Clinical research

Do statins influence the prognostic impact of non-sustained ventricular tachycardia after ST-elevation myocardial infarction?

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Aims The study evaluates the effect of statin therapy on the prognostic impact of non-sustained ventricular tachycardia (NSVT) occurring after acute ST-elevation myocardial infarction (STEMI).

Methods and results From the German Acute Coronary Syndrome Registry (ACOS), 3137 patients with STEMI and in-hospital Holter monitoring were analysed. Three hundred and forty-six (11.0%) patients had NSVT. When compared with patients with no documented NSVT, patients with NSVT were older, more often had myocardial infarction in their history, diabetes mellitus, and an ejection fraction <40%. Regarding frequency of drug application, medication at discharge did not (beta-blockers, ACE-inhibitors, amiodarone) or only slightly (acetylsalicylic acid, statins, and sotalol) differ between both groups. Multivariable analysis of 1 year mortality, adjusted for age, gender, diabetes, reperfusion therapy, ejection fraction <40%, and beta-blocker therapy showed the following results: In patients without statin treatment and no NSVT, 1 year mortality after STEMI was 9.2%, but increased to 25.0% [odds ratio (OR) 3.02; 95% confidence interval (CI) 1.47–6.20], if NSVT were present. In patients on statin treatment and no NSVT, 1 year mortality was only 3.2%, and in the presence of NSVT 1 year mortality was not significantly increased anymore (5.3%; OR 1.03; 95% CI 0.55–1.92).

Conclusion After STEMI, only in patients not on statin treatment, the occurrence of NSVT is associated with a significant and marked increase in 1 year mortality.

KEYWORDS
ST-elevation myocardial infarction;
Statin;
Non-sustained ventricular tachycardia;
Prognosis;
Risk stratification;
Pleiotropic effect

Introduction

The prognostic impact of non-sustained ventricular tachycardia (NSVT) after ST-elevation myocardial infarction (STEMI) under the condition of modern pharmacological treatment including beta-blockers and statins is controversial.1-6 As statins have been proven to be very effective in reducing mortality rates after myocardial infarction,7-9 association of NSVT with adverse outcome after STEMI could be influenced by these agents.
The beneficial effect of statins in patients after myocardial infarction has primarily been attributed to lowering of blood cholesterol and thereby attenuating the progression of arteriosclerosis. However, recent data suggest that the beneficial effects of statins may extend to mechanisms beyond cholesterol reduction. 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. There is evidence that many of these effects are the result of reduced synthesis of isoprenoid intermediates of the cholesterol biosynthetic pathway, which serve as lipid attachments for intracellular signalling molecules, thereby affecting various signal transduction pathways. By changing signalling pathways and by modifying the cholesterol/phospholipid ratio in cellular plasma membranes, the beneficial prognostic effect of statins may also result from a favourable modulation of the autonomic nervous system and/or from an increased electrical stability of myocytes. Recent data support this hypothesis, as rosuvastatin has been shown to improve heart rate and blood pressure variability in genetically dyslipidaemic mice; simvastatin has been shown to normalize autonomic neural control in experimental heart failure; pravastatin has been shown to reduce ventricular late potentials and ventricular arrhythmias in patients with acute myocardial infarction, and finally lipid-lowering drug therapy (mostly statins) has been shown to be associated with a reduced probability of recurrent ventricular tachycardias in patients with implantable defibrillators.

On the basis of the prospective multi-centre ‘Acute Coronary Syndrome Registry’ (ACOS), the present study therefore evaluates the hypothesis that statin therapy may attenuate the potential adverse prognostic association of NSVT documented in patients after STEMI.

### Methods

#### ACOS registry

ACOS is a prospective, multi-centre, observational study on current treatment of acute coronary syndromes (STEMI, non-STEMI, and unstable angina pectoris) in Germany. Patients were recruited from 155 hospitals throughout Germany within the period from June 2000 to December 2002. Every participating centre was committed by written consent to include every consecutive patient with ACOS. Written informed consent was obtained from all patients before participation in the registry. There were no further exclusion criteria.

The present study is an analysis of pre-specified, consecutive patients with STEMI and Holter monitoring during the initial hospital stay, who were discharged alive and either received or did not receive statins at discharge. Until 31 December 2003, a total of 3137 patients with STEMI, complete follow-up, and Holter monitoring were included in the study (Figure 1). The decision for performing Holter monitoring was at the discretion of the treating physician.

