Clinical experience with a low-dose fixed combination of perindopril plus indapamide in a primary-care setting: the PRETEND study

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PRETEND was a multicenter observational survey carried out in primary-care clinics across Spain. It was designed to determine general practitioners' perceptions regarding their clinical experience with the fixed low-dose combination of perindopril 2 mg plus indapamide 0.625 mg in everyday practice. A total of 3198 patients, mean age 62.4 ± 10.9 years, were included. Before combined therapy, blood pressure was 161.8 ± 13.0/94.6 ± 9.2 mmHg and after treatment it was 139.8 ± 12.1/82.9 ± 8.4 mmHg ($p < 0.001$). The blood pressure control rate increased from 1.1 to 38.7%. Most physicians considered the efficacy and tolerability of perindopril plus indapamide to be good or very good, and most patients were satisfied or very satisfied with the therapy.

Keywords: antihypertensive therapy, hypertension, indapamide, perindopril, perindopril plus indapamide, primary care

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In 1990, in a landmark observational analysis, MacMahon and colleagues demonstrated that lowering blood pressure (BP) is critical for reducing the risk of cardiovascular outcomes and preventing major coronary events [1]. Today, hypertension is recognized as one of the most common treatable diseases associated with significant cardiovascular morbidity and mortality. Current USA and European hypertension guidelines highlight the need to treat even small elevations of BP, particularly in high-risk patients such as those with diabetes and/or renal disease [2,3]. Whilst many clinical trials have focused on the early detection of hypertension and have documented some improvement in BP control rates, it remains a fact that overall BP management is relatively poor. Indeed, during long-term treatment, more than 50% of treated hypertensive patients have elevated BP and are at greater cardiovascular risk [4–8]. With regards to pharmacological intervention, it has been reported that usually approximately 50% of patients respond to monotherapy, although much lower rates have been observed [9], and with time this number decreases to 25% [10,11]. Combination therapy is required when monotherapy fails and in certain situations, such as treatment of patients with high-risk comorbidities (diabetes and/or renal disease), it may be the optimal first-line choice. Both the USA [2] and European guidelines [3] advocate low-dose combination therapy when patients fail monotherapy, rather than continuing to increase the dosage of a single agent. 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 compensatory responses [12]. In practice numerous antihypertensive combination regimens are currently available, and one of the most common is a fixed low-dose combination of an angiotensin-converting enzyme (ACE)-inhibitor plus a diuretic. Clinical studies have confirmed the antihypertensive efficacy and safety of low-dose ACE-inhibitor/diuretic combinations such as perindopril plus indapamide [12,13].

While randomized, clinical trials (RCTs) are clearly very important to benchmark the effectiveness and tolerability of therapeutic interventions in a controlled scientific manner, they do not always accurately represent 'real world' clinical practice [14–16]. RCTs are planned with a rigid design that reduces bias and ensures relatively high levels of compliance by patients and physicians; this in itself can result in better BP control in these studies (i.e., the protocol itself can have an impact on the results achieved) [16]. Observational studies provide an insight into drug efficacy and safety in a clinical practice setting when standards for compliance are possibly not as high as in RCTs, and patients are not monitored so routinely. Observational evidence provides a 'real life' insight into drug usage and this is invaluable in chronic diseases such as hypertension [17,18]. It is important to understand the effects of nonadherence to prescription instructions, the impact of adverse effects, lifestyle changes, as well as the lack of a positive effect of the drug *per se* on therapeutic efficacy/safety. Many observational studies have examined the effects of antihypertensive drugs in general practice from a clinical-outcomes and patient perspective, but information regarding the physicians' view of treatment with antihypertensive medication and its impact on disease management is limited.

Table 1. Clinical characteristics of the study population.

