

# Manidipine–delapril combination in the management of hypertension

Manuel Luque Otero

Hypertension Unit, Hospital Clinico San Carlos, Complutense University, Madrid, Spain

**Abstract:** High blood pressure (BP) is the major cardiovascular risk factor and the main cause of death around the world. Control of blood pressure reduces the high mortality associated with hypertension and the most recent guidelines recommend reducing arterial BP values below 140/90 mmHg for all hypertensive patients (130/80 in diabetics) as a necessary step to reduce global cardiovascular risk, which is the fundamental objective of the treatment. To achieve these target BP goals frequently requires combination therapy with two or more antihypertensive agents. Although the combination of a diuretic and an angiotensin converting enzyme inhibitor (ACEI) is the most commonly used in the clinical practice, the combination of an ACEI and a calcium channel blocker may have an additive antihypertensive effect, a favorable effect on the metabolic profile, and an increased target organ damage protection. The new oral fixed combination manidipine 10 mg/delapril 30 mg has a greater antihypertensive effect than both components of the combination separately, and in non-responders to monotherapy with manidipine or delapril the average reduction of systolic and diastolic BP is 16/10 mmHg. The combination is well tolerated and the observed adverse effects are of the same nature as those observed in patients treated with the components as monotherapy. However, combination therapy reduces the incidence of ankle edema in patients treated with manidipine.

**Keywords:** manidipine, delapril, manidipine–delapril combination, hypertension

## Introduction

Arterial hypertension is a very common condition and the main cause of mortality in the world (Lopez et al 2006). Elevation of arterial blood pressures, even at levels that are considered clinically normal, is associated with an increase in cardiovascular diseases (ischemic heart disease, cerebrovascular disease, peripheral arteriopathy, and heart failure (Prospective Studies Collaboration 2002)). Furthermore, there is an accumulation of risk factors (dyslipidemia, hydrocarbonate intolerance/diabetes) and target organ damage (microalbuminuria, left ventricular hypertrophy) that increases cardiovascular risk and accounts for the high morbidity–mortality associated with hypertension in hypertensive patients (Guidelines Committee 2003).

## Antihypertensive treatment reduces cardiovascular events

Since the beginning of the 1970s, treatment of hypertension has been known to reduce associated mortality (VAC 1970). Many meta-analyses have demonstrated the superiority of antihypertensive treatment versus placebo (BPLTT 2003, 2005). A controversy has existed for years regarding the superiority of some antihypertensive drugs over others, especially diuretics or beta-blockers versus calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB). However, a number of comparative studies have been published. From these we consider that the effect of the antihypertensive drugs, with some exceptions, is due

Correspondence: Manuel Luque Otero  
Hypertension Unit, Hospital Clinico San Carlos, Complutense University, 28040 Madrid, Spain  
Tel +34 91 3303125  
Fax +34 91 3303458  
Email mluqueo@telefonica.net

more to the reduction of arterial pressures than to specific effects of the different antihypertensive groups (Guidelines Committee 2003). The prevailing opinion has been that the protective effect of all classes of drugs against cardiovascular mortality is the same, with equal degrees of blood pressure (BP) reduction.

Another very important aspect of treatment is that its benefits are achieved even though the number of patients with well-controlled BP is moderate in such studies (Mancia et al 2002). Furthermore, the importance of the reduction of arterial pressures has been demonstrated again recently.

The VALUE (Valsartan Antihypertensive Long-Term Use Evaluation) study (Julius et al 2004) compared the effects of treatment based on valsartan (ARB) and amlodipine (CCB) on heart morbidity and mortality in high-risk hypertensive patients. At study end (72 months) or final visit the reductions in systolic BP (SBP) from baseline until study end were 15.2 mmHg and 17.3 mmHg in the valsartan and amlodipine groups, respectively. The difference between groups was substantial at 1 month (4.0 mmHg) but decreased to approximately 2.1 mmHg at 6 months and averaged 2.0 mmHg thereafter. As with SBP, the difference in diastolic BP (DBP) between groups was substantial at 1 month (2.1 mmHg) but decreased to 1.6 mmHg at 6 months and remained relatively constant thereafter. Targets of <140 mmHg SBP and <90 mmHg DBP were achieved in 56% of the valsartan group and 62% of the amlodipine group.

Although there was no significant difference in the primary composite end point (cardiac morbidity or mortality) in these high-risk patients treated with valsartan- or amlodipine-based regimens, a trend towards fewer fatal or non-fatal strokes in the amlodipine group was observed and there was a significant decrease in the incidence of fatal and non-fatal myocardial infarction in the amlodipine group. However, as the study progressed and the differences in SBP became smaller, the odd ratios for myocardial infarction approached unity. Thus, unequal BP reductions might account for the reduced incidence of myocardial infarction and stroke seen with amlodipine, particularly early in the study when these differences were greatest.

## Control of arterial blood pressure

The most recent European (Guidelines Committee 2003) and North American (Chobanian et al 2003) guidelines recommend reducing arterial BP values below 140/90 mmHg for all hypertensive patients over 18 years of age, including elderly patients, as long as it is tolerated clinically, as a necessary step to reduce global cardiovascular risk, which

is the fundamental objective of the treatment. For high-risk hypertensive subjects, such as diabetics, those having silent lesions of the target organ or established cardiovascular clinical disease, values below 130/80 mmHg should be reached and maintained. These should be even lower for patients with established kidney disease and nephrotic range proteinuria.

