The influence of low-dose atorvastatin on lipid levels and endothelial vascular function in patients with significant coronary artery stenosis

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Abstract

Background: Hyperlipidaemia is a well-established risk factor of the progression of coronary artery disease (CAD). Statins such as atorvastatin, as lipid-lowering agents, can not only normalise serum lipid levels, but also may improve endothelial function, reduce vascular inflammation and enhance plaque stability.

Aim: To evaluate the efficacy of a low-dose atorvastatin regimen (10 mg daily) in patients with CAD.

Methods: Seventy-nine patients with stable angina of II or III functional class and angiographically significant stenosis of coronary arteries (>70%) entered a 12-week treatment period with atorvastatin 10 mg/day. Lipid profile, which included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG) were assessed at baseline and after treatment at week 12. In addition, flow-mediated vasodilatation (FMD) and nitrate-induced dilation (NID) of the brachial artery were measured before and after treatment.

Results: Among 79 patients included in the study, in 54 (68%) the target TC value <5.0 mmol/l, and in 51 (65%) the LDL-C level <3.0 mmol/l were achieved. Atorvastatin decreased TC level by 31% (p<0.01), LDL-C level by 35% (p<0.01), TG level by 23% (p<0.01) and increased HDL-C level by 8% (p<0.01). FMD was increased by 61 % (p<0.01) and normalised in 88% of patients after 3-month therapy of atorvastatin. NID was increased by 16% (p<0.05).

Conclusion: Low-dose treatment with atorvastatin (10 mg daily) is effective in reducing blood lipids and is associated with the improvement of endothelial function in patients with CAD.

Key words: coronary artery disease, lipids, endothelium, low-dose atorvastatin

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Introduction

Hyperlipidaemia is a well-established risk factor for the progression of coronary artery disease (CAD) [1]. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are the lipid-lowering agents and are well-known for their ability to normalise patients' serum lipid levels [2]. Statins have unequivocally shown the importance of cholesterol lowering in the prevention of morbidity and mortality due to CAD [3]. However, the overall benefits observed with statins appear to be greater than what might be expected from changes in lipid levels alone, suggesting effects beyond cholesterol lowering [4]. Statins appear to have additional cholesterol-independent or pleiotropic effects, including the improvement of endothelial function, reduction of vascular inflammation and enhancement of plaque stability [5]. The optimal statin dosing in CAD patients has not yet been established and should take into account high economic expenditure.

The aim of this study was to evaluate the efficacy of a low-dose atorvastatin regimen (10 mg daily) in patients with CAD.

Methods

Seventy-nine patients aged 42-73 years (53 male, 26 female, mean age 56.8 \pm 5.7) with stable CAD were enrolled in the study. Patients were in the CCS II or III

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functional class (Canadian Cardiovascular Society Functional Classification of Angina Pectoris) and had heart failure (II or III NYHA functional class) with left ventricular (LV) ejection fraction >40%. All patients had angiographically significant stenosis of coronary arteries (>70%). Exclusion criteria consisted of acute coronary syndrome, diabetes or LV ejection fraction <40%.

Patients entered a 12-week treatment with atorvastatin 10 mg/day (Lipitor, Pfizer) in addition to standard therapy. Seventy-seven (97%) patients received antiplatelet agents, 73 (94%) received β -blockers, 63 (80%) received ACE-inhibitors and 69 patients (87%) received nitrates.

Lipid profile, which included total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), was assessed before and after 12 weeks of therapy (ELISA).

We also studied the endothelium-dependent vasorelaxation of the brachial artery to evaluate the endothelium vascular function [6]. We examined the endothelium-dependent vasorelaxation, which is measured as % flow-mediated vasodilatation (FMD), and endothelium-independent dilatation, which is measured as % nitrate--induced dilation (NID) of the brachial artery at baseline and after three months of therapy. We performed ultrasound measurement of the brachial artery diameter non-invasively both at rest and during reactive hyperaemia, which causes endothelium-dependent vasodilatation. We measured brachial artery diameters non-invasively using a 7.5 MHz ultrasound machine at rest, during reactive hyperaemia, and after sublingual nitroglycerine administration. Brachial artery diameter was measured using B-mode ultrasound images. Changes in the diameter of the brachial artery were measured at rest and for 60s after cuff deflation. Then, after 15 min. rest, sublingual nitroglycerine was administered, and 3 to 4 min. later the last scan was performed. Endothelial dysfunction was diagnosed if FMD was less than 10%.

