Amlodipine and valsartan: calcium channel blockers/angiotensin II receptor blockers combination for hypertension

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Despite the availability of numerous antihypertensive agents, many patients with hypertension fail to achieve the blood pressure goals set out in current guidelines. These patients remain at a high risk of cardiovascular morbidity and mortality and require effective treatment options to reduce that risk. Current guidelines recognize that many patients require multiple antihypertensive agents to achieve blood pressure goals. Numerous combination therapies are available, although there is currently no available fixed-dose alternative that combines the benefits of angiotensin receptor blockers and calcium channel blockers. This article explores the rationale for using multiple-mechanism therapy with the angiotensin receptor blocker valsartan and the calcium channel blocker amlodipine and discusses the clinical data supporting this novel approach to the treatment of hypertension.

Burden of cardiovascular disease & poor hypertension control in Europe

In Europe, cardiovascular disease (CVD) causes 4.35 million deaths per year (49% of all deaths) and costs the EU economy an estimated US$169 billion per year [1]. Hypertension, which is defined as a blood pressure (BP) greater than 140/90 mmHg [2], is one of the most common treatable risk factors for CVD [3]. Almost half of all European adults (aged 35–64 years) and a quarter of the world's adult population have hypertension [4,5].

Although it is well established that antihypertensive therapy can reduce the risk of CVD, rates of BP control remain suboptimal [6]. Current European guidelines set a BP target of less than 140/90 mmHg [2], which is not often achieved. The high frequency of uncontrolled hypertension was illustrated in the WHO Multinational mONItoring of trends and determinants in CArdiovascular disease (MONICA) project, which evaluated the prevalence and control of hypertension in two independent, cross-sectional surveys conducted between the early 1980s and mid-1990s in 24 populations in Europe, Australia, Canada and the USA [7]. These surveys demonstrated that among hypertensive individuals aged 35–64 years, only 13–38% of men and 17–54% of women were receiving BP-lowering treatment. Even when antihypertensive therapy is administered, many patients still do not achieve adequate BP control. The MONICA studies showed that 13–67% of treated men and 12–63% of treated women achieved BP control. Recent data suggest that no more than 10% of treated patients achieve BP targets in many European countries [3].

Inadequate control of BP exposes patients to a high risk of long-term cardiovascular (CV) complications, such as myocardial infarction (MI), heart failure, stroke, renal disease and premature mortality [8]. For individuals aged 40–69 years, the risk of CVD-related mortality doubles with each 20 mmHg increment in systolic BP (SBP) or 10 mmHg increase in diastolic BP (DBP) over a BP range of 115/75–185/115 mmHg [9]. CV complications arising from inadequately treated hypertension also impose a substantial financial burden due to increased hospitalization and healthcare costs [10].

Barriers to adequate blood pressure control

Poor control of hypertension can be attributed to several factors. These include patient-related factors (e.g., lack of knowledge or awareness of hypertension), environmental factors (e.g., smoking or sedentary lifestyle) and physician-related factors (e.g., inadequately aggressive treatment).

The asymptomatic nature of hypertension and lack of knowledge regarding target BP levels present major obstacles to achieving adequate BP control. Large-scale surveys conducted as part of the WHO MONICA project demonstrated that the percentage of individuals who were aware of their hypertension ranged from 30% in Belfast, UK, to 62% in Catalonia, Spain [7]. Although rates of awareness and treatment of hypertension increased during the 10-year study

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period, BP control remained far from adequate, suggesting that early and more aggressive treatment is critical, as are more comprehensive interventions, such as lifestyle changes and increased monitoring of BP levels.

Numerous environmental factors, such as smoking, alcohol consumption, caloric intake, salt and potassium intake and lack of physical activity, can adversely affect BP control. Although comprehensive lifestyle modification has been shown to improve BP control [11] and treatment guidelines stress the importance of adopting a healthy lifestyle [2], such interventions are generally underutilized [12] and compliance with these nonpharmacological measures is generally poor [13].

The term 'clinical inertia' describes a situation in which the physician recognizes that there is a problem, but fails to act [14]. Studies of physicians' behavior have shown that they frequently fail to increase the dose of antihypertensive medications or to try new treatments in patients with elevated BP [15]. For example, in a European survey published in 1993, 84% of physicians admitted to taking no action if a patient's BP was higher than the recommended goal [16].

Poor compliance with therapy is a major problem among patients with hypertension and is one of the main causes of failure to adequately control BP [17]. While many factors contribute to poor compliance, such as a patient's knowledge, attitudes and beliefs or medication cost, it is the complexity of the dosing regimen and drug-related side effects that most likely play the largest roles in medication compliance [17].

Meeting the blood pressure control challenge: European treatment guidelines

Current European treatment guidelines recommend that, in all patients with hypertension, BP should be reduced to below 140/90 mmHg, with a more stringent target of 130/80 mmHg in patients with additional risk factors (e.g., diabetes or renal disease) [2]. The European Society of Hypertension (ESH)–European Society of Cardiology (ESC) guidelines recommend initiating antihypertensive therapy based not only on BP, but also on the total level of CV risk, including people with high-normal BP (130–139/85–89 mmHg) and additional risk factors.