In spite of such exact recommendations, control of hypertensive patients is very deficient over almost all the world. Recent surveys in Europe have found an 18.7% rate of control in Germany in primary healthcare (Sharma et al 2004). In specialized care in Italy, the care level that generally has the greatest control, control rate is 11.9% (Mancia et al 2004). Rate of control was 42.1% in hospital-based hypertension units in Spain (Banegas et al 2002). The percentage of control is much lower in diabetic patients. Control tends to be better in North America than in Europe: for European countries on average only 8% of hypertensive individuals have their condition well controlled compared with 23% in Canada and the United States (persons 35–64 years of age) (Wolf-Meier et al 2003).

Different causes have been mentioned to explain poor control of arterial BP (Guidelines Committee 2003), including unknown or unsuspected secondary hypertension, limited treatment compliance, consumption of hypertensive substances or drugs, and failure to change life style (gaining weight or excessive drinking of alcohol). An important aspect to consider is that in spite of poor BP control, a significant percentage of hypertensive patients receive antihypertensive monotherapy. Furthermore, among the patients uncontrolled with monotherapy, treatment is not modified in most cases: for about three-quarters of visits in which elevated BP was recorded in treated hypertensives, physicians did not increase medications (Berlowitz et al 1998). Antihypertensive monotherapy leads to limited reduction in BP and manages to control only a moderate percentage of hypertensive subjects. Many physicians do not prescribe enough medication to control their patients.

In a recent meta-analysis (Law et al 2003) of 354 randomized, double-blind, placebo-controlled trials of the principal antihypertensive drugs, all categories of drug produced similar reductions in BP: 9.1 mmHg systolic and 5.5 mmHg diastolic at standard dose and 7.1 mmHg systolic and 4.4 mmHg diastolic (20% lower) at half standard dose. The drugs reduced BP from all pretreatment levels, more so from higher levels. The BP-lowering effects of different categories of drugs were additive. An increase in the doses of thiazides, beta-blockers, and CCBs increased the rate of adverse effects; symptoms caused by ACEIs (mainly cough) were not dose related.

## Combination of drugs in the treatment of hypertension

To achieve target BP goals frequently requires combination therapy with two or more antihypertensive agents. The proportion of patients requiring combination therapy will depend on baseline BP values. In ALLHAT (ALLHAT 2002), which recruited grade 1 and 2 hypertensives mostly on monotherapy, about 60% of the patients remained on monotherapy. In the HOT study (Hanson et al 1998), which recruited grade 2 and 3 hypertensives after washout from previous medication, monotherapy was successful in only 25%–40% of patients, according to the target DBP.

Since most hypertensive patients will require two or more antihypertensive medications to achieve their BP goals, the 2003 European Society of Hypertension/European Society of Cardiology guidelines (Guidelines Committee 2003) consider reasonable initiating therapy either with a low dose of a single agent or with a low dose combination of two agents. To initiate therapy with a combination of two drugs with different mechanisms of action increases the possibility that BP and its complications are controlled, and because fixed low-dose combinations are available the administration of two agents within a single tablet is possible, thus optimizing compliance. The seventh Report of the Joint National Committee (Chobanian et al 2003) recommends the addition of a second drug from a different class when use of a single agent in adequate doses fails to achieve the goal. In addition when BP is >20 mmHg above SBP goal or 10 mmHg above DBP goal, consideration should be given to initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations.

The initiation of therapy with more than one drug increases the likelihood of achieving the BP goal early. The use of multidrug combinations often produces greater BP reduction at lower doses of the component agents, resulting in fewer side-effects. The use of fixed-dose combinations may be more convenient and simplify the treatment regimen, and may cost less than the individual components prescribed separately.

Diuretic therapy is the logical add-on therapy following optimization of ACEI or ARB. The available evidence suggests that long-acting CCBs remain a logical, safe, and very effective addition, as recommended in the ESH/ESC guidelines.

## Combination of renin-angiotensin system blockade and CCB therapy

Angiotensin renin system inhibition, with both ACEIs and ARBs, plays a fundamental role in the antihypertensive treatment. Although it is still unknown what role angiotensin II plays

in the maintenance of high BPs in the hypertensive subject, its involvement in the physiopathology of target organ damage and in the main complications of hypertension is clear.

ACEIs reduce BP by reducing the circulating levels of angiotensin II. Although the role of the tissue renin–angiotensin system in pathophysiology remains unclear ACEIs inhibit ACE activity within the vessel wall and multiple tissues such as heart and brain.

The ACEIs reduce left ventricular hypertrophy more than other antihypertensive drugs (Klingbeil et al 2003). This is probably partly due to their effect on the cardiac renin-angiotensin system (RAS), but they also increase distensibility of the aorta and reduce the reflected arterial wave amplitude (London et al 1996). They reduce wall remodeling in the small resistance arteries, reducing the media thickness and media width to lumen ratio (Schiffrin et al 1994).

In the kidney, the ACEIs decrease constriction of the efferent arteriole induced by angiotensin II, reducing intraglomerular pressure and protecting the kidney, especially in hypertensive or normotensive diabetic subjects. They reduce morbidity–mortality and slow down progression toward renal failure in type 1 diabetics (Lewis et al 1993). They also reduce urinary excretion of albumin and progression of nephropathy with proteinuria (Jafar et al 2001). Administration of ACEI compared with placebo reduced the incidence of microalbuminuria in normoalbuminuric type 2 diabetic subjects (Ruggeneti et al 2005).

