

Role of Combination Therapy in the Treatment of Hypertension: Focus on Valsartan plus Amlodipine

Claudio Ferri

Giuseppe Croce

Giovambattista Desideri

University of L'Aquila, Department of Internal Medicine and Public Health, L'Aquila, Italy

ABSTRACT

Hypertension control is rare in clinical practice, particularly in high-risk patients. A large factor is therapeutic inertia deriving from poorly prescribed lifestyle changes, excess monotherapy use, and scarce on-treatment modifications. The use of drug combinations significantly improves blood pressure (BP) control; in particular, fixed combinations improve therapy without increasing daily pill intake, thereby favouring patient compliance and therapy continuation.

The most widely used fixed combination is based on thiazide diuretics added to either angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Several large-scale clinical trials have been conducted showing that these combinations are effective in lowering BP. However, thiazide diuretics can reduce the metabolic benefits derived from renin–angiotensin–aldosterone system (RAAS) inhibitors in high metabolic risk patients. In contrast, ACE inhibitors or ARBs combined with dihydropyridine calcium channel antagonists (DHPCAs) exert a marked antihypertensive effect without decreasing metabolic protection by RAAS blockade. In the recent JIKEI heart study, ~60% of patients affected by hypertension, heart failure, coronary heart disease or their combination in the valsartan arm were simultaneously treated with DHPCAs. Of note, a 39% reduction in the primary endpoint of combined morbidity and mortality was reported in the valsartan compared with the non-valsartan arm. Furthermore, in a recent multinational study, 83% of 3161 hypertensive patients treated with valsartan and the DHCPA amlodipine reported a

Address correspondence to: Claudio Ferri, University of L'Aquila, Department of Internal Medicine and Public Health, P.le Salvatore Tommasi, n.1, 67100 Coppito (AQ), Italy. Email: claudio.ferri@cc.univaq.it

controlled BP after 8 weeks of treatment. As expected, amlodipine did not negatively influence the metabolic profile of patients, thereby supporting the role of ARB+DHPCA combinations as effective and promising tools in hypertension treatment.

In summary, the combination of ARBs with DHPCAs is an effective strategy in hypertension treatment through synergy between their antihypertensive and vascular protective actions, persistent metabolic benefits deriving from RAAS inhibition, and reduced incidence of side effects.

Keywords: amlodipine; angiotensin-converting enzyme inhibitors; angiotensin receptor antagonists; dihydropyridine calcium channel antagonists; hypertension; treatment; valsartan

BLOOD PRESSURE CONTROL IN TREATED HYPERTENSIVE PATIENTS

In the most recent National Health and Nutrition Survey (NHANES 2003–2004) overall age-adjusted prevalence of hypertension in US residents was 29.3%.¹ The percentage of these patients who reached target blood pressure (BP) levels was 33.1% for all hypertensive patients and 63.9% for those receiving antihypertensive treatment.¹ The number of patients treated with antihypertensives who reached target BP levels has not changed from the 2001–2002 survey, even though more patients received antihypertensive therapy.^{1,2} Compared with the US, the prevalence of hypertension is even higher in European countries (44%).³ Despite this, hypertension treatment is less frequent in Europe (26.8%), ranging from 26% in Germany to 32% in Italy.³ Therefore, it is not surprising to note that only 8% of the whole hypertensive population in Europe reported a BP of <140/90 mmHg.³ Thus, it is evident that BP control in hypertensive patients is still

far from ideal in both the US and Europe, particularly in patients who are receiving antihypertensive medication.

Concordant with the above surveys, a recent pooled analysis conducted in 52,715 Italian hypertensive patients reported stable hypertension treatment in 69% of patients ($n=36,556$). Mean systolic (SBP) and diastolic blood pressure (DBP) were 148 ± 9 mmHg and 90 ± 5 mmHg, respectively,⁴ indicating that the mean SBP, rather than DBP, was abnormal. BP stratification was obtained in 40,829 individuals and demonstrated that about one third (32.6%) of uncontrolled hypertensives had mean BP of >160/100 mmHg. Thus – also based on the reported prevalence of other concomitant risk factors and target organ damage in the same analysis⁴ – it seems evident that most Italian hypertensive patients who received antihypertensive treatment for a high or very-high cardiovascular risk profile had an unchanged risk profile at the end of treatment.

In keeping with the above, similar findings have been found in a recent survey conducted in our unit. Indeed, in con-

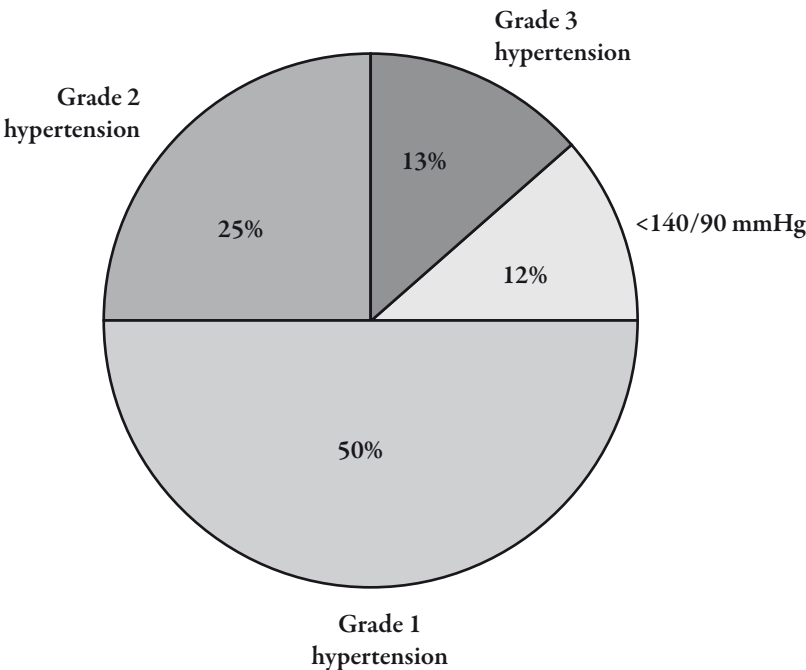
secutive outpatients who referred for the first time, following treatment by specialists or general practitioners, we observed that only 12% of patients had BP levels of <140/90 mmHg, while 38% had grade 2/3 hypertension despite being often prescribed antihypertensive medication (Figure 1). Even more perplexing, the vast majority of these patients were rarely affected by hypertension alone and usually presented with at least one additional cardiovascular risk factor (20% had ≥ 2 additional risk factors). Thus, it appears that a lack of BP control is not limited to low-risk patients, but also to those who have an increasing constellation of risk factors known as the metabolic syndrome.⁵ In line with this hypothesis, the recent European Action on Secondary Prevention Through Intervention to Reduce Events (EUROASPIRE)

III survey was conducted in 22 European countries and demonstrated that the majority of patients with known atherosclerotic disease were still not achieving BP, lipid and glucose targets.⁶ Therefore, according to these data, it is likely that approaches to cardiovascular disease prevention need to be revised and adjusted.

LACK OF HYPERTENSION CONTROL IN TREATED HYPERTENSIVE PATIENTS: A CALL TO ACTION

Lack of hypertension control is mainly responsible for the persistently elevated hypertension-related cardiovascular morbidity and mortality observed in treated patients.¹⁻⁴ Such effects persist despite several antihypertensive agents being

Figure 1. First visits in a hypertension and cardiovascular prevention outpatient unit in patients previously followed in other settings by either specialists or general practitioners.



available, and effective lifestyle-based antihypertensive strategies having clearly demonstrated effective BP reduction in the general hypertensive population⁷ as well as in hypertensives with additional cardiovascular risk factors.⁸ Additional interventions suggested to improve BP control have often been debated and include education programmes aiming to encourage and then maintain lifestyle changes in the long run, evaluation of physician approaches to cardiovascular risk factor control by quality and not economic indicators, implementation of simplified guidelines for patients and general practitioners, counselling with patients to improve awareness and collaboration in the management of hypertension, and increased use of home BP monitoring.^{7–12} The main aim of all of these measures is to reduce therapeutic inertia,^{9,10} i.e. the main culprit responsible for the lack of BP control in the vast majority of treated hypertensive individuals.

