Association of statin therapy with blood pressure control in hypertensive hypercholesterolemic outpatients in clinical practice

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ABSTRACT

Background: Some clinical evidence revealed that statins, apart from lowering cholesterol levels, also have an antihypertensive effect. Our aim was to evaluate the existence of a possible association of statin therapy with blood pressure (BP) control in clinical practice. **Materials and Methods:** Patients attending a hypertension/dyslipidemia clinic were prospectively evaluated. Those patients with a diagnosis of stage 1 hypertension and hypercholesterolemia who consented to participate were included in the study, either in the statin group (when taking a statin) or in the control group (when not taking a statin). Exclusion criteria included dementia, pregnancy, or breastfeeding, and history or evidence of stage 2 hypertension. Detailed clinical information was prospectively obtained from medical records. A total of 110 hypertensive patients were assigned to the study (82 in the statin group and 28 in the control group). **Results:** Although there were no significant differences ($P > 0.05$) in both groups concerning gender, body mass index, antihypertensive pharmacotherapy, and serum levels of high-density lipoprotein cholesterol and triglycerides, a higher BP control was observed in the statin group ($P = 0.002$). Significantly lower systolic BP (−6.7 mmHg, $P = 0.020$) and diastolic BP (−6.4 mmHg, $P = 0.002$) levels were reported in the statin group. Serum levels of low-density lipoprotein were also significantly lower in the statin group ($P < 0.001$). **Conclusions:** This observational study detected an association of statin therapy with BP control in hypertensive hypercholesterolemic patients in clinical practice. These findings raise the possibility that statin therapy may be useful for BP control in the studied population.

Key words: Antihypertensives, blood pressure, hypercholesterolemia, hypertension, Portugal, statins

INTRODUCTION

Hypertension is a major risk factor in the development of cardiovascular disease, with myocardial infarction and stroke being one of the most important health problems worldwide causing excess morbidity and mortality. The risk of cardiovascular morbidity and mortality is particularly marked when there is insufficient hypertension control and prevention at the community level. Randomized controlled trials (RCTs) have demonstrated that treating high blood pressure (BP) with medication can substantially reduce the risk of stroke by 35–40%, myocardial infarction by 20–25%, and heart failure by more than 50%.[1,2] Hypertension is often associated with other cardiovascular risk factors, including hypercholesterolemia that are present in over 40% of the hypertensive patients.[3] The concomitant presence of both hypertension and hypercholesterolemia in the same patient is associated with a higher rate of cardiovascular events that surpasses the separate contribution of each separate risk factor.[4] The prescription of both antihypertensive and cholesterol-lowering drugs is generally required in these patients.

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Inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (statins) are the most effective and widely used cholesterol-lowering agents in industrialized countries.[5] They significantly reduce the risk of cardiovascular events, particularly in patients showing a combination of high BP and hypercholesterolemia.[6] Although the long-term benefit of statin therapy is largely attributed to their cholesterol-lowering action, additional actions of these drugs, which are independent from 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibition, are thought to be involved in the cardiovascular protection observed shortly after the initiation of treatment.[7] Several RCTs have investigated the antihypertensive effect of statins in patients with hypertension associated with hypercholesterolemia.[8-10] An effect of statins on BP is potentially important and not improbable considering its reported effects on endothelial function, their interaction with the renin–angiotensin system, and their ability to affect large artery compliance.[9,11] However, most significant effects of statins on BP control were reported in controlled clinical trials,[8-10] which involve a highly motivated, closely controlled, and monitored patient population, where any supposed antihypertensive effects of statins would have a greater chance to be detected, when compared to the general population.

The objectives of our study were to prospectively investigate, in the setting of clinical practice, the potential association of self-administered statins with BP control in stage 1 hypertensive outpatients with hypercholesterolemia. We, thus, aimed to evaluate the existence of a possible relationship between statin therapy and BP control and BP levels in hypercholesterolemic hypertensive patients attending a hospital outpatient clinic (ambulatory setting) for routine follow-up.

MATERIALS AND METHODS

Settings

This study was conducted in a secondary care hypertension/dyslipidemia clinic in the university teaching hospital of Cova da Beira Hospital Centre, Covilhã, District of Castelo Branco, located in the Eastern Central Region of Portugal. This outpatient clinic is one of the most important clinics of this region of Portugal in the field of hypertension/dyslipidemia and serves a significant hypertensive population of Covilhã, with a population of 35,000 inhabitants.

