

# Fixed combinations in the management of hypertension: patient perspectives and rationale for development and utility of the olmesartan – amlodipine combination

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**Abstract:** Although the awareness and control of hypertension has increased, only 37% of hypertensive patients in the US achieve the conservative goal of <140/90 mmHg. Achieving optimal blood pressure (BP) control is the most important single issue in the management of hypertension, and in most hypertensive patients, it is difficult or impossible to control BP with one drug. Blocking two or more BP regulatory systems provides a more effective and more physiologic reduction in BP, and current guidelines have recommended the use of combination therapy as first-line treatment, or early in the management of hypertension. Fixed combination therapy is an efficacious, relatively safe, and may be cost-effective method of decreasing BP in most patients with essential hypertension. Similar to other combinations, fixed-dose combination tablets containing the dihydropyridine calcium channel blocker amlodipine and the angiotensin II receptor blocker olmesartan bring together two distinct and complementary mechanisms of action, resulting in improved BP control and potential for improved target organ protection relative to either class of agent alone.

**Keywords:** olmesartan – amlodipine, hypertension, combination therapy

## Introduction

Hypertension is a highly prevalent condition and an important modifiable risk factor for cardiovascular (CV) disease. Hypertension affects nearly 1 in 3 adults in the US, with a prevalence of 29.3% in a population  $\geq 18$  years old (Hajjar and Kotchen 2003; Ong et al 2007; Rosamond et al 2008), and as many 1.5 billion persons worldwide will have hypertension by 2025 (Kearney et al 2005).

Hypertension is the most common risk factor for CV death and disability in both developed and developing countries, and control of blood pressure (BP) significantly reduces these risks (Turnbull et al 2003; Kearney et al 2005). Observational studies have shown that mortality from ischemic heart disease and stroke in persons 40–89 years of age increases in log linear fashion with increases in both systolic (SBP) and diastolic BP (DBP) (Lewington et al 2002). For each increase in SBP of 20 mmHg or in DBP of 10 mmHg over the entire range from 115/75 mmHg, there is a twofold increase in mortality related to coronary artery disease and stroke.

Although the awareness and control of hypertension have increased, only 37% of hypertensive patients in the United States achieve the conservative goal of <140/90 mmHg (Ong et al 2007). Achieving optimal BP control is the most important single issue in the management of hypertension, and in most hypertensive patients, it is difficult or impossible to control BP with one drug. For example, in the very large Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) trial less than

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30% of more than 42,000 participants achieved goal BP (<140/90 mmHg) on monotherapy (Cushman et al 2002). In the Losartan Intervention For Endpoint (LIFE) trial, in which treatment to goal (<140/90 mmHg) was aggressively pursued in >9,000 patients with left ventricular hypertrophy (LVH) and an average baseline BP of 175/98 mmHg, >90% required more than one antihypertensive agent (Dahlöf et al 2002). Although participants in the LIFE trial had free medications and close follow-up, only 49% of patients assigned to losartan and 46% assigned to atenolol achieved the BP goal (<140/90 mmHg).

Based on clinical trials, current guidelines have recommended the use of combination therapy as first-line treatment, or early in the management of hypertension in patients with comorbidities that require prompt BP reduction. Initial treatment with 2 antihypertensive agents is suggested for persons with BP >20/10 mmHg above goal (Figure 1) (Chobanian et al 2003; Mancia et al 2007).

## Patient adherence

Patient adherence refers to the willingness and ability of an individual patient to follow health-related advice, take medication as prescribed, attend scheduled clinic appointments, and complete recommended tests and consultations (Murphy and Coster 1997). Poor adherence to medication regimens contributes to the practice – outcome gap, in which clinical guidelines are implemented but expected benefits are not realized. For example, in one study, nonadherence to medication was by far the leading cause of hospitalization in a series of 179 patients admitted to hospital with acute decompensation of pre-existing heart failure, being implicated in 42% of hospital admissions (Michalsen et al 1998). In another study of 1,015 outpatients with stable coronary heart disease, self-reported medication nonadherence was associated with a greater than 2-fold increased rate of subsequent CV events, such as coronary heart disease death, myocardial infarction, and stroke (Gehi et al 2007).

Multiple medications and complexity of treatment regimens are two of the determinants of poor medication adherence. A survey conducted by the National Council on Patient Information and Education showed that one-third of patients receive at least 2 prescriptions and 10% of patients receive 4 or more prescriptions after a visit to a primary care physician (Dezii 2000). This survey also has estimated that the adherence rate is in the range of 30% for chronic conditions.

There is a clear inverse relationship between complexity of the dosing regimen/number of drugs that patients have to take and patient adherence. Adherence to antihypertensive

