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ORIGINAL ARTICLE

# Effects of fluvastatin on insulin resistance and cardiac morphology in hypertensive patients

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**Among hypertensive patients, cardiovascular disease morbidity is common, even in those who are adequately treated. New pharmacological strategies to mitigate the burden of arterial hypertension are needed. This 12-month, randomized, double-blind placebo-controlled study investigated the effect of statin (fluvastatin) treatment on ambulatory blood pressure (ABP), exercise blood pressure (EBP), myocardial structure, endothelial function and insulin resistance in 50 hypertensive patients. At baseline, the groups were comparable in terms of demographic characteristics, ABP, EBP, endothelial function and homeostasis model assessment of insulin resistance (HOMA-IR). At the end of the study, there was no difference between groups in terms of resting systolic blood pressure. However, maximum systolic EBP was lower in the treatment group than in the placebo group (175 ± 18 vs 192 ± 23 mm Hg, $P<0.05$), as was left ventricular mass index (LVMI; 82 ± 15 vs 100 ± 23, $P<0.05$), and HOMA-IR index was lower after fluvastatin treatment (2.77 ± 1.46 vs 3.33 ± 1.73, $P<0.05$). Changes in lipid profile were not correlated with blood pressure, endothelial function, LVMI or HOMA-IR data. In hypertensive patients, fluvastatin can improve maximum systolic EBP, myocardial remodelling and insulin resistance, independently of lipid profile variations and endothelial function.**
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**Keywords:** endothelium/drug effects; pleiotropism; hydroxymethylglutaryl-CoA reductase inhibitors; insulin resistance; hypertrophy; left ventricular



## Introduction

The risk of adverse cardiovascular events increases dramatically when dyslipidaemia and hypertension co-exist,[1,2] and the simultaneous prescription of antihypertensive and hypolipidaemic agents is common. Addition of hypolipidaemic agents to hypertension treatment regimens can be beneficial, lessening target organ lesions and possibly reducing the number of cardiovascular events.[3] The 3-hydroxyl-3–methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, are the most effective low-density lipoprotein cholesterol-lowering drugs, with significant benefits in the prevention of primary and secondary cardiovascular disease.[4–9]

Endothelial dysfunction is an event that occurs early in atherosclerosis and in hypertension.[10] It is one of the potential mechanisms linking cholesterol with cardiovascular disease. In that context, insulin resistance and progressive endothelial dysfunction have a role in the pathogenesis of hypertension and atherosclerosis.[11] Recent studies have demonstrated that the so-called pleiotropic effects of statins can prevent cardiovascular remodelling in experimental models of human disease.[12,13] Dechend *et al.*,[14] studying transgenic rats, found that, in addition to the known lipid-lowering effect, statin treatment reduced hypertension, myocardial hypertrophy and vascular fibrosis. Other experimental studies, of rosuvastatin and pravastatin, have shown that statins slow the development of cardiovascular hypertrophy, inflammation and glucose intolerance.[13,15,16] Although these experimental results suggest that statins act simultaneously on endothelial function, insulin resistance and myocardial structure, efforts to translate such findings to the clinical setting have been unsuccessful.

This study investigated the effect of fluvastatin treatment on ambulatory blood pressure (ABP), exercise blood pressure (EBP), myocardial structure, endothelial function and insulin resistance in a group of patients under treatment for hypertension.

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## Materials and methods

We conducted a randomized, double-blind study comparing fluvastatin (20 mg) with placebo in patients with primary hypertension that was classified as stage 1 hypertension, as defined in The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7).[17] A total of 50 patients were enrolled in the study. The study was divided into two phases, the selection/washout phase (3 weeks) and the randomized treatment phase (12 months). During the selection/washout phase (visits 1 and 2, V1 and V2), patients received only placebo and were taken off any antihypertensive or hypolipidaemic agents. Patients entering the randomized treatment phase then received either placebo or fluvastatin throughout the 12-month study period, with evaluations every 2 months (visits V3–V8). All patients, regardless of group assignment, were treated for hypertension with enalapril. If necessary, the dose was increased or hydrochlorothiazide was added as follows: step 1—enalapril, 10 mg b.i.d.; step 2—enalapril, 20 mg b.i.d.; step 3—enalapril (20 mg b.i.d.) + hydrochlorothiazide (12.5 mg per day). With regard to previous therapies, both groups were comparable in terms of exposition to antihypertensive agents, before the wash-out period, with a median 62% use of thiazide diuretics and 54% use of renin–angiotensin system blockers in both groups, in comparable proportions.

