The Effect of Early and Intensive Statin Therapy on Ventricular Premature Beat or Nonsustained Ventricular Tachycardia in Patients With Acute Coronary Syndrome

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ABSTRACT

Background: To evaluate the prognostic value of early and intensive lipid-lowering treatment on ventricular premature beat or nonsustained ventricular tachycardia (NSVT) after acute coronary syndrome (ACS) (ST-elevation myocardial infarction [STEMI], non-STEMI, and unstable angina pectoris).

Hypothesis: Provided that early and intensive lipid-lowering treatment can reduce ventricular premature beat or non-sustained ventricular tachycardia after ACS.

Methods: A total of 586 patients with ACS were randomly divided into 2 groups: group A (with conventional statin therapy, to receive 10 mg/day atorvastatin, $n = 289$) and group B (early and intensive statin therapy, 60 mg immediately and 40 mg/day atorvastatin, $n = 297$). The frequency of ventricular premature beat and NSVT was recorded with Holter monitoring after hospitalization (24 hours and 72 hours).

Results: Seventy-seven (11.8%) patients had NSVT. When compared to patients with no documented NSVT, patients with NSVT were older and more often had myocardial infarction, diabetes mellitus, atrial fibrillation, and an ejection fraction $<40\%$ in their history. Ventricular premature beats decreased significantly in the early and aggressive treatment group (24 hours, $P < 0.01$; 72 hours, $P < 0.001$). A significant reduction in NSVT was seen in the early and aggressive (24 hours, $P < 0.01$; 72 hours, $P < 0.001$) group. No side effects were observed in either group.

Conclusions: Early and intensive lipid-lowering treatment can obviously decrease ventricular premature beats and NSVT.

Introduction

As statins have been proved to be very effective in reducing mortality rates after acute coronary syndrome (ACS), the beneficial effects of statins on patients after ACS has primarily been attributed to lowering blood cholesterol and thereby attenuating the progression of arteriosclerosis.^{1–4} However, recent data suggest that the beneficial effects of statins might extend to mechanisms beyond cholesterol reduction.^{5–7} These pleiotropic effects include improvement of endothelial function, inhibition of platelet function, and smooth muscle cell proliferation, enhancing stability of arteriosclerotic plaques and attenuating vascular inflammation. Recent evidence has shown that statins might exert antiarrhythmic effects both in experimental models and in humans.^{8–15}

Association of ventricular premature beat and nonsustained ventricular tachycardia (NSVT) with adverse outcome after ACS could be influenced by these agents. The early and intensive relationship for atorvastatin in patients with ACS during early hospitalization in terms of antiarrhythmic effects is unclear. In this study we analyzed the effects of early and intensive atorvastatin on the prognostic impact of ventricular premature beat and NSVT after ACS.

Methods

In the present study all data were recorded. Demographic data, patient's history, procedural information, outcomes, and follow-up data were recorded using 4 case report forms. The first form recorded the data necessary for diagnosis and specification of ACS (symptoms, electrocardiography, and cardiac enzymes). The second form included the patient's history (concomitant disease and previous cardiovascular events), and acute therapy

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Table 1. Comparison of Baseline Clinical Characteristics Between the 2 Groups

