Original Research

CARDIOLOGY

The Impact of Statin Treatment on Presentation Mode and Early Outcomes in Acute Coronary Syndromes

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Abstract

Objectives: The role of statin use in the treatment of acute coronary syndromes (ACS) is not clear. The aim of our study was to evaluate the role of statins in ACS. *Methods:* Using data from the Acute Myocardial Infarction in Switzerland (AMIS Plus) Project, we compared the effects of chronic statin use, statin therapy after admission and no statin therapy on presentation mode and outcomes in ACS. *Results:* Available data from the period 2001–2006 including 11,603 patients were analyzed. Major cardiac event rates and in-hospital mortality were more common in statin-naive patients compared to patients who received statins. *Conclusions:* Our results support the importance of statin treatment in ACS. Chronic statin therapy seems to alter the initial presentation of ACS but it is questionable whether it provides an additional effect on early outcomes compared to the establishment of statin therapy after admission in statin-naive patients.

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Introduction

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) were established in 1987 for treating hypercholesterolemia [1] and are now one of the most widely used drugs in coronary artery disease (CAD). Several randomized, placebo-controlled trials showed that statins can substantially reduce the incidence of clinical coronary disease in both primary and secondary prevention [2–5]. A 2004 meta-analysis of 97 randomized controlled trials investigating different lipid-lowering interventions showed that statins are the only lipid-lowering agents that reduce overall mortality and strokes in primary and secondary prevention of CAD [6]. The likely mechanisms of benefit are not solely attributed to the lipid-lowering effects of statins, but also to the variety of anti-inflammatory and antiproliferative effects, commonly described as pleiotropic effects [7–11].

While the benefits of statin therapy in patients with stable CAD are clearly recognized, there have been conflicting results on whether early use of statins reduces myocardial infarction or overall mortality in the first months following acute coronary syndrome (ACS). The MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) [12] and the PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) [13] trials both showed that high-dose atorva-

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statin (80 mg) when started within the first 10 days following ACS was superior to controls (placebo in the MIRACL study and 40 mg pravastatin in the PROVE IT trial) and reduced early cardiovascular morbidity. The A to Z trial [14] which compared simvastatin (40 mg) for 1 month followed by 80 mg thereafter to placebo found no difference in the primary outcome (composite of cardiovascular death, myocardial infarction, readmission for ACS, and stroke) during the first 4 months of follow-up. A recent meta-analysis of randomized controlled trials regarding statin initiation in ACS questioned the positive effect of these drugs on early outcomes such as death, myocardial infarction or stroke [15]. Another meta-analysis showed that early, intensive statin therapy reduces death and cardiovascular events after 4 months of treatment [16].

Little is known about the effect of chronic statin treatment on the presentation mode of ACS. In a recent case-control study statin and β-blocker use was shown to significantly alter the initial presentation of CAD [17]. In that study statin use was associated with lower odds of presenting with an acute myocardial infarction than with stable angina. Another observational study showed that patients who were already taking statins when they presented to the hospital were less likely to have ST segment elevation myocardial infarction (STEMI) [18].

Using data from the Acute Myocardial Infarction in Switzerland (AMIS Plus), a large national registry of ACS, we analyzed the effect of statin therapy on presentation mode and outcomes in ACS.

Methods

The AMIS Plus Registry

The AMIS Plus Project is a nationwide prospective registry of patients with ACS admitted to hospitals in Switzerland. The registry began in 1997, and patient recruitment has been ongoing since. Participating centers, ranging from community institutions to large tertiary facilities, provide blinded data for each patient through a standardized Internet- or paper-based questionnaire. The details of the AMIS Plus Project have been published elsewhere [19–21].

