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Effectiveness and Tolerability of Fixed-Dose Combination Enalapril plus Nitrendipine in Hypertensive Patients

Results of the 3-Month Observational, Post-Marketing, Multicentre, Prospective CENIT Study

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Abstract

Background and objective: Monotherapy with any class of antihypertensive drug effectively controls blood pressure (BP) in only about 50% of patients. Consequently, the majority of patients with hypertension require combined therapy with two or more medications. This study aimed to evaluate the effectiveness (systolic BP [SBP]/diastolic BP [DBP] control) and tolerability of the fixed-dose combination enalapril/nitrendipine 10 mg/20 mg administered as a single daily dose in hypertensive patients.

Methods: This was a post-authorization, multicentre, prospective, observational study conducted in primary care with a 3-month follow-up. Patients throughout Spain with uncontrolled hypertension (≥140/90 mmHg for patients without diabetes mellitus, or ≥130/85 mmHg for patients with diabetes) on monotherapy or with any combination other than enalapril + nitrendipine, or who were unable to tolerate their previous antihypertensive therapy, were recruited. Change from previous to study treatment was according to usual clinical practice. BP was measured once after 5 minutes of rest in the sitting position. Therapeutic response was defined as follows: 'controlled' meant controlled BP (<140/90 mmHg for nondiabetic patients, or <130/85 mmHg for diabetic patients); 'response' meant controlled BP, or a decrease in SBP of ≥20 mmHg and in DBP of ≥10 mmHg. The main laboratory test parameters

were documented at baseline and after 3 months. Patients aged >65 years, with diabetes, with isolated systolic hypertension (ISH; SBP ≥140 mmHg for patients without diabetes, SBP ≥130 mmHg for patients with diabetes) and who were obese (body mass index [BMI] ≥30 kg/m^2) were analysed separately.
Results: Of 6537 patients included, 5010 and 6354 patients were assessed in effectiveness and tolerability analyses, respectively. In the tolerability analysis population, there were 3023 men (47.6%) and 3321 women (52.4%). The mean (± SD) age of the tolerability analysis group was 62.8 (± 10.7) years. A total of 71.1% of the patients presented at least one clinical cardiovascular risk factor other than hypertension, with the most frequent being dyslipidaemia (42.3%), obesity (29.2%) and diabetes (23.9%). After 3 months of treatment, SBP and DBP showed mean (±SD) decreases of 26.5 (± 14.4) mmHg and 14.9 (± 9.0) mmHg, respectively, and 73.0% of patients responded to treatment while 40.9% achieved BP control (70.8%/36.1% in 2658 patients aged >65 years; 61.7%/46.8% in 1521 patients with diabetes; 55.3%/44.2% in 731 patients with ISH; 72.0%/36.4% in 1762 obese patients). Adverse events were reported in 10.8% of patients (n = 689). During the follow-up period, ten patients died and seven patients had serious adverse events; in no case was a causal relationship attributed to the study product.
Conclusions: The rate of SBP/DBP control achieved demonstrates the effectiveness of the fixed-dose enalapril/nitrendipine 10 mg/20 mg combination administered as a single daily dose in patients with essential hypertension not adequately controlled with monotherapy or with any combination other than enalapril + nitrendipine. The proportion and type of adverse events reported were as expected and have already been described for both components of the enalapril/nitrendipine 10 mg/20 mg combination. These results confirm the effectiveness of a strategy based on a fixed-dose enalapril/nitrendipine 10 mg/20 mg combination in reducing BP and achieving BP control goals.

Background

The overall prevalence of hypertension in the adult European population is 38%.[1] In Spain, there are an estimated 6–7 million hypertensive patients.[1] It has been demonstrated that increased blood pressure (BP), whether systolic (SBP) or diastolic (DBP), consistently increases the risk of cardiovascular (CV) disease, e.g. stroke, coronary artery disease, heart failure, peripheral vascular disease and sudden death.[1-3] The high prevalence of hypertension and the associated high risk of CV morbidity and mortality means that treatment of hypertension is a major challenge in clinical practice.[4]

