Pharmacological Reports
2010, 62, 883–890
ISSN 1734-1140

Hypotensive effect of atorvastatin is not related to changes in inflammation and oxidative stress

Agnieszka M. Kuklińska[1], Barbara Mroczko[2], Włodzimierz J. Musiał[1], Robert Sawicki[1], Anna Kozieradzka[1], Monika Usowicz-Szaryńska[1], Karol Kamiński[1], Małgorzata Knapp[1], Maciej Szmitkowski[2]

[1]Department of Cardiology, [2]Department of Biochemical Diagnostics, Medical University, M. Skłodowskiej-Curie 24A, PL 15-276, Białystok, Poland

Correspondence: Agnieszka Kuklińska, e-mail: agnieszka.kuklinska@gmail.com

Abstract:
We sought to determine if atorvastatin lowers blood pressure in patients with previously diagnosed and well-controlled essential arterial hypertension and if this effect could be related to anti-inflammatory and anti-oxidative effects. Among 92 patients with essential arterial hypertension, we studied 56 non-smoking and normolipemic: 39 were randomized to receive 80 mg atorvastatin daily for 3 months (statin-treated patients, ST), and the rest continued a previous hypotensive therapy (statin-free patients, SF). Blood pressure was measured using a 24-h ambulatory blood pressure measurement device. Serum levels of high-sensitivity C-reactive protein (hs-CRP), total antioxidant status (TAS) and plasma peroxides (assessed by Oxystat) were measured in both groups. The mean change in systolic BP (SBP) for atorvastatin was –5.7 mmHg (95% confidence interval CI, –4.1 to –7.2 mmHg), and the mean change in diastolic BP (DBP) was –3.9 mmHg (95% CI, –2.7 to –5.0 mmHg). No change in BP in SF patients was observed. In the ST group, hs-CRP and peroxides did not significantly decrease. In the SF group, concentrations of hs-CRP proceeded to decrease while peroxides increased. In the ST group, changes in hs-CRP correlated with changes in total cholesterol and low-density lipoprotein cholesterol ($r = 0.41$, $p = 0.013$ and $r = 0.35$, $p = 0.04$, respectively) but did not correlate with changes in BP. The hypotensive statin effect was independent of the hypolipemic effect. During three months of observation, TAS concentrations in both groups remained stable. In this randomized study, additionally administered atorvastatin to non-smoking and normolipemic patients with well-controlled essential arterial hypertension resulted in reduction of BP. This effect was not followed by significant changes in hs-CRP, TAS or Oxystat concentrations. The hypotensive effect of atorvastatin did not depend on anti-inflammatory, anti-oxidative or hypolipemic actions.

Key words:
arterial hypertension, atorvastatin, hs C-reactive protein, Oxystat, total antioxidant status

Abbreviations: ABPM – ambulatory blood pressure measurement, BP – blood pressure, CI – confidence interval, DBP – diastolic blood pressure, HDL – high-density lipoprotein cholesterol, hs-CRP – high-sensitivity C-reactive protein, HTN – essential arterial hypertension, LDL – low-density lipoprotein cholesterol, NO – nitric oxide, ox-LDL – oxidized low density lipoprotein, PGI_2 – prostacyclin, ROS – reactive oxygen species, SBP – systolic blood pressure, SD – standard deviation, SF – statin-free, ST – statin-treated, TAS – total antioxidant status, TC – total cholesterol, TG – triglycerides

Introduction

Statins, the most widely used drugs to treat hypercholesterolemia, can improve blood pressure control in hypertensive patients [4]. They have a pleiotropic effect that goes beyond lowering cholesterol levels.

Some of these actions – anti-inflammatory and anti-oxidative – could explain their hypotensive effect. Through reducing inflammation and oxidative stress, statins shift the balance from vasoconstriction to vasodilation [19].

Recent interest has been directed toward investigating the role of endothelial dysfunction and oxidative stress, which are important in the pathogenesis of arterial hypertension. Low-grade inflammation, measured as elevated levels of high-sensitivity C-reactive protein (hs-CRP), may be implicated in the development of endothelial dysfunction, which leads to arterial hypertension [14]. In addition, essential arterial hypertension (HTN) is associated with greater than normal lipoperoxidation and imbalance of anti-oxidant status, suggesting that oxidative stress is important in the pathogenesis of HTN [16].

