Effect of Statin Therapy Added to ACE-Inhibitors on Blood Pressure Control and Endothelial Functions in Normolipidemic Hypertensive Patients

Normolipidemik Hipertansif Hastalarda ACE İnhibitör Tedavisine Eklenen Statin Terapisinin Kan Basıncı Kontrolüne ve Endoteliyal Fonksiyonlarına Etkisi

Zülfikar Danaoğlu, MD, Hakan Kültürsay, MD, Meral Kayıkçıoğlu, MD
Levent Can, MD, Serdar Payzin, MD

From the Department of Cardiology, Ege University Medical School, *İzmir, Turkey*

Abstract

Objective: Endothelium-dependent vasodilatation is impaired in hypertension. Statins have been shown to improve endothelial functions in hyperlipidemic subjects. We aimed to investigate the effect of statins on endothelium-dependent flow mediated dilatation (FMD) and blood pressure (BP) in normocholesterolemic hypertensive patients.
Methods: This randomized prospective study consisted of 56 patients with newly diagnosed essential hypertension. All patients received angiotensin converting enzyme (ACE) inhibitor lisinopril (5 mg/day) as antihypertensive therapy, and half of them were randomized to simvastatin(20mg/day) irrespective of serum lipid levels. All subjects underwent brachial artery ultrasonographic examination for the measurement of FMD before randomization and at the end of 12 weeks treatment.
Results: A total of 39 patients completed the study (21 patients in the statin + ACE inhibitor group, and 18 patients in the ACE-inhibitor alone group). Blood pressure levels were substantially reduced in both groups after treatment. In statin+ ACE-inhibitor group systolic pressure reduced by 23% (p=0.0001) and diastolic BP reduced by 23% (p=0.0001). In ACE-inhibitor alone group these ratios were 20% (p=0.001) and 21% (p=0.001), respectively. Meanwhile, pulse pressure (PP) decreased by 25% in statin+ ACE-inhibitor group (P=0.0001) and by 16% in ACE inhibitor-alone group (p=0.0051). Baseline FMD was significantly impaired in overall patients with hypertension as compared with healthy controls (13 ± 8 vs. 24±8 %, P = 0.001). After treatment FMD decreased by 23% in lisinopril alone group (p=0.054). There were no correlations between FMD improvement, LDL reduction, BP or PP changes in both groups.
Conclusion: Addition of simvastatin to ACE-inhibitor treatment in newly diagnosed hypertensive patients with normal cholesterol levels, significantly reduced PP and facilitated BP control, but did not affect endothelium-dependent dilatation. Further long-term large scale studies are needed to clarify the effect of various statins on endothelial functions of either hypercholesterolemic or normocholesterolemic hypertensive patients.*(Anadolu Kardiyol Derg 2003; 3: 331-7)*
Key Words: Simvastatin; essential hypertension; endothelial functions, flow mediated dilatation