In this context, one of the most important tools in the fight against therapeutic inertia is represented by combination treatments.^{11,12} Fixed combination therapies are particularly able to significantly increase patient compliance and long-term stay on-treatment, reduce side effects and (when appropriately chosen) allow the achievement of lower SBP and DBP levels.¹³

COMBINATION TREATMENT IN ESSENTIAL HYPERTENSION

While initial guidelines on BP control emphasised the role of monotherapy, in recent years, clinical trials and daily practice experience have suggested that

such an approach is not effective in the majority of patients.^{14–16} In keeping with the above, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Blood Pressure (JNC 7) suggests that antihypertensive therapy should start with two drugs when a patient presents with a BP of >20 mmHg above SBP and/or >10 mmHg above DBP target.¹⁷ Furthermore, the more recently available European guidelines¹⁸ clearly state that the majority of hypertensive patients enrolled in trials start on a single agent but end up on combination therapy. Combination treatment is particularly encouraged in patients with higher risk profiles, more marked BP elevation and lower BP targets.¹⁸ Thus, statements from different expert panels concluded that combination treatment should be preferred in most hypertensive individuals. An explanatory flow chart – largely based on the European Guidelines¹⁸ – depicting the possible pathways leading to the more appropriate choice is shown in Figure 2.

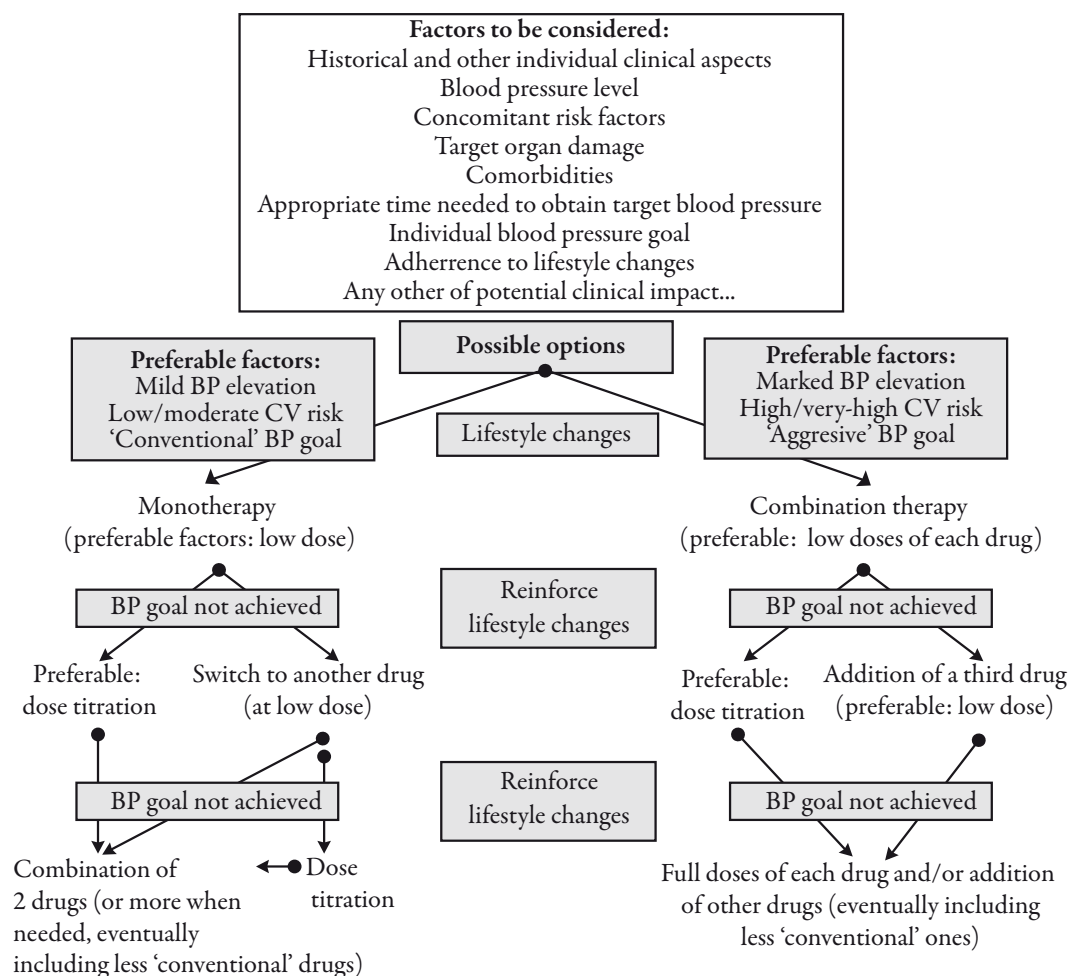
In summary, in contrast to previous approaches, current guidelines support the evidence that combination treatment is often necessary in the vast majority of hypertensive patients. In particular, the same guidelines also indicate that combination of two drugs should be considered as the initial treatment in most cases.

Combination Therapy Based on Angiotensin Receptor Blockers

Antihypertensive therapies based on angiotensin receptor blockers (ARBs) have been demonstrated to reduce composite outcomes comprising cardiovas-

Figure 2. Antihypertensive treatment in the general hypertensive population: a practical flow chart.¹⁸
BP=blood pressure; CV=cardiovascular.

Reproduced with permission from Mancia G, et al. *Management of Arterial Hypertension of the European Society of Hypertension. European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC).* J Hypertens. 2007;25:1105–1187.



cular and cerebrovascular events;¹⁹ slow down the progression from incipient to overt nephropathy in type 2 diabetic hypertensive patients;²⁰ reduce the progression of overt renal damage in type 2 diabetic patients;²¹ be effective in reducing outcomes in patients with heart failure²² and after an acute myocardial infarction;²³ and reduce cardiovascular morbidity and mortality in patients affected by either hypertension, coronary

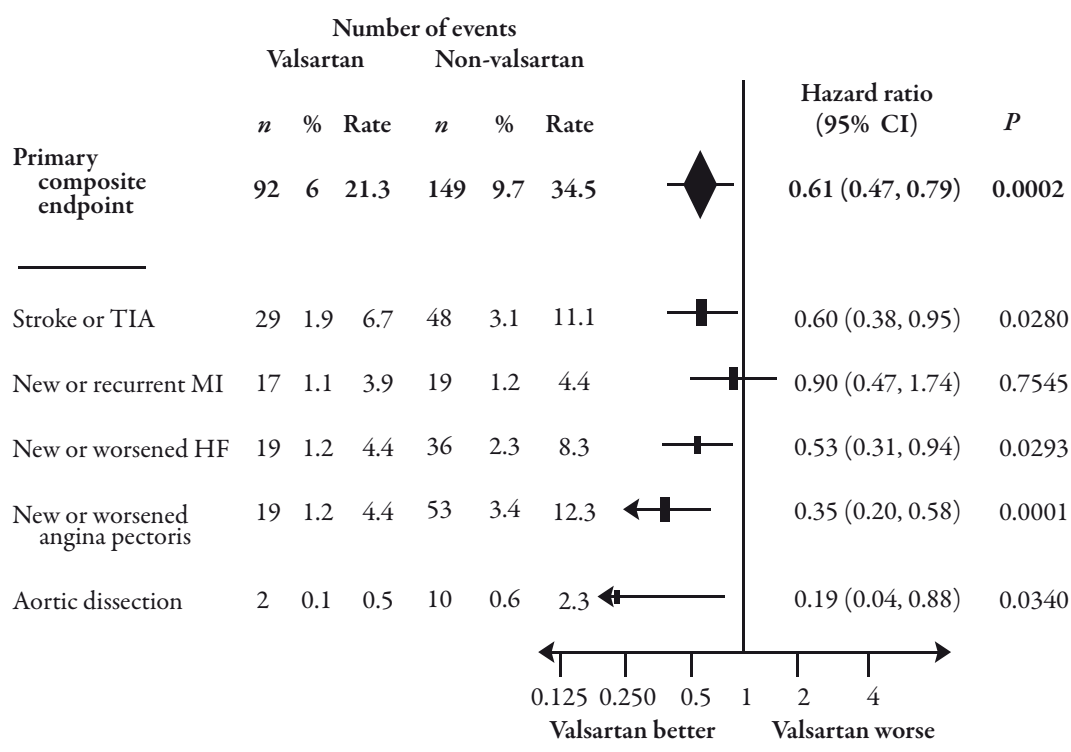
heart disease, heart failure or a combination of these diseases.²⁴ The majority of patients enrolled in the above trials received the ARB valsartan. Studies conducted in hypertensive individuals clearly showed that the ability of valsartan to reduce SBP and DBP levels was dose-dependent, with progressive BP decrements from 40 mg to 320 mg daily.²⁵ Accordingly, in the recent JIKEI heart study²⁴ SBP/DBP levels after a mean follow-up period of 3.1 years