Patients

The AMIS Plus registry included all patients with ACS: acute myocardial infarction, defined by characteristic symptoms and/or ECG changes and enzyme rises (total creatine kinase or creatine kinase MB fraction) of at least twice the upper limit of normal, ACS with minimal necrosis (symptoms or ECG changes compatible with ACS and cardiac enzymes lower than twice the upper limit of normal range and positive troponins) and unstable angina (symptoms or ECG changes compatible with ACS and normal cardiac enzymes). Valid data since 2001 on pretreatment and early treatment with statins were available and those data were analyzed. Baseline characteristics and outcomes are compared between patients on chronic statin therapy and who continued with the therapy after admission (group A), patients without statin pretreatment and in whom statin therapy was started after admission (group B), and patients without statin pretreatment who were not started on a statin when admitted (group C). Patients were also categorized as having ST segment elevation ACS (STEMI) or non-ST elevation myocardial infarction (NSTEMI) based on initial ECG findings. Classification of ST segment elevation-ACS included evidence of ACS as above and ST segment elevation and/or new left bundle branch block on the initial ECG. NSTEMI included patients with ischemic symptoms, ST segment depression or T wave abnormalities in the absence of ST elevation on the initial ECG. Major adverse cardiac events (MACE) were defined as a composed endpoint of reinfarction, stroke and/or in-hospital death. In March 2005 the AMIS Plus Questionnaire was revised and more angiographic parameters were added [e.g. vessel treated, left ventricular ejection fraction, thrombolysis in myocardial infarction (TIMI) flow at the end of percutaneous intervention (PCI)].

Statistical Analyses

Data are presented as percentages of valid cases for discrete variables and as mean ± SD and/or median for continuous variables. Differences in baseline characteristics were compared using t test and χ^2 test. A p value of <0.05 was considered significant. User-defined missing values are treated as missing. Statistics for each table are based on all cases with valid data in the specified ranges for all variables in each table. Odds ratios (OR) with 95% of confidence interval for OR of in-hospital mortality were calculated using logistic regression models. The following factors were included in the multivariate analysis: statin treatment, age, gender, history of CAD, hypertension, diabetes, dyslipidemia, smoking, overweight, ST segment elevation, Killip class and use of PCI. SPSS software (Chicago, Ill., USA; Version 13.0) was used for all statistical analyses.

Results

Baseline Characteristics

Of the 12,742 patients admitted for ACS and enrolled in the AMIS Plus registry from January 2001 through to March 2006, 11,603 patients (91.1%) were available for this analysis: 3,274 (28.2%) patients were on chronic statin treatment upon admission (group A) compared to 8,329 subjects (71.8%) who were statin naive. In these statin-naive patients, statin therapy was started in 5,567 patients (66.8%) after admission (group B), while 2,762 (33.2%) never received a statin (group C).

Baseline characteristics of the three groups are presented in table 1. Mean age was 66 ± 12 years in group A, 63 ±13 years in group B and 70 ± 14 years in group C. The proportion of males was similar in group A and B (75.8 vs. 74.8%) and lower in group C (65%).

Table 1. Baseline characteristics of the study population

|	Group A (n = 3,274)	Group B (n = 5,567)	Group C (n = 2,762)
Mean age (± SD), years	66 ± 12	63 ± 13	70 ± 14
Males, %	75.8	74.8	65.0
Known history of			
CAD, %	66.4	25.0	32.7
Hypertension, %	71.6	51.2	57.5
Diabetes, %	28.5	15.6	20.0
Dyslipidemia, %	88.8	57.2	41.1
Current smokers, %	32.2	42.8	33.4
Overweight (BMI >25), %	69.3	64.9	55.9

Presentation Mode, Complication and Outcome according to Statin Pretreatment

The proportion of STEMI was higher in statin-naive patients than in patients on chronic statin treatment (63 vs. 46%, p < 0.001) (fig. 1).

Complications and outcome of ACS patients according to statin pretreatment and statin start after admission are presented in table 2. The rate of occurrence of cardiogenic shock was slightly higher in patients with chronic statin pretreatment (group A) compared to patients without pretreatment but with statin start after admission (group B; 4.3 vs. 3.3%; p = 0.025). Patients without statin pretreatment and who were not started on a statin upon admission had a more than 2-fold higher rate of cardiogenic shock (10.3%, compared with group A and B, p < 0.001). Reinfarction was more common in patients of group C (2.3%) although not significantly different from reinfarction rates in group A (1.8%) and group B (1.8%; p = 0.34). Stroke rate was more common in group C (1.2%) than in group A (0.5%) and B (0.7%; p = 0.009). Need for respiratory support (intubation) was significantly different between the three groups: group A (3.6%), group B (2.5%) and group C (6.2%; p < 0.001).

