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# Pleiotropic and Lipid–lowering Effects of Statins in Hypertension

**Lulzim Selim Kamberi[1], Aurora Bedri Bakalli[1], Norma Muhamet Budima[1], Daut Rashit Gorani[1] Ahmet Muzaffer Karabulut[2], Kelmend Talat Pallaska[1]**
**University Clinical Centre of Kosova, Prishtina, Kosovo[1]**
**Department of Cardiology, Istanbul Medicine Hospital, Istanbul, Turkey[2]**

**Corresponding author:** Lulzim Kamberi, MD. University Clinical Centre of Kosova, nn, Mother Teresa, 10000 Prishtina, Kosovo, +377 44 14 56 80; E-mail: lulzimkamberi@gmail.com

**ORIGINAL PAPER**

SUMMARY

**Background.** Data on the lowering effects of statins in hypertensive patients have been mixed and highly controversial. Some studies shows reductions effects of statins in blood pressure, whereas others do not. The evidence in the literature on the effects of statins on blood pressure raises the possibility that statins may directly lower blood pressure in addition to reduce cholesterol levels–pleiotropic effects of statins. **Aim of the study.** The role of statins as additional treatment in patients with severe hypertension and advanced aortic atherosclerotic plaques. Methods. We enrolled 62 patients. Study has been approved by Committee of Ethics and patients signed a Term of Free Informed Consent. All patients were studied with transoesophageal echocardiography at baseline and 12 months after enrolment. Inclusion criteria were severe hypertension and presence of aortic atherosclerotic plaques. Patients have been divided into two groups; group A (treated with antihypertenives and statins) and group B (treated, just with antihypertensives). **Results.** Twenty patients, of totally 38, from group A (20/38 or 52.6%) had significantly plaque reduction. One patient of totally 24 (1/24 or 4.1% ) from group B had significantly atherosclerotic plaque reduction. Difference of plaques reduction between two groups was highly significant. Regarding blood pressure levels, statins users had significantly reduction on systolic and diastolic blood pressure compared to statins nonusers. **Conclusion.** Hypertensive patients with presence of AA plaques treated with antihypertensives and statins have more BP reduction compared will hypertensive patients treated with antihypertensives alone.

**Key words: statins, hypertension, atherosclerotic aortic plaque, pleiotropic effects of statin.**

## 1. INTRODUCTION

The effects of statins on blood pressure (BP) have been studied in several clinical trials. Some studies shows reductions effects of statins in blood pressure, whereas others do not (1, 2, 3, 4). Results of recent meta-analysis of some trials, related to effects of statins on BP, found that systolic but not diastolic BP was significantly lower in patients using statins (5). Many other controversial studies have been published about effect of statins in BP component (systolic or diastolic); different aspects of population (e.g. hypercholesterolemic, ages) stages of high BP, treatment etc. One study confirms in a large random sample of community individuals that statins significantly lowers systolic and diastolic BP. Statins lowered diastolic BP by a similar amount in users and nonusers of antihypertensive medication. Moreover, among nonusers of antihypertensive medications the BP-lowering effect of statins increased with higher levels of diastolic BP (6). Patients with controlled hypertension who are also hypercholesterolemic have no change in blood pressure levels with additional statin treatment (7, 8, 9), whereas others demonstrate that additional statin therapy led to a greater reduction in blood pressure in patients with uncontrolled hypertension (10, 11). The differences in study outcomes may relate to many factors as sample size, different antihypertensive drugs, methodology etc. Adjustment for total cholesterol level decreased the BP reducing effect of statins by a small amount. This suggests that the BP lowering effects of statins are mediated mostly by mechanisms other than cholesterol lowering–pleiotropic effects of statins (12). Pleiotropic effects of statins raise the possibility that these agents may directly lower BP in addition to reducing serum cholesterol levels. Statins activate endothelial nitric oxid synthase, downregulate angiotensin II type 1 receptors, reduce levels of endothelin-1 and decrease the

vascular production of reactive oxygen species (13, 14, 15, 16). Statins, finally, improve arterial compliance (2, 17). Of 96 patients with severe longstanding hypertension (investigated by transoesophageal echocardiography (TEE)), atherosclerotic plaques in thoracic aorta (AA plaques), grade 2 and/or grade 3 have been reported in 82.3% of cases (18). Previous studies have reported the role of lipid-lowering agents in the treatment of AA in patients with hyperlipidaemia and their effect on plaque regression (19). One study suggests that statins reduce the risk of AA progression and increase plaque thickness reduction (20).