Furthermore, the ACEIs have been shown to reduce insulin resistance associated with arterial hypertension and reduce the incidence of diabetes mellitus in long-duration studies compared with other classes of antihypertensive drugs (Mancia et al 2006).

CCBs are a group of antihypertensive agents constituted by 3 families: benzothiazepine (diltiazem), phenylalkylamine (verapamil), which are heart rate slowing, and dihydropyridines, which are predominantly vasodilators. Their mechanism of action is that of reducing cytosolic calcium content of the smooth muscle cells of the vessels, reducing their contraction and vasodilating the small arteries. CCBs block Ca entry through Ca channels. They block L type calcium channels (Pitt B 1997)

These are excellent antihypertensive agents. Their primary action is to block Ca entry through Ca channels, and they also restore nitric oxide availability (Taddei et al 2001) and tend to be more effective at high rather than low sodium intake (Luque Otero et al 1987), perhaps because they have a natriuretic effect. Their antihypertensive benefit is well

documented in the elderly, and in the presence of isolated systolic hypertension (Liu et al 1998).

CCBs reduce left ventricular hypertrophy, practically in the same way as the ACEIs (Klingbeil et al 2003). Their renal effects are controversial, perhaps because their vasodilator effect is limited to the afferent arteriole, and they tend to increase intraglomerular pressure (Zanchi et al 1995) that could eventually be associated with the progression of renal disease (Griffin et al 1995). In type 2 diabetics the dihydropyridine CCBs tend to have a neutral or adverse effect on proteinuria, whereas the non-dihydropyridine CCBs tend to reduce the rise in proteinuria. But these studies are really too small to enable definitive clinical conclusions to be drawn (Kloke et al 1998).

In contrast to the predominant action on the afferent arterioles of conventional types of CCB, the novel molecules such as manidipine acting on both afferent and efferent arterioles may correct glomerular hypertension, reduce microalbuminuria, and prevent the progression of renal disease (Tojo et al 1992).

Both in animal as well as human models, the CCBs reduce progression of arteriosclerosis plaques (Simon et al 2002). This has been demonstrated in comparative follow-up studies with other antihypertensive agents (Zanchetti et al 1998, 2002).

The combination of ACEIs and CCB is greatly used in clinical practice because both drug groups have different mechanisms of action that may be complementary. Table 1 shows the possible benefits of the combination of both drugs (Swales et al 2002).

Fixed dose combination of ACEI–CCB therapy was shown to be equally efficacious as ACEI–thiazide (Letellier et al 1994) or  $\beta$ -blocker–diuretic combinations (De Leuw et al 1997). However, the results of the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT) Study demonstrated that among 19,257 high risk hypertensives, treatment with the amlodipine–perindopril combination (if necessary to achieve the target BP) prevented more major cardiovascular events and induced less diabetes

than treatment with the atenolol–thiazide combination (if necessary), suggesting a superiority of the combined treatment with ACEI–CCB over betablocker–thiazide. The study was stopped prematurely after 5.5 years' median follow-up because compared with those allocated to the amlodipine-based regimen the patients allocated to the atenolol-based regimen had significantly higher mortality as well as worse outcomes on several other secondary endpoints: fatal and non-fatal stroke (327 vs 422; 0.77, 0.66–0.89,  $p = 0.0003$ ), total cardiovascular events and procedures (1362 vs 1602; 0.84, 0.78–0.90,  $p < 0.0001$ ), and all-cause mortality (738 vs 820; 0.89, 0.81–0.99,  $p = 0.025$ ). The incidence of developing diabetes was less on the amlodipine-based regimen (567 vs 799; 0.70, 0.63–0.78,  $p < 0.0001$ ). As occurred in the VALUE trial, compared with those allocated the atenolol–thiazide-based regimen, BP values were lower throughout the trial in those allocated the amlodipine–perindopril-based regimen. These differences were largest (5.9/2.4 mmHg) at 3 months, and the average difference throughout the trial was 2.7/1.9 mmHg. The higher BP lowering achieved in the amlodipine–perindopril group, particularly in the first year of follow-up, is likely to have contributed to the differential cardiovascular benefits (Dahlof et al 2005).

## Manidipine

Manidipine is a third-generation CCB with a long duration of action because of its high lipophilic nature, strong membrane binding, and slow release to calcium channels. Manidipine inhibits the calcium influx to the cell by antagonism on calcium channels (Okabe et al 1987). In addition, and in contrast with other CCBs, manidipine not only blocks the L-type calcium channels but also the T-type channels (Furukawa 2005) that are distributed in the sinoatrial node and participate in the pathogenesis of cardiac hypertrophy and in cardiac remodeling.

Manidipine is highly selective for the vasculature. Its antihypertensive effects have been well documented in clinical studies (McKeage and Scott 2004) and result from peripheral vasodilation without any significant modification of norepinephrine levels, suggesting a lack of sympathetic activation (Fogari et al 2000). Manidipine reduced BP in a dose-dependent manner between 10 and 40 mg daily and the usual dosage in clinical practice is established at between 10 and 20 mg daily. The antihypertensive effect of once-daily manidipine administration is maintained during the 24-hour period without disturbing the circadian BP rhythm (Fogari et al 1996). Manidipine has been compared with other CCBs such as amlodipine, felodipine, lercanidipine, and nifedipine

**Table 1** Possible benefits of the combination of calcium channel blockers and angiotensin converting enzyme inhibitors (adapted from Swales and Williams 2002)

More effective reduction in stroke
Reduction of left ventricular mass
Control of ventricular dysrhythmias
To improve cardiac filling and contractility
More effective prevention (and regression) of atherogenesis
Additional possible antiproteinuric effects
More favorable effects on the metabolic profile



(McKeage and Scott 2004), its antihypertensive effect being of a similar magnitude and dose-related. In contrast, fewer manidipine-treated patients experienced ankle edema than patients treated with amlodipine (Zanchetti et al 2001), perhaps reflecting a lesser activation of the sympathetic nervous system (Fogari 2005). There were no clinically relevant effects on heart rate with recommended dosages of manidipine (10 or 20 mg once daily).