The overall MACE rates were 6.5% in group A, 5.6% in group B and 15.3% in group C. The difference between group A and B was not significant, while the MACE rates of group C were significantly higher than those of group A and B (p < 0.001). Table 3 shows independent predictors for MACE in ACS patients. Immediate statin therapy (in statin-naive patients), age, history of diabetes, history of dyslipidemia, ST segment elevation, Killip class II–IV and use of primary PCI were significant predictors of MACE.

The unadjusted OR for in-hospital mortality for chronic statin therapy was 0.32 (95% CI 0.26–0.39; p <
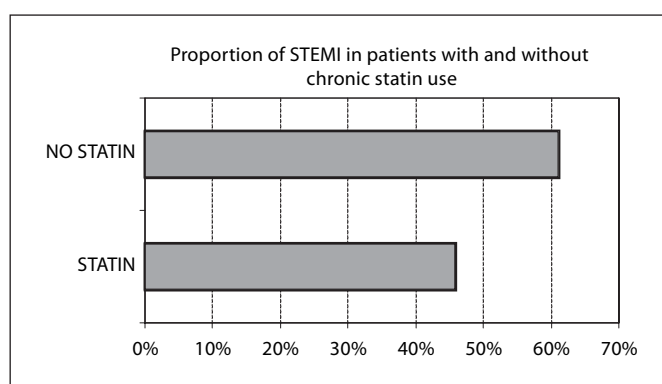
**Fig. 1.** Presentation mode of ACS according to statin pretreatment (n = 11,571).

0.001) and for statin therapy after admission (in statin-naive patients) OR was 0.25 (95% CI 0.21–0.30; p < 0.001). After adjustment for all variables the OR for chronic statin therapy was no longer significant (OR 0.76, CI 95% 0.53–1.08; p = 0.125), but statin therapy after admission (in statin-naive patients) remained significant even after adjustment for age, gender, history of CAD, hypertension, diabetes, dyslipidemia, smoking, overweight, ST segment elevation, Killip class and primary PCI.

Complication and Outcome in Various Risk Groups

MACE rates in various risk categories (age >70, diabetes, renal failure) are presented in figure 2. Group C had the highest MACE rates independently of the risk category (p < 0.001 for all comparisons of group C with group A and B). In group C the MACE rates were highest in patients with renal disease (29.4%), diabetes (23.1%) and patients older than 70 years (21.7%). The MACE

Table 2. Interventions, complications and outcome according to statin treatment

	Group A (n = 3,274)	Group B (n = 5,567)	Group C (n = 2,762)
Intervention			
Primary percutaneous intervention, %	48.2	56.7	36.1
Thrombolysis, %	6.3	10.8	10.4
Complication			
Cardiogenic shock, %	4.3	3.3	10.3
Reinfarction, %	1.8	1.8	2.3
Cerebrovascular incident, %	0.5	0.7	1.2
Outcome			
Major adverse cardiac event, %	6.5	5.6	15.3
In-hospital mortality, %	4.5	3.6	12.8
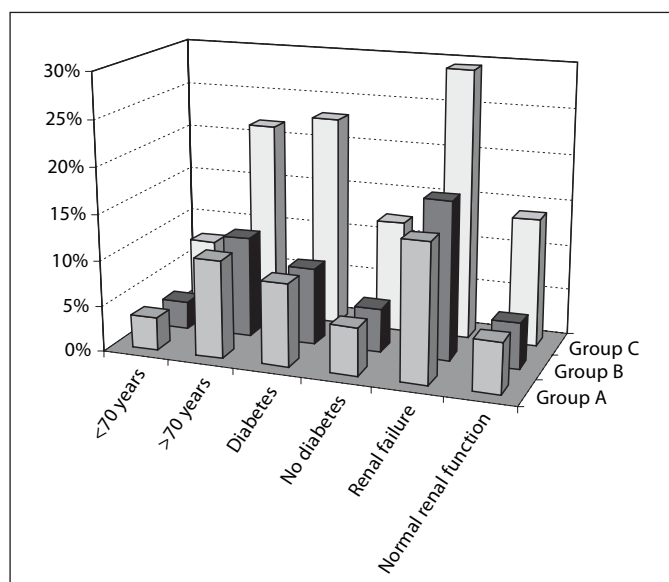
Fig. 2. MACE rates in various risk populations (n = 11,603).

