Original Research

Effect of Statin Pretreatment on the Outcome of ST-Segment Elevation Myocardial Infarction in Patients Without Prior History of Coronary Artery Disease

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Key words: **Statin, thrombolysis, ST-elevation myocardial infarction.**

Introduction: Early statin treatment has beneficial effects on the prognosis after acute coronary syndromes. We investigated the impact of prior statin treatment on the outcome of patients without a prior history of coronary artery disease (CAD) who presented with ST-elevation myocardial infarction (STEMI) and were treated with thrombolysis.

Methods: The study enrolled 1032 consecutive patients who satisfied the above criteria. They were categorized into two groups, based on their prior statin treatment for at least 3 months before admission: the statin-pretreatment group (n=124) and the statin-naïve group (n=908). All patients received high-dose statins during hospitalization and were prescribed statins after discharge. The primary outcome was the incidence of successful thrombolysis, as expressed by the percentage of patients with ≥50% ST-segment resolution and complete retrosternal pain resolution at 90 minutes. Secondary outcomes included reduction in high-sensitivity C-reactive protein (hs-CRP) and CK-MB levels, and in-hospital, short- and long-term cardiovascular mortality.

Results: ST-segment resolution ≥50% was observed in 63.7% of the statin-pretreatment group and in 49.1% of statin-naïve patients (p<0.01). Statin pretreatment was associated with lower hs-CRP and peak CK-MB levels (p<0.001). The statin-pretreatment group had lower 30-day mortality (5.6% vs. 12.3%, p<0.05), whereas no significant differences were detected in in-hospital or 3-year mortality.

Conclusions: Prior statin treatment in patients without a history of CAD who present with STEMI is associated with successful thrombolysis, decreased systemic inflammation, a lesser degree of myocardial damage, and a possible reduction in short-term mortality.

Manuscript received: May 18, 2012;
Accepted: November 26, 2012.

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Statin administration has been associated with significant mortality reduction, in both acute coronary syndromes (ACS) and stable coronary artery disease (CAD).[1,2] It has been shown that statin treatment was associated with a mortality benefit in primary prevention of CAD in high-risk individuals.[3] The benefit of statins in ACS seems to derive not only from their lipid-lowering properties but mainly from their pleiotropic effects, which are associated with plaque stabilization.[4,5]

Prior treatment with statins in patients admitted with ACS is associated with a reduced incidence of ST-segment elevation myocardial infarction (STEMI) compared to other presentations of CAD.[6,7] However, the impact of statin

pretreatment on the outcome of STEMI patients receiving reperfusion therapy with thrombolysis has not been thoroughly investigated.

Accordingly, we aimed to investigate the impact of prior statin treatment on the efficacy of thrombolytic therapy in patients without a prior history of CAD, who presented with STEMI and were treated with thrombolytic therapy.

Methods

Study population

We prospectively enrolled 1032 consecutive patients with STEMI who were admitted to the coronary care units of the Tzanio Piraeus Hospital and the "Sotiria" Athens Hospital during 2001-2006 and were treated with intravenous thrombolysis within 12 hours from symptom onset. STEMI was defined as continuous (refractory to nitrates) angina pectoris of ≥30 min duration, present upon admission, together with ST-segment elevation ≥2 mm in ≥2 contiguous precordial leads, or ≥1 mm in ≥2 contiguous limb leads, on the 12-lead electrocardiogram.

The study population was made up entirely of patients with no prior history of CAD, thus excluding patients with a history of myocardial infarction (ST-elevation or non ST-elevation), or previous percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery, a positive stress or ischemia study, or coronary artery stenosis greater than 50% in a previous angiogram. Patients in whom the ST-segment in the ECG could not be evaluated (left or right bundle branch block, permanent pacemaker), patients with contraindications for thrombolysis, patients with cardiogenic shock, and patients presenting more than 12 hours after symptom onset were also excluded. All patients provided written informed consent before their inclusion in the study. The study was approved by the institutional Ethics Committee and complied with the Declaration of Helsinki.

