EFFECT OF CONVENTIONAL AND MORE AGGRESSIVE ROSUVASTATIN TREATMENT ON MARKERS OF ENDOTHELIAL ACTIVATION

EFEKTI KONVENCIONALNE I AGRESIVNIJE TERAPIJE ROSUVASTATINOM NA MARKERE ENDOTELNE AKTIVACIJE

Arman S. Postadzhiyan[1], Anna V. Tzontcheva[2], Ivan Kehajov[3], Stanimir Kyurkchiev[3],
Margarita D. Apostolova[4], Bojidar Finkov[1]

[1]Clinic of Cardiology, St. Anne University Hospital, Sofia, Bulgaria
[2]Department of Clinical Laboratory and Clinical Immunology, Medical University, Sofia, Bulgaria
[3]Section of Molecular Immunology, Institute of Biology and Immunology of
Reproduction, Bulgarian Academy of Sciences, Sofia, Bulgaria
[4]Laboratory for Medical and Biological Research, Institute of Molecular Biology, BAS, Sofia, Bulgaria

Summary: Treatment of hypercholesterolemia with HMG-CoA reductase inhibitors results in an earlier reduction of morbidity and mortality than expected from trials using conventional cholesterol-lowering therapies. Possible explanations for this effect include improvement of endothelial function, plaque stabilization, and inhibition of the inflammatory response associated with atherosclerosis. In this study we assessed the effects of low and moderate dose rosuvastatin treatment, on circulating markers of endothelial activation in patients admitted for acute coronary syndromes without ST segment elevation. Thirty patients with unstable angina and non ST segment elevation myocardial infarction were randomized into two groups, and received rosuvastatin 10 mg/day (n =16) or rosuvastatin 20 mg/day (n =14) for 12 weeks. Circulating levels of soluble vascular cell adhesion molecule (sVCAM-1) and intercellular adhesion molecule-1 (sICAM-1) were measured at admission, and at the end of the study. Lipid values were significantly reduced in both treatment groups, but with significantly greater reduction in the aggressively treated group. Serum levels of sICAM-1 and sVCAM-1 were significantly decreased in both rosuvastatin-treated groups during 12 weeks of follow-up with a more pronounced decrease in the more aggressively treated group. Therefore, rosuvastatin modulates endothelial activation in patients after acute coronary syndromes.

Keywords: soluble adhesion molecules, statins, acute coronary syndromes, inflammation

Address for correspondence:

Prof. Dr Anna Tzontcheva
Medical University of Sofia
Chair of Clinical Laboratory
»Georgi Sofijski« 1
1431 Sofia, Bulgaria
Tel. +359 29520463
e-mail: annavtz@yahoo.com

Kratak sadržaj: Lečenje hiperhomocisteinemije inhibitorima HMG-CoA reduktaze ima za rezultat ranije smanjenje morbiditeta i mortaliteta nego što je očekivano na osnovu proba u kojima su korišćene konvencionalne terapije sa snižavanje holesterola. Moguća objašnjenja za takav efekat uključuju poboljšanje endotelne funkcije, stabilizaciju plaka, i inhibiciju inflamatornog odgovora povezanog sa aterosklerozom. U ovoj studiji razmatrani su efekti lečenja niskim i umerenim dozama rosuvastatina na cirkulišuće markere endotelne aktivacije kod pacijenata primljenih zbog akutnih koronarnih sindroma bez elevacije ST-segmenta. Trideset pacijenata sa nestabilnom anginom i infarktom miokarda bez elevacije ST-segmenta, podeljenih u dve grupe, primali su 10 mg (n=16) i 20 mg rosuvastatina dnevno (n=14) tokom 12 nedelja. Cirkulišući nivoi rastvorljivog vaskularnog ćelijskog adhezivnog molekula (sVCAM-1) i intercelularnog adhezionog molekula-1 (sICAM-1) izmereni su po prijemu pacijenata, kao i po završetku studije. Vrednosti lipida bile su značajno snižene u obe tretirane grupe, ali uz značajno veće smanjenje u agresivnije tretiranoj grupi. Nivoi sICAM-1 i sVCAM-1 u serumu bili su značajno sniženi u obe grupe tretirane rosuvastatinom tokom 12 nedelja praćenja, uz izraženije smanjenje u agresivnije tretiranoj grupi. Dakle, rosuvastatin moduliše endotelnu aktivaciju kod pacijenata posle akutnih koronarnih sindroma.

