

# Fixed combination of lercanidipine and enalapril in the management of hypertension: focus on patient preference and adherence

Claudio Borghi  
Francesca Santi

Internal Medicine, Aging and Kidney  
Disease Department, University  
of Bologna, Italy

**Abstract:** Hypertension is one of the most important and widespread risk factors for the development of cardiovascular disease. Once, combination therapy was traditionally reserved as a third-line or fourth-line approach in the management of hypertension. However, several major intervention trials in high-risk patient populations have shown that an average of 2–4 antihypertensive agents are required to achieve effective blood pressure control. Combination treatment should be considered as a first choice in patients at high cardiovascular risk and in individuals for whom blood pressure is markedly above the hypertension threshold (eg, more than 20 mmHg systolic or 10 mmHg diastolic), or when milder degrees of blood pressure elevation are associated with multiple risk factors, subclinical organ damage, diabetes, renal failure, or associated cardiovascular disease. A number of clinical trials have demonstrated that a fixed combination of lercanidipine and enalapril has better efficacy and tolerability than monotherapy with either agents. The fixed-dose formulation of lercanidipine–enalapril was well tolerated in all clinical trials, with an adverse event rate similar to that of the component drugs as monotherapy. The advantages of combination therapy include improved adherence to therapy and minimization of blood pressure variability. In addition, combining two antihypertensive agents with different mechanisms of action may provide greater protection against major cardiovascular events and the development of end-organ damage.

**Keywords:** hypertension, treatment, fixed-dose combination, lercanidipine, enalapril

## Introduction

Hypertension is one of the most important and widespread cardiovascular risk factors responsible for the development of cerebrovascular disorders, heart disease, and renal failure. Combination therapy was traditionally reserved as a third-line or fourth-line approach in the management of hypertension.<sup>1</sup> However, several major intervention trials in high-risk patient populations have shown that an average of 2–4 antihypertensive agents are required to achieve effective blood pressure control.<sup>2–8</sup> The European Society of Hypertension guidelines<sup>9</sup> comment on the possibility of starting antihypertensive treatment with a single drug at low dose or with combination therapy. In fact, the so-called “responder rate” (systolic and diastolic blood pressure reduction  $\geq 20$  mmHg and 10 mmHg, respectively) to any agent in monotherapy is approximately 50%,<sup>10</sup> and the ability of any agent used alone to achieve target blood pressure values ( $< 140/90$  mmHg) does not exceed 20%–30% in the overall hypertensive population, except in subjects with grade 1 hypertension.<sup>11,12</sup>

In most trials, a combination of two or more drugs has been the most widely used treatment regimen to reduce blood pressure effectively. Combination therapy

Correspondence: Francesca Santi  
Internal Medicine, Aging and Kidney  
Disease Department, University  
of Bologna, Via Albertoni 15,  
Bologna 40138, Italy  
Fax +39 05 1390 646  
Tel +39 05 1636 2212  
Email francesca.snt.santi@gmail.com

has been found to be more effective in high-risk patients and diabetics, and whenever lower blood pressure targets are needed.<sup>13</sup>

An obvious disadvantage of initiating treatment with two drugs is the potential exposure of some patients to an unnecessary agent. However, the advantages seem to be overwhelming. In fact, by using a combination, both drugs can be given in lower dosage, thus minimizing the risk of side effects compared with full-dose monotherapy. Furthermore, fixed low-dose combinations are available, allowing two agents to be administered in a single tablet, both simplifying and optimizing treatment and compliance. The advantages of combination therapy are well documented, with increased antihypertensive efficacy as a result of the simultaneous inhibition of different mechanisms of action, with a lesser incidence of adverse events, because of the possible compensatory responses and the lower doses used.<sup>14</sup>