Age (years), mean ± SD	62.4 ± 10.9
Female, n (%)	1631 (51)
Abdominal obesity (male >102 cm; female >88 cm), n (%)	1887 (59)
Cardiovascular risk factors, n (%)	
Dyslipidemia	1842 (57.6)
Smoking	1270 (39.7)
Diabetes	838 (26.2)
Family history of premature coronary disease	582 (18.2)
Vascular disease, n (%)	
Peripheral artery disease	345 (10.8)
Coronary artery disease	281 (8.8)
Congestive heart failure	230 (7.2)
Advanced retinopathy	196 (6.1)
Renal failure (serum creatinine >1.5/1.4 mg/dl [male/female])	169 (5.3)
Stroke	154 (4.8)
Clinical data, mean ± SD	
Baseline systolic BP (mmHg)	161.8 ± 13.0
Baseline diastolic BP (mmHg)	94.6 ± 9.2

n = 3198.
BP: Blood pressure; SD: Standard deviation.

The objective of this observational study was to assess, in a primary-care clinical practice setting, the efficacy and tolerability of a fixed-dose combination of perindopril 2 mg plus indapamide 0.625 mg, from both a patient's and a physician's perspective.

Patients & methods

The 'Percepción de las Recomendaciones Establecidas para el Tratamiento antihipertensivo En relación con la Necesidad de utilización de bajas Dosis en combinación' (PRETEND) study was a multicenter survey undertaken in the primary-care setting throughout Spain. The survey comprised two parts:

- Part 1: general practitioners (GPs) were questioned regarding their knowledge, agreement with and application of the 2003 European Society of Hypertension and European Society of Cardiology (ESH/ESC) hypertension guidelines [3] with regards to the use of combined therapy to lower BP (submitted for publication separately);
- Part 2: each investigator was questioned regarding their experience with perindopril 2 mg plus indapamide 0.625 mg for treating six consecutive patients with mild-to-moderate essential hypertension.

Each investigator was questioned regarding their clinical experience in treating adult male or female outpatients (≥ 18 years) with mild-to-moderate essential hypertension and an active clinical history at the health centre. Treatment consisted of a fixed-dose combination of perindopril 2 mg plus indapamide 0.625 mg administered for at least 6 weeks, and in practice it was administered to three separate groups:

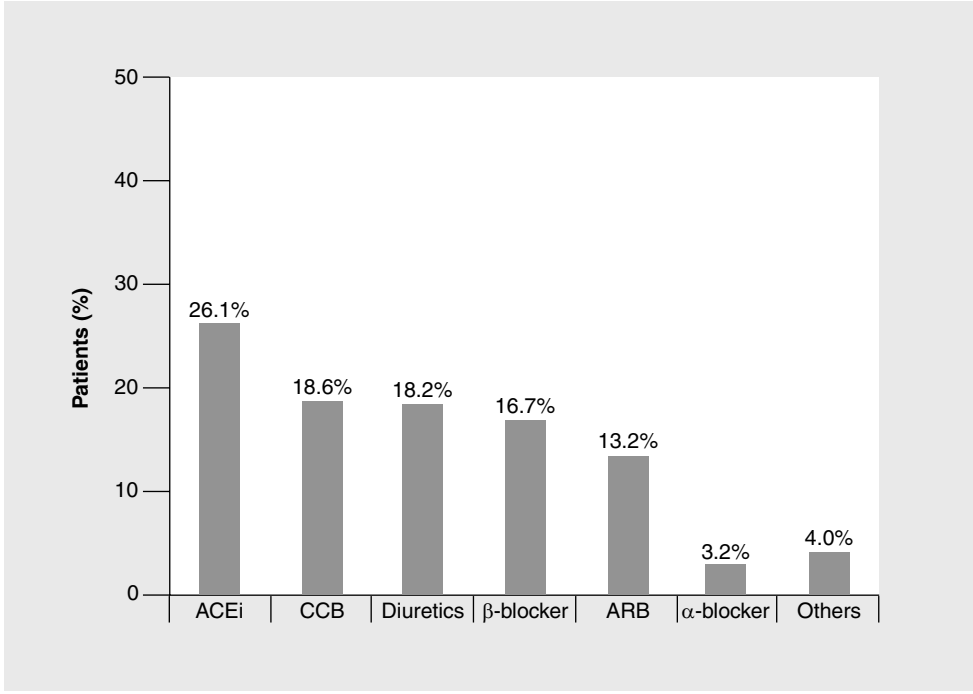
- As the first treatment for recently identified hypertensive patients
- As a substitute therapy for patients not responding to current treatment
- As add-on therapy to patients who achieved only a partial response to previous treatment