Statistical analysis

The results are expressed in terms of arithmetic means (X) \pm standard deviation (SD). The statistical significance of the difference between the means was evaluated by Student's t test. The correlation between parameters was analysed using the Pearson correlation test and a p value <0.5 was accepted as significant.

Results

All patients completed the entire treatment period. Among them, 23 (29%) had stable class II CAD and 56 (71%) had class III CAD. Forty-eight (61%) patients had arterial hypertension, 42 (53%) had NYHA class II heart failure, and 37 (47%) had NYHA class III. The mean LV ejection fraction was 51.5±4.7%.

Single-vessel disease was documented in 27 (34%) patients, two-vessel CAD in 32 (41%) patients, and three or more vessel disease in 20 (25%) patients. In patients with three or more stenosed coronary arteries, the mean LV ejection fraction was lower than in those with one or two coronary lesions (p<0.05).

In 82% of patients, the baseline TC level exceeded 5 mmol/l and LDL-C was >3 mmol/l in 88% of patients. TC level in patients with three stenosed coronary arteries was significantly higher than in patients with single- or two-vessel CAD (Figure 1). The strongest relationship was observed between the extent of CAD and LDL-C. CAD was correlated with the LDL-C level and was significantly more advanced in patients with two stenosed arteries as compared with one stenosed artery (p<0.01).

The mean baseline TC, LDL-C, HDL-C and TG levels were $5.93\pm0.59 \text{ mmol/l}$, $3.88\pm0.46 \text{ mmol/l}$, $0.84\pm0.12 \text{ mmol/l}$, and $2.16\pm0.44 \text{ mmol/l}$, respectively. Among the 79 patients included in the study, 54 (68%) achieved a target TC level <5.0 mmol/l and 51 (65%) pa-



Figure 1. Baseline lipid levels in patients with various degree of CAD



Figure 2. Effects of atorvastatin therapy on lipid levels

tients achieved LDL-C level <3.0 mmol/l after three months of treatment. Atorvastatin decreased TC level by 31% (p <0.01), LDL-C level by 35% (p <0.01) and TG level by 23% (p <0.01), and increased HDL-C level by 8% (p <0.01, Figure 2).

In 59 (75%) patients endothelial dysfunction was detected – the mean FMD was $8.36\% \pm 1.84$. In two patients with accompanying arterial hypertension and multi-vessel disease we observed a paradoxical vaso-constriction. After three months of therapy with atorvastatin, FMD increased significantly by 62% (p <0.01) and normalised in 88% of patients (Figure 3). The highest improvement was seen in patients with baseline lower relaxation. NID was increased by 15.6% (p <0.05). A significant negative correlation between FMD and TC (r=-0.48, p <0.01) and LDL-C (r=-0.51, p <0.01) was found. Endothelial dysfunction was present in 80% of patients with three stenosed coronary arteries.

Discussion

Hyperlipidaemia strongly enhances the progression of CAD and its treatment is essential for patients. A reasonable therapeutic strategy to reduce CAD progression is the use of a low-dose statin therapy and decrease LDL-C concentration <115 mg/dl as well as increase HDL-C >40 mg/dl. Statins appear to be the fundamental therapy in patients with established CAD as well as a mainstay for those with early evidence of atherosclerosis [7].

Atorvastatin is one of the most effective statins in reducing TC, LDL-C and TG levels [8]. Atorvastatin in a dose of 80 mg markedly reduces levels of atheroge-



Figure 3. Endothelial vascular function before and after treatment with atorvastatin

nic lipid fractions and favourably influences prognosis after coronary angioplasty, as has been shown in the AVERT study [8]. It has also been demonstrated that intensive lowering of LDL-C in patients with unstable angina reduces the incidence of clinical complications (MIRACL study) [7, 9]. However, treatment with atorvastatin in the maximum dose is associated with high costs.

The results of the HPS, PROVE-IT and ASCOT-LLA studies indicated that LDL-C reduction by 30-40% is needed to provide benefits that are similar to those seen in recent clinical trials. The ASCOT-LLA study showed that low-dose treatment with statins (10 mg) is highly beneficial for primary prevention in patients with hypertension at moderately high risk of cardiova-scular events [10]. In the CARDS [11] study the efficacy of low-dose atorvastatin in reduction of serum lipid levels and prevention of CAD in patients with diabetes II types has been demonstrated. The question about optimal dose of statins in patients with stable angina pectoris remains open.