Starting treatment with a two-drug combination therapy may allow blood pressure control to be achieved in a shorter time. This may be of critical importance in high-risk patients, because the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial demonstrated that in the first 6 months of treatment, a greater blood pressure reduction (23.8/22.2 mmHg) obtained in amlodipine-treated versus valsartan-treated patients was accompanied by a difference in cardiovascular event rate in favor of the more effectively treated group.<sup>4,9</sup>

Combination treatment should be considered as the first choice in patients at high cardiovascular risk and in individuals for whom blood pressure is markedly above the hypertension threshold (eg, more than 20 mmHg systolic or 10 mmHg diastolic), or when milder degrees of blood pressure elevation are associated with multiple risk factors, subclinical organ damage, diabetes, renal failure, or associated cardiovascular disease.<sup>9</sup>

In all these conditions, the need to obtain a larger blood pressure reduction could not be satisfied by monotherapy alone, and often more than two drugs are needed. Guidelines recommend various two-drug combinations of different classes of antihypertensive agents based on data derived from controlled interventional trials, but 3–4 drugs may be required depending on the patient's risk profile.

In clinical practice, numerous fixed-dose antihypertensive combination regimens are widely available, ie, a beta-blocker + hydrochlorothiazide, an angiotensin-converting enzyme inhibitor + hydrochlorothiazide, an angiotensin receptor blocker + hydrochlorothiazide, and a calcium channel blocker + angiotensin-converting enzyme inhibitor.<sup>15</sup>

Many studies have shown that newer antihypertensive agents, such as calcium channel blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors, provide additional benefits by reducing the incidence of cardiovascular events in patients with hypertension.<sup>4,16–18</sup> This review focuses on the fixed association of lercanidipine-enalapril, pointing out the potential advantages of such a combination.

## Lercanidipine

Calcium channel blockers are extensively used in clinical practice, and several randomized clinical trials have shown that calcium channel blockers are potent antihypertensive drugs with good tolerability both in the general hypertensive population and in a wide range of patients, alone or in combination.<sup>14,19</sup>

Lercanidipine is a third-generation dihydropyridine calcium channel blocker which inhibits calcium entry through L-type calcium channels in smooth muscle cells of the cardiovascular system, leading to peripheral vasodilatation<sup>20–22</sup> and so exerting its antihypertensive effect. It is a highly lipophilic drug and has a slower onset and longer duration of action than other dihydropyridines.<sup>23</sup> Furthermore, the drug is highly vasoselective because of the high proportion of L-type calcium channels in arteries and has shown less in vitro and in vivo negative inotropic activity than some other dihydropyridines.<sup>20</sup> Lercanidipine is a well tolerated drug with a low adverse event rate due to its long-lasting and vasoselective calcium entry blocking activity, and does not cause sympathetic activation and reflex tachycardia.<sup>24</sup> As a result, the overall adverse event rate is lower than that observed with other dihydropyridines.<sup>15</sup> The efficacy of lercanidipine has been evaluated in both noncomparative and comparative studies with other calcium channel blockers and different antihypertensive drugs, showing comparable effects in all cases.<sup>25–30</sup>

Some studies have suggested that lercanidipine may have antiatherogenic effects beyond blood pressure reduction.<sup>21,31–33</sup> Another reported benefit with lercanidipine is its renoprotective effect, which is related to its ability to induce both afferent and efferent arteriolar vasodilatation.<sup>34,35</sup> Lercanidipine was also superior to ramipril in reducing albumin excretion in diabetic patients with microalbuminuria.<sup>35</sup>

In diabetic patients with hypertension, treatment with lercanidipine was able to decrease the glycosylated hemoglobin level significantly, without negatively affecting glucose homeostasis, to enhance glucose tolerance, and to reduce fasting blood glucose, with either neutral or favorable effects on

the lipid profile.<sup>22,36</sup> Moreover, in diabetics with renal failure, lercanidipine had a good tolerability profile and a neutral effect on plasma lipids, with no impairment of renal function.<sup>37</sup>