In high-risk patients, rapid attainment of BP targets may have an important influence on clinical outcomes. This was supported by an analysis of data from the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial [18]. In VALUE, patients with hypertension and additional cardiac risk factors were rolled over from their current antihypertensive therapy to a regimen based on valsartan or amlodipine. The primary end point was a composite of cardiac morbidity and mortality. An analysis was carried out in the entire patient cohort comparing the outcomes in 'immediate responders' with those in 'delayed responders'. Immediate responders were defined as patients who had no increase in BP 1 month after switching to study medication or, among patients receiving no prior therapy, those with a SBP decrease at 1 month of 10 mmHg or greater. In this analysis, immediate responders had a significantly lower risk of cardiac events, stroke or death than delayed responders (**Figure 1**).

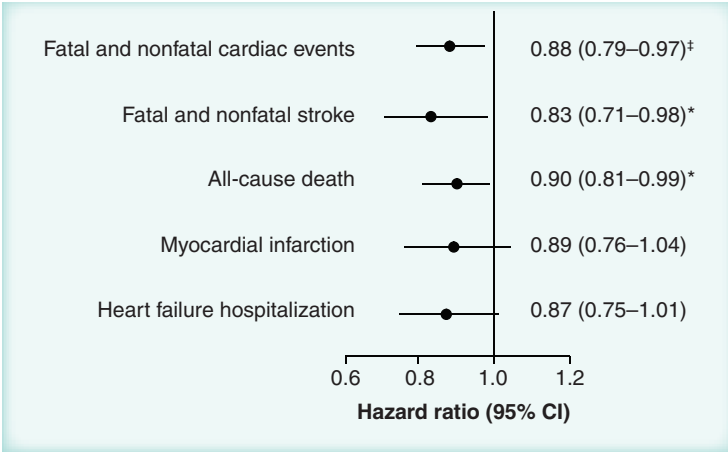
Further support for the association between time taken to reach BP targets and CV outcomes was provided in an open-label extension to the Systolic Hypertension in Europe (Syst-Eur) trial, which showed that patients who had originally received active therapy ('immediate' antihypertensive treatment) had a significantly lower risk of stroke (-28%) and CV complications (-15%), compared with patients who had originally received placebo ('delayed' therapy) [19]. These studies provide strong support for the hypothesis that rapid control of BP reduces the risk of CV events [20]. Therefore, there is a strong rationale for both prompt initiation of antihypertensive therapy and selection of agents that can achieve rapid reductions in BP.

The multifactorial nature of hypertension means that the majority of patients with hypertension will require at least two antihypertensive agents to achieve BP goals, especially given the more stringent targets currently being recommended [21]. This treatment strategy is endorsed by the various hypertension management guidelines, including those of the ESH–ESC, which state that '…to reach target BP, it is likely that a large proportion of patients will require combination therapy with more than one agent' [2].

Combination therapy

Fixed-dose combinations have a number of potential advantages compared with monotherapy or free combinations. Use of a fixed-dose combination may increase patient convenience by decreasing pill burden and simplifying

Figure 1. Hazard ratios for cardiovascular morbidity and mortality in immediate responders compared with nonimmediate responders in the VALUE study.



*p < 0.05.
‡p < 0.01.
CI: Confidence interval; VALUE: Valsartan Antihypertensive Long-term Use Evaluation.
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treatment. Improved convenience and a reduction in the complexity of a treatment regimen may translate into optimization of medication compliance and persistence, thus could conceivably help overcome one of the major barriers to effective BP control [17]. In addition, direct and indirect medical costs associated with managing high BP and associated CV complications are likely to decrease as a result of potential improvements in patient compliance with medications as well as the cardioprotective effects offered by each component.

Currently available combinations

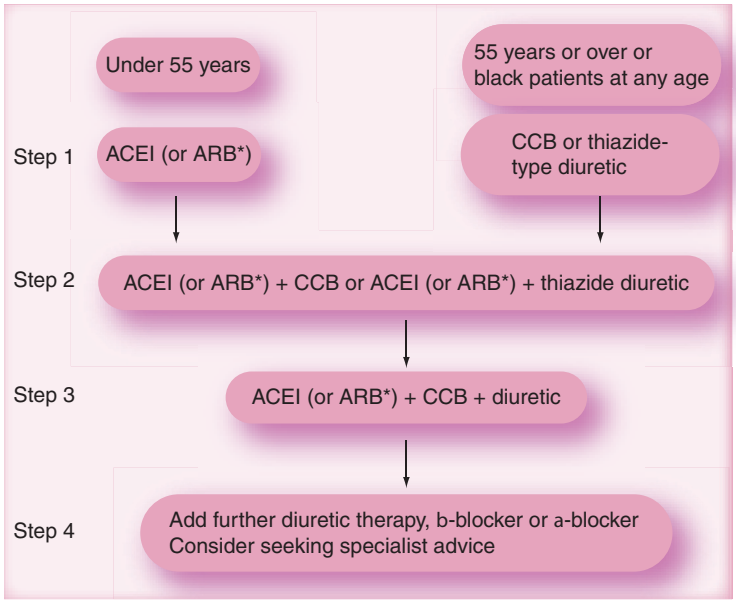
Numerous fixed combinations are available for the treatment of hypertension, including angiotensin-converting enzyme (ACE) inhibitors plus calcium channel blockers (CCBs), ACE inhibitors plus diuretics, angiotensin II receptor blockers (ARBs) plus diuretics, and β-blockers plus diuretics. A notable absentee from current combination therapies is the CCB/ARB combination, a therapeutic strategy that may be an appropriate choice for many patients with hypertension who are unable to attain BP goal [22]. The simultaneous blockade of two different pathways of BP control offered by a CCB/ARB has been shown to result in significantly greater BP reductions and improved BP control compared with its monotherapy components [23].

