Integrated Blood Pressure Control

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Complementary mechanisms of action and rationale for the fixed combination of perindopril and indapamide in treating hypertension – update on clinical utility

This article was published in the following Dove Press journal:
Integrated Blood Pressure Control
10 May 2010
Number of times this article has been viewed

Vivencio Barrios[1]
Carlos Escobar[2]

[1]Department of Cardiology, Hospital Ramon y Cajal, Madrid, Spain;
[2]Department of Cardiology, Hospital Infanta Sofia, Madrid, Spain

Abstract: Although reducing blood pressure is the most important approach to reduce cardiovascular outcomes in the hypertensive population, the majority of patients fail to attain the targets. Most patients with hypertension need at least 2 antihypertensive agents to achieve blood pressure goals. The 2007 European hypertension guidelines state that combined therapy is needed when monotherapy does not attain blood pressure objectives and as a first-line treatment in high-risk patients. This point has been reinforced in the 2009 update of the European guidelines. The advantages of combination therapy are well documented with the potential for increased antihypertensive efficacy as a result of different mechanisms of action, and a lower incidence of adverse effects because of the lower doses used and the possible compensatory responses. Moreover, the use of fixed dose combinations are specially recommended as they facilitate treatment compliance. The inhibition of the renin-angiotensin system appears to be very beneficial in the treatment of patients with hypertension along the cardiovascular continuum and the combination of a renin-angiotensin system inhibitor and a diuretic is particularly recommended. Many clinical trials have demonstrated the benefits of the fixed combination perindopril/indapamide in the treatment of hypertension. The aim of this manuscript is to update the published data on the efficacy and safety of this fixed combination.

Keywords: fixed dose, combination therapy, angiotensin-converting enzyme, diuretic

Introduction

Arterial hypertension, a major risk factor for the establishment and development of cerebrovascular, cardiovascular and renal diseases, is very prevalent worldwide. It has been estimated that about a quarter of the general population is hypertensive, a proportion that increases with age.[1–3] In Spain, 44% of the middle-aged population and 68% of patients aged 60 years or older exhibit hypertension.[1] In United States about 65 million people are hypertensive.[2,3] It has been calculated that hypertension is responsible for 1 of every 14 deaths for any reason and for 1 of every 2.5 cardiovascular deaths.[4]

Even small elevations above optimal systolic or diastolic blood pressure (BP) values increase the probability of cardiovascular outcomes.[5] Thus, in 18,876 healthy subjects, an increased risk of new onset heart failure in individuals with systolic BP 130–139 mmHg compared with those with optimal BP (<120 mmHg) has recently been reported, with a linear trend in heart failure risk across the normal range of systolic BP.[6] Similar findings have been reported in patients with ischemic heart disease.[7] A *post hoc* analysis of INVEST (International Verapamil SR-Trandolapril Study) trial, performed

Correspondence: Vivencio Barrios
Department of Cardiology, Hospital Ramon y Cajal Madrid 28034, Spain
Tel +34 91 336 8259
Fax +34 91 336 8665
Email vbarriosa@meditex.es;
vbarrios.hrc@salud.madrid.org

in 22,576 patients with hypertension and coronary artery disease, showed there was a steep reduction in cardiovascular risk in parallel to the proportion of visits with controlled BP, independent of baseline characteristics and mean on-treatment BP.[7] In the classical systematic review of Collins et al[8] a 42% stroke risk reduction ($P < 0.0001$) and a 14% coronary heart disease risk reduction in those hypertensives who attained BP goals, when compared to those treated but not adequately controlled, was reported. As a result, it is crucial not only to reduce BP values but to achieve BP goals in order to improve cardiovascular prognosis.[5]

Although in the last decades BP control rates have progressively improved (ie, in Spain, BP control has increased from <20% in 1990s to the current 40%),[9] they are far from optimal and this occurs everywhere (Italy about 31%, United Kingdom 36%, Germany 40% and France 46%).[2] However, after the results of EUROASPIRE III, it seems that this improvement has stopped or at least slowed.[10] EUROASPIRE surveys analyzed rates of modifiable cardiovascular risk factors in patients with coronary heart disease. EUROASPIRE I, II, and III were designed as cross-sectional studies and included the same selected geographical areas and hospitals in the Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, and Slovenia. These studies showed that although the proportion with raised total cholesterol has markedly decreased, from 94.5% in EUROASPIRE I to 76.7% in II, and 46.2% in III ($P < 0.0001$), the proportion of patients with raised BP (≥140/90 mmHg in patients without diabetes or ≥130/80 mmHg in patients with diabetes) remained unchanged (58.1% in EUROASPIRE I, 58.3% in II, and 60.9% in III; $P = 0.49$).[10]

These data suggest that, although in the general hypertensive population BP control rates are rising, this does not occur in those hypertensive patients at higher risk such as those with coronary heart disease. In fact, as cardiovascular risk increases, a lesser proportion of patients attain BP goals.[10,11] This is very relevant, since nowadays the majority of patients attended by specialists or general practitioners, belong to high- or very high-risk groups.[12,13] Furthermore, since the prevalence of diabetes, obesity and sedentary life style is growing, it is likely that the number of high risk hypertensive patients will rise in the future.[14]