#### Data processing

All data were centrally processed in the data processing centre of the Heart Centre Ludwigshafen. Demographic data, patients history, procedural, outcome, and follow-up data were recorded using four case report forms. The first form recorded the data necessary for diagnosis and specification of the acute coronary syndrome (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). The third form included elective diagnostic and therapeutic procedures (echocardiography, stress-test, Holter monitoring, and medication) and clinical events until discharge of the patient. Evaluation of Holter monitoring was decentralized and performed in each participating centre. Source data verification was performed by comparison of the registry data with hospital records in randomly selected patients in 20 randomly selected participating centres.

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![Figure 1](flow-chart.png)  
**Figure 1** Flow chart of patient recruitment and differentiation into subgroups.
With respect to therapeutic interventions, each participating centre was strongly advised to follow the actual national and international guidelines. On the basis of this advice, medical treatment, including statin treatment, was at the discretion and responsibility of the treating physician. The individual reasons for not treating patients with statins have not been asked in the registry. Follow-up was centrally achieved 12 ± 1 months after inclusion of the patient by the data processing centre of the Heart Centre Ludwigshafen. Members of the data processing centre contacted the study patients by telephone and completed the follow-up questionnaire (case report form four). Follow-up included documentation of symptoms, clinical events, medication, and rehabilitation during the follow-up period. If patients died during follow-up, death was confirmed by family members and additionally by either the family doctor or the local authorities.

**Diagnostic procedures**

For Holter monitoring, at least an 18 h continuous registration was required and mean heart rate, total number of ventricular beats, and total number of ventricular tachycardias had to be registered in the corresponding case report form. NSVT was defined as three or more consecutive premature ventricular beats with a rate of more than 100 beats per minute. Left ventricular function was measured by angiography (view: 30° right anterior oblique) or semi-quantitatively by echocardiography (four-chamber view).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of patients after STEMI either presenting with NSVT during Holter monitoring or not</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td><strong>NSVT (−)</strong></td>
</tr>
<tr>
<td>Statin (−)</td>
<td>Statin (+)</td>
</tr>
<tr>
<td>Age (years; mean ± SD)</td>
<td>69.3 ± 12.4</td>
</tr>
<tr>
<td>Male</td>
<td>63.5% (304/479)</td>
</tr>
<tr>
<td>Myocardial infarction in history</td>
<td>14.8% (71/479)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56.8% (272/479)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29.2% (140/479)</td>
</tr>
<tr>
<td>Ejection fraction &lt;40%</td>
<td>23.5% (108/459)</td>
</tr>
<tr>
<td>Sinus rhythm at admission</td>
<td>87.3% (418/479)</td>
</tr>
<tr>
<td>Atrial fibrillation at admission</td>
<td>10.2% (49/479)</td>
</tr>
<tr>
<td>Atrioventricular block at admission</td>
<td>2.7% (13/479)</td>
</tr>
</tbody>
</table>

Both groups are subdivided into patients either receiving statins at discharge or not.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Medication at hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medication at discharge</strong></td>
<td><strong>NSVT (−)</strong></td>
</tr>
<tr>
<td>Statin (−)</td>
<td>Statin (+)</td>
</tr>
<tr>
<td>ASS</td>
<td>90.2% (432/479)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>84.8% (406/479)</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>78.7% (377/479)</td>
</tr>
<tr>
<td>Sotalol</td>
<td>1.7% (3/179)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>5.6% (10/179)</td>
</tr>
</tbody>
</table>

STEMI was diagnosed in the presence of one of the following criteria: (i) persistent angina pectoris for ≥20 min plus ST-segment elevation of ≥1 mm in two or more standard leads or ≥2 mm in two or more continuous precordial leads, (ii) persistent angina pectoris for ≥20 min plus the presence of a left bundle branch block. Diagnosis was later confirmed by the increase of cardiac enzymes to more than twice the upper normal limit.

Stroke was defined as the occurrence of persistent specific neurological deficits irrespective of the aetiology.

**Statistical methods**

The aim of the study was to investigate the association of NSVT with adverse prognosis after STEMI under the conditions of modern medical treatment. The second step was to test the hypothesis based on recent scientific data that statins may influence this association.

Absolute numbers, per cent, mean, and standard deviation were computed to describe the patient population. Categorical variables were compared using the χ² or Fisher's exact test and continuous variables by using Wilcoxon rank-sum test. Evaluating the baseline characteristics, P-values were only used in a descriptive way to show differences among the four groups under investigation (Tables 1 and 2).