Study procedures

Demographic and clinical data were collected prospectively. Hypertension was defined as a history of treated or untreated arterial hypertension, or blood pressure >140/90 mmHg in two independent measurements. Diabetes mellitus was defined as a history of treated or untreated diabetes mellitus, fasting serum glucose ≥126 mg/dL or any serum glucose ≥200 mg/dL during hospitalization for STEMI. Dyslipidemia was defined as a history of treated or untreated dyslipidemia, or elevated levels of blood lipids on admission (total cholesterol ≥200 mg/dL and/or low-density lipoprotein cholesterol [LDL] ≥130 mg/dL). Prior medical treatment was recorded in detail, including information about prior statin therapy. Patients were prospectively divided into two groups, depending on whether they had been receiving statins for at least three months before the onset of the ACS.

Tissue-type plasminogen activator was used as a thrombolytic agent. Chewed aspirin 160-325 mg and a loading dose of 300 mg clopidogrel were administered upon admission. Unfractionated heparin was given as appropriate in a bolus of 60 U/kg (up to 5000) upon admission, followed by an intravenous infusion of 12 U/kg/h titrated to a therapeutic activated partial thromboplastin time. Heparin was continued in uncomplicated case subjects for 48 h. The pharmacological treatment after thrombolysis in all patients included aspirin, clopidogrel 75 mg, β-blockers, nitrates, and angiotensin-converting enzyme inhibitors, unless a contraindication was present.

All patients received high-dose statin treatment (40 mg atorvastatin or 40 mg simvastatin) immediately after thrombolytic administration and during the initial 24 hours of hospital stay, unless contraindicated, according to practice guidelines.[8,9]

On admission, venous blood samples were obtained before intravenous administration of any drugs. Coded plasma samples were stored at -80°C for central analysis of high-sensitivity C-reactive protein (hs-CRP) at the end of the study. hs-CRP was measured using a highly sensitive nephelometric method (Binding Site, Birmingham, UK). The lower limit of detection is 0.12 mg/L. For values below the limit of detection, the lower limit value was used for statistical analysis. Creatine kinase-MB (CK-MB) was measured on admission and 24 hours after admission. Laboratory results were studied and the peak value of CK-MB was recorded.

Electrocardiographic analysis

The analysis of electrocardiographic data was performed in the laboratory of Tzanio General Hospital by physicians who were blinded to the clinical data. Standard 12-lead ECGs were obtained at baseline and after 90 minutes. The ST-segment was measured 20 ms after the J-point, and the sum of ST deviations was measured at baseline and after 90 minutes.[10] The percentage resolution of ST-deviation from baseline to 90 minutes was calculated, and thrombolysis was

categorized as successful (≥50% ST-segment resolution) or failed (<50% ST-segment resolution).[11]

Follow up

In-hospital and long-term follow-up data were collected prospectively using pre-designed forms. Subjects were followed up at 30, 90, and 180 days, and every 180 days thereafter, for a period of 1200 days. Cardiovascular death was defined as sudden unexplained death or death due to fatal myocardial infarction, death after rehospitalization because of heart failure or possible acute myocardial ischemia, death due to cerebrovascular accident, and death due to complications of peripheral arterial disease. The diagnosis of cardiovascular death was verified by death certificates, hospital records, or telephone contact with the subjects' relatives or attending physicians. Events were adjudicated by a committee who were unaware of the study protocol.

Study outcomes

The primary outcome of this study was the incidence of successful thrombolysis in STEMI, as expressed by the percentage of patients with ≥50% ST-segment resolution and complete resolution of retrosternal pain. Secondary outcomes included reductions in hs-CRP and CK-MB levels, and in-hospital, short- and long-term cardiovascular mortality.

