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ORIGINAL ARTICLE

Reduction of in Long-Term Mortality Related to Higher Doses of Atorvastatin in Patients with Acute Coronary Syndromes

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Abstract

Background: Recent experimental studies have described reduction in inflammatory markers related to higher doses of statins in patients with acute coronary syndromes (ACS). However, the clinical implication of the dose of statin in the acute phase of the ACS remains uncertain.

Objective: To compare the outcomes in short and long terms among patients with acute coronary syndromes that received higher doses of atorvastatin versus low doses of atorvastatin started in the first 24 hours of hospital admission.

Methods: For such, the patients were divided in two groups: group I (N = 464): atorvastatin dose: 40 mg/day. Demographic data, laboratory exams, medications used and coronary treatment adopted were obtained. Statistical analysis: The primary outcome was mortality from all causes. The comparison between groups was made by T-test and Q-square. Multivariative analysis of in-hospital outcomes were determined by logistic regression, considered significant when $p < 0.05$. In long-term, the mortality and combined events by the Kaplan-Meier method were assessed, with median follow-up of 8.79 months.

Results: In the analysis of in-hospital outcomes, no significant differences were observed between groups I and II. In the long-term, group II presented lower mortality in comparison with group 9 (8.4% vs. 3.9%, $p = 0.013$).

Conclusions: Favorable and significant differences were observed in relation to long-term mortality in patients with ACS that received high doses of atorvastatin since the acute phase. (Int J Cardiovasc Sci. 2016;29(4):280-287)

Keywords: Acute Coronary Syndrome/mortality; Hidroxymethylglutaryl CoA Reductase Inhibitors; Hypertension; Cohort Studies.

Introduction

Various experimental studies have showed a reduction of inflammatory markers associated to higher doses of statins in patients with acute coronary syndrome (ACS).[1,2] In addition, in patients with previous acute myocardial infarction, the use of higher doses of statins is capable of decreasing mortality, and is recommended routinely by different medical societies.[3-5]

However, the clinical implication of the statin dose started in the acute phase of the ACS remains uncertain. Thus, this study aims to compare short and long-term outcomes between ACS patients that received higher atorvastatin doses versus low doses of atorvastatin started in the first 24 hours of hospital admission.

Methods

Study population

It is a retrospective and unicentric cohort study. All patients with ACS (N = 929) admitted from May 2010 to

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May 2015 in the emergency department were included. The patients were divided in two groups: group I: atorvastatin < 40 mg/day (N = 464); group II: atorvastatin ≥ 40 mg/day (N = 465). The dose of statin used was defined at the discretion of the Attending Physician of the case. Patients who did not start the use of atorvastatin in the first 24 hours were excluded from the case, as well as those that modified the initial doses throughout the monitoring.

All patients that met the criteria set forth by the latest guideline by the American Heart Association were considered as ACS.[3-5] ACS with supraunleveling of the ST segment was defined as a presence of thoracic pain with persistent alteration of the ST ≥0.1 mV segment in the leads of the frontal plane and ≥ 0.2 mV in the precordial leads, in at least two contiguous leads. ACS without ST supraunleveling was defined as the presence of thoracic pain linked to the electrocardiographic changes or troponin elevation/drop on admission or, in absence thereof, clinical features and risk factors consistent with unstable angina (thoracic pain at rest or on minimal exertion, severe or occurring in a growing standard). The clinical interventionist treatment performed to patients included in the study also followed recommendations set forth by the latest guidelines in force. Major bleeding was defined by the score of BARC[6] types 3 and 5, and minor bleeding by types 1 and 2. Reinfarction was considered in cases of recurrence of thoracic pain linked to the new troponin elevation. Ischemic cerebrovascular accident (ICVA) was considered when the patient displayed new focal motor neurological deficit confirmed through cranial computerized tomography. Rhabdomyolysis was considered in cases of CPK elevation above 10 times the upper limit of the method. Statin-related drug-induced hepatitis was considered if there was an elevation of transaminases at least 3 times the upper limit of normal.

The following data were obtained: age, sex, presence of diabetes mellitus, systemic arterial hypertension, smoking, dyslipidemia, family history of early coronary disease, previous coronary artery disease (angioplasty or previous myocardial revascularization surgery), cardiac insufficiency, previous ICVA, previous acute myocardial infarction, hemoglobin, creatinine, troponin peak, Killip classification, left ventricular ejection fraction, systolic blood pressure on admission, previous statin use, medications used in the first 24 hours after admission and coronary care adopted.