Long-term treatment with manidipine significantly reduced the left ventricular mass index in hypertensive patients with type 2 diabetes and microalbuminuria. After 2 years' treatment, manidipine produced a greater reduction of left ventricular mass index than lisinopril (14.9 g/m<sup>2</sup> vs –10.8 g/m<sup>2</sup> at 24 months) (Fogari et al 2005).

Unlike the conventional types of CCB, manidipine dilates both efferent and afferent arterioles in animal models (Hayasi et al 1996) thus reducing intraglomerular pressure. In hypertensive patients with microalbuminuria and type 2 diabetes, manidipine 10 or 20 mg once daily effectively lowered BP from baseline as well as ACEIs such as enalapril (Mancia et al 200; Luque et al 2005) or lisinopril. Manidipine and lisinopril significantly decreased albumin excretion rate (AER), but it was slightly but significantly more pronounced with lisinopril (at 24 weeks, –37.2 mg/24 hours,  $p < 0.001$  vs baseline) than with manidipine (–29.9 mg/24 hours,  $p < 0.05$  vs baseline) (Fogari et al 2005). In hypertensive type 2 diabetics with microalbuminuria and uncontrolled BP treated with ARBs or ACEIs, the addition of manidipine to the treatment caused a large reduction in both blood pressure (–18/6.5 mmHg) and AER (–60%). Over one third of the patients reached the AER target (<20 mg/min) (Martinez et al 2004).

Moreover, manidipine improved insulin resistance as assessed by glucose clamp technique in essential hypertensives (Iimura et al 1995) and in hypertensive type 2 diabetics (Suzuki et al 1996).

## Delapril

Delapril is a non-sulphydryl ACEI. It is an esterified pro-drug that is converted in vivo to its active metabolites — delapril diacid and 5-hydroxy delapril diacid. The vast body of evidence collected by various studies shows that delapril, at doses between 30 and 120 mg/day, is endowed with a significant antihypertensive effect (Onayama et al 1988). Once-daily administration of delapril maintains the antihypertensive action for 24 hours (Fogari et al 1997). Delapril is eliminated mainly through urine and in patients with marked renal impairment there is a need for dosage adjustment (Onoyama et al 1988).

The antihypertensive effect of delapril is similar that the obtained with other ACEIs and has renoprotective and cardioprotective actions, with a lower incidence of cough than captopril or enalapril (Saruta and Nishikawa 1991). Delapril increased the insulin sensitivity in hypertensive type 2 diabetic patients (Suzuki et al 1996).

## Manidipine–delapril

Pharmacokinetic studies of the combination demonstrated that co-administration of single oral doses of manidipine 10 mg and delapril 30 mg in healthy volunteers did not modify the pharmacokinetics of either drug or those of their major metabolites (Stockis et al 2003).

## Antihypertensive efficacy

### Dose finding

The optimum dosage of each component of the combination was determined in a study using a  $3 \times 3$  factorial design combining manidipine 5 or 10 mg, delapril 15 or 30 mg, or placebo administered once daily during 6 weeks. The study was randomized, double-blind, and 400 patients with mild to moderate hypertension were randomized. The most effective combination was 30 mg delapril and 10 mg manidipine once daily. The reduction of BP from baseline was 15/13 mmHg for SBP and DBP, respectively. The placebo-corrected reduction of BP, 11/9 mmHg, resulted in a good control of BP in 72% of the patients (Ambrosioni 1998; Bachelli et al 2002).

### Comparison with the components in monotherapy

The antihypertensive efficacy of the fixed combination manidipine 10 mg/delapril 30 mg is higher than the efficacy of its components administered in monotherapy, as was demonstrated in a randomized, double-blind study in essential hypertensives treated for 12 weeks with manidipine (134 patients), delapril (136 patients), and the fixed-combination (131). At the end of the study the mean reduction of DBP from baseline in the trough was 14 mmHg in the group treated with combination therapy, significantly higher than with delapril (10 mmHg,  $p < 0.001$ ) or manidipine (11 mmHg,  $p < 0.05$ ) alone. The reductions of SBP were also greater with the fixed combination (19 mmHg) than with delapril (14 mmHg,  $p < 0.01$ ) or manidipine (15 mmHg,  $p < 0.05$ ) monotherapy. At the end of the study 76% of the patients treated with the fixed combination of manidipine–delapril had DBP <90 mmHg, and 71% SBP <140 mmHg. The respective proportions for patients treated with delapril or manidipine alone were 57% and 54%, and 64% and 49% respectively (Zannad 2004).