The inclusion criteria were being between 18 and 65 years of age and having primary hypertension that was classified as stage 1. Exclusion criteria were as follows: stage 2 hypertension or any form of secondary hypertension; secondary dyslipidaemia; prior cardiovascular disease; endocrinopathy (including diabetes mellitus); pneumopathy or nephropathy of any origin; any pathology of the locomotor system that could interfere with the treadmill test; known hypersensitivity to fluvastatin; positive pregnancy test and breastfeeding. Written informed consent was obtained from all patients.

*Clinical evaluation*

The primary demographic and anthropometric data collected were age (years), weight (kg), height (m) and body mass index ($kg\,m^{-2}$). During all visits, blood pressure was calculated as the mean of three measurements taken while the patients were seated, in accordance with JNC 7 recommendations.[17]

*Clinical and biochemical parameters*

At months 0, 2, 4, 8 and 12, the following biochemical parameters were analysed: fasting glucose, fasting insulinaemia, low-density lipoprotein cholesterol, very low-density lipoprotein (VLDL) cholesterol, high-density lipoprotein cholesterol and triglycerides. Diabetes mellitus was diagnosed according to the American Diabetes Association criteria:[18] Symptoms of diabetes plus casual plasma glucose concentration $\geqslant 200\,mg\,dl^{-1}$ without regard to time since last meal or fasting plasma glucose concentration $\geqslant 126\,mg\,dl^{-1}$ (fasting defined as no caloric intake for 8 h) or 2-h post-load glucose $\geqslant 200\,mg\,dl^{-1}$ during oral glucose tolerance test. At months 0 and 12, pregnancy tests were carried out. At months 0, 6 and 12, albuminuria was measured by 12-h nocturnal immunoturbidimetry, and ABP was measured on the same day. At months 0 and 12, insulin resistance was calculated by the homeostasis model assessment of insulin resistance model assessment of insulin resistance (HOMA-IR) index,[19] calculated according to the following equation:

$$\text{HOMA-IR} = [\text{fasting insulin } (\mu U\,l^{-1}) \times \text{fasting glucose } (mmol\,l^{-1})]/22.5$$

The ABP was measured during a 24-h period at months 0, 6 and 12 using an automatic monitor (Model 90207; Spacelabs Healthcare, Issaquah, WA, USA) fitted on the non-dominant arm. A percentage of successful readings greater than 80% was considered adequate. At months 0, 6 and 12, treadmill exercise stress tests were carried out using computerized equipment (Challenger 5.0; Ecafix Indústria e Comércio Ltda, São Paulo, Brazil) including an electrocardiograph and cardiac monitor for continuous observation. To evaluate maximum systolic blood pressure during exercise (ExSBPmax), we measured blood pressure before the stress test and once per minute thereafter, during treadmill activity, using the Ellestad protocol.

At months 0, 6 and 12, patients underwent echocardiography (Model SIM 5000; Escote Biomedica, Florence, Italy) in order to determine the left ventricular mass index (LVMI), calculated in accordance with the American Society of Echocardiography guidelines.

At months 0, 6 and 12, endothelial function was evaluated by two independent, experienced radiologists. Measurements of the endothelium-dependent and endothelium-independent vasodilator capacity of the brachial artery were made using Doppler B-mode ultrasound.[20] Evaluations were made in separate tests:

*Endothelium-dependent phase*: Patients were put at rest, in the horizontal decubitus position, for 10 min. Intima–media thickness was measured in the right brachial artery, at 2–15 cm above the crook of the arm. Subsequently, a pneumatic cuff was inflated to 290 mm Hg for 5 min on the same arm, resulting in total interruption of regional blood flow. Fifteen seconds after deflating the cuff the maximum blood flow was measured during reactive hyperaemia. After 90 s, three consecutive brachial artery diameter measurements were taken during diastole.