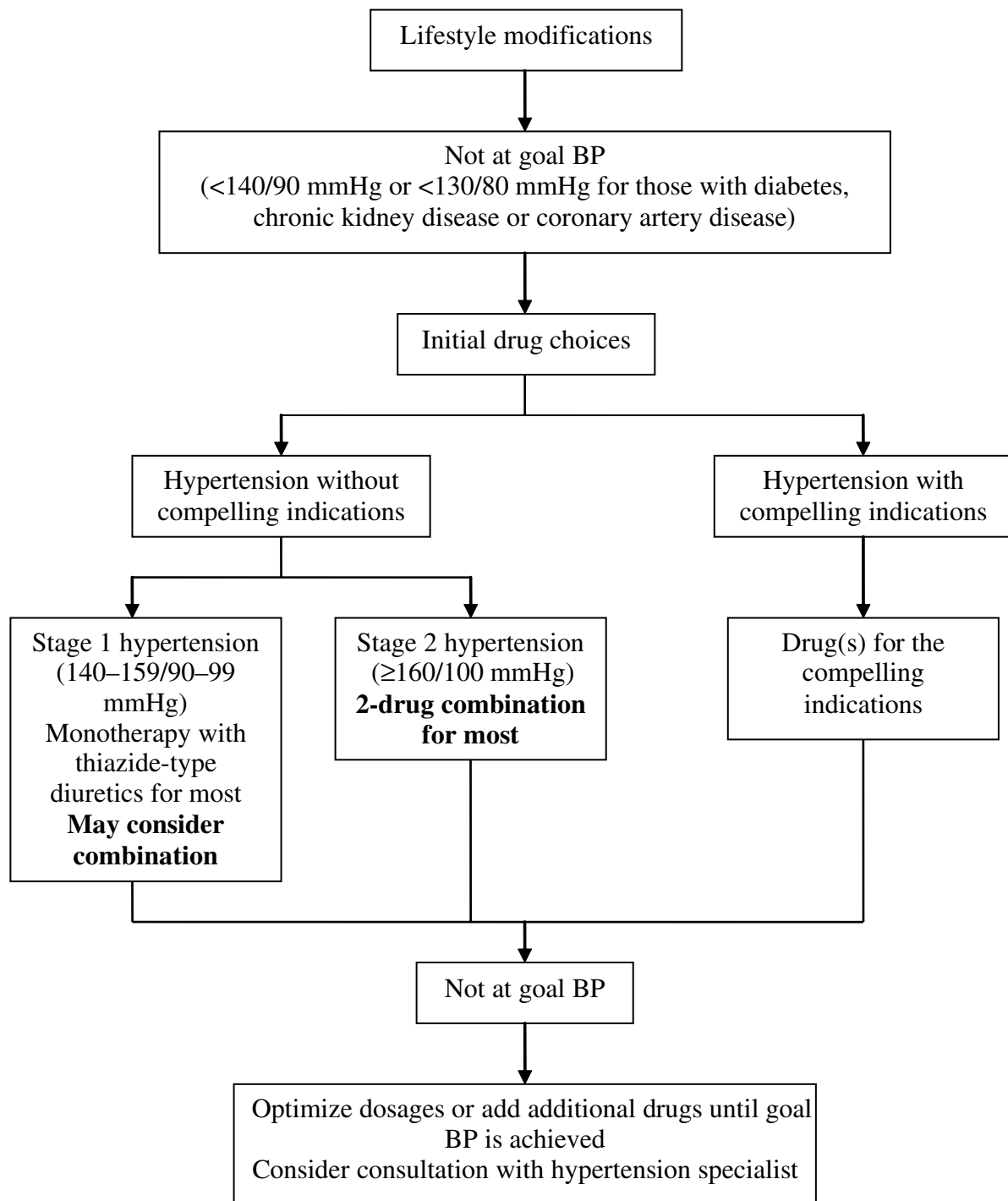
agents varies inversely with dosing frequency (Sica 1994). For example, among 198 Canadian hypertensives randomized to diltiazem twice-daily compared with amlodipine once-daily, those on the once-daily regimen took the medication more regularly than those on twice-daily dosing (Leenen et al 1997). Among 91 diabetic patients using oral antidiabetic agents, the adherence rate, defined as the percentage of doses taken during the observation period, fell from 79% on once-daily to 38% on 3-times daily dosing (Paes et al 1997).

Adherence to antihypertensive treatment is inversely related to achieved BP levels, ie, nonadherent patients tend to have higher BP than adherents. In a prospective study of 347 hypertensive patients, BP levels were compared between adherents and nonadherents with antihypertensive treatment (Khalil and Elzubier 1997). Patients were considered adherent if the number of pills prescribed or dispensed – the number of pills missed/number of pills prescribed or dispensed for the interval time  $\times 100$  was >80%. BP was significantly lower in adherent than in nonadherent patients.

Adherence rate is also inversely related to the number of drugs given. Patients are more adherent when they take a combination as a single tablet than if they are given the same drugs as 2 separate pills, even when dosed once daily (Neutel 2005). A meta-analysis of 9 studies which compared fixed-dose combinations versus free-drug components of the regimen separately for treatment of hypertension (4 studies), diabetes (2 studies), tuberculosis (2 studies), and human immunodeficiency virus (HIV) disease (1 study), showed that fixed-dose combinations decreased rate of nonadherence by 26% compared with free-drug component regimens (Bangalore et al 2007). A subgroup analysis of the four studies in hypertension showed that fixed-dose combinations decreased the risk of medication nonadherence by 24% compared with free-drug combinations (Figure 2) (Bangalore et al 2007).

Fixed-dose combination therapy is an efficacious, relatively safe, and possibly cost-effective method of decreasing BP in most patients with essential hypertension (Sica 2002). Initiating therapy with more than one agent offers the potential advantages of achieving BP control more rapidly and avoiding dose-related adverse effects of individual drugs by producing greater BP reductions at lower doses of the component agents. Fixed-dose combinations also have other advantages (Table 1) (Lewanczuk and Tobe 2007; Woodham and Oparil 2007).

