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Persistence on Treatment and Blood Pressure Control with Different First-Line Antihypertensive Treatments: A Prospective Evaluation

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We enrolled 347 hypertensive patients, randomly allocated them to different first-line treatments, and followed-up for 24 months. Persistence on treatment was significantly higher in patients treated with ARBs (68.5%) and ACE inhibitors (64.5%) vs. CCBs (51.6%), β-blockers (44.8%), and diuretics (34.4%). No ARB, ACE inhibitor, β-blocker, or diuretic was associated with a greater persistence in therapy as compared with the other molecules used in each therapeutic class. The rate of persistence was significantly higher in patients treated with lercanidipine vs. other CCBs (59.3% vs. 46.6%). Systolic and diastolic BP decreased more in patients treated with ARBs (-11.2/-5.8 mmHg), ACE inhibitors (-10.5/-5.1 mmHg), and CCBs (-8.5/-4.6 mmHg) when compared to β-blockers (-4.0/-2.3 mmHg) and diuretics (-2.3/-2.1 mmHg).

Keywords hypertension, antihypertensive drugs, persistence, blood pressure

Introduction

Pharmacological therapy with single or multiple antihypertensive drugs can reduce elevated blood pressure values (BP) in ≥80% of hypertensive patients (1), where it also prevents the morbidity and mortality attributable to hypertension (2,3). However, nearly three-fourths of hypertensive patients worldwide actually do not achieve a satisfactory blood pressure according to guidelines (4). This indicates that the actual benefits of blood pressure lowering treatment are less than predicted with a persistently elevated morbidity and mortality (5) and an increase in health care costs (6) associated with hypertension.

A major (and modifiable) reason for lack of BP control is failure by patients to take the medications as prescribed (7). The appropriate use of medications includes both

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compliance (taking medications at the prescribed intervals and dosing regimen) and persistence (continuous use of medications for the specified treatment time period). In the case of hypertension, both compliance and persistence should be maintained life-long. Poor compliance and persistence with antihypertensive medications is one likely explanation for the discrepancy between the efficacy of drug treatment established through clinical trials and the results observed in clinical practice (7). Compliance to antihypertensive treatment is influenced by many factors, including tolerability of the medication, complexity of the drug regimen, cost of the therapy, characteristics of the medical system and the physician, and the presence of symptoms associated with the disease (8,9).

Previous studies assessing determinants of the persistence/discontinuation of drug therapy were often limited by small sample size, short duration of follow-up, and lack of generalizability to the population treated in community-practice settings. Indeed, most of those studies were conducted as part of large-scale clinical trials (10) or involved a cohort of Medicaid and Medicare beneficiaries (11) or armed forces personnel (12). In many instances, the studies were retrospective and predated the introduction of the newest classes of better tolerated antihypertensive agents, such as the angiotensin II receptor antagonists (ARBs) (13). This can have important clinical implications according to the results of a retrospective study involving more than 12,000 patients and showing that the continuation of the initially prescribed therapy is significantly higher in patients treated with ARBs and ACEIs (14). This was confirmed by the results of a more recent analysis of prescription records of two additional cohorts of Canadian (15) and Italian (16) hypertensive patients.

However, none of these studies has prospectively investigated the problem of persistence on treatment with the different classes of antihypertensive drugs or assessed whether the differences in persistence on treatment might directly influence the extent of BP control in clinical practice. Furthermore, to the best of our knowledge, no data has been published about the possibility that differences in the long-term persistence on antihypertensive treatment can be detected among drugs with a different tolerability profile within the same class. This could be a relevant problem for some families of antihypertensive drugs such as the dihydropyridines CCBs, which have evolved from the first generation, short-acting compounds, to agents with long plasma and receptor half-life with a more favorable clinical profile and a better compliance (17).

The main aim of this study was to evaluate prospectively the long-term persistence on antihypertensive treatment of different classes of first-line antihypertensive drugs prescribed as monotherapy in patients with mild-to-moderate hypertension. We also investigated whether a difference in the persistence on treatment influenced BP control and if it could be detected within the class of dihydropyridine CCBs by comparing the third-generation CCB lercanidipine with other compounds of the same family.