Only patients with BP measurements carried out according to international guideline recommendations were included in the study [19]. BP was considered to be controlled when measurements were below 140/90 mmHg (<130/80 mmHg for diabetics) [3]. The GPs who agreed to take part applied a nonprobabilistic sampling process to select six consecutive patients who complied with the inclusion criteria. Biodemographic data, BP values before and after the use of perindopril plus indapamide, previous antihypertensive drugs, the main reasons for prescribing the fixed-dose combination, and all concomitant treatments were recorded. Patients were questioned regarding their degree of satisfaction with the use of the combined therapy.

Statistical analysis

Various statistical tests were performed depending on the nature of variables being compared. The χ^2 test was used to analyze the relationship between categorical variables. However, when more than 20% of the cells had an expected frequency lower than five the Fisher's exact test was used. Comparison of continuous variables between groups was performed using the Student's t-test. Database recording was subjected to internal consistency rules and ranges to control inconsistencies/inaccuracies in the collection and tabulation of data (SPSS version 12.0, Data Entry). All data were recorded and analyzed independently to prevent bias. Results are presented as mean ± standard deviation unless stated otherwise and a p-value of less than 0.05 was considered statistically significant.

Figure 1. Previous antihypertensive treatments (as monotherapy or in combination regimens).



ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blockers.

Results

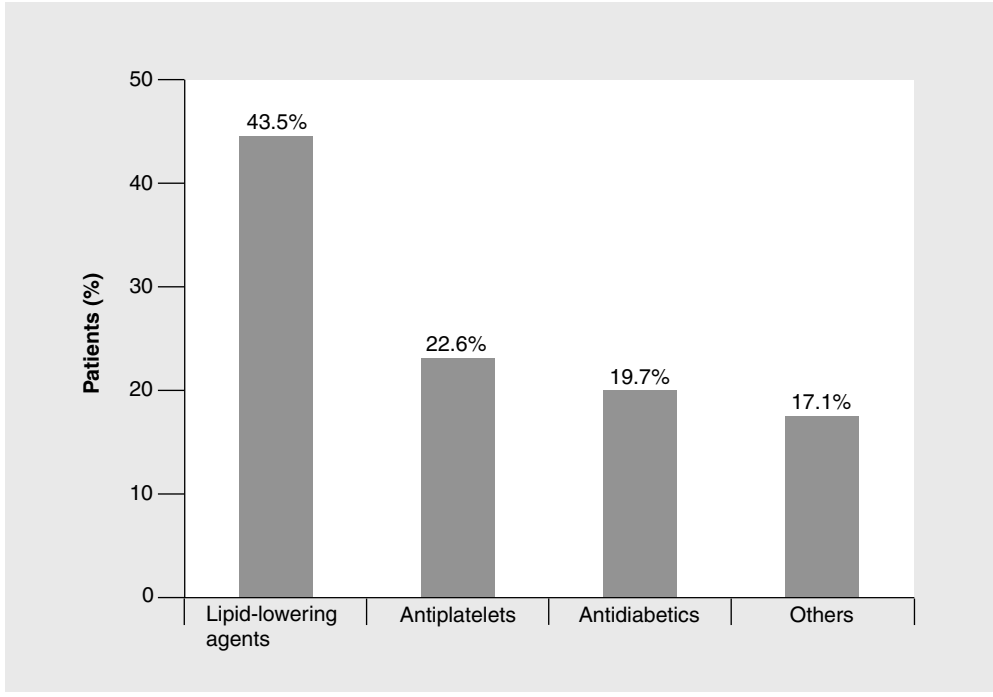
A total of 621 primary-care physicians participated in the study, which was performed from October 2005 to March 2006. They had an average of 20.8 ± 7.5 years' clinical experience: 73.3% worked in an urban environment and 26.7% in a rural setting. More than a half of the respondents (59.8%) performed at least 40 consultations per day.

