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The effect of early and intensive statin therapy on ventricular premature beat or non-sustained ventricular tachycardia in patients with acute coronary syndrome

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Abstract

Background: *Our study's aim was to evaluate the prognostic value of early and intensive lipid-lowering treatment on ventricular premature beat or non-sustained ventricular tachycardia (NSVT) after acute coronary syndrome (STEMI, non-STEMI, and unstable angina pectoris).*

Methods: *Some 586 patients with acute coronary syndrome were randomly divided into two groups: Group A (with conventional statin therapy, to receive 10 mg/day atorvastatin, n = 289) and Group B (given 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 via Holter monitoring after hospitalization (24 h and 72 h).*

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

Conclusions: *Early and intensive lipid-lowering treatment can clearly decrease ventricular premature beats and NSVT.* (Cardiol J 2010; 17, 4: 381–385)

Key words: acute coronary syndrome, atorvastatin, ventricular premature beat, non-sustained ventricular tachycardia

Introduction

Statins have been proven to be very effective in reducing mortality rates after acute coronary syndrome (ACS). This beneficial effect has primarily been attributed to lowering blood cholesterol and thereby attenuating the progression of arteriosclerosis [1–4]. However, recent data suggests that the beneficial effects of statins may extend to mecha-

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nisms 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]. The association of ventricular premature beat (VPB) and non-sustained ventricular tachycardia (NSVT) with adverse outcome after ACS could be influenced by these agents. The early and intensive relationship between 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 VPB and NSVT after acute coronary syndrome.

Methods

In the present study, all data was recorded. Demographic data, the patient's history, procedural details, the outcome, and follow-up data were recorded using four 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 (medication, coronary angiography and reperfusion therapy). Case report form three 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 thrice by one professional physician. Diagnostic procedures for Holter monitoring involvedat least a 72-hour continuous registration; mean heart rate, total number of VPBs and total number of ventricular tachycardias had to be registered in the corresponding case report form. NSVT was defined as three or more consecutive VPBs with a rate of more than 100 beats per minute. Left ventricular function was measured by angiography, or semi-quantitatively by echocardiography (four-chamber view).

Some 586 consecutive patients with ACS who were admitted to our institution 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 after admission, while Group B (early and intensive statin therapy, n = = 297) received 60 mg immediately and 40 mg/day atorvastatin thereafter. All but seven of the patients completed the study. A further four patients in Group A and three 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 two groups for the comparison of baseline clinical characteristics adjusted for age, gender, body mass index, prior myocardial infarction, blood pressure, prior percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), 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 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 analysis

The primary aim of our study was to investigate the association of VPB and NSVT with adverse prognosis after ACS under the conditions of modern medical treatment. The second aim was to test the hypothesis based on recent scientific data that statins may influence this association. Absolute numbers, percent, mean, and standard deviation were computed to describe the patient population. Categorical variables were compared using the χ^2 or Fisher's exact test. Evaluating the baseline characteristics, p-values were only used in a descriptive way to show differences among the two 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%, and sinus rhythm at admission, atrial fibrillation, and atrioventricular block. These variables were selected according to their clinical relevance. P-value < 0.05 was considered to be statistically significant. All statistical analyses were carried out using the Statistical Package for Social Science (SPSS, version 12.0.2, 24 March 2005).

Results

For this study, 579 patients with ACS were randomly divided into two 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 then 40 mg/day atorvastatin, n = 297). The results show that early and intensive statin therapy compared to

Table 1. Comparison of baseline clinical characteristics between the two groups.

