funds for the preparation of the manuscript were provided by Daiichi Sankyo, Inc, Parsippany, New Jersey. Editorial support for this article was provided by Vrinda Mahajan, PharmD, of Peloton Advantage, LLC, Parsippany, New Jersey. The opinions expressed in the current article are those of the author. The author received no honorarium/fee for service or other form of financial support related to the development of this article.

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Fixed-dose Triple-Combination Hypertension Treatments