The aim of the present study was to evaluate if high dose atorvastatin added to the standard antihypertensive therapy lowers blood pressure and if this effect depends on anti-inflammatory or anti-oxidative mechanisms.

Materials and Methods

Selection of the study population

Among 92 patients referred to our outpatient clinic with previously diagnosed and well-controlled HTN, we studied 56 non-smoking and normolipemic patients with a median age of 53 years (25%; 75% quartile range: 44; 64), 32 of whom were males. Thirty-nine of them were randomized to receive 80 mg atorvastatin daily for 3 months (statin-treated patients, ST), and the rest continued a previous hypotensive therapy (statin-free patients, SF). When a patient fulfilled the inclusion criteria and gave written consent, he or she was registered as a study participant. The physician then contacted an independent study at the registration office, from which the randomization code was obtained. Sixty patients were planned to be randomized in an open-label manner in the proportion of 2:1 (ST:SF). This sample size provides a power of 80% to detect a clinical difference of treatment groups in the primary endpoint at 5% level of significance.

Blood pressure was measured in the ambulatory condition using a 24-h ambulatory blood pressure measurement device (ABPM, Tracker Reynolds NIBP2, Reynolds Medical, Hertford, UK). Cuffs of an appropriate size were used on the nondominant arm with the automatic readings provided at 10 min intervals during the day (from 6:00 a.m. to 10:00 p.m.) and 20 min intervals during the night (from 10:20 p.m. to 05:40 a.m.). Automatic deflation of the equipment was no more than 2 mmHg per second. All patients were instructed to engage in normal activities, refrain from strenuous exercise and keep the arm extended at the time of cuff inflations. Only recordings with more than 85% valid values were analyzed. Based on recent recommendations, HTN was diagnosed when the median 24-h value of systolic blood pressure (SBP) was 125–130 mmHg and/or the median value of diastolic blood pressure (DBP) exceeded 80 mmHg [12]. Patients with a known secondary reason for HTN, any history of symptoms of coronary artery disease, diagnosed diabetes mellitus, renal dysfunction (eGFR < 60 ml/min) or symptoms of heart failure were excluded. All patients were treated according to the current guidelines [12]. Only two patients received aspirin.

The study design was compliant with the Helsinki Declaration of 1975 as revised in 1996 and it was approved by the local institutional committee on human research (Institutional Review Board – Local Bioethics Committee of Białystok Medical University). Informed consent of all participants studied for the report was obtained.

Blood sampling and biochemical measurements

Venous blood samples were obtained between 8:00 a.m. and 10:00 a.m. from fasting patients. After 20 min, venous blood samples for hs-CRP and total anti-oxidant status (TAS) were collected into tubes with clotting activation system and for peroxides into tubes containing EDTA. All samples were centrifuged within 2 h after drawing and stored at –80°C until assayed.

Serum levels of hs-CRP were determined using the immunoturbidimetric method (CRP High-sensitivity assay kits, Thermo Electron Corporation, Ratastie, Finland) according to the manufacturer's instructions. The intra-assay CV% is reported by the manufacturer of the assay kits as 2.3% at an hs-CRP mean concentration of 2.41 mg/l.

TAS was measured using the enzymatic method with peroxidase by commercially available RANDOX TAS kits (Randox, Ardmore, United Kingdom) according to the manufacturer's instructions. In this method, ABTS® (2,2 azino-di-[3-ethylbenzthiazoline sulfonate]) is incubated with a peroxidase metmyo-

globin and H_2O_2 to produce the radical cation ABTS®$^{*+}$. This cation has a relatively stable blue-green color, which is measured at 600 nm. Antioxidants in the added serum sample suppress this color production to a degree that is proportional to their concentration.

Plasma concentrations of peroxides were measured using the colorimetric assay kit Oxystat (Biomedica, Wien, Austria), according to the manufacturer's instructions. Results show a direct correlation between free radicals and circulating biological peroxides, which allows the characterization of the oxidative status in biological samples. The peroxide concentration is determined by the reaction of the biological peroxides with peroxidase and subsequent color reaction using TMB (tetramethylbenzidine) as a substrate. After addition of a stop solution, the colored liquid is measured photometrically at 450 nm. The intra-assay coefficient of variation is referred to by the manufacturer of assay kits as 3.1% at a peroxide mean concentration of 221 μmol/l, SD = 6.9 μmol/l.