Multiple logistic regression analysis was used to compare clinical outcome in the different groups by calculating the odds ratio (OR) and the 95% confidence interval (CI). In this analysis,
adjustment was performed for the following variables: age, gender, diabetes mellitus, reperfusion therapy, ejection fraction <40%, and beta-blocker therapy at discharge. These variables were selected according to their clinical relevance and potential impact on long-term prognosis, as shown by earlier studies. To determine whether the model was linear in the logit for continuous variables, a method of designing variables described by Hosmer and Lemeshow was used. Interactions among the variables ‘statin therapy’ and ‘NSVT’ were checked in the multivariable model.

Kaplan–Meier curves were used to describe differences in the survival rates between the groups. The differences between survival curves were assessed by a log-rank test. A P-value < 0.05 was considered to be statistically significant. All P-values are the results of two-tailed tests. The tests were performed using the SAS statistical package, version 8.02 (SAS Institute, Cary, NC, USA).

Results

From the 3137 patients included in the study, 346 (11.0%) had NSVT documented by in-hospital Holter monitoring (Figure 1). The number of NSVT, as documented by Holter monitoring, in this group exhibited a large variation ranging from one episode in 25% of cases to a maximum of 900 episodes in one case (median: 2 NSVT; lower quartile: 1 NSVT; upper quartile: 5 NSVT).

Table 1 shows the baseline characteristics of patients with and without NSVT either under statin therapy or not. In general, patients with NSVT were older (67.0 ± 12.3 vs. 63.4 ± 12.6 years, P < 0.0001), more often had myocardial infarction in their history (20.5 vs. 11.3%, P < 0.0001), had an ejection fraction <40% (33.4 vs. 19.9%, P < 0.0001), and had atrial fibrillation slightly more often (7.2 vs. 4.8%, P = 0.048) at admission.

At discharge, 78.0% of the patients with documented NVST and 82.8% of the patients without NSVT were on statin therapy (P = 0.027). Distribution of the various types of statins given at hospital discharge was as follows: atorvastatin, 44.3%; simvastatin, 34.7%; pravastatin, 10.2%; cerivastatin, 4.0%; fluvastatin, 3.7%; lovastatin, 3.1%. The other medication at discharge is given in Table 2.

Univariable analysis of the total population showed that patients with STEMI and documented NSVT had NSVT documented by in-hospital Holter monitoring (Figure 1). The number of NSVT, as documented by Holter monitoring, in this group exhibited a large variation ranging from one episode in 25% of cases to a maximum of 900 episodes in one case (median: 2 NSVT; lower quartile: 1 NSVT; upper quartile: 5 NSVT).

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Univariable analysis of the total population showed that patients with STEMI and documented NSVT had increased mortality during follow-up (Figure 2). After multivariable analysis adjusted for age, gender, diabetes, early reperfusion, ejection fraction <40%, and chronic beta-blocker therapy confirmed documented NSVT after STEMI being associated with a significant increase of 1 year mortality in the group of patients not on statin therapy, whereas statin therapy was associated with a decrease of mortality regardless of the presence or absence of NSVT. Furthermore, if patients were on statin therapy, NSVT were not associated with adverse long-term prognosis anymore (Table 2). To formally assess the hypothesis that statin treatment influences the prognostic impact of NSVT after STEMI (1 year all-cause mortality), the interaction term between statin treatment and NSVT was determined and shown to be statistically significant (OR 0.39; 95% CI 0.15–0.98; P = 0.047).

Statin therapy was also associated with a reduced rate of non-fatal major adverse events (sum of non-fatal re-infarction and non-fatal stroke) during follow-up, but these changes did not reach the level of significance [patients with documented NSVT: statin (−) vs. statin (+) 10.0/6.7%, P = 0.42; patients without NSVT: statin (−) vs. statin (+) 6.3/4.2%, P = 0.07].

Discussion

The present study shows the occurrence of NSVT after STEMI being associated with an increased long-term mortality. However, this adverse effect only applies for patients not on statin therapy. Statins significantly reduce long-term mortality irrespective of the absence or presence of NSVT; moreover, the data suggest that statins are able to markedly attenuate the association of NSVT with adverse outcome after STEMI, maintaining beneficial effects on outcome.

