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Statin pretreatment and presentation patterns in patients with coronary artery disease

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Abstract

Background: *Knowledge on the impact of pretreatment statin therapy on presentation of patients with coronary artery disease (CAD) is incomplete. The aim of this study was to investigate the impact of statin pretreatment on presentation patterns of patients with CAD.*

Methods: *The study included 12,989 consecutive patients with CAD who underwent coronary angiography. The primary outcome was presentation as stable angina or acute coronary syndrome (ACS) according to statin pretreatment.*

Results: *At the time of presentation, 8147 (62.7%) patients were receiving statins and 4842 (37.3%) patients were not receiving statins. Presentation pattern in patients receiving statins vs. those not receiving statins was: stable angina in 5939 (72.9%) vs. 2102 (43.4%) patients; odds ratio (OR) = 3.50, 95% confidence interval (CI) 3.25–3.78; p < 0.001; unstable angina in 1435 (17.6%) vs. 1011 (20.9%) patients; OR = 0.81, 95% CI 0.74–0.89; p < 0.001; non-ST-segment elevation myocardial infarction (NSTEMI) in 463 (5.7%) vs. 505 (10.4%) patients; OR = 0.52, 95% CI 0.45–0.59; p < 0.001; and ST-segment elevation myocardial infarction (STEMI) in 310 (3.8%) vs. 1224 (25.3%) patients; OR = 0.11, 95% CI 0.10–0.13; p < 0.001. Gensini score (median [25th to 75th percentiles]) was significantly higher in patients on statins presenting with stable angina (26.5 [13.0–59.5] vs. 21.0 [10.5–47.4]; p < 0.001) or ACS (39.3 [17.5–77.0] vs. 37.0 [18.0–64.0]; p = 0.001). In multivariable analysis, statin therapy was an independent correlate of reduced presentation with ACS (adjusted OR = 0.35 [0.32–0.39]; p < 0.001) or STEMI (adjusted OR = 0.18 [0.16–0.22]; p < 0.001).*

Conclusions: *Despite having a higher coronary atherosclerotic burden, patients with CAD on statin therapy have reduced odds for presentation with ACS and STEMI compared to patients not receiving statins.* (Cardiol J 2013; 20, 1: 52–58)

Key words: acute coronary syndrome, angina, atherosclerosis, myocardial infarction, statins

Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality worldwide. Ample evidence shows that progression of atherosclerosis and, in particular, transition from stable to unstable coronary atherosclerotic plaque(s) underlies clinical manifestations of CAD including presentation with acute coronary syndrome (ACS). Earlier angiographic studies [1–3] have shown that

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acute coronary occlusions resulting in ACS occur preferentially at the sites of non-critical coronary narrowing. However, recent studies in more contemporaneous series of patients and with the use of advanced imaging technology have shown that majority of acute myocardial infarctions (AMI) occur at the sites of critical coronary stenoses [4, 5]. In a recent study of patients with stable and unstable CAD, we showed that severe stenoses (those causing ≥ 75% narrowing) mediate almost all the risk related to atherosclerotic burden for presentation as unstable CAD [6]. In this study, we hypothesized that, widespread use of statins and antithrombotic therapy in more contemporaneous series of patients, through their lipid-lowering, plaque-stabilizing, anti-inflammatory and antithrombotic effects may have changed the natural course of atherosclerotic plaque reducing plaque vulnerability to rupture allowing plaques to reach critical degrees of lumen obstruction without clinical events [6]. Although, a low incidence of cardiac events [7–9], reduced odds of presenting with AMI [10, 11] and reduced incidence of plaque rupture [12, 13] by statin pretreatment have been reported, knowledge on the impact of statin therapy on presentation patterns of patients with CAD remains far from complete. We undertook this study to investigate the impact of statin pretreatment on the presentation patterns of patients with CAD undergoing percutaneous coronary intervention (PCI).