Baseline Clinical Characteristics	Conventional Statin Therapy (n = 285)	Early and Intensive Statin Therapy (n = 294)	Statistic Value	P Value
Age, y, mean $\pm$ SD	58.45 $\pm$ 10.54	60.87 $\pm$ 9.89	$t = 0.368$	0.683
Sex (male/female)	198/87	211/83	$\chi^2 = 0.776$	0.378
Systolic pressure	138.82 $\pm$ 12.42	139.37 $\pm$ 11.83	$t = 0.463$	0.385
Diastolic pressure	86.42 $\pm$ 7.31	87.42 $\pm$ 8.36	$t = 0.547$	0.576
BMI, kg/m ²	23.62 $\pm$ 3.01	24.68 $\pm$ 2.94	$t = 0.337$	0.585
Past medical history				
Myocardial infarction	32	34	$\chi^2 = 0.052$	0.887
PCI	56	60	$\chi^2 = 0.007$	0.864
CABG	9	8	$\chi^2 = 0.505$	0.448
Cardiac inadequacy	19	17	$\chi^2 = 0.347$	0.561
Risk factors				
Systemic hypertension	168	172	$\chi^2 = 0.067$	0.548
Diabetes mellitus	98	101	$\chi^2 = 0.239$	0.617
Smoking	102	99	$\chi^2 = 0.533$	0.584
Alcohol abuse	16	19	$\chi^2 = 0.667$	0.412
EF <40%	26	28	$\chi^2 = 0.237$	0.624
Sinus rhythm at admission	274	283	$\chi^2 = 0.007$	0.918
Atrial fibrillation	11	16	$\chi^2 = 0.234$	0.641
Atrioventricular block	40	43	$\chi^2 = 0.247$	0.638
Combination therapy				
Diuretic	39	41	$\chi^2 = 0.372$	0.537
β -blockers	245	251	$\chi^2 = 0.014$	0.901
Ca ²⁺ channel blockers	71	76	$\chi^2 = 0.277$	0.684
ACE-inhibitors	285	294	$\chi^2 = 0.000$	0.991
Abbreviations: ACE, angiotensin converting enzyme; BMI, body mass index; CABG, coronary artery bypass graft; EF, ejection fraction; PCI, percutaneous coronary intervention; SD, standard deviation.				

(medication, coronary angiography, and reperfusion therapy). The case report form included elective diagnostic and therapeutic procedures (echocardiography, Holter monitoring, and medication), and clinical events until discharge of the patient.

Evaluation of Holter monitoring was performed by 1 professional physician 3 times. Diagnostic procedures for Holter monitoring for at least 72 hours of continuous registration was required, and mean heart rate, total number of ventricular premature beats, and total number of ventricular tachycardias had to be registered in the corresponding case report form. NSVT was defined as 3 or more consecutive premature ventricular beats with a rate of more than 100 beats per minute. Left ventricular function was measured by angiography or semiquantitatively by echocardiography (4-chamber view).

There were 586 consecutive patients with ACS who were admitted to our institution and were randomly assigned, in a double-blind manner, to receive atorvastatin treatment. Group A (with conventional statin therapy, $n = 289$) received 10 mg/day atorvastatin within the first 24 hours of admission, and group B (early and intensive statin therapy, $n = 297$) received 60 mg immediately and then 40 mg/day atorvastatin after admission. A total of 579 patients completed the study. Furthermore, 4 patients in group A and 3 patients in group B were excluded after completion because they died. Excluded patients were evenly distributed over both treatment groups (χ^2 , 0.58; $P = 0.75$). There were no differences between the 2 groups for the comparison of baseline clinical characteristics adjusted for age, gender, body mass index, prior myocardial infarction (MI), blood pressure, prior

Table 2. Comparison of the Numbers of Ventricular Premature Beats Between the 2 Groups

Group	No.	Ventricular Premature Beats in 24 Hours (Episode)	Ventricular Premature Beats in 24–72 Hours (Episode)	Total Ventricular Premature Beats in 72 Hours (Episode)
Conventional statin therapy	285	1243 ± 104	1568 ± 121	2658 ± 127
Early and intensive statin therapy	294	532 ± 83	562 ± 87	1073 ± 91
<i>P</i> value		0.006	0.003	<0.001

Table 3. Baseline Characteristics of Patients After ACS Either Presenting With Nonsustained Ventricular Tachycardia During Holter Monitoring or Not