The prevalence of NSVT after STEMI in this study is in the same range as reported in previous studies. Patients with or without NSVT did not largely differ in discharge medication including ACE-inhibitors, beta-blockers, and statins. In both groups, only a minority of the patients obtained specific anti-arrhythmic drugs at discharge. As expected, however, patients with NSVT more often had previous myocardial infarction and severely reduced left ventricular function. In multivariable analysis, taking these parameters into account,
only NSVT was associated with a trend to adverse prognosis. Indeed, the independent prognostic value of NSVT in the era of modern treatment of myocardial infarction including thrombolysis, PCI, beta-blockers, and statins is controversial and has been questioned previously.\(^2\)\(^{-4}\),\(^3\)\(^3\),\(^3\)\(^4\)

The situation completely changes if the prognostic value of NSVT is evaluated within the subgroups of patients either receiving or not receiving statins. Whereas in patients without statin treatment the occurrence of NSVT was associated with an almost three-fold increase of 1 year mortality, NSVT had no independent predictive value on long-term mortality anymore, if patients received statins at discharge.

The present study only investigates all-cause mortality after STEMI, and the data of the ACOS registry do not allow the differentiation of the individual cause of death on a reliable basis. As differences in the classification of death adopted in different recent trials and inter-observer discordance may complicate classification,\(^3\)\(^5\) the use of total mortality has been advocated as the most reliable endpoint in myocardial infarction studies.\(^3\)\(^6\) Still, it is well known that a significant portion of the patients, who die within 1 year after STEMI, die from sudden death.\(^3\)\(^6\) 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.\(^3\)\(^5\),\(^2\)\(^6\) This assumption would be in line with recent data showing statins to improve autonomic neural control and increase electrical stability of the myocardium.\(^2\)\(^7\)\(^{2\)\(^9\) In addition, in patients with coronary artery disease and implanted cardioverter defibrillator lipid-lowering therapy (the majority of patients receiving statins) was associated with a reduction of the recurrence of ventricular tachycardia.\(^3\)\(^0\) However, further investigations are necessary to confirm the clinical significance of these observations and to clarify the potentially underlying mechanisms. Furthermore, other protective mechanisms have to be additionally taken into account as improvement of endothelial function has also been shown to occur early after starting statin therapy.\(^1\)\(^4\)

In the present study, in both groups (NSVT vs. no NSVT) statin therapy was associated with a reduced number of non-fatal major adverse events (re-infarction and/or stroke) within 1 year of follow-up, but this effect did not reach the level of significance. Lack of significance could be the result of the relatively small number of non-fatal adverse events during this time period. Furthermore, with regard to the group of patients with NSVT, the subgroups either receiving or not receiving statins were small. Prolongation of the follow-up period would be necessary to get clarification.

**Study limitations**

The present investigation is not a randomized, controlled study evaluating the effect of statins on patients with STEMI and NSVT. However, randomization of these patients in two groups either receiving or not receiving statins is not actually possible for ethical reasons. Therefore, the present prospective and well-defined registry appears to be an acceptable way for evaluation of the therapeutic effect of statins in certain subgroups. Moreover, this study included all patients with STEMI as presented in clinical practice, suggesting a sufficient clinical impact of the results.

In the ACOS registry, performance of in-hospital Holter monitoring was at the discretion of the treating clinician.
Appendix

The following list presents the participants of the ACOS-registry:


Table 3 Multivariable analysis of 1 year all-cause mortality of patients after acute STEMI, adjusted for age, gender, diabetes, reperfusion, ejection fraction <40%, and chronic beta-blocker therapy

<table>
<thead>
<tr>
<th>Total mortality</th>
<th>NSVT (−)</th>
<th>NSVT (+)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin (−)</td>
<td>9.2 %</td>
<td>25.0 %</td>
<td>3.02</td>
<td>1.47-6.20</td>
</tr>
<tr>
<td>(43/466)</td>
<td>(18/72)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin (+)</td>
<td>3.2 %</td>
<td>5.3 %</td>
<td>1.03</td>
<td>0.55-1.92</td>
</tr>
<tr>
<td>(72/2273)</td>
<td>(14/263)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>0.67</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.43-1.04</td>
<td>0.12-0.67</td>
<td></td>
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</tr>
</tbody>
</table>

The analysis differentiates between the groups being on treatment with statins at discharge or not and presenting with NSVT during Holter monitoring or not.

Conclusion

In conclusion, after STEMI, it is only in patients not on statin treatment that the occurrence of NSVT is associated with a significant and marked increase in 1 year mortality. Under statin treatment, however, NSVT is not associated with an adverse long-term prognosis, suggesting that statins may have an additional effect beyond cholesterol lowering and plaque stabilization, which may be associated with a stabilization of myocardium against pro-arrhythmic events.

Supplementary material

Supplementary material is available at European Heart Journal online.

Acknowledgements

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References

8. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial


