

Exforge[®] (amlodipine/valsartan combination) in hypertension: the evidence of its therapeutic impact

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Abstract

Introduction: Hypertension is an important risk factor for cardiovascular disease and its management requires improvement. New treatment strategies are needed.

Aims: This review analyses one of these strategies, which is the development of effective and safe combination therapy. Indeed, at least two antihypertensive agents are often needed to achieve blood pressure control. Exforge[®] (Novartis) is a new drug combination of the calcium channel blocker, amlodipine, and the angiotensin II receptor blocker, valsartan.

Evidence review: The amlodipine/valsartan combination is an association of two well-known antihypertensive products with specific targets in cardiovascular protection, namely calcium channel blockade and antagonism of the renin-angiotensin-aldosterone system. This kind of association, with neutral metabolic properties and significant antihypertensive efficacy, could be a useful new antihypertensive product. Currently available data have shown that this new combination is well-tolerated and effective even in severe hypertension.

Clinical value: Clinical trials are ongoing for further assessment of the efficacy, compliance, and safety of this combination and its congeners. No data exist to prove that the amlodipine/valsartan combination is better than other antihypertensive strategies for cardiovascular or renal protection, but some trials with other combination therapies show such potential advantage.

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Key words: arterial hypertension, treatment, combination therapy, calcium channel blocker, amlodipine, angiotensin II receptor blocker, valsartan

Core evidence clinical impact summary for Exforge (amlodipine/valsartan) in hypertension

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Improvement in cardiovascular morbidity and mortality	Clear (for each agent alone)	Trials on both drugs as monotherapy have shown either direct protection against cardiovascular events or surrogate benefit by reducing blood pressure
Reduced atrial fibrillation	Moderate	Reduced recurrent atrial fibrillation
Patient acceptability	Limited	Low rate of adverse events
Improvement in quality of life	Moderate	Less edema, better tolerability
Disease-oriented evidence		
Effective control of blood pressure	Clear	Combination more effective than monotherapy
Economic evidence		
Cost effectiveness as antihypertensive therapy	Limited	No studies to show the long term efficacy for lowering blood pressure and decreasing morbidity or mortality in spite of higher cost of the fixed combination

Scope, aims, and objectives

This article discusses the place of combination therapy in arterial hypertension (HTN) and concentrates on the potential advantage of Exforge® (Novartis), the first commercially available combination of a dihydropyridine calcium channel blocker (CCB) (amlodipine) and an angiotensin II receptor blocker (ARB) (valsartan). These are two of the most commonly prescribed antihypertensive drugs in their classes. Their combination aims to secure better control of blood pressure (BP) along with simultaneous cardiovascular and renal risk reduction and few side effects. The scope of this article is in the area of human hypertension and its treatment, with particular focus on amlodipine, valsartan, and their combination.

Methods

An extensive literature search on amlodipine/valsartan was conducted as follows.

Peer reviewed articles and abstracts (English-language only) were identified from Medline, EMBASE, BIOSIS, the National Institute for Health and Clinical Excellence (NICE), and the York University Centre for Reviews and Dissemination Database (<http://www.crd.york.ac.uk/crdweb/>) using the terms “antihypertensive combination, amlodipine, valsartan, CCB, and ARB”.

PubMed was used for the terms “amlodipine and valsartan” with the search limits “clinical trial, meta-analysis, practice guideline, randomized controlled trial, hypertension treatment”, and English language only. Forty-nine records were found, of which 11 were reviews on the topic. Only 15 of the records appeared relevant to the combination of both drugs. The search also produced records of trials that compared amlodipine and valsartan; they were included in this review to substantiate the evidence of the efficacy and tolerability of each individual drug.

A search on the site of the European Medicines Agency (EMA), (www.emea.europa.eu), was also done with Exforge as the topic searched. EMBASE and BIOSIS were also consulted with the same search keywords, but the records that were identified were already found in the PubMed results. For NICE, no records were found. From the York University Centre for Reviews and Dissemination Databases, four records were identified, but for the purpose of the present article, none were judged relevant. The results of the literature search are shown in Table 1.

The main aims of all the studies selected were the efficacy of antihypertensive effect and tolerability.

Most of these articles were the results of prospective, randomized, either double-blind or open-label multicenter studies, placebo- or active-treatment controlled, with samples including men and women of a mean age around 60 years. Additional references were obtained from the authors' files.

Disease overview

Hypertension is a well-known risk factor for cardiovascular disease, affecting more than 1 billion people worldwide. Recently,

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	49	12
records excluded	34	
records included	15	1
Additional studies identified	46	1
Total records included	61	
Level 1 clinical evidence (systematic review, meta analysis)	10	
Level 2 clinical evidence (RCT)	37	
Level ≥3 clinical evidence trials other than RCT	11	2
Economic evidence	3	

For definitions of levels of evidence, see inside back cover or *Core Evidence* website (<http://www.coremedicalpublishing.com>).
RCT, randomized controlled trial.