### Efficacy in non-responders to monotherapy with the components

The antihypertensive efficacy of the fixed combination manidipine 10 mg/delapril 30 mg once daily in non-responders to monotherapy with either component was assessed in an open label phase III study in patients with moderate hypertension. The patients were included in the study if their DBP was  $>90$  mmHg (95% of the patients) or they experienced adverse events (5% of the patients) with either manidipine 20 mg od ( $n = 152$ ) or delapril 30 mg twice daily. After 12 weeks of follow-up the mean reductions from baseline in sitting SBP and DBP were 16/10.1 mmHg in the group previously treated with manidipine, and 15.8/11 mmHg in the non-responders to delapril; both reductions were statistically significant. The rate of normalized DBP ( $\leq 90$  mmHg) and responder rate (DBP reduction  $\geq 10$  mmHg) was 79% in the patients previously treated with manidipine and 82% in non-responders to delapril (Zoppi et al 2003).

### Evaluation of antihypertensive action by 24-hour ambulatory BP monitoring

The fixed combination of manidipine–delapril produced significant and smooth reductions in BP values, which persisted during the 24-hour interval. This was demonstrated in essential hypertensives inadequately controlled by monotherapy with either component who were treated with the fixed combination for 8 weeks. A 24-hour ambulatory BP monitoring recording was performed before and at the end of the combination therapy. BP control over 24 hours was quantified by the trough-to-peak ratio and the smoothness index. Compared with placebo, the fixed combination of manidipine and delapril produced a statistically significant ( $p < 0.01$ ) decrease in sitting clinic (18/14 mmHg) and 24-hour blood pressure (12/10 mmHg) without affecting heart rate. At the end of the 8-week combination treatment period, the rate of normalized patients was 73%. Treatment with the fixed combination was associated with a positively high smoothness index and with a relatively good trough-to-peak ratio (0.46/0.60). These results support the use of fixed manidipine–delapril combination in the treatment of mild to moderate hypertensive patients inadequately controlled by monotherapy (Mugellini et al 2005).

### Comparison with other combinations of antihypertensive drugs

To compare the antihypertensive efficacy of the fixed combination manidipine 10 mg/delapril 30 mg with the standard combination of an ACEI and a diuretic, hypertensive

patients were randomized in a 2:1 ratio after a 2-week single-blind placebo to receive delapril 30 mg ( $n = 106$ ) or enalapril 20 mg ( $n = 54$ ) during 8 weeks. Non-responders (sitting DBP  $\geq 85$  mmHg) received delapril 30 mg plus manidipine 10 mg or enalapril 20 mg plus hydrochlorothiazide (HCTZ) 12.5 mg once daily for an additional 8-week period. After 16 weeks the mean reduction of DBP was similar with the two treatments (delapril  $-14$ , enalapril  $-15$  mmHg) with no differences between manidipine–delapril and enalapril–HCTZ treatments. More than 50% of the patients in both groups had their DBP controlled (Mugellini et al 2004a).

The efficacy of the combination manidipine–delapril was compared with the irbesartan–HCTZ combination in 80 mild to moderate hypertensives with concomitant type 2 diabetes. After an initial 4-week period on placebo patients were randomly assigned to receive delapril 30 mg or irbesartan 150 mg once daily for 8 weeks. Thereafter, manidipine 10 mg was added to delapril and HCTZ 12.5 mg as added to irbesartan for a further 8 weeks. Both delapril and irbesartan significantly reduced SBP and DBP and no differences in BP-lowering efficacy was found either between the two monotherapies (delapril: from 161/101 mmHg at baseline to 146/90 mmHg; irbesartan: from 160/100 at baseline to 144/89 mmHg) or between the two combination therapies (BP at the end of the 8 weeks follow-up 134/80 mmHg in both groups). There were no significant changes in fasting blood glucose and plasma insulin, and the diabetic control as assessed by HbA1c concentration was not influenced by both treatments. The manidipine–delapril combination gave a greater improvement in fibrinolytic function, greater decrease in PAI-I activity, and greater increase in t-PA activity, while the irbesartan–HCTZ combination gave a worse fibrinolytic function (Mugellini et al 2004b).

Two other studies have been presented as abstracts. One compared the BP-lowering effects of the manidipine–delapril combination with that of ramipril–HCTZ or valsartan–HCTZ in hypertensive type 2 diabetic patients. Patients were first randomized to receive delapril 30 mg, ramipril 2.5 mg, or valsartan 80 mg during 6 weeks. Those patients with DBP  $>90$  mmHg after 6 weeks of treatment received a second drug: manidipine 30 mg in those treated with delapril, HCTZ 12.5 mg in those treated with either ramipril or valsartan, for an additional 44 weeks. The mean decrease of BP was similar in the three groups, as was the proportion of patients controlled. The conclusion of the study was that the BP lowering of the three combinations tested was similar (Rizzoni et al 2005). The other study (Trimarco et al 2005)

included patients not controlled in monotherapy randomized to receive the combination delapril 30 mg/manidipine 10 mg or lisinopril 20 mg/HCTZ 12.5 mg for 12 weeks. BP was reduced significantly with both treatments (manidipine–delapril:  $-21.5/-15.7$  mmHg, lisinopril–HCTZ:  $-23.8/-16.2$  mmHg) and the percentage of patients with BP  $<140$  and  $90$  mmHg was slightly higher, although non significantly, in patients treated with manidipine–delapril than in those treated with lisinopril–HCTZ (60% vs 54%).

### Log-term administration of the combination

The long-term effects of the treatment with the fixed combination manidipine 10 mg/delapril 30 mg was assessed in a multicenter non-comparative follow-up study of 309 mild to moderate hypertensives. Patients with DBP  $>95$  mmHg after 4 weeks of treatment with the fixed combination were given additional therapy with HCTZ 12.5 mg. The antihypertensive efficacy of the fixed combination was maintained during the 50 weeks of follow up. BP reduction from baseline after 4 weeks of treatment was  $-16.6/-9.3$ , and at the end of the study the BP reduction reached  $-21.8/-14.3$  mmHg. The percentage of patients with DBP  $\leq 90$  mmHg was 80.6% and the rate of patients with both SBP and DBP  $\leq 140$  and  $90$  mmHg was 55.3% (Karpati et al 2003).