Although it is well known that the majority of hypertensive patients will need more than 1 antihypertensive drug to attain BP objectives (particularly those at higher risk),[15,16] several surveys have reported that combined therapy is actually underused.[9–12] The 2007 European guidelines for the management of arterial hypertension, indicate that combined therapy is required when monotherapy fails to attain BP goals. They also show that a combination of 2 drugs at low doses as first line treatment, can be prescribed when total cardiovascular risk is high or very high, or when initial BP values are in the range of grade 2 or 3.[5] The evidence that in the vast majority of hypertensives effective BP control can only be achieved by combination of at least 2 antihypertensive agents continues to grow, as a last update of European guidelines shows. Moreover, the combination of 2 antihypertensive drugs may offer advantages also for treatment initiation, particularly in patients at high cardiovascular risk in which early BP control may be desirable.[17] Fortunately, although the use of combined therapy is still low and far from optimal, its prescribing has improved in the last decade.[18,19]

The use of a combination of 2 antihypertensive agents at fixed doses in a single tablet should be preferred, since decreasing the number of pills that have to be taken daily has been associated with an improvement in compliance, and consequently, better BP control rates during follow-up.[20] As current recommendations report, there are several 2-drug fixed combinations suitable for clinical use. However, trial evidence of outcome reduction has been obtained particularly for the combination of a diuretic or a calcium channel blocker, with an angiotensin-converting enzyme (ACE) inhibitor, or a diuretic with an angiotensin receptor blocker. Importantly, the use of the angiotensin receptor blocker/calcium channel blocker combination also appears to be rational and effective.[17] As a result, these combinations should be recommended for priority use. This manuscript aims to update the published data on the efficacy and safety of the fixed combination perindopril plus indapamide.

Renin-angiotensin system and organ damage

Although the renin-angiotensin aldosterone system (RAAS) is important for the cardiovascular system homeostasis, the BP control, and the sodium and water balance, its excessive activation promotes the development and worsening of cardiovascular disease.[21] Angiotensin II is associated with all phases of cardiovascular disease, from the early (hypertension), to the mid (left ventricular hypertrophy and microalbuminuria), to the late stages (myocardial infarction, heart failure stroke, and renal disease).

Left ventricular hypertrophy is one of the most relevant subclinical organ damage in patients with hypertension.[5] Although many factors have been involved in the establishment and development of left ventricular hypertrophy

in hypertension, it is likely that the RAAS activity and the increased afterload are the main ones.[22] Its presence increases 2- to 5-fold the risk of major cardiovascular events.[23] However, left ventricular hypertrophy regression, or at least reduction, is associated with a better prognosis.[5] Although the most important point in the treatment of hypertensive population with left ventricular hypertrophy is BP reduction, several trials have reported that RAAS inhibitors could be recommended as first-line therapy in this setting.[5,24,25]

It is well known that renal disease and hypertension are closely related. Hypertension is one of the most frequent causes of new-onset renal disease and their progression toward end-stage renal failure and conversely, chronic kidney disease promotes the development of hypertension.[26] Microalbuminuria is an early manifestation of renal involvement in patients with hypertension, particularly in diabetic population. The presence of microalbuminuria in this context has been related to an increase of mortality, and its reduction with a better prognosis.[5] Many clinical trials have shown that RAAS inhibition is a very effective therapeutic strategy in hypertensive patients with renal impairment.[27,28] RAAS inhibition promotes a decrease of glomerular pressure, a decline of albumin excretion rate due to the dilatation of efferent arterioles, and a reduction of local inflammation and growth in the glomerulus. This translates into a reduced vascular trophic remodelling and results in different and additive beneficial effects on renal function and structure.[26]

Endothelial dysfunction is a predictor of cardiovascular events in hypertensive patients.[29,30] Endothelial dysfunction as well as vascular endothelial cell apoptosis occurs in the early atherosclerotic lesions, but also as cardiovascular disease progresses.[31] This endothelial impairment damages the functioning of endothelium, affecting nitric oxide bioavailability, promoting vasoconstriction, inflammation, thrombosis and platelet activation what finally provokes the development of atherosclerotic disease.[32] By contrast, ACE inhibitors improve endothelium-dependent vasodilation in hypertensive patients, protecting them from ischemic heart disease.[33]

Pharmacology and rationale for the combination of perindopril and indapamide

Perindopril is a prodrug that is rapidly absorbed in the gastrointestinal tract after oral administration. Bioavailability of perindopril is 61%–85%. The biotransformation of perindopril to perindoprilat, the active metabolite, is approximately 20%. Notably, food intake may reduce hepatic biotransformation to perindoprilat. The peak plasma concentration and the peak pharmacological activity of perindoprilat occur at 3 to 4 hours and 4 to 6 hours, respectively, after oral administration of perindopril. The rates of protein binding of perindoprilat are low (<30%). Free perindoprilat is eliminated via the urine. Although the elimination half-life of the free fraction of perindoprilat is between 3 and 5 hours, the terminal half-life of the dissociation of perindoprilat from plasma and tissue ACE is about 25 to 30 hours. The steady-state concentration of perindoprilat is reached within 4 days when chronically administered.[34–36]

Indapamide is an oral diuretic with natriuretic properties that acts in the proximal segment of the distal tubule. Interestingly, the main effect of indapamide is on sodium and chloride excretion, but with less effect on potassium or uric acid urine excretion. Nevertheless, there is an appreciable increase in urinary volume only at doses greater than 2.5 mg/day. Despite these renal effects, it has been suggested that the reduction in vascular reactivity to pressor amines caused by indapamide has a more important role in its antihypertensive effect.[34,37,38]

