Effects of combined statin and ACE inhibitor therapy on endothelial function and blood pressure in essential hypertension - a randomised double-blind, placebo controlled crossover study

Piotr Ruszkowski, Anna Masajtis-Zagajewska and Michał Nowicki

Abstract

Background: The aim of this study was to compare the influence of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors on endothelial function and blood pressure in patients with essential hypertension on long-term angiotensin-converting enzyme inhibitor therapy.

Method: The study was designed as a prospective, double-blind, randomised, placebo controlled, crossover clinical trial. Twenty patients with essential hypertension were treated with an angiotensin-converting enzyme inhibitor; the control group included 10 healthy subjects. Hypertensive patients received in random order 80 mg of fluvastatin daily or placebo for 6 weeks. The following parameters were assessed at baseline and after each treatment period: serum lipids, flow-mediated vasodilation, activity of von Willebrand factor, concentration of vascular endothelial growth factor, C-reactive protein and 24-hour blood pressure profile.

Results: Hypertensive patients did not differ from healthy subjects with respect to age, body mass and biochemical parameters, with the exception of C-reactive protein, which was higher in hypertensive patients (P=0.02). After statin therapy, low-density lipoprotein cholesterol (P<0.0001), C-reactive protein (P=0.03), von Willebrand factor (P=0.03) and vascular endothelial growth factor (P<0.01) decreased and flow-mediated vasodilation improved (P<0.001). Statins had no significant effect on blood pressure.

Conclusions: Statins added to angiotensin-converting enzyme inhibitors may improve endothelial function and ameliorate inflammation independently of blood pressure.

Keywords
Arterial hypertension, endothelium-mediated vasodilation, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, angiotensin-converting enzyme inhibitor

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Introduction

Arterial hypertension is a major risk factor for the progression of atherosclerosis and cardiovascular events.1 The activation of the renin–angiotensin–aldosterone system (RAAS) plays a key role in the pathogenesis of arterial hypertension.2 Apart from its vasoconstrictive properties, angiotensin II causes an increase in the activity of the sympathetic nervous system as well as the stimulation of aldosterone secretion and the release of several growth factors, cytokines, vasopressin and endothelin-1.3

The endothelium plays an important role in blood pressure (BP) regulation and in the pathogenesis of arterial
hypertension. Endothelial cells secrete a number of biologically active substances that regulate vessel wall tension. Endothelium-derived contracting factors belong to the second group that includes several highly potent factors such as endothelin-1 and angiotensin II.4

For the past decades the drugs interfering with the RAAS have been used as the first line treatment of hypertension. However, the mechanisms behind their complex effects have not been fully elucidated. The drugs that are currently used in the treatment of hypertension and act by way of the RAAS include a direct renin inhibitor, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin type 1 receptor blockers (ARBs) and aldosterone antagonists. ACEIs decrease aldosterone secretion and thereby inhibit sodium retention in response to a decrease in BP.5 Apart from that, they also inhibit endothelin-1 secretion,6 improve endothelium activity7 and weaken adrenergic stimulation in response to vessel dilation.8

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are a class of lipid-lowering compounds that have a well-established role in the treatment of hypercholesterolemia and the prevention of cardiovascular disease. The mechanisms of the beneficial effect of statins, apart from a marked decrease of serum lipids, comprise the pleiotropic effects such as the improvement of endothelium-mediated vasodilation,9,10 reduction of oxidative stress,11,12 inflammation13–15 and downregulation of the angiotensin II type 1 receptor.16

Statins may also have an antihypertensive effect that is probably mediated by an increase in nitric oxide bioavailability resulting in increased endothelium-dependent vasodilation response, and a reduction in endothelin-1 secretion and free radical formation.12,17,18 A synergistic action of statins and RAAS inhibitors has been postulated; however, the data from clinical studies are scarce.19 The effect may be linked to a reduced expression of type 1 angiotensin receptors and a blockade of intracellular pathways associated with angiotensin II action.16

The aim of this randomised placebo controlled crossover study was to assess the effect of statins added to chronic ACEI therapy on the endothelial function and BP control in patients with arterial hypertension.

Materials and methods

Study design

The study was designed as a randomised double-blind, placebo controlled crossover trial. The patients were randomly selected to receive either fluvastatin (80 mg/day in a single evening dose) or identically looking placebo tablets for the first 6 weeks. After a 2-week-long wash-out period the therapy with either placebo or fluvastatin continued for another 6 weeks. The measurements were taken three times, i.e. at baseline and after each treatment period. The study design is shown in Figure 1.

