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Lynn Moran

Tyler Fugate

Yufei Xiang

Christopher Cianci

Martin E. Matsumura MD
Lehigh Valley Health Network, Martin_E.Matsumura@lvhn.org

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CLINICAL STUDY

Statin Pretreatment Is Protective Despite an Association With Greater Coronary Artery Disease Burden in Patients Presenting With a First ST-Elevation Myocardial Infarction

Lynn Moran, DO; Tyler Fugate, DO; Yufei Xiang, MD, MS; Christopher Cianci, BS; Sherrine Eid, MPH; Martin Matsumura, MD

The relationship of chronic pre-event statin use with coronary disease severity at the time of presentation with a first acute ST-elevation myocardial infarction (STEMI) is unknown. A retrospective review was performed of consecutive patients presenting with STEMI and without a prior history of vascular disease, divided into those whom had been treated with statins before presentation (n=50) and those whom were not pretreated (n=231). Patients pretreated with statins were more likely to have left main (24.0% vs 8.3%; P=.001) or 3-vessel disease (44.0% vs 25.1%; P=.007) vs untreated patients. After matching for risk factors, a trend toward higher likelihood of 3-vessel disease persisted in the statin pretreatment group (47.6% vs 28.6%; P=.07). Significantly lower peak troponin-I levels (87.8 mg/dL vs 134.5 mg/dL; P=.006) were found in patients pretreated with statins, suggesting that statin pretreatment is protective in patients with STEMI despite the presence of greater disease burden. This finding supports the concept that statin therapy alters the natural history of coronary artery disease development leading to a first STEMI and is cardioprotective in those patients who experience a first STEMI. (Prev Cardiol. 2008;11:21–25) ©2008 Le Jacq

From the Cardiovascular Research Institute, Penn State College of Medicine/Lehigh Valley Hospital, Allentown, PA
Address for correspondence:
Martin Matsumura, MD, Division of Cardiology, Penn State College of Medicine/Lehigh Valley Hospital, Allentown, PA 18036
E-mail: mem2y@hotmail.com
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It is well established that statins are associated with a reduced risk of a first cardiac event and a reduction in both early and late adverse outcomes following an acute cardiac event.[1,2] One aspect of the protective effect of statins in patients presenting with an acute coronary syndrome (ACS) appears to involve a reduction in myonecrosis associated with percutaneous coronary intervention (PCI) in this setting.[3] This finding is consistent with the growing body of literature supporting reduced myonecrosis in patients pretreated with statins undergoing elective PCI.[4,5] There are several potential mechanisms to explain this phenomenon, including a reduction in microembolization during PCI, an improvement in target vessel endothelial function, and a direct anti-inflammatory effect of statin therapy.[5]

While the positive effect of statins on patient outcomes across a wide spectrum of coronary disease presentations is unequivocal, the effect of chronic statin therapy on degree and severity of coronary artery disease (CAD) in patients presenting with a first ST-elevation myocardial infarction (STEMI) is unknown. Just as pretreatment with aspirin was previously identified as an independent risk factor in ACS,[6] it seems plausible that patients who present with STEMI despite chronic statin therapy may represent a subgroup of patients with more aggressive, higher risk CAD. Therefore, in the present study we tested the hypothesis that prior treatment with statins may be associated with alterations in CAD burden in patients presenting with a first STEMI, and we examined whether this alteration in disease burden modulates the protective effect of statin therapy in this setting.

METHODS

A retrospective review was performed using a search of a computerized database of all patients admitted between January 2004 and June 2006 to

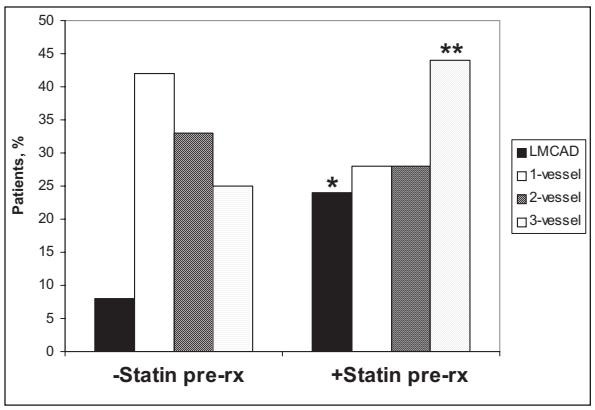

*Figure 1. Comparison of percentage of number of diseased vessels and left main coronary artery disease (LMCAD) between statin pretreated (+ statin pre-rx) and nonstatin pretreated (– statin pre-rx) groups (*P=.001 vs nonstatin pretreated for LMCAD; **P=.007 vs nonstatin pretreated for 3-vessel CAD).*