Özet

Amaç: Hipertansiyonda endotel bağımlı vazodilatasyon (EBVD) bozulmaktadır. Statinlerin hiperlipidemik bireylerde endotel fonksiyonları üzerine olumlu etkileri gösterilmiştir. Bu çalışmada statin tedavisinin dislipidemisi olmayan hipertansif olgularda endotel fonksiyonları ve kan basıncı (KB) üzerine olan etkisi araştırılmıştır.
Yöntem: Çalışmaya yeni esansiyel hipertansiyon tanısı almış ve daha önceden ilaç kullanmayan 56 olgu prospektif olarak alındı. Tüm olgulara antihipertansif olarak bir anjiyotensin dönüştürücü enzim inhibitörü (ACE-İ) olan lisinopril (5 mg/g) ile başlandı. Olguların yarısı ise lipid düzeylerinden bağımsız olarak simvastatin (20mg/g) tedavisine randomize edildi. Olgular 12 haftalık tedavi öncesi ve sonrasında yüksek rezolüsyonlu vasküler ultrasonografi (USG) (7.5 mHz problu) ile brakiyal arterlerinin reaktif hiperemiye (EBVD) ve ayrıca dil altı nitrogliserine (endotelden bağımsız vazodilatasyon) yanıt açısından değerlendirildiler.
Bulgular: Çalışmayı 39 hasta tamamlayabildi (statin+ACE-İ grubunda 21 hasta ve tek başına ACE-İ alan grupta 18 hasta). Tedavi sonucunda her iki grupta da KB düzeylerinde yeterli düşme oldu. Statin+ACE-İ grubunda sistolik KB %23 (p=0.0001) ve diyastolik KB %23 (p=0.0001) azalırken, tek başına ACEI- İ alan grupta bu oranlar sırasıyla %20 (p=0.001) ve %21 (p=0.001) idi. Aynı zamanda nabız basıncı (NB) statin+ ACE-İ grubunda anlamlı azalmıştı (-%25, p=0.0001). Tek başına ACE-İ alan grupta ise NB azalması %16 (p=0.005) idi. Tüm hipertansif hastalarda bazal EBVD, sağlıklı kontrollere göre anlamlı derecede bozulmuştu (%13±8'e karşın %24±8, P=0.001). Tedavi sonrasında EBVD, sadece lisinopril alan grupta düzeldi (-%23, p=0.054), ancak bu düzelme istatistiksel olarak anlamlı değildi. Brakiyal arterlerinin reaktif hiperemideki değişimi LDL düzeylerindeki azalma, KB veya NB daki değişimlerle korelasyonu saptanmadı.
Sonuç: Yeni tanı almış esansiyel hipertansiyonlu olup normal kolesterol düzeylerine sahip hastalarda ACE-İ tedavisine statin eklenmesi NB'nı anlamlı azaltırken, KB kontrolünü kolaylaştırmaktadır, ancak endotel bağımlı vazodilatasyona bir etkisi saptanmamıştır. Bununla birlikte çeşitli statinlerin endotel fonksiyonlarına olan etkisine açıklık getirmek için gerek normo-kolesterolemik gerekse hiperkolesterolemik hipertansiflerde daha geniş ve uzun dönem çalışmalara gereksinim vardır. *(Anadolu Kardiyol Derg 2003; 3: 331-7)*
Anahtar Kelimeler: Simvastatin; esansiyel hipertansiyon, endotel fonksiyonu, endotel bağımlı vazodilatasyon

Adress for correspondence: Dr. Zulfikar Danaoğlu - Erzincan, Tel: +90.232 3742695, Fax: +90.232 3746618, E-mail: mekay@med.ege.edu.tr

Introduction

It is well established that endothelial functions are impaired in patients with essential hypertension (1, 2). In clinical studies, antihypertensive treatment with angiotensin-converting enzyme inhibitors (ACEI's) was found to improve vasodilating properties and to reduce vascular damage (3-4). Previous studies have shown that statins can improve endothelial functions which might be in part due to non-lipid-lowering effects (5). Recently several studies have found that a blood pressure reduction is associated with the use of statins (6), and addition of a statin to ACEI's have been shown to improve blood pressure control in hypertensive patients with hyperlipidemia (7-8). Moreover, recent animal data indicate that HMG-CoA reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species (9). The aim of the present study was to evaluate whether adding of statin therapy to ACEI's could influence the endothelium dependent vasodilatation (EDD) in patients with essential hypertension in the absence of hyperlipidemia.

Methods

Study population and study design: This randomized prospective clinical study included 56 patients with newly diagnosed stage I and II hypertensive disease (essential hypertension) who were not taking any lipid-lowering or antihypertensive drugs. To be eligible patients had to have diastolic blood pressure > 90 mm Hg and, and systolic blood pressure > 140 mm Hg.

The exclusion criteria were hyperlipidemia (total cholesterol levels >240 mg/dl or triglycerides >150 mg/dl), diabetes mellitus, a history of atherosclerotic vascular disease, heart failure, and liver or renal disease. All subjects with endocrine, inflammatory, metabolic, or malignant diseases, women of childbearing potential, postmenopausal women receiving hormone replacement therapy, patients with physical or psychosocial disorders that could interfere with protocol adherence, and patients with known hypersensitivity to statins or ACE inhibitors were also excluded. Twenty healthy volunteers with normal blood pressure selected among the hospital staff (14 males and 6 females) constituted the control group. The study protocol was approved by the institutional review board.