Ključne reči: rastvorljivi adhezioni molekuli, statini, akutni koronarni sindromi, inflamacija

Introduction

Soluble forms of adhesion molecules are found in the circulation and are believed to be derived from endothelial cell shedding (1, 2). Acute coronary syndromes (ACSs) are associated with higher circulating levels of adhesion molecules compared with stable coronary artery disease and healthy controls, suggest-

ing that ACS may be associated with endothelial activation or damage (3, 4). In prospective studies, high levels of adhesion molecules have independently predicted long-term risk of atherosclerosis and coronary heart disease (5, 6). In addition, among patients with stable coronary artery disease and acute coronary syndromes, extreme quartiles of soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cellular adhesion molecule-1 (sVCAM-1) predict clinical events over 2 years (4, 7).

Previous studies have shown that statin treatment improves the prognosis in patients with acute coronary syndromes (8, 9). The reduction of clinical events secondary to lipid lowering has traditionally been attributed to reduction of cholesterol deposition and facilitation of cholesterol efflux from coronary plaques. However, several studies have recently suggested that the beneficial effects of statins in atherosclerotic disease may not be limited to the lipid-lowering effects of these drugs. Thus, both in vivo and in vitro studies have shown immunomodulatory effects of statins (10, 11). These agents have been shown to improve endothelial function and to reduce the elevated levels of adhesion molecules observed in patients with dyslipidemia (12). In the present study we examined the impact of early initiation of low and moderate-dose rosuvastatin treatment on the concentration of soluble intercellular adhesion molecule-1 (sICAM-1) and vascular cells adhesion molecule (VCAM-1) during the first 12 weeks of post non ST elevation ACS.

Materials and Methods

Patients

Thirty patients with unstable angina or non STEMI were included in this study immediately after their admission to the Hospital. Unstable angina (UA) patients had ischemic chest pain at rest within the preceding 48 hours that had developed in the absence of an extracardiac precipitating cause with either ST segment depression of >0.1 mV or T wave inversion in two or more contiguous leads on the presenting 12 lead ECG. Patients with non ST elevation myocardial infarction had similar diagnostic criteria along with elevation of serum creatine kinase, without the evolution of pathological q waves. Subjects with acute or chronic inflammatory diseases, malignancies, renal insufficiency, severe liver disease, on immunosuppressive and antibiotic treatment were excluded from the study. Also excluded were patients with acute ST elevation myocardial infarction, diabetes mellitus, and history of myocardial infarction, surgical intervention or major trauma within the preceding month or in use of lipid-lowering agents during the past 6 months.

Protocol

This trial was a randomized prospective study, which included 30 patients admitted with ACS. The randomization was carried out by the adaptive dynamic random allocation method irrespective of serum lipid levels. During the admission, patients were allocated into two groups, and received rosuvastatin 10 mg/day (n=16, mean age 57.25±2.2 years) or rosuvastatin 20 (n=14, mean age 57.64±3.1 years) for 12 weeks. All patients were under treatment with the same medications during the acute phase of the episode (heparin, aspirin, nitrates, beta blockers, ACE inhibitors), according to the guidelines.

Biochemical measurements

Blood samples from ACS patients were collected after admission in the ICU prior to the onset of the antiischemic and anticoagulant therapy and after 12 weeks with a closed Vacutainer system (Beckton Dickinson, NJ, USA) using differentiating gel ensuring serum separation without any haemolysis. The serum was separated after centrifugation at 3000 g for 10 min up to 1 hour after taking the samples and frozen at -80°C for future analysis.