In our study we used a low dose of atorvastatin (10 mg) in patients with stable angina pectoris. Administration of atorvastatin in low dose (10 mg) significantly reduced TC, LDL-C and TG concentrations. Furthermore, this significant improvement in parameters reduced both relative and absolute risk of coronary events and total mortality.

Atorvastatin is known to exert additional cholesterol-independent or pleiotropic effects on various aspects of cardiovascular disease, including improvement of endothelial function, reduction of vascular inflammation and enhancing plaque stability. The vascular endothelium is a dynamic endocrine organ that regulates vascular tone, local homeostasis and the fibro--inflammatory-proliferative processes. Endothelial dysfunction is a generalised phenomenon, present at various levels of the cardio-vascular system, and is evident very early in the atherosclerotic process [5]. Vascular endothelial function is an important and clinically relevant therapeutic target in cardiovascular diseases [4]. An important characteristic of endothelial dysfunction is the impaired synthesis, release, and activity of endothelial-derived nitric oxide (NO). Statins increase endothelial NO production by stimulating and up-regulating endothelial NO synthase as well as attenuate endothelial dysfunction in the presence of atherosclerotic risk factors [4].

In the present study we showed that 75% of patients with stable angina have endothelial dysfunction. In patients with three and more stenosed coronary arteries, FMD was significantly lower than in patients with one or two stenosed arteries. This endothelial dysfunction is associated with the extent of coronary atherosclerosis. Low-dose atorvastatin increased FMD by 61% after three months of therapy and restored endothelial dysfunction. NID was increased by 16%, which is probably associated with improvement of the elastic properties of the vascular wall. Thus, low-dose atorvastatin demonstrated the ability to increase FMD and restored endothelial dysfunction.

Conclusions

Low-dose treatment with atorvastatin (10 mg daily) is effective in reduction of blood lipid levels and improves endothelial vascular function.

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Wpływ małej dawki atorwastatyny na poziom lipidów i funkcję śródbłonka naczyniowego w chorobie wieńcowej

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Streszczenie

Wstęp: Hiperlipidemia jest znanym czynnikiem ryzyka rozwoju choroby wieńcowej (CAD). Statytyny, w tym atorwastatyna, nie tylko obniżają stężenie lipidów ale mogą również poprawiać funkcję śródbłonka, hamować procesy zapalne w naczyniach oraz poprawiać stabilność blaszki miażdżycowej.

Cel: Ocena skuteczności małej dawki atorwastatyny u chorych z CAD.

Metodyka: Do badania włączono 79 chorych ze stabilną CAD i angiograficznie potwierdzonym istotnym (>70%) zwężeniem naczynia wieńcowego, u których zastosowano przez 12 tygodni atorwastatynę w dawce 10 mg/dobę. Parametry lipidowe oceniano przed włączeniem leczenia i po 12 tygodniach terapii. Ponadto oceniano wazodilatację zależną od przepływu (*flow-mediated vasodilatation*, FMD) i zależną od nitratów (*nitrate-induced dilation*, NID) w tętnicy ramieniowej przed i po zakończeniu leczenia.

Wyniki: Spośród 79 chorych docelowe stężenie całkowitego cholesterolu <5.0 mmol/l uzyskano po leczeniu atorwastatyną u 54 (68%) chorych, a LDL-cholesterolu <3.0 mmol/l u 51 (65%) pacjentów. Atorwastatyna obniżyła stężenie cholesterolu całkowitego o 31% (p <0.01), LDL-cholesterolu o 35% (p <0.01), trójglicerydów o 23% (p<0.01), zwiększyła zaś stężenie HDL-cholesterolu o 8% (p <0.01). Po leczeniu atorwastatyną wartości FMD wzrosły o 61% (p <0.01) i uległy normalizacji po leczeniu u 88% chorych. Również wartości NID wzrosły istotnie o 16% po leczeniu atorwastatyną (p <0.05).

Wnioski: Atorwastatyna zastosowana w niskiej dawce (10 mg/dobę) nie tylko skutecznie obniża stężenie lipidów, ale również poprawia funkcję śródbłonka naczyniowego.

Słowa kluczowe: choroba wieńcowa, atorwastatyna, śródbłonek, lipidy

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