Baseline Clinical Characteristics	No NSVT (n = 502)	NSVT (n = 77)	<i>P</i> Value
Age, y, mean ± SD	58.37 ± 10.84	66.8 ± 9.34	<0.001
History of myocardial infarction	7.5% (38/502)	36.3% (28/77)	<0.001
History of systemic hypertension	58.1% (292/502)	62.3% (48/77)	0.624
History of diabetes mellitus	31.4% (158/502)	53.2% (41/77)	0.008
Smoking	34.6% (174/502)	35.1% (27/77)	0.423
EF <40%	6.7% (34/502)	25.9% (20/77)	<0.001
Sinus rhythm at admission	96.4% (484/502)	88.3% (68/77)	0.864
Atrial fibrillation	3.5% (18/502)	11.7% (9/77)	0.007
Atrioventricular block	14.1% (71/502)	15.6% (12/77)	0.495

Abbreviations: EF, ejection fraction; NSVT, nonsustained ventricular tachycardia; SD, standard deviation.

percutaneous coronary intervention (PCI), coronary artery bypass graft, history of heart failure, hypertension, diabetes mellitus, smoking, alcohol abuse, ejection fraction <40%, sinus rhythm at admission, atrial fibrillation, atrioventricular block, beta-blocker use, calcium-blockers, or angiotensin converting enzyme (ACE) inhibitor use (Table 1). The protocol was approved by the institutional review board at our institution and informed consent was obtained from all study patients.

Statistical Methods

The aim of the study was first to investigate the association of ventricular premature beat and NSVT with adverse prognosis after ACS under the conditions of maximum medical treatment. The second step was to test the hypothesis based on recent scientific data that statins might influence this association. Absolute numbers, percent, mean, and standard deviation were computed to describe the patient population. Categorical variables were compared using χ^2 or Fisher exact test. Evaluating the baseline characteristics, *P* values were only used in a descriptive way to show differences between the 2 groups under investigation (Tables 1–4). In this analysis, adjustment was performed for the following variables: age, history of myocardial infarction, systemic hypertension, diabetes mellitus, smoking, ejection fraction <40%, sinus rhythm at admission, atrial fibrillation, and atrioventricular block. These variables were selected according to their clinical relevance. A *P* value <0.05 was considered to be statistically significant. All statistical analyses were carried out with the Statistical Package for Social Science version 16.0 (SPSS, Inc., Chicago, IL).

Results

For this study, 579 patients with ACS were randomly divided into 2 groups: group A (with conventional statin therapy, to receive 10 mg/day atorvastatin, *n* = 289) and group B (early and intensive statin therapy, 60 mg immediately, 40 mg/day atorvastatin, *n* = 297). The results show that early and intensive statin therapy compared with conventional statin therapy can significantly reduce the ventricular premature beats in 24 hours or in 24 to 72 hours (*P* = 0.006; *P* = 0.003). The statistic for total ventricular premature beats in 72 hours was *P* < 0.001, suggesting statistical significance. The mean heart rate in the 2 groups was for group A, 81.3 ± 6.7; and for group B, 79.6 ± 6.4; *P* = 0.783, suggesting no statistical significance.

Table 3 shows the baseline characteristics of patients with and without NSVT during Holter monitoring either under early and intensive statin therapy or conventional

Table 4. Comparison of the Number of Patients With Nonsustained Ventricular Tachycardia and the Number of Nonsustained Ventricular Tachycardias Between the 2 Groups

Group	NSVT in 24 Hours (Patients)	Total NSVT in 24 Hours (Episode)	Total NSVT in 24–72 Hours (Episode)	Total NSVT in 72 Hours (Episode)
Conventional statin therapy	23.2 (56/285)	363 ± 32	132 ± 36	583 ± 31
Early and intensive statin therapy	7.1 (21/294)	186 ± 27	78 ± 31	207 ± 29
<i>P</i> value	0.008	0.007	0.007	<0.001

Abbreviations: NSVT, nonsustained ventricular tachycardia.

statin therapy. In general, patients with NSVT were older (66.8 ± 9.34 vs 58.37 ± 10.84 years, $P < 0.001$), more often had myocardial infarction in their history (36.3% vs 7.5%, $P < 0.001$), had an ejection fraction $<40\%$ (25.9% vs 6.7%, $P < 0.001$), and had atrial fibrillation more often (11.7% vs 3.5%, $P = 0.007$) at admission.

