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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Statins decrease mean platelet volume irrespective of cholesterol lowering effect

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Abstract

Background: Recent clinical observations have demonstrated that the beneficial effects of statins are not limited to LDL lowering effect. They have also favourable effects on platelet activation, endothelial function, inflammation, and coagulation cascade.

Aim: To investigate the effects of statins on mean platelet volume (MPV) which is a simple measure of platelet activation volume in patients who have been prescribed statins. Atorvastatin and rosuvastatin were also compared in respect to effects on MPV.

Methods: One hundred and forty five patients were retrospectively included in the study from the outpatient cardiology clinic. Patients who had been given statin treatment were recruited based on the records. Baseline and 4–8 weeks biochemical analysis and haematological measurements and cardiovascular risk factors were recorded.

Results: Both statins significantly decreased the MPV. MPV of patients did not show any significant correlation with lipid parameters. Linear regression analysis revealed that there were no statistically significant associations of Δ MPV with the Δ LDL-cholesterol (beta coefficient = 0.13; p = 0.24), Δ HDL-cholesterol (beta coefficient = 0.17; p = 0.18) or Δ triglyceride (beta coefficient = –0.11; p = 0.21) after statin treatment. Both statins had comparable effects on lipid parameters at the end of the one month follow up period.

Conclusion: Statins significantly reduce MPV irrespective of cholesterol levels, and atorvastatin and rosuvastatin have comparable effects in this regard.

Key words: statin, mean platelet volume, platelet activation

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INTRODUCTION

Statins are the most commonly used drugs in the world, due to their antihyperlipidaemic effect. Statins inhibit cholesterol synthesis in the liver by blocking the conversion of 3-hydroxy-3-methyl-glutaryl-CoA to mevalonate, which is the rate-limiting step in the mevalonate pathway. They have also some effects, namely pleiotropic, which are not directly related to cholesterol lowering [1]. Lowering of low-density lipoprotein (LDL) plasma levels has been shown to reduce primary and secondary cardiovascular events including myocardial infarction (MI), stroke, and all cause mortality [1]. Recent clinical observations have demonstrated that the beneficial effects of statins are not limited to LDL lowering effect; they decrease the cardiovascular complication rates and survival very quickly and independently of their cholesterol lowering effect [2–4]. Pretreatment with statins one week before elective angioplasty reduced procedure-related MI by more than 80% [5]. They also have favourable effects on platelet activation, endothelial function, inflammation, and coagulation cascade [6–19].

Mean platelet volume (MPV) which is a simple measure of platelet activation, has recently become an interesting topic in cardiovascular research. When platelets become activated, MPV increases and change from quiescent discs to swollen spheres. Large platelets are more adhesive and likely to aggregate than small ones [20]. Accordingly, we aimed to investigate the effects of statins on MPV in patients who had been prescribed statins according to the Adult Treatment

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Panel-III guidelines [1]. Atorvastatin and rosuvastatin were also compared in respect to effects on MPV.

METHODS

Patients

One hundred and forty five patients were retrospectively included in the study from the outpatient cardiology clinic. Patients who had been given statin treatment were recruited based on the records. Patients who had been given statins in combination with other drugs such as anti-hypertensives or anti-diabetics or anti-ischaemics were not included in the study. Baseline medications had not been changed during the follow up period except for the initiation of statins. Atorvastatin had been given in four alternative dosages; 10 mg (25 patients), 20 mg (36 patients), 40 mg (9 patients), and 80 mg (4 patients), and rosuvastatin in three different dosages; 10 mg (46 patients), 20 mg (21 patients) and 40 mg (4 patients). Baseline and 4–8 weeks biochemical analysis and haematological measurements (complete blood count) and cardiovascular risk factors were recorded. Risk factors and treatment goals were evaluated in patients with primary hypercholesterolaemia according to the Third Report of the National Cholesterol Education Program (NCEP-III) [1].