## 2. METHODS

All of the 62 patients, enrolled in the study,approved by Committee of Ethics, signed a Term of Free Informed Consent. Inclusion criteria were severe hypertension (stage 2 by JNC 7) (21) not treated (different reasons) for at least 1 year and presence of aortic (thoracic part) atherosclerotic (AA) plaques. Patients has been divided into two groups; group A and group B. Group A, 38 patients, has been treated with same antihypertensive medication including ACE-inhibitors (lisinopril 20 mg), diuretics (HCTZ 25 mg)), beta-blockers (bisoprolol 5 mg ) and statins (atorvastatin 20 mg ); whereas, 24 patients of group B, has been treated with same antihypertensive drugs but without statins. All of the patients selected to be with normal value of glicemia and lipid profile. A complete medical history, physical examination, clinical evaluation (heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse pressure and electrocardiography (ECG) were recorded), transthoracic echocardiography (TTE) and TEE were used by expert cardiologists for clinical evaluation. The procedure that we used for performing TEE in our laboratory has been reported (18). Patients were studied with TEE at baseline and 12 months after enrolment in the study. Data from multiplane views of the thoracic aorta were obtained in detail. Exactly same images of the position and extension of the plaques were used at follow-up for every patient measuring their distance (in millimeters) from the incisors, and dividing the short-axis plane of the aorta into four perpendicular clockwise sectors. Aorta has been divided as ascending aorta, and descending aorta using orientation landmark, right pulmonary artery and the left subclavian artery respectively. Aortic plaque progression was defined as an increase in maximal plaque thicknes by ≥1 mm or regression was defined as a decrease in maximal thickness of atheromatous plaque by ≤1mm. Atherosclerotic plaques were defined as moderate (those with a thickness between 1 and 3.9 mm) and severe aortic plaques (those with a thickness ≥4 mm) (22). All examinations were recorded, reviewed and measured by two independent senior cardiologists blinded to each other. BP was measured and recorded three to four times at home following the recommendations of the American Heart Association (23). The results were analyzed by a standard method of descriptive statistics using Pivot Table of Excel Office 2007 and Simple Interactive Statistical Analysis (SISA).

## 3. RESULTS

Table 1. depicts the baseline demographic data of the study population, number of patients included in the study and their TEE findings related to AA plaque; also in the same table are presented comparison between groups and subgroups. Mean age shows no significant differences between groups or subgroups studied (Table 1). Twenty patients, of totally 38, from group A (20/38 or 52.6%) had significantly plaque reduction referred as subgroup rA; 18 patients of the group A (18/38 or 47.4%) had not or not significantly plaque reduction-subgroup nrA. None of the patients had atherosclerotic plaque progression.

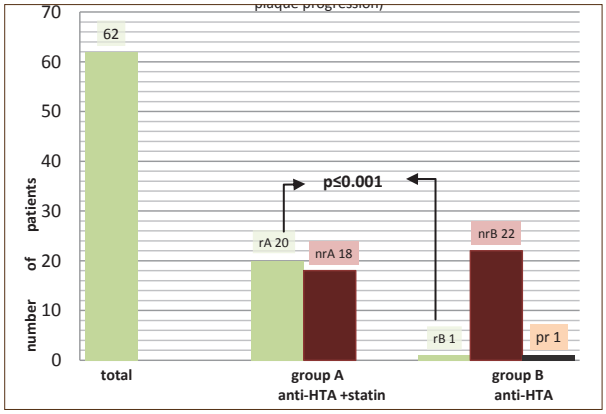


Diagram 1. Represent total number of patients, group A (with nr of pt with plaque reduction (rA) and no plaque reduction (nrA)) and group B (with nr of pt with plaque reduction (rB), no plaque reduction (nrB) and plaque progression)