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Methods

The study was carried out in a cohort of 347 uncomplicated mild-to-moderate hypertensive patients consecutively referred to our Hypertension Clinic for a clinical evaluation of their hypertension. The following patient characteristics have been used as inclusion criteria:

1. age between 18 and 80 years,
2. no antihypertensive treatment during the last six months,
3. no history of major CV diseases (e.g., previous stroke, myocardial infarction, heart failure, major arrhythmias) requiring complex pharmacological treatment,

4. no history of intolerance/hypersensitivity for nor resistance to specific classes of antihypertensive drugs,
5. no compelling indications for a specific class of antihypertensive drugs according to ESC-ESH Guidelines (18), and
6. capacity to comply with the study protocol.

Patients have been randomly allocated to treatment with one of the following classes of antihypertensive drugs: ACE inhibitors, ARBs, CCBs, diuretics, and ß-blockers, as well as to a single-blind study design. Patients treated with CCBs have been randomly stratified to lercanidipine in comparison to any other CCB according to a 1:1.5 proportion. No methodological constraint was applied to the choice of CCBs other than lercanidipine. Before inclusion into the study, all patients underwent a complete clinical cardiovascular examination including blood pressure (BP) measurement and standard 12-lead electrocardiogram. Resting supine and standing systolic and diastolic BP were measured by mercury sphygmomanometer to the nearest 2 mmHg. The mean of three consecutive BP determinations at 1-min intervals was recorded. An identical procedure was used for the assessment of heart rate. Secondary causes of hypertension have been excluded with clinical and biochemical evaluation according to a standardized protocol including determination of plasma renin activity, plasma aldosterone, renal function, and electrolyte balance. Patients have been followed-up at a six-month interval and for a cumulative period of 24 months from randomization. Blood pressure and heart rate have been measured in occasion of each control according to the baseline procedure.

At the same time-interval, any change in the initially prescribed therapy and the relative causes were reported in the case report form. Persistence with antihypertensive treatment has been simply defined as the continued use of a medication or medications according to initial prescription (i.e., no discontinuation) over the period of follow-up. Persistence has been determined as a dichotomous variable at the specified time-intervals of the protocol. The proportion of patients persistent at any scheduled interval and the average duration of persistence (i.e., the average time from treatment initiation to discontinuation) have been then calculated. In patients where the treatment was discontinued before the end of follow-up, persistence has been quantified as the time-interval between randomization and treatment discontinuation. If no discontinuation occurred, persistence has been censored at the end of the follow-up. In those patients who did not show a reduction of systolic BP values $\geq 10\%$ by monotherapy after six months of treatment, a second drug has been added. For the purpose of the data analysis, they have been considered according to their initial treatment allocation. Patients who needed the addition of a third drug to control BP have been excluded from the study.

The study protocol has been approved by the Ethics Committee of the St. Orsola-Malpighi Hospital, and all patients provided written informed consent to participate before inclusion in the study.

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Outcome Variables

The main study outcome was the proportion of patients who persisted with the initially prescribed antihypertensive treatment in each drug class and over the cumulative period of 24 months. We considered as "not persistent" all patients who withdrew from treatment as well as those who switched to a different class of drugs. Secondary objectives were the extent of systolic and diastolic BP decrease in the different subgroups of patients, as well

as a comparison between the persistence on treatment between patients treated with lercanidipine vs. other first-line antihypertensive drugs, including the other CCBs.

Statistical Analysis

Results are expressed as means ± SD. Statistical analysis was carried out by using a SPSS statistical package (Version 9.6.2 for Windows; SPSS Inc., Chicago, Illinois, USA). The study sample size was calculated according with the hypothesis of a difference between ARBs and diuretics of 25% in terms of persistence on treatment, with an α-error of 0.05 and a power of the study of 80%. Drop-out rate was estimated at 10%. The data have been analyzed according to an intention-to-treat approach by considering any patients according to its initial drug allocation. Observed differences in the continuation of initial therapy were compared between ARBs and the antihypertensive drug class having the next highest rate of continuation using unadjusted, two-sided, chi-square tests and an α level of 0.05. The odds ratio (OR) for continuation with the initial drug therapy was then calculated by unconditioned logistic regression using the same statistical package. Potential predictors of persistence tested in the logistic regression model included age (≥65 and <65 years), sex, antihypertensive drug class (ARBs, ACE inhibitors, CCBs, β-blockers, thiazide diuretics), and dosing frequency (once or twice per day). Confidence intervals (CIs) for the estimated ORs, and significance tests for the differences from the null value were calculated using estimated standard errors.