Lawes et al. (2008) summarized the worldwide burden of disease attributable to high BP and found that 7.6 million premature deaths and 92 million disability-adjusted life years were attributed to high BP. Half of strokes and ischemic heart disease worldwide were attributable to high BP. About half this burden was in people with HTN, the remainder was in those with lesser degrees of high BP. The prevalence of HTN varies according to the country, with a range between 5% in rural India to 70% in Poland (Kearney et al. 2004).

The economic impact of HTN is enormous, representing \$US24 billion in the US in 1995, and more than one-third of that cost is due to drug treatment (Pardell et al. 2000). Further, Goetzel et al. (2004) suggest that HTN carries a high per-employee cost, even higher than that of heart disease, depression, or arthritis.

Despite the effort to increase the awareness and treatment of HTN, recent data for the US show that only 39% of patients have their BP adequately controlled (Ma & Stafford 2008). In Europe, BP control was achieved in only 12% of Polish hypertensives and up to 36% of Spanish hypertensives (Erdine 2007). These statistics show the need to change the landscape of BP management.

Current therapy options

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of HTN (Chobanian et al. 2003) recommends a BP treatment goal of <140/90 mmHg for most patients and <130/80 mmHg for those with diabetes mellitus or chronic kidney disease. These targets conform to the more recent European guidelines (Mancia et al. 2007). These target BP goals should reduce the long-term risk of cardiovascular disease and death. In most hypertensive subjects, optimal control of the BP will depend on effective and trouble-free medication.

Choosing the appropriate medications for individual patients and adherence to these regimens are the key factors for successful treatment of HTN. Diuretics remain an important drug class with a large amount of evidence for their efficacy. They are also

inexpensive, but they have potential adverse metabolic side effects. When used alone, they are often stopped during the first year of their use, with a one-year persistence rate of only 34% (Hasford et al. 2002).

Medications that act on the renin-angiotensin-aldosterone system (RAAS) are now frequently prescribed because they block important renal mechanisms that play a crucial role in salt and volume homeostasis, and because of additional extrarenal actions. They also reduce major cardiovascular events in high-risk patients (Yusuf et al. 2000, 2008).

For their part, calcium antagonists have regained popularity in spite of worries about short-acting calcium antagonists (Alderman et al. 1997). They have been used in many recent hypertension treatment trials (e.g. ALLHAT, VALUE, ASCOT) and may have utility because of their neutral metabolic effects and also potential antiatherosclerotic properties.

The current market share in the US for angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) is near 50%, while that of calcium blockers is 20% (Stafford et al. 2006). These are thus major drug classes for the treatment of hypertension.

Unmet needs

Of the unmet medical needs in the management of HTN, there is strong evidence to support simpler treatment regimens that effectively control BP and that are still used by patients in the long term because they are well tolerated.

Major trials, such as LIFE, ASCOT, and VALUE, have shown that up to 80% of hypertensive patients need more than one antihypertensive agent to get to and maintain their BP goal. In the Hypertension Optimal Treatment study (HOT), an average of 3.3 drugs were required to attain a diastolic BP goal of <80 mmHg (Hansson et al. 1998). Furthermore, the JNC7 recommendations state that “when BP is more than 20 mmHg above systolic goal or above 10 mmHg diastolic goal, consideration should be given to initiate with 2 drugs, either as separate prescriptions or in fixed-dose combinations” (Chobanian 2003).

For those with reduced kidney function, the number of medications needed to control BP rises as the glomerular filtration rate (GFR) falls (K/DOQI clinical practice guidelines 2004) (Fig. 1). Combination therapy thus appears to be an attractive option for the 10% of hypertensives who have stage II hypertension or more and for those with chronic kidney disease and HTN.

Combination therapy could improve adherence to therapy (“compliance”), due to reduction of the daily pill intake (Osterberg & Blaschke 2005). Better adherence to HTN therapy could enhance individual and population-level BP control. Some authors consider that improvement of treatment compliance could yield the greatest gain both in cost effectiveness and efficiency (Mar & Rodriguez-Artalejo 2001).

In addition, BP has multiple regulatory pathways, including the sympathetic nervous system, RAAS, and total body sodium.