| Group / p value Nr. of pt. 62 / subgroups | A 38 | | B 24 | | p≤0.005; S rA/nrA rA/rB rA/nrB nrA/nrB | | |
|---|---|---|---|---|---|---|---|
| AA plaque | r* | nr** | r | nr | pr$ | | |
| Nr. | 20 (52.6%) | 18 (47.4%) | 1 | 22 | 1 | S | |
| Male | 7 | 5 | 0 | 11 | 1 | | |
| Mean age ± st. dev | 62.46 ± 8.02 | 61.80 ± 7.67 | | 62.80 ± 6.80 | | NS | NS NS |
| Smoker | 9 | 10 | 0 12 | 1 | NS | NS | |
| SBP& (ABPM£) ± st. dev | 138.2 ± 3.21 | 140.1 ± 3.38 | | 143.39 ± 2.12 | | NS | S S |
| DBP¥( ABPM) ± st. dev | 89.17 ± 3.21 | 90.95 ± 2.94 | | 93.28 ± 3.32 | | NS | S NS |

Table 1. Detailes about values and statistical findings. * reduction; ** nonreduction; $ progression; & systolic blood pressure; ¥ diastolic blood pressure; £ ambulatory blood pressure measurement

One patient of totally 24 (1/24 or 4.1% ) from group B had significantly atherosclerotic plaque reduction-subgroup rB; one patient had atherosclerotic plaque progression-pr.

Difference of plaques reduction between two groups was highly significant (diagram 1). Regarding BP levels, statins users had significantly reduction on systolic BP compared to statins nonusers.

Systolic BP (SBP) was lowest in subgroup rA, followed by SBP of nrA and than nrB. Diastolic BP (DBP) was lowest in subgroup rA, followed bt DBP of nrA and than nrB.

## 4. DISCUSSION

The role of statins in reduction of AA plaques have been reported (19, 20). We have found (in TEE of control) that hypertensive patients treated with anti-HTA and statins (group A) showed significantly more AA plaques reduction 20/38 or 52.6%, compared to hypertensive patients treated with anti-HTA but without statins 1/24 or 4.1%). AA plaque reduction of group A of 52.6% was greater than those reported of 38.3% (19) but our study group of patients was very specific (severe hypertension not treated for long time).

The effects of statins on BP have been studied in several clinical trials with controversial results (1, 2, 3, 4, 7, 8, 9). Strazzullo et al. in meta-analysis trials (5) found that systolic BP was significantly lower in patients using statins. Leonelo, confirms in a large random sample of patients that statins significantly lowers systolic and diastolic BP (6). The results of our study group of patients, followed for 12 months, shows that all patients (group A and group B) had significantly BP reduction.

Highest decrease of high blood pressure was achieved in patients of group A with AA plaque reduction (rA); systolic/diastolic BP was 138.2 ± 3.21 / 89.17±3.20, respectively, followed by patients of the same group but without AA plaque reduction (nrA); systolic/diastolic BP was 140.1 ± 3.38 / 90.95±2.94, respectively, and finally significant reductions of BP but not as in group A (two subgroups of group A) had patients of group B without AA plaque reduction (nrB); systolic/diastolic was 143.39 ± 2.12 / 93.28±3.32, respectively. Reduction of BP (systolic and diastolic) was significantly lower in group A with AA plaque reduction compared with group B without AA plaque reduction; rA vs. nrB. Systolic, but not diastolic; BP reduction was also significantly lower in group A with no AA reduction compared to group B with no AA plaque reduction nrA vs. nrB.

But, reduction of BP was always much more in group A with antihypertensive and statin, than in group B with antihypertensive without statins. BP reduction was more in group A with AA reduction subgroup rA than in group A without AA plaque reduction subgroup nrA; both subgroups were treated with antihipertensives and statins but, BP reduction was more in group with AA plaques reduction; we suppose that this is because of pleiotropic effects of statins (13, 14, 15, 16) and their effect in improvement of arterial compliance (2, 17).

## 5. CONCLUSION

Hypertensive patients with presence of AA plaques treated with antihypertensives and statins have more BP reduction compared will hypertensive patients treated with antihypertensives alone. Atherosclerotic plaque reduction, as a result of statins treatment, has much more reduction effect on lowering of BP (addition to antihypertensives) than if reduction of atherosclerotic plaque was not achieved despite treatment with statins (addition to antihypertensives).

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