The following clinical and demographic parameters were recorded: age, sex, hypertension (known hypertension treated with antihypertensive drugs, two or more blood pressure recordings greater than 140/90 mm Hg), diabetes mellitus (known diabetes treated with diet or drugs or both; or either a fasting serum glucose of more than 126 mg/dL). Current cigarette smoking was defined as active smoking within the past 12 months. Coronary artery disease was defined as > 50% luminal narrowing of epicardial coronary arteries, and normal coronary arteries were defined as absence of significant coronary stenosis (< 50%) in any epicardial coronary arteries in whom coronary angiography was performed previously. All patients had ≥ 2 coronary risk factors and elevated levels of LDL cholesterol (LDL-C) > 130 mg/dL.

Exclusion criteria

Patients with any of the following conditions were excluded: moderate to severe valvular heart disease, chronic hepatitis, chronic renal failure, alcohol abuse, hypersensitivity to statins, current usage of drugs such as oral contraceptives, systemic steroids, heparins, oral anticoagulants and immunosuppressives. Patients with acute coronary syndromes, recent MI or cerebrovascular event (< 3 months), acute or chronic heart failure, acute infections, haematological diseases such as polycythemia vera, thrombophilia, or active malignancies were not included in the study. Fifty four (73%) patients on atorvastatin treatment and 71 (70%) patients on rosuvastatin treatment had already been receiving either aspirin or clopidogrel during enrollment; that is why the possible effect of these drugs on MPV has been mostly eliminated due to the inclusion process.

Haematological variables, including MPV, platelet count, red blood cell and white blood cell count were measured by cell analysers (BC 5500 Auto Hematology Analyzer CHINA).

Statistical analysis

Results are expressed as the mean ± standard deviations and percentages. Baseline measurements and 4–8 weeks later measurements were compared by paired t-test and χ^2. Patients were also divided into two groups: group 1 (atorvastatin) and group 2 (rosuvastatin). Effects of atorvastatin and rosuvastatin were also compared by using independent samples t-test and χ^2 where suitable. Pearson correlation analysis was performed to analyse the relation between MPV and lipid parameters. Delta differences (Δ) of MPV, LDL-C, triglyceride, high-density lipoprotein cholesterol (HDL-C) were calculated by subtracting the values of before-statin treatment from that of after-treatment. Linear regression analysis was made to find a possible correlation of Δ MPV with Δ LDL, Δ HDL, and Δ triglyceride levels. Differences were considered significant at $p < 0.05$ (two-tailed). Statistical analyses were performed by using SPSS 15.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

The patients' clinical characteristics are presented in Table 1. There were no statistically significant differences between group 1 and group 2 regarding the demographics and cardiovascular risk factors (Table 1).

Both statins had comparable effects on lipid parameters at the end of the one month follow up period. Meanwhile both statins significantly decreased the MPV.

The MPV of patients did not show any significant correlation with lipid parameters before (LDL-C: $r = –0.04$, $p = 0.61$; HDL-C: $r = 0.09$, $p = 0.26$; triglyceride: $r = 0.03$, $p = 0.68$) or after statin treatment (LDL-C: $r = –0.02$, $p = 0.78$; HDL-C: $r = 0.14$, $p = 0.09$; triglyceride: $r = –0.02$, $p = 0.79$) (Figs. 1, 2). Comparison of atorvastatin and rosuvastatin did not yield any difference in respect to MPV and Δ MPV levels (Table 2). Linear regression analysis revealed that there were no statistically significant associations of Δ MPV with the Δ LDL-C (beta coefficient = 0.13, $p = 0.24$), Δ HDL-C (beta coefficient = 0.17, $p = 0.18$), or Δ triglyceride (beta coefficient = –0.11, $p = 0.21$) after statin treatment.

DISCUSSION

The main finding of our study is that statin treatment had significantly decreased MPV approximately one month later, and this effect had no relation to cholesterol levels or cholesterol lowering effect. Additionally rosuvastatin and atorvastatin had comparable effects on MPV.