Patients

The patients with arterial hypertension had been receiving an ACEI in unmodified dose for at least the past 6 months. Baseline clinical and biochemical characteristics of all study subjects are presented in Table 1. The control group comprised 10 healthy persons with normal BP without any chronic or acute disease or any medication.

The main inclusion criteria included essential hypertension diagnosed according to European Society of Cardiology (ESC)-European Society of Hypertension (ESH) criteria, the treatment with an ACEI in an unmodified dose for at least the past 6 months, hypertensive Keith Wagener Barker stage 2 or 3 retinopathy, left ventricular hypertrophy and total serum cholesterol level below 250 mg/dl. Exclusion criteria included any clinical or laboratory signs suggesting a secondary form of hypertension, the use of statins or fibrates in the past 6 months, history of statin intolerance, chronic kidney disease stage 3a or higher (i.e. CKD-EPI estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²), diabetes mellitus, liver disease, cancer, hyper or hypothyroidism, acute or chronic inflammation and chronic heart failure (New York Heart Association (NYHA) stage 3 or 4). Apart from the study-related medication, the doses of all other drugs were unchanged throughout the study.

The local ethics committee approved the study protocol. All subjects were informed about the aims and design of the study and provided a written informed consent prior to the recruitment.

Office and ambulatory BP and heart rate

Ambulatory BP monitoring. BP and heart rate were recorded three times, i.e. at baseline and at the end of each treatment period. Office BP was recorded using a mercury sphygmomanometer in a sitting position after 15 minutes of rest, and the measurement protocol included three consecutive measurements with 3 minute intervals at each visit. The same person, a trained nurse, took all BP measurements. Mean BP was calculated as diastolic BP plus 1/3
of pulse pressure (systolic BP – diastolic BP). Ambulatory BP monitoring was measured using a Mobil-O-Graph device, version 12 (IEM GmbH, Stolberg, Germany). During the day the measurements were taken every 15 minutes and during the night every 30 minutes.

**Flow-mediated dilation**

Flow-mediated dilation (FMD) of the brachial artery, consisting of inducing reactive hyperemia by cuff obstruction of the forearm using high-resolution ultrasonography, was measured to assess endothelial function according to the guidelines. Ultrasound measurements were performed with a GE LOGIC device 400 with a linear scanning 8.2–11 MHz probe. With the participant supine, the right arm was placed in a supporting cradle, a BP cuff placed around the forearm and the ultrasound transducer was placed on the arm proximal to the elbow with the aid of a sterotactic stand. A three-lead ECG was connected to the ultrasound machine to enable measurement of the cardiac cycle.

A 30-second baseline period of scanning of the brachial artery was recorded prior to cuff inflation. The cuff was then inflated to 250 mmHg for 5 minutes to achieve total brachial artery occlusion. Recording recommenced at 15 seconds post occlusion and continued for 3 minutes.

The pre and post occlusion cine clips were then transferred to a computer for measurement by automated edge detection software (Brachial Artery Analyser; MIA-LLC, Coralville, USA). All measurements were obtained during diastole. The point of maximum dilation was identified and the maximum diameter was obtained by averaging five images from consecutive cardiac cycles. The FMD was calculated using the equation:

$$\text{FMD} \, (\%) = \frac{\text{peak diameter} - \text{baseline diameter}}{\text{baseline diameter}} \times 100.$$ 

**Blood tests**

Blood samples were obtained after an overnight fasting and collected in ethylenediaminetetraacetic acid (EDTA) tubes and promptly centrifuged at 2000 g at 2–8°C for 10 minutes. The plasma was stored in aliquots at −70°C. The biochemical parameters measured at each study visit included serum creatinine (eGFR – calculated using the CKD-EPI abbreviated formula), total cholesterol, high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol, triglycerides, uric acid, sodium, potassium, creatine kinase, C-reactive protein, vascular endothelial growth factor (VEGF) and von Willebrand factor (vWF).

Body mass and body mass index were measured during each visit.