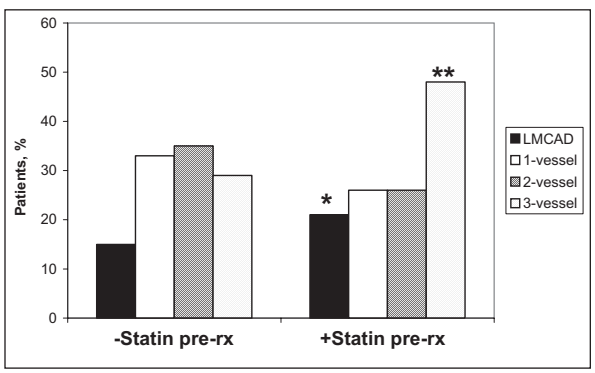

*Figure 2. Comparison of percentage of number of diseased vessels and left main coronary artery disease (LMCAD) between statin pretreated (+ statin pre-rx) and nonstatin pretreated (– statin pre-rx) groups, matched for age, sex, tobacco use, and hypertension (*P=.421; **P=.07).*

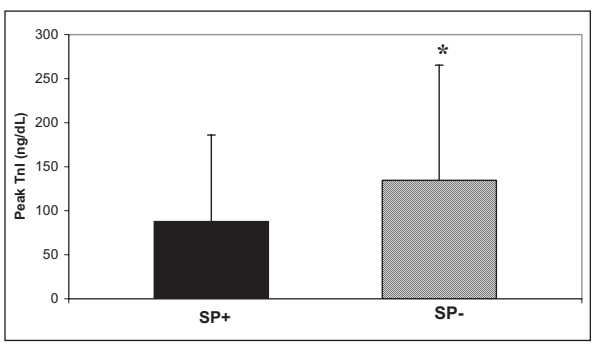

*Figure 3. Comparison of peak troponin-I (TnI) levels for statin pretreated (SP+) vs nonstatin pretreated (SP–) patients (*P=.006).*

Lehigh Valley Hospital (Allentown, PA) with the diagnosis of STEMI. Data regarding past medical history, medicine use, admitting laboratory studies, and hospital course were extracted from an electronic medical record database. Patients included in the review were those who had no prior history of coronary, cerebral, or peripheral vascular disease by either clinical events or abnormal diagnostic testing. Additionally, patients with a history of diabetes mellitus were not included in the study. Patients with a pre-event history of angina were included if the diagnosis of CAD was not confirmed with diagnostic testing. Statin use before presentation was recorded from the admission history and nursing notes. Patients were excluded if they were taking nonstatin lipid-lowering agents, including fibrates, fish oil, cholesterol-binding agents, or niacin.

All patients in the study underwent diagnostic cardiac catheterization within 4 hours of presentation or transfer to the study center. Coronary anatomy and degree of stenoses were determined by the catheterizing physician with at least 2 views of each coronary artery. A coronary artery (including the STEMI culprit vessel) was defined as being diseased if the major epicardial vessel or any major branches had >50% stenosis. Left ventricular ejection fraction was assessed qualitatively at the time of cardiac catheterization by ventriculography in 2 planes. Serum lipid levels were assessed within 48 hours of admission, in the fasted state. Cardiac troponin-I (TnI) levels were measured immediately on presentation and at 6 and 24 hours after admission.

Patients were stratified into statin pretreatment (SP+) or no statin pretreatment (SP–) groups for analysis based on whether they had been prescribed a statin >7 days before presentation. The baseline and end point analyses were performed with unpaired *t* tests for continuous data and chi-square tests for categorical data with SigmaStat software (Systat Software, Inc, San Jose, CA). The Institutional Review Board of Lehigh Valley Hospital approved the study.