(range, 1–3.9 years) were 131/77 mmHg in a cohort of 1541 Japanese patients at high cardiovascular risk randomised to receive valsartan treatment instead of placebo ($n=1540$ patients), in both cases in addition to conventional treatment. Therefore, achieved BP in the JIKEI heart study was markedly below the threshold of 140/90 mmHg and very close to the levels of <130/80 mmHg that have been recommended by more recent European guidelines in high-risk individuals.¹⁸ Achievement of these BP levels was accompanied by significant reductions of the primary composite and secondary endpoints in patients taking valsartan at

a dose ranging from 40 to 160 mg once daily (mean dose, 76 mg daily) compared with those taking placebo (Figure 3). Of note, at the end of the JIKEI heart study about two thirds of patients were on simultaneous treatment with a dihydropyridine calcium channel antagonist (DHP-CA), one third with an angiotensin-converting enzyme (ACE) inhibitor, one third with a beta blocker and 10% with a diuretic.²⁴ Thus, based on the JIKEI heart study findings it is evident that most high-risk patients require the prescription of ARBs in appropriate combination with another antihypertensive treatment to obtain optimal BP control.

Figure 3. Reduction in incidence of primary and secondary endpoints in valsartan- and non-valsartan-treated patients in the JIKEI heart study.²⁴ CI=confidence interval; HF=heart failure; MI=myocardial infarction; TIA=transient ischaemic attack.

Reprinted from The Lancet, Vol 369, Mochizuki S, et al. Valsartan in a Japanese population with hypertension and other cardiovascular disease (JIKEI heart study): a randomised, open-label, blinded endpoint morbidity-mortality study. Pages 1431–1439. Copyright 2007, with permission from Elsevier.



Thiazide diuretics have historically represented the most widely used combination drug with ARB-based therapy.²⁶ ARBs provide enhanced activity when combined with 12.5 or 25 mg hydrochlorothiazide (HCTZ), thereby providing an important option for tighter BP control.²⁷ In turn, response to HCTZ is also enhanced by the use of ARBs and patients exhibiting a low response to HCTZ monotherapy often report significant BP reductions when the diuretic is combined with an ARB.²⁷

In keeping with this, in the recent COMparative Study of efficacy of Irbesartan/HCTZ with valsartan/HCTZ using home blood pressure Monitoring in the treatment of mild-to-moderate hypertension (COSIMA), the addition of ARBs was able to induce further BP reductions in 464 patients unresponsive to previous diuretic monotherapy.²⁸ However, in the COSIMA study patients received 12.5 mg HCTZ daily as additional treatment to the ARBs irbesartan (150 mg daily) or valsartan (80 mg daily).²⁷ In clinical practice, most patients require the use of higher doses of HCTZ, i.e. 25 mg daily, reporting greater BP reduction but also potential increments in thiazide-related side effects. Thus, in the INCLUSIVE trial²⁹ patients ($n=844$) who still had uncontrolled SBP levels following 4 weeks of treatment with monotherapy were treated sequentially with placebo (4–5 weeks), HCTZ 12.5 mg once daily (2 weeks), irbesartan 150 mg/HCTZ 12.5 mg once daily (8 weeks), and finally with irbesartan 300 mg/HCTZ 25 mg (8 weeks). The mean change in SBP from placebo phase to week 18 (intention-to-treat, $n=736$ patients) was $-21.5\pm$

14.3 mmHg ($P<0.001$), while the mean change in DBP was -10.4 ± 8.7 mmHg ($P<0.001$). Overall, 77% (95% confidence intervals [CI]: 74%, 80%) of patients achieved a SBP of <140 mmHg, 83% (95% CI: 80%, 86%) achieved a DBP of <90 mmHg, and 69% (95% CI: 66%, 72%) achieved dual SBP/DBP goals. Although combination treatment was well tolerated, only one patient manifested with hypotension with the addition of low-dose HCTZ (12.5 mg) versus eight patients among those receiving the full daily dose (i.e. 25 mg). Similarly, three versus eight patients reported fatigue in the 12.5 mg compared with the 25 mg HCTZ groups, respectively.²⁹ Thus, the use of HCTZ 25 mg daily enhanced BP response to irbesartan and was effective, although possibly associated with very modestly worse tolerability.

However, the possibility that diuretics, in general, and HCTZ, in particular, might counteract, at least in part, some of the benefits deriving from renin–angiotensin–aldosterone system (RAAS) inhibitors is supported by two recent post-hoc analyses of the VALUE trial.^{30–32} In the first of these analyses, valsartan, compared with amlodipine, was able to significantly reduce the incidence of new-onset type 2 diabetes mellitus in hypertensive patients at high cardiovascular risk.³¹ Significant protection was still evident in valsartan-treated hypertensives when a more recent definition of fasting hyperglycaemia was used, as well as in patients taking diuretics and/or beta blockers in addition to ARB treatment.³¹ However, new-onset type 2 diabetes mellitus occurred in 15.8% of these latter patients compared with 9.8%

of valsartan-treated patients as a whole. Thus, metabolic protection by valsartan persisted, but was mildly reduced by the addition of beta blockers and/or diuretics. Concordantly, the second post-hoc analysis³² of the VALUE trial showed that new-onset type 2 diabetes mellitus had detrimental effects on cardiovascular prognosis, inducing an increment in the hazard ratio for total cardiac morbidity of 1.43 (95% CI: 1.16, 1.77; $P=0.0008$), supporting the notion that reduced metabolic protection induced by beta blockers and/or diuretics added to previous ARB treatment might negatively influence, at least in part, individual cardiovascular prognosis.

Rationale for the Combination of ARBs with DHPACs

Apart from the evident cardiovascular benefits deriving from the combination of the ARB valsartan with calcium antagonists coming from the recent JIKEI heart study,²⁴ the possibility that simultaneous angiotensin II type 1 (AT_1) receptor and voltage-dependent calcium channel blockade may result in a marked synergy with regard to individual BP-lowering action and vascular protective properties derives from different experimental studies.

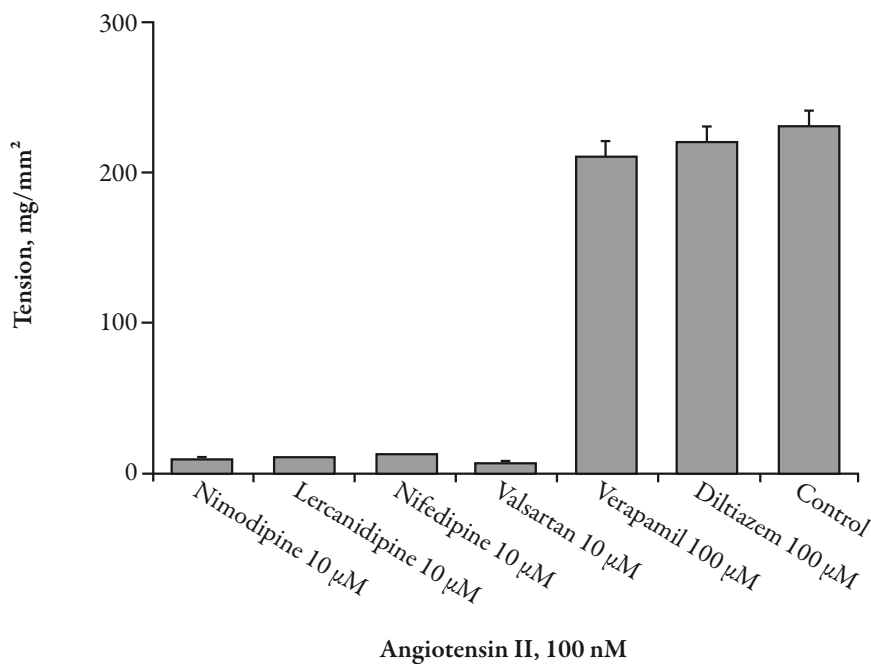
As is known, the AT_1 receptor plays an important role in the structural and functional integrity of the arterial wall.³³ Most of the AT_1 -mediated vascular effects, including vascular contraction, are dependent on activation of a number of intracellular pathways and cytosolic free Ca^{++} concentration which, in turn, is increased by angiotensin II via the same receptor.^{34,35} Although based on cytosolic free Ca^{++} con-