Results

The baseline characteristics of the study population (n=347) and the distribution of first-line antihypertensive drugs are reported in Table 1. In all, 196 patients were male and 151 were female; the mean age was 58±6 and 62±5 years, respectively. No differences have been observed among the different subgroups with regard to age, gender distribution, and baseline systolic and diastolic BP. Thiazide diuretics and non-lercanidipine CCBs were equally prescribed as the initial drug in 18.1% of the population, followed by ACE inhibitors and β-blockers (17.5%) and ARBs (15.2%). Lercanidipine was prescribed as first-line antihypertensive therapy in the 13.2% of patients. About 80% (78.1%) of the patients have been treated with monotherapy for the whole period of observation. Combination treatment was used in a small proportion of patients enrolled in the study (n=15/347) without significant differences among the various subgroups (see Table 1), number of patients treated, antihypertensive drug distribution, or drop-in rated (data not shown). These patients were those defined as non-responders to monotherapy for experiencing a systolic blood pressure reduction of less than 10% with a single drug.

After 24 months, the percentage of subjects continuing their initial ARB (68.5%) and ACE inhibitor (61.5%) medication was higher than the percentage of those continuing the treatment with CCBs (51.6%, $p < 0.05$), β-blockers (48.8%, $p < 0.05$), and thiazide diuretics (34.4%, $p < 0.01$; see Figure 1). The main reason for drug discontinuation was the occurrence of adverse effects in more than two-thirds of the population, not achieving the primary end-point of persistence. In most cases (84%), the change in therapy was decided in agreement with the patient general practitioner or with other colleagues, while the 16% of patients changed their therapy without discussing it with specialists of our center. The main duration of persistence with treatment was 20.3±9 months for ARBs, 18.7±8 months for ACE inhibitors, 17.1±9 months for CCBs, and 15.8±8 and 14.1± 9 months for ß-blockers and thiazide diuretics, respectively ($p < 0.005$ for trend). No ARB, ACE inhibitor,

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Table 1
Baseline characteristics of the studied population

	Diuretics	ß-blockers	ACEI	ARB	CCB	Lercanidipine	Overall
Number of patients	63	61	61	53	63	46	347
Age (yrs)	59.1 ± 5	59.7 ± 6	59.6 ± 5	58.9 ± 6	59.3 ± 6	59.4 ± 5	59.4 ± 6
Age > 65 yrs (%)	21(33.3)	19 (31.1)	22 (36.0)	17 (32.0)	25 (39.7)	18 (39.1)	122 (35.1)
Gender (M/F)	36/27	34/27	32/29	30/23	38/25	26/20	206/141
SBP (mmHg)	156 ± 15	157.2 ± 13	152.5 ± 12	154.3 ± 13	153.3 ± 12	153.8 ± 12	154.1 ± 12
DBP (mmHg)	99.3 ± 9	100.2 ± 7	98.7 ± 8	99.1 ± 7	97.4 ± 7	98.1 ± 7	99.1 ± 7
Heart rate (b/min)	78 ± 3	77 ± 5	78 ± 5	76 ± 4	79 ± 5	78 ± 5	78.2 ± 4
Combination therapy (n, %)	2 (3.1%)	3 (5.0%)	3 (4.9%)	3 (6.1%.)	3 (4.7%)	1 (2.1%)	15 (4.3%)

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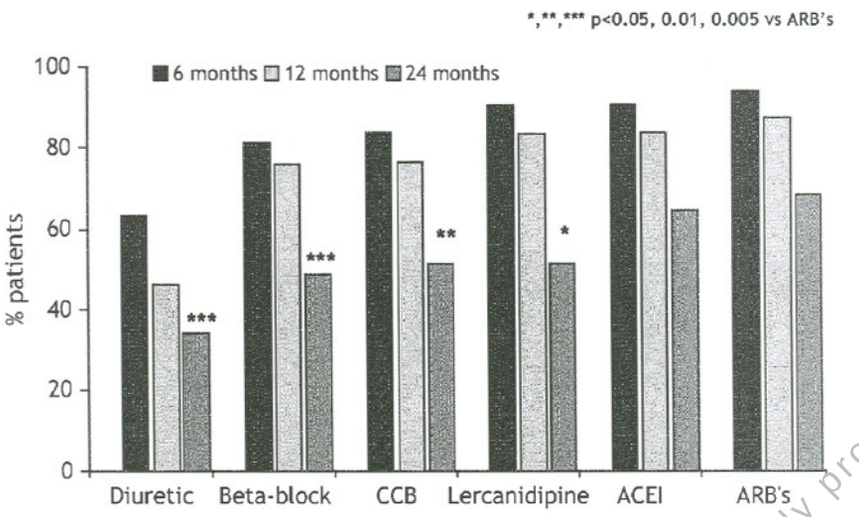