### Tolerability

Tolerability of the fixed combination manidipine 10 mg/delapril 30 mg has been assessed in the clinical studies previously reviewed. In the long-term study, after 50 weeks of follow up (Karpati et al 2003) 43.4% of the patients reported adverse events but only 14.2% seemed to be related to therapy. The most frequently reported adverse event among the 263 patients allocated to the combination manidipine 10 mg/delapril 30 mg was cough (2.7%) and the second was ankle edema (1.9%). Fifteen patients withdrew from the study due to adverse events.

Compared with other combinations of drugs manidipine–delapril has a similar incidence of adverse events to lisinopril–HCTZ (Trimarco et al 2005), enalapril–HCTZ (Mugellini et al 2004), ramipril–HCTZ, and valsartan–HCTZ (Rizzoni et al 2005).

In the phase III studies the tolerability of the fixed combination was similar to that the observed with its components in monotherapy (Zannad 2004). In a study published as an abstract (Fogari et al 2003) monotherapy with manidipine elevated pretibial subcutaneous tissue pressure and ankle-foot volume. But after treatment with the combination manidipine 10 mg/delapril 30 mg once daily, the increases in these

measures of ankle edema were significantly less than those with manidipine alone.

In all the studies there were no significant changes in biochemical and metabolic parameters in the patients receiving the fixed combination of manidipine 10 mg/delapril 20 mg

## Concluding comments

Control of BP is a very important objective in reducing the high morbidity and mortality observed in hypertensive patients. Current guidelines recommend achieving goal BPs below those acceptable in the past. Thus combination therapy is required to achieve BP targets in a large proportion of patients with hypertension. Moreover, the current international guidelines for the management of hypertensive patients recommend these combinations for first-line treatment.

The combination of a CCB with an ACEI has been shown to have an additive antihypertensive effect because every drug lowered BP by different mechanism, both reducing peripheral resistance with little effects on cardiac output. In addition to the favorable effects of each of its components on target organ damage, this combination has been shown to be superior in terms of morbidity and mortality to the classical combination of diuretics and beta-blockers.

The fixed combination of delapril 30 mg/manidipine 10 mg is an effective and well tolerated antihypertensive therapy, increasing the BP decrease in patients with poor response to delapril or manidipine monotherapy. Its effect was similar to the effects obtained with other fixed combinations of ACEIs or ARBs with diuretics.

## References

- Banegas JR, Segura J, Ruilope LM, et al. 2004. Blood pressure control and physician management of hypertension in hospital hypertension units in Spain. *Hypertension*, 43:1338–44.
- Bachelli S, Degli Esposti D, Alberici M, et al. 2002. Effects of the combination of different doses of manidipine and delapril in hypertensive patients. *Am J Hypertens*, 15:45–6A.
- Berlowitz DR, Ash AS, Hickey EC, et al. 1998. Inadequate management of blood pressure in a hypertensive population. *N Engl J Med*, 339:1957–63.
- [BPLTT] Blood Pressure Lowering Treatment Trialists' Collaboration. 2003. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed, overviews of randomised trials. *Lancet*, 362:1527–35.
- [BPLTT] Blood Pressure Lowering Treatment Trialists' Collaboration. 2005. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med*, 165:1410–19.
- Chobanian AV, Bakris G, Black H, et al. 2003. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure: The JNC 7 Report. *JAMA*, 289:2560–72.