*Endothelial-independent phase*: Patients were put at rest again for 10 min, and brachial artery diameter and regional blood flow were measured as above. Subsequently, 5 mg of isosorbide mononitrate was





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administered sublingually in pill form, followed by an additional measurement of the arterial diameter and regional blood flow.

*Statistical analysis*

For comparisons between the two groups, we used the Student's *t*-test for categorical variables and the Wilcoxon test or Mann–Whitney test, as appropriate, for continuous variables. To test for differences over time, we used analysis of variance with repeated measures. The chi-square test was used to compare proportions between groups. Pearson's correlation test was used in order to identify correlations between variables. For all tests, values of $P<0.05$ were considered statistically significant.

## Results

Baseline patient demographic data and test results during the randomization period (visit V2) are shown in Table 1. During the wash-out phase, six patients were excluded: four due to stage 2 hypertension and two due to a diagnosis of diabetes mellitus. An additional four patients, three in the fluvastatin arm and one in the placebo arm, dropped out of the study. In the placebo group, one patient was excluded because of the need for hypolipidaemic treatment. Therefore, 39 patients completed the 12-month treatment period. The mean age was 51 years. Males accounted for 10% of the placebo group and 31.6% of the fluvastatin group. There was no severity of hypertension imbalance before the wash-out period. There were no statistically significant differences between the groups in terms of body mass index or lipid profile. Similarly, during randomization no significant differences between groups were observed in the values obtained for uric acid, creatinine, microalbuminuria, HOMA-IR index, blood pressure (ABP or ExSBPmax) or LVMI. During the study period, there were no differences between the groups in terms of the type or number of antihypertensive drugs taken (mean, 1.5 prescriptions per patient).

At the end of the 12-month study period, no statistically significant differences were found between the placebo and fluvastatin groups in terms of high-density lipoprotein cholesterol or triglyceride plasma levels (Table 2). In addition, there were no differences in terms of serum creatinine or microalbuminuria values. Over the course of the study, there was, as expected, a significant reduction in low-density lipoprotein cholesterol in the fluvastatin group but not in the placebo group.

Blood pressure measurements are shown in Table 3. No significant differences in ABP or resting blood pressure were observed. However, compared with patients in the placebo group, those treated with fluvastatin demonstrated a statistically significant ($P<0.05$) reduction in ExSBPmax by the end of treatment (Figure 1), with a concomitant reduction in LVMI (Figure 2). No association between systolic exercise blood pressure and/or changes in left

**Table 1** Baseline characteristics

| | *Placebo* N = *20* | *Fluvastatin* N = *19* | P |
|---|---|---|---|
| Age, years | 51 ± 8 | 51 ± 10 | 0.78 |
| Male | 10.00% | 31.6% | |
| Bmi V2 | 29 ± 5 | 27 ± 3 | 0.86 |
| CHOL V2, mg dl$^{-1}$ | 252 ± 3 | 2 239 ± 4 | 0 0.26 |
| HDL V2, mg dl$^{-1}$ | 51 ± 12 | 44 ± 13 | 0.12 |
| LDL V2, mg dl$^{-1}$ | 161 ± 38 | 165 ± 32 | 0.76 |
| TG V2, mg dl$^{-1}$ | 187 ± 175 | 195 ± 149 | 0.87 |
| Uric acid V2, mg dl$^{-1}$ | 4.6 ± 1 | 4.9 ± 1.7 | 0.43 |
| Creatinine V2, mg dl$^{-1}$ | 0.88 ± 0.19 | 0.88 ± 0.16 | 0.98 |
| MICRO V2, mg per g cr | 11.3 ± 15.3 | 6.3 ± 6.8 | 0.2 |
| HOMA-IR V2 | 4.38 ± 6.13 | 3.34 ± 1.73 | 0.48 |
| Pre SBP V2, mm Hg | 151 ± 15 | 149 ± 16 | 0.61 |
| ExSBPmax V2, mm Hg | 187 ± 20 | 190 ± 20 | 0.66 |
| ABP SBP V2, mm Hg | 138 ± 12 | 139 ± 14 | 0.78 |
| ABP DBP V2, mm Hg | 86 ± 9 | 87 ± 11 | 0.77 |
| ABP SL V2, % | 57 ± 31 | 54 ± 28 | 0.76 |
| ABP DL V2, % | 46 ± 28 | 43 ± 30 | 0.76 |
| LVMI V2 | 116 ± 34 | 99 ± 36 | 0.13 |