All enrolled patients received lisinopril 5 mg/day as a starting antihypertensive therapy and half of them were randomized to statin treatment (simvastatin 20mg/day) irrespective of their serum lipid levels. The patients were instructed to maintain the same diet (containing 120 mmol of sodium and 2200 kcal, 30% of which came from fatty acids (10% saturated fatty acids) throughout the study. Patients did not receive any other drugs that can affect the lipid levels, and endothelial functions throughout the study.

At baseline, all patients underwent physical examinations, ECG, echocardiography, chest X-ray films, and fasting blood chemistry to exclude secondary hypertension, hepatic or renal impairments, diabetes, coagulation and fibrinolytic abnormalities, or other metabolic disorders. All subjects underwent brachial artery ultrasonographic examination for the measurement of endothelium dependent flow mediated dilation (FMD) and endothelium-independent nitrate mediated dilation (NMD) before randomization and at the end of 12 weeks treatment. Compliance to treatment regimens was assessed at each visit by pill count.

Blood pressure was measured with a mercury sphygmomanometer after 5 minutes of rest, as recommended by the 6th Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (10). Patients were seated with their arm bared and supported at heart level. Two readings, separated by 2 minutes, were obtained and averaged. Additional readings were obtained if these readings differed by >5 mm Hg. Pulse pressure was calculated by subtraction of diastolic blood pressure from systolic blood pressure. Mean blood pressure was calculated by the addition of two thirds of the pulse pressure to diastolic blood pressure. Body mass index was calculated by dividing the weight in kilograms by the square of the height in meters.

Laboratory assessment: Before treatment, and at each visit, 12-hour overnight fasting blood samples were obtained from each patient for determinations of total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, apolipoprotein (Apo) A1 and apolipoprotein B. A complete blood count and measurements of serum creatine kinase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transpeptida-

se, blood urea nitrogen, serum creatinine, uric acid, and a urine examination were performed as safety evaluations. All the lipoprotein analyses for lipid determination were carried out after an overnight fast on two occasions. Total cholesterol, high density lipoprotein (HDL) cholesterol and triglycerides were assessed enzymatically on an automatic analyzer (Techicon Dax 48, Bayer Diagnostics, Tokyo, Japan). The low density lipoprotein (LDL) cholesterol was calculated by the Friedewald formula: {LDL = total cholesterol-(TG/5+HDL} (11). The apoproteins B and A1 values were assessed by immunoturbidometry (Hitachi BM 704, Boehringer-Mannheim, Germany).

Vascular assessment: The noninvasive determination of endothelial dysfunction was performed according to the method described by Celermajer et al. (12). Imaging studies of the brachial artery were performed using a high-resolution ultrasound machine (Hewlett-Packard SONOS 2500, Andover, Massachusetts) equipped with a 7.5-MHz linear-array transducer. All vasoactive medications were withheld for 24 hours before the procedure. The subjects remained at rest in the supine position for at least 15 min before the examination started. Subject's right arm was comfortably immobilized in the extended position to allow consistent recording of the brachial artery 2–4 cm above the antecubital fossa. All ultrasound images were recorded on S-VHS videotape for subsequent blinded analysis. Recordings of both B-mode and pulsed Doppler spectral curve were taken at rest, during reactive hyperemia (endothelium-dependent vasodilatation), and following the sublingual application of isosorbide dinitrate (endothelium-independent vasodilatation). After baseline measurements, a sphygmomanometer cuff, placed around the right upper arm proximal to the imaged artery segment, was inflated to the pressure of 240 mmHg for 4.5 minutes. To verify that suprasystolic compression of the brachial artery caused adequate increase in blood flow, flow velocity was measured at rest and within 15 sec after cuff deflation. Blood flow, pressure and end-diastolic diameter were recorded at 30 sec intervals for 300 sec after cuff release and at 6, 8 and 10 min until recovery to baseline values. After reestablishing of baseline conditions 15 to 20 minutes later, measurements of arterial diameter and flow velocity were repeated, followed by sublingual isosorbide dinitrate administration at a dose of 5 mg in order to assess endothelium-independent vasodilatation. Four minutes later, measurements of arterial diameter and flow velocity were repeated. The arterial diameter was measured in millimeters as the distance between the anterior wall media-adventitial interface ("m" line) and the posterior wall intima-lumen interface at end-diastole, coincident with the R wave on the continuously recorded electrocardiogram at 2 sites along the artery. The maximum FMD and NMD diameters were calculated as the average of the three consecutive maximum diameter measurements after hyperemia and nitroglycerin, respectively. The FMD and NMD were then calculated as the percent change in diameter compared with baseline resting diameters.