Methods

Patients

This study included a consecutive series of 12,989 patients with CAD who underwent coronary angiography and PCI in our hospital between March 2000 and December 2009. Eligible for the study were patients with the clinical diagnosis of stable CAD or ACS confirmed by coronary angiography, in whom the information of statin use before admission was available. The diagnosis of stable angina was based on the presence of chest pain that did not change its pattern in the preceding 2 months. Unstable angina was diagnosed using Braunwald's criteria [14]. Non-ST-segment elevation myocardial infarction (NSTEMI) was diagnosed in the presence of chest pain highly suggestive of myocardial ischemia, elevated troponin level (4^{th} generation cardiac troponin T > 0.03 μg/L), documentation of significant CAD (culprit lesions) in coronary angiography, but no ST-segment elevation in the electrocardiogram. ST-segment elevation myocardial infarction (STEMI) was diagnosed in the presence of chest pain lasting ≥ 20 min associated with ST-segment elevation in the electrocardiogram (ST-segment elevation of ≥ 0.1 mV in ≥ 2 limb leads or ≥ 0.2 mV in ≥ 2 contiguous precordial leads or complete left bundle branch block of new onset) and documentation of culprit coronary lesions in coronary angiography. All patients gave informed consent for coronary angiography and PCI. The study has been carried out in accordance with the Declaration of Helsinki and has been approved by the institutional ethics committee.

Definitions of risk factors

Data on history of disease, statin therapy before admission and cardiovascular risk factors were collected in every patient. Hypercholesterolemia was defined as a documented total cholesterol value ≥ 220 mg/dL or prior or ongoing treatment with a lipid lowering agent. Arterial hypertension was diagnosed when a patient was receiving active treatment with antihypertensive drugs or if on 2 separate occasions the systolic blood pressure was 140 mm Hg or greater or the diastolic blood pressure 90 mm Hg or greater. Criteria for the diagnosis of diabetes were: active treatment with insulin or oral hypoglycemic agents on admission; documentation of an abnormal fasting blood glucose (> 125 mg/dL); blood glucose > 200 mg/dL at any time; or abnormal glucose tolerance test based on the World Health Organization criteria. Smokers were defined as those currently smoking any tobacco. Body mass index was calculated using patients' weight and height measured during the hospital course. The glomerular filtration rate was estimated using the Cockcroft-Gault formula [15].

Coronary angiography and stent implantation

Digital angiograms were analyzed offline with an automated edge detection system (CMS; Medis Medical Imaging Systems, Nuenen, The Netherlands) in the core angiographic laboratory. CAD was diagnosed in the presence of coronary stenoses ≥ 50% lumen obstruction in, at least, 1 of the 3 major coronary arteries. Coronary atherosclerotic burden was estimated using the Gensini score [16]. A culprit lesion was described in the presence of an acute occlusion, intraluminal filling defects (or thrombus), ulcerated plaques with contrast-filled pocket protruding into plaque with or without delayed contrast wash-out, extraluminal contrast, dissection or intraluminal flaps. The complexity of lesions was defined according to the modified American College of Cardiology/American Heart Association grading

Table 1. Baseline data, type of intervention and therapy at discharge according to statin therapy on admission.