Figure 1. Rate of persistence on treatment after 6, 12, and 24 months in different subgroups of patients treated with ARBs, ACEIs, CCBs, lercanidipine, ß-blockers, and diuretics.

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β-blocker, or diuretic was associated with a higher persistence in therapy as compared to the other molecules used in each therapeutic class. Among the subgroup of patients treated with CCBs, the rate of stay-on-therapy was higher in those treated with lercanidipine (59.3% vs. 46.6%, $p < 0.05$ vs. others CCBs).

In the logistic regression model of persistence on treatment, using ARBs as reference term, patients taking ACE inhibitors were more likely to continue their initial antihypertensive therapy (ACE inhibitors: OR=0.94, 95% CI: 0.79–0.99) followed by users of CCBs (OR=0.76; 95% CI: 0.54–0.85), β-blockers (OR=0.67; 95% CI: 0.57–0.79), and thiazide diuretics (OR=0.56; 95% CI: 0.38–0.84). Patients treated with lercanidipine (OR=0.84, 95% CI: 0.61–0.88) were more likely to persist on treatment than patients taking other CCBs (OR=0.70; 95% CI: 0.51–0.79). There was a clinically uncertain but statistically significant relationship between female sex and continuation of the initial therapy (OR=1.08; 95% CI: 1.02–1.15). Age ≥ 65 years was associated with higher persistence (OR=0.79; 95% CI: 0.74–0.84), while the prescription of drugs requiring multiple doses increased the rate of discontinuation when compared to once-daily dosing (OR=1.40; 95% CI: 1.29–1.52).

The decrease of systolic and diastolic BP in response to treatment was largely proportional to the rate of persistence on treatment and greater in patients treated with ARBs, ACE inhibitors, and CCBs (see Figure 2). The difference was clearly enhanced in those patients where the initial treatment was not replaced by a different antihypertensive drug after discontinuation (see Figure 3). No ARB, ACE inhibitor, β-blocker, or diuretic was associated with a higher BP control as compared to the other molecules used in each therapeutic class. The treatment with lercanidipine was associated with a trend toward a better BP control vs. other CCBs with a difference that achieved a statistical significance after 24 months of treatment.

Discussion

The results of the present study confirm that the rate of persistence on initial antihypertensive treatment is prospectively higher for hypertensive patients treated with ARBs and