Although the use of β-blocker/diuretic therapy is much more effective at lowering BP in patients with hypertension than either of its constituents alone [24], there are reports of a greater risk of diabetes, itself a major risk factor for CVD, with this combination [25]. The use of β-blocker/diuretic combinations has declined in light of the findings from the Losartan Intervention For Endpoint reduction in hypertension study (LIFE) [26] and the Anglo–Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) [27], which showed that β-blockers may provide less protection for patients with hypertension than other classes of antihypertensive agents. ASCOT-BPLA showed that an amlodipine-based regimen reduced the risk of major cardiovascular events to a greater extent than an atenolol-based regimen, although there was no significant difference for the primary end point (nonfatal MI and fatal coronary heart disease), possibly owing to the early termination of the trial. The lower levels of protection afforded by β-blockers in the ASCOT-BPLA may have been due in part to a smaller antihypertensive effect, although the difference in CV protection appeared to be too great to be explained by BP alone [27]. The reductions in BP may also have been achieved more rapidly in the amlodipine group than in the atenolol group (the difference between groups was greatest at 3 months), which could be consistent with the hypothesis that rapid responders have a lower risk of cardiovascular outcomes than delayed responders. The results from ASCOT-BPLA provided the rationale for a recent update to the UK National Institute for Health and Clinical Excellence (NICE) guidelines, which now state that β-blockers are not a preferred initial therapy for hypertension (**Figure 2**) [28]. An analysis of the influence of concomitant β-blocker/diuretic therapy in VALUE adds further data to what is known about the metabolic disadvantages from this combination in terms of the increased risk of new-onset diabetes [29].

ACE inhibitors & ARBs in combination with diuretics

There is a strong rationale for treatment with combinations of an ACE inhibitor or ARB plus a diuretic, based on substantially increased percentages of patients achieving target BP reductions, compared with component monotherapies. In addition, inhibiting the renin–angiotensin system (RAS) with an ACE

Figure 2. Updated UK National Institute of Clinical Excellence guidelines for the treatment of newly diagnosed hypertension.



*If ACEI not tolerated.
ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; CCB: Calcium channel blocker.
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inhibitor or ARB prevents or reverses the effects of diuretics on serum glucose, lipids and potassium [30]. According to the recent update of the UK NICE guidance [28], ACE inhibitors or ARBs are the preferred first-choice treatment option for hypertensive patients aged less than 55 years and are the preferred second-line option for patients aged 55 years or over (**Figure 2**).

ACE inhibitors in combination with CCBs

The combination of ACE inhibitors and CCBs has been shown to provide greater BP-lowering efficacy than the component monotherapies [24,31–33]. ACE inhibitor/CCB combinations have been shown to be particularly effective at reducing BP in patients with hypertension and renal failure, without compromising remaining renal function [34,35], and in patients with Type 2 diabetes [36]. ASCOT-BPLA provided compelling evidence of the benefits of combination therapy with a CCB (amlodipine) and a RAS inhibitor (perindopril). ASCOT was a multicenter, prospective, randomized, controlled trial of 19,257 patients aged 40–79 years with hypertension and with at least three other CV risk factors. Patients were assigned to amlodipine plus perindopril or atenolol plus bendroflumethiazide. There were significant differences in BP in favor of the CCB/RAS inhibitor combination and, although the differences in the primary composite CV end point were not significant (risk reduction 10%; $p = 0.1$), the CCB/RAS inhibitor combination reduced the risk of stroke by 23%, total CV events and procedures by 16%, CV deaths by 24% and new-onset diabetes by 30% compared with β-blocker/diuretic therapy. By contrast, recent results from the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial indicated that the ACE inhibitor ramipril did not significantly reduce the incidence of new-onset diabetes, compared with placebo, in 5269 patients with impaired fasting glucose or impaired glucose tolerance (or both) and no pre-existing CVD [37]. However, the divergence of the Kaplan–Meier curves late in the study suggested that there might be a benefit in terms of diabetes prevention after 3.5 years [37], indicating that the study may have been under-powered or of too short a duration. Results from ongoing studies, such as the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, will provide additional information on the efficacy of RAS inhibitors for reducing new-onset diabetes.