There is broad consensus that reducing BP has a major clinical impact.[2,3] It has been demonstrated that a long-term reduction of 10 mmHg in SBP or of 5 mmHg in DBP can reduce the risk of death due to stroke by 40% and of death due to coronary artery disease or CV disease by 30%.[2] Antihypertensive treatment should therefore be given without delay to achieve the goal of controlling BP based on the overall CV risk of each patient, or of reaching the lowest possible BP levels, if well tolerated, according to the 2007 European recommendations for hypertension management.[2] However, monotherapy with any class of antihypertensive drug effectively controls BP in only about 50% of patients with

hypertension.[5,6] Consequently, about half of patients with hypertension require combined therapy with two or more medications.[2]

The difficulty of controlling BP may be attributed to diverse factors, including low acceptance of treatment and poor compliance with therapy by patients.[7,8] Other factors may be the poor efficacy of certain drug classes in some groups of patients, the tolerability profile of the drug, and use of inadequate dosages.[1,2] A variety of pharmacodynamic mechanisms may explain why monotherapy is less effective than combination therapy. It has been reported that monotherapy can activate BP regulatory mechanisms that counteract the effects of therapy, thus reducing the antihypertensive power of some drug classes.[9] This seems to be confirmed by the effects of combined therapy involving low doses of two antihypertensive drugs that have different, but complementary, mechanisms of action.[10-12] A synergistic effect between the two drugs occurs and an additive antihypertensive effect is obtained.[10-12] In fact, it has been demonstrated in clinical practice that use of fixed-dose combined treatment with a single daily administration regimen favours therapeutic compliance, which in turn helps to increase the percentage of patients who achieve BP control.[13] Overall, use of a fixed-dose combination enables BP control in up to 80% of patients with hypertension.[1,14]

The combination of a calcium channel antagonist (calcium channel blocker [CCB]) with an ACE inhibitor produces a complementary effect,[15,16] which translates into larger reductions in BP than are obtained with either drug as monotherapy.[17-19] ACE inhibitors are the antihypertensive agents of choice in hypertensive patients with type 1 and 2 diabetes mellitus and proteinuria.[1,20] Tolerability is another favourable aspect of combined therapy, which is characterized by a lower incidence of adverse effects than occurs with the components of the combination when these are administered as monotherapy at the same dose.[1,11,21] In particular, the combination of enalapril/nitrendipine 10 mg/20 mg creates a potent vasodilator effect by simultaneously inhibiting angiotensin II formation and the breakdown of bradykinin while blocking the entry of calcium in the smooth muscle fibres of the vascular wall.

The impact of ACE inhibitor + CCB combinations on CV risk was evaluated in the Syst-Eur (Systolic Hypertension in Europe) study, which demonstrated a reduction in the risk of stroke and CV events in older adults with isolated systolic hypertension (ISH) treated with a CCB and an ACE inhibitor and/or hydrochlorothiazide.[22-24] The Syst-Eur study also demonstrated a reduction in the rate of dementia.[25] Recently, the results of the ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension) study[26] confirmed the findings of the Syst-Eur study. This study compared the effects of initial treatment with two fixed-dose combinations, ACE inhibitor + CCB versus ACE inhibitor + hydrochlorothiazide, in the prevention of CV morbidity and mortality in high-risk patients with hypertension. The results demonstrated a higher rate of BP control in patients treated with the ACE inhibitor + CCB combination and a reduction of more than 20% in CV morbidity and mortality relative to the ACE inhibitor + hydrochlorothiazide treatment arm ($p < 0.001$).

The CENIT study (Study of the Effectiveness and Tolerability of the Enalapril + Nitrendipine Combination in Hypertensive Patients) was carried out to evaluate the effectiveness and tolerability of a fixed-dose enalapril/nitrendipine 10 mg/20 mg combination in patients with hypertension not controlled with monotherapy or with any combination other than enalapril/nitrendipine 10 mg/20 mg, or with previous intolerance of a drug combination, in the primary-care setting.

Patients and Methods

Study Design

This was an observational, post-marketing, multicentre, prospective study conducted in a primary care setting in Spain, with a follow-up period of 3 months.

Study Population

We recruited patients aged ≥18 years diagnosed with essential hypertension who were treated in primary-care centres but who were unable to achieve BP control with monotherapy or with a combination of two antihypertensive agents (not enalapril and/or nitrendipine), or who were intolerant of their previous treatment, and in whom treatment with a fixed-dose enalapril/nitrendipine 10 mg/20 mg combination was indicated. Change from previous treatment to the study drug was implemented before starting the study, and according to usual clinical practice at the time the study was designed. Addition of another antihypertensive agent was allowed when necessary.