Abbreviations: ABP DBP, ambulatory blood pressure, diastolic blood pressure; ABP DL, ambulatory blood pressure, diastolic load; ABP SBP, ambulatory blood pressure, systolic blood pressure; ABP SL, ambulatory blood pressure, systolic load; BMI, body mass index; CHOL, cholesterol; ExSBPmax, maximum systolic blood pressure during exercise; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LVMI, left ventricular mass index; MICRO, microalbuminuria; Pre SBP, pre-exercise systolic blood pressure; TG, triglycerides; V2, visit 2 (washout phase).
Data are means ± s.d.

**Table 2** Lipid profile and renal function

| | *Placebo* N = *20* | *Fluvastatin* N = *19* | P |
|---|---|---|---|
| CHOL V2, mg dl$^{-1}$ | 252 ± 32 | 239 ± 40 | 0.26 |
| CHOL V5, mg dl$^{-1}$ | 236 ± 32 | 208 ± 31 | 0.008* |
| CHOL V8, mg dl$^{-1}$ | 240 ± 35 | 207 ± 36 | 0.008* |
| HDL V2, mg dl$^{-1}$ | 51 ± 12 | 44 ± 13 | 0.12 |
| HDL V5, mg dl$^{-1}$ | 53 ± 12 | 47 ± 15 | 0.15 |
| HDL V8, mg dl$^{-1}$ | 53 ± 14 | 48 ± 15 | 0.27 |
| LDL V2, mg dl$^{-1}$ | 161 ± 38 | 165 ± 32$^{\dagger}$ | 0.76 |
| LDL V5, mg dl$^{-1}$ | 151 ± 37 | 129 ± 22 | 0.04* |
| LDL V8, mg dl$^{-1}$ | 155 ± 27 | 127 ± 30$^{\dagger}$ | 0.008* |
| TG V2, mg dl$^{-1}$ | 187 ± 175 | 195 ± 149 | 0.78 |
| TG V5, mg dl$^{-1}$ | 167 ± 101 | 185 ± 172 | 0.76 |
| TG V8, mg dl$^{-1}$ | 177 ± 106 | 185 ± 143 | 0.84 |
| Cr V2, mg dl$^{-1}$ | 0.88 ± 0.19 | 0.88 ± 0.16 | 0.98 |
| Cr V5, mg dl$^{-1}$ | 0.91 ± 0.11 | 0.92 ± 0.16 | 0.71 |
| Cr V8, mg dl$^{-1}$ | 0.94 ± 0.13 | 0.91 ± 0.15 | 0.54 |
| MICRO V2, mg per g Cr | 11 ± 15 | 6 ± 7 | 0.2 |
| MICRO V5, mg per g Cr | 14 ± 19 | 6 ± 6 | 0.1 |
| MICRO V8, mg per g Cr | 10 ± 15 | 4 ± 3 | 0.13 |

Abbreviations: CHOL, cholesterol; Cr, creatinine; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; Micro, microalbuminuria; TG, triglycerides; V2, visit 2 (washout phase); V5, visit 5 (month 6); V8, visit 8 (month 12).
Data are means ± s.d.
*$P<0.05$ fluvastatin vs placebo; $^{\dagger}P<0.05$ fluvastatin V2 vs fluvastatin V8.