Characteristic	With statins (n = 8147)	Without statins (n = 4842)	P
Age [years]	67.4 [59.8; 74.3]	67.5 [59.2; 75.3]	0.297
Women	1761 (21.6)	1278 (24.4)	< 0.001
Arterial hypertension	5945 (73.0)	3010 (62.2)	< 0.001
Hypercholesterolemia	7022 (86.2)	2105 (43.5)	< 0.001
Diabetes	2377 (29.2)	1252 (25.9)	< 0.001
On insulin therapy	788 (9.7)	374 (7.7)	< 0.001
Body mass index [kg/m^2]	27.0 [24.7; 29.7]	26.6 [24.4; 29.4]	< 0.001
Current smoker	996 (12.2)	1040 (21.5)	< 0.001
Prior myocardial infarction	3236 (39.7)	895 (18.5)	< 0.001
Prior coronary artery bypass surgery	1594 (19.6)	362 (7.5)	< 0.001
Glomerular filtration rate [mL/min]	80.8 [61.3; 102.6]	78.5 [59.0; 100.8]	< 0.001
C-reactive protein [mg/L]	1.91 [0.85; 5.00]	3.54 [1.40; 10.40]	< 0.001
Number of affected coronary arteries:			< 0.001
1	973 (11.9)	1281 (26.5)	
2	2041 (25.1)	1389 (28.7)	
3	5133 (63.0)	2172 (44.8)	
Multivessel disease	7174 (88.1)	3561 (73.5)	< 0.001
Complex lesions	6065 (74.4)	3762 (77.7)	< 0.001
Gensini score	30.0 [14.0; 65.0]	30.0 [13.5; 57.0]	0.002
Patients with stable angina	26.5 [13.0; 59.5]	21.0 [10.5; 47.4]	< 0.001
Patients with ACS	39.3 [17.5; 77.0]	37.0 [18.0; 64.0]	0.001
Vessel treated:			< 0.001
Left main coronary artery	407 (5.0)	174 (3.6)	
Left descending coronary artery	2973 (36.5)	2114 (43.7)	
Left circumflex coronary artery	2043 (25.1)	1087 (22.4)	
Right coronary artery	2282 (28.0)	1355 (28.0)	
Bypass graft	442 (5.4)	112 (2.3)	
Left ventricular ejection fraction (%)	58.0 [49.0; 62.0]	55.0 [45.0; 62.0]	< 0.001
Type of intervention:			< 0.001
Coronary stenting	7247 (89.0)	4557 (94.1)	
Balloon angioplasty	900 (11.0)	285 (5.9)	

Data are median [25th; 75th percentiles] or number of patients (%); ACS — acute coronary syndrome

system. Class B2 and C lesions were considered complex. Left ventricular ejection fraction (LVEF) was measured using the area-length method on left ventricular angiograms [17].

Stent implantation and periprocedural care were performed according to standard criteria. Antiplatelet therapy consisted of clopidogrel (300 mg or 600 mg as a loading dose followed by 75 mg/day for at least 4 weeks) and aspirin (200 mg/day administered orally and continued indefinitely).

Outcome

The main outcome analysis was presentation pattern according to statin therapy on admission. Clinical presentation as stable angina, unstable angina, NSTEMI or STEMI in groups with or without statin therapy at the time of admission was analyzed.

Statistical analysis

Data are presented as median (25th to 75th percentiles) or counts and proportions (%). The normality of distribution of continuous data was assessed using the Kolmogorov-Smirnov test. Continuous data were compared with the Kruskal-Wallis rank-sum test. Categorical data were compared with χ^2 test. Multiple logistic regression model was used to test the association between statin therapy before admission and clinical presentation as ACS or STEMI (2 separate models). All variables of Table 1 except for type of inter-

Table 2. Clinical presentation in groups with and without statins.

Clinical presentation	With statins	Without statins	Odds ratio [95% CI]	P
All patients (n = 12,989)	N = 8147	N = 4842		
Stable angina	5939 (72.9)	2102 (43.4)	3.50 [3.25; 3.78]	< 0.001
Unstable angina	1435 (17.6)	1011 (20.9)	0.81 [0.74; 0.89]	< 0.001
NSTEMI	463 (5.7)	505 (10.4)	0.52 [0.45; 0.59]	< 0.001
STEMI	310 (3.8)	1224 (25.3)	0.11 [0.10; 0.13]	< 0.001
Patients ACS (n = 4948)	N = 2208	N = 2740		
Unstable angina	1435 (65.0)	1011 (36.9)	3.17 [2.82; 3.57]*	< 0.001
NSTEMI	463 (21.0)	505 (18.4)	1.17 [1.02; 1.35]*	0.025
STEMI	310 (14.0)	1224 (44.7)	0.20 [0.17; 0.23]*	< 0.001

Data are number of patients (%);*Shows the odds of presentation patterns within the group of patients with acute coronary syndrome (ACS); CI — confidence interval; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

vention were entered into the models. All analyzes were performed using S-plus statistical package (S-PLUS, Insightful Corp, Seattle, Washington). A 2-tailed $p < 0.05$ was considered to indicate statistical significance.