Statistical analysis: SPSS (Chicago, Illinois) for Windows (Version 10.0) was used for all statistical analysis. Data are presented as percentages for discrete variables and as mean± SD for continuous variables. A p value of <0.05 (two-sided) was regarded as statistically significant. Comparison of groups was tested by Chi-square and Mann Whitney U tests. Paired t test or Wilcoxon Signed rank tests were performed to compare the continuous variables before and 3 months after the treatment regimens according to the distribution pattern of the variables.

Results

Of the initial 56 patients, 17 were lost during follow-up: four patients with persistent cough related to the ACEI, one patient with high postprandial blood glucose levels, 3 patients requiring more aggressive antihypertensive treatment, and 9 subjects who did not complete the protocol. A total of 39 patients (10 men, 29 women) completed the study (21 patients in the statin + ACE inhibitor group, and 18 patients in the ACE inhibitor alone group).

Table 1 lists the baseline demographic characteristics of the study groups. No significant differences were observed between age, gender, sex distribution, and coronary risk factors. During the entire study, body mass index did not vary significantly. Mean dietary compliance did not change significantly in both groups during the study. Compliance with the medication regimen was average 96% for both groups. Smoking habits in both groups remained unchanged. Serum creatinine, glucose, urea, bilirubin, uric acid, creatinine phosphokinase, aspartate aminotransferase, and alanine aminotransfera-

Table 1: Baseline characteristics of patients

	Simvastatin + Lisinopril	Lisinopril alone
n	21	18
Gender (m/f)	4/17	6/12
Mean age (yr, mean±SD)	52 ± 3	54 ± 4
Cigarette smoking (%)	19	22
Weight (kg)	71.7±9	74.0±11
Family history (%)	47	50
p = NS for all parameters.		

se levels were not affected by the treatments. Serum potassium level slightly increased (+ 0.9 meq/dl) in both groups.

The mean lipid and lipoprotein values at baseline and at the end of 12 weeks period in both groups are presented in Table 2. Baseline values did not differ among the groups. Plasma total cholesterol, triglycerides, and LDL cholesterol, decreased from baseline levels by 17% (p=0.0001), 23% (p=0.103), and 16% (p=0.041), respectively, in statin+ACEI group. The HDL cholesterol levels increased by 3% in this combination (p=0.450). Howe-

Table 2: Comparison of plasma lipid levels and blood pressure between groups

	Simvastatin + Lisinopril	Lisinopril Only	
	(n = 21)	(n = 18)	P value
Total Cholesterol (mg/dl)			
Baseline	194±22	188±30	0.48
3rd month	161±36	180±41	0.13
Triglycerides (mg/dl)			
Baseline	153±73	136±69	0.46
3rd month	132±57	129±74	0.89
LDL Cholesterol (mg/dl)			
Baseline	118±15	109±22	0.14
3rd month	101±31	114±28	0.18
HDL Cholesterol (mg/dl)			
Baseline	46±6	46±14	1.0
3rd month	48±7	47±12	0.75
Systolic BP (mm Hg)			
Baseline	160±11	158±14	0.62
3rd month	122±9	126±19	0.40
Diastolic BP (mm Hg)			
Baseline	99±9	104±10	0.12
3rd month	76±6	82±8	0.01
Mean BP (mmHg)			
Baseline	140±9	140±14	1.0
3rd month	107±7	113±8	0.02
Pulse pressure			
Baseline	61±11	54±14	0.09
3rd month	46±8	46±10	1.0
FMD %			
Baseline	16±7	13±8	0.22
3rd month	16±7	18±7	0.54
NMD% (baseline)	21±8	19±9	0.41

All values are expressed as mean±SD
BP: blood pressure, FMD: flow mediated vasodilatation, NMD: nitrate mediated vasodilatation.
To convert values for cholesterol in mg/dl to millimoles per liter, multiply by 0.026, and values for triglycerides in mg/dl to millimoles per liter, multiply by 0.011.

ver, there were no significant changes in any of the lipid parameters in the ACEI alone group.