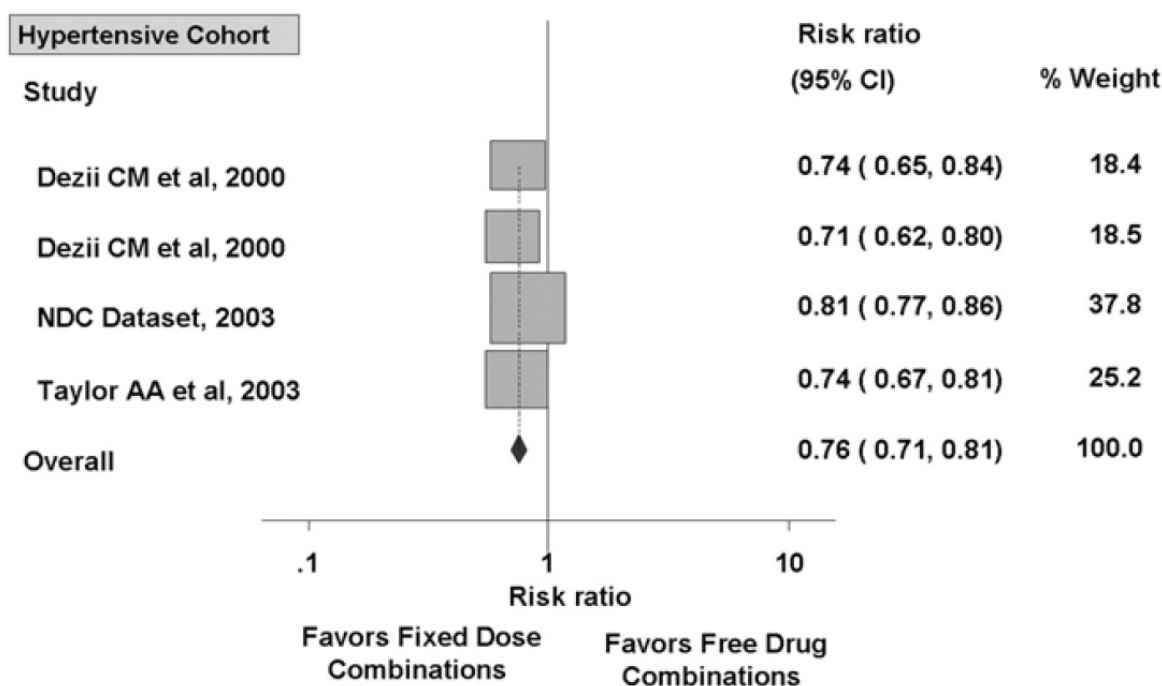
Adherence to antihypertensive treatment increases with fixed-dose combinations (Figure 3). Adherence to a fixed-dose combination of the calcium channel blocker (CCB) amlodipine with the angiotensin converting-enzyme (ACE)



**Figure 1** Algorithm for treatment of hypertension. BP, blood pressure. Modified from Chobanian et al (2003).

inhibitor benazepril has been compared with adherence to free-dose combination therapy of the two agents in a retrospective analysis of data obtained from a pharmacy claims database in the US (Wanovich and Kerrish 2004). Patients who received 2 or more prescriptions for the fixed-dose combination ( $n = 2,839$ ) or the two components separately

( $n = 3,367$ ) were identified and followed up for an average of 259 days and 247 days, respectively. Adherence to fixed-dose combination therapy was significantly greater than for free combination therapy, 88% vs 69%, respectively. In another study, hypertensive subjects receiving once-daily, single-capsule, fixed-dose combination of amlodipine – benazepril



Heterogeneity  $\chi^2 = 6.30$  ( $p = 0.10$ )

Publication Bias (Egger's)  $p = 0.05$

**Figure 2** Effect of fixed-dose combinations versus free-drug combination on the risk of medication nonadherence in cohort with hypertension. Reprinted from Bangalore S, Kamalakkannan G, Parkar S, et al 2007. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 120:713–19. Copyright © 2007, with permission from Elsevier.

demonstrated significantly better medication adherence than subjects receiving an ACE and a CCB as separate components, 80.8% vs 73.8%, respectively (Taylor and Shoheiber 2003). The average annual cost of CV-related care per subject was also significantly lower in hypertensive patients receiving the fixed-dose.

The most important reason for use of combination therapy in clinical practice is that combining two antihypertensive agents with complementary mechanisms of action produces significantly greater BP reducing efficacy than either of the components as monotherapy (Chrysant 1994; Chrysant et al

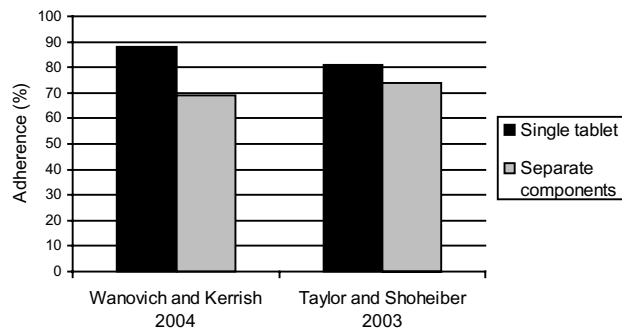
2004; Hasebe 2005). As hypertension is multifactorial and many pathophysiologic factors contribute to high BP, the combination of agents with different (and complementary) mechanisms of action provides more complete blockade of pressor mechanisms with less activation of counter-regulatory mechanisms. For example, diuretics activate the renin-angiotensin-aldosterone system (RAAS), reduce volume, and make BP more angiotensin dependent. Concomitant administration of an ACE inhibitor or an angiotensin II receptor blocker (ARB) blocks angiotensin II generation or action, minimizing the compensatory pressor effect of diuretic-induced RAAS activation and producing an additive BP-lowering effect.

Combination therapy also improves tolerability by reducing dose-dependent side effects (clinical or metabolic) of individual components. Upward dose titration in an attempt to avoid the addition of a second agent often leads to increases in dose-dependent side effects, resulting in discontinuation of therapy. Appropriate combination therapy can also improve tolerability if one component can neutralize the adverse effects of the second agent. For example, the tendency for thiazides to cause hypokalemia is blunted by concomitant use of potassium-sparing diuretics, ACE inhibitors, or ARBs. In

**Table 1** Advantages of fixed-dose combination therapy

- Increased compliance, simplified titration, and convenience of use.
- Potentiation of antihypertensive effects of single compounds.
- Additive or synergistic effects.
- Enhancing effect in specific populations.
- Attenuation in adverse events.
- Decreases in diuretic-induced metabolic changes with ACE inhibitors or ARBs.
- Decrease in calcium channel antagonist-related peripheral edema with ACE inhibitors or ARB.
- Improved overall results, greater BP response, and lower cost.