A total of 3198 patients were included in the study (mean age 62.4 ± 10.9 years; 51% women). The clinical characteristics of the study population are presented in **Table 1**. The most frequently associated risk factors were abdominal obesity (59%), dyslipidemia (57.6%) and diabetes (26.2%). Peripheral arterial disease was documented in 10.8% of the population.

The low-dose fixed combination of perindopril plus indapamide was used in 37.6% as the first-line treatment for high BP. In 38.3% it was used as a substitute for a previous therapy (in 85% because of poor BP control and in 15% because of poor tolerability). In the final 24.1%, it was added to a treatment regimen that was not controlling BP adequately. In patients who had previously been treated with antihypertensive medication, the drugs most commonly administered were ACE-inhibitors (26.1%), calcium channel blockers (18.6%) and diuretics (18.2%) (**Figure 1**). Approximately two-thirds of patients (69.4%) were receiving concomitant medications: lipid-lowering drugs (43.5%), antiplatelet drugs (22.6%) and antidiabetic therapy (19.7%) being the most frequently administered (**Figure 2**).

Prior to perindopril plus indapamide being administered, mean systolic BP (SBP) was 161.8 ± 13.0 mmHg and diastolic BP (DBP) 94.6 ± 9.2 mmHg. Following treatment with the low-dose combination, BP was reduced to 139.8 ± 12.1/82.9 ± 8.4 mmHg, respectively (both $p < 0.001$). SBP was reduced by 22.0 mmHg (95% CI: 21.6–22.5) and DBP 11.7 mmHg (95% CI: 11.5–12.1). BP changes are shown in **Figure 3**. The degree of BP control improved from 1.1–38.7% with combined therapy. SBP control increased from 3.1–44.1% and DBP from 20.5–77.5% (**Figure 4**). The BP control rates of the study population according to the reasons for prescribing the low-dose combination (as first-line therapy, as substitutive or as additional therapy) are shown in **Table 2**. Prior to perindopril plus indapamide being administered, BP control rates for the total population, and the individual subgroups based on reasons

Figure 2. Concomitant treatments.



for prescribing the combination, were clearly very low. The improvement following the introduction of low-dose perindopril plus indapamide was both clinically and statistically ($p<0.001$) significant (**Figure 4 & Table 2**).

Most GPs (88.8%) considered the efficacy of combined therapy as good or very good (44.7% very good). With regards tolerability, 96.2% of GPs considered it good or very good (50.3% very good). In total, 92% of patients were satisfied or very satisfied with combined therapy.