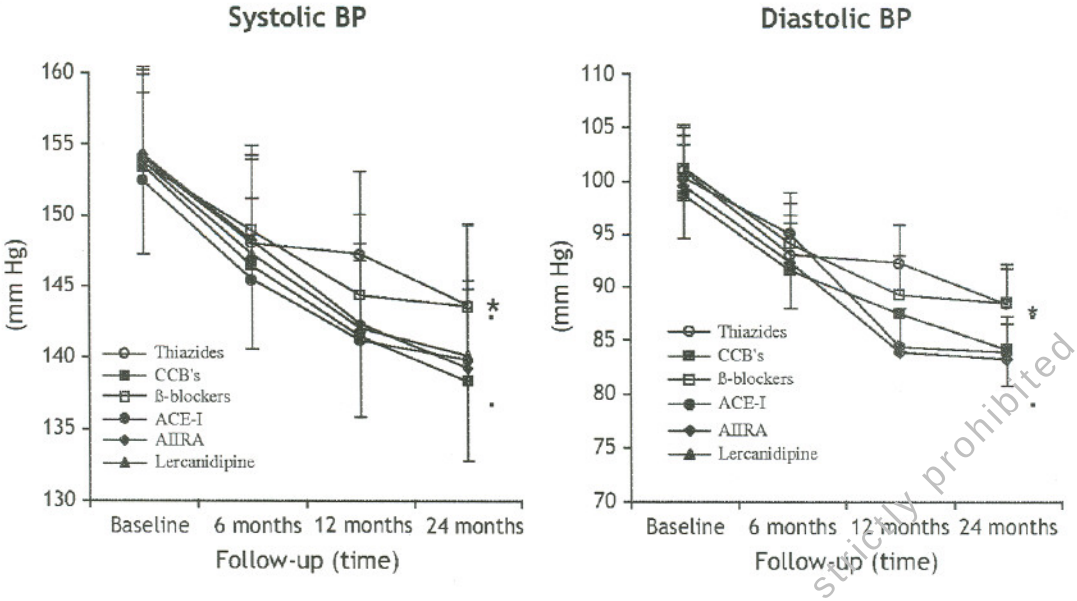

Figure 2. Systolic blood pressure decrease over 24 months in the overall population of patients (n=347) initially allocated to the different classes of antihypertensive drugs.

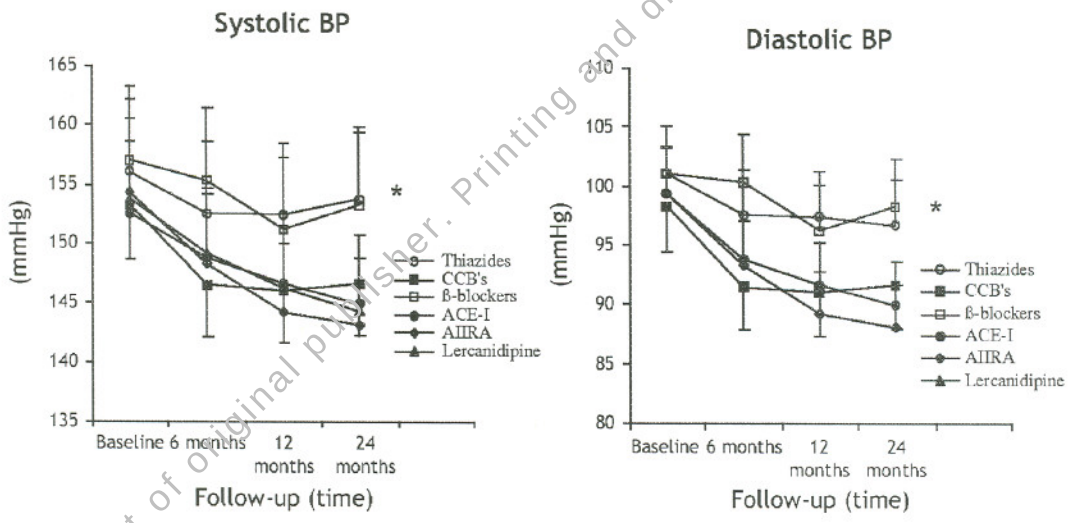

Figure 3. Systolic blood pressure decrease over 24 months in the selected population of patients allocated to different drug classes and not replacing the antihypertensive treatment after withdrawal.

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ACE inhibitors as first-line drugs. The extent of persistence on treatment might significantly differ within patients treated with compounds belonging to the same class of drugs but bearing a different tolerability profile (e.g., calcium-channel blockers). In addition, the study supports the evidence that the extent of persistence on treatment influences the clinical outcome of antihypertensive therapy with a larger blood pressure decrease in those patients treated with drugs, leading to a higher rate of stay-on-therapy.

The present findings are in agreement with previously published data demonstrating that the highest rate of long-term (24 months) compliance to antihypertensive therapy can be achieved in patients treated with drugs inhibiting the renin-angiotensin system and