Table 3. Independent predictors for MACE in ACS patients

	OR	95% CI	Significance
Chronic statin therapy (group A)	0.83	0.61–1.12	0.226
Immediate statin therapy (group B)	0.77	0.59–0.99	0.047
Age (per year)	1.05	1.04–1.06	<0.001
Gender	1.03	0.83–1.29	0.769
Diabetes	1.58	1.25–1.99	<0.001
Hypertension	0.88	0.71–1.11	0.285
Dyslipidemia	0.75	0.60–0.94	0.014
Smoking	1.13	0.88–1.45	0.322
History of CAD	1.13	0.91–1.42	0.275
Overweight (BMI >25)	0.84	0.68–1.03	0.095
ST segment elevation	1.39	1.11–1.72	0.003
Killip class II	2.30	1.81–2.93	<0.001
Killip class III	3.40	2.36–4.90	<0.001
Killip class IV	9.69	6.15–15.3	<0.001
PCI primary	0.68	0.54–0.87	0.002

rates were comparable in group A and B for patients younger than 70 years (3.6 vs. 3.0%), patients older than 70 years (10.7 vs. 11.0%), patients with diabetes (9.0 vs. 8.4%) and without diabetes (5.2 vs. 4.8%), and also for patients with (15.0 vs. 17.2%) and without renal disease (5.5 vs. 5.0%).

TIMI Flow according to Statin Treatment

TIMI flow rates at the end of the PCI were available for 1,432 patients and are shown in table 4. TIMI III flow rates were higher in group A and B compared to group C but this did not reach statistical significance.

Discussion

In our population of ACS patients the proportion of STEMI was 61% in statin-naive patients but only 46% in patients already on chronic statin therapy. Our observation that statin therapy indeed has an impact on the presentation mode of ACS (STEMI vs. NSTEMI/unstable angina) is consistent with the results of the GRACE (Global Registry of Acute Coronary Events) register [18] where patients already taking statins were less likely to have STEMI on admission. Our analysis is also in accordance with the results of Go et al. [17] who recently re-

ported that patients on statin and β-blocker therapy present with stable angina rather than acute myocardial infarction. While the benefit of statin therapy on presentation mode of ACS is plausible to explain (e.g. plaque stabilization), absolute proof that statins can really alter the mode of presentation of CAD still has to be obtained in a prospective trial. If confirmed, the findings could have a substantial impact on future patient care because NSTEMI and unstable angina are associated with a better prognosis than STEMI.

Patients on chronic statin therapy and patients who were started on statins after admission had similar rates of reinfarction, cerebrovascular incidents and in-hospital mortality. Cardiogenic shock was slightly less common in group B (3.3%) compared to group A (4.3%) and markedly high in group C (10.3%). The rate of major cardiac events was 6.5% for the group with chronic statin therapy and 5.6% for the group with in-hospital statin start. Patients who never received statins had excessively high rates of complications, e.g. cardiogenic shock (10.3%) and in-hospital mortality (12.8%). The MACE rate in this group of patients was very high (15.3%). MACE rates were consistently higher in group C even when different risk populations were compared (>70 years, <70 years, patients with and without diabetes and patients with and without renal disease). Patients in group B had significantly lower (34%, p = 0.0006) in-hospital mortality than patients in group C. Patients in group A also had lower in-hospital mortality when compared to group C (OR 0.76) but this did not reach statistical significance (p = 0.125).

The clearly better outcomes and lower complication rates of statin-pretreated patients were also observed in the GRACE [18] and PRISM (Platelet Receptor Inhibition in Ischemic Syndrome Management) [22] studies. However, in both these studies the withdrawal of previous statin therapy resulted in worse outcomes. Interestingly, in our study better outcomes were observed in patients who were started on statins upon admission compared to patients already on chronic statin therapy and who continued with the therapy while hospitalized; patients with statin start after admission had lower in-hospital mortality and lower rates of cardiogenic shock. Our analysis included the time period 2001–2006 and patients who were started on statin upon admission most likely received high-dose therapy, since both the MIRACL [12] and the PROVE IT [13] study (published in 2001 and 2004, respectively) reported benefits of high-dose statin (i.e. 80 mg of atorvastatin) therapy in patients with ACS. The fact that group A (compared to group B) included patients

Table 4. TIMI flow rates (in %) after PCI in different statin groups

	TIMI flow			
	0	I	II	III
Group A (n = 457)	3.9	0.9	5.7	89.5
Group B (n = 836)	1.9	1.2	7.4	89.5
Group C (n = 139)	4.3	2.2	6.5	87.1
	n.s.	n.s.	n.s.	n.s.

n.s. = No significant differences between the groups.

who were older and had a higher prevalence of diabetes, CAD, dyslipidemia and hypertension might also have influenced their worse outcome.