**Abbreviations:** ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure.



**Figure 3** Medication adherence with combination of amlodipine/benazepril single-tablet compared to same combination as separate components.

a prospective 8-week study of 1,346 hypertensive patients, the incidence of hypokalemia was lower in those assigned to receive valsartan – hydrochlorothiazide (HCTZ) than in those assigned to HCTZ monotherapy (Pool et al 2007). Further, the peripheral edema caused by the dihydropyridine CCB amlodipine is reduced with ARBs or ACE inhibitors (Messerli et al 2000; Neutel et al 2005; Philipp et al 2007). For example, in a prospective randomized double-blind study of 1,079 hypertensive patients who were assigned to receive amlodipine/benazepril or amlodipine or nifedipine monotherapy, the incidence of edema was 15% in the high-dose nifedipine group and 24% in the high-dose amlodipine group and was greatly reduced in patients treated with any dose of combination therapy (1.5%–3.8%) or low-dose CCB (4.9%–5.4%) (Messerli et al 2000). In another prospective study of 1,911 patients, the incidence of peripheral edema was significantly lower in patients randomized to receive the ARB valsartan plus amlodipine than in patients treated with amlodipine monotherapy (5.4% vs 8.7%, respectively;  $p = 0.014$ ) (Philipp et al 2007).

## Overview of currently available fixed combinations

The very earliest outcome trial of antihypertensive therapy, the Veteran's Administration Cooperative Study on Antihypertensive Agents, demonstrated dramatic reductions in CV outcomes with a triple combination of HCTZ, reserpine, and hydralazine compared with placebo (Veterans Administration Cooperative Study 1967). Fixed-dose combinations of newer antihypertensive drugs have been developed in recent years, in response to the realization that most patients require multiple antihypertensive agents for BP control (Prisant et al 1995). The currently available fixed-combination therapies are listed in Table 2.

ACE inhibitor – diuretic or ARB – diuretic combinations are the most commonly used fixed-dose combination

antihypertensive agents because of an additive effect on BP reduction related to complementary mechanisms of action of the components and the favorable vascular, metabolic, cardiac, and renoprotective effects of the ACE inhibitors and ARBs (Lewis et al 1993; Weir and Dzau 2001; Chobanian et al 2003). Randomized controlled clinical trials that compared the combination versus monotherapy with either ACE inhibitor or HCTZ have generally demonstrated greater BP-lowering efficacy with low-dose combinations over higher-dose monotherapy with either single agent. In a representative trial, patients were randomized to 8 weeks of placebo, lisinopril 10 mg, HCTZ 12.5 mg, HCTZ 25 mg, or combination therapy with lisinopril 10 mg and either HCTZ

**Table 2** Currently available combination antihypertensives in US in 2007

### ACE inhibitors and diuretics

Benazepril – HCTZ  
Captopril – HCTZ  
Enalapril – HCTZ  
Lisinopril – HCTZ  
Fosinopril – HCTZ  
Quinapril – HCTZ  
Moexipril – HCTZ

### ARBs and diuretics

Losartan – HCTZ  
Valsartan – HCTZ  
Irbesartan – HCTZ  
Telmisartan – HCTZ  
Olmesartan – HCTZ  
Candesartan – HCTZ  
Eprosartan – HCTZ

### Potassium-sparing diuretics and HCTZ

Amiloride – HCTZ  
Spironolactone – HCTZ  
Triamterene – HCTZ

### BBs and diuretics

Metoprolol – HCTZ  
Timolol – HCTZ  
Atenolol – Chlorthalidone  
Bisoprolol – HCTZ  
Nadolol – Bendroflumethiazide  
Propranolol – HCTZ

### ACE inhibitors and CCB

Enalapril – Diltiazem  
Benazepril – Amlodipine  
Enalapril – Felodipine  
Trandolapril – Verapamil

### ARBs and CCBs

Valsartan – Amlodipine  
Olmesartan – Amlodipine

**Abbreviations:** ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BB,  $\beta$ -blockers; CCB, calcium-channel blockers; HCTZ, hydrochlorothiazide.