Total cholesterol, HDL cholesterol and triglycerides were determined according to routine laboratory techniques. LDL-cholesterol was calculated using the Friedewald formula. Quantitative detection of serum concentrations of sVCAM-1 and sICAM-1 was performed using an enzyme linked immunosorbent assay (ELISA) technique employing a commercially available assay kit (BenderMed Systems, Vienna, Austria). The intra- and interassay coefficients of variation were 3.1%, 5.2% for VCAM-1 and 4.1%, 7.6% for ICAM-1 respectively.

Statistical analysis

Statistical analyses within groups were performed by the paired sample t-test for normal distribution and Wilcoxon signed rank test for nonparametric testing, as appropriate, while analyses between groups were performed by the independent sample t-test and Mann-Whitney U-test, as appropriate. Data are presented as mean ± standard deviation (SD) and 95% confidence interval unless otherwise stated. Only two-tailed probabilities were used for testing statistical significance. A p value <0.05 was regarded as statistically significant. All analyses were performed with SPSS, 13.0 version for Windows.

Results

Baseline characteristics for each group are presented in *Table I*, showing no significant differences between the two treatment groups. Furthermore, no

Table I Baseline characteristics.

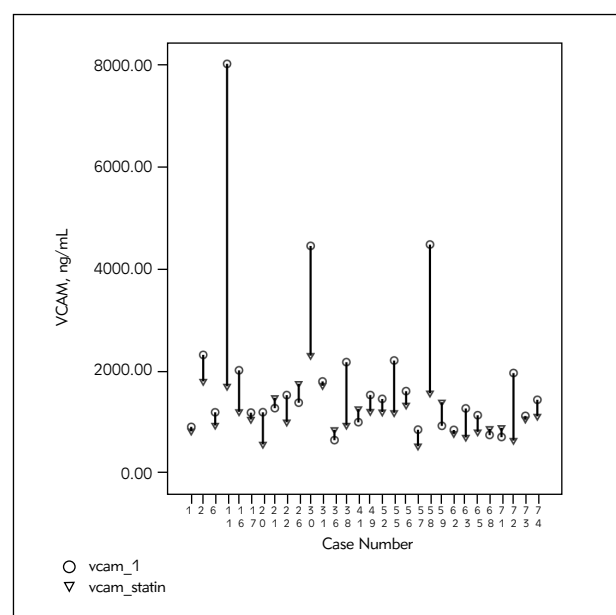| Variable	Rosuvastatin 10 mg n=16	Rosuvastatin 20 mg n=14	p
Age	57.25±2.22	57.64±3.1	0.34
Male gender	7 (23%)	9 (30%)	0.22
Hypertension	9 (30%)	9 (30%)	0.72
Smoking	7 (23.3%)	6 (20%)	0.62
Family history	5 (16.7%)	7 (23.3%)	0.46
cTnT	0.29±0.13	0.46±0.18	0.91
EF %	58.5±2.1	58.8±2.6	0.46
BMI	26.8±1	26.9±1	0.34
Cholesterol, mmol/L	5.66±0.28	6.07±0,32	0.4
Triglycerides, mmol/L	1.76±0.17	1.93±0,25	0.6
HDL-C, mmol/L	0.99±0.03	0.91±0,03	0.14
LDL-C, mmol/L	3.86±0.29	4.27±0.28	0.3
sVCAM-1, ng/mL	1235(831.3–1476.3)	1327.4(1039.5–1989.7)	0.21
sICAM-1, ng/mL	476.8(424.3–516.8)	439.4(362.1–607.3)	0.92

Table II Effects of rosuvastatin on lipid profile.