Table 2 additionally shows the efficacy of treatments on resting blood pressure measurements. Systolic and diastolic blood pressure levels were substantially reduced in both groups after 12 weeks of treatment. Blood pressure regulation was obtained in statin+ACEI group with reduction of systolic blood pressure by 23% (p=0.0001) and diastolic blood pressure by 23% (p=0.0001). In the ACEI alone group these values were 20% (p=0.001) and 21% (p=0.001), respectively. Mean arterial pressure decreased significantly in both groups (by 24% in statin+ACEI group, p=0.0001; by 19% in ACEI alone group, p=0.001). Meanwhile, pulse pressure decreased significantly only in the statin+ACEI group (-25%, p=0.0001). The mean change observed in pulse pressure of the ACEI alone group was -16% (p=0.05) .

Brachial artery Doppler findings are presented in Table 2. Baseline FMD was significantly impaired in overall patients with hypertension as compared with healthy control subjects (13 ± 8% vs. 24±8%, respectively, p = 0.001). The FMD, NMD measurements at baseline did not differ statistically among the treatment groups. At the end of the 12 weeks follow up period, FMD slightly increased in patients receiving only lisinopril (23%, p=0.054), but this improvement was not statistically significant. Meanwhile there was no significant improvement in statin group's FMD values. Correlation analyses revealed that there were no significant correlation between FMD improvement and LDL reduction, blood pressure changes or pulse pressure changes in both groups.

Discussion

Experimental and clinical investigations have demonstrated that endothelium-dependent vascular relaxation is impaired in hypertensive subjects (1, 2). There are several reports suggesting that HMG-CoA reductase inhibitors can improve endothelial function and the endothelium-dependent arterial vasodilatation that are typically altered in patients with increased plasma cholesterol level (13, 14). Statins may cause vasodilatation and decrease in blood pressure by restoring the endothelial dysfunction that frequently accompanies hypertension (6-8). Moreover, experimental evidence indicates that the effect of statins on the endothelium might be in part due to nonlipid effects (5). However in humans there are no data regarding possible additional effects of statin treatment on endothelial functions in normocholesterolemic hypertensives. Starting out from this point, we aimed to investigate the effect of statin treatment on endothelium-dependent dilatation and blood pressure in a very selected sample of never-treated essential hypertensive patients with normal cholesterol levels.

In our 12 weeks study, both groups showed significant reductions in systolic and diastolic blood pressure levels. But this reduction was more striking in the statin+ACEI group. These observed changes in blood pressure were consistent with the results of recent studies, which have found a blood pressure reduction associated with the use of statins. In two animal studies, both lovastatin and pravastatin significantly decreased mean arterial pressure in spontaneously hypertensive rats after a few weeks of treatment (15,16). Similarly, in 26 healthy normotensive individuals with high plasma cholesterol levels, systolic blood pressure increase triggered by the mental arithmetic test was blunted after 6 weeks of treatment with lovastatin (17). In a randomized, double-blind, placebo-controlled crossover study, pravastatin has blunted the diastolic blood pressure increase induced by angiotensin II and norepinephrine after 3 weeks of treatment (18). In two other studies, fluvastatin (40 mg/day) significantly decreased systolic and diastolic blood pressures after 3 months of treatment in hypertensive patients with hypercholesterolemia and this effect was independent from cholesterol lowering mechanism (19-20). In another study, Borghi et al. demonstrated that the use of statins for 3 months in combination with antihypertensive drugs can improve blood pressure control in patients with uncontrolled hypertension and high serum cholesterol levels (21). Meanwhile, such an effect was not confirmed on either normotensive or hypertensive patients in whom blood pressure was controlled (22-24). Glorioso et al. (6) also demonstrated that the HMG-CoA reductase inhibitor pravastatin significantly lowers blood pressure in patients with coexisting essential hypertension and primary hypercholesterolemia. All these data might be the explanation of significant reduction in stroke observed in both the CARE and LIPID studies (25-26).