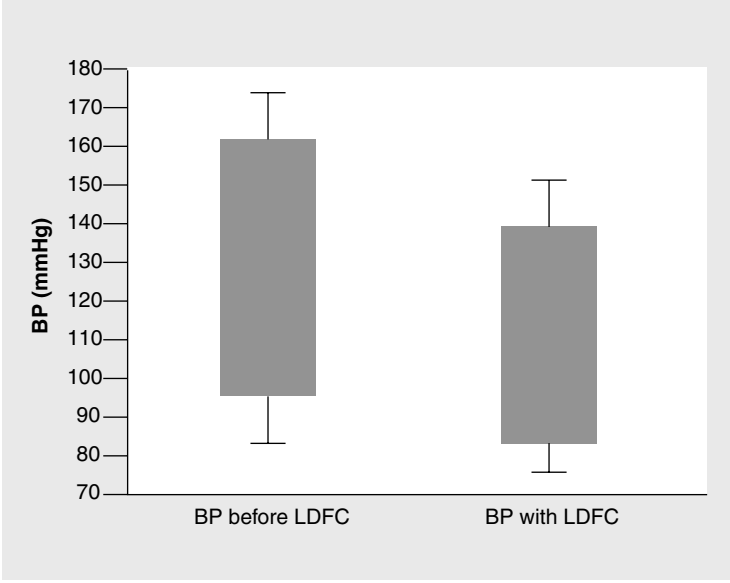
Discussion

It has been shown that observational studies provide an insight into drug efficacy and tolerability that can differ from findings obtained in RCTs [16]. General practice observational surveys such as this have their limitations, since they are based on active questioning and physicians may tend to overestimate the results obtained. However, they provide very useful insight into physician and patient behavior and response that cannot be obtained from RCTs. In chronic diseases such as hypertension it is important for the physician to have as much information as possible regarding the posology, efficacy, tolerability/safety and compliance of treatment, which is generally long term. The aim of the current observational survey was to assess the perception of patients and physicians, and the level of BP control, in a large cohort of Spanish patients with mild-to-moderate hypertension. The survey involved a wide range of physicians across Spain working in very busy general practice with its attendant high workload (e.g., 60% of physicians attended at least 40 patients per day).

Combination therapy with an ACE-inhibitor plus diuretic has been shown to produce BP-control rates as high as 80% in patients with mild-to-moderate hypertension [11]. In addition, a fixed combination of the two drugs helps improve compliance by reducing the number of tablets that need to be taken [20]. Based on the findings from RCTs and observational studies, low-dose perindopril plus indapamide has been shown to be an effective antihypertensive regimen [20–30]. For example, in the STRATHE trial, a low-dose combination of perindopril plus indapamide produced normalization of BP in significantly more patients compared with 'sequential monotherapy' (involving a β-blocker, an angiotensin-receptor blocker and then a calcium channel antagonist) or a 'stepped-care' strategy (involving an angiotensin-receptor blocker and a diuretic). Furthermore, the improvement in efficacy was not associated with an increase in adverse effects [12].

In the current study, a fixed low-dose combination of perindopril plus indapamide was associated with a higher rate of BP control than

Figure 3. Changes in blood pressure.

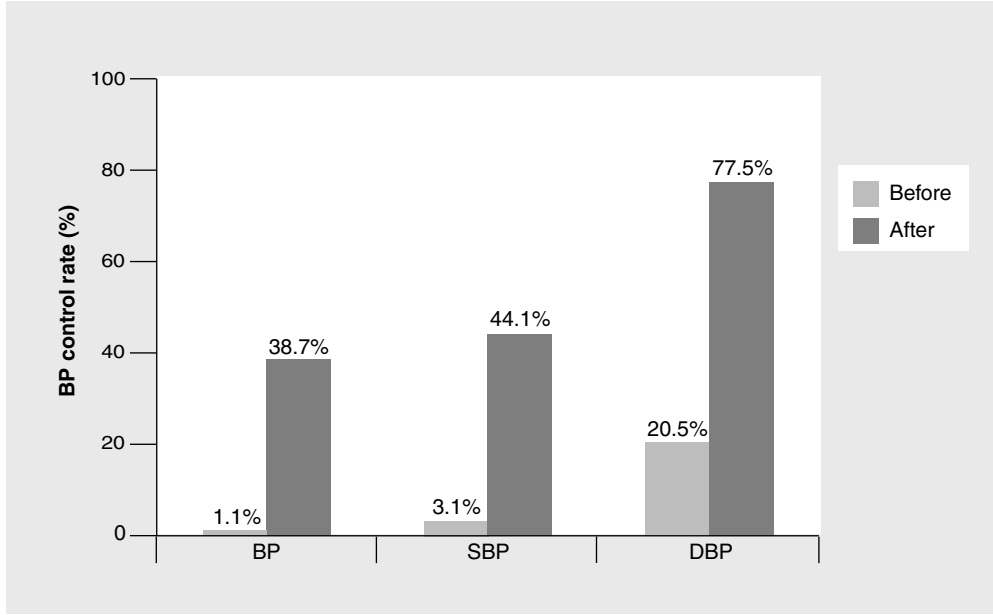


BP: Blood pressure; LDFC: Low-dose fixed combination.