Statistical analysis

Results are expressed as the means ± SD or CI and medians with 25% to 75% interquartile ranges as appropriate (continuous variables) or as proportions (categorical variables). Associations between continuous and categorical variables were examined using the Mann-Whitney U test, and associations between categorical variables were examined using the χ^2 test. Concomitant treatment during observation was assessed using Cochrane's Q test. The Wilcoxon signed-rank test was performed for the repeated measurements. Associations of hs-CRP changes and hypotensive and hypolipemic effects were assessed using Pearson's correlation analysis. Multiple regression analysis was performed to indicate factors that were associated with blood presure changes during statin treatment. All analyses were carried out using Statistica 8.0 (StatSoft, Tulsa, OK, USA); $p < 0.05$ was considered statistically significant.

Tab. 1. Changes in blood pressure values, changes in lipid profiles and antihypertensive treatment in statin-treated and statin-free patients

Blood pressure	Atorvastatin treatment		p	Standard treatment		p
	Baseline	After 3 months		Baseline	After 3 months	
Systolic BP, mmHg the mean ± SD	129.0 ± 11.0	123.3 ± 8.9	< 0.05	129.5 ± 13.0	128.5 ± 9.7	0.9
Diastolic BP, mmHg the mean ± SD	76.0 ± 9.0	72.1 ± 8.6	< 0.05	74.0 ± 7.6	74.0 ± 7.6	0.8
TC, mg/dl, the mean ± SD	196 ± 35.4	137.9 ± 40.5	< 0.05	157.3 ± 33.9	135.9 ± 27.9	0.02
LDL, mg/dl, the mean ± SD	124.5 ± 32.6	74.4 ± 33.7	< 0.05	92.7 ± 28.2	70.5 ± 24.4	0.4
HDL, mg/dl, the mean ± SD	48.0 ± 11.4	45.7 ± 10.8	0.08	45.1 ± 9.8	45.6 ± 8.6	0.8
TG, mg/dl, the mean ± SD	117.6 ± 50.7	89.8 ± 50.6	< 0.05	97.7 ± 34.0	99.4 ± 50.5	0.02
Antihypertensive treatment						
ACEI, %	65.9			76.5		0.4
ARB, %	6.8			5.9		0.9
CA, %	29.6			41.2		0.4
BB, %	52.3			58.8		0.6
Diuretics, %	50.0			70.1		0.1

BP – blood pressure; SD – standard deviation; TC – total cholesterol; LDL – low-density lipoprotein cholesterol; HDL – high-density lipoprotein cholesterol; TG – triglycerides: ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CA – calcium antagonists; BB – beta-blockers

Results

The baseline systolic and diastolic blood pressures in statin-treated and statin-free groups were similar: 129.0 mmHg (± 11) *vs.* 129.5 mmHg (± 13.0), p = 0.8 for SBP and 76.0 mmHg (± 9.0) *vs.* 74.0 mmHg (± 7.6), p = 0.6 for DBP, respectively (Tab. 1). The proportion of antihypertensive agents was similar between groups (Tab. 1).

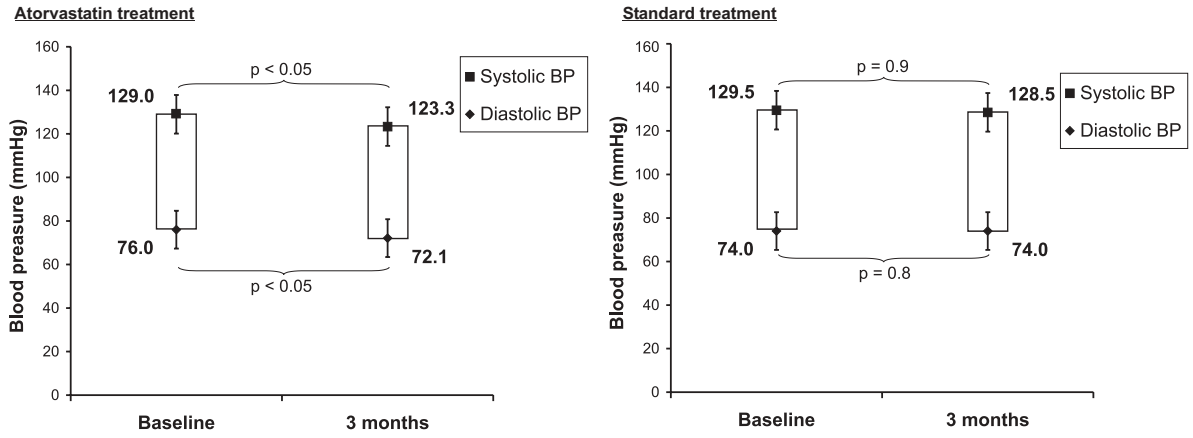

Fig. 1. Changes in blood pressure in one group receiving atorvastatin and one group receiving standard treatment. BP blood pressure