Troponin-I was measured using the kit Elecsys 2010 (Siemens Healthcare Diagnostics Inc., United States of America) kit, 4th generation immunoassay, considering the 99% percentile of the method the value of 0.04 ng/ml. The total cholesterol measures and its fractions were determined by the Siemens ALDL Dimension (Siemens Healthcare Diagnostics Inc., United States of America) kit.

The work was submitted and approved by the ethics and research committee (CAPPesq Opinion: 1.095.729). The free and informed consent form was completed by all patients in the study.

Statistical analysis

The primary outcome was in-hospital mortality from all causes. The secondary outcome was combined events (cardiogenic shock, reinfarction, death, ICVA and bleeding). A descriptive analysis was made using averages, minimum and maximum values. The comparison between groups was made through Q-square for the categorical variables. For continuous variables, when the Komolgorov-Smirnov normality test showed normal distribution, the variables were calculated using T-test. If the distribution did not follow the normality standard, we used the Mann-Whitney U test. The multivaried analysis was performed through logistic regression for outcomes in which the univariate analysis presented significant result only. All baseline characteristics presented by table 1 were considered as variables in the analysis, and considering as significant $p < 0.05$.

In the long-term, the patients were monitored by an average period of 8.79 through telephone contact and electronic medical record review. 785 patients 84.5% of the initial sampling) remained in this assessment. The outcomes described in this period were mortality from all causes, reinfarction, cardiac insufficiency and combined events (reinfarction, cardiac insufficiency and mortality). The long-term analysis was performed through the Kaplan-Meier method. It was considered significant $p < 0.05$. All patients were referred to the post discharge consultation in 14 days, and a new consultation in 6 months, performing ischemia or catheterization tests requested according to medical evaluation from the staff in charge. All stents used were conventional, and all patients remained using aspirin and clopidogrel for at least 12 months.

In the in-hospital analysis, incidences of rhabdomyolysis and statin-related drug-induced hepatitis were observed.

All calculations were performed using the SPSS Statistics Base v10.0 software for Windows.

Results

The mean age was of 63 years, and approximately 61% were male. The most prevalent risk factor was systemic

arterial hypertension in 81% of the cases. In relation to the treatment, the performance of percutaneous coronary intervention was observed in 31.7% in group I and 31.2% in group II ($p = 0.38$). Coronary artery bypass surgery was performed to 9.5% of group I versus 12.5% in group II ($p = 0.145$). ACS without ST supraunleveling was the diagnosis in 79.3% of the patients in group I and 79.4% in group II ($p = 0.973$).

In group II, a higher prevalence of dyslipidemia was observed (56.3% vs. 49.1%, $p = 0.028$), a greater use of beta-blockers (75.2% vs. 63.1%, $p < 0.0001$), angiotensin converting enzyme inhibitors (55.9% vs. 45.5%, $p = 0.001$), clopidogrel (72.3% vs. 65.1%, $p = 0.018$) and a greater prevalence of prior statin use (48.6% vs. 39.7%, $p = 0.007$) in comparison with group I, respectively. The baseline characteristics of the studied population are in table 1.

Table 1
Comparative baseline clinical characteristics between patients with ACS according to the dose of atorvastatin used