Results

Baseline characteristics

Overall, there were 12,989 patients included. At the time of admission, 8147 (62.7%) patients were on statin therapy and 4842 (37.3%) patients were not receiving statins. Baseline characteristics of patients are shown in Table 1. With the exception of age, all other characteristics appear to differ significantly in groups with or without statins at the time of admission. In general, patients on statin therapy appear to have a more adverse cardiovascular risk profile, a higher atherosclerotic burden and more extensive CAD than patients not receiving statins at the time of admission. The predominant factor underlying the difference in the atherosclerotic burden (Gensini score) was the proportion of patients with a high atherosclerotic burden (those in the 4th quartile of Gensini score) in the statin therapy group. On the other hand, patients receiving statins had lower levels of C-reactive protein and slighty but significantly higher glomerular filtration rates and LVEF (Table 1). Coronary stents were implanted in 11,804 (91.0%) patients and balloon angioplasty without stent placement was performed in 1185 (9.0%) patients.

Clinical presentation

Overall, 8041 (62.0%) patients presented with stable angina and 4948 (38.0%) patients presented with ACS (Table 2; Fig. 1). As seen in the Table 2, pre-treatment with statins markedly increased the odds for presentation with stable angina and decreased the odds for presentation with ACS (unstable angina, NSTEMI or STEMI). When presentation was assessed only for patients with ACS, then pretreatment with statins significantly increased the odds for presentation with unstable angina or NSTEMI and decreased the odds for presentation with STEMI (Table 2; Fig. 2).

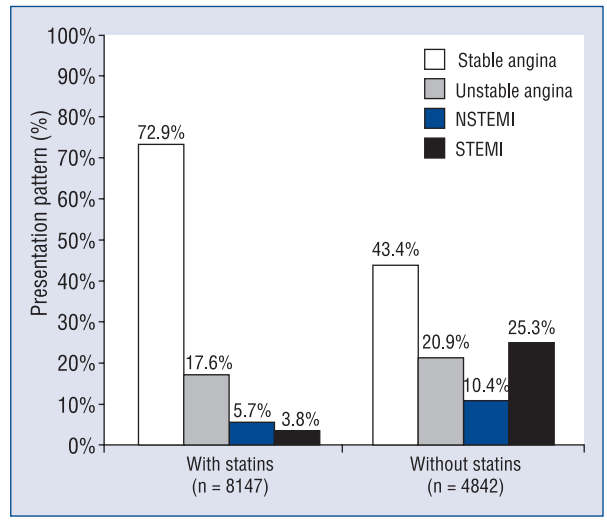

Figure 1. Presentation patterns according to statin therapy on admission; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction.

Correlates of presentation with ACS and STEMI

The association between statin pretreatment and clinical presentation was adjusted for potential confounders using the multivariable logistic regression (see Methods for variables entered into the

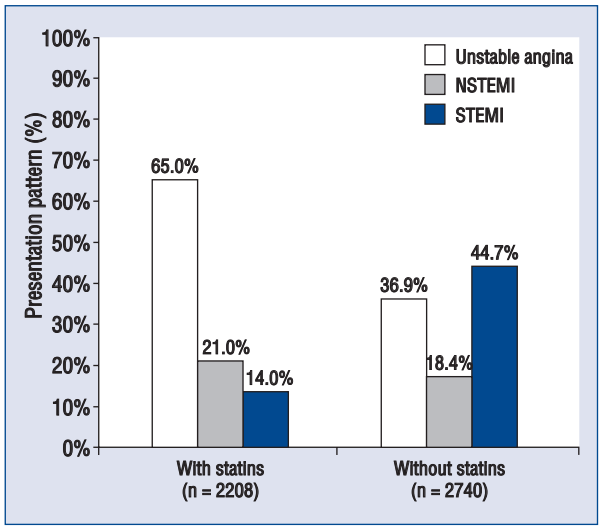

Figure 2. Presentation patterns according to statin therapy on admission in patients with acute coronary syndrome; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction.

model). When applied to test the association between statin pre-treatment and presentation with ACS vs. presentation with stable angina, statin pretreatment remained a significant independent correlate of decreased presentation with ACS (adjusted odds ratio [OR] = 0.35, 95% confidence interval [CI] 0.32–0.39; $p < 0.001$). Other independent associates of presentation with ACS and the direction of associations are shown in Table 3. When applied to test the association between statin pre-treatment and presentation with STEMI, again, statin pretreatment remained a significant correlate of decreased presentation as STEMI (adjusted OR = 0.18, 95% CI 0.16–0.22; $p < 0.001$). Other independent associates of presentation with STEMI and the direction of associations are shown in Table 4.