Table 1. Clinical and demographic characteristics of patients

Variables	Total (n = 145)	Atorvastatin (n = 74)	Rosuvastatin (n = 71)	P
Age [years]	54 ± 9	54 ± 9	54 ± 9	0.98
Gender (male)	77 (53%)	39 (53%)	38 (54%)	0.92
Coronary artery disease	51 (35%)	26 (35%)	25 (35%)	0.99
Hypertension	78 (54%)	39 (53%)	39 (55%)	0.79
Diabetes mellitus	41 (28%)	21 (28%)	20 (28%)	0.97
Smoking	47 (32%)	24 (32%)	23 (32%)	0.99
Hyperlipidaemia	52 (35%)	26 (35%)	26 (35%)	0.85
Renin–angiotensin system blockers	75 (55%)	38 (53%)	37 (57%)	0.72
Calcium channel blockers	44 (33%)	22 (34%)	22 (31%)	0.58
Beta-blockers	63 (44%)	29 (42%)	34 (47%)	0.15
Nitrates	24 (17%)	16 (22%)	8 (13%)	0.20
Aspirin	90 (62%)	45 (61%)	45 (63%)	0.85
Clopidogrel	13 (9%)	9 (13%)	4 (7%)	0.53

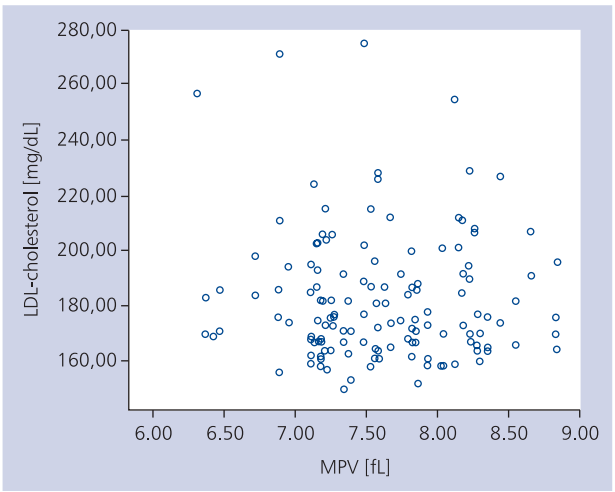

Figure 1. LDL-cholesterol and mean platelet volume (MPV) before statin treatment

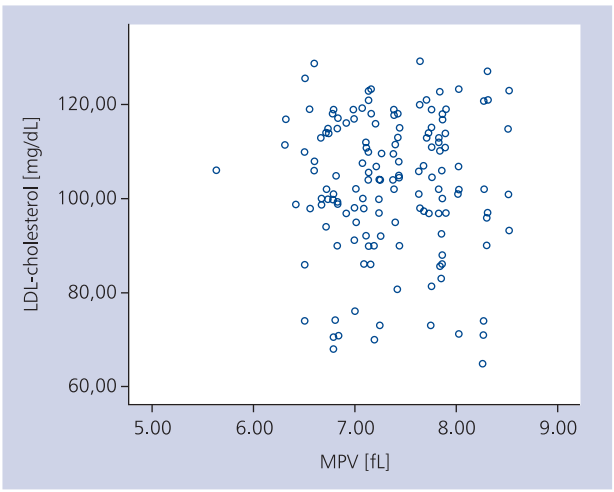

Figure 2. LDL-cholesterol and mean platelet volume (MPV) after statin treatment

The anti-thrombotic effects of statins are well known and documented in the literature. The inhibition of platelet-dependent thrombus generation in hypercholesterolaemic subjects by statins does not correlate with the lipid-lowering effect, suggesting that other lipid-independent effects of statins may contribute to its anti-aggregatory activity [21, 22]. While inhibiting HMG-CoA reductase and mevolanate formation, statins also inhibit the synthesis of important isoprenoid intermediates [23]. These intermediates serve as important lipid attachments for the posttranslational modification of a variety of proteins [24]. Additionally, statins via pleiotropic effects exert an antiplatelet activation either by upregulation of eNOS in platelets [25], or PPAR dependent mechanism [26], or thromboxan dependent mechanism or modifying intraplatelet redox imbalance [27]. Whatever the mechanism underlying antiplatelet action, it is important to document an obvious end-point. In this regard, MPV which is a simple laboratory measurement has significantly decreased after statin treatment. This effect has no relation to cholesterol levels. Additionally both atorvastatin and rosuvastatin have shown comparable effects on MPV, suggesting a class effect rather than a single molecule. The effect of rosuvastatin on MPV has also been shown in a relatively low number of patients recently [28].