- Dahlöf B, Sever PS, Poulter NR, et al. 2005. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomized controlled trial. *Lancet*, 366:895–906.
- De Leeuw PW, Kroon AA. 1997. Fixed low-dose combination of an angiotensin converting enzyme inhibitor and a calcium channel blocker drug in the treatment of essential hypertension. *J Hypertens*, 15(Suppl 2):39–42.
- Fogari R, Zoppi A, Lusardi P, et al. 1996. Evaluation by 24-hour ambulatory blood pressure monitoring of efficacy of manidipine hydrochloride 10, 20 or 40 mg once daily as compared to placebo in treating mild to moderate essential hypertension: a double-blind, randomized, parallel group, placebo-controlled study. *Blood Press*, 5(Suppl 5):16–23.
- Fogari R, Zoppi A, Mugellini A, et al. 1997. Efficacy of delapril in the treatment of mild to moderate essential hypertension: evaluation by 24-hour ambulatory blood pressure monitoring. *Adv Ther*, 14:254–61.
- Fogari R, Zoppi A, Corradi L, et al. 2000. Effects of different dihydropyridine calcium antagonists on plasma norepinephrine in essential hypertension. *J Hypertens*, 18:1871–5.
- Fogari R, Malamani G, Derosa G, et al. 2003. Effect of delapril addition to manidipine on ankle oedema and subcutaneous tissue pressure in hypertensive patients [abstract no. P-205]. *Am J Hypertens*, 16:113A.
- Fogari R. 2005. Ankle edema and sympathetic activation. *Drugs*, 65(Suppl 2):21–7.
- Fogari R, Mugellini A, Zoppi A, et al. 2005. Effect of successful hypertension control by manidipine or lisinopril on albuminuria and left ventricular mass in diabetic hypertensive patients with microalbuminuria. *Eur J Clin Pharmacol*, 61:483–90.
- Furukawa T, Nukada T, Miura R, et al. 2005. Differential blocking action of dihydropyridine Ca<sup>2+</sup> antagonists on a T-type Ca<sup>2+</sup> channel (alpha1G) expressed in *Xenopus* oocytes. *J Cardiovasc Pharmacol*, 45:241–6.
- Griffin KA, Picken MM, Bidani AK. 1995. Deleterious effects of calcium channel blockers on pressures transmissions and glomerular injury in rat remnant kidneys. *J Clin Invest*, 96:793–800.
- Guidelines Committee. 2003. European Society of Hypertension–European Society of Cardiology Guidelines for the Management of Arterial Hypertension. *J Hypertens*, 21:1011–53.
- Hansson L, Zanchetti A, Carruthers SG et al. 1998. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*, 351:1755–62.
- Hayasi K, Nagahama T, Oka K, et al. 1996. Disparate effects of calcium antagonists on renal microcirculation. *Hypertens Res*, 19:31–6.
- Iimura O, Shimamoto K, Masuda A, et al. 1995. Effects of a calcium channel blocker, manidipine, on insulin sensitivity in essential hypertensives. *J Diab Camp*, 9:215–19.
- Jafar TH, Schmid CH, Landa M, et al. 2001. Angiotensin converting enzyme inhibitors and progression of nondiabetic renal disease. *Ann Intern Med*, 135:733–87.
- Julius S, Kjeldsen SE, Weber M, et al. 2004. Outcomes in hypertensive patients at high cardiovascular risk treated with valsartan- or amlodipine-based regimens: VALUE, a randomised trial. *Lancet*, 363:2022–31.
- Karpati P, Alberici M, Tocci G, et al. 2003. Long-term tolerability and efficacy of the fixed combination of manidipine and delapril in patients with essential hypertension. *High Blood Press Cardiovasc Prev*, 10:1–6.
- Klingbeil AU, Schneider M, Martus P et al. 2003. A meta-analysis of the effect of treatment of left ventricular mass in essential hypertension. *Am J Med*, 115:41–6.
- Kloke HJ, Branten AJ, Huysmans FT, et al. 1998. Antihypertensive treatment of patients with proteinuric renal diseases: risks or benefits of calcium channel blockers? *Kidney Int*, 53:1559–73.
- Law MR, Wald NJ, Morris JK, et al. 2003. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ*, 326:1407–8.
- Letellier P, Overlack A, Agnes E. 1994. Perindopril plus nifedipine versus perindopril plus hydrochlorothiazide in mild to severe hypertension: a double-blind multicentre study. The Multicentre Study Group on Treatment Association with Perindopril. *J Hum Hypertens*, 8:145–9.
- Lewis EJ, Hunsicker LG, Bain RP, et al. 1993. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*, 329:1456–62.
- London GM, Pannier B, Vicaute E, et al. 1996. Antihypertensive effects and arterial hemodynamic alterations during angiotensin converting enzyme inhibition. *J Hypertens*, 14:1139–46.
- Lopez A, Mathers CD, Ezzati M, et al. 2006. Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet*, 367:1747–57.
- Liu L, Wang JG, Gong L, et al. 1998. Comparison of active treatment and placebo for older Chinese patients with isolated systolic hypertension. *J Hypertens*, 16:1823–9.
- Luque Otero M, Fernández Pinilla C, Catalán P, et al. 1987. Acute antihypertensive effect of nifedipine on high and low salt diet. *J Cardiovasc Pharmacol*, 10 (Suppl 10):S147–8.
- Luque Otero M, Martell Claros N, on behalf of the Study Investigators Group. 2005. Manidipine versus enalapril monotherapy in patients with hypertension and type 2 diabetes mellitus: a multicenter, randomized, double-blind, 24-week study. *Clin Ther*, 27:166–73.
- Mancia G, Omboni S, Agabiti-Rosei E, et al. 2000. Antihypertensive efficacy of manidipine and enalapril in hypertensive diabetic patients. *J Cardiovasc Pharmacol*, 35:926–31.
- Mancia G, Grassi G. 2002. Systolic and diastolic blood pressure control in antihypertensive trials. *J Hypertens*, 20:1461–4.
- Mancia G, Volpe R, Boros S, et al. 2004. Cardiovascular risk profile and blood pressure control in Italian hypertensive patients under specialist care. *J Hypertens*, 22:51–7.
- Mancia G, Grassi G, Zanchetti A. 2006. New-onset diabetes and antihypertensive drugs. *J Hypertens*, 24:3–10.
- Martinez-Martin FJ, Saiz-Satjes M. 2004. Addition of manidipine in type 2 diabetic patients with uncontrolled hypertension and microalbuminuria. *J Hypertens*, 22(Suppl 2):s245.
- McKeage K, Scott LJ. 2004. Manidipine: a review of its use in the management of hypertension. *Drugs*, 64:1923–40.
- Mugellini A, Dobovisek J, Planinc D, et al. 2004. Efficacy and safety of delapril plus manidipine compared with enalapril plus hydrochlorothiazide in mild to moderate essential hypertension: results of a randomized trial. *Clin Ther*, 26:1419–26.
- Mugellini A, Preti P, Zoppi A, et al. 2004. Effect of delapril–manidipine combination vs irbesartan-hydrochlorothiazide combination on fibrinolytic function in hypertensive patients with type II diabetes mellitus. *J Hum Hypertens*, 18:687–91.
- Mugellini A, Vaccarella A, Celentano A, et al. 2005. Fixed combination of manidipine and delapril in the treatment of mild to moderate essential hypertension: evaluation by 24-hour ambulatory blood pressure monitoring. *Blood Pressure*, 14(Suppl 1):6–13.
- Okabe K, Terada K, Kitamura K, et al. 1987. Selective and long lasting inhibitory actions of the dihydropyridine derivative, CV-4093, on calcium currents in smooth muscle cells of the rabbit pulmonary artery. *J Pharmacol Exp Ther*, 243:703–10.
- Onoyama K, Nanishi F, Okuda S, et al. 1988. Pharmacokinetics of a new angiotensin I converting enzyme inhibitor (delapril) in patients with deteriorated kidney function and in normal control subjects. *Clin Pharmacol Ther*, 43:242–9.
- Pitt B. 1997. Diversity of calcium antagonists. *Clin Ther*, 19(Suppl A):3–17.
- Prospective Studies Collaboration. 2002. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*, 360:1903.
- Rizzoni D, Bevilacqua M, Gobbato C, et al. 2005. Blood pressure lowering effects of delapril and manidipine, in hypertensive patients with type 2 diabetes, not adequately controlled by monotherapy [abstract]. *High Blood Press Cardiovasc Prev*, 12:180(abstract no. 8.6).