Tab. 2. Changes in biochemical parameters in the course of atorvastatin and standard treatment

	Atorvastatin treatment		p	Standard treatment		p
	Baseline	After 3 months		Baseline	After 3 months	
hs-CRP, mg/l the mean SD	3.5 ± 4.6	2.5 ± 2.3	0.1	4.8 ± 9.5	4.6 ± 11.9	0.5
Oxystat, µmol/l the mean SD	326.8 ± 194	316.5 ± 160	0.5	249.1 ± 139.8	275.5 ± 166.5	0.9
TAS, mmol/l the mean SD	1.5 ± 0.2	1.5 ± 0.4	0.3	1.4 ± 0.3	1.4 ± 0.3	0.8

hs-CRP – high-sensitivity C-reactive protein; TAS – total antioxidant status; SD – standard deviation

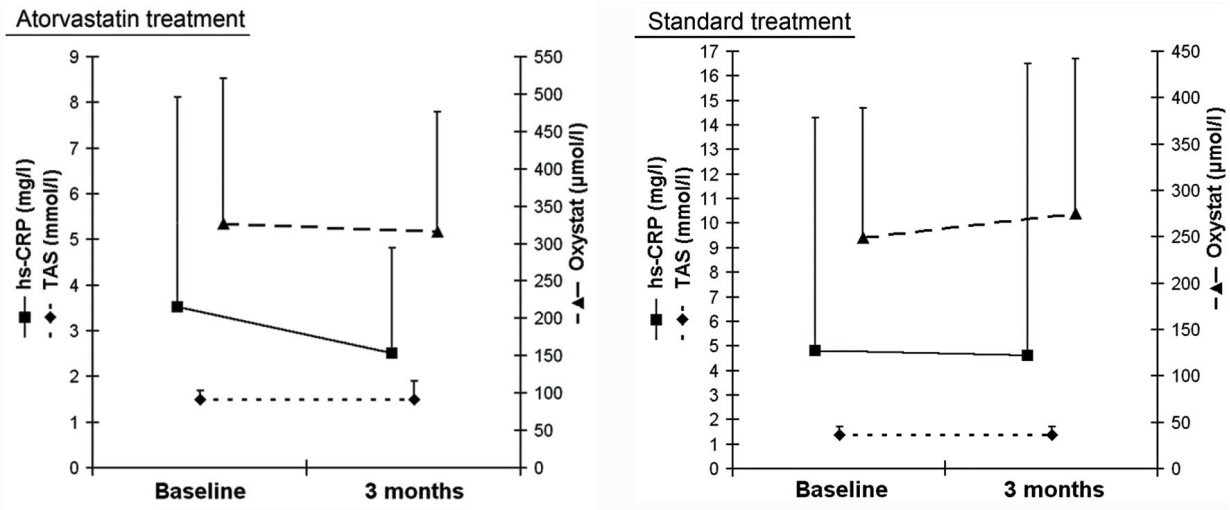

Fig. 2. Changes in hs-CRP, TAS and Oxystat concentrations in one group receiving atorvastatin and one group receiving standard treatment. hs-CRP – high-sensitivity C-reactive protein; TAS – total antioxidant status; Oxystat – an assay for plasma concentrations of peroxides