	Rosuvastatin 10 mg			Rosuvastatin 20 mg		
	Baseline	3 months	p	Baseline	3 months	p
Cholesterol, mmol/L	5.66±0.28	4.49±0.18	<0.001	6.07±0.32	4.24±0.16	<0.001
Triglycerides, mmol/L	1.76±0.17	1.3±0.13	<0.001	1.93±0.25	1.37±0.18	<0.001
HDL-C, mmol/L	0.99±0.03	1.05±0.04	<0.001	0.91±0.03	1.06±0.03	<0.001
LDL-C, mmol/L	3.86±0.29	2.67±0.2	<0.001	4.27±0.28	2.27±0.11	<0.001

significant differences in lipids and markers of endothelial activation were observed at baseline.

The changes in lipid values from baseline to 12 weeks in the two treatment groups are shown in *Table II*.
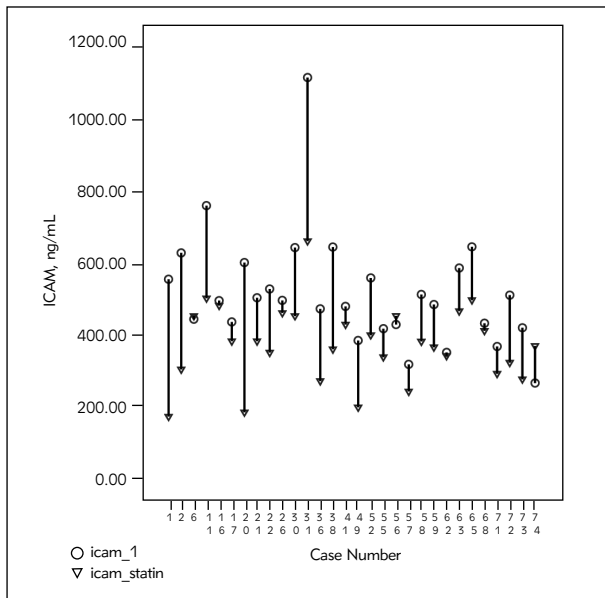
Serum levels of total cholesterol, triglycerides and LDL-cholesterol in patients decreased after 3 months of treatment with rosuvastatin. The decrease in total cholesterol and LDL cholesterol was significantly larger in the more aggressively treated group (p<0.05 for all comparisons).

After 3 months, patients in the 20 mg rosuvastatin group demonstrated a significant decrease in serum levels of sICAM-1 and sVCAM-1 (*Table III, Figure 1* and *2*). Also in the 10 mg-rosuvastin group, there was a significant decrease of sICAM-1 (*Figure 3*). However, no changes in sVCAM-1 levels were observed in this group of patients (*Table III, Figure 4*). There were no significant differences in changes between the two treatment groups for either soluble adhesion molecule levels, but for sICAM-1 we found a trend towards lower concentrations in the moderately treated group (p=0.07).
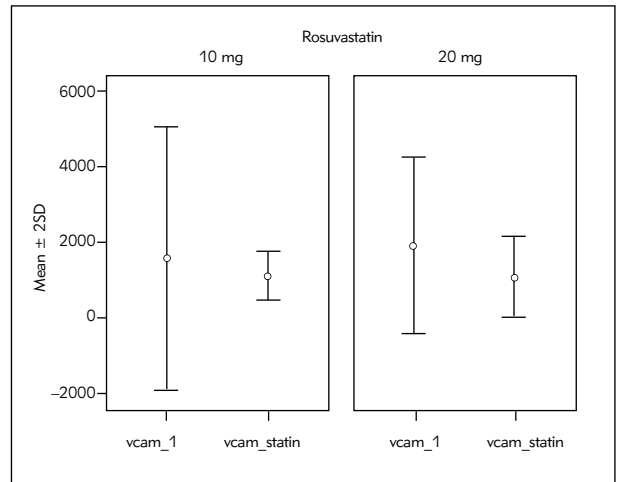

Figure 1 Intraindividual changes in levels of s-VCAM-1 in patients during the study.