Since it has been shown that MPV is an independent risk factor for MI or recurrent MI and associated with acute coronary syndrome or cardiovascular risk factors [29–32], it is noteworthy not to have large platelets. The question of how we should decrease MPV has already been raised [33].

Table 2. Comparison of biochemical and haematological parameters in patients receiving statin treatment

Variables		Atorvastatin (n = 74)	Rosuvastatin (n = 71)	P
Total cholesterol	Before*	259 ± 33	257 ± 32	0.66
	After	165 ± 22	163 ± 23	0.59
Triglyceride	Before*	196 ± 100	174 ± 92	0.07
	After	137 ± 88	130 ± 70	0.29
HDL-cholesterol	Before*	40 ± 11	40 ± 10	0.90
	After	35 ± 9	33 ± 8	0.56
LDL-cholesterol	Before*	178 ± 19	185 ± 25	0.05
	After	102 ± 15	103 ± 14	0.56
Platelet [$\times 10^3$]	Before	284 ± 63	281 ± 65	0.79
	After	284 ± 61	281 ± 63	0.98
Mean platelet volume [fL]	Before*	7.65 ± 0.55	7.55 ± 0.58	0.25
	After	7.37 ± 0.56	7.33 ± 0.46	0.66
Glucose [mg/dL]		112 ± 54	113 ± 43	0.99
Urea [mg/dL]		18 ± 9	17 ± 8	0.90
Creatinine [mg/dL]		1.02 ± 0.28	0.97 ± 0.20	0.24
Aspartate amino transferase		26 ± 9	26 ± 18	0.99
Alanin amino transferase		23 ± 10	22 ± 14	0.62
White blood cell [/mL]		6,585 ± 2,440	6,759 ± 2,265	0.65
Haemoglobin [g/dL]		13.2 ± 1.3	13.5 ± 1.1	0.18
Δ Total cholesterol		94 ± 41	94±40	0.59
Δ HDL-cholestrol		5 ± 15	7 ± 12	0.54
Δ LDL-cholesterol		76 ± 23	81 ± 27	0.17
Δ Triglyceride		61 ± 131	31 ± 88	0.19
Δ Mean platelet volume [fL]		0.25 ± 0.23	0.19 ± 0.29	0.11

*$p < 0.001$ vs. after

Although most of the patients with coronary artery disease and those who have hypercholesterolaemia according to NCEP receive statins, to have a lower MPV and subsequent beneficial effects is another reason behind the rationale of using statins.

One might expect that use of other drugs and antiplatelet drugs, namely aspirin and clopidogrel, would affect MPV. Since all the patients had continued to receive their baseline medications during the follow up period, we may assume that the change in MPV could be attributable to the statin effect solely. Additionally all the other drugs were comparable in both statin groups and had not been changed during the follow up period.

CONCLUSIONS

Statins significantly reduce MPV irrespective of cholesterol levels, and atorvastatin and rosuvastatin have comparable effects in this regard.

Conflict of interest: *none declared*

References

1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation, 2002; 106: 3143–3421.
2. Schwartz GG, Olsson AG, Ezekowitz MD et al. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. The MIRACL study: a randomized controlled trial. JAMA, 2001; 285: 1711–1718.
3. de Lemos JA, Blazing MA, Wiviott SD et al. A to Z Investigators. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes (phase Z of the A to Z trial). JAMA, 2004; 292: 1307–1316.
4. Ray KK. Cannon CP. McCabe CH et al. PROVE IT-TIMI 22 Investigators. Early and late benefits of high-dose atorvastatin in patients with acute coronary syndromes: results from the PROVE IT-TIMI 22 trial. J Am Coll Cardiol, 2005; 46: 1405–1410.
5. Pasceri V, Patti G, Nusca A et al. ARMYDA Investigators Randomized trial of atorvastatin for reduction of myocardial dam-