RESULTS

A total of 281 patients were identified who met the study criteria. Of these, 231 patients (82.2%) were placed in the SP– group and 50 patients (17.8%) were placed in the SP+ group. The clinical characteristics of the 2 groups are summarized in the Table. Significantly more patients in the SP+ group had a history of hypertension (59.2% vs 30.3%; *P*=.001). Other demographics and past medical diagnoses were not different between groups. Nonstatin medicine use did not differ between the 2 groups, with the exception of greater use of angiotensin receptor antagonists in the SP+ group (14.0% vs 3.8%; *P*=.012). Of note, aspirin use did not differ significantly between the 2 groups.

Statin pretreated patients were administered variable formulations and doses of statins, with type of statin, mean dose, and dose range summarized in the Table. As would be expected, patients in the SP+ group had significantly lower mean values for total cholesterol (154.4 mg/dL vs 178.7 mg/dL; *P*=.019) and low-density lipoprotein cholesterol (91.3 mg/dL vs 118.9 mg/dL; *P*=.045), and a higher mean

Table. Clinical characteristics, medicine use, and lipid profiles of patients with (SP+) and without (SP–) statin pretreatment before STEMI

	SP+ (N=50)	SP– (N=231)	*P* VALUE
Age, mean, y	83.54	70.75	.466
Sex, male	59.1%	71.4%	.093
Tobacco use	44.9%	56.4%	.145
Hypertension	59.2%	30.3%	.001
CAD Family history	42.5%	44.2%	.840
Medicine use			
Aspirin	20.0%	8.0%	.062
ARB	14.0%	3.8%	.012
ACEI	2.0%	6.1%	.412
Calcium channel blocker	8.0%	3.1%	.227
β-Blocker	6.0%	3.4%	.645
Diuretic	16.0%	6.5%	.112
Statin, mg (mean dose, range)			
Atorvastatin	48.0% (18.8, 10–80)	N/A	
Simvastatin	40.0% (20.8, 5–80)	N/A	
Pravastatin	4.0% (30.0, 20–40)	N/A	
Fluvastatin	4.0% (60.0, 40–80)	N/A	
Rosuvastatin	2.0% (10.0, 10.0)	N/A	
Lovastatin	2.0% (20.0, 20.0)	N/A	
Admission TC, mg/dL	154.43	178.67	.019
Admission LDL, mg/dL	91.26	118.92	.045
Admission HDL, mg/dL	40.55	36.27	.004
Admission TG, mg/dL	132.79	161.82	.099

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N/A, not applicable; STEMI, ST-elevation myocardial infarction; TC, total cholesterol; TG, triglycerides.

high-density lipoprotein cholesterol (40.6 mg/dL vs 36.3 mg/dL; *P*=.004) vs SP– patients. While SP+ patients had a lower mean value for triglycerides, this was not statistically significant.

Angiographic data are depicted in Figure 1. At catheterization, SP+ patients had significantly higher frequency of both left main and 3-vessel CAD (24.0% vs 8.3% and 44.0% vs 25.1%; *P*=.001 and *P*=.007, respectively). Angiographic data were reanalyzed after SP+ patients were matched on demographics and risk factors 1:1 with SP– patients. Results are summarized in Figure 2. After matching, a nonsignificant trend toward increased risk of 3-vessel disease persisted in the SP+ group (47.6% vs 28.6%; *P*=.07). The relationship between statin pretreatment and risk of left main CAD did not persist after matching analysis.

Clinical outcome data are summarized in Figure 3. SP+ patients had a significantly lower peak measurement of TnI vs SP– patients (87.8 ng/mL vs 134.5 ng/mL; *P*=.006). Other outcome data were not significantly different between the 2 groups, including death (4.1% vs 1.7%; *P*=.305), shock and/or need for intra-aortic balloon pump (16.3% vs 9.6%; *P*=.169), or need for urgent bypass surgery (19.1% vs 13.5%; *P*=.319). Likewise, there was no significant difference between the 2 groups in terms of predischarge ejection fraction (47.4% vs 52.2%; *P*=.54).