**Statistical analysis**

The results are expressed as mean ± SD or median (interquartile range). Statistical significance was defined as $P<0.05$. The normality of data distribution was checked

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**Table 1.** Baseline clinical and biochemical characteristics of the patients with arterial hypertension and the control group.

|                          | Patients mean±SD | Controls mean±SD | $P$ value |
|--------------------------|------------------|-----------------|-----------|
| Age (years)              | 56.5 ± 7.7       | 53.1 ± 5.8      | ns        |
| Sex (female/male)        | 8/12             | 4/6             |           |
| BMI (kg/m²)              | 26.5 ± 2.7       | 25.0 ± 2.2      | ns        |
| Heart rate (/min)        | 68 ± 12.4        | 73 ± 10.3       | ns        |
| MAP-ABMP (mmHg)          | 91.7 ± 12.2      | 89.6 ± 9.8      | ns        |
| Fasting glucose (mg/dl)  | 102 ± 12.2       | 99.2 ± 11.2     | ns        |
| Triglycerides (mg/dl)    | 160.8 ± 79.9     | 155.3 ± 126.3   | ns        |
| Total cholesterol (mg/dl)| 220.7 ± 17.9     | 216.2 ± 26.2    | ns        |
| HDL-cholesterol (mg/dl)  | 55.0 ± 14.0      | 57.7 ± 17.2     | ns        |
| LDL-cholesterol (mg/dl)  | 135.6 ± 26.3     | 57.7 ± 17.2     | ns        |
| Sodium (mmol/l)          | 138.4 ± 2.7      | 141.0 ± 2.7     | 0.02      |
| Potassium (mmol/l)       | 4.2 ± 0.5        | 4.3 ± 0.2       | ns        |
| Creatinine (mg/dl)       | 0.84 ± 0.2       | 0.81 ± 0.2      | ns        |
| Uric acid (mg/dl)        | 5.0 ± 1.1        | 4.7 ± 1.3       | ns        |
| Creatine kinase (U/l)    | 125.1 ± 81.7     | 111.8 ± 48.1    | ns        |
| Alanine transaminase (U/l)| 26.8 ± 12.0    | 27.0 ± 13.6     | ns        |
| VEGF (pg/ml)             | 590.7 ± 437.3    | 503.5 ± 257.0   | ns        |
| vWF (% n)                | 128.1 ± 36.3     | 137.1 ± 32.9    | ns        |
| hs-CRP (mg/dl)           | 0.41 ± 0.5       | 0.12 ± 0.1      | 0.02      |
| Diameter of brachial artery (mm) | 4.22 ± 0.8 | 3.96 ± 0.8     | ns        |

BMI: body mass index; MAP-ABMP: mean arterial pressure-ambulatory blood pressure monitoring; LDL: low-density lipoprotein; HDL: high-density lipoprotein; VEGF: vascular endothelial growth factor; vWF: von Willenbrand factor; hs-CRP: high sensitivity C-reactive protein.
by the Kolmogorov–Smirnov test. Within-group comparisons were performed using the t-test or Wilcoxon’s test. Pearson or Spearman’s correlation coefficients were used to assess relations between the variables depending on the normality of data distribution. Statistical analysis of treatment outcome was carried out using the parametric approach to crossover trials, including the evaluation of potential carryover effects.

**Results**

**Characteristics of the studied patients**

The study group comprised 20 patients (eight women, 12 men, mean age 56.4±7.5 years with mean body mass index 26.5±2.7 kg/m²) with a diagnosis of arterial hypertension and 10 healthy subjects who served as a reference group. Table 1 shows the demographic and clinical characteristics of the study participants. Eleven patients were taking ramipril as a monotherapy 10 mg per day and nine patients were taking perindopril 10 mg per day. All patients completed the study according to the protocol and no clinically relevant side effects or study medications were observed during the therapy.

**Office and 24-hour BP**

No significant differences in mean, systolic or diastolic office BP during treatment with fluvastatin or placebo were observed (94.6±8.2 mmHg; P=0.8 vs. 95.2±7.7 mmHg; P=0.78, respectively) (Table 2). After treatment with fluvastatin there was a significant increase in daytime systolic, diastolic and mean BP. Daytime BP was unchanged after placebo. The changes in nighttime systolic, diastolic and mean BP after both fluvastatin and placebo therapy were not significant.

**Flow-mediated dilation**

A significant one-minute change in the dilation of the brachial artery in response to reactive hyperemia was found after fluvastatin treatment (P<0.001). During placebo the change in FMD was not significant (P=0.23) (Figure 2). A 2-minute change in FMD after fluvastatin was not significant (P=0.22).

**Biochemical parameters**

Table 3 shows the effect of fluvastatin on the serum concentration of sodium, potassium, creatinine, eGFR, uric acid, creatine kinase, alanine transaminase, vWF and VEGF after both the statin and placebo period.