Atorvastatin significantly reduced total cholesterol (TC), low-density lipoprotein (LDL) and triglycerides (TG) concentrations (Tab. 1). In SF patients, TC and TG concentrations also significantly decreased. After three months of treatment, BP values significantly decreased in ST patients (Tab. 1). The mean change in systolic BP for atorvastatin was –5.7 mmHg (95% CI, –4.1 to –7.2 mmHg) and the mean change in diastolic BP was –3.9 mmHg (95% CI, –2.7 to –5.0 mmHg) (Fig. 1). This hypotensive effect was not observed in SF patients: for SBP, p = 0.9 and for DBP, p = 0.8 (Tab. 1, Fig. 1). During atorvastatin treatment, hs-CRP and peroxide concentrations decreased, but the alterations were not significant (Tab. 2, Fig. 2). In the SF group, hs-CRP decreased while peroxides levels increased, though neither change was significant (Tab. 2, Fig. 2). After three months of atorvastatin therapy, TAS concentrations did not change; a similar result was found in the SF group (Tab. 2, Fig. 2). There were no significant correlations between CRP and BP changes. Changes in CRP correlated with changes in TC and LDL (r = 0.41, p = 0.013 and r = 0.35, p = 0.04, respectively) (Fig. 3). In the multiple regression analysis, both systolic and diastolic blood pressure value reductions were influenced by the baseline values of SBP and DBP and the use of atorvastatin. Blood pressure decrease both systolic and diastolic was not altered by hs-CRP reduction, which was observed after statin treatment (Tab. 3). The hypotensive statin effect was independent of the hypolipemic effect (Fig. 4).

Discussion

Statins, in addition to their unquestionable ability to decrease lipid levels, have other biological actions, mostly relevant to improvement of endothelial function and arterial compliance. Some data indicate the direct effect of statins on blood pressure. After three months of atorvastatin treatment, Ferrier et al. [6] showed a mean change of –6 mmHg in SBP in a group of patients with isolated systolic hypertension. In our hypertensive patients, atorvastatin signifi-

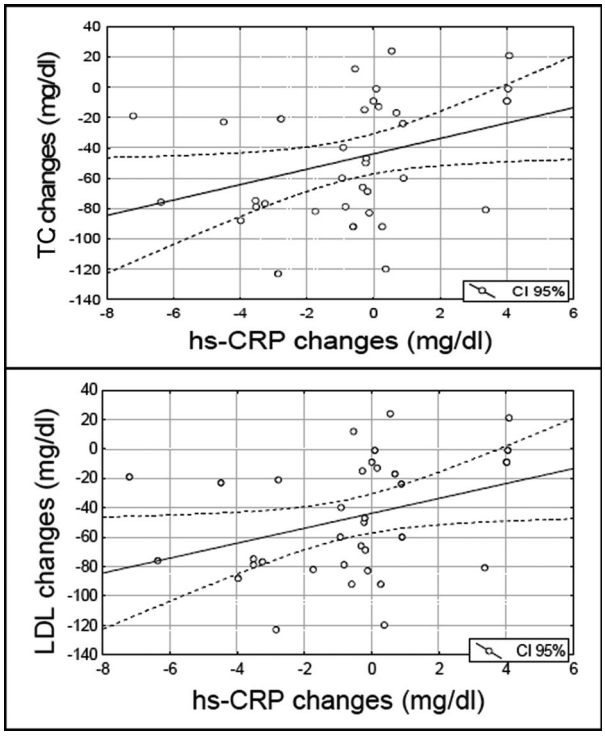

Fig. 3. Correlations between hs-CRP and TC and LDL concentrations (p = 0.013 and p = 0.04, respectively). hs-CRP – high-sensitivity C-reactive protein; TC – total cholesterol; LDL – low-density lipoprotein cholesterol

Tab. 3. Multiple regression analysis

Systolic blood pressure (R^2 = 0.63, p = 0.00001)		
	Beta	p
Age	–0.07	0.56
Baseline SBP	–0.72	0.000003
Atorvastatin	–0.31	0.007
TC change after 3 months	–7.4	0.42
Hs-CRP change after 3 months	0.03	0.76
TAS change after 3 months	–0.3	0.06
Diastolic blood pressure (R^2 = 0.39, p = 0.00039)		
	Beta	p
Age	–0.22	0.11
Baseline DBP	–0.45	0.001
Atorvastatin	–0.29	0.04
TC change after 3 months	–0.21	0.14
Hs-CRP change after 3 months	0.10	0.47
TAS change after 3 months	–0.21	0.09

SBP – systolic blood pressure; DBP – diastolic blood pressure; TC – total cholesterol concentration; hs-CRP – high-sensitivity C-reactive protein; TAS – total antioxidant status