**Table 3** Blood pressure results

| | *Placebo* N = *20* | *Fluvastatin* N = *19* | P |
|---|---|---|---|
| ABP SBP V2, mmHg | 138 ± 12 | 139 ± 14 | 0.78 |
| ABP SBPV5, mm Hg | 132 ± 12 | 126 ± 13 | 0.13 |
| ABP SBPV8, mm Hg | 131 ± 11 | 126 ± 12 | 0.2 |
| ABP DBP V2, mm Hg | 86 ± 9 | 87 ± 11 | 0.77 |
| ABP DBP V5, mm Hg | 82 ± 10 | 80 ± 10 | 0.44 |
| ABP DBP V8, mm Hg | 82 ± 8 | 80 ± 7 | 0.43 |
| ABP SLV2, % | 57 ± 31 | 54 ± 28 | 0.76 |
| ABP SLV5, % | 41 ± 31 | 28 ± 29 | 0.18 |
| ABP SLV8, % | 40 ± 29 | 27 ± 26 | 0.17 |
| ABP DLV2, % | 46 ± 28 | 43 ± 29 | 0.76 |
| ABP DLV5, % | 34 ± 26 | 27 ± 28 | 0.4 |
| ABP DLV8, % | 32 ± 23 | 22 ± 21 | 0.16 |
| ExSBPmax V2, mm Hg | 187 ± 20 | 190 ± 20 | 0.66 |
| ExSBPmax V5, mm Hg | 196 ± 19 | 189 ± 18 | 0.27 |
| ExSBPmax V8, mm Hg | 192 ± 23 | 175 ± 18 | 0.032* |
| Pre SBP V2, mm Hg | 151 ± 15 | 149 ± 16 | 0.61 |
| Pre SBP V5, mm Hg | 140 ± 16 | 136 ± 13 | 0.4 |
| Pre SBP V8, mm Hg | 136 ± 11 | 131 ± 12 | 0.31 |

Abbreviations: ABP DBP, ambulatory diastolic blood pressure; ABP DL, ambulatory blood pressure, diastolic load; ABP SBP, ambulatory systolic blood pressure; ABP SL, ambulatory blood pressure, systolic load; ExSBPmax, maximum systolic blood pressure during exercise; Pre SBP, pre-exercise systolic blood pressure; V2, visit 2 (washout phase); V5, visit 5 (month 6); V8, visit 8 (month 12).
Data are means ± s.d.
*$P<0.05$ for fluvastatin vs placebo.

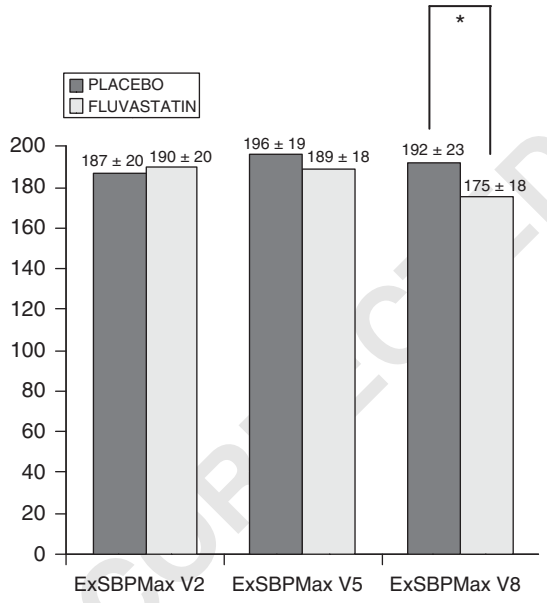


**Figure 1** Maximum systolic blood pressure during exercise (ExSBPmax), in mmHg, at visits V2 (washout), V5 (month 6) and V8 (month 12). *$P<0.05$ for fluvastatin vs placebo.

ventricular mass index was observed. These results remained consistent when the proportion of hypertrophic patients between groups was considered (64.1% hypertrophic and 35.9% non-hypertrophic).