Statistical analysis

With a sample size of 1000 patients, the study had 80% power to detect, with a 5% level of significance, a 15% difference in the percentage of cases with ≥50% ST-segment resolution after thrombolytic administration in the statin-pretreatment group compared to the statin-naïve group, assuming a statin pretreatment prevalence of 15% in patients without prior history of CAD and a 50% successful thrombolysis rate in the statin-naïve group.[6,12]

All statistical analysis was performed using SPSS Statistics version 19.0 (SPPS Inc., Chicago IL, USA). Data were expressed as mean ± SD for continuous variables and as percentages for categorical variables. Differences between groups were assessed with the χ^2 test or Fisher's exact test for categorical variables, and with Student's t-test and the Mann–Whitney test for continuous variables, as appropriate. Analysis of survival in each group was assessed using the Kaplan–Meier method, while the log-rank test was used to assess differences between the two curves. A p-value <0.05 indicated statistical significance.

Results

Baseline characteristics

A total of 1032 patients were evaluated. The mean age was 59.4 ± 9.8 years. The statin-pretreatment group consisted of 124 patients (12.0%) treated with statins for at least 3 months before admission, while the statin-naïve group consisted of the remaining 908 patients (88.0%). The mean time from pain onset to the start of thrombolysis was 3.61 ± 1.30 hours. The baseline clinical characteristics of the patients are summarized in Table 1. There were no significant differences between the two groups. Furthermore, no significant differences were detected between the two groups in concomi-

Table 1. Baseline clinical characteristics and electrocardiographic analysis.

	Statin pretreatment	Statin-naïve	p
Number of patients (n)	124	908	
Age (years)	58.6 ± 9.8	59.8 ± 9.8	0.19
Sex (male) (%)	97 (78.2)	748 (82.2)	0.29
Coronary risk factors, n (%):			
Current smokers	66 (53.2)	464 (51.1)	0.66
Hypertension	64 (51.6)	489 (53.9)	0.64
Hypercholesterolemia	124 (100)	536 (59)	<0.0001
Diabetes mellitus	29 (23.4)	253 (27.9)	0.29
Family history of coronary artery disease	55 (44.4)	419 (46.1)	0.70
Anterior myocardial infarction, n (%)	81 (65.3)	568 (62.6)	0.55
Time to thrombolysis (hours)	3.61 ± 1.3	3.61 ± 1.36	0.99
Number of leads with ST-segment elevation >1mm	4.33 ± 1.51	4.33 ± 1.56	0.98
Height of ST-segment elevation at admission (mm)	4.57 ± 1.43	4.54 ± 1.43	0.76

All values are expressed as mean ± SD or n (%).

tant medications before admission (β-blockers, angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers, antiplatelet therapy).

Results from the baseline electrocardiographic analysis are also presented in Table 1. There were no statistically significant differences between the two groups regarding either the extent of epicardial ischemia, estimated by the number of leads with >1 mm ST elevation, or the amplitude of the highest ST elevation. The primary outcome, ≥50% ST-segment resolution at 90 minutes following thrombolytic administration (accompanied by resolution of anginal pain), was observed in 63.7% of the patients with statin pretreatment versus 49.1% of the statin-naïve patients ($p<0.01$).

Serum levels of hs-CRP at admission in the statin-pretreatment group were significantly lower compared to the statin-naïve group (1.16 ± 1.25 vs. 1.82 ± 1.48 mg/dL, $p<0.001$; Figure 1A). Furthermore, analysis of myocardial necrosis biomarkers revealed that peak CK-MB after the first 24 hours was significantly lower in patients with statin pretreatment (136.66 ± 90.38 vs. 165.63 ± 73.31 U/L, $p<0.001$; Figure 1B). Serum levels of CK-MB and hs-CRP did not have a normal distribution and were assessed using the Mann–Whitney test.

Kaplan–Meier curves for cardiovascular survival are presented in Figure 2. In-hospital cardiovascular mortality was lower in the statin-pretreatment group (4.8%; n=6) compared to statin-naïve patients (6.9%; n=63), although the difference did not reach statistical significance ($p=0.38$).