Indapamide has high lipid solubility and as a consequence, its absorption from the gastrointestinal tract is fast (30 to 60 minutes after oral administration), and complete. Indapamide is bound to plasma proteins in 79% and has a relatively low apparent volume of distribution of approximately 60 L. Plasma elimination half life is biphasic and between 14 and 25 hours. The steady-state concentration of indapamide is reached within 3 to 4 days when chronically administered. Indapamide is widely metabolized in the Liver, principally by CYP2C9 and CYP3A4 isozymes, and by cytosolic hydrolysis enzymes. The main route of elimination is the urine, and 20 to 23% in the feces. In contrast to hydrochlorothiazide, indapamide does not adversely affect lipid profile or glucose tolerance either in hypertensive patients with diabetes.[34,37,38]

The combination of perindopril, an ACE inhibitor, and indapamide, a chlorosulphamoyl diuretic, is recommended as one of the antihypertensive combinations of priority use by the last update of European hypertension guidelines.[17] Due to their synergistic mechanisms of action, the doses at which this combination is given is up to 2 times lower than the usual dose used for monotherapy, showing a higher antihypertensive effect with lesser side effects. On the one hand, as indapamide depletes the cell of sodium and of calcium, this reduces the vascular response to angiotensin II and on the other hand, perindopril blocks the activation of RAAS and sympathetic nervous system induced by indapamide. Moreover, the

potassium depletion caused by indapamide is buffered by perindopril due to its potassium-sparing effect. Notably, the co-administration of perindopril and indapamide does not change their pharmacokinetic properties when compared to both drugs in monotherapy, and this facilitates its administration.[34,39]

Efficacy and safety of the combination perindopril/indapamide

Hypertension

Several randomized clinical trials and observational studies have analyzed the benefits of the fixed combination perindopril/indapamide in the treatment of hypertensive population. In a study performed in stable hypertensive patients with systolic BP >130 mmHg and/or diastolic BP > 85 mmHg, even with up to 2 antihypertensive drugs, excluding ACE inhibitors, angiotensin II receptor blockers or a diuretic, patients were randomized to receive perindopril 2 mg/indapamide 0.625 mg or cilazapril 2.5 mg once daily for a period of 12 weeks after a 2-week placebo run-in phase.[40] Although systolic BP was significantly reduced by both groups, diastolic BP was significantly reduced only by the combination perindopril/indapamide. Notably, the response rate, defined as systolic BP ≤ 140 mmHg and diastolic BP ≤ 90 mmHg at the last visit or a >20 mmHg reduction in systolic BP and/or >10 mmHg reduction in diastolic BP, was significantly higher with the combination (100%) than with cilazapril (70%) ($P = 0.0086$). Interestingly, there was no difference in the number of adverse events between the 2 groups.

In the STRATHE trial, the efficacy and the tolerability of three different strategies in the treatment of hypertension (low-dose combination, sequential monotherapy and stepped-care) were compared.[41,42] Hypertensive patients were randomized to a 9-month treatment. In the 'low-dose combination' group (n = 180), perindopril (2 mg) and indapamide (0.625 mg) were first administered with the possibility of increasing the doses in 2 steps up to 4 and 1.25 mg respectively. In the 'sequential monotherapy' group (n = 176), the treatment was initiated with atenolol (50 mg), replaced if necessary by losartan (50 mg), and afterwards by amlodipine (5 mg). In the 'stepped-care' group (n = 177), valsartan, was given first at a 40 mg dose, then at a 80 mg dose, to be finally co-administered with hydrochlorothiazide 12.5 mg if required. The main results of this study showed that the proportion of patients that achieved BP goals, was significantly higher in the 'low-dose combination' group (62%) than in the 'sequential monotherapy' (49%, $P = 0.02$) and the 'stepped-care' group (47%, $P = 0.005$). Moreover, the percentage of patients that normalized their BP was significantly greater in the 'low-dose combination' group (56%) than in the 'sequential monotherapy' (42%, $P = 0.002$) or in the 'stepped-care' group (42%, $P = 0.004$). Interestingly, these better BP results were not obtained at the expense of a worsening tolerability.

The Optimax II study was performed to assess whether the pre-existence of metabolic syndrome defined by the NCEP-ATP III criteria, had any impact on BP control in hypertensive patients receiving a fixed perindopril/indapamide combination therapy.[43] A total of 24,069 hypertensive patients were prospectively included and the follow-up lasted 6 months. About 30% of patients exhibited metabolic syndrome. Patients were divided in 3 groups: previously untreated, who received the combination therapy as initial treatment; previously treated but with unsatisfactory results and/or treatment intolerance, they had its previous treatment switched to perindopril/indapamide; and previously treated, with good treatment tolerance but uncontrolled BP, who received the study treatment in adjunction to the previous one. The normalization rates were 70.3%, 68.4%, and 64.1%, respectively, ($P < 0.0001$). Interestingly, the pre-existence of metabolic syndrome did not show any significant influence on these figures.

A meta-analysis was performed to assess the efficacy and safety profiles (through review of randomized, controlled trials) of the fixed, low-dose combination perindopril 2 mg and indapamide 0.625 mg given as first-line antihypertensive therapy in patients with mild to moderate hypertension.[44] In this systematic review, a total of 11 trials (5,936 individuals) were reviewed. In the 5 studies that compared perindopril indapamide versus placebo, the combination significantly reduced both systolic and diastolic BP values. In the other 6 studies, perindopril indapamide was compared to other antihypertensive therapies (perindopril 4 mg/day in monotherapy, losartan 50 mg/day, irbesartan 150 mg/day, enalapril 40 mg/day), showing significantly higher reductions in BP values with the combination perindopril/indapamide. Adverse events and withdrawals were not significantly different between perindopril indapamide and control groups.