Study design

From July 2009 to September 2009, we conducted a cross-sectional study of patients attending the hypertension/dyslipidemia medical clinic. All outpatients attending the medical clinic during that period were asked to give their signed informed consent to be enrolled in the study. The study was approved by the institutional ethics committee for the use of humans in research, and written informed consent was obtained from all participants before their enrollment in the study.

Clinical data for this study, including BP measures, lipid profile, medications prescribed, and medical problems, were prospectively obtained from the Hospital Electronic Medical Records (HEMR) database. The HEMR database of Cova da Beira Hospital Centre comprises detailed patient-level clinical and administrative information of all patients who utilized, at least once, this hospital's services. Available information includes patient demographics, medical problems, various measures of physiological status, and medications prescribed. This database is authorized by the Portugal Department of Health, the government department responsible for public health issues, and patient data confidentiality was ensured. This database was accessed at clinic attendance of patients.

Study population

Eligible participants were all adults (aged ≥18 years) with an established medical diagnosis of stage 1 hypertension (BP measurements, in the clinic, of systolic BP 140–159 mmHg and/or diastolic BP 90–99 mmHg, as defined in current international guidelines[12]) and hypercholesterolemia (fasting total serum cholesterol ≥200 mg/dL). Furthermore, all included patients had been on established antihypertensive treatment for at least 6 months. The recruited hypertensive hypercholesterolemic patients were included either in the statin group (when taking a statin for at least 6 months) or in the control group (when not taking a statin) and BP control and BP levels of both groups were compared. Exclusion criteria included dementia, pregnancy, or breastfeeding, and history or evidence of stage 2 hypertension (BP measurements, in the clinic, of systolic BP ≥ 160 mmHg and/or diastolic BP ≥ 100 mmHg). Hypertensive hypercholesterolemic patients taking a statin for less than 6 months were also excluded.

BP measurements

BP was measured in a seated position after a 5-min rest period, using a mercury sphygmomanometer or automatic device (Omron M4-I), with the mean of two consecutive measurements spaced by 1–2 min. Additional measurements were taken if the first two were quite

different. The BP clinic measurement was performed by several nurses blinded to the study.

According to the seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), hypertensive patients without diabetes and chronic kidney disease (CKD) with BP <140/90 mmHg were considered to have their BP controlled.[1] For hypertensive patients with diabetes or CKD, BP control was defined as BP measurements <130/80 mmHg.[1]

Medication adherence assessment

The assessment of medication adherence was determined using a validated five-item compliance scale[13] derived from the four-item scale developed by Morisky *et al.*[14,15] Low medication adherence was defined as answering 'yes' to three or more of five questions.[13] The five-item scale was reported to have predictive validity in that it was able to discriminate levels of hypertension control[14] and to discriminate cases of hypertensive emergency or urgency from hypertensive controls.[16] Cronbach's coefficient alpha,[17] a measure of the internal consistency of the scale, was 0.71 for the five-item scale,[13] better than the 0.61 for the original four-item scale.[14]

Statistical analysis

Demographic variables, clinical data, BP values, and lipid profile of patients included in the study, and also prescribing metrics were examined on a descriptive basis and expressed as the mean ± SD (standard deviation), frequency, and percentages. Student's *t*-test and Mann–Whitney rank-sum test were used to compare continuous variables and χ^2-test and Fisher's exact test were used to test for differences between categorical variables. A logistic regression model was used to adjust the odds ratio (OR) of controlled BP associated with statin therapy for the length of antihypertensive treatment. All statistical analyses were carried out using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA), and a *P*-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