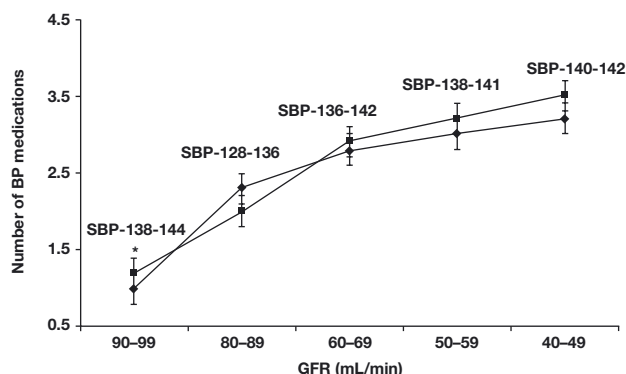


Fig. 1 | Relationship between level of baseline GFR and number of antihypertensive medications needed to achieve BP goal. SBP reflects BP ranges in the studies reviewed. Adapted from studies reviewed in 2004 Disease Outcomes Quality Initiative–Blood Pressure (DOQI -BP) guidelines. Black squares are diabetic studies; black diamonds are nondiabetic studies. This figure is reprinted by permission of the American Society of Nephrology and by Dr George Bakris, from NephSAP 4:101, 2005, the Nephrology Self-Assessment Program published by the American Society of Nephrology. BP, blood pressure; GFR glomerular filtration rate; SBP, systolic BP.

Combination therapy relies on efficient and complementary blockade of more than one of these, by separate and different agents, and without resorting to a high dose of either. This was shown by Andreadis et al. (2005) who noted that low-dose ARBs and CCBs had comparable effects in patients with grade I and II HTN. In patients who were not controlled by low-dose monotherapy, low-dose combination therapy using agents blocking different BP control pathways was more effective than was high-dose monotherapy. Such a complementary advantage was also reported by Stergiou et al. (2005) who showed that adding amlodipine or chlorthalidone to valsartan was more effective than add-on therapy with benazepril.

Additional reasons for inadequate BP control could derive from a suboptimal approach by physicians (Berlowitz et al. 1998). Yet the role of BP reduction in cardiovascular risk prevention is quite clear, and a greater reduction in BP yields greater reduction in risk (Staessen et al. 2005; LeLorier 2006). Getting to goal BP may require more than one antihypertensive drug.

Over the years, several combinations with fixed-dose drugs have been developed and shown to be effective. Some have had specific indications based on hemodynamic and metabolic criteria (van Zwieten 2003). These have included:

1. Thiazide diuretics and either beta blocker, ACE inhibitor, or ARB, for uncomplicated HTN, for heart failure, or left ventricular hypertrophy, respectively.
2. CCB and betablocker for HTN and coronary artery disease, or CCB and ACE inhibitor for HTN with kidney disease or with high cardiovascular risk.

The side effects of diuretics, beta blockers, and ACE inhibitors may limit the benefit of combinations using these drugs and also decrease patient adherence to treatment.

The combination of amlodipine/valsartan has been developed to try to improve efficacy and tolerability and thus deliver the promise of better treatment. Both amlodipine and valsartan have a favorable side effect profile, so their combination is attractive. Both drugs act on different mechanisms of hypertension and thus could be complementary in the benefit that they offer.

Pharmacodynamic profile

The CCB is effective in low-renin HTN and the ARB in high-renin HTN, thus combining both classes could improve the success of treatment. Both drugs have generally neutral effects on metabolic parameters such as blood lipid levels and insulin sensitivity, although plasma norepinephrine levels are increased with amlodipine therapy. This effect is not attenuated when combined therapy is used (de Champlain 2007).

Amlodipine

Amlodipine is a third generation CCB that acts on specific high-affinity binding sites in the L-type calcium channel complex of vascular smooth muscle cells. This causes vasodilatation of arteries and arterioles by reducing the influx of calcium into vascular smooth muscle. Calcium channels play important roles in cardiac contractility and electrophysiology but much higher concentrations of amlodipine are needed *in vitro* to influence those functions (Burgess et al. 1987). Its protein binding and elimination kinetics help to explain its long duration of action. Amlodipine produces a gradual onset of action and a prolonged effect that enables once-daily dosing. This explains the high trough-to-peak ratio of the antihypertensive effect and reduced variability of BP with once-daily administration. The vasodilatation can induce flushing, headache, and ankle edema.

Experimental data indicate that amlodipine has the potential to produce an antiatherosclerotic effect in humans, in part due to antioxidant effect or its endothelin antagonistic properties. Amlodipine can improve endothelium dysfunction, thanks to reduction of calcium influx, and, by its R-enantiomer, facilitate the action of nitric oxide or its production. In kidney transplant patients, amlodipine can also increase the glomerular filtration rate and renal blood flow, and decrease plasma uric acid concentration (Chanard et al. 2003).