Combining ACE inhibitors and CCBs also results in a lower incidence of peripheral edema than with CCB monotherapy [30]. ACE inhibitors are generally well tolerated, although chronic dry cough may be problematic for approximately 20% of patients [38].

ARBs in combination with CCBs

The use of a combination of an ARB and CCB has several potential benefits (**Table 1**), although the magnitude of effects on some aspects (e.g., costs associated with prevention of new-onset diabetes or angina) have yet to be quantified. Multiple-mechanism therapy with these agents has the potential to achieve rapid and additive BP-lowering efficacy by targeting the two key pathways involved in the regulation of BP [39,40]. ARBs target the RAS by blocking the angiotensin II, type 1 (AT_1) receptor, thereby promoting vasodilation and sodium and water excretion, and reducing activation of the sympathetic nervous system (SNS). CCBs stimulate peripheral vasodilation by blocking calcium channels in vascular smooth muscle cells. Targeting both of these key mechanisms has important benefits in terms of overcoming potential counter-regulatory mechanisms.

Table 1. Summary of potential benefits of CCB/ARB multiple-mechanism therapy, such as amlodipine/valsartan.

Potential benefits	Clinical consequences
Enhanced BP-lowering efficacy	Potentiation of the antihypertensive effect of a single compound Additive effect Neutralization of counter-regulatory mechanisms
Improved tolerability profile	Reduction in adverse events Not necessary to increase dose, thus reduction in dose-related adverse events Attenuation of adverse events (e.g., amlodipine-related peripheral edema)
Protective benefits	Benefits beyond BP lowering, e.g., - Reduced risk of new-onset diabetes mellitus - Anti-angina effects
Increased compliance and persistence	Simplified treatment regimen (compared with combination therapy given as separate pills) Offers convenience to patients Once-daily dosing Less complex treatment regimen/reduced pill burden
Potential health economic benefits	Cost likely to be less than two individual components Cost savings may also arise from: - Improved efficacy/getting to BP goal quicker and avoiding adverse cardiovascular outcomes - Improved tolerability profile - Less direct and indirect health costs

ARB: Angiotensin II receptor blocker; BP: Blood pressure; CCB: Calcium channel blocker.
From [40].

Therapy with an ARB and a CCB has the potential to provide prompt reductions in BP that would be expected to reduce the risk of CV morbidity and mortality. In addition, ARBs and CCBs have both been associated with protective benefits beyond BP control. For example, ARBs and CCBs have anti-atherosclerotic properties that are mediated through different mechanisms. A recent study in patients with untreated hypertension demonstrated that treatment with amlodipine achieved reductions in arterial stiffness, in part owing to reduced 24-h BP variability, whereas valsartan achieved similar decreases in arterial stiffness without affecting BP variability, possibly as a result of pleiotropic effects [41]. There is also evidence to suggest that long-acting CCBs are associated with improvements in left ventricular hypertrophy owing to improved 24-h BP control, while ARBs have been shown to reduce CV fibrosis and renal impairment [42]. In addition, the ARB valsartan has been shown to reduce the risk of new-onset diabetes, while the CCB amlodipine has been shown to have anti-angina benefits [27,43]. While anti-angina benefits are not unique to CCBs (similar benefits may be obtained with β-blockers), the different benefits of ARBs and CCBs provide a strong rationale for combining these two classes.

As well as improved efficacy, multiple-mechanism therapy would be expected to have benefits in terms of safety and tolerability. The mode of action of ARBs has the potential to attenuate adverse effects associated with CCBs [39,40]. In particular, the peripheral edema associated with CCBs results from their potent vasodilatory effects and may be offset by the action of ARBs, which promote both arterial and venous dilation. Furthermore, since it is more likely that BP control can be achieved without having to resort to increasing drug doses, adverse effects associated with high doses of CCBs may be minimized [2,40].

Combination of amlodipine & valsartan

Valsartan

Valsartan is a potent and highly selective ARB. By blocking the binding of angiotensin II (the main effector peptide of the RAS) to the AT_1 receptor, valsartan is able to:

- Produce balanced arterial and venous dilatation
- Increase sodium and water secretion
- Reduce aldosterone release
- Reduce SNS activity

These all contribute to BP reduction [44]. Valsartan may also enable increased activation of the AT_2 receptor. Although the functions of this receptor have not yet been fully elucidated,

it is thought to mediate effects opposed to those of the AT_1 receptor, including vasodilation, nitric oxide production, bradykinin production and antiproliferative effects [45,46]. The clinical effects of such AT_2 receptor activation have yet to be established and have not been explored in comparative studies of ACE inhibitors and ARBs. The safety and BP-lowering efficacy of valsartan has been demonstrated in several clinical trials including a large number of patients [43,47–49]. Valsartan provides double-digit BP lowering with 24-h control and is an effective antihypertensive treatment in a broad range of patient populations, including mild-to-moderate and moderate-to-severe hypertensive patients and the elderly.