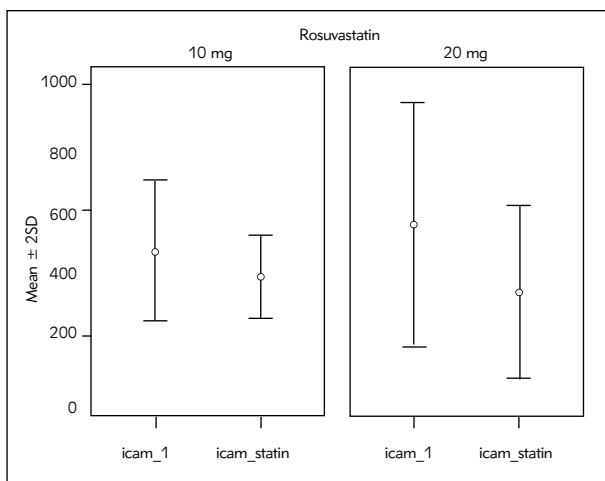**Table III** Effects of rosuvastatin on adhesion molecule levels.

	Rosuvastatin 10 mg			Rosuvastatin 20 mg		
	Baseline	3 months	p	Baseline	3 months	p
sVCAM-1 median, ng/mL 25- and 75-percentile	1235 (831.3–1476.3)	1120.2 (839.7–1341.2)	0.43	1327.4 (1039.5–1989.7)	962.4 (603.4–1570.3)	0.01
sICAM-1 median, ng/mL 25- and 75-percentile	476.8 (424.3–516.8)	385,5 (348.5–453.9)	0,004	439,4 (362.1–607.3)	324,7 (188.5–447.5)	0.01

Figure 2 Intraindividual changes in levels of s-ICAM-1 in patients during the study.

Figure 3 Mean changes ± 2 SD of sICAM-1 in the two rosuvastatin treated groups.

No correlations were found between changes in LDL-cholesterol over 12 weeks and changes in s-ICAM-1 (r=0.198, p=0.29) and sVCAM-1 (r=0.193, p=0.31) during the same period. The Spearman's cor-

Figure 4 Mean changes ± 2 SD of sVCAM-1 in the two rosuvastatin treated groups.

relation coefficients between hsCRP and sICAM-1 (r=0.059, p=0.7) and sVCAM-1 (r=0.15, p=0.4) are low and not statistically significant.

Discussion

ACS is a diffuse process involving the entire coronary vasculature (13). Although mechanical revascularization by percutaneous coronary intervention may address the culprit lesion, recurrent events may reflect disease progression or instability elsewhere in the vascular tree. Stabilization of vulnerable plaques or modulation of the so-called vulnerable patient is becoming recognized as an important target for systemic therapy (14–16). The rapid pleiotropic effects of statins on inflammation, endothelial function, and coagulation are likely to be particularly beneficial in patients with ACS in whom these systems are deranged.

Inhibition of HMG CoA reductase by statins inhibits cholesterol synthesis and isoprenoid production. This results in reduced prenylation of small G-proteins such as Rho and, in turn, NF-κB activation. By inhibiting HMG CoA reductase, statins can prevent the biosynthesis of isoprenoids such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. Inhibition of Rho geranylgeranylation by statins can reduce

leukocyte adhesion and fibrinolytic activity (17, 18). A recent report suggests an additional mechanism which is independent of mevalonate production – statins bind to a novel allosteric site within the β2-integrin leukocyte function–associated antigen–1 (LFA-1), preventing binding to the counter receptor on the endothelial surface (ICAM-1) (19).

In addition, statins can induce endothelial nitric oxide synthase (eNOS) accumulation in endothelial cells, an effect dependent on the inhibition of Rho geranylgeranylation (20), reduce the activation of monocyte/macrophage system (21), the cytotoxicity of T-lymphocytes (22) and the balance between Th-1/Th-2 subclass (23) Hence, statins modify the immune response in ACS via reductions in inflammatory cell number, adhesion, and activation at potentially vulnerable sites along the wall.