calcium-channel blockers (14,15). Conversely, Jones et al. (13) analyzed the United Kingdom MediPlus primary care database and excluded any significant difference in the six-month rate of continuation in patients treated with the four major classes of antihypertensive drugs (i.e., thiazide diuretics, beta-blockers, calcium antagonists, and ACE inhibitors). Unfortunately, most of the available data are retrospective in nature (14,15) or based on a short period of observation (13) and do not allow any definite conclusions about the differences in persistence with the antihypertensive treatment in clinical practice. Some prospective evidence might be achieved by the analysis of data collected in clinical trials that usually describe a rate of persistence higher than those reported by the present study, ranging from 80–90% over a period of 3–5 years (19,20). However, large-scale clinical trials usually tend to overestimate the rate of persistence on antihypertensive treatment because of selection bias and behavior reinforcement; consequently, their results can not be directly applied to clinical practice. The results of the present study have been achieved in a sample of relatively unselected hypertensive patients, treated in agreement with the European Guidelines for Hypertension management (18), and describe a situation more comparable to the real setting of daily clinical practice. Of course, our data also could somewhat overestimate the persistence rate in the "real world," because we excluded those patients with a known resistance to a specific antihypertensive drug class; however, this reproduces the behavior of the physician in the everyday clinical practices, and the study was carried out in a specialist center (with the consequent different psychological effect on the patient).

Interestingly, our results confirm that the rate of stay-on-therapy is higher for the patients treated with the better tolerated antihypertensive drugs (e.g., ARBs, ACE inhibitors). This is in agreement with the clinical observation that for many patients, the worsening of the quality of life that follows the use of antihypertensive medications is even more disturbing than the symptomless elevation of blood pressure and might result in the discontinuation of poorly tolerated drugs. We also suggest the possibility that a difference in the tolerability profile among compounds belonging to the same class of antihypertensive drugs can differently influence the patient's persistence on treatment. In particular, we specifically tested this hypothesis only within the population of patients with CCB treatment, where a greater persistence on therapy has been observed in those subjects treated with lercanidipine. This is in agreement with some consistent observations demonstrating a better tolerability profile of lercanidipine when compared with other drugs of the same class (21,22). We did not investigate the same hypothesis within the other classes of antihypertensive drugs, where the presence of possible differences among various compound cannot be ruled out.

Our findings suggest the importance of persistence on treatment for the management of hypertension. In particular, the higher the proportion of patients who persist on treatment, the greater the blood pressure decrease in response to antihypertensive drugs. This supports the hypothesis that the overall impact of the blood pressure-lowering treatment in clinical practice may actually result from the interaction between the absolute antihypertensive effect of drugs and their capacity to positively promote the persistence on treatment. In the hypertensive cohort of the Brisighella Heart Study, the subject proportion who achieved effective blood pressure control over time was directly proportional to the use of ACE inhibitors as first-line drugs and inversely related to the prescription of diuretics (23). Better blood pressure control was associated with a lesser rate of major CV events, including coronary artery disease and stroke. Unfortunately, no information on compliance to treatment has been collected in the Brisighella study, whose interesting results require additional confirmation in other investigational settings.

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We are also aware of some limitations of this study. First, we assessed the compliance to treatment rate only indirectly as well as the prescribed treatment discontinuation rate, and we do not have any specific information about prescription filling or pill count. However, the study was aimed at investigating the extent of persistence on treatment in the "real world," and for this reason, we have decided to exclude from the protocol any measure of drug compliance and to focus on the rate of discontinuation as measure of "clinical" compliance. A further limitation is represented by the fact that the study has separately considered only one calcium-channel blocker (lercanidipine) to support the hypothesis that the persistence on treatment might significantly differ among compounds belonging to the same class. The reason for such a choice was in the large amount of data that suggest a measurable difference between the tolerability profile of lercanidipine and other CCBs, particularly amlodipine. Because most of the difference is due to a lower rate of subjective adverse events in patients treated with lercanidipine (i.e., 40–50%), this would have increased the chance to detect a significant difference in the proportion of patients persisting on the same treatment over time. Finally, the exclusion of patients with previous intolerance/hypersensivity for specific antihypertensive drug classes could have overestimated the persistence in treatment with some drug, but as for the above cited limitation, due to the exclusion of patients with a known resistance to a specific antihypertensive drug class, this reproduces the standard behavior of the physician in the everyday clinical practice.

In conclusion, the results of the present study support a close relationship between the tolerability profile of the different classes of antihypertensive drugs and the long-term persistence on treatment. We also demonstrated that the rate of stay-on-therapy can significantly differ among patients even within the same pharmacological family, especially as it regards non-dihydropyridinic calcium antagonists. Finally, in our patient sample, the greater the persistence on treatment, the better the extent of blood pressure control. Additional studies are needed to assess whether these differences are maintained on a longer period, and whether the observed differences are associated with better health outcomes.

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