The serum total cholesterol and LDL-cholesterol level decreased significantly after treatment with fluvastatin (from 221±18 to 166±36 mg/dl, from 136±26 to 89±29 mg/dl; P<0.0001). No significant changes in serum triglycerides, HDL-cholesterol, creatine kinase, alanine transaminase and fasting glucose levels were observed during the study.

There was a significant correlation between baseline serum VEGF and serum LDL-cholesterol (r=0.49, P=0.03) and serum creatinine (r=0.57, P=0.01). There was also a significant correlation between the changes in the LDL-cholesterol level and vWF during fluvastatin treatment (r=−0.53, P=0.02).
There were significant correlations between brachial artery dilation and age ($r=-0.45$, $P=0.04$), plasma glucose ($r=0.58$, $P=0.01$), serum triglycerides ($r=0.45$, $P=0.04$) and HDL-cholesterol ($r=-0.47$, $P=0.004$) after one minute.

**Discussion**

The study showed that the addition of an inhibitor of HMG-CoA reductase to a long-term ACEI therapy in patients with essential hypertension may result in a moderate improvement in FMD of the brachial artery after reactive hyperemia and in a decrease in plasma high sensitivity CRP and VEGF levels and vWF activity. The results of our study did not confirm any significant effect of statins on the control of BP in patients with arterial hypertension.

The study was designed to explore further the concept that the combination of statins and ACEI could be particularly well suited for patients with arterial hypertension and its systemic complications. The effect of statins on BP have been studied in a number of clinical trials which, however, provided conflicting results. Studies on the potential hypotensive effect of statins have also provided conflicting results.
The main concept of our study was that statins could provide additional benefits in patients with arterial hypertension that has been well controlled with an ACEI. That issue has been the subject of only a few studies despite its potential clinical relevance. Danaoglu et al.\textsuperscript{32} performed a similarly designed study in 39 patients with newly diagnosed essential hypertension. The patients were randomly assigned to two parallel groups: one that received simvastatin 20 mg per day irrespective of serum lipid levels and the second that received a fixed dose of 5 mg lisinopril per day for 12 weeks. Our study was designed as a randomised placebo controlled crossover trial, and the patients had to have good BP control on an ACEI that was given for at least 6 months prior to the study. The study of Danaoglu et al.\textsuperscript{32} showed that the combination of simvastatin and ACEI treatment significantly reduced BP, but did not have any effect on endothelium-dependent dilation.

Another study performed by Gismondi et al.\textsuperscript{33} showed that the combination of statins and RAAS inhibitors improved both BP control and endothelial function in diabetes patients with arterial hypertension. That study had some limitations as it was designed as an open randomised clinical trial that compared two active treatments. The patients were classified as users or non-users of statins and all were randomly assigned to benazepril 10 mg per day or losartan 50 mg per day. Statin users exhibited a greater reduction of both systolic and diastolic BP. The meta-analysis of Strazzullo et al.\textsuperscript{31} confirmed that statin effects on BP may be limited to diabetes patients. However, the significant effect was seen only with regard to systolic but not diastolic BP. Most of the trials included in the meta-analysis had a small sample size and were not designed to test the effect of statins on BP.

Another meta-analysis of large prospective controlled studies found a small but statistically significant reduction of systolic BP in all patients taking statins.\textsuperscript{34} In studies that included hypertensive patients, the decrease in BP during statin therapy was larger than in those who did not receive statins, and statins effectively reduced systolic BP only in diabetes patients. The meta-analysis did not include any assessment of the effect of a combined treatment with statins and ACEIs on BP.\textsuperscript{34}

In the seminal HOPE-3 trial over 12,000 patients at moderate risk of cardiovascular disease were randomly assigned to receive candesartan/hydrochlorothiazide, rosuvastatin, or placebo in a combination or alone. In the patients receiving the combination therapy, there was a larger decrease in serum LDL and a greater decrease in systolic BP than in those who received placebo. The group on the combination therapy also had significantly lower rates of cardiovascular death and non-fatal events.\textsuperscript{35,36}

In our study, the addition of fluvastatin to an ACEI induced a similar effect on BP to placebo. The results of our study corroborate those of Koh et al.\textsuperscript{21} In contrast to most previous studies our protocol included not only the measurement of office BP but also a 24-hour ambulatory BP recording.