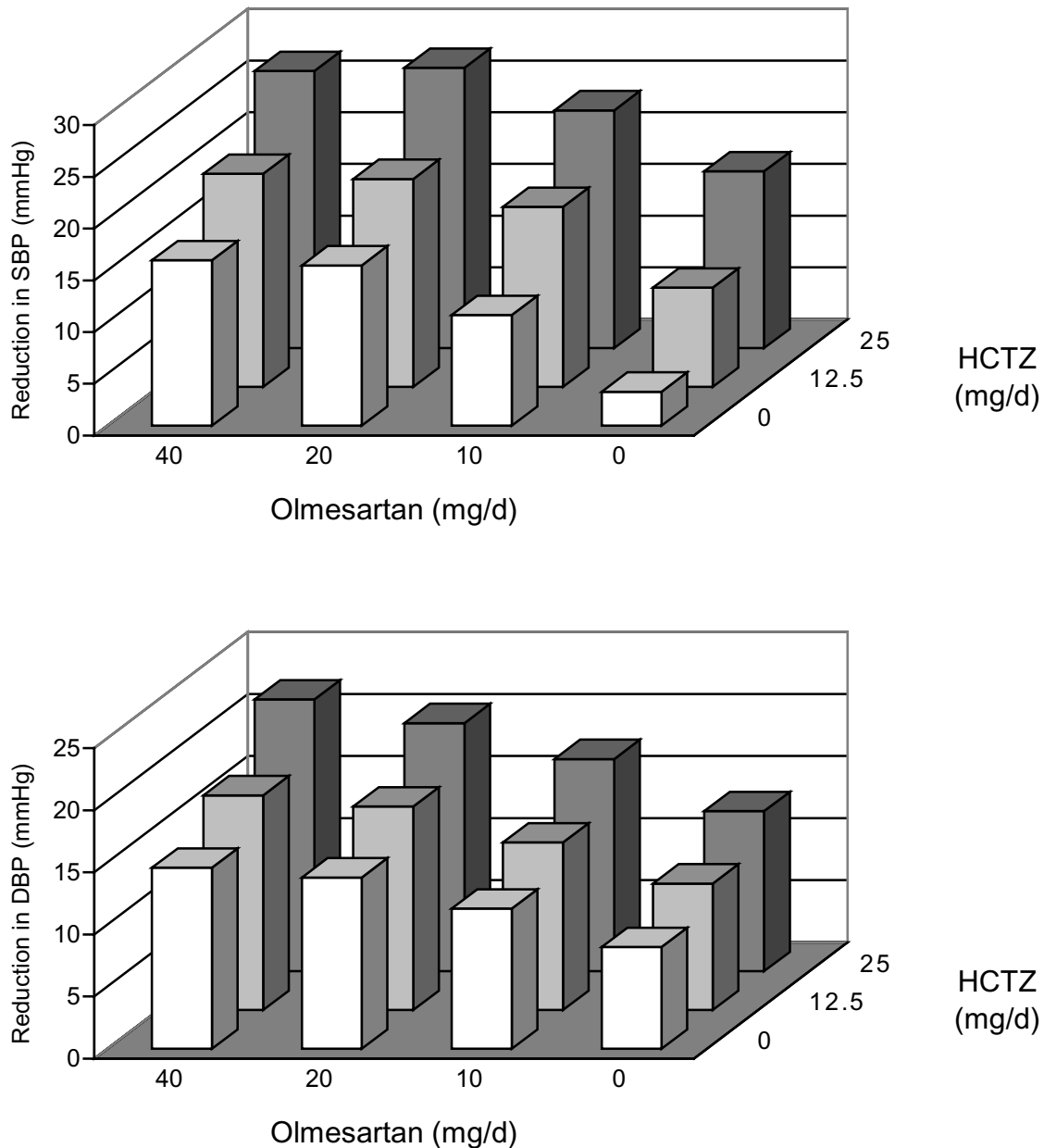
12.5 mg or 25 mg (Chrysant 1994). Monotherapy with either agent lowered DBP by 6–8 mmHg over placebo, and combination therapy produced a further 6–7 mmHg reduction in DBP. BP response rate, defined as a decrease in DBP of >10 mmHg or achieving a goal of <90 mmHg, was higher with combination therapy (70%–80%) than with lisinopril or HCTZ monotherapy (40%–50%).

Similarly, studies of ARB – diuretic combinations have demonstrated significantly greater reductions in SBP and DBP compared with monotherapy with either individual agent. A representative factorial study evaluated the efficacy of regimens that included either olmesartan 10–40 mg a day, HCTZ 12.5 or 25 mg a day, placebo, or the combination of olmesartan and HCTZ (Chrysant et al 2004). The greatest effect on BP was noted in the arm receiving 40 mg of olmesartan and 25 mg of HCTZ, in which SBP decreased by 23.5 mmHg and DBP by 13.7 mmHg more than with placebo (Figure 4). The addition of diuretic to placebo or to any dose of olmesartan produced an additional BP response compared with placebo or olmesartan alone. Control (<140/90 mmHg) rates were greater in patients taking the highest dose of the combined agents than in those taking the highest doses of monotherapies.

ACE inhibitor – CCB combinations also have additive antihypertensive effects and offer the added advantage of minimizing adverse effects of individual components (eg, edema with dihydropyridine CCBs). The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) presented evidence that a CCB – ACE inhibitor combination is more effective in lowering BP and reducing risk of mortality and major CV events than traditional therapy with a  $\beta$ -blocker (BB) – thiazide combination (Dahlöf et al 2005; Poulter et al 2005). ASCOT included 19,257 hypertensive patients randomly assigned to either amlodipine-based treatment (with the option of adding perindopril) or to atenolol-based treatment (with the option of adding bendroflumethiazide). BP control was defined as <140/90 mmHg in patients without diabetes and <130/80 mmHg with diabetes. The CCB – ACE inhibitor combination lowered BP by an average of 2.7/1.9 mmHg more than the BB – diuretic combination throughout the 5.5 year median follow-up period. Significant reductions in a number of outcomes (all-cause mortality, nonfatal myocardial infarction, and new-onset diabetes) were noted with CCB – ACE inhibitor compared with BB – diuretic. Importantly, by the end of the trial only 15% and 9% of participants were taking amlodipine or atenolol monotherapy, respectively, providing additional evidence for the inadequacy of monotherapy for BP control.

Similar to the ACE inhibitor – CCB combination, ARB – CCB combinations have showed efficacy in reducing BP. The Nifedipine and Candesartan Combination Study (NICE Combi) randomized 258 hypertensive patients to receive controlled-release nifedipine 20 mg plus candesartan 8 mg in combination or up-titration of candesartan 12 mg monotherapy (Hasebe et al 2005). BP reduction was significantly greater in the combination therapy group (12.1/8.7) than in the up-titrated monotherapy group (4.1/4.6,  $p < 0.0001$ ) after 8 weeks of follow-up. The NICE Combi study provides additional evidence that low-dose fixed combination therapy is more effective in reducing BP than monotherapy in high-dose.