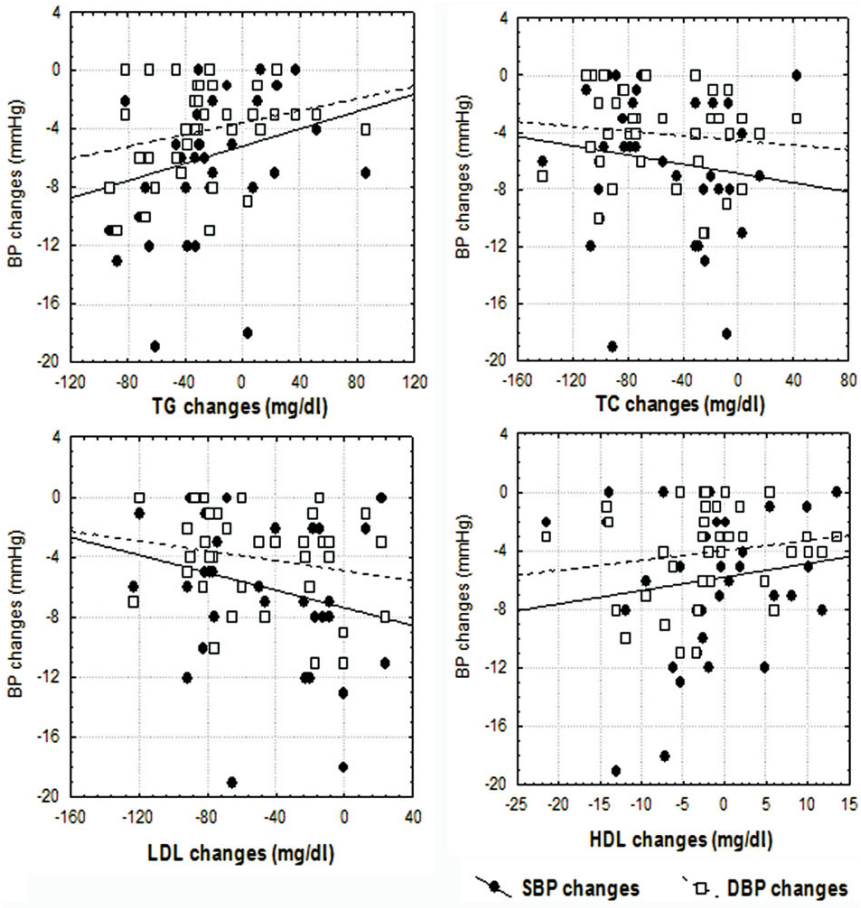

Fig. 4. Correlation between blood pressure changes and lipid profile values during statin therapy (the partial correlations, all p = ns). BP – blood pressure; TC – total cholesterol; TG – triglycerides; HDL – high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol

cantly reduced BP values and we obtained not only a significant reduction of SBP but also DBP values in the course of three months of atorvastatin treatment.

The hypotensive effect of statins could be masked by the action of antihypertensive agents administered simultaneously. However, Borghi et al. [3] demonstrated that the use of statins in combination with antihypertensive drugs can improve blood pressure control in patients with uncontrolled hypertension. Even though our non-smoking and normolipemic patients received a standard treatment of HTN, they received the beneficial hypotensive effect of additionally administered atorvastatin. Baseline BP values were similar in both groups and during the study antihypertensive treatment did not change in the ST, or SF group, which additionally emphasize atorvastatin hypotensive effect. Statins can decrease vasoconstriction and pressor response to vascular agonists, like angiotensin II [13]. This effect could be the explanation for the reported interaction between statins and some classes of antihypertensive agents [2]. In light of recent data, we also wanted to verify if atorvastatin therapy would improve BP control. Our patients, although well treated, had an additional hypotensive effect when they received atorvastatin. The BP response to statins was strongly influenced not only by the use of the statin but also by the baseline systolic and diastolic blood pressure values. Interestingly, age did not influence BP responses.

Anti-inflammatory and anti-oxidative effects are, among other possible explanations, easier to elucidate as potential hypotensive mechanisms of statins.