In the study of Nazzaro et al.\textsuperscript{22} and Danaoglu et al.,\textsuperscript{32} the patients were naive to antihypertensive therapy. It is of note that Borghi et al.\textsuperscript{37} showed that the BP-lowering effect of statins may be seen only in patients with high BP at baseline. Bawa et al.\textsuperscript{38} showed a significant improvement of both systolic and diastolic BP in patients who received a ACEI alone or a combination of a ACEI and statin. However, the latter group showed a larger decrease in systolic BP compared with the group that received an ACEI alone.\textsuperscript{38} Such results are consistent with studies in which a greater fall in systolic BP was observed in statin users compared with non-users. Studies by Hashimoto et al.\textsuperscript{39} and Ikeda et al.\textsuperscript{40} showed a greater reduction in systolic BP in hypertensive patients who also received statins. Our study did not confirm these findings. The similar negative result was also obtained in the PHYLLIS (Plaque Hypertension Lipid Lowering Italian Study) randomised double-blind trial in which the patients receiving antihypertensive treatment consisting of either hydrochlorothiazide or lisinopril and pravastatin were compared with those who did not receive statins.\textsuperscript{27} Our study did not confirm these significant effects of statins on the control of BP in patients with arterial hypertension. BP was higher after statins, after these the increase was not significant. This fact may be the result of the relatively short time of statin treatment and the small group of patients. In addition, patients in our study had satisfactory BP control.

Endothelial dysfunction may lead to increased endothelial adhesiveness to leukocytes and the release of multiple procoagulant and vasoactive molecules, cytokines and growth factors.\textsuperscript{41} Several studies showed that a proper structure and function of the endothelium plays an important role in cardiovascular prevention. A loss of endothelial integrity is observed in many diseases and seems to be associated with the development of cardiovascular complications.\textsuperscript{42}

Zhang et al.\textsuperscript{43} performed a meta-analysis of the effects of statins on the brachial artery FMD in patients with diabetes mellitus and showed a significant improvement of absolute FMD values. Koh et al.\textsuperscript{21} randomly assigned the patients to three groups that received ramipril, simvastatin or their combination. They found that the combination of statins and ACEIs induced a greater increase in FMD than each medication alone. Similar results were obtained by Gismondi et al.\textsuperscript{33} who showed that a statin group showed a greater FMD response than a non-statin group. Tan et al.\textsuperscript{44} studied diabetes patients with dyslipidemia and found a marked improvement in FMD with atorvastatin compared with placebo. In contrast, no improvement in FMD after atorvastatin was observed by Van Venrooij et al.\textsuperscript{45} and by Beisilzhen et al. after cerivastatin or simvastatin.\textsuperscript{46} In our study, which included patients who had already been on an ACEI, a statistically significant improvement in brachial
artery FMD was observed after the administration of fluvastatin. These results are similar to those found in other studies but the direct comparison of our results is difficult due to their different designs and clinical characteristics of study populations.21

VEGF is released by the endothelial cells and its serum level is recognised as a good biomarker of angiogenesis.47 The measurement of serum VEGF can provide information on the link between the pathogenesis of arterial hypertension and inflammation.48 Increased serum VEGF was also found in patients with left ventricular hypertrophy.49 vWF is a multifunctional plasma protein that plays an important role in vascular injury and therefore may serve as an endothelial marker.50 Serum vWF measurement was frequently used to estimate endothelial dysfunction in hypertensive patients.51 The studies showed that the vWF level decreased after antihypertensive therapy.51 The baseline serum vWF concentration in our study was similar in hypertensive patients and in healthy subjects. The addition of statin led to a decrease in the vWF level; however, that effect was not significant when corrected for placebo.

The studies of endothelial function may be difficult due to the confounding effects of various factors that may influence vascular wall structure and function. Therefore our patients were carefully selected and the subjects with advanced kidney disease, uncontrolled diabetes, inflammation and heart failure were excluded.

The limitations of our study may include a small sample size because only 20 hypertensive patients were included, which may not be sufficient to demonstrate small intergroup differences of the efficacy of study drugs. Second, the duration of each treatment period was only 6 weeks. Therefore our study needs to be recognised as hypothesis-generating and larger and longer studies are warranted to confirm the findings.

Conclusions
The study showed that the addition of an inhibitor of HMG-CoA reductase to long-term ACEI therapy in patients with essential hypertension may result in a moderate improvement of FMD of the brachial artery after reactive hyperemia and ameliorate inflammation independently of BP.

Declaration of conflicting interests
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ORCID iD
Anna Masajtis-Zagajewska https://orcid.org/0000-0001-8860-2089

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