centration and then also on AT_1 -mediated Ca^{++} mobilisation from the intracellular storage pool,³⁶ increments in cytosolic free Ca^{++} in angiotensin II-stimulated vascular smooth cells mainly depend on external Ca^{++} influx.³⁴ Angiotensin II-induced Ca^{++} influx in vascular smooth muscle cells involves dihydropyridine-sensitive calcium channels, receptor-gated calcium channels, dihydropyridine-insensitive cation channels, Ca^{++} -operated Ca^{++} release and membrane-bound Na^+/Ca^{++} exchanger.^{34,37,38} However, external calcium influx across the vascular smooth muscle cell membrane seems to be mainly related to dihydropyridine-sensitive calcium channels since angiotensin II was unable to induce contraction of isolated aortic rings from male Sprague-Dawley rats in calcium-free Krebs.³⁹ Of note, the vascular response to angiotensin II was less evident when aortic endothelium was removed and more pronounced in rats made diabetic by streptozotocin than in non-diabetic rats,³⁹ thereby suggesting hyperglycaemia enhances the vascular responsiveness to AT_1 blockade. Even more interestingly, angiotensin II-induced vascular contraction in the presence of external calcium was abolished by the AT_1 receptor inhibitor valsartan as well as by DHPACs (Figure 4), thereby indicating AT_1 -mediated dihydropyridine-sensitive calcium channel activation was the main mechanism responsible for AT_1 -induced cytosolic free Ca^{++} increment and the consequent aortic ring contraction. Also, non-DHPACs were unable to reduce the vascular response to angiotensin II in the presence of external calcium (Figure 4). Thus, it is evident that angiotensin II-induced vascular contraction is mediated by the AT_1 receptor, but also by the activa-

Figure 4. Effect of dihydropyridine and non-dihydropyridine calcium channel antagonists on angiotensin II-induced contractions in isolated thoracic rat aorta ($n=10$).³⁹

Copyright retained by: Arun KH, Kaul CL, Ramarao P. *AT₁ receptors and L-type calcium channels:*

functional coupling in supersensitivity to angiotensin II in diabetic rats. Cardiovasc Res. 2005;65:374–386.



tion of dihydropyridine-sensitive calcium channels. Based on these in-vitro findings, it is also evident that simultaneous AT₁ receptor and dihydropyridine-sensitive calcium channel blockade may manifest with a significant synergy in clinical practice, by acting on the same pathways leading to cytosolic free Ca⁺⁺ increase and then reciprocally potentiating their vascular dilative and protective properties (Figure 5).

In addition to the above, valsartan could also potentiate the BP-lowering effects of amlodipine by reducing sympathetic tone. Indeed, while amlodipine induces a modest adrenergic activation,⁴⁰ ARBs can reduce the adrenergic tone, particularly by inhibiting α_1 -adrenoceptor activity.^{40,41} Thus, the hypotensive actions of valsartan can also be related to sympathetic tone inhibition. This latter effect

of valsartan may be of particular clinical relevance since it could abolish the adrenergic tone increment that can be encountered in patients treated with DHPCAs.

Antihypertensive Efficacy of the Valsartan and Amlodipine Combination

Data supporting the existence of a marked synergy between valsartan and DHPCAs derive from several sources of in-vivo evidence. The majority of valsartan-treated patients participating in the JIKEI heart study were simultaneously treated with DHPCAs, and this study reported a significant reduction in both primary and secondary cardiovascular endpoints (Figure 3).²⁴ In addition, in a multinational, multicentre, double-blind, placebo-controlled, parallel-group trial

Vasoconstrictive role of angiotensin II: co-operative antagonism by AT₁ receptor and dihydropyridine Ca⁺⁺ blockers

A

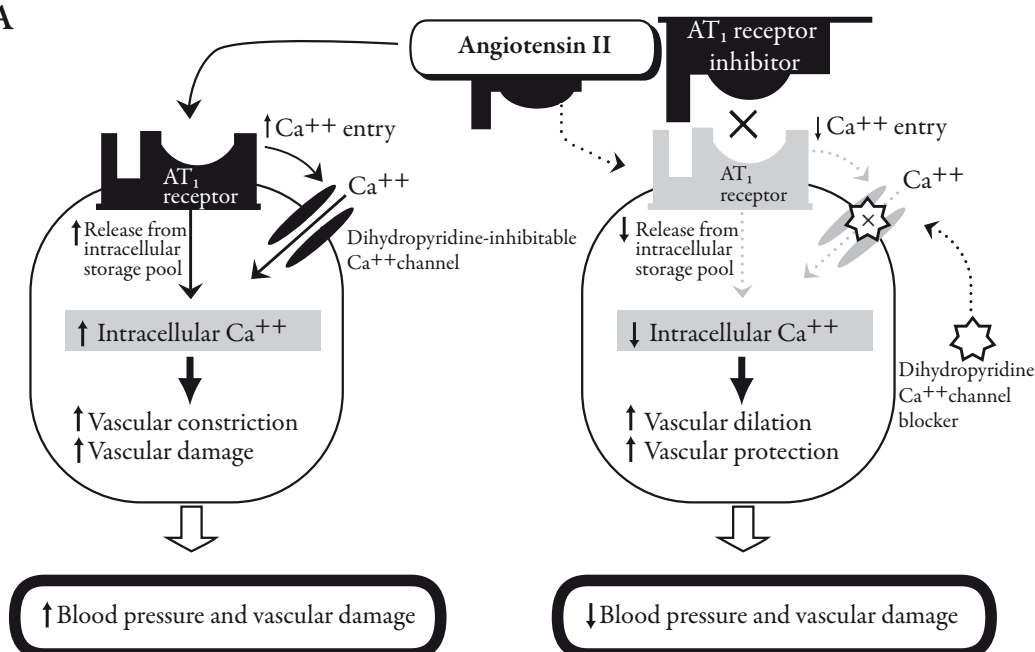


Figure 5A. Vasoconstriction is dependent on intracellular Ca⁺⁺ availability. Angiotensin II induces vasoconstriction by augmenting intracellular Ca⁺⁺ availability. In turn, this latter depends on angiotensin II type 1 (AT₁)-mediated Ca⁺⁺ release from intracellular storage pool and Ca⁺⁺ entry through dihydropyridine-inhibitable channels (left size). Thus, AT₁ receptor and dihydropyridine Ca⁺⁺ channel blockers co-operate in inducing vasodilation and vascular protection (right size).