Amlodipine

Amlodipine besylate is a long-acting dihydropyridine CCB and a potent peripheral and coronary vasodilator. Amlodipine impedes the transmembrane influx of calcium ions into vascular smooth muscle cells and cardiac muscle cells. Since amlodipine is more selective for vascular smooth muscle than for cardiac muscle, it reduces peripheral vascular resistance without affecting cardiac conduction or myocardial contractility [50]. A large number of clinical trials have demonstrated that amlodipine is highly effective at reducing BP [27,51] and is of particular benefit in certain patient populations, including elderly and black patients [28,52–54]. Overall, amlodipine is well tolerated and is associated with a low incidence of adverse events [50]. The most frequently reported adverse event associated with amlodipine is dose-related peripheral edema, which results from a mismatch between arteriolar and venular dilation favoring fluid extravasation [50]. However, less than 2% of patients who develop edema require discontinuation of amlodipine treatment [55].

Amlodipine/valsartan

The complementary benefits reported in the VALUE trial with therapies based on valsartan and amlodipine, respectively [43], provide a strong rationale for combining these two highly effective and well-tolerated agents as a multiple-mechanism therapy. Valsartan- and amlodipine-based therapies were both effective at reducing BP, although the reductions were slightly greater in the amlodipine-treated patients than in the valsartan recipients, with differences between the two groups of 1.5/1.3 mmHg after 1 year. Despite the differences in BP, the frequency of the primary composite end point (cardiac mortality and morbidity) was similar in the two treatment groups (10.6% with valsartan

Table 2. Completed amlodipine/valsartan Phase IIb/III clinical trials.

Trial	Design	Treatment	Patients
Efficacy: multifactorial trial	Multicenter, double-blind, randomized, placebo-controlled, parallel group	8 weeks of amlodipine 2.5 and 5 mg; valsartan 40, 80, 160 and 320 mg; all possible combinations; and placebo	1911 adults with mild-to-moderate, uncomplicated, diastolic hypertension
Efficacy: multifactorial trial	Multicenter, double-blind, randomized, placebo-controlled, parallel group	8 weeks of amlodipine 10 mg; valsartan 160 and 320 mg alone and in combination; and placebo	1250 adults with mild-to-moderate uncomplicated diastolic hypertension
Nonresponder trial	Multicenter, double-blind, randomized, active-controlled, parallel group	8 weeks of amlodipine/valsartan (5/160 and 10/160 mg) versus valsartan 160 mg	947 adults with mild-to-moderate uncomplicated diastolic hypertension not adequately controlled on valsartan 160 mg
Nonresponder trial	Multicenter, double-blind, randomized, active-controlled, parallel group	8 weeks of amlodipine/valsartan (10/160 mg) compared with amlodipine 10 mg	944 adults with mild-to-moderate uncomplicated diastolic hypertension not adequately controlled on amlodipine 10 mg
Safety and efficacy in severe hypertension	Multicenter, double-blind, randomized, active-controlled, parallel group	6 weeks of amlodipine/valsartan (5/160–10/160 mg) versus lisinopril/hydrochlorothiazide (10/12.5–20/12.5 mg)	130 adults with severe, uncomplicated essential diastolic hypertension

and 10.4% with amlodipine). However, there were differences between the two treatment regimens for several secondary outcomes: amlodipine-treated patients developed fewer nonfatal MIs and there was a trend towards fewer fatal and nonfatal strokes [43], while valsartan reduced the risk of hospitalizations for heart failure [18]. The finding that some outcomes were favored with valsartan-based therapy and others with a regimen based on amlodipine is intriguing and suggests that further investigation is warrented to explore the potential to achieve further improvements in overall CV morbidity and mortality by combining the two agents.

The amlodipine/valsartan combination is under investigation as a therapy for the treatment of hypertension in patients whose BP is not adequately controlled on amlodipine or valsartan monotherapy, and as replacement therapy for patients taking amlodipine and valsartan as a free combination. Amlodipine/valsartan has been evaluated in an extensive Phase IIb/III clinical trial program, consisting of five multicenter, randomized, controlled trials in more than 5000 patients with hypertension (**Table 2**). Two of these studies were multifactorial trials conducted in adult patients with mild-to-moderate, uncomplicated, essential diastolic hypertension and two were non-responder trials in adult patients with mild-to-moderate, uncomplicated essential hypertension not adequately controlled on either valsartan 160 mg monotherapy or on amlodipine 10 mg monotherapy.