ACE inhibitor – CCB combination therapy has become widely used due to high efficacy in reducing BP and high tolerability. Evidence that both CCBs and ACE inhibitors have beneficial effects on endothelial function (Taddei et al 2000) has also led to the hypothesis that, for the same BP effects, an ACE inhibitor – CCB combination may have outcome advantages over an ACE inhibitor – diuretic combination. Further, it has been hypothesized that the neutral metabolic effects of amlodipine, in contrast to the adverse metabolic effects of diuretics, translate into better clinical outcomes, even when each agent is combined with an ACE inhibitor. The latter argument has provided the rationale for the Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, the first randomized controlled blinded study to compare prospectively the effects of 2 fixed combinations of antihypertensive drugs, benazepril – amlodipine and benazepril – HCTZ on CV disease outcomes in high-risk hypertensive patients (Jamerson et al 2004). The primary study endpoint is a composite of CV mortality and morbidity and the secondary endpoints include new onset diabetes, progression of renal disease, and hospitalization for congestive heart failure. Early unblinded results from 10,704 participants from both treatment groups combined have shown higher BP control rates compared with previous clinical trials (Jamerson et al 2007). The 6-month BP control rate (<140/90 mmHg) was 73% in the overall trial (78% in the US); 43% of diabetics and 40% of patients with renal disease achieved the more aggressive BP goal of <130/80 mmHg. Serious hypotensive events occurred in only 1.8%, suggesting that these combinations are appropriate and safe for hypertensive patients who are at high-risk. Final results of ACCOMPLISH will provide insight into whether CCB – RAAS inhibitor combination therapy offers advantages over diuretic-RAAS inhibitor combinations in



**Figure 4** Reduction (model fitted) in seated systolic blood pressure (SBP) (upper panel) and seated diastolic blood pressure (DBP) (lower panel) for 12 groups in the factorial design by olmesartan medoxomil and hydrochlorothiazide (HCTZ) dosage. Adapted by permission from Macmillan Publishers Ltd: Chrysant SG, Weber MA, Wang AC, et al 2004. Evaluation of antihypertensive therapy with combination of olmesartan medoxomil and hydrochlorothiazide. *Am J Hypertens* 17:252–9. Copyright © 2004.

lowering BP, minimizing adverse effects, and preventing morbid and mortal CV events.

## Amlodipine Pharmacology

Dihydropyridine CCBs act by decreasing  $\text{Ca}^{2+}$  entry to cells through the L-type  $\text{Ca}^{2+}$  channel (Krum 1997; Messerli 2003). Decreased availability of intracellular  $\text{Ca}^{2+}$  in arterial smooth muscle cells prevents actin and myosin from interacting, resulting in vasodilation (Prisant 2005). Dihydropyridine

CCBs also facilitate natriuresis by increasing renal blood flow, dilating afferent arterioles, and increasing glomerular filtration pressure.

Amlodipine is a long-acting third generation dihydropyridine CCB that is the most commonly used agent in its class for the treatment of hypertension (Abernethy and Schwartz 1999; Basile 2004). More than 90% of amlodipine is absorbed and 95% of circulating amlodipine is bound to plasma proteins. It does not have an extensive hepatic first-pass metabolism, which contributes to its prolonged effect.

The time to peak effect of amlodipine is 10–14 hours; its elimination half-life is 35–45 hours and steady-state plasma levels are reached after 7–8 days of consecutive daily dosing (Prisant 2005). About 90% of amlodipine is converted to inactive metabolites via hepatic metabolism, and 60% of the metabolites are excreted in the urine. In patients with chronic kidney disease, the pharmacokinetics of amlodipine are minimally changed. In hepatic disease, diminished systemic clearance may necessitate dosage adjustments. Aging slows the metabolism of amlodipine, presumably secondary to the accompanying decrease in hepatic blood flow, sometimes necessitating dosage adjustments in the elderly (Prisant 2005; Weir 2008). Amlodipine may cause reflex tachycardia early in the course of therapy or at very high doses, but this sympathoexcitatory effect is not evident with usual clinical doses or with long term treatment (Weir 2008).

## Efficacy and safety

Amlodipine effectively lowers BP and is also effective in reducing CV disease outcomes, both morbid and mortal, with the exception of heart failure. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), more than 40,000 high risk hypertensive patients were randomly assigned to receive chlorthalidone, amlodipine, lisinopril, or doxazosin (ALLHAT 2002). Participants were men and women aged 55 years or older who had stage 1 or stage 2 hypertension with at least 1 additional risk factor for coronary heart disease events. ALLHAT tested the hypothesis that the newer drug classes (CCBs, ACE inhibitors,  $\alpha$ -blockers) are superior to the thiazide-like diuretics in preventing fatal and nonfatal coronary events. Thus, due to the design of the trial, the effects of a RAAS inhibitor-CCB combination could not be tested. ALLHAT is the only large outcome trial in hypertension that has included a racially/ethnically diverse patient population (35% Black, 19% Hispanic) and a large (36%) population of diabetics. Amlodipine was as effective as chlorthalidone in reducing the primary combined endpoint of fatal coronary heart disease or nonfatal myocardial infarction. In addition, amlodipine was effective in reducing combined coronary heart disease events and end-stage renal disease. However, incidence of heart failure was 38% higher in patients assigned to amlodipine than patients assigned to chlorthalidone in the absence of concomitant RAAS inhibitor therapy in either group. There was no significant difference in adverse effects between amlodipine and chlorthalidone based therapy, refuting previous claims that dihydropyridine CCBs precipitate coronary events.