In hypertensive patients with metabolic syndrome, lercanidipine appeared to have a better tolerability profile and was associated with fewer vasodilatation-related adverse effects than other dihydropyridine calcium channel blockers.<sup>15</sup> Lercanidipine also reduces the signs and symptoms of ischemia, and improves heart function in patients with angina.<sup>38</sup>

## Enalapril

The renin-angiotensin-aldosterone system plays a key role in regulating the homeostasis of fluids, electrolytes, and systemic vascular resistance. Overactivation of this system, especially through excessive production of its effector peptide, angiotensin II, has been related to the genesis and development of cardiovascular disease. Angiotensin-converting enzyme inhibitors are able to diminish plasma levels of angiotensin II by blocking the last step of its activation. This results in reduced vascular resistance, leading to a decrease in blood pressure values.<sup>14,39</sup>

Enalapril, one the most commonly prescribed angiotensin-converting enzyme inhibitors in clinical practice in a number of European countries, is an orally administered prodrug that is hydrolyzed to the active metabolite, enalaprilat, which decreases plasma levels of angiotensin II by inhibiting the last step of its activation. The reduction of angiotensin II leads to peripheral vasodilatation and reduced vascular resistance, decreasing blood pressure values.<sup>21,39,40</sup> Enalapril is a dose-dependent antihypertensive drug, with its maximum effect occurring 6–8 hours after administration and a total duration of effect of 24–36 hours.<sup>40</sup> Enalapril has been shown to be an effective antihypertensive agent, with positive effects on cardiovascular risk factors, prevention of decline in renal function and other organ damage,<sup>41–44</sup> like progression of intima media thickness in the carotid artery, an independent risk factor for cardiovascular and cerebrovascular disease.<sup>43</sup> The cardiovascular protection associated with enalapril may be caused by potentiation of the effects of bradykinin.<sup>45</sup> Further, in a randomized, double-blind, six-year trial in patients with diabetes and normoalbuminuria at baseline, enalapril reduced the development of microalbuminuria.<sup>42</sup>

## Combination of enalapril–lercanidipine

Because calcium channel blockers do not share the mode of action of renin-angiotensin-aldosterone system inhibitors,

a combination of these agents should provide synergistic and complementary effects. Indeed, in patients with newly diagnosed stage 1 or 2 hypertension and in patients with inadequate blood pressure control after conventional low-dose monotherapy, combination therapy with a calcium channel blocker and an angiotensin-converting enzyme inhibitor may be particularly effective.<sup>46,47</sup>

Calcium channel blockers are potent vasodilators that induce reflex activation of the sympathetic system and the renin-angiotensin-aldosterone system. As a result, the use of an angiotensin-converting enzyme inhibitor may buffer this excessive activation. Moreover, since calcium channel blockers promote a negative sodium balance and an increase in angiotensin II levels, this may reinforce the antihypertensive effect of angiotensin-converting enzyme inhibition.<sup>48</sup> On the other hand, the concomitance of both treatments may reduce the incidence of adverse events, in particular peripheral edema, due to an increase in intracapillary pressure as a consequence of selective diminution of precapillary arteriolar tone during blockade of calcium entry. Angiotensin-converting enzyme inhibitors reduce the lower extremity edema caused by calcium channel blockers, likely because of their ability to dilate both the arterial vascular bed and the venous capacitance vessels.<sup>49</sup>

In the SELECT (Systolic Evaluation of Lotrel Efficacy and Comparative Therapies) study, calcium channel blocker and angiotensin-converting enzyme inhibitor combination therapy with amlodipine and benazepril, respectively, was significantly more effective in reducing systolic blood pressure and pulse pressure in patients with severe systolic hypertension than either agent used alone.<sup>50</sup> The combination of manidipine and delapril was also more effective in reducing blood pressure than either drug used alone, achieving blood pressure control in 73% of treated patients.<sup>51</sup>