No significant differences between the placebo and fluvastatin groups were found for artery diameter or blood flow (endothelium-dependent or endothelium-independent), either during randomization or at the end of the 12-month study period (Table 4). Endothelial function was not found to correlate with ExSBPmax or LVMI, at any time during the study. In addition, at the study endpoint, lipid profile was not correlated with endothelial function, LVMI, ExSBPmax or HOMA-IR index.

The HOMA-IR index values for the placebo and fluvastatin groups are shown in Figure 3. There was no difference in anti-hypertensive drugs therapy before the wash-out period and between the wash-out phase and the end of the study, but there was a significant reduction in the HOMA-IR index in the fluvastatin group.

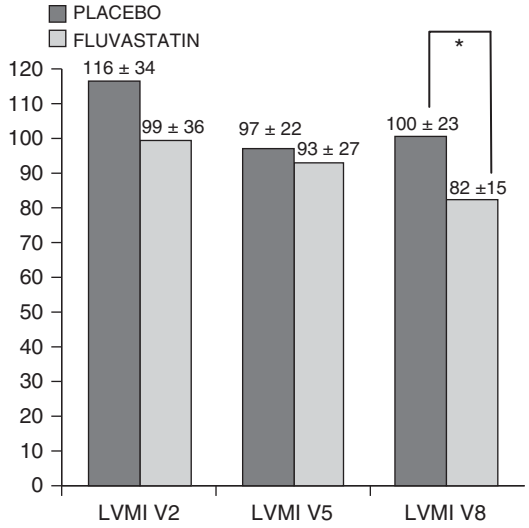


**Figure 2** Left ventricular mass index (LVMI) at visits V2 (washout), V5 (month 6) and V8 (month 12). *$P<0.05$ for fluvastatin vs placebo.

**Table 4** Endothelium results

| | *Placebo* *N = 20* | *Fluvastatin* *N = 19* | P |
|---|---|---|---|
| FEDF % V2 | 701 ± 330 | 762 ± 613 | 0.71 |
| FEDd % V2 | 10 ± 9 | 9 ± 11 | 0.74 |
| FEIF % V2 | 7 ± 52 | 10 ± 42 | 0.29 |
| FEId % V2 | 8 ± 10 | 10 ± 13 | 0.58 |
| FEDF % V8 | 598 ± 392 | 763 ± 451 | 0.26 |
| FEDd % V8 | 10 ± 9 | 14 ± 13 | 0.27 |
| FEIF % V8 | 30 ± 70 | 4 ± 29 | 0.08 |
| FEId % V8 | 23 ± 32 | 10 ± 9 | 0.13 |

Abbreviations: FEDd, final endothelium dependent diameter; FEDF, final endothelium dependent flux; FEId, final endothelium independent diameter; FEIF, final endothelium independent flux; V2, visit 2 (washout phase); V8, visit 8 (month 12).
Data are means ± s.d.

## Discussion

In the population studied (patients with stage 1 hypertension and without cardiovascular disease),





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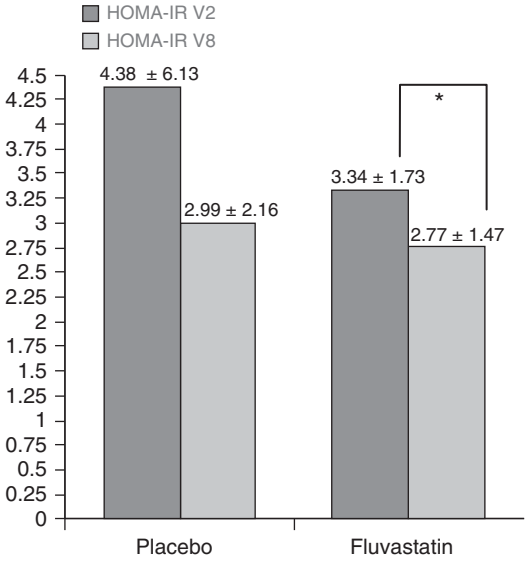


**Figure 3** Insulin sensitivity. Homeostasis model assessment of insulin resistance (HOMA-IR) index at visits V2 (washout) and V8 (month 12). *$P<0.05$ for V2 vs V8.

adding fluvastatin to the hypertension treatment regimen resulted in consistent reductions in LVMI and HOMA-IR index by the end of treatment. Similarly, ExSBPmax was reduced in the fluvastatin group, despite similar office blood pressure and ABP. We found that neither the lipid profile nor its variations (data not shown) correlated with LVMI, insulin resistance parameters or ExSBPmax.