The patients were followed for a mean period of 984 ± 127 days. Thirty-day follow-up data were available for 98.5% of the patients (n=1017). After thirty days, a statistically significant reduction in cardiovascular mortality was evident for patients pretreated with statins ($p<0.05$). Specifically, 7 of 124 statin-pretreated

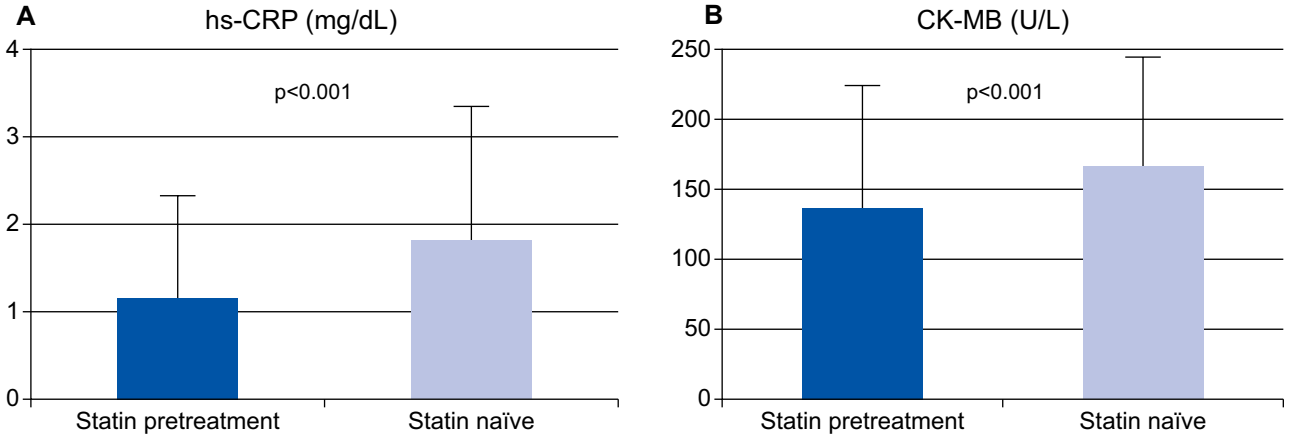

Figure 1. Levels of (A) high-sensitivity C-reactive protein (hs-CRP) and (B) creatine kinase-MB (CK-MB) in the statin-pretreatment and the statin-naïve group. Boxes represent mean and whiskers ± 1SD.