Data from the trials show that calcium channel blocker therapy plus additional add-on treatment is able to not only lower blood pressure, but also to improve patient outcomes. The HOT (Hypertension Optimal Treatment) trial showed that intensive lowering of blood pressure with calcium channel blocker-based therapy led to a low rate of cardiovascular events.<sup>52</sup> In the Syst-Eur (Systolic Hypertension in Europe) and Syst-China (Systolic Hypertension in China) studies, nitrendipine plus a diuretic and an angiotensin-converting enzyme inhibitor reduced the rate of cardiovascular complications in elderly patients with isolated systolic hypertension.<sup>53,54</sup>

Data from the ASCOT study showed that treatment with amlodipine plus perindopril (an angiotensin-converting

enzyme inhibitor, added as required) versus atenolol (a beta-blocker) plus bendroflumethiazide (a diuretic, added as required) was more effective in reducing the risks of non-fatal myocardial infarction or fatal coronary heart disease, fatal and nonfatal stroke, total cardiovascular events and procedures, all-cause mortality, and diabetes in patients with hypertension and at least three other cardiovascular risk factors.<sup>55</sup> The ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) trial compared the effectiveness of a maximally titrated, fixed-dose combination of benazepril (an angiotensin-converting enzyme inhibitor) and amlodipine (a dihydropyridine calcium channel blocker) with the combination of benazepril and hydrochlorothiazide in reducing cardiovascular morbidity and mortality. The trial was stopped early because of a 20% reduction in cardiovascular risk recorded in the benazepril plus amlodipine group, so demonstrating that combination treatment with benazepril plus amlodipine reduces progression of chronic kidney disease and cardiovascular or all-cause mortality in high-risk hypertensive patients. Differences in blood pressure control throughout the study could not account for these findings.<sup>56</sup>

A number of clinical trials have demonstrated that the fixed combination of lercanidipine and enalapril has better efficacy and tolerability than monotherapy with either agent<sup>57–60</sup> (Table 1). In a trial performed in hypertensive patients nonresponsive to lercanidipine, after 12 weeks of treatment with fixed-combination lercanidipine–enalapril, a significantly greater proportion of patients had normalized blood pressure compared with patients treated with lercanidipine as monotherapy (22% versus 12%,  $P=0.012$ ).<sup>59</sup> Similarly, in another study carried out in hypertensive patients nonresponsive to enalapril, after 12 weeks of treatment with

this fixed combination, there was a trend towards better blood pressure control in the population treated with the fixed combination compared with enalapril as monotherapy (24% versus 17%).<sup>58</sup>

A randomized, double-blind, placebo-controlled study showed that reduction in blood pressure was greater in patients who received the lercanidipine–enalapril combination than in those assigned to receive either component as monotherapy.<sup>6</sup> In fact, all active treatments significantly reduced mean 24-hour blood pressure and systolic blood pressure in the office compared with placebo, but the lercanidipine–enalapril combination was significantly more effective than the active components as monotherapy. Moreover, a higher proportion of patients treated with the lercanidipine–enalapril combination achieved their target blood pressure compared with those treated with lercanidipine or enalapril alone (45% versus 18% versus 19%, respectively). In addition, lercanidipine was noninferior to hydrochlorothiazide as add-on therapy in diabetic patients with hypertension who had not responded to enalapril alone.<sup>57</sup>

The fixed-dose formulation of lercanidipine–enalapril was well tolerated in all published clinical trials, with an adverse effect rate similar to that of the component drugs as monotherapy.<sup>57–60</sup> Adverse effects were generally transient and of mild severity, and there were no reports of peripheral edema.<sup>57–60</sup> Although infrequent, the most prevalent adverse events related to the use of the lercanidipine–enalapril combination were cough, dizziness, and vertigo. Interestingly, no clinically significant differences in heart rate were observed between the treatment groups, and 24-hour heart rate remained stable on all treatments.<sup>60</sup> The absence of negative effects of the combination on lipid and glucose metabolism appears to be an added advantage in the treatment of hypertensive population.<sup>39</sup>

**Table 1** Effect of fixed association of enalapril–lercanidipine on blood pressure control

Reference	Patients, n	Duration	Intervention	Outcome
Agrawal et al <sup>57</sup>	174	20 weeks	Lercanidipine + enalapril 20 mg versus hydrochlorothiazide + enalapril 20 mg	SBP –9.6 versus –6.0 mmHg DBP –9.3 versus –7.4 mmHg
Recordati SpA <sup>58</sup>	338	12 weeks	Enalapril 20 mg versus lercanidipine 10 mg + enalapril 20 mg	SBP –6.7 versus –9.8 mmHg DBP –7.5 versus –9.2 mmHg
Recordati SpA <sup>59</sup>	337	12 weeks	Lercanidipine 10 mg versus lercanidipine 10 mg + enalapril 10 mg	SBP –2.3 versus –7.7 mmHg DBP –4.3 versus –7.1 mmHg
Puig et al <sup>60</sup>	75	4 months	Lercanidipine 10 mg versus enalapril 20 mg alone or in combination versus placebo	SBP –5 versus –5.9 versus 16.9 mmHg, versus placebo
Rump <sup>61</sup>	8440	3 months	Enalapril 10 mg + lercanidipine 10 mg or enalapril 10 mg + lercanidipine 20 mg	SBP –28.4 mmHg DBP –13.5 mmHg
Gil Guillén et al <sup>65</sup>	1562	6 months	Lercanidipine + enalapril 20 mg alone or in combination	SBP –25.4 mmHg DBP –13.6 mmHg

**Abbreviations:** SBP, systolic blood pressure; DBP, diastolic blood pressure.

In an observational study which examined more than 8000 patients, physician (general practitioners and specialist in internal medicine) subjective assessment of the lercanidipine–enalapril combination was positive, the efficacy of the fixed combination was assessed by 94% as “very good” to “good”. The physicians also assessed tolerability in 97% of the patients as “very good” or “good”, and assessed compliance as “very good” or “good” in 97% of patients.<sup>61</sup>

## Conclusion

The main advantages of combination therapy include improved adherence to therapy<sup>62</sup> and minimization of blood pressure variability. In addition, combining two antihypertensive agents with different mechanisms of action may provide greater protection against major cardiovascular events and end-organ damage.<sup>9</sup> Combinations of two drugs in a single tablet, usually at low doses, (but sometimes at both lower and higher doses), are now widely available. Although the fixed doses of the components in the combination limits the flexibility of upward and downward treatment strategies, fixed combinations reduce the number of tablets to be taken by the patient, and this has some advantage for compliance with treatment.<sup>62,63</sup>

Fixed-dose combinations can substitute extemporaneous combinations that have successfully controlled blood pressure, but, when used at low doses, they can also be considered for first-step treatment.<sup>9</sup> Guidelines recommend various two-drug combinations of different classes of antihypertensive agents based on data derived from controlled interventional trials, but advise that 3–4 drugs may be required, depending on the patient’s risk profile.

In contrast, many studies have shown that newer antihypertensive agents, including calcium channel blockers, angiotensin receptor blockers, and angiotensin-converting enzyme inhibitors, provide additional benefits by reducing the incidence of cardiovascular events in patients with hypertension.<sup>4,16–18</sup> In addition, cases of new-onset diabetes are less common with newer antihypertensive agents than with older therapies, such as diuretics and beta-blockers.<sup>64</sup> Whether this is due to the deleterious effect of the older agents on glucose metabolism or to a positive effect of the newer agents remains to be clarified.<sup>19</sup> A fixed combination of lercanidipine and enalapril has been shown to be effective in controlling calcium channel blocker levels and data about tolerability and patient compliance, indicating that this combination is a suitable, effective, and safe treatment for hypertension.

## Disclosure

The authors report no conflicts of interest in this work.

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