	Atorvastatin dose		p
	< 40 mg/day (N = 464)	≥ 40 mg/day (N = 465)	
Age (average)	63.5	61.83	0.533
Male (%)	60.1	61.1	0.768
Diabetes Mellitus (%)	36.4	42.2	0.132
SAH (%)	80.4	82.2	0.491
Tobacco use (%)	44.2	44.2	0.532
Positive FH for CAD (%)	10.9	14.6	0.098
Dyslipidemia (%)	49.1	56.3	0.028
Statins – previous use (%)	48.6	39.7	0.007
CI (%)	7.8	6.7	0.52
Previous CVA (%)	6.7	7.9	0.455
Previous AMI (%)	36.2	40.0	0.234
Previous CABS (%)	14.7	18.7	0.097
Previous CA (%)	25.0	28.8	0.19
Hb (mg/dL) (average)	13.8	14.01	0.147
Troponin Peak (average) (ng/dL)	7.08	6.85	0.097
Cr (mg/dL) (average)	1.31	1.19	0.11
SBP (mmHg) (average)	134.2	134.9	0.241
LVEF (%) (average)	52.1	52.4	0.101
Killip > 2 (%)	18.9	17.0	0.433
AAS (%)	95.9	97.8	0.14
Beta-blocker (%)	63.1	75.2	< 0.0001
Glycoprotein inhibitor IIb/IIIa	9.9	11.2	0.529
Enoxaparin (%)	71.8	77.2	0.057
Clopidogrel (%)	65.1	72.3	0.018
Ezetimibe (%)	2.2	2.2	0.996
Fibrates (%)	2.2	1.7	0.631
ACEI (%)	45.5	55.9	0.001

SBP: systolic blood pressure; SAH: systemic arterial hypertension; FH: family history; CAD: coronary arterial disease; CI: cardiac insufficiency; CVA: cerebrovascular accident; AMI: acute myocardial infarction; CABS: coronary artery bypass surgery; CA: coronary angioplasty; Hb: hemoglobin; Cr: creatinine; LVEF: left ventricular ejection fraction; GPI: glycoprotein inhibitor; ACEI: angiotensin converting enzyme inhibitor.

The evaluation of the lipid profile requested for the admission of patients showed similarities between groups I and II regarding the LDL-cholesterol values (107.4 mg/dL vs. 112.7 mg/dL, $p = 0.542$), HDL-cholesterol (39.0 mg/dL vs. 39.1 mg/dL, $p = 0.702$) and total cholesterol (176.9 mg/dL vs. 183.1 mg/dL, $p = 0.873$). Triglyceride values were significantly higher in group II in comparison with group I (161.1 mg/dL vs. 138.3 mg/dL, $p = 0.035$), respectively.

In the comparison of outcomes, the univariate analysis did not show significant differences between groups I e II in relation to combined events (20.9% vs. 20%, $p = 0.251$) and mortality (4.3% vs. 4.1%, $p = 0.865$), respectively. The results of the univariate analysis comparing different in-hospital outcomes between the groups are found in table 2.

In the long-term, lower mortality was observed in group II in comparison with group I (3.9% vs. 8.4%, $p = 0.013$), respectively. The other outcomes presented similar results between the groups. The results of the long-term evolution according to the dose of atorvastatin are found in table 3 and figure 1.

No complications related to the use of statin, such as rhabdomyolysis and drug-induced hepatitis. were described.

Table 2
Results of the univariate analysis comparing different in-hospital outcomes between patients with ACS according to the atorvastatin dose

	Atorvastatin dose		p
	< 40 mg/day	≥ 40 mg/day	
Reinfarction (%)	0.6	0.9	0.519
Cardiogenic shock (%)	8.0	5.4	0.205
Bleeding (%)	7.8	9.0	0.508
ICVA (%)	0.2	0.6	0.228
Mortality (%)	4.3	4.1	0.865
Combined events (%)	20.9	20.0	0.251

ICVA: ischemic cerebrovascular accident.

Table 3
Results of the long-term evolution comparing different outcomes between the patients with ACS according to the atorvastatin dose

	Atorvastatin dose		p
	< 40 mg/day	≥ 40 mg/day	
Reinfarction (%)	5.9	8.9	0.259
IC (%)	16.3	16.2	0.683
Mortality (%)	8.4	3.9	0.013
Combined events (%)	30.6	29.0	0.251

IC: cardiac insufficiency.