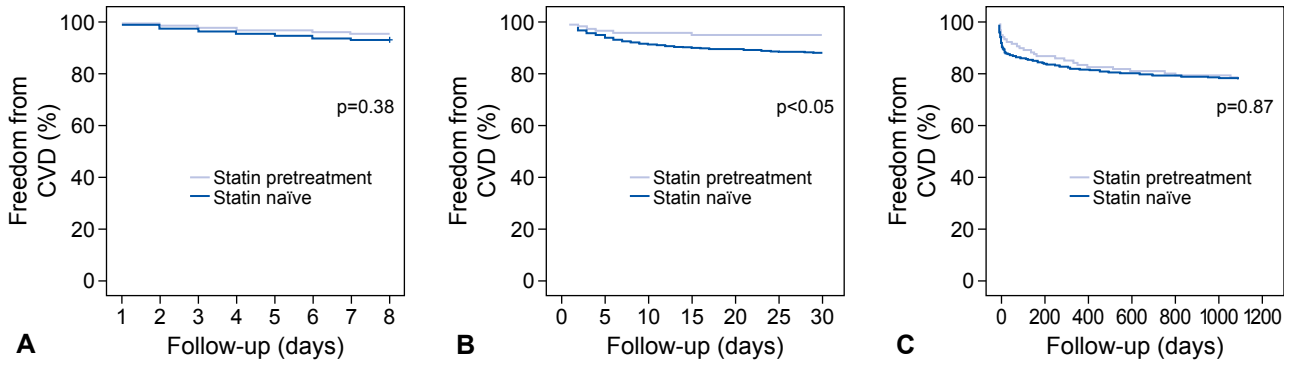

Figure 2. Kaplan–Meier curves for (A) in-hospital cardiovascular survival, (B) 30-day cardiovascular survival, (C) 3-year cardiovascular survival, in the statin-pretreatment and the statin-naïve group. Cardiovascular mortality was lower at 30 days in the statin-pretreatment group. CVD – cardiovascular death.

patients (5.6%) died of a cardiovascular cause within 30 days, while cardiovascular death was observed in 112 of 908 patients (12.3%) in the statin-naïve group.

Follow-up data at 3 years were available for 1009 patients (97.8%). During this period, 27 deaths from cardiovascular causes (21.8%) were recorded in patients pretreated with statins, while in statin-naïve patients death from cardiovascular causes was observed in 22.4% (n=202) of the cases (p=0.876).

Discussion

The main findings of the present study are: 1) in patients with no prior history of CAD who presented with STEMI and were treated with thrombolysis, prior treatment with statins was associated with successful thrombolysis, as assessed by the percentage of patients achieving ≥50% ST-segment resolution at 90 minutes after thrombolysis and complete retrosternal pain resolution; 2) patients receiving statins before admission had lower levels of peak CK-MB and hs-CRP, indicating a smaller infarct size and a lesser extent of inflammatory activation; 3) prior treatment with statins may be associated with lower 30-day mortality, without any differences being evident during hospital stay or at 3-year follow up.

Very early high-dose statin administration in the setting of ACS is associated with a significant reduction in mortality.[1,6,13-19] However, the effect of statin pretreatment in patients with STEMI who are treated with thrombolysis has not been extensively investigated. Our study is the first to show that statin pretreatment is associated with successful thrombolysis, as expressed by the percentage of patients with ≥50% ST-segment resolution and complete retrosternal pain resolution. Statin pretreatment has been associated with a greater degree of ST-segment resolution in a small study of STEMI patients receiving thrombolytic treatment.[20] Experimental studies have shown that statins promote vascular fibrinolysis after plaque rupture,[21,22] while concomitantly decreasing lipid oxidation, inflammation, matrix metalloproteinase-2 and cell death, and increasing the content of tissue inhibitor of metalloproteinase-1 and collagen.[23] Via these pathways, statins increase fibrous cap thickness and decrease the lipid core size of atheromatous plaque,[24] morphological features associated with successful thrombolysis and reduced distal embolization.[20,25,26] The cardioprotective effect of statins against ischemia-reperfusion injury has been proven in experimental studies and is attributed to the improvement in endothelial function and the attenuation of the production of reactive oxygen species.[20,23] Finally, it has been suggested that statins exert pharmacological ischemic preconditioning effects by opening mitochondrial ATP-sensitive potassium channels.[27] These effects might contribute to reduced myocardial damage during ischemia-reperfusion. The aforementioned findings are in accordance with our study, where statin pretreatment was associated with an absolute reduction of 14.6% in the primary outcome of ≥50% ST-segment resolution and complete retrosternal pain resolution.

Prior treatment with statins in patients with myocardial infarction undergoing primary PCI has been associated with attenuation of the inflammatory process, improved coronary flow and myocardial perfusion, and a reduction in the extent of myocardial necrosis.[28-31] Additionally, in experimental observations statin administration was associated with reduced inflammatory activation,[4] while statin pretreatment before reperfusion exerted a cardioprotective effect by reducing infarct size.[32-34] Indeed, our results indicate that statin pretreatment is also associated with attenuation of inflammation and a reduction in myocardial damage in STEMI patients treated with thrombolysis.