High-sensitivity CRP levels are higher in patients with arterial hypertension than in normal individuals [22]. Recent studies have demonstrated the contribution of low grade inflammation, measured as hs-CRP levels, in various patients with hypertension, including those with "white-coat" or resistant hypertension [14, 17]. CRP could be an independent risk factor for the development of hypertension [1]. The results of the ICEBERG study disclosed that the use of hs-CRP might be helpful in stratifying hypertensive patients into specific risk groups [9]. Thus, hs-CRP is an important biomarker in hypertensive patients with re-

gard to assessment of risk, diagnosis and prediction of complications. Regarding the anti-inflammatory effect of statins, it was reasonable to assess hs-CRP concentration in the course of atorvastatin treatment in hypertensive patients. In our study we found a decrease in hs-CRP concentration in the group of patients receiving atorvastatin. Although the change was insignificant, it was larger than in the statin-free group. However, changes of CRP did not correlate with changes in BP, and BP reduction was not altered by CRP reduction. The changes in CRP were only concomitant with cholesterol reduction, which seems to be the main (and probably only) mechanism of the benefit of statins.

Recent studies have shown that increased production of oxygen-derived free radicals (reactive oxygen species, ROS) could play an important role in the development and consolidation of HTN. ROS production (termed "oxidative stress") is associated with endothelial dysfunction [8]. Peroxides cause vascular contraction. Therefore, the latest theories indicate that the increase in vasoconstriction, which contributes to arterial hypertension, is associated with a greater production of free radicals. Oxystat is an assay that measures total peroxide concentration [5]. We found an insignificant decrease in peroxide concentration, measured by Oxystat, in patients receiving atorvastatin compared to the statin-free group.

On the other hand, it is worth noting that essential hypertension is associated not only with greater than normal lipoperoxidation but also with a decrease in anti-oxidant status. In fact, this imbalance in the pro-oxidant and anti-oxidant status shifts in hypertensive patients. Decreased TAS was found in patients with sustained and "white-coat" hypertension [21]. Lantos et al. [11] found that TAS values were below the normal range in hypertensive patients and increased gradually following antihypertensive treatment. In contrast to the above results and to our expectations, we found no differences in TAS concentrations in the course of atorvastatin treatment or in the statin-free group.

We did not prove that the hypotensive statin effect was related to anti-inflammatory or anti-oxidative actions. Among various pleiotropic statin mechanisms of action, perhaps others could be more responsible for this effect. Increased production of contracting factors, like oxidized low-density lipoprotein (ox-LDL), a marker of oxidative stress, and decreased production of vasodilators, like nitric oxide (NO) and prostacyclin (PGI_2), may also play an important role in the development and consolidation of HTN [7, 10, 18, 20]. The potential influence of statins on these mechanisms could be the essence of their hypotensive effect.

To assess blood pressure, we used a precise ambulatory blood pressure measurement device. It measures more accurately than clinic blood pressure the extent of blood pressure reduction induced by treatment and is not influenced by the "white coat" effect [15]. This accuracy could be why, despite insignificant changes in measured biomarkers, we showed a significant reduction of BP values in patients who received atorvastatin. Interestingly, in both groups, during three months of observation, TAS concentrations did not change. This may be explained by the small sample size of the study.

Moreover, in our study, the hypolipemic effect was present in both groups. Both groups of patients followed a hypolipemic diet, which could be the reason for the decrease in cholesterol levels observed in the patients not treated with statins. The decrease in TC and TG observed in the patients not treated with statins was probably due to following a strict hypolipemic diet. However, the hypotensive effect, which was observed only in the statin-treated group, was independent of lipid-lowering.

Conclusions

Our study suggests that the treatment of hypertensive patients with a high dose of atorvastatin lowers blood pressure, even when added to standard antihypertensive therapy. However, this effect, independent of lipid-lowering, is not related to the beneficial anti-inflammatory or anti-oxidative statin effect.

Study limitations

The main limitation of this study is the relatively small number of patients enrolled, due to the strict inclusion criteria. Therefore, the interpretation of results and discussion should be performed with caution. However, the patients were included prospectively and were investigated thoroughly, so the authors consider the results obtained as being representative. Objectively, this study was designed as a cross-over trial; therefore, the present report has a pilot character and it will be strengthened by further publications.

Acknowledgment:
Work supported by The State Committee for Scientific Research (grant No. N 402 075 31/2290).