Valsartan

Valsartan is a specific blocker of the binding of angiotensin II to the AT₁ receptor, blocking the vasoconstrictor effect and the adrenal aldosterone secretion induced by this peptide. Valsartan does not significantly increase bradykinin concentrations, in contrast to ACE inhibitors. It reduces BP without increasing the heart rate. It has a 24-hour effect on BP control due to blockade of the AT₁ receptor, but there may be an increase in angiotensin II concentration acting on AT₂ receptors, with consequent vasodilatation. In the kidneys, especially at the renal tubular level, the stimulation of AT₂ could mediate natriuresis which could also contribute to the antihypertensive

effect (Padia et al. 2006 ; Franco et al. 2008). Stopping valsartan intake is not associated with rebound of the BP level.

Pharmacokinetic profile

Limited data are available on the pharmacokinetic properties of fixed-dose combinations of amlodipine/valsartan. No drug interaction studies have been conducted with fixed-dose combinations and other drugs.

Amlodipine

When orally absorbed, peak plasma concentrations of amlodipine are reached in 6–8 hours and its bioavailability is 64–80%. It has an inherently long half-life of between 30 and 50 hours with gradual onset of action and a prolonged effect, which is useful for once-daily dosing, and no rebound of HTN when the drug is abruptly stopped. It has 98% plasma protein binding and is extensively metabolized in the liver to inactive metabolites (EMA 2007; Plosker & Robinson 2008).

Amlodipine can interfere with the metabolism of some drugs through the enzyme CYP3A, because this enzyme constitutes the pathway of its catabolism. Any substance that induces or inhibits CYP3A could affect amlodipine concentration, and amlodipine could also modify the concentration of the coadministered drug (Wilkinson 2005). An increase in cyclosporin concentrations may occur but is of limited clinical significance.

Valsartan

Peak plasma concentrations of valsartan are reached 3 hours after oral administration. Its bioavailability is 23% and this is not influenced by food. Its half-life is 6 hours and its plasma protein binding is over 95%. Like amlodipine, it is metabolized by the liver. Valsartan is eliminated mainly as unchanged drug in the faeces (83% of the dose) and urine (13% of a dose). It is not metabolized by the CYP system and thus has little interference with other drugs. In hepatic failure its concentration is increased. In renal impairment, its dosage does not need modification and it is not removed by dialysis. Its main contraindication is pregnancy, because antagonists of the RAAS may be teratogens. Valsartan can worsen kidney function in patients with bilateral renal artery stenosis, and in this condition of use requires surveillance of serum potassium and creatinine (EMA 2007; Plosker & Robinson 2008).

Clinical evidence with amlodipine

The long-acting third-generation dihydropyridine calcium antagonist amlodipine is one of the most commonly used antihypertensive agents, and is approved for the treatment of HTN and angina at doses from 2.5 to 10 mg/day. It has no effects on lipids or insulin sensitivity, but it can increase plasma norepinephrine levels. It has been shown to activate the sympathetic system during the day and to decrease the parasympathetic activity during the night (Karas 2005).

Amlodipine has been studied in patients with coronary artery disease and shows benefit compared with placebo or enalapril in terms of

cardiovascular events, with a trend towards an antiatherosclerotic effect even in normotensive patients who have coronary heart disease (Nissen et al. 2004). It may exert a preferential effect in lowering central aortic pressures (CAFE Investigators 2006).

Amlodipine is not recommended as first-line treatment in hypertensives with proteinuric renal disease because it may aggravate proteinuria (Nathan et al. 2005; Bakris et al. 2008). It is possible that this is related to an increase in glomerular capillary pressure that may occur in patients taking amlodipine (Delles et al. 2004). Compared with RAAS blockers, amlodipine use in proteinuric kidney disease was not as useful in preventing renal disease progression (Agodoa et al. 2001; Lewis et al. 2001).

Clinical evidence with valsartan

Valsartan is an ARB that has been marketed for HTN since 1996. It is available in the US at 80–320 mg/day and in Europe at 80–160 mg/day. Valsartan is approved for the treatment of HTN, for congestive heart failure, and also for postmyocardial infarction patients in some countries.

Valsartan has also been described as having antiinflammatory properties reducing the high sensitivity C-reactive protein level, as shown in the Val-MARC trial. However, this antiinflammatory effect has not been confirmed in the VIVALDI study comparing valsartan with telmisartan (Ridker et al. 2006; Galle et al. 2008).

Comparisons of amlodipine and valsartan

Although not the focus of this review, some comparisons of amlodipine and valsartan are relevant to the discussion of the combination of both drugs.