The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial compared the effects of amlodipine and valsartan as first-line therapy in reducing CV outcomes in hypertensive patients at high CV risk (Julius et al 2004). Amlodipine treatment was associated with a more prompt and robust reduction in BP than valsartan treatment, particularly early in the trial when participants were on monotherapy. In the study as a whole, amlodipine treatment was associated with a significantly greater reduction in the incidence of nonfatal myocardial infarction compared with valsartan treatment. Subanalysis of VALUE results reported that patients treated with amlodipine monotherapy had a 22% higher risk of heart failure than those treated with valsartan monotherapy; there were no other significant outcome differences (Julius et al 2006). These data are consistent with the findings in ALLHAT that amlodipine does not prevent heart failure as effectively as some other antihypertensive drugs. However, data from Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study showed that amlodipine does not increase CV morbidity or mortality in patients with severe heart failure, suggesting that this CCB does not worsen established heart failure (Packer et al 1996).

In ASCOT, the amlodipine – perindopril regimen was more effective in reducing BP and preventing CV events than the atenolol – bendroflumethiazide regimen (Dahlöf et al 2005). BP was, on average, 2.7/1.9 mmHg lower in the amlodipine group than in the atenolol group during 5.7 years of follow-up. Amlodipine  $\pm$  perindopril was also superior in preventing fatal and nonfatal stroke, total CV events and procedures, and all-cause mortality than atenolol  $\pm$  bendroflumethiazide. Interestingly, the incidence of fatal and nonfatal heart failure did not differ between amlodipine- and atenolol-based regimens, suggesting that blocking the RAAS neutralizes the adverse effects of amlodipine monotherapy. By the end of the trial, 85% of patients assigned to amlodipine and 91% of those assigned to atenolol were taking at least 2 antihypertensive agents, reinforcing the concept that combination therapy is needed to control BP in high risk hypertensive patients. There was a significant difference in favor of the amlodipine-based regimen in the proportion of patients who stopped the trial therapy because of serious adverse events.

Amlodipine has been proven effective in decreasing left ventricular mass in hypertensive patients. In a 1-year prospective study of 59 patients with diastolic hypertension who were randomized to lisinopril or amlodipine, amlodipine decreased left ventricular mass as effectively as lisinopril ( $-11.0$  g/m<sup>2</sup> vs  $-12.6$  g/m<sup>2</sup>, respectively) (Beltman et al 1988).



Further, in the Effects of Amlodipine and Lisinopril on Left Ventricular Mass and Diastolic Function (ELVERA) trial, which compared amlodipine with lisinopril therapy in 166 elderly patients with hypertension (95–115/160–220 mmHg), amlodipine and lisinopril reduced left ventricular mass and improved diastolic function to a similar extent after 2 years of follow-up (Terpstra et al 2001).

## Olmesartan Pharmacology

ARBs lower BP by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle and other cell types (Ruddy and Kostis 2005). Olmesartan medoxomil, the most recently developed ARB, is rapidly and completely bioactivated by ester hydrolysis in the gut wall to the pharmacologically active compound olmesartan, with peak plasma concentrations achieved between 1 and 3 hours and an elimination half-life of 12–18 hours (Laeis et al 2001; Schwocho and Masonson 2001). The absolute bioavailability of olmesartan medoxomil after oral administration is 26%–28.6%. Steady-state plasma concentrations are reached within the first few days, and accumulation is not noted on long-term dosing. Olmesartan is not metabolized; 35%–50% of the systemically available active compound is excreted unchanged in the urine and the remainder in the bile. Olmesartan medoxomil has minimal or no inhibitory activity on human cytochrome p450 (Laeis et al 2001; Schwocho and Masonson 2001). Olmesartan has a unique mechanism of binding to the AT1 receptor that appears to contribute to its sustained duration of AT1 receptor blockade (Miura et al 2006, 2008). This involves the “double chain domain”, whereby olmesartan binds to the receptor at 2 sites, a –OH group and an  $\alpha$ -COOH group, whereas other ARBs bind only at the –OH group. It has been shown that olmesartan produces more sustained inhibition of the pressor effects of infused angiotensin than other ARBs in normotensive adults, suggesting a more prolonged blockade of the AT1 receptor. It has been hypothesized (but not proven) that this sustained pressor inhibition is a function of the “double chain domain” binding.

## Efficacy and safety

Olmesartan reduces BP rapidly and effectively in hypertensive patients. An analysis of 7 randomized, double-blind, placebo-controlled, parallel-group studies compared the safety and efficacy of olmesartan monotherapy with placebo in patients with essential hypertension (Neutel 2001). Olmesartan produced dose-dependent BP reductions in both

DBP and SBP within 1 week of initiating treatment, and the response was nearly maximal within 2 weeks.

At traditionally recommended starting doses, olmesartan reduces BP more effectively than other ARBs (Oparil et al 2005). A 588 patient, multicenter, randomized, double-blind, trial that compared once-a-day therapy with the recommended starting doses of losartan, valsartan, and irbesartan showed a significantly greater reduction in sitting cuff DBP at trough with olmesartan (11.5 mmHg) than with losartan, valsartan, and irbesartan (8.2, 7.9, and 9.9 mmHg, respectively,  $p < 0.005$  olmesartan vs losartan;  $p < 0.05$  olmesartan vs valsartan and irbesartan) (Oparil et al 2001). Reductions in cuff SBP with the four ARBs had the same numerical trend, but differences between treatments were not statistically significant due to variability in the data. The reduction in mean 24-hour DBP with olmesartan (8.5 mmHg) was significantly greater than reductions with losartan and valsartan (6.2 and 5.6 mmHg, respectively,  $p < 0.05$ ) and showed a trend toward significance compared with the reduction in DBP with irbesartan (7.4 mmHg;  $p = 0.087$ ). The reduction in mean 24-hour SBP with olmesartan (12.5 mmHg) was significantly greater than those with losartan and valsartan (9.0 and 8.1 mmHg, respectively) and equivalent to the reduction with irbesartan (11.3 mmHg). All drugs were well tolerated.