References:

1. Bautista LE, López-Jaramillo P, Vera LM, Casas JP, Otero AP, Guaracao AI: Is C-reactive protein independent risk factor for essential hypertension? J Hypertens, 2001, 19, 857–861.
2. Borghi C, Dormi A, Veronesi M, Sangiorgi Z, Gaddi A; Brisighella Heart Study Working Party: Association between different lipid-lowering treatment strategies and blood pressure control in the Brisighella Heart Study. Am Heart J, 2004, 148, 285–292.
3. Borghi C, Prandin MG, Costa FV, Bacchelli S, Degli Esposti D, Ambrosioni E: Use of statins and blood pressure control in treated hypertensive patients with hypercholesterolemia. J Cardiovasc Pharmacol, 2000, 35, 549–555.
4. Borghi C, Veronesi M, Prandin MG, Dormi A, Ambrosioni E: Statins and blood pressure regulation. Curr Hypertens Rep, 2001, 3, 281–288.
5. De Groot H: Oxystat technique in study of reactive oxygen species. Methods Enzymol, 1990, 186, 443–448.
6. Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM, Kingwell BA: Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol, 2002, 39, 1020–1025.
7. Gryglewski RJ: Prostacyclin among prostanoids. Pharmacol Rep, 2008, 60, 311.
8. Higashi Y, Noma K, Yoshizumi M, Kihara Y: Endothelial function and oxidative stress in cardiovascular diseases. Circ J, 2009,73, 411–418.
9. Kozan O, Buyukoztruk K, Ilerigelen B, Kabakci G, Koylan N; ICEBERG Investigators: The impact of plasma high-sensitivity C-reactive protein levels on cardiovascular risk stratification of hypertensive patients: results of the ICEBERG study. J Clin Hypertens (Greenwich), 2007, 9, 500–505.
10. Kuklinska AM, Mroczko B, Musial WJ, Usowicz-Szarynska M, Sawicki R, Borowska H, Knapp M et al.: Diagnostic biomarkers of essential arterial hypertension: the value of prostacyclin, nitric oxide, oxidized-LDL, and peroxide measurements. Int Heart J, 2009, 50, 341–351.
11. Lantos J, Röth E, Czopf L, Nemes J, Gál I: Monitoring of plasma total antioxidant status in different diseases. Acta Chir Hung, 1997, 36, 188–189.
12. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G et al.: 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J, 2007, 28, 1462–1536.
13. Nickenig G, Bäumer AT, Temur Y, Kebben D, Jockenhövel F, Böhm M: Statin-sensitive dysregulated AT1 receptor function and density in hypercholesterolemic men. Circulation, 1999, 100, 2131–2134.
14. Ozdogan M, Bozcuk H, Coban E: Low-grade inflammation in white-coat hypertension. Med Sci Monit, 2007, 13, CR570–573.
15. Parati G, Pomidossi G, Casadei R, Mancia G: Lack of altering reactions to intermittent cuff inflations during noninvasive blood pressure monitoring. Hypertension, 1985, 7, 597–601.
16. Russo C, Olivieri O, Girelli D, Faccini G, Zenari ML, Lombardi S, Corrocher R: Anti-oxidant status and lipid peroxidation in patients with essential hypertension. J Hypertens, 1998, 16, 1267–1271.
17. Salles GF, Fiszman R, Cardoso CR, Muxfeldt ES: Relation of left ventricular hypertrophy with systemic inflammation and endothelial damage in resistant hypertension. Hypertension, 2007, 50, 723–728.
18. Taddei S, Virdis A, Ghiadoni L, Salvetti G, Salvetti A: Endothelial dysfunction in hypertension. J Nephrol, 2000, 13, 205–210.
19. Tesfamariam B: The effects of HMG-CoA reductase inhibitors on endothelial function. Am J Cardiovasc Drugs, 2006, 6, 115–120.
20. Toikka JO, Niemi P, Ahotupa M, Niinikoski H, Rönnemaa T, Viikari JS, Hartiala JJ et al.: Decreased large artery distensibility in borderline hypertension is related to increased in vivo low-density lipoprotein oxidation. Scand J Clin Lab Invest, 2002, 62, 301–306.
21. Yildiz A, Gür M, Yilmaz R, Demirbađ R, Celik H, Aslan M, Koçyiđit A: Lymphocyte DNA damage and total antioxidant status in patients with white-coat hypertension and sustained hypertension. Turk Kardiyol Dern Ars, 2008, 36, 231–238.
22. Zdrojewski T, Chwojnicki K, Bandosz P, Konarski R, Wyrzykowski B: Distribution of C-reactive protein and its relation to arterial hypertension in a country representing a high-risk region for cardiovascular diseases. Blood Press, 2006, 15, 20–26.

Received:
August 24, 2009; in revised form: March 9, 2010.