Recently, addition of a statin to ACEI treatment has been shown to improve blood pressure control

in hypertensive patients with hyperlipidemia. In an open phase 3 design study, Nazzaro et al. (8) used simvastatin with enalapril in 30 hypertensive patients with hyperlipidemia for 14 weeks. During their combination treatment, a significant additive effect on hypercholesterolemia, structural vascular damage, blood pressure, and FVR was observed. Similarly, Sposito et al. (7) observed a greater reduction in blood pressure after 16 weeks of statin (lovastatin-20mg/d or pravastatin-10mg/d) plus ACEI (enalapril-20 mg/d or lisinopril-40mg/d). All these data were obtained from subjects with high cholesterol levels. These findings might suggest that ACEI and statin treatments possess a distinct and additive positive vascular effect that may critically modify the structural characteristics and functional responses of peripheral arteries during stressful stimuli in hypercholesterolemic hypertensive subjects.

In our selected population, the HMG-CoA reductase inhibitor simvastatin when combined with an ACEI significantly decreased peripheral pulse pressure which is a good surrogate marker of large arterial stiffness. There is now increasing evidence that high pulse pressure is an independent risk factor for cardiovascular mortality in different populations (27). To the best of our knowledge, there is only one study dealing with the effects of statins on pulse pressure. Glorioso et al. (6) have observed a mean of 3 mmHg decrease with pravastatin in hypercholesterolemic patients. In our study simvastatin combined with an ACEI, decreased pulse pressure significantly in normocholesterolemic hypertensive patients, but in the ACEI alone group the decrease of this parameter was not statistically significant. The mechanism behind this is unclear but may be related to the beneficial effect of statins on endothelial function. But our results on the FMD of the groups did not support this expectation: the addition of a statin to an ACEI in normocholesterolemic hypertensive patients did not show an additional benefit on endothelium-dependent dilatation. Baseline FMD was better in the statin group which might be a selection bias. The high percent of female patients in the statin group might also have affected the baseline FMD. But, although the baseline FMD was worse in the statin group, the improvement in ACEI alone group was also not significant. Our result is consistent with the Kuroedov et al's findings (28). In their normocholesterolemic hypertensive patients, 1 month of treatment with simvastatin (10 mg/day) did not cause substantial increase of endothelium-dependent vasodilatation which was assessed by photoplethysmography of cutaneous vessels (norepinephrine and histamine). These results may suggest that the mechanism of endothelial dysfunction in hypertensive patients with high cholesterol levels is different than normocholesterolemic hypertensive patients. However, Wassmann et al. (29), demonstrated that the 30 day treatment of spontaneously hypertensive rats with atorvastatin causes a significant reduction of systolic blood pressure and a profound improvement of endothelial dysfunction mediated by a reduction of free radical release in the vasculature. They have assessed endothelial dysfunction by carbachol-induced vasorelaxation in aortic segments. Their suggestion was that the underlying mechanism could in part be based on the statin-induced down-regulation of angiotensin I receptor expression. The inconsistency of these results might be based on the type of the statins used. The mechanism responsible for the beneficial effect of statins on pulse pressure and blood pressure control may also be related to their interaction with angiotensin II receptors (30).

As a conclusion, addition of simvastatin to ACEI treatment in newly diagnosed hypertensive patients with normal blood cholesterol levels, significantly reduced pulse pressure and facilitated the blood pressure control, but did not affect the endothelium-dependent arterial vasodilatation. Further long term large scale studies are needed to clarify the effect of various statins on endothelial functions of either hypercholesterolemic or normocholesterolemic hypertensive patients.

Acknowledgment: This study was funded as project by EUTF-EBİLTEM.

References

1. Lockette W, Otsuka Y, Carretero O. The loss of endothelium-dependent vascular relaxation in hypertension. Hypertension 1986;8 (Suppl):II61-6.
2. Panza JA, Quyyumi AA, Brush JE Jr, Epstein SE. Abnormal endothelium-dependent vascular relaxation in patients with essential hypertension. N Engl J Med 1990; 323: 22-7.
3. Taddei S, Virdis A, Ghiadoni L, Mattei P, Salvetti A. Effects of angiotensin converting enzyme inhibition on endothelium-dependent vasodilatation in essential hypertensive patients. J Hypertens 1998;16:447-56.
4. Izzo JL Jr. The role of the renin-angiotensin system in vascular health: use of ACE inhibition to improve vascular function. Heart Dis 2000;2:380-3.