Wogen et al. (2003) compared patient adherence with amlodipine, lisinopril, or valsartan therapy in people treated for HTN. In a usual-care setting, patients receiving valsartan rather than lisinopril or amlodipine appear to be more compliant with treatment, due to less subjective side effects. Moreover, Elliott et al. (2007) reported that, probably for the same reasons, the risk of discontinuation of four antihypertensive drugs (hydrochlorothiazide, amlodipine, lisinopril, and valsartan) was different. The lowest risk of discontinuation was seen with the ARB, followed by the ACE inhibitor, then the CCB, with the highest discontinuation rate being noted with the thiazide. This could be explained by a superior tolerance profile of ARB compared with the other antihypertensive classes.

For cardiovascular protection, an action on oxidative stress may be beneficial. Dihydropyridine CCBs have antioxidant and antiinflammatory effects that may be independent of their BP-lowering action and that yield synergistic vasoprotective activity with RAAS blockers (Mason et al. 2003). The reduction of oxidative stress and plasma methyl arginine, an endogenous inhibitor of nitric oxide synthase, has also been noted in patients with chronic renal failure treated with either amlodipine or valsartan (Aslam et al. 2006). However, valsartan seems to

be more effective than amlodipine in restoring endothelial function and decreasing oxidative stress in essential HTN (Hirooka et al. 2008).

Clinical evidence with amlodipine/valsartan combination

Exforge is a fixed-dose combination of amlodipine, as the besilate salt, and valsartan, in the form of film-coated tablets. Fixed-dose combinations of amlodipine (5 or 10 mg) and valsartan (160 or 320 mg) have been available in the US and several countries in Europe since September 2007 for once-daily oral administration in patients with HTN who have not had an adequate response to amlodipine (or another dihydropyridine CCB) or valsartan (or another ARB alone) as monotherapy. Exforge was recently approved by the FDA as initial or first-line therapy in patients likely to need multiple drugs to achieve their BP goals.

There have been only a few studies testing this combination of the two drugs. The addition of valsartan 80 mg/day to amlodipine 5 mg/day in patients not controlled with amlodipine 5 mg alone has been shown to improve exercise performance assessed by measurements of cardiac output and total peripheral resistance at rest and at peak exercise (Maeda et al. 2006). As noted above, in hypertensives not controlled with valsartan as monotherapy, a combination of amlodipine and valsartan has been shown to be well-tolerated, safe, and effective (Stergiou et al. 2005). Combination amlodipine/valsartan was very effective in lowering BP in patients in whom monotherapy with various other antihypertensives was incompletely effective (Allemann et al. 2008). In this study, a variety of drugs were used at baseline as monotherapy before the use of amlodipine/valsartan. Poldermans et al. (2007) showed that amlodipine/valsartan combination therapy was as effective in patients with stage II hypertension as lisinopril/hydrochlorothiazide combination therapy.

While several trials have been designed to test the antihypertensive efficacy of this combination, very few studies have been devoted to analyze its potential benefit in terms of cardiovascular or renal protection. The particular case of atrial fibrillation was tested by Fogari et al. (2008), who showed that amlodipine/valsartan combination therapy was better than atenolol/amlodipine in preventing recurrent atrial fibrillation in hypertensive diabetics, although comparisons with an ACE inhibitor and a CCB or a diuretic would be more appropriate comparators in this patient population.

Currently, no information on albuminuria is available for the amlodipine/valsartan combination. Nonetheless, Fogari et al. (2007a) showed that the amlodipine/telmisartan combination has been very useful in decreasing urinary albumin excretion in hypertensive diabetic patients with microalbuminuria. The clinical development program for amlodipine/valsartan fixed combination products has included bioequivalence studies and phase III clinical efficacy/safety studies, including placebo- and active-controlled studies to justify proposed dosages. All of these studies showed efficacy in all grades of HTN, as well as efficacy in nonresponders to monotherapy or to previous combination therapy (Table 2).

Table 2 | Randomized trials with amlodipine/valsartan combination in hypertension