Contradictory results have been published about the effect of statins on sICAM-1 and sVCAM-1 plasma/serum concentrations in patients with various clinical manifestations of ischemic heart disease. In a number of small population studies, different authors have noted that treatment with statins diminished sICAM-1 concentrations in subjects with hypercholesterolemia or CHD (24–26). However, Wiklund et al. (27) observed a small and inconsistent effect of Simvastatin and Atorvastatin treatment in hypercholesterolemic patients. Furthermore, Jilma et al. (28) demonstrated that Atorvastatin, Simvastatin, or Pravastatin did not modify sICAM-1 concentrations after 3 months of treatment in subjects with moderate hypercholesterolemia. Blanco-Colio et al. (29) investigated the effect of 10-, 20-, 40- and 80 mg Atorvastatin on sICAM-1 and MCP-1 levels in 2117 patients with CHD in Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration Trial and found no statistically significant differences between the various doses used. Although Atorvastatin had a weak effect on sICAM-1 concentrations in the whole population [–2.2 % change (95% confidence interval –3.8 to –0.6%); P =.006], in the highest quartile all doses of Atorvastatin diminished sICAM-1 plasma levels by more than 10% in subjects at high cardiovascular risk, indicating that Atorvastatin has a greater effect in subjects with higher systemic inflammation. In patients with ACS, short term treatment with 10 mg Atorvastatin prevented the increase of sVCAM-1 in 47 normocholesterolemic patients with unstable angina (30) and 24 patients with STEMI (31). In the large PROVE-IT TIMI 22 study Ray et al. (32) found no significant difference between intensive (80 mg Atorvastatin) and standard (40 mg Pravastatin) regiment on sICAM-1 levels at 30 days. However, when considering the relation among statin therapy,

sICAM-1 levels, and clinical outcomes, the authors found that the risk of adverse events for patients with a sICAM-1 level >231 ng/ml appeared more marked among those allocated to standard dose statin therapy (each odds ratio >2.1). The observed pattern raises the hypothesis that the risk associated with sICAM-1 may be attenuated by treatment with intensive statin therapy (each odds ratio <1.5).

In this study we have analyzed the effect of two rosuvastatin regimens on sICAM-1 and sVCAM-1 concentration in patients with high risk ACS defined by the levels of soluble adhesion molecules. We observed that the treatment with rosuvastatin diminished both markers of endothelial activation during the 12 week follow-up. We found out a trend towards lower concentrations of sICAM-1 in patients randomized to 20 mg rosuvastatin, in addition to the previously observed significant lowering of low-density lipoprotein and C-reactive protein. There was no correlation between sCAMs and low-density lipoprotein and hsCRP at month 3 and the effect of rosuvastatin on soluble CAMs did not appear to be explained by changes in lipids or inflammatory markers.

However, standard statin therapy did not significantly alter sVCAM-1 levels at 30 days. The present observations with sVCAM-1 are analogous to the observations with Aspirin and Clopidogrel in which each drug decreases the risk of adverse clinical events in subjects with high CRP levels but does not decrease CRP significantly (33–35). A potential mechanistic explanation for our clinical observations is, that among subjects with increased endothelial activation, a more potent statin regimen could bind to lymphocyte function-associated antigen-1 on inflammatory cells to a greater extent, thus interfering with downstream effects of increased endothelial activation rather than decreasing endothelial activation itself. This hypothesis raises the possibility that novel therapeutic strategies that target inhibition of adhesion molecules may be of benefit in ACS, as has been demonstrated in animal models and in patients with inflammatory bowel disease (36, 37).

Conclusion

Our findings support the hypothesis that statins decrease endothelial injury and activation in patients with acute coronary syndromes. In addition, we found that a more aggressive regimen with early initiation of 20 mg rosuvastatin significantly decreases sICAM-1 levels. Future studies are required to elucidate the optimal dose of statin treatment in patients with ACS and high levels of markers of inflammatory and endothelial activation.