The exclusion criteria were: foreseeable poor compliance, clinical follow-up or cooperation; high risk of discontinuing treatment during follow-up; and the contraindications listed in the product information of the enalapril/nitrendipine 10 mg/20 mg combination. The latter were of greatest relevance to patients who were hypersensitive to this product, those with a history of angioedema related to previous treatment with an ACE inhibitor, and patients with hereditary or idiopathic angioedema, haemodynamic instability or severe renal or kidney insufficiency.

Sample size was estimated with respect to the objective of assessing the tolerability of the study treatment, and therefore a higher sample size was required. It was estimated that 10 000 patients would need to be recruited in order to detect unusual adverse reactions (specifically, at least five cases with an adverse reaction with an incidence of 0.1%), given a security level of 95% and an estimated 10% withdrawal of patients.[27] Ultimately, 6537 patients were recruited.

Effectiveness and Tolerability Endpoints

Effectiveness was evaluated by measuring SBP and DBP once in the clinic after 5 minutes' rest in the sitting position at each study visit (baseline, 1 month and 3 months). BP was measured independently of time since the last dose of the previous medication. Analytical determinations were made of the lipid profile, glucose, uric acid, urea and creatinine on an optional basis according to physician discretion during follow-up.

Therapeutic response was defined as follows: 'responders' had controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients) or a reduction of ≥20 mmHg in SBP and ≥10 mmHg in DBP; 'controlled' patients had controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients). Values of <130/85 mmHg were considered as goal BP for diabetic patients according to the guidelines used at the time the study was designed.[28]

Adherence to hypertensive therapy was evaluated using a validated Spanish version of the Morisky-Green test, which includes four dichotomous questions about adherence to treatment.[29,30] Good compliance was considered when the Morisky-Green overall test score was three or higher (on a 0–4 point scale). Information was also collected in the case report form on vital statistics and general clinical characteristics, including life habits associated with a greater CV risk (smoking and alcohol [ethanol] consumption, lack of physical activity [defined as walking less than half an hour per day or participating in sports less than twice a week]) and clinical CV risk factors (presence of diabetes, previous CV pathology, dyslipidaemia or other possible clinical factors registered by the investigator). Finally, adverse events were recorded spontaneously by the patient or detected by the investigator during the follow-up period. Adverse events were classified according to the WHO-Adverse Reaction Terminology (ART) criteria.[31]

Statistical Analysis

The tolerability analysis included all patients who met the screening criteria established in the protocol other than patients with baseline data only and patients with incomplete baseline data for whom the occurrence of adverse events, poor tolerability or death were not specified as the reason for withdrawal.

The effectiveness analysis included all patients actually treated (rather than intention to treat).

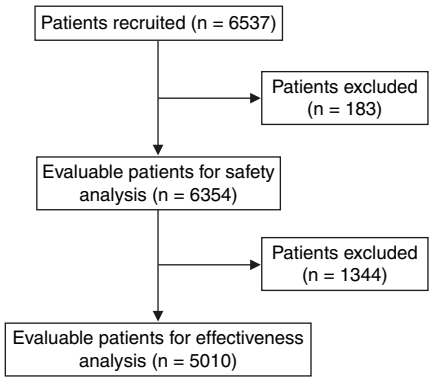

Fig. 1. Diagrammatic representation of recruited and evaluated patients.

Accordingly, patients lacking minimum data on use of the drug combination and the primary study endpoint (compliance) were excluded. Patients with baseline data only or incomplete baseline data and no or minimal follow-up data were also excluded.

Data were processed using SPSS program version 11.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were described using central trend measures (mean) and dispersion measures (standard deviation). Categorical variables were described using absolute and relative frequency tables. All statistical comparisons (chi-squared [χ^2] test, Mann-Whitney U test and Wilcoxon test) were conducted and are reported independently of the result, together with the p-value obtained.

Independent analyses were made of the following patient subgroups: age >65 years, diabetes, ISH (SBP ≥140 mmHg and DBP <90 mmHg in non-diabetics, ≥130 mmHg and <85 mmHg in patients with diabetes) and obesity (body mass index [BMI] ≥30 kg/m^2).