The remaining trial in the Phase IIb/III clinical program was a randomized, multicenter, double-blind, active-controlled study that evaluated the overall safety profile of amlodipine/valsartan compared with that of the ACE inhibitor lisinopril in combination with hydrochlorothiazide (HCTZ) in 130 adult patients with severe, uncomplicated diastolic hypertension (mean sitting DBP ≥110 and <120 mmHg) [56]. This study showed that 2 weeks of treatment with amlodipine/valsartan 5/160 mg followed by 4 weeks of amlodipine/valsartan 10/160 mg resulted in clinically significant reductions in SBP (35.8 mmHg) and DBP (28.6 mmHg) that were numerically greater than those observed with lisinopril plus HCTZ (SBP 31.8 mmHg, DBP 27.6 mmHg). In a *post hoc* subanalysis of 26 patients with a mean sitting SBP of at least 180 mmHg at baseline; reductions of 43.0/26.1 mmHg were recorded for amlodipine/valsartan and 31.2/21.7 mmHg for lisinopril/HCTZ. Full results from this study are expected to be published in 2007.

Amlodipine/valsartan was also found to have a favorable overall safety profile [56]. Adverse events were reported in similar numbers of patients receiving amlodipine/valsartan and lisinopril/HCTZ, and most events were not related to the study drug and were mild or moderate in severity. In addition, a 6-week cross-over study in 42 patients with mild-to-moderate hypertension has shown that valsartan/amlodipine results in a lower incidence of ankle edema (four patients, 9.5%) than amlodipine monotherapy (eight patients; 19.0%) [57]. Edema associated with amlodipine results from an imbalance between dilation of the arterioles and venules, which tends to promote fluid extravasation [40]. Use of valsartan in combination with amlodipine may redress this imbalance by promoting more equal arteriolar and venular dilation.

Outlook

The major, ongoing challenge in the current era of hypertension management is achieving BP goals. There are several reasons why patients fail to achieve target BP values, including inadequate efficacy with current therapeutic regimens and a need for simplified treatment and dosing regimens with favorable tolerability profiles in order to enhance medication compliance. To this end, the use of combination therapy is likely to become standard practice for the management of hypertension within the next few years. Indeed, there has been interest in the 'polypill' concept, in which multiple medications (e.g., a statin, several low-dose antihypertensives, aspirin and folic acid) are used to reduce multiple risk factors [58]. While this concept remains controversial, the benefits of antihypertensive combination therapy are well established. Although many combination agents are currently available, the development of CCB/ARB combinations is likely to add new and powerful options that could help many patients to achieve BP goals. Amlodipine/valsartan is the first such combination to be developed, although fixed-dose combinations of olmesartan/amlodipine and telmisartan/amlodipine are also being evaluated. Amlodipine/valsartan delivers powerful BP-lowering via a potent dual CCB/ARB mechanism of action and exhibits additional benefits characteristic of each component. Therefore, this new modality is likely to provide a valuable addition to the antihypertensive therapeutic armamentarium, offering clinically

important benefits in patients for whom getting to and remaining at BP goal is currently a challenge. With data already available demonstrating the efficacy and tolerability of amlodipine/valsartan in patients with severe hypertension, the results of ongoing trials are eagerly awaited.

Disclosure

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Highlights

- Hypertension is the most common treatable risk factor for cardiovascular disease (CVD) and, thus, represents an important worldwide public health challenge.
- Even when identified and treated, most patients with hypertension do not get to blood pressure (BP) goal.
- Most patients with hypertension need at least two antihypertensive agents to achieve BP control.
- Although various combination therapies are currently available for the treatment of hypertension, development of more powerful therapies is necessary to help implement guideline recommendations that call for more aggressive treatment options and early BP control.
- Amlodipine/valsartan is an antihypertensive agent that lowers BP via calcium channel blockade and angiotensin receptor blockade. This potent dual mechanism of action is also likely to attenuate compound-specific adverse events, such as amlodipine-related peripheral edema.
- Clinical trials are ongoing to assess the efficacy and safety of amlodipine/valsartan in various patient populations, the results of which are eagerly anticipated. Currently available data show that amlodipine/valsartan is a well-tolerated agent that gets patients with severe hypertension to their BP goal.

Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M: Economic burden of cardiovascular diseases in the enlarged European Union. *Eur. Heart J.* 27, 1610–1619 (2006).
2. ESH/ESC Guidelines Committee: 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J. Hypertens.* 21, 1011–1053 (2003).
3. Wolf-Maier K, Cooper RS, Kramer H *et al.*: Hypertension treatment and control in five European countries, Canada, and the United States. *Hypertension* 43, 10–17 (2004).

• **Survey illustrating the low levels of blood pressure (BP) control achieved in Europe and the USA.**

4. Wolf-Maier K, Cooper RS, Banegas JR *et al.*: Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. *JAMA* 289, 2363–2369 (2003).
5. Kearney PM, Whelton M, Reynolds K *et al.*: Global burden of hypertension: analysis of worldwide data. *Lancet* 365, 217–223 (2005).
6. Kaplan NM, Opie LH: Controversies in hypertension. *Lancet* 367, 168–176 (2006).
7. Antikainen RL, Moltchanov VA, Chukwuma C Sr *et al.*: Trends in the prevalence, awareness, treatment and control of hypertension: the WHO MONICA Project. *Eur. J. Cardiovasc. Prev. Rehabil.* 13, 13–29 (2006).
8. Chobanian AV, Bakris GL, Black HR *et al.*: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 289, 2560–2572 (2003).
9. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R: Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 360, 1903–1913 (2002).
10. Hansson L, Lloyd A, Anderson P, Kopp Z: Excess morbidity and cost of failure to achieve targets for blood pressure control in Europe. *Blood Press.* 11, 35–45 (2002).