DISCUSSION

The value of statin therapy in reducing the risk of a first myocardial infarction is supported by a wealth of clinical data.[7] Recent data have suggested that in addition to reducing the risk of cardiac events, statins may influence the way that patients present with CAD. Analysis of the Global Registry of Acute Coronary Events (GRACE) database noted that, compared with patients without prior statin use, chronic statin users presenting with ACS were less likely to have ST elevation on their initial electrocardiogram.[7] A recent study demonstrated that statins increase the likelihood that patients will present with stable effort angina rather than an ACS.[8] These data support a protective effect of statins against high-risk CAD presentations. Likewise, several recent studies have demonstrated significantly improved outcomes among patients who are treated with statins early in the course of ACS.[9,10] However, these studies have not specifically examined the comparative outcomes of patients who present with STEMI despite statin treatment vs those who are statin-naive. While the effect of statin pretreatment on clinical outcomes in

STEMI has not been fully defined, it seems almost a certainty that the overall effect of chronic statin use is protective at the time of STEMI. In support of this concept is a recent study demonstrating increased likelihood of infarct-related artery patency in patients treated with statins before STEMI, an angiographic finding known to be associated with improved clinical outcomes.[11]

The present study demonstrates a protective effect of statin pretreatment in patients without a history of vascular disease or equivalent who present with a first STEMI. The finding of reduced infarct size as defined by peak TnI in statin pretreated patients was particularly compelling in that it was apparent despite the presence of increased CAD burden in the statin pretreated group. The finding of reduced myonecrosis despite greater CAD burden is in contrast to prior studies that concluded that the presence of multivessel CAD at the time of STEMI presentation was linked to both poorer initial PCI results and increased risk of death or recurrent myocardial infarction at 1 year post-STEMI,[12] providing further evidence of a protective effect of statin pretreatment in our patients.

Why do patients who are chronically treated with statins appear to have higher-risk CAD at the time of presentation with STEMI? One possibility is that the occurrence of STEMI despite chronic treatment with statins identifies patients with particularly aggressive CAD. A similar relationship was noted in patients taking aspirin persistently and presenting with ACS.[6] An obvious alternative explanation for the relationship between statin use and CAD burden is that the use of lipid-lowering therapy is simply a "marker" for patients with higher risk profiles who are felt to be at a significant enough risk for CAD events that statin therapy is warranted. Interestingly, the 2 patient groups differed in terms of risk factors only in the prevalence of hypertension, which was significantly more common among the SP+ patients. However, when we attempted to match patients in the 2 groups to eliminate the imbalance in risk factors, a trend toward increased CAD burden persisted in the SP+ group, although the difference was not statistically significant. Regardless, the finding of increased CAD burden in STEMI patients pretreated with statins is to the best of our knowledge a novel finding and has implications for the early risk stratification and management of patients who present with a first STEMI.

The present study, while compelling, is retrospective and as such has inherent weaknesses. Because the patient population studied was not part of a closed medical system, the authors were unable to ascertain the length of time each of the pretreated patients had been prescribed statin therapy. Thus, an association of length of pretreatment with outcomes could not be assessed. Likewise, baseline lipid profiles of both groups before STEMI presentation could not be compared. It is likely that the statin pretreated group had significantly worse dyslipidemia before the institution of therapy, and the contribution of this risk factor to disease burden at the time of STEMI cannot be ignored. However, our population appears to be similar to that of prior studies with regard to the rate of statin use among patients who present with a first STEMI. A recent study assessing the Framingham Risk Score in men presenting with a first acute myocardial infarction found a 25% rate of statin use in patients with risk factors similar to those of our study population, which was notable for a 18% rate of statin use.[13] The higher rate of treatment with drugs modulating the renin-angiotensin system (angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers combined) in the SP+ group is worth noting, as increased use of these classes of drugs may have a cardioprotective effect at the time of STEMI; angiotensin-converting enzyme inhibitors, in particular, have been shown to be associated with increased coronary patency in patients presenting with STEMI.[11]

CONCLUSIONS

The present study adds to the growing body of literature supporting the benefit of statin therapy not only in prevention of coronary events, but also in improvement of outcomes in patients presenting with acute coronary events. Our study is unique in that it suggests that statin pretreated patients may have greater CAD burden at presentation with a first STEMI, despite the finding of decreased infarct size in this group. Further studies are needed to confirm this finding and determine the effect, if any, of this relationship on clinical outcomes.

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