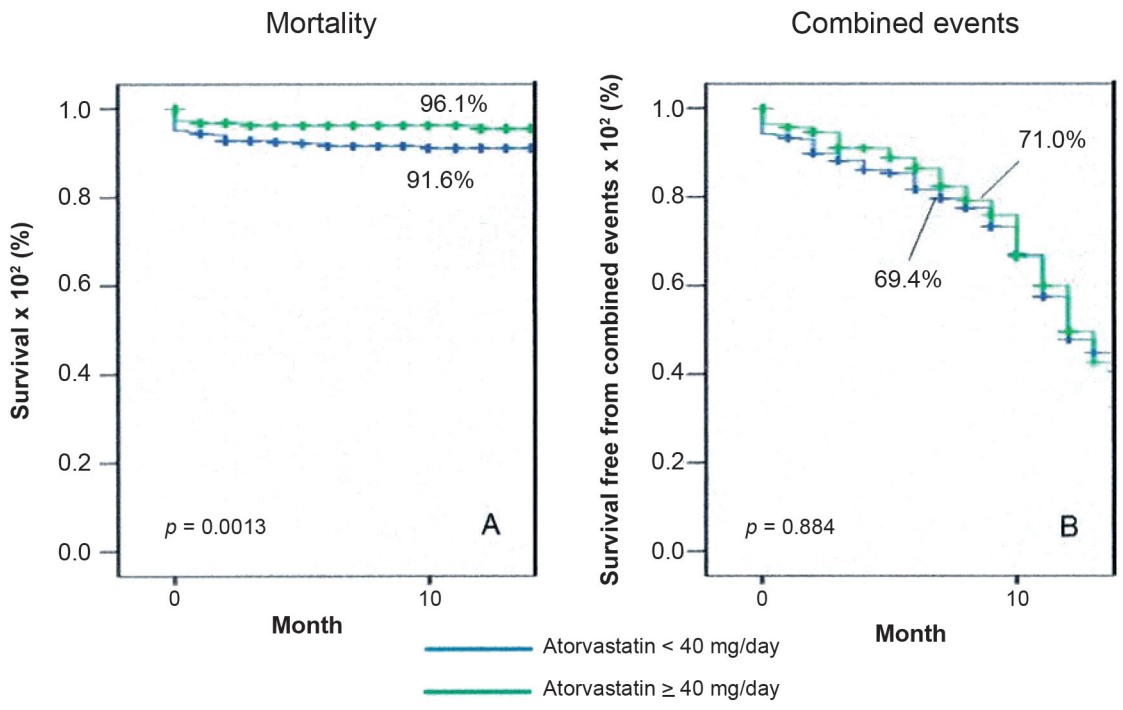

Figure 1
Long-term evolution of patients with ACS according to the used atorvastatin dose.
A: comparative evolution of survival. B: comparative evolution of survival free from combined events.

Discussion

Guidelines by the American Heart Association and by the European Society of Cardiology alike recommend to start the routine use of high doses of statins in ACS patients at an early stage (Class Indication IIa; Level of Evidence B).[3-5] Corroborating what the literature suggests, we observe a decrease in mortality in the long term in patients using higher doses of atorvastatin from the start, following average monitoring of only 8.79 months. In in-hospital evolutions, we did not observe significant differences between the groups according to the statin dose. The long-term result becomes important, as studies comparing different doses of the same statin introduced in the acute stage of the ACS were not described.

One of the great questionings regarding the dose or type of statins to be used in the acute stage in ACS patients is if the benefit stems only from the reduction of LDL-cholesterol or if it depends on other factors, such as pleiotropic or anti-inflammatory effects.[2,7,8] Various previous studies showed that higher doses of more potent statins are capable of reducing in a significant manner the levels of C-reactive protein, both in the acute phase of the ACS and in patients with chronic coronary disease.[1,9]

With the purpose of evaluating the direct relation between the reduction of LDL-cholesterol and the reduction of coronary events in patients with ACS, the IMPROVE-IT trial was published.[2] This study compared in 18,144 patients the introduction in the acute stage of simvastatin + ezetimibe versus placebo + ezetimibe, with the occurrence of combined events (death, acute myocardial infarction, ICVA, unstable angina and need for revascularization) as the primary outcome 30 days after the randomization. A 9% reduction to the rate of events in patients who received ezetimibe ($p = 0.007$) was observed. The average levels of LDL-cholesterol were smaller in patients who did not present events comparatively to those who had a primary outcome (58.3 mg/dL vs. 59.6 mg/dL, $p < 0.001$), endorsing the idea that the benefit originates only from the value of cholesterol, and not

from the type or dose of drug used.[2] It is worth to stress that, although it is a recent publication, this study did not assess the use of high potency statin and no longer follows the orientation of the current guidelines.