- Ruggenenti P, Fassi A, Ilieva AP, et al, for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. 2004. preventing microalbuminuria in type 2 diabetes. *N Engl J Med*, 351:1941–51.
- Saruta T, Nishikawa K. 1991. Characteristics of a new angiotensin converting enzyme inhibitor: delapril. *Am J Hypertens*, 4:23S–28S.
- Schiffrin EL, Deng LY, Larochelle P. 1994. Effects of a beta-blocker or a converting enzyme inhibitor on resistance arteries in essential hypertension. *Hypertension*, 23:83–91.
- Sharma A, Wittchen H-U, Kirch W, et al, for the HYDRA Study Group. 2004. High prevalence and poor control of hypertension in primary care: cross-sectional study. *J Hypertens*, 22:479–86.
- Simon A, Gariépy J, Chironi G, et al. 2002. Intima-media thickness: a new tool for diagnosis and treatment of cardiovascular risk. *J Hypertens*, 20:159–70.
- Stockis A, Gengler C, Goethals F, et al. 2003. Single oral dose pharmacokinetic interaction study of manidipine and delapril in healthy volunteers. *Arzneimittelforschung*, 53:627–34.
- Suzuki S, Ohtomo M, Ssatoh Y, et al. 1996. Effect of manidipine and delapril on insulin sensitivity in type 2 diabetic patients with essential hypertension. *Diab Res Clin Pract*, 33: 43–51.
- Swales P, Williams B. 2002. 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 Aldosterone Syst*, 3:79–89.
- Taddei S, Virdis A, Ghiadoni L, et al. 2001. Restoration of nitric oxide availability after calcium antagonist treatment in essential hypertension. *Hypertension*, 37:943–8.
- The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. 2002. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA*, 288:2981–97.
- Tojo A, Kimura K, Matsuoka H, et al. 1992. Effects of manidipine hydrochloride on the renal microcirculation in spontaneously hypertensive rats. *J Cardiovasc Pharmacol*, 20:895–9.
- Trimaco B, Arcucci O, Gacionig G, et al. 2005. Evaluation of different combination of antihypertensive drugs in hypertensive patients not adequately controlled by previous monotherapy [abstract]. *High Blood Press Cardiovasc*, 12:180(abstract no. 8.5).
- [VAC] Veterans Administration Cooperative Study Group on Antihypertensive Agents. 1970. Effects of treatment on morbidity in hypertension: II results in patients with diastolic blood pressure average 90 through 114 mm Hg. *JAMA*, 213:1143–9.
- Watanabe H. 2003. Block of T-type calcium channel by dihydropyridine calcium antagonists. *Teikyo Medical Journal*, 26:425–33.
- Wolf-Maier K, Cooper RS, Banegas JR, et al. 2003. Hypertension prevalence and blood pressure levels in 6 European countries, Canada and the United States. *JAMA*, 289:2363–9.
- Zanchetti A, Omboni S, La Commarre P, et al. 2001. Efficacy, tolerability, and impact on quality of life of long-term treatment with manidipine or amlodipine in patients with essential hypertension. *J Cardiovasc Pharmacol*, 38:642–50.
- Zanchetti A, Rosei EA, Dal Palu C, et al. 1998. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. *J Hypertens*, 16:1667–76.
- Zanchetti A, Bond MG, Hennig M, et al. 2002. European Lacidipine Study on Atherosclerosis investigators Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. *Circulation*, 106:2422–7.
- Zanchi A, Brunner HR, Waeber B, et al. 1995. Renal hemodynamic and protective effects of calcium antagonist in hypertension. *J Hypertens*, 13:1363–75.
- Zannad F. 2004. Multicentre, randomised, parallel group, double-blind, phase III study to compare the antihypertensive effects and tolerability of delapril and manidipine monotherapy to delapril plus manidipine (CHF 1521 fixed combination) in patients with mild to moderate essential hypertension (Data on file). Chiesi Farmaceutici A.p.A.
- Zoppi A, Mugellini A, Preti P, et al. 2003. Effects of the fixed combination of manidipine plus delapril in the treatment of hypertension inadequately controlled by monotherapy with either component: a phase III, multicenter, open-label, clinical trial. *Curr Ther Res*, 64:422–33.