References

1. Fassbender K, Kaptur S, Becker P, Groschl J, Hennerici M. Adhesion molecules in tissue injury: kinetics of expression and shedding and association with cytokine release in humans. Clin Immunol Immunopathol 1998; 89: 54–60.

2. Leeuwenberg JF, Smeets EF, Neefjes JJ, Shaffer MA, Cinek T, Jeunhomme TM, Ahern TJ, Buurman WA. E-selectin and intercellular adhesion molecule-1 are released by activated human endothelial cells in vitro. Immunology 1992; 77: 543–9.

3. Mulvihill N, Foley JB, Ghaisas N, Murphy R, Crean P, Walsh M. Early temporal expression of soluble cellular adhesion molecules in patients with unstable angina and subendocardial myocardial infarction. Am J Cardiol 1999; 83: 1265–7.

4. Postadzhiyan A, Tzontcheva A, Kehayov I, Finkov B. Circulating soluble adhesion molecules ICAM-1 and VCAM-1 and their association with clinical outcome, troponin T and C-reactive protein in patients with acute coronary syndromes Clinical Biochemistry 2008; 41: 126–33.

5. Hwang SJ, Ballantyne CM, Sharrett AR, Smith LC, Davis CE, Gotto AM Jr, Boerwinkle E. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. Circulation 1997; 96: 4219–25.

6. Malik I, Danesh J, Whincup P, Bhatia V, Papacosta O, Walker M, Lennon L, Thomson A, Haskard D. Soluble adhesion molecules and prediction of coronary heart disease: a prospective study and metaanalysis. Lancet 2001; 358: 971–6.

7. Blankenberg S, Rupprecht HJ, Bickel C, Peetz D, Hafner G, Tiret L, Meyer J. Circulating cell adhesion molecules and death in patients with coronary artery disease. Circulation 2001; 104: 1336 –42.

8. Kinlay S, Schwartz GG, Olsson AG, et al.: Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study Investigators. High-dose atorvastatin enhances the decline in inflammatory markers in patients with acute coronary syndromes in the MIRACL study. Circulation 2003; 108: 1560–6.

9. Ridker PM, Cannon CP, Morrow D, et al.: Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352: 20–28.

10. Liao JK: Beyond lipid lowering: the role of statins in vascular protection. Int J Cardiol 2002; 86: 5–18.

11. Ray KK and Cannon CP. Early Time to Benefit with Intensive Statin Treatment: Could It Be the Pleiotropic Effects? Am J Cardiol 2005; 96[suppl]: 54F–60F

12. O'Driscoll G, Green D, Taylor RR: Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. Circulation 1997; 95: 1126–31.

13. Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. N Engl J Med 2002; 347: 5–12.

14. Libby P, Aikawa M. Mechanisms of plaque stabilization with statins. Am J Cardiol 2003; 91(suppl 4A): 4B–8B.

15. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies, part I. Circulation 2003; 108: 1664 –72.

16. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, Badimon JJ, Stefanadis C, Moreno P, Pasterkamp G, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies, part II. Circulation 2003; 108: 1772–8.

17. Rasmussen LM, Hansen PR, Nabipour MT, et al.: Diverse effects of inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase on the expression of VCAM-1 and E-selectin in endothelial cells. Biochem J 2001, 360(Pt 2): 363–70.

18. Yoshida M, Sawada T, Ishii H, et al.: HMG-CoA reductase inhibitor modulates monocyte-endothelial cell interaction under physiological flow conditions in vitro: involvement of Rho GTPase-dependent mechanism. Arterioscler Thromb Vasc Biol 2001; 21: 1165–71.

19. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med 2001; 7: 687–92.

20. Laufs U, La Fata V, Plutzky J, et al.: Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. Circulation 1998; 97: 1129–35.

21. Luan Z, Chase AJ, Newby AC. Statins inhibit secretion of metalloproteinases-1, -2, -3, and -9 from vascular smooth muscle cells and macrophages. Arterioscler Thromb Vasc Biol 2003; 23: 769–75.