Table 4 shows that early and intensive statin therapy compared with conventional statin therapy can significantly reduce the cases with NSVT ($P = 0.008$) and NSVT in 24 hours or in 24 to 72 hours ($P = 0.007$). The statistic for total NSVT in 72 hours was $P < 0.001$, suggesting statistical significance. Almost all patients showed good tolerance of 20 mg/day atorvastatin. All of these results of the present study indicate that early and intensive statin therapy with (60 mg immediately, 40 mg/day) atorvastatin is more efficacious than and as safe as 10 mg/day atorvastatin when administered to patients during early hospitalization for ACS.

Discussion

It is well known that a significant portion of the patients who die after ACS, die from sudden death because of severe arrhythmias.¹³ In some early experimental animal models, researchers have demonstrated that statins can significantly decrease reperfusion injury and limit MI size.^{5,6} Many studies show that patients with ACS who are treated with statins early—within 24 hours of hospitalization—have lower in-hospital morbidity and mortality risks than patients not treated with statins,^{2–4} but the effectiveness of antiarrhythmias in the patients with ACS receiving immediate and intensive statin therapy was not clear. The present study shows that the occurrence of ventricular premature beats and NSVT after ACS is associated with increased mortality. However, this adverse effect only applies for patients not on statin therapy. Atorvastatin significantly reduces mortality irrespective of the absence or presence of ventricular premature beats and NSVT. The present study also shows that atorvastatin is able to markedly attenuate the association of ventricular premature beats and NSVT with adverse outcomes after ACS.¹⁶ Patients with and without ventricular premature beats and NSVT did not largely differ in medication, including ACE-inhibitors and beta-blockers. As expected, however, patients with ventricular premature beats and NSVT were older and more often had previous myocardial infarction, severely reduced left ventricular function and atrial fibrillation. Taking these parameters into account, only ventricular premature beats and NSVT were associated with a trend toward an adverse prognosis. Indeed, the independent prognostic value of ventricular premature beats and NSVT in the era of modern treatment of myocardial infarction, including thrombolysis, PCI, beta-blockers, and statins is controversial and has been questioned previously. The situation completely changes if the prognostic value of ventricular premature beats and NSVT is evaluated within the patients receiving immediate and intensive statin therapy.^{17–19} In the present study, early and intensive atorvastatin therapy can significantly decrease the recurrence of ventricular premature beats and NSVT. It might therefore be suggested that one of the beneficial mechanisms of statins

could be to rapidly affect signaling pathways in cell membranes of the myocardium and/or the autonomic nervous system, thereby protecting patients from life-threatening arrhythmias.^{20–22} This assumption would be in line with recent data showing statins to improve autonomic neural control and increase electrical stability of the myocardium. Atorvastatin is a highly lipophilic drug that becomes easily embedded in the membrane having overlapping locations in the hydrocarbon core adjacent to the phospholipid head groups.^{23–26} Moreover, the blocking effects could be attributed to an effect on the lipid content of the membrane.²⁷

Conclusion

The present study supports the experimental data, as the benefit likely has to do with immediately improving autonomic neural control and increasing electrical stability of the ischemic myocardium, as well as having an antiarrhythmic effect. Because the drug is going to be used anyway, it should be started right away because there might be an added benefit that occurs quite early.