previous therapy, and it was also notable that high rates were documented in patients who received the combination as the first line of treatment. Interestingly, the most frequently administered previous antihypertensive therapies in these patients, and which failed to control BP in most cases, were ACE-inhibitors, calcium channel antagonists and diuretics. A recent study involving 12,954 hypertensive patients treated in primary care (a high proportion on monotherapy) showed that only approximately a quarter achieved good BP control, and this rate was even worse in patients at high risk, such as those with diabetes [31]. With usual care, monotherapy provides effective BP control in no more than approximately 30–40% patients with mild-to-moderate hypertension. There is increasing evidence showing that the use of low-dose combination therapy, as first-line treatment or as add-on therapy, facilitates much greater levels of BP control [2]. However, the results of our survey indicate that despite guidelines that clearly define when to use combination therapy, a significant proportion of physicians do not follow this advice, and this almost certainly helps explain the poor BP-control rates recorded in daily clinical practice in Spain.

The effectiveness of drugs used to control BP is a balance between BP-lowering efficacy and long-term tolerability. The latter is important as it appears to be one of the main causes for poor compliance. The situation is made more difficult by the fact that polypharmacy is common in patients with hypertension and this increases the risk of adverse effects occurring. Thus, the use of well-tolerated drugs may result in better patient adherence and, almost certainly, better BP control [32–34]. In Spain, it has been estimated that almost a third of the hypertensive population are noncompliant [35].

Figure 4. Blood pressure, diastolic and systolic blood pressure control rates.



BP: Blood pressure; DBP: Diastolic blood pressure; SBP: Systolic blood pressure.
*p < 0.001 between before use of low-dose fixed combination and after it.

Table 2. BP control rates of the study population and according to the reasons for the use of the low-dose fixed combination of perindopril plus indapamide

	BP (mmHg)	BP control rates (%)	BP control rates (%)		
			First therapy group	*Substitute group*	*Additional therapy group*
Before treatment with LDFC	BP<140/90	1.1	0	2.4	0
	SBP<140	3.1	1.8	3.8	1.8
	DBP<90	20.5	18.6	23.5	20.1
After treatment with LDFC	BP<140/90	38.7	41.9	37.0	36.2
	SBP<140	44.1	49.1	41.6	40.6
	DBP<90	77.5	78.4	78.4	76.7

BP: Blood pressure; DBP: Diastolic blood pressure; LDFC: Low-dose fixed combination; SBP: Systolic blood pressure.

Therefore, a good tolerability profile is clearly very important for antihypertensive medications so as to facilitate good compliance. Our results show that the majority of patients treated with perindopril plus indapamide reported a high degree of satisfaction with the treatment, and this helps to explain the good efficacy and tolerability profile exhibited by the combination.

Conclusion

In conclusion, the PRETEND study demonstrates a high degree of satisfaction of GPs in Spain with the use and effectiveness of a fixed low-dose combination of perindopril plus indapamide in daily clinical practice. Most patients were also satisfied or very satisfied with the use of this fixed combination.

Future perspective

It is of growing concern that despite the introduction of new and very potent antihypertensive drug classes, hypertension remains poorly controlled in clinical practice. Results from RCTs clearly do not always translate into effective BP control in the community. In the future, well-designed 'practice studies' will increasingly augment findings from RCTs, and it is also our view that low-dose combination therapy will become more popular, as it will help increase compliance, reduce adverse effects and improve overall effectiveness. Indeed, clinical findings have recently been published from the ADVANCE study, which provide further support for low-dose combination therapy in terms of improving cardiovascular protection in a high-risk population (diabetics) [36].

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Executive summary

- Despite many clinical trials reporting excellent responses to antihypertensive therapy, it remains a fact that in everyday clinical practice, overall blood-pressure (BP) control is poor.
- Observational studies in everyday practice remain the best means of determining the impact of compliance, tolerability, concomitant therapies, and so on, on BP control.
- In this study, performed in Spain, a low-dose combination of perindopril plus indapamide significantly increased the percentage of blood-pressure responders (1.1% to 38.7%).
- Most general practitioners (~90%) considered the efficacy of perindopril plus indapamide to be good or very good.
- In total, 92% of patients were satisfied or very satisfied with the combination therapy.

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