In the present study, statin pretreatment was associated with a significant reduction in short-term mortality, without being associated with a reduction in in-hospital or in long-term mortality. However, the study sample was inadequate for showing a mortality benefit, and thus our results should be interpreted cautiously. The lower 30-day mortality observed in the statin-pretreatment group could be attributed to the increased efficacy of thrombolytic therapy and the smaller infarct size in these patients. Furthermore, despite all patients being treated with high-dose statins early after admission, patients with statin pretreatment had an additional benefit, as in order for statins to exert their plaque stabilizing effect in full, administration should take place over several months.[19] Similarly, statin pretreatment was found to be an independent predictor of 30-day mortality in STEMI patients undergoing primary PCI.[35] Results from the GRACE registry also suggest that patients treated with statins before admission present more often with non-ST-elevation myocardial infarction instead of STEMI, and are associated with a better prognosis.[6]

Conversely, statin pretreatment was not associated with a significant mortality benefit during the initial hospital stay. However, early intensive in-hospital lipid-lowering therapy administered to both groups could have attenuated a possible effect of statin pretreatment. Accordingly, no significant difference has been detected in early outcomes between statin-pretreated patients and statin-naïve patients

who received statins early during hospitalization for ACS.[6,16,36] Furthermore, considering the low mortality rate in both groups (<7%), a very large sample size would be required to demonstrate a benefit.

Finally, long-term mortality was not different between the two groups. The latter finding was not surprising, as both groups received intensive statin therapy during their hospital stay and after discharge, according to guidelines,[8,9] thus leading to a late "catch-up" effect. Furthermore, the presence of other factors affecting long-term mortality, such as the extent of CAD and subsequent revascularization, was not assessed and might have played an important role in long-term survival.[37,38]

Clinical implications

Our study corroborates the role of statins in primary prevention by underscoring the potential benefits of prior treatment with statins in patients who undergo thrombolysis for STEMI. Despite the impediments to performing a randomized study for assessing the impact of statin pretreatment on patients developing ACS, such observations, along with prospective randomized data in primary prevention studies,[3] indicate a role for chronic statin treatment in the reduction of ACS morbidity.

Study limitations

One of the limitations of the study is that detailed information about clinical presentation, angiographic extent of CAD, and revascularization status were not recorded, and thus such data are not available. However, it is important to point out that consecutive patients were enrolled. Therefore, differences in clinical presentation, if present, could also be attributed to the prior administration of statins.[5] Furthermore, such factors have been shown to be associated with cardiovascular mortality, but not with ST-segment resolution, the primary outcome of the study. The inclusion of that information, and mainly the patients' revascularization status, could help elucidate whether statin pretreatment contributes to reducing short-term cardiovascular mortality.

A second limitation was that this was a non-randomized prospective observational study. However, patients included had no prior history of CAD; thus, no baseline differences were present between the groups apart from hypercholesterolemia. Thirdly, although the sample study was sufficient to detect a difference in the percentage of patients with successful thrombolysis, prospective recruitment of a sample size large enough to detect differences in mortality would be very difficult in patients with no prior history of CAD. Nevertheless, our study is the largest prospective study to investigate the effect of statin pretreatment on the outcome of STEMI treated with thrombolysis. Fourthly, despite the meticulous follow up, three of 124 patients in the statin-pretreatment group (2.4%) and 12 of the 908 statin-naïve patients (1.3%) were lost to follow up. However, even if all these patients had been associated with an event, our findings would not be affected. Finally, data on the type and doses of prior statin treatment were not analyzed, because of the relatively small sample size.

Conclusions

Prior statin treatment in patients with no history of CAD who present with STEMI is associated with a greater efficacy of thrombolytic therapy, as expressed by the percentage of patients with ≥50% ST-segment resolution and complete retrosternal pain resolution. Furthermore, statin pretreatment is associated with decreased systemic inflammation and a reduction in the final infarct size. Prior statin treatment may be associated with lower short-term mortality, without, however, a significant in-hospital or 3-year mortality benefit.

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