Results

Evaluable Patients

The overall group of patients recruited and evaluable for the analysis is shown in figure 1. A total of 6537 patients were recruited by 1345 investigators throughout Spain. Of this group, 6354 patients (97.20%) were considered evaluable for tolerability after exclusion of 183 patients who had only baseline data (1.71%), deficient baseline data (0.93%), were treated with monotherapy (0.14%) or were aged <18 years (0.02%). Of these patients, 5010 (76.64%) were evaluable for the effectiveness analysis after exclusion of 1344 patients who attended all their scheduled visits but had incomplete data on two tests (10.02%), who attended two scheduled visits but had incomplete data on one test (6.85%), had data for only one visit (3.61%), had only baseline data (3.55%) or had deficient baseline data (0.14%).

Characteristics of the Patients Analysed

The baseline characteristics of the patients are summarized in table I. Women made up 52.3% of the group, and they had a higher mean age and BMI than the men in the population (Mann-Whitney U test, $p < 0.01$). The population contained 32.1% smokers or ex-smokers who had

Table I. Baseline characteristics of the populations analysed, by sex

Characteristic	Total (n = 6354)			Males (n = 3023)			Females (n = 3321)			p-Value[a]
	n	mean	SD	n	mean	SD	n	mean	SD	
Age (y)	6285	62.82	10.72	2984	61.29	10.47	3295	64.20	10.75	<0.01
Weight (kg)	6112	76.55	12.17	2915	80.96	11.05	3191	72.54	11.74	<0.01
Height (cm)	6043	164.18	8.51	2890	169.79	6.50	3148	159.04	6.69	<0.01
BMI (kg/m^2)	6036	28.42	4.16	2889	28.09	3.50	3142	28.73	4.67	<0.01
SBP	6345	164.52	14.01	3021	163.75	13.67	3315	165.19	14.27	<0.001
DBP	6345	95.52	8.56	3021	96.06	8.27	3315	95.04	8.79	<0.001

a Statistically significant differences by sex (Mann-Whitney U test, $p < 0.05$).

BMI = body mass index; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure.

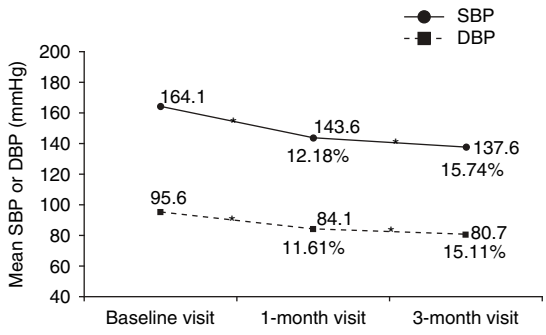

Fig. 2. Evolution of blood pressure in the overall study population. Percentage under the line corresponds to the mean percentage reduction relative to the baseline measurement. **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure. * Wilcoxon test between 1 month and baseline, and between 3 months and baseline: $p < 0.001$.

smoked for >5 years, 22.6% alcohol users and 52.3% with a sedentary lifestyle. With respect to the presence of clinical CV risk factors other than hypertension, 71.1% had at least one additional clinical CV risk factor: 42.3% dyslipidaemia, 29.2% obesity and 23.9% diabetes. A family history of CV disease was present in 43.5% of cases. In the population included in the study, the mean time to diagnosis of hypertension was 6.4 years and the most frequent reason for changing antihypertensive treatment was inefficacy (91.1%).

Effectiveness

The primary endpoint analysis of the main variable is shown in figure 2. The mean (±SD) reductions in BP at the end of the follow-up period were 26.5 (± 14.4) mmHg and 14.9 (± 9.0) mmHg, respectively, for SBP and DBP. The evolution of BP control and response achieved at each study visit is shown in figure 3. At 3 months of treatment, 73.0% of patients were responders and 40.9% exhibited BP control. The profile of responders was a younger person with lower BMI than nonresponders (Mann-Whitney U test, $p < 0.05$). Responders also had a lower prevalence of diabetes and dyslipidaemia (χ^2 test, $p < 0.05$).

Evaluation of Morisky-Green test scores disclosed that adherence to therapy with the fixed-dose combination of enalapril/nitrendipine 10 mg/20 mg was notable at both the 1-month (89.70%) and 3-month (94.61%) follow-up visits.

The evolution of BP reduction according to compliance is shown in figure 4. Compliant patients had higher rates of BP response to treatment (73.8%) and BP control (31.7%) than noncompliant patients (69.0% response, χ^2 test, $p = 0.005$; 24.4% control, χ^2 test, $p < 0.001$).