Co-operative antagonism by AT₁ receptor and dihydropyridine Ca⁺⁺ blockers : ↑vascular protection and ↓side effects

B

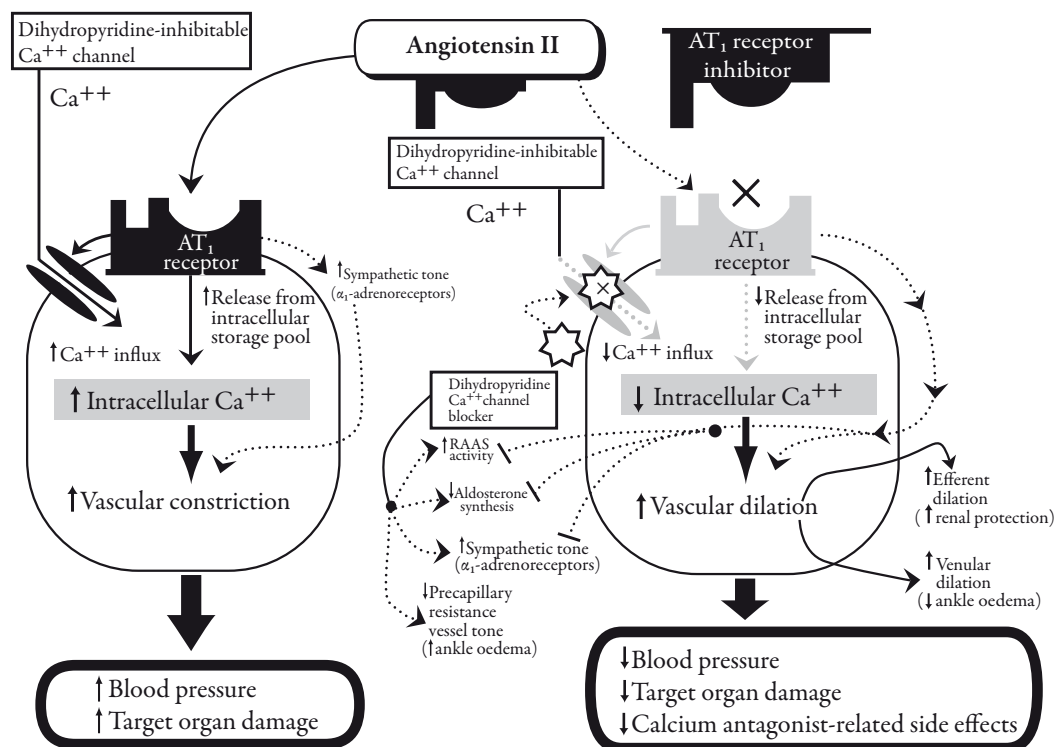


Figure 5B. Vasoconstriction is dependent on intracellular Ca⁺⁺ availability. Angiotensin II induces vasoconstriction by augmenting intracellular Ca⁺⁺ availability. In turn, this latter depends on angiotensin II type 1 (AT₁)-mediated Ca⁺⁺ release from intracellular storage pool and Ca⁺⁺ entry through dihydropyridine-inhibitable channels (left size). Thus, complementary antihypertensive actions exerted by AT₁ receptor and dihydropyridine Ca⁺⁺ channel antagonists also include a decrement in α₁-adrenergic tone, thereby counteracting its mild increase induced by dihydropyridine Ca⁺⁺ channel antagonists (right size). Combination of AT₁ receptor and dihydropyridine Ca⁺⁺ channel antagonists also modulates cutaneous microcirculation and thereby reduces ankle oedema due to the use of Ca⁺⁺ channel antagonists as monotherapy. Similar complementary action on intrarenal resistance vessels leads to increased renal protection. Finally, the modest renin–angiotensin–aldosterone system (RAAS) activation that may also be consequent to the use of dihydropyridine calcium antagonists is also blunted by AT₁ blockade. In turn, both this latter and calcium channel blockers directly reduce aldosterone synthesis and secretion.

Philipp et al.²⁵ recently evaluated 1911 essential hypertensive patients who were randomised to receive either amlodipine 2.5 or 5.0 mg once daily, valsartan 40 to 320 mg once daily, the combination of amlodipine 2.5 or 5.0 mg with valsartan 40 to 320 mg once daily, or placebo over a period of 8 weeks. Cumulative analysis of data showed that 1022 patients were randomised to amlodipine plus valsartan, 507 to valsartan, 254 to amlodipine, and 128 to placebo treatments. According to in-vitro findings, clinical results showed an evident dose response for all combinations, the highest response rate being associated with the highest dose of com-

bination therapy (amlodipine 5 mg plus valsartan 320 mg; 91.3%) (Figure 6A).

Additionally, Philipp et al.²⁵ also evaluated 1250 hypertensive patients, who were randomised to a similar valsartan dose but a higher amlodipine dose over a period of 8 weeks. Interestingly, BP decrements were again found to be dose-dependent but the two doses of combination therapy were associated with similar response rates (amlodipine 10 mg plus valsartan 160 mg, 88.5%; amlodipine 10 mg plus valsartan 320 mg, 87.5%) (Figure 6B). This suggests that the commonly available/used doses of both valsartan and amlodipine are characterised

Figure 6. Effect of combined valsartan and amlodipine therapy on systolic (SBP) and diastolic blood pressure (DBP) of patients with mild-to-moderate essential hypertension.²⁵

Reprinted from Clinical Therapeutics, Vol 29. Philipp T, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Pages 563–580. Copyright 2007, with permission from Excerpta Medica, Inc.

(A) Least-squares mean reduction in (i) sitting DBP and (ii) sitting SBP at the end of Study 1. The standard errors of the means for all reductions in part (i) ranged from 0.65 to 0.67 mmHg; in part (ii), they ranged from 1.03 to 1.06 mmHg.

* $P < 0.05$ vs placebo; † $P < 0.05$ vs the same dose of valsartan monotherapy; ‡ $P < 0.05$ vs the same dose of amlodipine monotherapy.

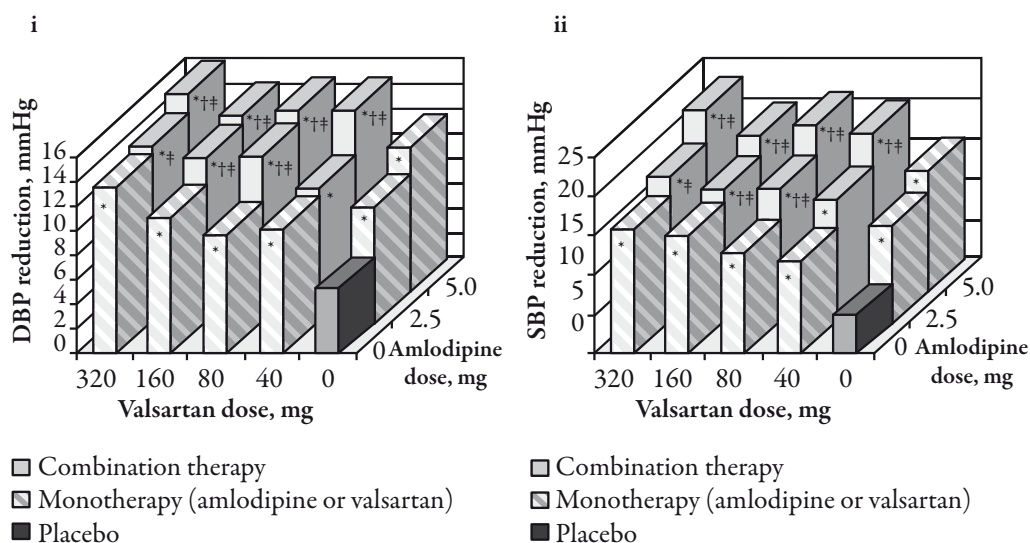
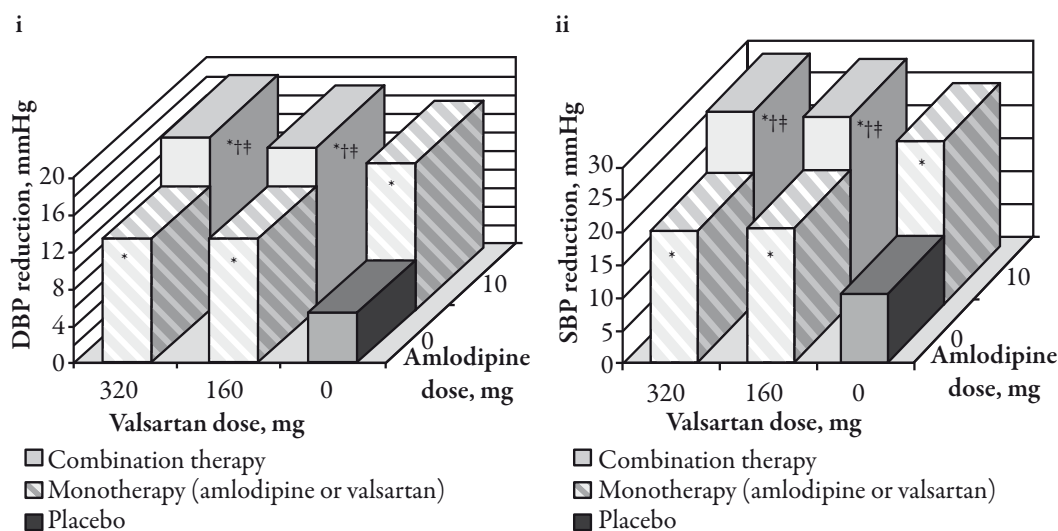


Figure 6. (Continued)

Reprinted from *Clinical Therapeutics*, Vol 29. Philipp T, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. Pages 563–580. Copyright 2007, with permission from Excerpta Medica, Inc.

(B) Least-squares mean reduction in (i) sitting DBP and (ii) sitting SBP at the end of Study 2. The standard errors of the means for all reductions in part (i) ranged from 0.62 to 0.63 mmHg; in part (ii), they ranged from 0.96 to 0.97 mmHg.

* $P < 0.05$ vs placebo; † $P < 0.05$ vs the same dose of valsartan monotherapy; ‡ $P < 0.05$ vs the same dose of amlodipine monotherapy.



by optimal BP responses. Also, comparisons of two different combination regimens based on either the ACE inhibitor lisinopril 10–20 mg plus HCTZ 12.5 mg, or valsartan 160 mg plus amlodipine 5–10 mg showed a marked BP response in hypertensive patients treated with the second combination (SBP –35.8 mmHg after 6 weeks, DBP –28.6 mmHg after 6 weeks; $P < 0.001$ vs baseline in both cases).⁴² Therefore, controlled clinical trials indicate that the combination of amlodipine plus valsartan is associated with significantly greater BP reductions from baseline compared with amlodipine or valsartan monotherapy. In keeping with this, 77.9% of pa-

tients in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, who were randomised to losartan, received calcium channel blockers and reported a significant decrease in the pre-defined renal endpoint of worsening of kidney failure,⁴³ thereby indicating that combination of ARBs with DHPCAs can also be used in high-risk conditions, including type 2 diabetes mellitus with overt renal damage. A review of available data supports the notion that the combination of RAAS and calcium channel antagonists can be very effective in the treatment of hypertension and further improve BP control.⁴⁴

Safety Profile of the Valsartan and Amlodipine Combination

Some post-hoc evidence from the VALUE trial suggests that the combination of valsartan with diuretics and/or beta blockers modestly attenuates the metabolic benefits derived from RAAS blockade.^{31,32} Obviously, this does not mean that a low-dose thiazide cannot be added in principle to RAAS inhibitors, and this also applies to other diabetogenic drugs, i.e. beta blockers. Indeed, it is obvious that the use of diuretics and/or beta blockers is often necessary in hypertensive patients. However, thiazides and beta blockers may limit the metabolic benefits that are known to derive from RAAS blocking agents. Their use, at the higher doses, should be prescribed only when necessary in patients with metabolic disturbances or at high risk for developing type 2 diabetes mellitus. Therefore,

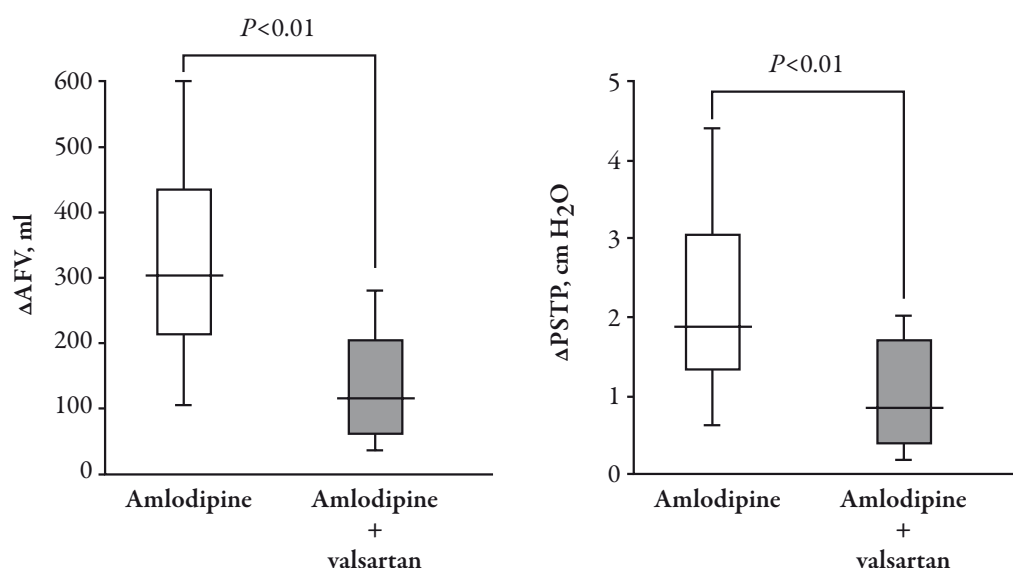
combinations of ARBs and DHPCAs appear the more rational choice in these patients when monotherapy is not able to normalise BP.

Apart from the metabolic aspect, it is of particular interest to note that the two studies evaluating the antihypertensive efficacy of valsartan plus amlodipine combinations^{25,42} also showed that side effects were modest and occurred to a lesser extent in patients taking valsartan plus amlodipine compared with those on amlodipine alone.²⁵ In particular, the incidence of ankle oedema was lower (5.4% vs 8.7%, respectively; $P=0.014$). The incidence of headache was also lower in patients treated with valsartan plus amlodipine compared with those on amlodipine alone (4.3% vs 7.6%, respectively; $P<0.01$).

The reasons leading to the reduced occurrence of the more common side ef-

Figure 7. Effects of amlodipine (10 mg once daily) monotherapy or valsartan (160 mg once daily) plus amlodipine (10 mg once daily) on ankle foot volume (left) and pretibial subcutaneous tissue pressure (right) in 80 hypertensive patients.⁴⁹

Copyright retained by: Fogari R, Zoppi A, Derosa G, et al. J Hum Hypertens. 2007;21:220–224.



fects observed in patients treated with DHPCAs are unclear. However, a certain reduction in ankle oedema has been already reported in two previous studies conducted in hypertensive patients treated with amlodipine in combination with ACE inhibitors^{45,46} and in a previous observation based on the evaluation of ankle oedema by the use of the water displacement technique, i.e. the ancient Archimedes principle.⁴⁷ Furthermore, evaluation of skin blood flow by laser Doppler flowmetry and of leg weight in hypertensive patients treated with amlodipine showed that enalapril restrained fluid extravasation and increment in leg weight induced by amlodipine, probably because of enalapril-related venodilation.⁴⁸ Similar findings might be taken into account to explain the protection against amlodipine-related ankle oedema that was exerted by valsartan.⁴⁰ In accordance with this, a recent study measured two objective measures of ankle oedema, i.e. ankle foot volume and pretibial subcutaneous tissue pressure in 80 hypertensive patients who after a 4-week period on placebo were randomised to amlodipine 10 mg, or valsartan 160 mg, or amlodipine 10 mg plus valsartan 160 mg for 6 weeks according to an open-label, blinded-endpoint, crossover design.⁴⁹ At the end of the placebo period and of each treatment period, ankle foot volume and pretibial subcutaneous tissue pressure were measured. As expected, amlodipine and valsartan monotherapy significantly reduced SBP (−16.9 and −14.5 mmHg, respectively; $P<0.01$ vs baseline) and DBP (−12.9 and −10.2 mmHg, respectively; $P<0.01$ vs baseline) but the reduction

was greater with the combination (−22.9 mmHg for SBP, $P<0.01$ vs monotherapy; −16.8 mmHg for DBP, $P<0.01$ vs monotherapy). Amlodipine but not valsartan monotherapy significantly increased both ankle foot volume (amlodipine, +23%; $P<0.01$ vs baseline) and pretibial subcutaneous tissue pressure (amlodipine, +75.5%; $P<0.001$ vs baseline). Compared with amlodipine monotherapy, the valsartan/amlodipine combination produced a less marked increase in ankle foot volume (+6.8%; $P<0.01$ vs amlodipine monotherapy) and pretibial subcutaneous tissue pressure (+23.2%; $P<0.001$ vs amlodipine monotherapy) (Figure 7). Ankle oedema was clinically evident in 24 patients with amlodipine and in six patients with the combination, thereby supporting a role for valsartan in counteracting the microcirculatory changes responsible for calcium channel blocker-induced oedema formation. Indeed, while angiotensin II is able to induce the constriction not only of arteries but also of veins due to the high amount of AT₁ receptors that are present at the venous level,⁵⁰ DHPCAs mainly dilate large and small arteries and reduce precapillary arteriolar resistance (Figure 5).⁵¹ In keeping with this, complementary actions of ARBs and calcium antagonists might also explain the reasons leading to improved renal outcome in the recent RENAAL study,⁴³ whose patients were treated with losartan in frequent combination with calcium antagonists. In fact, while ARBs reduce systemic BP and preferentially reduce vascular efferent resistance, thereby reducing capillary intraglomerular pressure, blockade of

dihydropyridine-sensitive calcium channels reduces systemic BP and dilates both afferent and efferent arterioles.

In addition to the above explanation, valsartan could have reduced amlodipine-related peripheral oedema because of changes in the sympathetic tone. While amlodipine induces a modest degree of sympathetic activation,⁴⁰ ARBs can reduce the adrenergic tone, particularly by inhibiting α_1 -adrenoceptor activity.^{40,41} In contrast to this, the selective α_1 -adrenoceptor antagonist doxazosin had very modest effects on cutaneous microcirculation⁵² and seems to be ineffective in reducing amlodipine-induced peripheral oedema. Thus, while the hypotensive action of valsartan may be mediated in part by the inhibition of the sympathetic tone in patients with hypertension (Figure 5),⁴⁰ such activity is unlikely to be responsible for the observed reduction in ankle oedema in patients treated with valsartan plus amlodipine compared to those treated with amlodipine alone.

CONCLUSION

Effective reduction in BP is rare in clinical practice, particularly in high-risk hypertensive patients. Clinical trials and epidemiological evidence support the notion that BP decrements within the range of normality significantly improves survival and morbidity. RAAS blockade has been proven to be effective in reducing BP as well as mortality/morbidity outcomes in hypertensive patients. However, ARB monotherapy is not always sufficient to induce an effective BP reduction. In this case, combination therapy is necessary.

In contrast to thiazides, DHPCAs do

not have unfavourable metabolic actions⁵³ and are able to protect the cardiovascular system not only by reducing BP but also through blood pressure-independent mechanisms. Furthermore, since angiotensin II-induced vasoconstriction depends on external calcium, the addition of DHPCAs to ARB treatment provides additional BP decrements. Accordingly, combination of RAAS blocking agents with DHPCAs has been proven to be particularly useful in the management of hypertension and to reduce cardiovascular, cerebrovascular and renal outcomes even in patients with type 2 diabetes mellitus, overt renal failure, coronary heart disease and heart failure. In addition, due to the inhibition of adrenergic tone and venular dilation, ARBs are also able to significantly reduce ankle oedema, i.e. a minor side effect that can be observed in patients taking DHPCAs and can limit long-term adherence to therapy. Accordingly, the valsartan/amlodipine combination has been demonstrated to induce satisfying BP decrements in more than 80% of a large cohort of hypertensive patients.²⁵ In this regard, the modest RAAS activation that can be encountered after DHPCA administration⁵⁴ can be also suppressed by ARBs.⁵⁵

Based on a recent meta-analysis⁵⁶ that stressed the role of fixed combinations in improving long-term adherence to therapy, as well as another study that highlighted the tendency of many hypertension physicians to use approaches that diverge from guideline recommendations,⁵⁷ the use of fixed combinations, in general, and of RAAS plus calcium channel blocking agents, in particular, seems to represent an extremely attrac-

tive tool in cardiovascular prevention in essential hypertensive patients. Finally, the combination of ARBs and DHPCAs is also likely to represent a more fruitful opportunity to obtain the more possible advantages from the suggested ancillary properties that might be responsible for the BP-independent benefits deriving from amlodipine and ARB monotherapies.⁵⁸

REFERENCES

- Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension*. 2007;49:69–75.
- Cheung BM, Ong KL, Man YB, Lam KS, Lau CP. Prevalence, awareness, treatment, and control of hypertension: United States National Health and Nutrition Examination Survey 2001–2002. *J Clin Hypertens*. 2006;8:93–98.
- 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*. 2003;289:2363–2369.
- Volpe M, Tocci G, Trimarco B, et al. Blood pressure control in Italy: results of recent surveys on hypertension. *J Hypertens*. 2007;25:1491–1498.
- Weycker D, Nichols GA, O’Keeffe-Rosetti M, et al. Risk-factor clustering and cardiovascular disease risk in hypertensive patients. *Am J Hypertens*. 2007;20:599–607.
- Kindermann M, Adam O, Werner N, Böhm M. Clinical Trial Updates and Hotline Sessions. Presented at the European Society of Cardiology Congress 2007: (FINESSE, CARESS, OASIS 5, PRAGUE-8, OPTIMIST, GRACE, STEEPLE, SCAAR, STRATEGY, DANAMI-2, ExTRACT-TIMI-25, ISAR-REACT 2, ACUITY, ALOFT, 3CPO, PROSPECT, EVEREST, COACH, BENEFIT, MERLIN-TIMI 36, SEARCH-MI, ADVANCE, WENBIT, EUROASPIRE I-III, ARISE, getABI, RIO). *Clin Res Cardiol*. 2007;96:767–786.
- Elmer PJ, Obarzanek E, Vollmer WM, et al. PREMIER Collaborative Research Group. Effects of comprehensive lifestyle modification on diet, weight, physical fitness, and blood pressure control: 18-month results of a randomized trial. *Ann Intern Med*. 2006;144:485–495.
- Lien LF, Brown AJ, Ard JD, et al. Effects of PREMIER lifestyle modifications on participants with and without the metabolic syndrome. *Hypertension*. 2007;50:609–616.
- Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. *Hypertension*. 2006;47:345–351.
- Guthrie B, Inkster M, Fahey T. Tackling therapeutic inertia: role of treatment data in quality indicators. *BMJ*. 2007;335:542–544.
- Basile J, Black HR, Flack JM, Izzo JL Jr. The role of therapeutic inertia and the use of fixed-dose combination therapy in the management of hypertension. *J Clin Hypertens*. 2007;9:636–645.
- Fahey T, Schroeder K, Ebrahim S. Educational and organisational interventions used to improve the management of hypertension in primary care: a systematic review. *Br J Gen Pract*. 2005;55:875–882.
- Nesbitt SD. Antihypertensive combination therapy: optimizing blood pressure control and cardiovascular risk reduction. *J Clin Hypertens*. 2007;9(suppl 4):26–32.

14. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. FEVER Study Group. The Felodipine Event Reduction (FEVER) study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. *J Hypertens*. 2005;23:2157–2172.
15. Patel A, MacMahon S, Chalmers J, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet*. 2007;370:829–840.
16. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033–1041.
17. Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.
18. Mancia G, De Backer G, Dominiczak A, et al. Management of Arterial Hypertension of the European Society of Hypertension. European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–1187.
19. Dahlöf B, Devereux RB, Kjeldsen SE, et al. LIFE Study Group. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995–1003.
20. Viberti G, Wheeldon NM. MicroAlbuminuria Reduction with VALsartan (MARVAL) Study Investigators. Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. *Circulation*. 2002;106:672–678.
21. Lewis EJ, Hunsicker LG, Clarke WR, et al. Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851–860.
22. Cohn JN, Tognoni G. Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345:1667–1675.
23. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893–1906.
24. Mochizuki S, Dahlöf B, Shimizu M, et al. Heart Study Group. Valsartan in a Japanese population with hypertension and other cardiovascular disease (JIKEI heart study): a randomised, open-label, blinded endpoint morbidity-mortality study. *Lancet*. 2007;369:1431–1439.
25. Philipp T, Smith TR, Glazer R, et al. Two multicenter, 8-week, randomized, double-blind, placebo-controlled, parallel-group studies evaluating the efficacy and tolerability of amlodipine and valsartan in combination and as monotherapy in adult patients with mild to moderate essential hypertension. *Clin Ther*. 2007;29:563–580.
26. Waeber B. Combination therapy with ACE inhibitors/angiotensin II receptor antagonists and diuretics in hypertension. *Expert Rev Cardiovasc Ther*. 2003;1:43–50.

27. Pool JL, Glazer R, Weinberger M, Alvarado R, Huang J, Graff A. Comparison of valsartan/hydrochlorothiazide combination therapy at doses up to 320/25 mg versus monotherapy: a double-blind, placebo-controlled study followed by long-term combination therapy in hypertensive adults. *Clin Ther*. 2007;29:61–73.
28. Bobrie G, Delonca J, Moulin C, Giacomino A, Postel-Vinay N, Asmar R. COmparative Study of efficacy of Irbesartan/HCTZ with valsartan/HCTZ using home blood pressure Monitoring in the treAtment of mild-to-moderate hypertension (COSIMA) Investigators. A home blood pressure monitoring study comparing the antihypertensive efficacy of two angiotensin II receptor antagonist fixed combinations. *Am J Hypertens*. 2005;18:1482–1488.
29. Neutel JM, Saunders E, Bakris GL, et al. INCLUSIVE Investigators. The efficacy and safety of low- and high-dose fixed combinations of irbesartan/hydrochlorothiazide in patients with uncontrolled systolic blood pressure on monotherapy: the INCLUSIVE trial. *Clin Hypertens*. 2005;7:578–586.
30. Julius S, Kjeldsen SE, Weber M, et al. VALUE Trial Group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022–2031.
31. Kjeldsen SE, Julius S, Mancia G, et al. VALUE Trial Investigators. Effects of valsartan compared to amlodipine on preventing type 2 diabetes in high-risk hypertensive patients: the VALUE trial. *J Hypertens*. 2006;24:1405–1412.
32. Aksnes TA, Kjeldsen SE, Rostrup M, Omvik P, Hua TA, Julius S. Impact of new-onset diabetes mellitus on cardiac outcomes in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial population. *Hypertension*. 2007;50:467–473.
33. Voors AA. Vascular benefits of angiotensin receptor blockers. *Expert Opin Investig Drugs*. 2007;16:987–997.
34. Lu HK, Fern RJ, Luthin D, et al. Angiotensin II stimulates T-type Ca^{2+} channel currents via activation of a G protein, Gi. *Am J Physiol*. 1996;271:C1340–C1349.
35. Desideri G, Bravi MC, Tucci M, et al. Angiotensin II inhibits endothelial cell motility through an AT1-dependent oxidant-sensitive decrement of nitric oxide availability. *Arterioscler Thromb Vasc Biol*. 2003;23:1218–1223.
36. Neusser M, Tepel M, Golinski P, et al. Different calcium storage pools in vascular smooth muscle cells from spontaneously hypertensive and normotensive Wistar-Kyoto rats. *J Hypertens*. 1994;12:533–538.
37. Carraro-Lacroix LR, Malnic G. Signaling pathways involved with the stimulatory effect of angiotensin II on vacuolar H^{+} -ATPase in proximal tubule cells. *Pflugers Arch*. 2006;452:728–736.
38. Fuller AJ, Hauschild BC, Gonzalez-Villalobos R, et al. Calcium and chloride channel activation by angiotensin II-AT1 receptors in preglomerular vascular smooth muscle cells. *Am J Physiol Renal Physiol*. 2005;289:F760–F767.
39. Arun KH, Kaul CL, Ramarao P. AT1 receptors and L-type calcium channels: functional coupling in supersensitivity to angiotensin II in diabetic rats. *Cardiovasc Res*. 2005;65:374–386.
40. de Champlain J, Karas M, Assouline L, et al. Effects of valsartan or amlodipine alone or in combination on plasma catecholamine levels at rest and during standing in hypertensive patients. *J Clin Hypertens*. 2007;9:168–178.
41. Batenburg WW, van Esch JH, Garrelds IM, et al. Carvedilol-induced antagonism of angiotensin II: a matter of alpha1-adrenoceptor blockade. *J Hypertens*. 2006;24:1355–1363.

42. Poldermans D, Glazes R, Kargiannis S, et al. Tolerability and blood pressure-lowering efficacy of the combination of amlodipine plus valsartan compared with lisinopril plus hydrochlorothiazide in adult patients with stage 2 hypertension. *Clin Ther*. 2007;29:279–289.
43. Brenner BM, Cooper ME, de Zeeuw D, et al. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861–869.
44. Swales P, Williams B. Calcium channel blockade in combination with angiotensin-converting enzyme inhibition or angiotensin II (AT(1)-receptor) antagonism in hypertensive diabetics and patients with renal disease and hypertension. *J Renin Angiotensin Aldosterone Syst*. 2002;3:79–89.
45. Kuschnir E, Acuña E, Sevilla D, et al. Treatment of patients with essential hypertension: amlodipine 5 mg/benazepril 20 mg compared with amlodipine 5 mg, benazepril 20 mg, and placebo. *Clin Ther*. 1996;18:1213–1224.
46. Messerli FH, Oparil S, Feng Z. Comparison of efficacy and side effects of combination therapy of angiotensin-converting enzyme inhibitor (benazepril) with calcium antagonist (either nifedipine or amlodipine) versus high-dose calcium antagonist monotherapy for systemic hypertension. *Am J Cardiol*. 2000;86:1182–1187.
47. Fogari R, Malamani GD, Zoppi A, et al. Effect of benazepril addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens*. 2003;17:207–212.
48. Pedrinelli R, Dell’Omo G, Melillo E, Mariani M. Amlodipine, enalapril, and dependent leg oedema in essential hypertension. *Hypertension*. 2000;35:621–625.
49. Fogari R, Zoppi A, Derosa G, et al. Effect of valsartan addition to amlodipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients. *J Hum Hypertens*. 2007;21:220–224.
50. Pastore L, Tessitore A, Martinotti S, et al. Angiotensin II stimulates intercellular adhesion molecule-1 (ICAM-1) expression by human vascular endothelial cells and increases soluble ICAM-1 release in vivo. *Circulation*. 1999;100:1646–1652.
51. Williams SA, Rayman G, Tooke JE. Dependent oedema and attenuation of postural vasoconstriction associated with nifedipine therapy for hypertension in diabetic patients. *Eur J Clin Pharmacol*. 1989;37:333–335.
52. Iabichella ML, Dell’Omo G, Melillo E, Pedrinelli R. Calcium channel blockers blunt postural cutaneous vasoconstriction in hypertensive patients. *Hypertension*. 1997;29:931–937.
53. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007;369:201–207.
54. Atkins CE, Rausch WP, Gardner SY, Defrancesco TC, Keene BW, Levine JF. The effect of amlodipine and the combination of amlodipine and enalapril on the renin-angiotensin-aldosterone system in the dog. *J Vet Pharmacol Ther*. 2007;30:394–400.
55. Ohbayashi Y, Tsutamoto T, Sakaguchi T, et al. Effect of an angiotensin II type 1 receptor blocker, valsartan, on neurohumoral factors in patients with hypertension: comparison with a long-acting calcium channel antagonist, amlodipine. *J Cardiovasc Pharmacol*. 2003;42(suppl 1):S71–S74.
56. Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120:713–719.

57. Malacco E, Ferri C, Grandi AM, Kilama MO, Sogliani AG, Vigna L. Treatment of hypertension and adherence to treatment guidelines in clinical practice: an Italian study. *Adv Ther*. 2005;22:96–106.
58. Wang J, Franklin SS, Safar M. Prevention of stroke and myocardial infarction by amlodipine and angiotensin receptor blockers: a quantitative overview. *Hypertension*. 2007;50:151–158.