age during coronary intervention: results from the ARMYDA (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) study. Circulation, 2004; 110: 674–678.
6. Koh KK. Effects of HMG-CoA reductase inhibitor on hemostasis. Int J Cardiol, 2000; 76: 23–32.
7. Takemoto M, Liao JK. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Arterioscler Thromb Vasc Biol, 2001; 21: 1712–1719.
8. Thompson PD, Moyna NM, Michael White C et al. The effects of hydroxy-methyl-glutaryl co-enzyme A reductase inhibitors on platelet thrombus formation. Atherosclerosis, 2002; 161: 301–306.
9. Inoue I, Goto S, Mizotani K et al. Lipophilic HMG-CoA reductase inhibitor has an anti-inflammatory effect: reduction of MRNA levels for interleukin-1beta, interleukin-6, cyclooxygenase-2, and p22phox by regulation of peroxisome proliferator-activated receptor alpha (PPARalpha) in primary endothelial cells. Life Sci, 2000; 67: 863–876.
10. Sukhova GK, Williams JK, Libby P. Statins reduce inflammation in atheroma of nonhuman primates independent of effects on serum cholesterol. Arterioscler Thromb Vasc Biol, 2002; 22: 1452–1458.
11. Shimada K, Miyauchi K, Daida H. Early intervention with atorvastatin modulates TH1/TH2 imbalance in patients with acute coronary syndrome: from bedside to bench. Circulation, 2004; 109: e213–e214.
12. Rezaie-Majd A, Maca T, Bucek RA et al. Simvastatin reduces expression of cytokines interleukin-6, interleukin-8, and monocyte chemoattractant protein-1 in circulating monocytes from hypercholesterolemic patients. Arterioscler Thromb Vasc Biol, 2002; 22: 1194–1199.
13. Bickel C, Rupprecht HJ, Blankenberg S et al. AtheroGene Group. Influence of HMGCoA reductase inhibitors on markers of coagulation, systemic inflammation and soluble cell adhesion. Int J Cardiol, 2002; 82: 25–31.
14. Porreca E, Di Febbo C, Amore C et al. Effect of lipid-lowering treatment on factor VII profile in hyperlipidemic patients. Thromb Haemost, 2000; 84: 789–793.
15. Undas A, Brummel KE, Musial J et al. Simvastatin depresses blood clotting by inhibiting activation of prothrombin, factor V, and factor XIII and by enhancing factor Va inactivation. Circulation, 2001; 103: 2248–2253.
16. Undas A, Brummel-Ziedins KE, Potaczek DP et al. Atorvastatin and quinapril inhibit blood coagulation in patients with coronary artery disease following 28 days of therapy. J Thromb Haemost, 2006; 11: 2397–2404.
17. Masamura K, Oida K, Kanehara H et al. Pitavastatin-induced thrombomodulin expression by endothelial cells acts via inhibition of small G proteins of the Rho family. Arterioscler Thromb Vasc Biol, 2003; 23: 512–517.
18. Bourcier T, Libby P. HMG CoA reductase inhibitors reduce plasminogen activator inhibitor-1 expression by human vascular smooth muscle and endothelial cells. Arterioscler Thromb Vasc Biol, 2000; 20: 556–562.
19. Zhou Q, Liao JK. Pleiotropic effects of statins. Circ J, 2010; 74: 818–826
20. Martin JF, Trowbridge EA, Salmon G et al. The biological significance of platelet volume: its relationship to bleeding time, thromboxane B2 production and megakaryocyte nuclear DNA concentration. Thromb Res, 1983; 32: 443–460.
21. Gaddam V, Li DY, Mehta JL. Anti-thrombotic effects of atorvastatin — an effect unrelated to lipid lowering. J Cardiovasc Pharmacol Ther, 2002; 7: 247–253.
22. Puccetti L, Bruni F, Bova G et al. Effect of diet and treatment with statins on platelet-dependent thrombin generation in hypercholesterolemic subjects. Nutr Metab Cardiovasc Dis, 2001; 11: 378–387.
23. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature 1990; 343: 425–430.
24. Takemoto M, Liao J. Pleiotropic Effects of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase inhibitors. Arterioscler Thromb Vasc Biol, 2001; 21: 1712–1719.
25. Laufs U, Gertz K, Huang P et al. Atorvastatin upregulates type III nitric oxide synthase in thrombocytes, decreases platelet activation, and protects from cerebral ischemia in normocholesterolemic mice. Stroke, 2000; 31: 2442–2449.
26. Haramaki N, Ikeda H, Takenaka K et al. Fluvastatin alters platelet aggregability in patients with hypercholesterolemia: possible improvement of intraplatelet redox imbalance via HMG-CoA reductase. Arterioscler Thromb Vasc Biol, 2007; 27: 1471–1477.
27. Ali FY, Armstrong PC, Dhanji AR et al. Antiplatelet actions of statins and fibrates are mediated by PPARs. Arterioscler Thromb Vasc Biol, 2009; 29: 706–711.
28. Coban E, Afacan B. The effect of rosuvastatin treatment on the mean platelet volume in patients with uncontrolled primary dyslipidemia with hypolipidemic diet treatment. Platelets, 2008; 19: 111–114.
29. Endler G, Klimesch A, Sunder-Plassmann H et al. Mean platelet volume is an independent risk factor for myocardial infarction but not for coronary artery disease. Br J Haematol, 2002; 117: 399–404.
30. Martin JF, Bath PMW, Burr ML. Influence of platelet size on outcome after myocardial infarction. Lancet, 1991; 338: 1409–1411.
31. Pizzulli L, Yang A, Martin JF et al. Changes in platelet size and count in unstable angina compared to stable angina or noncardiac chest pain. Eur Heart J, 1998; 19: 80–84.
32. Senaran H, Ileri M, Altinbaş A et al. Thrombopoietin and mean platelet volume in coronary artery disease. Clin Cardiol, 2001; 24: 405–408.
33. Yetkin E. Mean platelet volume not so far from being a routine diagnostic and prognostic measurement. Thromb Haemost, 2008; 100: 3–4.