Another antihypertensive drug needed to be added in 12.0% of patients after 1 month and in 12.6% of patients after 3 months; hydrochlorothiazide was the most frequent antihypertensive treatment added.

A reduction was observed between baseline and the 3-month visit in almost all laboratory parameters investigated (table II), with the exception of urea and high-density lipoprotein (HDL) cholesterol, which increased. Statistically significant reductions in glucose, creatinine, uric acid and triglyceride levels, and a significant increase in HDL cholesterol level (Wilcoxon test, $p < 0.01$), were observed. However, these variations were not considered clinically relevant.

Tolerability

Almost 10% of patients (9.99%, n = 635) withdrew from the study early, generally because of intolerable adverse events (7.49%, n = 473) or missed visits (1.55%, n = 99).

As illustrated in table III, in the overall group of patients included in the study, 10.84% (n = 689)

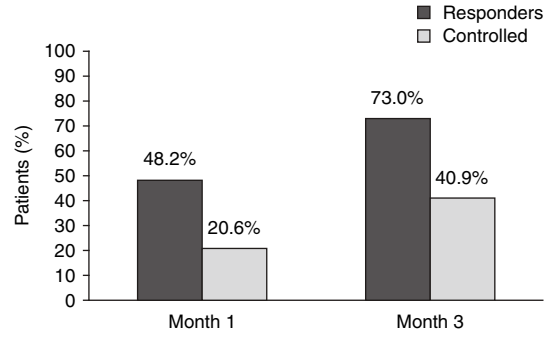

Fig. 3. Evolution of blood pressure (BP) control and response in the overall study population. Responder patients were defined as having controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients) or a reduction of ≥20 mmHg in systolic BP and ≥10 mmHg in diastolic BP. Controlled patients had controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients).

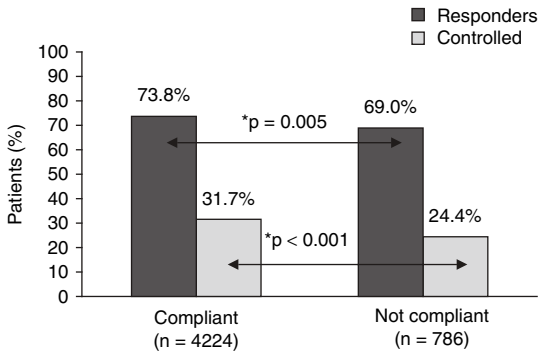

Fig. 4. Evolution of blood pressure (BP) control and response according to compliance in the overall study population. Controlled patients had controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients). Responder patients were defined as having controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients) or a reduction of ≥20 mmHg in systolic BP and ≥10 mmHg in diastolic BP. Adherence to hypertensive therapy was evaluated using a validated Spanish version of the Morisky-Green test. * Statistically significant differences (Pearson chi-squared [χ^2] test).

reported some adverse event. Oedema (4.41%), flushing (2.48%) and headache (1.78%) were the most frequently reported adverse events. Only 0.77% (49 patients) reported coughing.

During the follow-up period, ten patients died; in no case was a causal relationship attributed to the study product. Seven patients had serious adverse events, including hypotensive episodes (three cases at the initiation of therapy), palpitations and tachycardia (two cases), intense facial reddening, abdominal pain (one case) and peripheral vertigo (one case).

Analysis of Subgroups

Four independent analyses of patient subgroups were conducted to evaluate effectiveness and tolerability specifically in groups of particular clinical interest in the overall hypertensive population: patients aged >65 years and those with diabetes, ISH or obesity. The age, degree of BP response and control achieved, and the presence of adverse reactions in each patient subgroup, are described in table IV and figure 5. Analysis revealed that 70.8% of >65-year-old patients were responders to treatment after 3 months, as were 61.7%, 55.3% and 72.0% of patients with diabetes, ISH and obesity, respectively. In turn, 36.1% achieved BP control after 3 months in the >65-year-old group, as did 46.8%, 44.2% and 36.4% of patients with diabetes, ISH and obesity, respectively.

Discussion

The results of the present observational study of 6537 patients with hypertension not controlled by previous monotherapy or by a variety of combinations provide valuable information about the use of this strategy in routine clinical practice.