Trial	Design	Treatment	Patients
Efficacy (Philipp et al. 2007; Smith et al. 2007) EMEA study 2201 + 2307	Multicenter, double-blind, randomized, placebo-controlled, parallel group	8 weeks of amlodipine 2.5, 5 mg; valsartan 40, 80, 160, and 320 mg, all possible combinations and placebo	1911 patients with mild-to-moderate diastolic HTN
Efficacy (Philipp et al. 2007; Smith et al. 2007) EMEA study 2201 + 2307	Multicenter, double-blind, randomized, active-controlled, parallel group	8 weeks of amlodipine/valsartan (5/160 mg and 10/160 mg) compared with valsartan 160 mg	1250 patients with mild-to-moderate diastolic HTN
Efficacy and safety in severe HTN (Poldermans et al. 2007) EMEA study 2308	Multicenter, double-blind, randomized, active-controlled, parallel group	8 weeks of amlodipine/valsartan (5/160 mg and 10/160 mg) compared with valsartan 160 mg	947 adults with mild-to-moderate HTN uncontrolled by valsartan 160 mg
Efficacy and safety EX-FAST (Alleman et al. 2008) EMEA study 2401 mild-to-moderate HTN	Multicenter, double-blind, randomized, active-controlled, parallel group	16 weeks of amlodipine 5 or 10 mg/valsartan 160 mg compared with previous monotherapy	894 patients receiving the combination (443 with amlodipine 5 mg and 451 with amlodipine 10 mg) with mild-to-moderate HTN uncontrolled by monotherapy
Efficacy and safety EX-EFFeCTS study (Destro et al. 2008) EMEA study 2403	Multicenter, double-blind, randomized, active-controlled, parallel group	8 weeks amlodipine/valsartan vs amlodipine monotherapy in systolic stage II HTN	646 patients with stage II and III HTN receiving either the amlodipine 5 or 10 mg/valsartan 160 mg combination (n=322) or amlodipine monotherapy 5 or 10 mg (n=324)
Nonresponder study ExPress-C trial (Trenkwalder et al. 2007)	Open-label, simple arm	5 weeks amlodipine/valsartan 10/160 mg compared with ramipril 5 mg/felodipine 5 mg	105 patients with stage II HTN uncontrolled by ramipril/felodipine after 5 weeks
Nonresponder study (Brachmann et al. 2008) EXPRESS-M trial	Open-label, simple arm	8 weeks amlodipine/valsartan compared with amlodipine or felodipine monotherapy	181 patients stage II HTN uncontrolled by CCB monotherapy

CCB, calcium channel blocker; EMEA, European Medicines Agency; HTN, hypertension.

To date, some clinical trials with combinations of both drugs have been published, with a focus on BP control but without using home or ABPM, and only one study has been published on systolic HTN (Destro et al. 2008). Several studies have shown the efficacy of each component drug in reducing BP and cardiovascular events, as reviewed above.

Published randomized studies

1. Combination therapy with amlodipine/valsartan has been compared with that of amlodipine or valsartan monotherapy in two large randomized double-blind, placebo-controlled studies and their subgroup analyses (Philipp et al. 2007; Smith et al. 2007). These studies included 3161 patients with mild-to-moderate HTN. The primary efficacy endpoint was the change from baseline in mean sitting diastolic (D) BP at the end of the 8-week study period. Secondary endpoints were the percentage of patients achieving a DBP <90 mmHg or a >10 reduction from baseline, and change of mean systolic (S) BP.

The efficacy of the combination was better than either monotherapy at the same dose. More than 80% of patients treated with amlodipine/valsartan 5/80 mg, 5/160 mg, or 5/320 mg met the criteria for response. This was also the case when the amlodipine dose in the combination was 10 mg.

The same group (Philipp et al. 2007) showed that ~50% of the patients treated with the combination of amlodipine 10 mg and valsartan 320 mg achieved the BP goal of <140/90 mmHg at 2 weeks. The combination therapy was associated with greater reductions in BP than each separate

monotherapy or placebo across all patient subgroups, including those aged >65 years, black patients, and those with stage II HTN (Smith et al. 2007).

2. A large, randomized, double-blind, phase IIIb–IV trial in almost 900 patients evaluated a direct switch to amlodipine/valsartan 5/160 mg or 10/160 mg once daily in patients whose BP was previously uncontrolled by monotherapy with various antihypertensive agents (Alleman et al. 2008). Patients whose BP was uncontrolled with the combination after 8–12 weeks could receive diuretics. BP control was achieved in 76% and 71% of patients after 8 weeks of combination with amlodipine/valsartan 10/160 mg or 5/160 mg, respectively. For both dosage regimens, the magnitude of SBP reductions was similar regardless of the class of antihypertensive drug used prior to randomization.
3. Brachmann et al. (2008) recently showed that the addition of an ARB to CCB-based antihypertensive therapy may be associated with enhanced efficacy and reduced risk of adverse events. In this 8-week, open-label, single-arm trial, the efficacy and tolerability of the combination of amlodipine and valsartan was evaluated in patients not responding adequately to treatment with amlodipine or felodipine alone. Patients aged ≥18 years with moderate essential hypertension (defined as mean sitting SBP ≥160 and <180 mmHg) were treated for 4 weeks with amlodipine 5 mg or felodipine 5 mg once daily. At week 4, patients not adequately responding were treated for an additional 4 weeks with a fixed dose combination of once-daily amlodipine/valsartan 5/160 mg. Of 214 patients treated for 4 weeks with amlodipine 5 mg or felodipine 5 mg,

181 failed to achieve mean sitting SBP <140 mmHg. These 181 nonresponders were treated for an additional 4 weeks with amlodipine/valsartan 5/160 mg: over half of them achieved target BP level (<140/90 mmHg).