Wpływ statyn na zmniejszenie średniej objętości płytek krwi niezależnie od ich działania hipolipemizującego

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Streszczenie

Wstęp: W najnowszych badaniach klinicznych wykazano, że korzystne efekty stosowania statyn nie ograniczają się do zmniejszenia stężenia cholesterolu frakcji LDL. Korzystny wpływ tych leków wynika również z ich oddziaływania na aktywację płytek, czynność śródbłonka, proces zapalenia i kaskadę krzepnięcia.

Cel: Celem niniejszej pracy była ocena wpływu statyn na średnią objętość płytek krwi (MPV), która jest prostym wskaźnikiem aktywacji płytek. Porównano ponadto wpływ atorwastatyny i rosuwastatyny na średnią MPV.

Metody: Do badania włączono retrospektywnie 145 pacjentów przychodni kardiologicznej. Chorych przyjmujących statyny rekrutowano na podstawie dokumentacji medycznej. Na początku badania i po 4–8 tygodniach przeprowadzono analizy biochemiczne oraz oceniono czynniki ryzyka sercowo-naczyniowego.

Wyniki: Obie statyny spowodowały istotnie zmniejszenie MPV. Nie stwierdzono znamiennych korelacji między MPV a parametrami lipidowymi. Na podstawie analizy regresji liniowej wykazano brak statystycznie istotnych zależności między zmianą MPV a zmianą stężeń cholesterolu frakcji LDL (współczynnik beta = 0,13; p = 0,24), cholesterolu frakcji HDL (współczynnik beta = 0,17; p = 0,18) i triglicerydów (współczynnik beta = –0,11; p = 0,21) po leczeniu statynami. Wpływ obu statyn na parametry lipidowe oceniany w momencie zakończenia miesięcznego okresu obserwacji był porównywalny.

Wnioski: Statyny istotnie obniżają średnią objętość płytek krwi, niezależnie od stężenia cholesterolu; wpływ atorwastatyny i rosuwastatyny jest pod tym względem podobny.

Słowa kluczowe: statyny, średnia objętość płytek krwi, aktywacja płytek krwi

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