The overall effectiveness results coincide with results previously obtained in several clinical trials, which show that monotherapy results in BP control in only 50% of patients,[5,6] whereas combinations achieve BP control in up to 80% of patients.[32-35]

Moreover, the fixed-dose enalapril/nitrendipine 10 mg/20 mg combination was a therapeutic

Table II. Laboratory parameters (at baseline and at month 3)[a]

Parameter	n	Mean	SD	p-Value
Glucose (mg/dL)				
Baseline	1411	113.32	33.68	<0.001
Month 3	1411	109.22	28.98	
Urea (mg/dL)				
Baseline	1073	40.75	11.49	NS
Month 3	1073	40.88	10.54	
Creatinine (mg/dL)				
Baseline	1372	1.02	0.39	<0.001
Month 3	1372	0.99	0.33	
Uric acid (mg/dL)				
Baseline	1237	5.54	1.82	<0.01
Month 3	1237	5.43	1.69	
Total cholesterol (mg/dL)				
Baseline	1027	146.84	24.77	NS
Month 3	1027	139.12	22.44	
HDL cholesterol (mg/dL)				
Baseline	1313	50.93	14.03	<0.001
Month 3	1313	52.58	14.84	
Triglycerides (mg/dL)				
Baseline	1400	150.45	66.99	<0.001
Month 3	1400	140.11	54.12	

a Results are for patients with data at the baseline visit and at 3 months of follow-up.

HDL = high-density lipoprotein; **NS** = not significant.

Table III. Description and incidence of adverse drug reactions (ADRs) in the overall study population

Adverse reaction	Patients with ADR		No. of ADRs
	n[a]	%	
Oedema	280	4.41	326
Flushing	158	2.48	177
Headache	113	1.78	121
Others[b]	298	4.69	398
Total no. of patients with ADRs	689	10.84	
Total no. of ADRs			1022
Total no. of patients	6354	100.00	

a Some patients reported more than one ADR.

b Includes all other ADRs that occurred, of which the most frequent (present in >2% of patients) were dizziness, cough, hypotension, tachycardia, skin rash and palpitations.

strategy that produced a marked reduction in SBP and DBP in the first month of treatment in patients with stage I (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and stage II hypertension (SBP 160–179 mmHg and/or DBP 100–109 mmHg), not controlled previously, in a routine clinical practice setting. This combination strategy is, therefore, consistent with current recommendations for hypertension management, which give priority to the prompt control of BP in order to reduce the risk of CV disease, particularly in the case of failure of previous strategies.[4]

The present study also shows the importance of simple therapeutic regimens, such as the fixed-dose enalapril/nitrendipine 10 mg/20 mg combination used in this study, for facilitating compliance and enhancing effectiveness.[7] Compliant patients experienced a significantly larger mean reduction in SBP and DBP than noncompliant patients from the beginning of treatment to the first month. These results suggest that appropriate therapeutic compliance influences the effectiveness of treatment from the very onset of therapy.

Analysis of high-risk patient subgroups (those aged >65 years or with diabetes, ISH or obesity) confirmed the difficulty of achieving BP control.[4] Nonetheless, evidence of the benefit of treatment with the enalapril/nitrendipine 10 mg/20 mg combination in older patients, regardless of whether they have ISH or they are diabetic or nondiabetic,[24] for reduction in the risk of stroke, CV disease and dementia[4,24] reveals that this strategy has a favourable therapeutic impact.

It should be noted that, although studies with an observational design do not allow a controlled, blinded comparison of the efficacy of different therapeutic strategies, the effectiveness results that are obtained provide a perspective on the use of the product in large populations that are similar to those seen in routine clinical practice.

The tolerability results of the present study highlight a substantially lower withdrawal rate because of adverse events (7.5%) than has been documented in clinical trials of both components of the enalapril/nitrendipine 10 mg/20 mg combination as monotherapy (20.2% with enalapril

Table IV. Description of age, degree of blood pressure (BP) response and control, and the presence of adverse reactions in different subgroups of patients analysed

Variable	Age >65 y (n = 2658)	Diabetes mellitus (n = 1521)	ISH (n = 731)	Obesity (n = 1762)
Age (y) [mean (SD)]	72.7 (5.4)	65.4 (9.4)	69.5 (10.4)	63.1 (10.4)
Males [n (%[a])]	1101 (41.5)	632 (41.6)	294 (40.3)	706 (40.1)
Patients with BP response[b] at 3-month visit [n (%[a])]	1451 (70.8)	705 (61.7)	308 (55.3)	963 (72.0)
Patients with BP control[c] at 3-month visit [n (%[a])]	740 (36.1)	534 (46.8)	246 (44.2)	487 (36.4)
Patients with adverse reactions [n (%[a])]	328 (12.3)	176 (11.6)	96 (13.1)	228 (12.9)

a Percentages calculated from the total number of patients in each group for the degree of control and response (2050, 1142, 557 and 1338, respectively).

b Defined as having controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients) or a reduction of ≥20 mmHg in systolic BP and ≥10 mmHg in diastolic BP.

c Defined as having controlled BP (<140/90 mmHg for nondiabetic patients or <130/85 mmHg for diabetic patients).