Although the results of controlled randomized trials are very important, they are selective and significant differences may remain between them and the 'real world' of general practice. Therefore, it is not always reliable to translate these results to clinical practice.[45,46] In this context, observational studies may be useful to determine

the impact of compliance, tolerability and BP control in daily clinical activity.[47,48] In a descriptive, multicenter survey carried out in primary care setting across Spain, general practitioners were asked about their own experience in the use of the fixed combination perindopril 2 mg plus indapamide 0.625 mg in hypertensive patients for a minimum of 6 weeks.[47] They found in 3,198 patients, that BP control rates increased from 1.1% at baseline, to 38.7% with the combination (Figure 1). Moreover, the great majority of physicians considered the efficacy and tolerability of the combination perindopril and indapamide as good or very good (88.8% and 96.2%, respectively). Furthermore, most patients (92%) were satisfied or very satisfied with the therapy. Another study with a similar design, but including specialists, was performed including a total of 5,126 patients with hypertension and diabetes.[48] At baseline, 1.7% of the general practitioners' patients and 1.3% of the specialists' patients had their BP controlled, and with the combined therapy, BP control rates increased to 30.7% and 29.8%, respectively ($P < 0.001$ vs baseline and not significantly different between groups) (Figure 1). Approximately 85% of physicians considered the efficacy and tolerability of combined therapy as 'good' or 'very good' and 93% of the patients were 'satisfied' or 'very satisfied' with the combined therapy.

Organ damage

The fixed combination perindopril/indapamide has been shown to be an effective therapy for the treatment of patients with hypertension and subclinical organ damage.[49–52] In the PICXEL study,[49] the efficacy of a strategy based on first-line combination with perindopril/indapamide versus monotherapy with enalapril in reducing echocardioghraphic left ventricular hypertrophy in hypertensive patients was compared. After 1 year, treatment

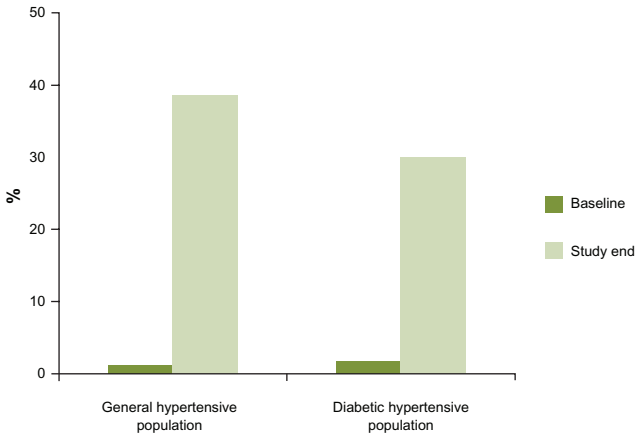

Figure 1 Changes in blood pressure control rates (%) during the study in PRETEND and PRETENDIABETES studies with the fixed combination perindopril 2 mg plus indapamide 0.625 mg. Drawn from data of.[47,48]

systolic and diastolic BP decreased significantly more in the perindopril/indapamide than in the enalapril group ($P < 0.0001$ and $P = 0.003$, respectively). Moreover, the left ventricular mass index decreased by 13.6 ± 23.9 g/m^2 with perindopril/indapamide ($P < 0.0001$ vs baseline) and 3.9 ± 23.9 g/m^2 with enalapril ($P < 0.005$ vs baseline and $P < 0.0001$ between groups) (Figure 2). Both treatments were well tolerated. In an ancillary study of the PICXEL trial, the fixed combination perindopril/indapamide reduced 24-hour and daytime systolic BP as well as pulse pressure significantly more than enalapril treatment ($P < 0.01$). No significant between-group differences were noted for diastolic BP or for night-time measurements. Trough/peak ratios were higher with perindopril/indapamide than with enalapril. Moreover, more patients required dose increases with enalapril (87%) than with perindopril/indapamide (71%).[50]

The effects of the combination perindopril/indapamide on kidney disease have also been assessed.[51] For this purpose, the combination of perindopril/indapamide was compared with enalapril monotherapy on albumin excretion rate (AER) in patients with type 2 diabetes, albuminuria, and hypertension in a 12-month, randomized study. After a 4-week placebo period, patients with albuminuria >20 and <500 μg/min, were randomized to a combination of 2 mg perindopril/0.625 mg indapamide or to 10 mg daily enalapril. After a 12-week period, doses were adjusted on the basis of BP to a maximum of 8 mg perindopril/2.5 mg indapamide or 40 mg enalapril. Combined therapy exhibited higher systolic and diastolic BP reductions than enalapril (−3.0, $P = 0.012$ and −1.5, $P = 0.019$, respectively) and higher AER reduction (−42% vs −27%, $P = 0.002$) (Figure 3). The greater AER reduction remained significant after adjustment for mean BP. Adverse events were similar in the 2 groups.

In a post hoc analysis of the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial, the effects of BP lowering and intensive glucose control on the incidence and progression of retinopathy in type 2 diabetes patients were analyzed.[52] The main results of this study showed that although BP lowering or intensive glucose control did not significantly reduce the incidence and progression of retinopathy, consistent trends towards a benefit were observed, with significant reductions in some lesions observed with both interventions. These effects of the 2 treatments were independent and additive.

Cardiovascular events

Several and important trials have specifically studied the efficacy of the combination perindopril/indapamide on cardiovascular events.[53–63] The PROGRESS (perindopril protection

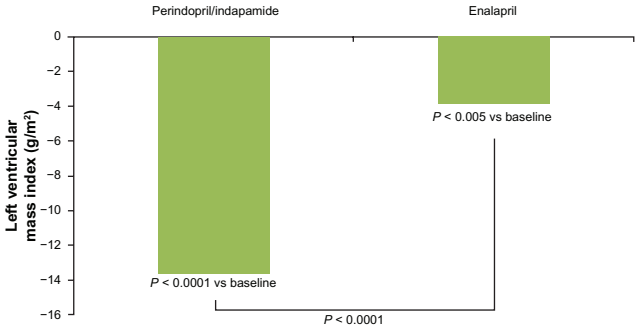

Figure 2 Effect of the combination perindopril/indapamide (2 mg/0.625 mg up to 8 mg/2.5 mg) and enalapril (10 mg up to 40 mg/daily) on left ventricular mass index (g/m^2). Data from data of the PICXEL study.[49]

against recurrent stroke study) trial, was designed to determine the effects of a BP-lowering regimen in hypertensive and non-hypertensive patients with a history of stroke or transient ischemic attack.[54–56] A total of 6,105 subjects from 172 centers in Asia, Australasia, and Europe were randomized to active treatment consisting of a flexible regimen based on perindopril (4 mg daily), with the addition of indapamide at the discretion of treating physicians (n = 3051) or placebo (n = 3054). The primary end point of the study was total stroke (fatal or non-fatal). After a 4-year follow-up, perindopril/indapamide reduced BP by 9/4 mmHg. Those treated with perindopril/indapamide exhibited a 28% relative risk reduction (95% CI 17–38, $P < 0.0001$) in the primary outcome, and a 26% risk reduction for total major vascular events. There were similar reductions in the risk of stroke in hypertensive and non-hypertensive subgroups (all $P < 0.01$). The combination perindopril/indapamide reduced BP by 12/5 mmHg and stroke risk by 43%, whereas perindopril in monotherapy reduced BP by 5/3 mmHg, without a discernable reduction in the risk of stroke.

In the ADVANCE trial,[57–61] the effects of the routine administration of the combination perindopril/indapamide on serious vascular events in patients with diabetes, irrespective of initial BP levels or the use of other BP-lowering drugs were assessed. After a 6-week active run-in period, 11,140 patients with type 2 diabetes were randomized to the combination perindopril/indapamide or placebo, in addition to current therapy. The primary endpoints were a composite of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease. After a mean of 4.3 years of follow-up, those assigned to perindopril/indapamide had a mean reduction in systolic BP of 5.6 mmHg and diastolic BP of 2.2 mmHg. The relative risk of a major macrovascular or microvascular event was reduced by 9% ($P = 0.04$). The relative risk of death from cardiovascular disease was reduced by 18% ($P = 0.03$) and death from any cause by 14% ($P = 0.03$) (Table 1). The fixed combination of perindopril and indapamide was well tolerated. The authors concluded that the results of the ADVANCE trial suggest that over 5 years, 1 death of any cause would be averted among every 79 patients assigned to active therapy.

A recent combined analysis using individual data from ADVANCE, EUROPA, and PROGRESS studies was performed to determine the consistency of the treatment effect of a perindopril-based regimen in patients with vascular disease or at high risk of vascular disease.[62] All-cause mortality and major cardiovascular outcomes during a follow-up of about 4 years in 29,463 patients randomly assigned to a perindopril-based treatment regimen or placebo were analyzed. The perindopril-based regimens were associated with a significant reduction in all-cause mortality (HR 0.89; $P = 0.006$), cardiovascular mortality (HR 0.85; $P = 0.004$), non-fatal myocardial infarction (HR 0.80; $P < 0.001$), stroke (HR 0.82; $P = 0.002$), and heart failure (HR 0.84; $P = 0.015$).

The results of the HYVET (Hypertension in the Very Elderly Trial) study have been very important to clarify how the management of the hypertensive population aged 80 years or older should be.[63] In this study, 3,845 patients from Europe, China, Australasia, and Tunisia, who were ≥80 years and had a sustained systolic BP ≥ 160 mmHg, were randomized to receive either indapamide (sustained release, 1.5 mg) or matching placebo. Perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target BP of 150/80 mmHg. The primary end point was fatal or nonfatal stroke. After 2 years of treatment, mean BP was 15.0/6.1 mmHg lower in the active-treatment group than in the placebo group. Active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke ($P = 0.06$), a 39% reduction in the rate of death from stroke

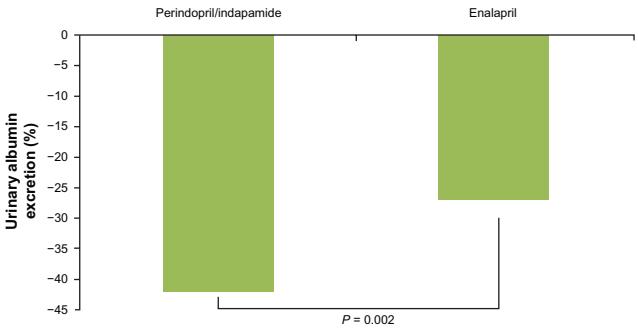

Figure 3 Effect of the combination perindopril/indapamide (2 mg/0.625 mg up to 8 mg/2.5 mg) and enalapril (10 mg up to 40 mg/daily) on urinary albumin excretion (% of change from baseline). Data from data of the PREMIER study.[51]

Table 1 Main results of ADVANCE trial[57]

Variables	Relative risk reduction	Hazard ratio (95% CI)	*P*
Major macrovascular or microvascular event	9%	0.91 (0.83–1.00)	0.041
Death from cardiovascular disease	18%	0.82 (0.68–0.98)	0.027
Death from any cause	14%	0.86 (0.75–0.98)	0.025

Abbreviation: CI, confidence interval.

($P = 0.05$), a 21% reduction in the rate of death from any cause ($P = 0.02$), a 23% reduction in the rate of death from cardiovascular causes ($P = 0.06$), and a 64% reduction in the rate of heart failure ($P < 0.001$) (Table 2).

Safety and tolerability

The fixed combination perindopril plus indapamide is a safe and well-tolerated drug, with a low incidence of adverse events. In general, drug-related adverse events are mild and transient with a very low discontinuation rate (about 2%). The most frequent adverse events reported with the fixed combination perindopril (2–4 mg) plus indapamide (0.625–1.25 mg) are cough (4.4%), headache (3.1%), asthenia (1.6%), dizziness (1.4%) and flu-like symptoms (1.2%). Due to their complementary mechanisms of action, hyponatremia and hypokalemia are uncommon with perindopril/indapamide therapy. This antihypertensive combination does not adversely affect lipid profile or glucose tolerance even in hypertensive patients at risk.[34]

The combination perindopril and indapamide is contraindicated in patients with a history of previous hypersensitivity to either of the active compounds, perindopril or indapamide, in subjects with bilateral renal artery stenosis (or unilateral in subjects with only one kidney), in patients with severe renal insufficiency (creatinine clearance below 30 mL/min), as well as during pregnancy and for lactating women.[34] It should be noted that these contraindications are the same for all RAAS blockers.

Conclusions and place in therapy

The majority of patients with hypertension often require more than one drug to achieve BP goals. The last update of the European guidelines for the management of arterial hypertension recommends the use of fixed combinations in those patients that require more than one antihypertensive drug to attain BP objectives. The combination of an ACE inhibitor with a diuretic is highly recommended in this context. Many trials have demonstrated the beneficial effects of perindopril on the whole spectrum of the cardiovascular continuum.

Clinical trials have shown that perindopril/indapamide is an effective and well-tolerated fixed-dose antihypertensive combination. As expected, it provides greater antihypertensive efficacy than either component taken as monotherapy. This combination has been demonstrated to reduce left ventricular mass index as well as albumin excretion rate, probably beyond its antihypertensive effect. But, moreover, relevant controlled randomized clinical trials such as ADVANCE, PROGRESS or HYVET have importantly shown that treatment with perindopril/indapamide reduces cardiovascular outcomes in different contexts, such as the diabetic population, a history of cerebrovascular disease or the elderly.

The ACCOMPLISH trial showed that not all antihypertensive fixed combinations have the same impact on cardiovascular outcomes. In this trial, the benazepril–amlodipine combination was superior to benazepril–hydrochlorothiazide in reducing cardiovascular events in a hypertensive population with a high proportion of patients with diabetes and obesity.[64] It should be kept in mind that in this situation, a thiazide may worsen glucose and lipid profiles and this could influence outcomes. However, indapamide does not have these deleterious effects on lipid and glucose profiles. Although both indapamide and thiazides are diuretics, their mechanisms of action differ, as well as their clinical benefits on vascular protection. Moreover, the evidence on the benefits of perindopril in outcome trials is much more

Table 2 Main results of HYVET trial[63]

Variables	Relative risk reduction	95% confidence interval	*P*
Fatal or nonfatal stroke	30%	−1 to 51	0.06
Death from stroke	39%	1 to 62	0.05
Death from any cause	21%	4 to 35	0.02
Death from cardiovascular causes	23%	−1 to 40	0.06
Rate of heart failure	64%	42 to 78	<0.001

robust than that with benazepril. As a result, the results of ACCOMPLISH should not be directly applied to the fixed combination perindopril-indapamide.

As a result, as 2007 ESH/ESC guidelines recommend, the fixed combination perindopril/indapamide at low doses could be suitable in the treatment of hypertensive patients at high or very high risk, as initial therapy.

Acknowledgments/disclosures

The authors have no conflicts of interests directly related with this manuscript.

References

1. Banegas JR, Rodríguez-Artalejo F, de la Cruz Troca JJ, et al. Blood Pressure in Spain: distribution, awareness, control and benefits of a reduction in average pressure. *Hypertension*. 1998;32:998–1002.
2. Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. *Arch Intern Med*. 2007;167:141–147.
3. Ong KL, Cheung BM, Man YB, et al. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999–2004. *Hypertension*. 2007;49:69–75.
4. Banegas JR, Rodriguez-Artalejo F, Graciani A, et al. Mortality attributable to cardiovascular risk factors in Spain. *Eur J Clin Nutr*. 2003;57 Suppl 1:S18–S21.
5. Mancia G, De Backer G, Dominiczak A, et al. 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.
6. Britton KA, Gaziano JM, Djoussé L. Normal systolic blood pressure and risk of heart failure in US male physicians. *Eur J Heart Fail*. 2009;11:1129–1134.
7. Mancia G, Messerli F, Bakris G, et al. Blood pressure control and improved cardiovascular outcomes in the International Verapamil SR-Trandolapril Study. *Hypertension*. 2007;50:299–305.
8. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335:827–838.
9. Barrios V, Banegas JR, Ruilope LM, et al. Evolution of blood pressure control in Spain. *J Hypertens*. 2007;25:1975–1977.
10. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet*. 2009;373:929–940.
11. Barrios V, Escobar C, Calderon A, et al. Blood pressure and lipid goal attainment in the hypertensive population in the primary care setting in Spain. *J Clin Hypertens (Greenwich)*. 2007;9:324–329.
12. Barrios V, Escobar C, Calderon A, et al. CONTROLRISK Investigators Cardiovascular risk profile and risk stratification of the hypertensive population attended by general practitioners and specialists in Spain. The CONTROLRISK study. *J Hum Hypertens*. 2007;21:479–485.
13. Marquez-Contreras E, Coca A, de la Figuera M, et al. Cardiovascular risk profile of uncontrolled hypertensive patients. The Control-Project study. *Med Clin (Barc)*. 2007;128:86–91.
14. Ryden L, Standl E, Bartnik M, et al. Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: Executive summary. The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2007;28:88–136.
15. Sica DA. Rationale for fixed-dose combinations in the treatment of hypertension: the cycle repeats. *Drugs*. 2002;62:44–62.
16. Motwani JG. Combining renin-angiotensin-aldosterone system blockade with diuretic therapy for treatment of hypertension. *J Renin Angiotensin Aldosterone Syst*. 2002;3:72–77.
17. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009 Oct 15. [Epub ahead of print].
18. Amar J, Vaur L, Perret M, et al. PRATIK study investigators. Hypertension in high-risk patients: beware of the underuse of effective combination therapy (results of the PRATIK study). *J Hypertens*. 2002;20:779–784.
19. Coca A. Blood pressure control among treated hypertensive patients by Primary Care in Spain. The 2003 Controlpres study. *Hipertension*. 2005;22:5–14.
20. Bangalore S, Kamalakkannan G, Parkar S, et al. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med*. 2007;120:713–719.
21. Volpe M. Angiotensin II: an amplifier of cardiovascular risk. *Curr Hypertens Rep*. 2004;6:247–248.
22. Schmieder RE. The role of non-haemodynamic factors of the genesis of LVH. *Nephrol Dial Transplant*. 2005;20:2610–2612.
23. Levy D, Garrison RJ, Savage DD, et al. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med*. 1990;322:1561–1566.
24. Klingbeil AU, Schneider M, Martus P, et al. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med*. 2003;115:41–46.
25. Escobar C, Barrios V, Calderón A, et al. Electrocardiographic left ventricular hypertrophy regression induced by an angiotensin receptor blocker-based regimen in hypertensive patients with the metabolic syndrome: data from the SARA Study. *J Clin Hypertens (Greenwich)*. 2008;10:208–214.
26. Barrios V, Escobar C, Echarri R, et al. New therapeutic progress in the cardio-renal protection of the hypertensive patient with a focus on olmesartan. *Hot Topics in Hypertension*. 2009;8:7–16.
27. Yusuf S, Sleight P, Pogue J, et al; for the Hearth Outcomes Prevention Evaluation (HOPE) Study Group. Effects of angiotensin-converting enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145–153.
28. Wachtell K, Olsen MH, Dahlof B, et al. Microalbuminuria in hypertensive patients with electrocardiographic left ventricular hypertrophy: the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. *J Hypertension*. 2002;20:405–412.
29. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. *Circulation*. 2000;101:1899–1906.
30. Tardiff JC. Angiotensin-converting enzyme inhibitors and atherosclerotic plaque: a key role in the cardiovascular protection of patients with coronary artery disease. *Eur Heart J Supple*. 2009;11 Suppl E:E9–E16.
31. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. *Arterioscler Thromb Vasc Biol*. 2003;23:168–175.
32. Behrendt D, Ganz P. Endothelial function. From vascular biology to clinical applications. *Am J Cardiol*. 2002;90:40L–48L.
33. Buus NH, Jorgensen CG, Mulvany MJ, et al. Large and small artery endothelial function in patients with essential hypertension – effect of ACE inhibition and beta-blockade. *Blood Press*. 2007;16:106–113.
34. COVERSYL PLUS® Data sheet. In Information for health professionals. http://www.medsafe.govt.nz/profs/datasheet/c/CoversylPlustab.htm. Last update 2006 March 03. Accessed January 2010.
35. Song JC, White CM. Clinical pharmacokinetics and selective pharmacodynamics of new angiotensin converting enzyme inhibitors: an update. *Clin Pharmacokinet*. 2002;41:207–224.