Discussion

The main findings of present study can be summarized as follows: (1) Statin pretreatment markedly change the pattern of presentation of patients with angiography-proven CAD. Specifically, therapy with statins before admission significantly increased the proportion of patients presenting with stable CAD and reduced the proportion of patients presenting with ACS as compared with patients not on statin therapy at the time of admission. (2) Patients on statin therapy at the time of coronary events have a significantly higher atherosclerotic burden (estimated by Gensini score) despite presentation with stable CAD or ACS. (3) Within the group of patients with ACS those on statins presented more often with unstable angina and NSTEMI and less often with STEMI. Of note, either in the whole group of patients or only in patients with ACS, statin pretreatment markedly reduced the occurrence of STEMI. Considering that a substantial number of patients with obstructive CAD are not being treated with statins [18], current findings may offer further evidence for the benefits of statins in patients with CAD and draw attention for a broader use of statins in these patients.

Anatomopathological studies have shown that the rupture-healing cycle(s) are part of the natural history of atherosclerotic plaques [19]. Although, the vast majority of these cycles may remain clinically silent [19], evidence available suggest that they contribute to plaque progression leading to progressive narrowing and tighter stenoses [20, 21] or acute coronary events [19, 22]. The so-called

Table 3. Independent predictors of presentation with acute coronary syndromes.

Characteristic	Adjusted odds ratio [95% confidence interval]	P
Statins on admission	0.35 [0.32; 0.39]	< 0.001
Male sex	1.37 [1.24; 1.52]	< 0.001
Arterial hypertension	0.77 [0.70; 0.84]	< 0.001
Current smoking	1.59 [1.41; 1.79]	< 0.001
Hypercholesterolemia	1.11 [1.01; 1.23]	0.039
Previous myocardial infarction	0.59 [0.53; 0.65]	< 0.001
Previous coronary artery bypass surgery	0.65 [0.56; 0.77]	< 0.001
Multivessel disease (vs. single vessel)	1.15 [1.03; 1.30]	0.012
C-reactive protein (for 5 mg/L increase)	1.09 [1.08; 1.11]	< 0.001
Gensini score (for a 10-point increase)	1.06 [1.05; 1.07]	< 0.001
Left ventricular ejection fraction (for a 10% decrease)	1.26 [1.21; 1.31]	< 0.001

Table 4. Independent predictors of presentation with ST-segment elevation myocardial infarction.

Characteristic	Adjusted odds ratio [95% confidence interval]	P
Statins on admission	0.18 [0.16; 0.22]	< 0.001
Male sex	1.38 [1.17; 1.62]	< 0.001
Arterial hypertension	0.47 [0.41; 0.54]	< 0.001
Diabetes	1.22 [1.04; 1.43]	0.015
Current smoking	2.04 [1.73; 2.40]	< 0.001
Hypercholesterolemia	1.11 [1.01; 1.23]	0.039
Previous myocardial infarction	0.34 [0.28; 0.41]	< 0.001
Previous coronary artery bypass surgery	0.41 [0.31; 0.56]	< 0.001
Multivessel disease (vs. single vessel)	1.54 [1.31; 1.82]	< 0.001
C-reactive protein (for 5 mg/L increase)	1.04 [1.03; 1.05]	< 0.001
Glomerular filtration rate (for 10 mL/min decrease)	1.05 [1.02; 1.08]	0.003
Gensini score (for a 10-point increase)	1.09 [1.07; 1.11]	< 0.001
Left ventricular ejection fraction (for a 10% decrease)	1.56 [1.47; 1.65]	< 0.001