• **Cost-of-illness model illustrating the large burden associated with inadequate control of hypertension.**

11. Elmer PJ, Obarzanek E, Vollmer WM *et al.*: Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. *Ann. Intern. Med.* 144, 485–495 (2006).
12. Chobanian AV: Control of hypertension – an important national priority. *N. Engl. J. Med.* 345, 534–535 (2001).
13. Munger MA: Critical overview of antihypertensive therapies: what is preventing us from getting there? *Am. J. Manag. Care* 6(4 Suppl.), S211–S221 (2000).
14. Phillips LS, Branch WT, Cook CB *et al.*: Clinical inertia. *Ann. Intern. Med.* 135, 825–834 (2001).
15. Berlowitz DR, Ash AS, Hickey EC *et al.*: Inadequate management of blood pressure in a hypertensive population. *N. Engl. J. Med.* 339, 1957–1963 (1998).
16. Menard J: Critical assessment of combination therapy development. *Blood Press.* 1(Suppl.), 5–9 (1993).
17. Burnier M: Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *Am. J. Hypertens.* 19, 1190–1196 (2006).
18. Weber MA, Julius S, Kjeldsen SE *et al.*: Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. *Lancet* 363, 2049–2051 (2004).
19. Staessen JA, Thijisq L, Fagard R *et al.*: Effects of immediate versus delayed antihypertensive therapy on outcome in the Systolic Hypertension in Europe Trial. *J. Hypertens.* 22, 847–857 (2004).
20. Basile JN, Chrysant S: The importance of early antihypertensive efficacy: the role of angiotensin II receptor blocker therapy. *J. Hum. Hypertens.* 20, 169–175 (2006).
21. Milani RV: Reaching for aggressive blood pressure goals: role of angiotensin receptor blockade in combination therapy. *Am. J.*

Manag. Care 11(7 Suppl.), S220–S227 (2005).

22. Messerli F: A rationale for combination therapy. In: *Clinician's Manual on Combination Therapy and Hypertension*. Messerli F (Ed.). Science Press, London, UK (2003).
23. Andreadis EA, Tsourous GI, Marakomichelakis GE *et al.*: High-dose monotherapy vs low-dose combination therapy of calcium channel blockers and angiotensin receptor blockers in mild to moderate hypertension. *J. Hum. Hypertens.* 19, 491–496 (2005).

•• **Prospective, randomized clinical trial demonstrating BP goal achievement in a greater number of patients treated with low-dose angiotensin receptor blocker/calcium channel blocker combination versus high-dose monotherapy.**

24. Frishman WH, Burris JF, Mroczek WJ *et al.*: First-line therapy option with low-dose bisoprolol fumarate and low-dose hydrochlorothiazide in patients with stage I and stage II systemic hypertension. *J. Clin. Pharmacol.* 35, 182–188 (1995).
25. Mason JM, Dickinson HO, Nicolson DJ *et al.*: The diabetogenic potential of thiazide-type diuretic and β-blocker combinations in patients with hypertension. *J. Hypertens.* 23, 1777–1781 (2005).
26. Dahlof B, Devereux RB, Kjeldsen SE *et al.*: Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet* 359, 995–1003 (2002).
27. Dahlof B, Sever PS, Poulter NR *et al.*: Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT–BPLA): a Multicenter randomised controlled trial. *Lancet* 366, 895–906 (2005).

•• **Randomized, controlled clinical trial demonstrating the superior protection afforded with amlodipine, compared with atenolol.**

28. National Collaborating Centre for Chronic Conditions: *Hypertension: Management of Hypertension in Adults in Primary Care: Partial Update*. London: Royal College of Physicians, London, UK (2006).
29. Kjeldsen SE, Julius S, Mancia G *et al.*: Effects of valsartan compared to amlodipine on preventing Type 2 diabetes in high-risk hypertensive patients: the VALUE trial. *J. Hypertens.* 24, 1405–1412 (2006).

•• **Analysis demonstrating that valsartan reduces new-onset diabetes compared with amlodipine.**