ISH = isolated systolic hypertension.

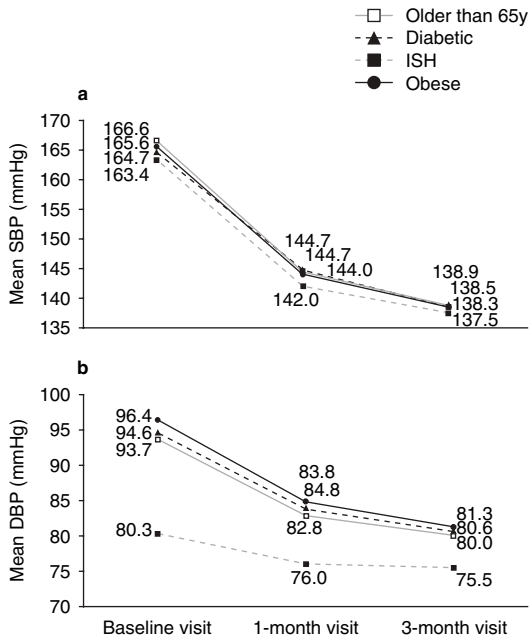

Fig. 5. Evolution of systolic blood pressure [SBP] (**a**) and diastolic blood pressure [DBP] (**b**) in the different subgroups of patients analysed. **ISH** = isolated systolic hypertension.

and 15.0% with nitrendipine).[36] The overall incidence of adverse events (10.8%) was also lower than that obtained with enalapril and nitrendipine as monotherapy,[17] and lower than that obtained in a previous clinical trial with the same combination of enalapril/nitrendipine 10 mg/20 mg (19.8%), which was also conducted in Spain.[33] The incidence of oedema (4.4%) was also lower than reported in this previous clinical trial (11.1%) and the incidence of cough (0.8%) was particularly low. These results support the tolerability of enalapril/nitrendipine 10 mg/20 mg, even though they must be interpreted in light of the spontaneous adverse event reporting system used in the present study. In addition, the neutral effect of the fixed-dose enalapril/nitrendipine 10 mg/20 mg combination on the biochemical parameters investigated underlines the benefits of using this strategy in patients with hypertension and carbohydrate and lipid metabolism disorders.[4] The statistically significant reduction in glucose values in patients should be emphasized, particularly as it is consistent with results observed in previous studies of diabetic hypertensive patients.[34] This relevant clinical effect implies an important difference between enalapril/nitrendipine 10 mg/20 mg and other combinations that included a diuretic, as has been pointed out in previous studies such as the STAR (Study of Trandolapril/Verapamil SR and Insulin Resistance) study.[35]

Although tolerability is evaluated in observational studies on the basis of spontaneous reporting by patients and questioning by the investigator, the large sample studied and its representativeness of the general population allow for the identification of adverse events not detected previously in the context of strictly screened populations, as found in clinical trials. The tolerability results of the present study did not reveal adverse events that have not been communicated previously with use of ACE inhibitors or CCBs, or any increase in incidence that compromises the benefit/risk profile of a fixed-dose enalapril/nitrendipine 10 mg/20 mg combination.

The present study has several limitations. A total of 1344 patients (21.1%) were excluded from the effectiveness analysis and this high percentage must be considered a limitation to interpretation of the effectiveness results. Likewise, the study did not include a control group. Furthermore, different groups of patients were assessed jointly for the effectiveness analysis, and this may have biased the overall effectiveness results. However, this limitation was partially offset by performance of additional analysis on four subgroups of patients (those aged >65 years, and those with diabetes, ISH or obesity).

Conclusion

Therapy with a fixed-dose enalapril/nitrendipine 10 mg/20 mg combination is effective in routine clinical practice for lowering BP and facilitating the achievement of the recommended goals for controlling hypertension, with a tolerability profile showing a favourable benefit/risk ratio.

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