A total of 222 patients attended the medical clinic during

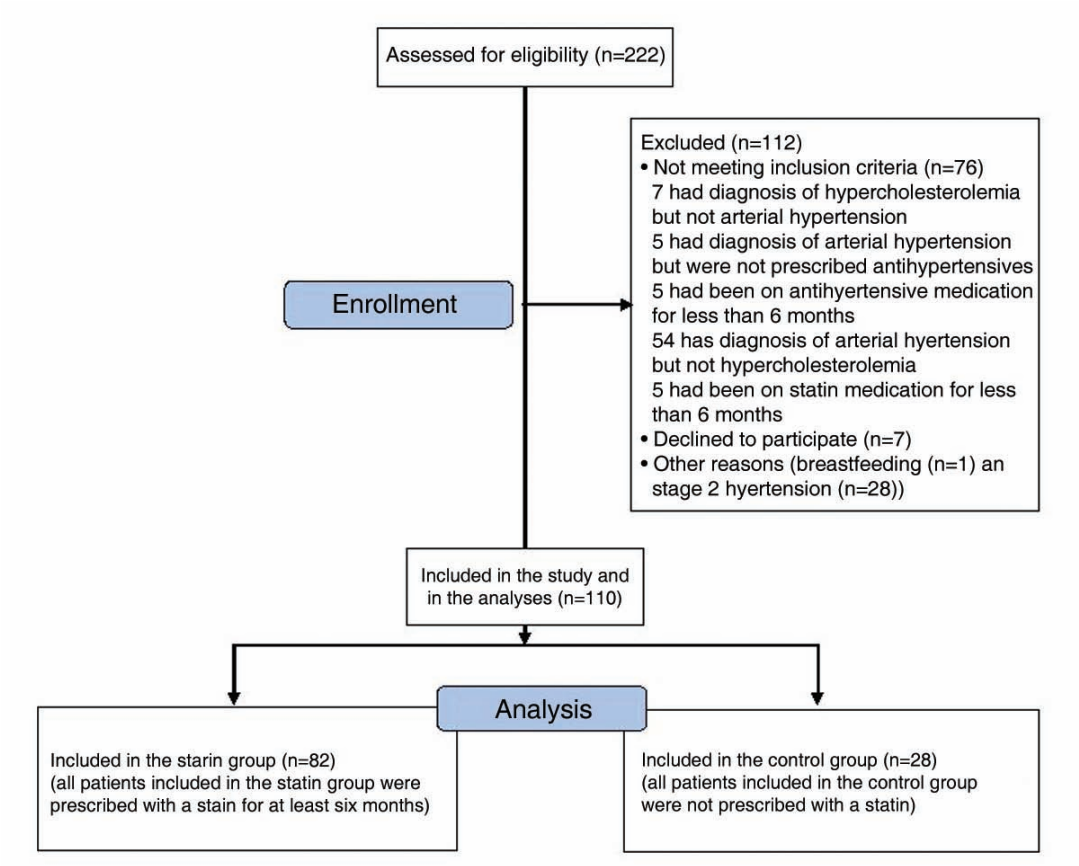

Figure 1: Diagram of patient enrollment

the recruitment period (from July 2009 to September 2009), and all were assessed for eligibility. Of these, 76 were excluded from our study because they did not meet the inclusion criteria, 28 were excluded because of stage 2 hypertension, 1 was excluded because of breastfeeding, and 7 were excluded because they declined to participate (did not sign the informed consent). Of the 110 hypertensive hypercholesterolemic patients meeting the inclusion criteria and consenting to participate, 82 were included in the statin group and 28 were included in the control group [Figure 1].

The overall mean age of the included patients was 59.7 ± 9.5 years, 40.0% being male and 60.0% female. Among these hypertensive hypercholesterolemic patients, 82 (74.5%) were taking a prescribed statin for at least 6 months and were included in the statin group, whereas the remaining 28 (25.5%) were not taking a statin and were included in the control group [Table 1]. In the statin group, patients were receiving both dietary advice and a statin. In the control group, patients were receiving dietary advice alone as a therapeutic measure to control hypercholesterolemia. The use of a statin was considered only when dietary measures alone had proven to be insufficient to control hypercholesterolemia. All statins currently licensed for human use in Portugal were prescribed (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin).

There were no significant differences between patients in the statin group and the control group concerning age (mean 60.2 ± 9.6 years vs. 58.1 ± 9.4 years; $P = 0.306$), gender (39.0% males vs. 42.9%; $P = 0.718$), and body mass index (mean 29.8 ± 4.7 kg/m^2 vs. 29.8 ± 4.6 kg/m^2; $P = 0.963$). Likewise, the proportion of patients with diabetes and/or chronic kidney disease, the number and class of antihypertensive drugs used, and the high-density lipoprotein cholesterol (HDL-C) and triglyceride fasting serum levels did not significantly differ in both groups. Conversely and as expected, fasting total serum cholesterol and low-density lipoprotein cholesterol (LDL-C) levels were significantly lower in the statin group. In addition, the mean duration of antihypertensive drug treatment was significantly higher in the statin group (10.1 vs. 6.9 years, $P = 0.031$), which might represent a possible confounding variable [Table 1].