However, another study with 1.355 patients with ACS, randomized for early treatment with atorvastatin 10 mg/day *versus* atorvastatin 20 – 40 mg/day showed, at the end of an average monitoring of two years, to not have differences between the groups in relation to combined events (death, acute myocardial infarction, need for revascularization, unstable angina and ICVA), despite a greater reduction of the LDL-cholesterol levels on patients who used higher statin doses (decline of 26.6% vs. 20.2%, $p < 0.001$).[8] This reinforces the hypothesis that maybe only the LDL-cholesterol levels are not the determinant factors of the occurrence of outcomes, and that even higher doses (≥ 40 mg/day de atorvastatin) may bring even greater benefits, as observed in our study. Interestingly, the initial LDL-cholesterol of the group with greater clinical benefit was significantly greater, which makes us think that either the reduction was more intense and, thus, so was the clinical benefit, or that is not the main point of reference is not the initial LDL level, but the intensity of the treatment administered.

In 2001, the MIRACL[10] study compared the use of atorvastatin 80 mg/day against placebo in 3,086 patients with ACS without ST supraunleveling, both introduced in the first 24 to 96 hours following hospital admission. Significant differences were observed between the two groups in relation to combined events with lower incidence in patients who received atorvastatin (14.8% vs. 17.4%, $p = 0.048$).[10] This study is used so far as one of the main grounds of the guidelines. However, the high dose of atorvastatin was compared only with placebo, which makes the evidence for the deployment of 80 mg of statin important, but impossible to perform correlations with lower doses, as presented in our study.

Distinctly, aiming to compare different statin types, the IDEAL[11] study compared the use of 80 mg/day of torvastatin versus 20 – 40 mg/day of simvastatin in 8,888 patients. Statin could be introduced up to 2 months following the ACS event, and not necessarily in the acute stage. At the end of a five-year monitoring, a reduction of combined events in the group that used atorvastatin (37.9% vs. 44.7%, $p = 0.04$)[11-13] was observed. This reinforces the fact that higher doses of statins may bring benefits. However, as opposed to our study, the comparison was made between different statin types. In addition, the late introduction of the statin removes the possibility of analyzing the effect in the acute moment of the ACS.

The A to Z[14] study followed a similar line and studied the introduction of 40 mg/day of simvastatin in the first month after the coronary event followed by an increase of the dose to 80 mg/day versus placebo for 4 months followed by 20 mg/day simvastatin. A total of 16.7% of the patients receiving placebo/simvastatin presented combined events versus 14.4% in the group undergoing a more intensive treatment, without significant differences ($p = 0.14$). However, there were differences in mortality from cardiovascular causes, which occurred in 5.4% in the group that received placebo versus 4.1% in the intensive treatment group ($p = 0.05$) by the end of 24 months.[14] This result stresses our findings, as it coincides with the reduction of mortality in the long-term without changes in the incidence of combined events.

Thus, we observed that the use of higher doses of statins from the ACS stage of the ACS probably brings clinical benefits in the long-term. The same line of thinking may be used in comparison with the use of more potent statins. However, this comparison between different doses of a same potent statin type in the acute stage of the ACS had not been previously described.

Limitations

It is a retrospective study presenting certain differences between the analyzed groups. The dose of statin used was defined at the discretion of the Attending Physician of the case, and it may be related to the severity of the patient in question. Regarding the two groups, differences regarding the prescription of certain drugs that could influence the prognosis, such as beta-blockers, angiotensin-converting enzyme inhibitors and clopidogrel are observed. The outpatient evaluation following hospital discharge was performed according to the routine of the institution, without inference from the study in the adjustment of conduct. The LDL-cholesterol levels were dosed in the beginning, but no specific control was performed by the study.

Conclusion

Favorable and significant differences were observed in relation to mortality in the long-term in patients with ACS who received high doses of atorvastatin from the acute stage.

Author contributions

Conception and design of the research:Soeiro AM, Soeiro MCFA. Acquisition of data: Soeiro AM, Bossa AS, Zullino CN, Leal TCAT, Biselli B, Soeiro MCFA. Analysis and interpretation of the data: Soeiro AM, Zullino CN, Leal TCAT, Soeiro MCFA. Statistical analysis: Soeiro AM, Bossa AS, César MC. Writing of the manuscript: Soeiro AM. Critical revision of the manuscript for intellectual content: Soeiro AM, Serrano Jr. CV, Oliveira Jr. MT.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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