4. Poldermans et al. (2007) showed that better BP control was achieved with the combination of amlodipine/valsartan 5/160 mg or 10/160 mg than with the combination of lisinopril 10 or 20 mg and hydrochlorothiazide 12.5 or 25 mg in adult patients with stage II HTN. Mean sitting SBP/DBP was reduced by 36/29 mmHg and 32/28 mmHg, respectively, but this was not statistically significant. Subgroup analyses showed that both combination regimens reduced BP from baseline in two important patient groups; those aged >65 years at baseline and those with SBP >180 mmHg at baseline (i.e. stage III HTN).
5. Trenkwalder et al. (2007) tested the efficacy of treatment with the combination of ramipril 5 mg and felodipine 5 mg. In patients who were resistant to this combination, they evaluated the efficacy of switching to amlodipine/valsartan 10/160 mg. The amlodipine/valsartan combination led to a significant additional BP reduction, of 15 mmHg for SBP and 7 mmHg for DBP ($P<0.001$). Moreover, there was a better safety and tolerability profile for amlodipine/valsartan compared with ramipril/felodipine.
6. Destro et al. (2008) assessed the efficacy and safety of amlodipine/valsartan versus amlodipine monotherapy in patients with systolic stages II and III HTN (sitting SBP between 160 and 200 mmHg) in a randomized, double-blind, 8-week trial. A total of 646 patients were enrolled, of whom 322 were treated with amlodipine/valsartan 5/160 mg (group 1) and 324 were treated with amlodipine 5 mg for 2 weeks (group 2). For the remainder of the study, there was a dose increase to 10/160 mg in group 1 and 10 mg in group 2. At week 4, if patients were not controlled (SBP <130 mmHg), open label hydrochlorothiazide 12.5 mg could be added.

At week 4, the change from baseline SBP was significantly greater with amlodipine/valsartan compared with amlodipine monotherapy (decrease in SBP of 30 mmHg versus 24 mmHg; $P<0.0001$). By the end of the study, SBP was reduced from a baseline of 171 to 137 mmHg in the amlodipine/valsartan arm compared with 145 mmHg in the amlodipine treatment arm ($P<0.0001$). The difference in response was similar whatever the subgroup analysis (i.e. the elderly, those with severe HTN, obese patients, or those with diabetes mellitus).

Tolerability and safety

The most frequently reported adverse events with amlodipine/valsartan were ankle edema, headache, nasopharyngitis, upper respiratory tract infection, and dizziness. The aggregate frequency of adverse events was not different for amlodipine monotherapy (46%) as compared with amlodipine/valsartan combination (44%) but was higher than that reported for valsartan alone (40%) (Philipp et al. 2007). The frequency of ankle edema was greatest with amlodipine alone (9%), followed by the combination (5%), and was least common with valsartan monotherapy (2%). For the placebo group, the frequency of edema was 3% (Philipp et al. 2007).

Ankle edema was studied in detail by Fogari et al. (2007b). Objective ankle foot volume and pretibial subcutaneous tissue pressure were masked endpoints after 6 weeks of amlodipine monotherapy or amlodipine/valsartan combination therapy. Ankle edema was most common in those on amlodipine monotherapy, least common in those on valsartan monotherapy, and of intermediate frequency in those on combination therapy. The ankle edema with CCB may be due to high capillary hydrostatic pressure from precapillary vasodilatation. Several drug classes have relevant venodilating potential, including ACE inhibitors, ARBs, and nitrates. The use of valsartan, which has a mixed vasodilating effect on arteriolar and venular sites, may decrease the postcapillary pressure thereby normalizing transcapillary pressure and reducing edema. Another mechanism explaining a less frequent development of edema with the combination of amlodipine and valsartan could be the natriuretic effect of angiotensin blockade.

In the study published by Poldermans et al. (2007), most of the adverse events were not considered to be related to the study drugs. Mild-to-moderate adverse events were reported in 41% of patients treated with amlodipine/valsartan and 32% in the group treated with lisinopril/hydrochlorothiazide. Headache (11%) and peripheral edema (8%) were reported mainly in the amlodipine/valsartan group whereas diarrhea and pharyngitis occurred mainly in the lisinopril/hydrochlorothiazide group (6% for both). Cough occurred in 3% of those on lisinopril, but in fewer than 2% of those in the amlodipine/valsartan combination.

Economic evidence

In HTN without any other associated cardiovascular risk factor, the treatment cost increases as the target for HTN is lowered but this effect is attenuated when the population tested is older or has higher cardiovascular risk. Cost effectiveness may be better for older compared to younger people and for higher starting levels of BP. Cost effectiveness of treatment for HTN is also improved in secondary prevention or in the presence of diabetes (Jönsson et al. 2003).