Blood pressure control according to the JCN 7 guidelines was significantly higher ($P = 0.002$) in the statin group (54.9%) when compared with the control group (21.4%; Table 1). Accordingly, significantly lower systolic BP (−6.7 mmHg, $P = 0.020$) and diastolic BP (−6.4 mmHg, $P = 0.002$) levels were observed in the statin group [Figure 2].

In the light of these results, since the mean duration of

Table 1: Clinical characteristics of the study population

Characteristics	Statin group (*n* = 82)	Control group (*n* = 28)	*P*-value for difference
Mean age (years)	60.2 ± 9.6	58.1 ± 9.4	0.306
Gender (male/female; %)	39.0/61.0	42.9/57.1	0.718
Body mass index (kg/m2)	29.8 ± 4.7	29.8 ± 4.6	0.963
Loop diuretics (%)	15.9	10.7	0.560
Thiazide diuretics (%)	58.5	64.3	0.590
Potassium-sparing diuretics (%)	2.4	3.6	1
Renin inhibitors (%)	1.2	0.0	1
ACE inhibitors (%)	34.1	39.3	0.624
Angiotensin II receptor antagonists (%)	56.1	53.6	0.823
Calcium channel blockers (%)	41.5	25.0	0.120
Beta blockers (%)	45.1	39.3	0.590
Central alpha-2 agonists (%)	7.3	0.0	0.199
Number of antihypertensive drugs per patient	2.6 ± 1.5	2.4 ± 1.1	0.401
Number of years in antihypertensive drug treatment	10.1 ± 7.1	6.9 ± 4.2	0.031*
Total cholesterol (mg/dL)	185.5 ± 39.5	221.3 ± 52.1	<0.001*
LDL cholesterol (mg/dL)	107.1 ± 36.2	140.5 ± 40.9	<0.001*
HDL cholesterol (mg/dL)	50.8 ± 11.7	47.4 ± 8.4	0.169
Triglyceride (mg/dL)	141.9 ± 61.1	172.3 ± 105.0	0.074
Diabetes or chronic kidney disease (%)	22.0	17.9	0.647
BP controlled (JCN 7 guidelines) (%)	54.9	21.4	0.002*
Low, self-reported medication adherence, score ≥ 3 (%)	47.6	57.1	0.380

*Values are mean ± SD unless otherwise stated, *statistically significant difference (P-value < 0.05), ACE, Angiotensin-converting enzyme; BP, Blood pressure; HDL, High-density lipoprotein; LDL, low-density lipoprotein*

antihypertensive drug treatment was significantly higher in the statin group, this variable was included into a logistic regression model to adjust the OR of controlled BP associated with statin therapy in hypertensive hypercholesterolemic patients [Table 2].

The crude model presented in Table 2 confirms that statin therapy increases the likelihood of having the BP controlled [OR 4.46; 95% confidence interval (CI) 1.64–12.15]. After adjusting for the length of antihypertensive treatment, the same statistically significant relationship is observed [OR 5.23; 95% CI 1.86–14.67], confirming the hypothesis that statin therapy may be useful for BP control in the studied population.

DISCUSSION

Previous studies found a possible relationship between hyperlipidemia and hypertension that coexist very often in the same patients and exert a cumulative effect on the risk of cardiovascular events.[3,18,19] Several RCTs revealed that statins, beyond their lipid-lowering properties, are also able to significantly reduce systolic and diastolic BP.[8-10,20] However, the capacity of statins to affect systemic BP in clinical practice is still debated and a demonstration of a better BP control, according to JNC 7 guidelines, in self-administered hypertensive, hypercholesterolemic statin outpatients is still lacking. The data recently provided by the Plaque Hypertension Lipid-Lowering Italian Study (PHYLLIS) trial, which enrolled both stage 1 and 2 hypertensive hypercholesterolemic patients (systolic BP 150–210 mmHg and diastolic BP 95–115 mmHg), do not confirm the conclusion of previous studies that statins exert a BP-lowering effect.[21] The results of PHYLLIS revealed that the administration of a statin in hypertensive hypercholesterolemic patients in whom BP is effectively reduced by concomitant antihypertensive treatment does not have an additional BP-lowering effect,[21] which seems to be in line with a few previous studies.[22,23]