5. Rosenson RS. Non-lipid-lowering effects of statins on atherosclerosis. Curr Cardiol Rep 1999;1:225-32.
6. Glorioso N, Troffa C, Filigheddu F, et al. Effect of the HMG-CoA reductase inhibitors on blood pressure in patients with essential hypertension and primary hypercholesterolemia. Hypertension 1999;34:1281-6.
7. Sposito AC, Mansur AP, Coelho OR, Nicolau JC, Ramires JA. Additional reduction in blood pressure after cholesterol-lowering treatment by statins (lovastatin or pravastatin) in hypercholesterolemic patients using angiotensin-converting enzyme inhibitors (enalapril or lisinopril). Am J Cardiol 1999 ;83:1497-9.
8. Nazzaro P, Manzari M, Merlo M, et al. Distinct and combined vascular effects of ACE blockade and HMG-CoA reductase inhibition in hypertensive subjects. Hypertension 1999;33:719-25.
9. Wassmann S, Laufs U, Baumer AT, Muller K, et al. HMG-CoA reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species. Hypertension 2001;37:1450-7.
10. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI), The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413-46.
11. Friedewald WT, Levy RI, Frederickson DS. Estimation of concentration of low density lipoprotein cholesterol in plasma, without the use of preparative ultracentrifuge. Clin Chem 1972;18:499-502.
12. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992; 340:1111-5.
13. Egashira K, Hirooka Y, Kai H, et al. Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. Circulation 1994;89:2519-24.
14. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-Co enzyme A reductase inhibitor, improves endothelial function within 1 month. Circulation 1997;95:1126-31.
15. Wilson TW, Alonso Galicia M, Roman RJ. Effects of lipid-lowering agents in the Dahl salt-sensitive rat. Hypertension 1998;31:225–31.
16. Jiang J, Roman RJ. Lovastatin prevents development of hypertension in spontaneously hypertensive rats. Hypertension 1997;30:968–74.
17. Sung BH, Izzo JL Jr, Wilson MF. Effects of cholesterol reduction on blood pressure response to mental stress in patients with high cholesterol. Am J Hypertens 1997;10:592-9.
18. Straznicky NE, Howes LG, Lam W, Louis WJ. Effects of pravastatin on cardiovascular reactivity to norepinephrine and angiotensin II in patients with hypercholesterolemia and systemic hypertension. Am J Cardiol 1995;75:582–6.
19. Abetel G, Poget PN, Bonnabry JP. Hypotensive effect of an inhibitor of cholesterol synthesis (fluvastatin): a pilot study. Schweiz Med Wochenschr 1998;128:272–7.
20. Jarai Z, Kapocsi J, Farsang C, et al. Effect of fluvastatin on serum lipid levels in essential hypertension. Orv Hetil 1996;137:1857–9.
21. 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;35:549-55.
22. O'Callaghan CJ, Krum H, Conway EL, et al. Short term effects of pravastatin on blood pressure in hypercholesterolaemic hypertensive patients. Blood Press 1994;3:404–6.
23. D'Agostino RB, Kannel WB, Stepanians MN, D'Agostino LC. Efficacy and tolerability of lovastatin in hypercholesterolemia in patients with systemic hypertension. Am J Cardiol 1993;71:82–7.
24. Kool M, Lustermans F, Kragten H, et al. Does lowering of cholesterol levels influence functional properties of large arteries? Eur J Clin Pharmacol 1995;48:217–23.
25. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335:1001-9.
26. Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349-57.
27. Kingwell BA. Large artery stiffness: implications for exercise capacity and cardiovascular risk. Clin Exp Pharmacol Physiol 2002 ;29: 214-7.
28. Kuroedov AY, Nikolaeva AA. Effect of simvastatin on parameters of vascular reactivity in patients with hypertension and various baseline levels of blood lipids. Cardiology 2001;4:123-8.
29. Wassmann S, Laufs U, Baumer AT, et al. HMG-CoA reductase inhibitors improve endothelial dysfunction in normocholesterolemic hypertension via reduced production of reactive oxygen species. Hypertension 2001;37:1450-7.
30. Borghi C, Veronesi M, Prandin MG, Dormi A, Ambrosioni E. Statins and blood pressure regulation. Curr Hypertens Rep 2001;3:281-8.