The differences in BP reduction with olmesartan compared with other ARBs are attenuated at higher doses. In an 12-week, randomized, double-blind, forced titration study, 723 hypertensive patients were assigned to receive olmesartan, losartan, and valsartan (Giles et al 2007). Patients were randomized to olmesartan 20 mg, losartan 50 mg, valsartan 80 mg, or placebo, all once daily. Doses were titrated to 40, 100, and 160 mg once daily for olmesartan, losartan, and valsartan, respectively, after 4 weeks of treatment. At week 8, doses were titrated to 50 mg twice daily for losartan and 320 mg once daily for valsartan; olmesartan remained at the maximum recommended dose of 40 mg once daily. All three medications significantly reduced mean seated DBP from baseline compared with placebo. At week 8, patients receiving olmesartan 40 mg once daily had significantly greater reductions in mean seated DBP than those receiving losartan (–15.2/–12.9 vs –10.9/–9.4 mmHg, respectively,  $p < 0.001$ ); there was no significant difference compared with valsartan. A significantly greater percentage of patients achieved BP goals ( $<140/90$  mmHg) with olmesartan compared with losartan and valsartan (39.7, 19.8, and 29.0%, respectively,  $p < 0.001$  vs losartan and  $p = 0.031$  vs valsartan).

Olmesartan has vasoprotective and antiinflammatory effects that are unrelated to BP reduction. In the European

Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis (EUTOPIA) study, investigators compared the antiinflammatory effects of olmesartan alone and with pravastatin in patients with essential hypertension and microinflammation (Fliser et al 2004). Olmesartan treatment significantly reduced serum levels of high-sensitivity C-reactive protein (CRP), high-sensitivity tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) compared to placebo independently of BP reduction. Treatment with pravastatin alone did not significantly alter inflammation markers. The Vascular Improvement with Olmesartan medoxomil Study (VIOS) tested the hypothesis that suppression of RAAS with olmesartan reverses abnormal remodeling of resistance vessels and has favorable effects on central hemodynamics compared to suppression of sympathetic drive with the BB atenolol despite equivalent BP control (Smith et al 2007). In the presence of nearly physiological BP control, olmesartan reversed small resistance vessel remodeling virtually back to normal, while atenolol had little to no effect on the vascular wall. Further, olmesartan, but not atenolol, reduced the augmentation index. Thus, olmesartan has favorable effects on surrogate endpoints, but results of outcome trials are not yet available.

## **Olmesartan – amlodipine combination**

### **Pharmacology**

The pharmacokinetics of the olmesartan – amlodipine combination are equivalent to the pharmacokinetics of amlodipine and olmesartan medoxomil administered separately (Haworth et al 2007a; Rohatagi et al 2007; Salazar et al 2007). The bioavailability of the combination is well below 100%, and is not affected by food (Haworth et al 2007b).

### **Efficacy and safety**

The combination of olmesartan and amlodipine in a single tablet effectively reduces BP and attenuates the adverse events of the amlodipine component in hypertensive patients. An 8-week, multi-center, double-blind, randomized, placebo-controlled, parallel-group, factorial study of 1,940 subjects with mild to severe hypertension (seated DBP ranging from 99 to 120 mmHg) compared BP responses with placebo, monotherapy with amlodipine 5 mg or 10 mg, with olmesartan medoxomil 10, 20, or 40 mg, and combination therapy with amlodipine – olmesartan medoxomil at doses of 5/10, 5/20, 5/40, 10/10, 10/20, and 10/40 mg (Chrysant et al 2007).

All combinations produced greater mean reductions in BP than either drug alone. The highest dose combination, amlodipine 10 mg plus olmesartan 40 mg, reduced SBP by 30.1 mmHg, a 53% greater reduction than with 10 mg amlodipine alone. DBP was reduced by 19 mmHg, compared with 12.7 mmHg for amlodipine alone. Addition of olmesartan to amlodipine decreased the amlodipine-related adverse effects. All combinations of amlodipine 10 mg with olmesartan demonstrated less peripheral edema than amlodipine 10 mg monotherapy.

## **Patient perspective**

Although recent guidelines and advisory statements are recommending lower thresholds and goals for antihypertensive treatment, approximately two-thirds of patients do not achieve the goals. Population characteristics, such as increased life expectancy, higher obesity rates, and decreased physical activity, as well as provider characteristics, including inadequate attention to SBP elevations and the more aggressive BP goals recommended by recent guidelines, are factors that predispose to antihypertensive treatment resistance. For patients with difficult-to-control hypertension, the fixed-dose combination offers many advantages, such as convenience of use, fewer adverse events, greater antihypertensive potency, and lower cost.

## **Conclusions**

Combination therapy is recommended by treatment guidelines and has become widely accepted by health care providers for the therapy of hypertension. Fixed-dose combinations provide effective antihypertensive treatment by achieving BP goals more frequently, improving patient adherence, and decreasing adverse effects.

Use of effective combination therapies blocks two or more BP regulatory systems, thus providing more effective and more physiologic reduction in BP than most monotherapies. Outcomes studies support inclusion of ARBs, such as olmesartan, and CCBs, such as amlodipine, in antihypertensive drug regimens.

## **Disclosures**

Dr. Pimenta has no conflicts. Dr. Oparil has received grants-in-aid from Abbott Laboratories, AstraZeneca, Aventis, Biovail, Boehringer Ingelheim, Bristol Myers-Squibb, Forest Laboratories, GlaxoSmithKline, Novartis, Merck and Co, Pfizer, Sankyo Pharma, Sanofi-Synthelabo, and Schering-Plough; has served as consultant for Bristol Myers-Squibb,

Daiichi Sankyo, Merck and Co, Novartis, Pfizer, Sanofi Aventis, and The Salt Institute; and is a member of Board of Directors for Encysive Pharmaceuticals.

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