In this cross-sectional study, statin therapy was not only associated with an improved lipid profile, through significantly lower fasting total serum cholesterol and LDL-C levels, but also with a higher BP control in stage 1 hypertensive hypercholesterolemic patients from the Eastern Central Region of Portugal. After adjusting for the length of antihypertensive treatment, statin therapy increased 5.23 times the odds of having the BP controlled, this relationship being statistically significant (95% CI 1.86–14.67). The magnitude of systolic and diastolic BP reduction (−6.7 mmHg and −6.4 mmHg, respectively, $P < 0.05$) observed in the statin group when compared to the control group is in agreement with data obtained in some RCTs.[24]

Table 2: Odds ratio of controlled BP associated with statin therapy according to the length of antihypertensive treatment

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Statin therapy	4.46 (1.64–12.15)†	5.23 (1.86–14.67)†

**Results are adjusted for the length of antihypertensive treatment, †Values are significant at the 0.05 level (two-sided), CI, confidence interval; OR, odds ratio.*

These findings may have some reasonable clinical implications since they help to emphasize the role of statins in the prevention of cardiovascular diseases, particularly in hypertensive hypercholesterolemic patients with stage 1 arterial hypertension. However, adequately powered epidemiological studies need to be considered to test the efficacy and safety of statin therapy in BP control and prevention of cardiovascular events.

Several limitations of this study must be mentioned. First, the sample size power to detect small differences between groups may be questionable. Even though the association observed is statistically significant, the increased precision of confidence intervals is desired. From a methodological point of view, this is a small cross-sectional study and our results must be considered exploratory in nature. Second, the evaluation of BP control is also subject to criticism since it is based on the measurements performed in one single medical appointment. These BP measurements may or may not be representative of the adequacy of BP control in hypertensive patients. Third, we were unable to obtain objective measurements of patient medication compliance

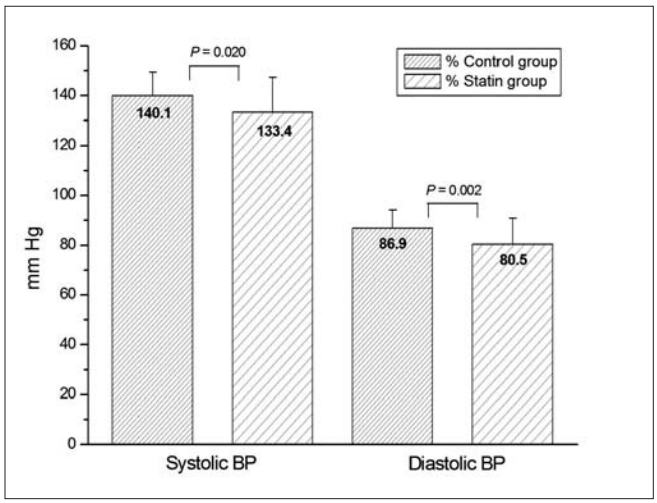

Figure 2: Significant lower systolic blood pressure (−6.7 mmHg, $P = 0.020$) and diastolic blood pressure (−6.4 mmHg, $P = 0.002$) levels were observed in the statin group when compared with the control group. Error bars indicate standard deviation. BP, blood pressure

(e.g., drug level in biologic fluids, biologic markers, direct patient observation) and compare them in both groups. Finally, we did not evaluate whether some combinations of certain statins and antihypertensive drugs might result in a more effective BP control than others, and we did not investigate whether the effect of statins on BP was dose related or not.

In conclusion, our results are aligned with the majority of the medical literature suggesting a statistically significant BP-lowering effect of statins, feasible to be achieved in hypertensive hypercholesterolemic patients in a clinical practice setting. Our findings suggest that, in stage 1 hypertensive patients in whom the prescription of a statin is simultaneously indicated (e.g., because of concomitant hypercholesterolemia), this can improve BP control and reduce, to some extent, the dose and number of antihypertensive drugs required to achieve satisfactory hypertension control. Therefore, our findings might have useful implications for effective and safe prevention of cardiovascular events, particularly in stage 1 hypertensive hypercholesterolemic patients in whom BP is not effectively controlled solely by concomitant antihypertensive treatment. Further studies are needed in this population to clarify the exact magnitude of the effect of statins on BP control, as well as its clinical relevance.

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