vulnerable plaques — characterized by large necrotic core, surrounded by a thin fibrotic cap and infiltrated by various inflammatory cells — are prone to rupture and coronary events [22]. Numerous prior studies including those using up-to-date imaging technologies [12, 13, 23–25] have demonstrated that statins, through their lipid-lowering and pleiotropic effects stabilize atherosclerotic plaques and thus prevent, modify or delay acute coronary events. As shown in the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial, a 53.2% reduction in the LDL-cholesterol by 40 mg/day rosuvastatin was associated with a 6.7% reduction in the total plaque volume over a 2-year follow-up [26]. Morphological studies in transplanted hearts have also shown a marked reduction in the plaque inflammation by statins [27]. A slowdown of plaque progression by statins [28] or atheromatous plaque rupture and healing without significant plaque modification in patients receiving statin and antithrombotic therapies [29] have also been reported.

These studies showed that statins may have changed the natural course of atherosclerotic plaques and their relationship with clinical presentation and events in patients with CAD. Thus, the widely-held concept that mild-to-moderate plaques have e propensity to become instable and thus pose a greater risk for coronary events than tighter plaques seems to loose ground in the statin era. Several recent studies have shown that high-grade stenoses are important predictors of presentation with STEMI [4, 5, 30] or other ACS [6]. A recent study by Zaman et al. [30] showed that most baseline lesions showed significant luminal narrowing when examined < 3 months before STEMI. In a recent study, we showed that almost the entire risk related to atherosclerotic burden for presenting with unstable angina was mediated by stenoses ≥ 75% of lumen obstruction [6]. A prior publication of the Global Registry of Acute Coronary Events (GRACE), showed that patients who were already taking statins at the time of presentation were less likely to have ST-segment elevation or AMI [11]. A prior case-control study of 1384 patients presenting with AMI or angina, showed that statin and beta-blocker use was associated with lower odds of presenting with AMI than with stable angina [10]. By demonstrating a positive effect of statin therapy across the whole spectrum of patients with CAD in terms of a marked reduction of the presentation with ACS and in particular of the presentation with STEMI, the present study seems to corroborate these studies in a large series of patients with angiography-proven CAD.

The finding that atherosclerotic burden was higher in patients on statin therapy despite reduced severity of clinical presentation is important for several reasons, Firstly, this finding may imply that statin therapy through plaque-stabilizing effects may have reduced plaque propensity to rupture allowing plaques to reach advanced stages without complications and clinical events. Supporting these views, a higher CAD burden at the time of presentation for STEMI in patients pretreated with statins [31] and a high coronary atherosclerotic burden in asymptomatic patients with familial hypercholeste-

rolemia receiving statin therapy [32] have been described. Secondly, higher atherosclerotic burden at the time of presentation may explain the observed shift in the presentation patterns toward more benign clinical forms for at least 2 reasons: first, coronary occlusions at the site of a critical stenosis functionally might be less important than coronary occlusion of mild-to-moderate stenoses because the amount of coronary flow that is interrupted might be already small and, second, critical stenoses might have promoted collateral development which further attenuates the clinical presentation of acute coronary occlusion. There are reports that statins may enhance coronary collateral formation in patients with severe CAD [33]. Thirdly, within the group of patients presenting with ACS, these effects may explain the increased proportions of unstable angina and NSTEMI, known to have a higher atherosclerotic burden than patients with STEMI [34]. Finally, these findings may offer an explanation for the observed trend of reduced incidence of STEMI [35] potentially implicating widespread statin use in contemporary patients.

Conclusions

In conclusion, statin pretreatment markedly change the pattern of presentation of CAD. The proportion of patients presenting with stable angina was markedly increased and the proportions of patients presenting with ACS and STEMI were markedly decreased in patients receiving statins compared to patients not receiving stations at the time of hospital admission. Despite reduced severity of clinical presentation in patients receiving statins, these patients had a significantly higher atherosclerotic burden as compared to patients not receiving statins at the time of coronary events. The study offers support for a broader use of statins in patients with obstructive CAD.

Conflicts of interest: none declared

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