Our study suggests that in ACS, chronic statin therapy might not have any additional effects on early outcomes over the establishment of statin therapy after admission.

The benefit of statin therapy seems to be accentuated in high-risk populations, such as older patients or those with diabetes or renal function impairment, as shown in figure 2. In our study patients in group C had a mean age of 70 years, being older than patients in group A (66 years) and group B (63 years). This fact suggests that, paradoxically, an effective and well-tolerated therapy is being withheld from older people, who are known to have a worse prognosis. However, more patients in group C needed respiratory support compared to groups A and B, which might partly explain the reason for statin withdrawal in this group of patients.

TIMI-III flow rates were higher in patients receiving statins but failed to show statistical significance. Recently, Iwakura et al. [23] reported that chronic pretreatment with statins is associated with the reduction of the no-reflow phenomenon in patients with reperfused acute myocardial infarction.

Study Limitations

Despite the prospective and multicenter character of our study one has to keep in mind that we present data from a registry and not a randomized controlled trial. Neither the dose of statins nor the time point at which statin therapy was started was defined.

There were noticeable baseline differences in several important prognostic factors between our primary comparison groups. Although we attempted to control for the effects of potential confounding factors, it is conceivable

that differences in other unmeasured factors may have influenced our study findings. The results should therefore be interpreted with caution.

Conclusions

Our findings provide additional evidence for the importance of statin therapy in the treatment of ACS. Chronic statin therapy seems to alter the initial presentation of ACS but it is questionable whether there is an additional effect on early outcomes compared to the establishment of statin therapy after admission in statin-naive patients. The benefit of statin therapy is accentuated in high-risk populations such as the elderly, diabetics or patients with renal failure. Despite the fact that bias due to group differences cannot be excluded and that we present data from a registry, not data from a randomized controlled trial, our results favor the early establishment of statin therapy in ACS; statin therapy achieves a remarkable reduction in mortality and this benefit is consistent in various risk groups.

Appendix 1

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AMIS Plus Participants
The following hospitals participated from 1997 to 2006 in the AMIS registry on which this report is based (in alphabetical order): Altdorf, Kantonsspital Altdorf: Dr. R. Simon; Altstätten, Kantonales Spital Altstätten: Dr. P.-J. Hangartner/Dr. M. Rhyner; Baden, Kantonsspital Baden: Dr. M. Neuhaus; Basel, Kantonsspital Basel: PD Dr. P. Hunziker; Basel, St. Claraspital: Dr. C. Grädel; Bern, Inselspital: Prof. B. Meier/PD Dr. S. Windecker; Biel, Spitalzentrum Biel: Dr. H. Schläpfer; Brig-Glis, Oberwalliser Kreisspital: Dr. D. Evéquoz; Bülach, Spital Bülach: Dr. R. Pampaluchi/Dr. A. Ciurea-Löchel/Dr. M. Kruhl; Chur, Rätisches Kantons- und Regionalspital Chur: Dr. P. Müller; Chur, Kreuzspital: Dr. V. Wüscher/Dr. R. Jecker; Davos Platz, Spital Davos: Dr. G. Niedermaier; Dornach, Spital Dornach: Dr. A. Koelz; Flawil, Kantonales Spital Flawil: Dr. T. Langenegger; Frauenfeld, Kantonsspital Frauenfeld: Dr. H.-P. Schmid; Fribourg, Hôpital cantonal de Fribourg: Dr. B. Quartenoud; Frutigen, Spital Frutigen: Dr. S. Moser/Dr. Kuengolt Bietenhard; Genève, Hôpitaux universitaires de Genève (HUG): Dr. J.-M. Gaspoz; Glarus, Kantonsspital Glarus: Dr. W. Wojtyna; Grenchen, Spital Grenchen: Dr. P. Schlup/Dr. A. Oestmann; Grosshöchstetten, Bezirksspital Grosshöchstetten:

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