The large majority of trials in the treatment of HTN have shown that the benefit from the treatment correlates with the decrease in BP. Recently some trials have suggested a benefit in addition to the BP decrease when using CCB and/or a blocker of the RAAS such as was observed in the LIFE or ASCOT trials (Dahlöf et al. 2002, 2005). However, the combination of two blockers of the RAAS (i.e. ACE inhibitor and ARB) has not demonstrated such benefit. In the VALIANT study, the combination of valsartan and captopril increased the rate of adverse events (Pfeffer et al. 2003). Similarly, in the Valsartan Heart Failure Trial (Val-HeFT), the combination of valsartan and ACE inhibitors or beta blocker was associated with a higher rate of adverse events (Cohn & Tognai 2001). In the ONTARGET trial, the combination of ramipril and telmisartan conferred no additional benefit compared with monotherapy in high cardiovascular risk populations (Yusuf et al. 2008). Considering absolute cost, paying for amlodipine and valsartan separately is cheaper, as shown in Table 3. However, the problem of compliance is inversely linked to the number of pills to be taken, which may cancel that small cost advantage (Osterberg & Blaschke 2005).

Table 3 | Average wholesale price (AWP) for Exforge and its separate components

Drug	AWP for 30 days (\$US)
Amlodipine 5 mg	10.34
Amlodipine 10 mg	14.19
Valsartan 160 mg	58.56
Valsartan 320 mg	74.09
Exforge 5/160 mg	85.86
Exforge 5/320 mg	108.91
Exforge 10/160 mg	97.39
Exforge 10/320 mg	123.63

The AWP is a prescription drugs term referring to the average price at which wholesalers sell drugs to physicians, pharmacies, and other customers.

Patient group/population

For the amlodipine/valsartan combination, the population who may benefit from its use are those patients with stage II or III HTN and those who have not sufficiently responded to an antihypertensive monotherapy. An additional population of interest is those with chronic kidney disease, especially when the estimated GFR is less than 60 mL/min/1.73m².

No specific drug interaction studies have been conducted with this combination, but interaction of the individual single agents with other drugs exists and should be kept in mind (see above).

In April 2008, the EMEA published information about the avoidance of this drug combination throughout pregnancy. Since the fourth of December 2007, the FDA has approved the use of valsartan for treating children with HTN, so amlodipine/valsartan could now be used in patients under 18 years of age but not in patients allergic to amlodipine or other medicines in the dihydropyridine class or with allergy to valsartan.

Regarding safety, it should be kept in mind that this combination includes a blocker of the action of angiotensin II. Thus, in all clinical situations such as fever, dehydration, or diarrhea, in which the renal blood flow must autoregulate to avoid renal insufficiency, the ARB must be stopped and amlodipine alone continued if the patient still requires antihypertensive therapy. Potassium and creatinine should be monitored in those with moderate renal impairment. Moreover, in therapeutic conditions that predispose to hyperkalemia (e.g. use of NSAIDs, spironolactone, or ACE inhibitors, as well as acute or chronic renal insufficiency), the presence of the ARB valsartan could mean that the combination may need to be stopped. Caution is advised when prescribing fixed-dose amlodipine/valsartan to patients with hepatic impairment, or biliary obstruction, or when increasing the dosage of the combination in elderly patients. Bilateral renal artery stenosis is another contraindication for the use of this combination.

Dosage, administration, and formulation

In the US, Exforge is available as film-coated tablets of amlodipine 5 and 10 mg and valsartan 160 and 320 mg, to be administered

once daily, taken with water, with or without food. Although a direct switch from monotherapy to the fixed dose may be appropriate for some patients, individual dose titration with amlodipine and valsartan is generally recommended before changing to a fixed-dose combination (EMEA 2007).

Clinical value

As reviewed, this combination is effective in terms of reduction in BP. HTN is an important risk factor for cardiovascular complications and its management still needs improvement. The development of new strategies to improve the BP control is welcome. The development of efficient and safe combination therapy is one of these strategies as many patients with HTN need at least two antihypertensive agents to achieve BP control. Exforge is a new drug combination associating two well-tested antihypertensive products: the CCB amlodipine and the ARB valsartan. The amlodipine/valsartan combination is an association with potential advantages in cardiovascular protection.

Clinical trials are ongoing to assess the efficacy and safety of this combination, and it is likely that others will follow. Currently available data have shown that this new formulation is well tolerated and effective even in severe HTN. Its cost, however, remains high compared with the individual component drugs and economic studies quantifying the possible benefit associated with improved compliance would be welcome.

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