36. Brugts JJ, Ferrari R, Simoons ML. Angiotensin-converting enzyme inhibition by perindopril in the treatment of cardiovascular disease. *Expert Rev Cardiovasc Ther*. 2009;7:345–360.
37. Robinson DM, Wellington K. Indapamide sustained release: a review of its use in the treatment of hypertension. *Drugs*. 2006;66:257–271.
38. Schiavi P, Jochemsen R, Guez D. Pharmacokinetics of sustained and immediate release formulations of indapamide after single and repeated oral administration in healthy volunteers. *Fundam Clin Pharmacol*. 2000;14:139–146.
39. Matheson AJ, Cheer SM, Goa KL. Perindopril/indapamide 2/0.625 mg/day: a review of its place in the management of hypertension. *Drugs*. 2001;61:1211–1229.
40. Sung SH, Wu TC, Lin SJ, Chen JW. Efficacy of a very-low-dose combination of perindopril and indapamide – preterax compared with cilazapril monotherapy in patients with inadequate blood pressure control – a randomized, double-blind, add-on study. *J Chin Med Assoc*. 2008;71:247–253.
41. Mourad JJ, Waeber B, Zannad F, et al. Comparison of different therapeutic strategies in hypertension: a low-dose combination of perindopril/indapamide versus a sequential monotherapy or a stepped-care approach. *J Hypertens*. 2004;22:2379–2386.
42. Waeber B, Mourad JJ. Application in the STRATHE trial of a score system to compare the efficacy and the tolerability of different therapeutic strategies in the management of hypertension. *Vasc Health Risk Manag*. 2008;4:249–252.
43. Mourad JJ, Lameira D, Guillausseau PJ. Blood pressure normalization by fixed perindopril/indapamide combination in hypertensive patients with or without associate metabolic syndrome: results of the OPTIMAX 2 study. *Vasc Health Risk Manag*. 2008;4:443–451.
44. Kang S, Wu YF, An N, Ren M. A systematic review and meta-analysis of the efficacy and safety of a fixed, low-dose perindopril-indapamide combination as first-line treatment of hypertension. *Clin Ther*. 2004;26:257–270.
45. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med*. 2000;342:1887–1892.
46. Steg PG, Lopez-Sendon J, Lopez de Sa E, et al. External validity of clinical trials in acute myocardial infarction. *Arch Intern Med*. 2007;167:68–73.
47. Barrios V, Escobar C, Divison JA, Medialdea F. Clinical experience with a low-dose fixed combination of perindopril plus indapamide in a primary-care setting: the PRETEND study. *Therapy*. 2007;4:677–683.
48. Barrios V, Escobar C, Divison JA, Medialdea F. Low-dose fixed combination of perindopril plus indapamide in the diabetic hypertensive population. *Expert Rev Cardiovasc Ther*. 2008;6:1063–1069.
49. Dahlöf B, Gosse P, Guéret P, et al. Perindopril/indapamide combination more effective than enalapril in reducing blood pressure and left ventricular mass: the PICXEL study. *J Hypertens*. 2005;23:2063–2070.
50. Asmar R, Garcia-Puig J, Gosse P, et al. Ambulatory blood pressure in hypertensive patients with left ventricular hypertrophy: efficacy of first-line combination perindopril/indapamide therapy. *Vasc Health Risk Manag*. 2007;3:371–380.
51. Mogensen CE, Viberti G, Halimi S, et al. Effect of low-dose perindopril/indapamide on albuminuria in diabetes: preterax in albuminuria regression: PREMIER. *Hypertension*. 2003;41:1063–1071.
52. Beulens JW, Patel A, Vingerling JR, et al. Effects of blood pressure lowering and intensive glucose control on the incidence and progression of retinopathy in patients with type 2 diabetes mellitus: a randomised controlled trial. *Diabetologia*. 2009;52:2027–2036.
53. Campbell DJ. A review of Perindopril in the reduction of cardiovascular events. *Vasc Health Risk Manag*. 2006;2:117–124.
54. 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.
55. PROGRESS Collaborative Group. Effects of a perindopril-based blood pressure lowering regimen on cardiac outcomes among patients with cerebrovascular disease. *Eur Heart J*. 2003:24:475–484.
56. Hisatomi A, Craig A, Teruo O, et al; for the PROGRESS Collaborative Group. Perindopril-based blood pressure lowering reduces major vascular events in Asian and Western participants with cerebrovascular disease: the PROGRESS trial. *J Hypertens*. 2010;28:395–400.
57. Patel A; ADVANCE Collaborative Group, MacMahon S, 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.
58. Chalmers J, Joshi R, Kengne AP, et al; ADVANCE Collaborative Group. Efficacy and safety of fixed combination of perindopril and indapamide in type 2 diabetes: results from ADVANCE in context of available evidence. *J Hypertens*. 2008;26 Suppl 3:S23–S30.
59. Waeber B, de la Sierra A, Ruilope LM. The ADVANCE trial: clarifying the role of perindopril/indapamide fixed-dose combination in the reduction of cardiovascular and renal events in patients with diabetes mellitus. *Am J Cardiovasc Drugs*. 2009;9:283–291.
60. Zoungas S, de Galan BE, Ninomiya T, et al. Combined effects of routine blood pressure lowering and intensive glucose control on macrovascular and microvascular outcomes in patients with type 2 diabetes: New results from the ADVANCE trial. *Diabetes Care*. 2009;32:2068–2074.
61. Du X, Ninomiya T, de Galan B, et al; ADVANCE Collaborative Group. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. *Eur Heart J*. 2009;30:1128–1135.
62. Brugts JJ, Ninomiya T, Boersma E, et al. The consistency of the treatment effect of an ACE-inhibitor based treatment regimen in patients with vascular disease or high risk of vascular disease: a combined analysis of individual data of ADVANCE, EUROPA, and PROGRESS trials. *Eur Heart J*. 2009;30:1385–1394.
63. Beckett NS, Peters R, Fletcher AE, et al. HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358:1887–1898.
64. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.