References

- Briel M, Schwach G, Thompson PL, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. *JAMA*. 2006;295:2046–2056.
- Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363–2372.
- Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
- Cheung BM, Launder IJ, Lau CP, et al. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *Br J Clin Pharmacol*. 2004;57:640–651.
- Greenwood J, Steinman L, Zamvil SS. Statin therapy and autoimmune disease: from protein prenylation to immunomodulation. *Nat Rev Immunol*. 2006;6:358–370.
- Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. *Nat Rev Drug Discov*. 2005;4:977–987.
- Robinson JG, Smith B, Maheshwari N, et al. Pleiotropic effects of statins: benefit beyond cholesterol reduction? a meta-regression analysis. *J Am Coll Cardiol*. 2005;46:1855–1862.
- Drogemuller A, Seidl K, Schiele R, et al; MITRA Study Group. Prognostic value of non-sustained ventricular tachycardias after acute myocardial infarction in the thrombolytic era: importance of combination with frequent premature beats. *Z Kardiol*. 2003;92:164–172.
- Pliquett RU, Cornish KG, Peuler JD, et al. Simvastatin normalizes autonomic neural control in experimental heart failure. *Circulation*. 2003;107:2493–2498.
- Kayikcioglu M, Can L, Evrengul H, et al. The effect of statin therapy on ventricular late potentials in a myocardial infarction. *Int J Cardiol*. 2003;90:63–72.
- Mitchell LB, Powell JL, Gillis AM, et al; AVID Investigators. Are lipid-lowering drugs also antiarrhythmic drugs? An Analysis of the Antiarrhythmic Versus Implantable Defibrillators (AVID) Trial. *J Am Coll Cardiol*. 2003;42:81–87.
- Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. *Circulation*. 2004;110:1061–1068.

13. Ellison KE, Hafley GE, Hickey K, et al. Effect of beta-blocking therapy on outcome in the Multicenter UnSustained Tachycardia Trial (MUSTT). *Circulation*. 2002;106:2694–2699.
14. Priori SG, Aliot E, Blomstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J*. 2001;22:1374–1450.
15. Hallstrom AP, McAnulty JH, Wilkoff BL, et al. Patients at lower risk of arrhythmia recurrence: a subgroup in whom implantable defibrillators may not offer benefit. *J Am Coll Cardiol*. 2001; 37: 1093–1099.
16. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.
17. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295:1556–1565.
18. Hulten E, Jackson JL, Douglas K, et al. The effect of early, intensive statin therapy on acute coronary syndrome: a meta-analysis of randomized controlled trials. *Arch Intern Med*. 2006;166:1814–1821.
19. De Lemos JA, Blazing MA, Wiviott SD, 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.
20. Decher N, Kumar P, Gonzalez T, et al. Binding site of a novel Kv1.5 blocker: a “foot in the door” against atrial fibrillation. *Mol Pharmacol*. 2006;70:1204–1211.
21. Starke-Peterkovic T, Turner N, Vitha MF, et al. Cholesterol effect on the dipole potential of lipid membranes. *Biophys J*. 2006;90: 4060–4070.
22. Nerbonne JM, Kass RS. Molecular physiology of cardiac repolarization. *Physiol Rev*. 2005;85:1205–1253.
23. Maguy A, Hebert TE, Nattel S. Involvement of lipid rafts and caveolae in cardiac ion channel function. *Cardiovasc Res*. 2006;69: 798–807.
24. Gauthereau MY, Salinas-Stefanon EM, Cruz SL. A mutation in the local anaesthetic binding site abolishes toluene effects in sodium channels. *Eur J Pharmacol*. 2005;528:17–26.
25. Shafer TJ, Bushnell PJ, Benignus VA, et al. Perturbation of voltage-sensitive Ca²⁺ channel function by volatile organic solvents. *J Pharmacol Exp Ther*. 2005;315:1109–1113.
26. Gingrich KJ, Tran S, Nikonov IM, et al. Halothane inhibition of recombinant cardiac L-type Ca²⁺ channels expressed in HEK-293 cells. *Anesthesiology*. 2005;103:1156–1163.
27. Joksovic PM, Brimelow BC, Murbarth J, et al. Contrasting anesthetic sensitivities of T-type Ca²⁺ channels of reticular thalamic neurons and recombinant Ca(v)3 channels. *Br J Pharmacol*. 2005;144:343–350.

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