Baseline clinical characteristics	Conventional statin therapy (n = 285)	Early and intensive statin therapy (n = 294)	Statistical value	P
Age (years; mean ± SD)	58.45 ± 10.54	60.87 ± 9.89	t = 0.368	0.683
Sex (male/female)	198/87	211/83	χ^2 = 0.776	0.378
Systolic pressure [mm Hg]	138.82 ± 12.42	139.37 ± 11.83	t = 0.463	0.385
Diastolic pressure [mm Hg]	86.42 ± 7.31	87.42 ± 8.36	t = 0.547	0.576
Body mass index [kg/m^2]	23.62 ± 3.01	24.68 ± 2.94	t = 0.337	0.585
Past medical history:				
Myocardial infarction	32	34	χ^2 = 0.052	0.887
PCI	56	60	χ^2 = 0.037	0.864
CABG	9	8	χ^2 = 0.505	0.448
Cardiac inadequacy	19	17	χ^2 = 0.347	0.561
Risk factors:				
Systemic hypertension	168	172	χ^2 = 0.387	0.548
Diabetes mellitus	98	101	χ^2 = 0.239	0.617
Smoking	102	99	χ^2 = 0.533	0.584
Alcohol abuse	16	19	χ^2 = 0.667	0.412
Ejection fraction < 40%	26	28	χ^2 = 0.237	0.624
Sinus rhythm at admission	274	278	χ^2 = 0.007	0.918
Atrial fibrillation	11	16	χ^2 = 0.234	0.641
Atrioventricular block	40	43	χ^2 = 0.247	0.638
Combination therapy:				
Diuretic	39	41	χ^2 = 0.372	0.537
Beta-blockers	246	251	χ^2 = 0.014	0.901
Ca^{2+}channel blockers	71	76	χ^2 = 0.277	0.684
ACE-inhibitors	285	294	χ^2 = 0.000	0.991

PCI — percutaneous coronary intervention; CABG — coronary artery bypass graft; ACE — angiotensin-converting enzyme

Table 2. Comparison of the numbers of ventricular premature beats (VPB) between the two groups.

Group	N	VPB in 24 h (episode)	VPB in 24–72 h (episode)	Total VPB in 72 h (episode)
Conventional statin therapy	285	1243 ± 104	1568 ± 121	2658 ± 127
Early and intensive statin therapy	294	532 ± 83	562 ± 87	1073 ± 91
P		0.006	0.003	< 0.001

Table 3. Baseline characteristics of patients after acute coronary syndrome either presenting with non-sustained ventricular tachycardia (NSVT) during Holter monitoring or not.

Baseline clinical characteristics	No NSVT (n = 502)	NSVT (n = 77)	P
Age (years; 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
Ejection fraction < 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

Table 4. Comparison of the numbers of patients with non-sustained ventricular tachycardia (NSVT) and the number with NSVT between the two groups.

Group	NSVT in 24 h (patients)	Total NSVT in 24 h (episode)	Total NSVT in 24–72 h (episode)	Total NSVT in 72 h (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
p	0.008	0.007	0.007	< 0.001

conventional statin therapy can significantly reduce VPB whether over 24 hours or between 24–72 hours ($p = 0.006$; $p = 0.003$). The statistic for total VPBs in 72 hours was $p < 0.001$, suggesting statistical significance. The mean heart rate in the two groups was: Group A 81.3 ± 6.7; 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 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 to conventional statin therapy can significantly reduce the cases with NSVT ($p = 0.008$) whether over 24 hours or in 24–72 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 these results of our 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 proportion of the patients who die after ACS, die suddenly because of severe arrhythmias [13]. In some early experimental animal models, researchers have demonstrated that statins can significantly decrease reperfusion injury and limit myocardial infarction size [5, 6]. Many studies show that patients with ACS treated with statins early (i.e. within 24 h of hospitalization) would have lower in-hospital morbidity and mortality risks than patients not treated with statins [2–4], but the effectiveness regarding antiarrhythmias in the patients with ACS receiving immediate and intensive statin therapy were not clear. The present study shows the occurrence of VPBs and NSVT after ACS being associated with an increased mortality. However, this adverse effect only applies to patients not on statin therapy. Atorvastatin significantly reduces mortality, irrespective of the absence or presence of VPBs and NSVT. The present study shows that atorvastatin are able to markedly attenuate the association of VPBs and NSVT with adverse outcomes after ACS [16]. Patients with or without VPBs and NSVT did not largely differ in medication including angiotensin-converting enzyme-inhibitors, beta-blockers etc.

As expected, however, patients with VPBs 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 VPB and NSVT were associated with a trend to adverse prognosis. Indeed, the independent prognostic value of VPB 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 VPB 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 VPB and NSVT. It may therefore be suggested that one of the beneficial mechanisms of statins could be to rapidly affect signalling 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 into the membrane having overlapping locations in the hydrocarbon core adjacent to the phospholipid headgroups [23–26]. Moreover, the blocking effects could be attributed to an effect on the lipid content of the membrane [27].

Conclusions

The present study supports the experimental data, as the benefit is probably due to immediately improving autonomic neural control and increasing electrical stability of the ischemic myocardium, as well as having an antiarrhythmia effect.

Since you're going to use the drug anyway, you might as well start it right away, given that there might be an added benefit that occurs quite early.

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