Several studies have analysed the impact of HMG-CoA reductase inhibitors on blood pressure in different patient populations, with inconsistent results. Although some studies have found that statin therapy reduces blood pressure,[21–26] there is no consensus yet on this observation.[24] In 1999, Glorioso *et al.*[26] demonstrated an attenuation of blood pressure in hypercholesterolaemic, hypertensive patients after a four-month course of pravastatin. In a subsequent study, Terzoli *et al.*[27] detected a reduction in ABP, but not in resting blood pressure, in a cohort treated with statins and anti-hypertensive drugs. Recently, in a discerning meta-analysis of 20 randomized, controlled studies, Strazzullo *et al.*[28] demonstrated a slight but significant reduction in blood pressure following HMG-CoA reductase inhibitor treatment. In our study, we found that blood pressure reduction occurred independently of changes in cholesterol levels. In agreement with Terzoli *et al.*,[27] we found that statin treatment affected ExSBPmax but detected no effect on resting blood pressure. It is of note that patients in our study population were not selected based on their lipid profiles and did not have any cardiovascular disease that might influence blood pressure. In addition, unlike the studies cited here, our study included standardized treatment of hypertension for all study subjects, such that any difference in blood pressure in the treatment group would be primarily attributable to statin therapy.

Wassmann *et al.*[29] reported a reduction in blood pressure among spontaneously hypertensive rats treated with atorvastatin and found the reduction to be associated with changes in the vasodilation of aortic segments. The authors hypothesized that the improvement in endothelial function was due to downregulated expression of the angiotensin II receptor $AT_1$. The clinical relevance of these observations was recently demonstrated by Ott *et al.*[30] in a study of 22 hypercholesterolaemic patients treated with rosuvastatin for 6 weeks. That study found an increase in basal nitric oxide synthase activity in patients treated with statins as compared with patients in the placebo group. Our study of endothelial function did not reveal variations in artery diameter or blood flow between groups, and, in accordance with Ott *et al.*,[30] did not demonstrate any correlation between endothelial function and treatment-related changes in lipid profile, or between endothelial function and blood pressure. The absence of an association with endothelial function was consistent, regardless of the type of blood pressure measurement (office blood pressure, ABP or ExSBPmax). Different methods for measuring endothelial function might explain why our results differed from those of Ott *et al.* In addition, hypercholesterolaemia was not considered during the selection of our patient population, which might have resulted in a lesser degree of endothelial dysfunction and subsequently less change during treatment. Finally, patients in our study already showed some degree of insulin resistance at randomization, an effect that might have influenced our endothelial function results, despite the improved HOMA-IR index seen in the fluvastatin group. In fact, although the numbers in the diabetes group might be too small for clear interpretation, findings from the ARBITER 2 trial showed that abnormal glucose metabolism could affect the analysis of vascular structure.[11] Despite a decrease in the carotid artery intima–media thickness in patients treated with the combination of statin and niacin, a similar improvement was not observed in patients who had abnormal glycaemic status at the beginning of treatment.[11]

Our study demonstrated that fluvastatin treatment improves insulin resistance (HOMA-IR index). The effect of statin treatment on insulin sensitivity is controversial. The validity of HOMA-IR has been evaluated by comparison with some gold standard methods. HOMA-IR has been shown to correlate well with insulin resistance index derived from the euglycaemic clamp and from directly measured insulin sensitivity.[31] Sari *et al.*[32] found no improvement in HOMA-IR in 42 hypercholesterolaemic patients treated with atorvastatin in a non-randomized, open-label study. In contrast with our cohort, the patients studied by Sari *et al.* had insulin resistance indices within the normal range (mean,