22. Blanco-Colio LM, Munoz-Garcia B, Martin-Ventura JL, et al. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors decrease Fas ligand expression and cytotoxicity in activated human T lymphocytes. Circulation 2003; 108: 1506–13.

23. Hakamada-Taguchi R, Uehara Y, Kuribayashi K, et al. Inhibition of hydroxymethylglutaryl-coenzyme a reductase reduces Th1 development and promotes Th2 development. Circ Res 2003; 93: 948 –56.

24. Ascer E, Bertolami MC, Venturinelli ML, et al. Atorvastatin reduces proinflammatory markers in hypercholesterolemic patients. Atherosclerosis 2004; 177: 161–6.

25. Patti G, Chello M, Pasceri V, et al. Protection from procedural myocardial injury by atorvastatin is associated with lower levels of adhesion molecules after percutaneous coronary intervention. J Am Coll Cardiol 2006; 48: 1560–6.

26. Seljeflot I, Tonstad S, Hjermann I, et al. Reduced expression of endothelial cell markers after 1 year treatment with simvastatin and atorvastatin in patients with coronary heart disease. Atherosclerosis 2002; 162: 179–85.

27. Wiklund O, Mattson-Hulten L, Hurt-Camejo E, et al. Effects of simvastatin and atorvastatin on inflammatory markers in plasma J Intern Med 2002; 251: 338–47.

28. Jilma B, Joukhadar C, Derhasching U, et al. Levels of adhesion molecules do not decrease after 3 months of statin therapy in moderate hypercholesterolemia. Clin Sci (Lond) 2003; 104: 189–93.

29. Blanco-Colio LM, Martın-Ventura JL, de Teresa E, Farsang C, Gaw A, et all of the ACTFAST investigators Elevated ICAM-1 and MCP-1 plasma levels in subjects at high cardiovascular risk are diminished by atorvastatin treatment. Atorvastatin on Inflammatory Markers study: A substudy of Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration. Am Heart J 2007; 153: 881–8.

30. Tousoulis D, Antoniades C, Katsi V, et al. The impact of early administration of low-dose atorvastatin treatment on inflammatory process, in patients with unstable angina and low cholesterol level. Int J Cardiol 2006; 109: 48–52.

31. Stefanadi E, Tousoulis D, Antoniades C, Katsi V, Bosinakou E, Vavuranakis E et all. Early initiation of low-dose atorvastatin treatment after an acute ST-elevated myocardial infarction, decreases inflammatory process and prevents endothelial injury and activation. Int J Cardiol 2008; in press

32. Ray KK, Morrow DA, Shui A, et al. Relation between soluble intercellular adhesion molecule-1, statin therapy, and long-term risk of clinical cardiovascular events in patients with previous acute coronary syndrome (from PROVE IT-TIMI 22). Am J Cardiol 2006; 98: 861 –5.

33. Kennon S, Price CP, Mills PG, Ranjadayalan K, Cooper J, Clarke H, Timmis AD. The effect of aspirin on C-reactive protein as a marker of risk in unstable angina. J Am Coll Cardiol 2001; 37: 1266–70.

34. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997; 336: 973–9.

35. Chew DP, Bhatt DL, Robbins MA, Mukherjee D, Roffi M, Schneider JP, Topol EJ, Ellis SG. Effect of clopidogrel added to aspirin before percutaneous coronary intervention on the risk associated with C-reactive protein. Am J Cardiol 2001; 88: 672–4.

36. Gill V, Doig C, Knight D, Love E, Kubes P. Targeting adhesion molecules as a potential mechanism of action for intravenous immunoglobulin. Circulation 2005; 112: 2031–9.

37. Van Assche G, Rutgeerts P. Physiological basis for novel drug therapies used to treat the inflammatory bowel diseases. I. Immunology and therapeutic potential of antiadhesion molecule therapy in inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol 2005; 288 (suppl): G169–G174.