30. Chrysant SG: Fixed low-dose drug combination for the treatment of hypertension. *Arch. Fam. Med.* 7, 370–376 (1998).
31. Cappuccio FP, Markandu ND, Singer DR, MacGregor GA: Amlodipine and lisinopril in combination for the treatment of essential hypertension: efficacy and predictors of response. *J. Hypertens.* 11, 839–847 (1993).
32. Jamerson KA, Nwose O, Jean-Louis L *et al.*: Initial angiotensin-converting enzyme inhibitor/calcium channel blocker combination therapy achieves superior blood pressure control compared with calcium channel blocker monotherapy in patients with stage 2 hypertension. *Am. J. Hypertens.* 17, 495–501 (2004).
33. Morgan T, Anderson A, Hopper J: Enalapril and nifedipine in essential hypertension; synergism of the hypotensive effects in combination. *Clin. Exp. Hypertens*. 10, 779–789 (1988).
34. ter Wee PM, Epstein M: Angiotensin-converting enzyme inhibitors and progression of nondiabetic chronic renal disease. *Arch. Intern. Med.* 153, 1749–1759 (1993).
35. ter Wee PM, De Micheli AG, Epstein M: Effects of calcium antagonists on renal hemodynamics and progression of nondiabetic chronic renal disease. *Arch. Intern. Med.* 154, 1185–1202 (1994).
36. Bakris GL, Barnhill BW, Sadler R: Treatment of arterial hypertension in diabetic humans: importance of therapeutic selection. *Kidney. Int.* 41, 912–919 (1992).
37. DREAM Trial Investigators, Bosch J, Yusuf S *et al.*: Effect of ramipril on the incidence of diabetes. *N. Engl. J. Med.* 355, 1551–1562 (2006).
38. Semple PF: Putative mechanisms of cough after treatment with angiotensin converting enzyme inhibitors. *J. Hypertens.* 13(Suppl.), S17–S21 (1995).
39. Quan A, Chavanu K, Merkel J: A review of the efficacy of fixed-dose combinations olmesartan medoxomil/hydrochlorothiazide and amlodipine besylate/benazepril in factorial design studies. *Am. J. Cardiovasc. Drugs* 6, 103–113 (2006).
40. Sica DA: Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. *Drugs* 62, 443–462 (2002).
41. Ichihara A, Kaneshiro Y, Takemitsu T, Sakoda M: Effects of amlodipine and valsartan on vascular damage and ambulatory blood pressure in untreated hypertensive patients. *J. Hum. Hypertens.* 20, 787–794 (2006).
42. Ishimitsu T, Kobayashi T, Honda T *et al.*: Protective effects of an angiotensin II receptor blocker and a long-acting calcium channel blocker against cardiovascular organ injuries in hypertensive patients. *Hypertens. Res.* 28, 351–359 (2005).
43. Julius S, Kjeldsen SE, Weber M *et al.*: Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 363, 2022–2031 (2004).

•• **Clinical trial demonstrating the protective and complementary benefits of amlodipine and valsartan.**

44. Schmieder RE: Mechanisms for the clinical benefits of angiotensin II receptor blockers. *Am. J. Hypertens.* 18(5 Pt 1), 720–730 (2005).
45. Maggioni AP, Latini R: The angiotensin-receptor blockers: from antihypertensives to cardiovascular all-round medications in 10 years? *Blood Press.* 11, 328–338 (2002).
46. Weber MA: The angiotensin II receptor blockers: opportunities across the spectrum of cardiovascular disease. *Rev. Cardiovasc. Med.* 3, 183–191 (2002).
47. Cohn JN, Tognoni G: A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N. Engl. J. Med.* 345, 1667–1675 (2001).
48. Viberti G, Wheeldon NM: Microalbuminuria reduction with valsartan in patients with Type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation* 106, 672–678 (2002).
49. Wogen J, Kreilick CA, Livornese RC, Yokoyama K, Frech F: Patient adherence with amlodipine, lisinopril, or valsartan therapy in a usual-care setting. *J. Manag. Care Pharm.* 9, 424–429 (2003).
50. Clavijo GA, de C, IV, Weart CW: Amlodipine: a new calcium antagonist. *Am. J. Hosp. Pharm.* 51, 59–68 (1994).
51. Neaton JD, Grimm RH Jr, Prineas RJ *et al.*: Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. *JAMA* 270, 713–724 (1993).

52. ALLHAT Collaborative Research Group: Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 288, 2981–2997 (2002).
53. Messerli FH: Evolution of calcium antagonists: past, present, and future. *Clin. Cardiol.* 26(2 Suppl. 2), II12–II16 (2003).
54. Pascual J: Hypertension control in the elderly with amlodipine. *Curr. Med. Res. Opin.* 16, 33–36 (2000).
55. Cocco G, Alfiero R: A double-blind dose-response study of amlodipine in patients with stable angina pectoris. *Eur. Heart J.* 12, 169–174 (1991).
56. Poldermans D, Gamboa R, Fomina I *et al.*: Comparative safety and blood pressure (BP)-lowering efficacy of a combination of amlodipine + valsartan and lisinopril + hydrochlorothiazide in patients with stage 2 hypertension. *J. Clin. Hypertens.* 8(5 Suppl. A), A96 (2006).
•• **Study demonstrating that amlodipine/valsartan is highly efficacious in lowering BP and is well tolerated in patients with stage 2 hypertension.**
57. Fogari R, Perrone T, Musca F *et al.*: Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. *J. Hypertens.* 24(Suppl. 4), S34 (2006).
•• **Study demonstrating that adding valsartan to amlodipine reduced ankle foot volume and was associated with a lower incidence of peripheral edema.**
58. Wald NJ, Law MR: A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 326, 1419 (2003).