1.8 ± 0.6 for the HOMA-IR index). That factor, together with the short 3-month study period of Sari *et al.*, might explain why that study detected no improvement in HOMA-IR. As in our study, Sonmez *et al.*[33] reported an improvement in insulin resistance in 35 hypercholesterolaemic patients treated with fluvastatin. We also found that there was no correlation between changes in patient lipid profile and the observed improvement in insulin resistance, suggesting potential fluvastatin pleiotropism. It also appears that this benefit increases in direct proportion to the magnitude of the change in insulin resistance. In fact, in 25 female patients with metabolic syndrome, the administration of pravastatin resulted in pronounced improvements in insulin resistance.[34]

A *post hoc* analysis of the West of Scotland Coronary Prevention Study demonstrated pravastatin's benefits in a large population sample, showing a 30% reduction in the incidence of diabetes mellitus,[35] although that finding was not confirmed in another major study.[36] On the other hand, the study of Koh *et al.*[37] addressed whether atorvastatin might decrease insulin sensitivity and increase ambient glycaemia in hypercholesterolaemic patients. It is not clear why atorvastatin has beneficial metabolic actions in some studies but not in others. The mechanisms by which statins might act to improve insulin resistance remain unclear. An improvement in endothelial function would be one reasonable hypothesis. However, data collected in our study do not support that theory.

The effect of statins on ventricular remodelling has recently been considered more thoroughly. Using an murine model of angiotensin II-induced hypertension, Xu *et al.*[15] showed improvement in diastolic left ventricular dysfunction with pravastatin, as well as improvements in hypertrophy and left ventricular remodelling. In agreement with our findings, the attenuation of ventricular hypertrophy observed by Xu *et al.* was not associated with changes in blood pressure or lipid profile. The authors found that the improvement in myocardial remodelling was associated with a downregulation of local mitogens (transforming growth factor-β and metalloproteinases) and of cytokines (interleukin-6 and transforming growth factor-α). These results confirm the findings of a previous study by Cirricone *et al.*,[38] in which the impact of ventricular volume overload was attenuated by rosuvastatin treatment in Sprague–Dawley rats. Statin use resulted in lower transforming growth factor-β, fibronectin and procollagen expression in ventricular tissue. In human subjects, few studies have investigated the possible benefits of statins on ventricular morphology and function. De Lorgeril *et al.*[39] showed an improvement in cardiac performance, as measured by cardiac stress scintigraphy, in 32 patients treated with simvastatin for 12 weeks. In another study, the impact of simvastatin on ventricular function was studied in hypercholesterolaemic patients during 6 months of treatment.[40] In contrast to the benefits seen in our study, statin treatment did not result in significant alteration of left ventricular function, as evaluated by echocardiography. As with conflicting data on the impact of statins on insulin resistance, it is possible in this case that the amount of time needed to show a benefit from HMG-CoA reductase inhibitors on ventricular remodelling was greater than that encompassed by the study period.

In summary, our study demonstrates simultaneous benefits of treatment with a HMG-CoA reductase inhibitor (fluvastatin) on blood pressure during exercise, insulin resistance and ventricular remodelling in patients under treatment for hypertension. The observed benefits were not associated with other effects of statin treatment, including the reduction in low-density lipoprotein cholesterol levels and changes in endothelial function. It is likely that the results are explained by statin pleiotropism.

*What is known about topic*
- Some studies have demonstrated blood pressure reduction with statin therapy.
- Some studies of statins have reported beneficial effects on cardiovascular hypertrophy, inflammation and glucose intolerance.
- The effect of statins on insulin sensitivity is controversial.

*What this study adds*
- Patients treated with fluvastatin showed a reduction in exercise maximum systolic blood pressure at the end of treatment.
- Fluvastatin treatment led to a reduction in left ventricular mass index.
- Fluvastatin treatment led to a significant reduction in insulin resistance in the treatment group.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgements

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