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Archives of Medical Research ■ (2018) ■

Archives of Medical Research

PRELIMINARY REPORT

Reduction of No Reflow with a Loading Dose of Atorvastatin before Primary Angioplasty in Patients with Acute ST Myocardial Infarction

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Received for publication June 18, 2018; accepted October 25, 2018 (ARCMED_2018_149).

Background. No reflow defined as an altered myocardial reperfusion and failure at microvascular level is a frequent complication in acute myocardial infarction that attenuates beneficial effect of reperfusion therapy leading to poor outcomes. There is not enough evidence to support that previous use of statins improves coronary flow in patients undergoing primary percutaneous coronary intervention (PCI).

Aim of study. To determine if a loading dose of 80 mg of atorvastatin before primary angioplasty reduces the frequency of no reflow, hs-CRP, IL6 intracoronary levels, and major combined cardiovascular events at 30 d.

Methods. In this controlled clinical trial, we randomly assigned 103 adult patients within the 12 h of acute ST-elevation myocardial infarction (STEMI) to receive 80 mg of atorvastatin additional to standard treatment (AST) before performing primary PCI versus standard treatment (ST) alone. The primary outcomes were the occurrence of no reflow and high sensitivity C-reactive protein (hs-CRP) and interleukin 6 levels and secondary outcomes were major adverse cardiovascular events at 30 d.

Results. 103 patients were analyzed, 49 (48%) received AST, 54 (52%) ST. Frequency of no reflow among groups was 27 vs. 63% respectively, $p \leq 0.0001$. hs-CRP level was 2.69 mg/dL

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https://doi.org/10.1016/j.arcmed.2018.10.006

for AST vs. 2.2 mg/dL in ST, meanwhile IL-6 levels were 5.2 pg/mL vs. 6.35 pg/mL respectively, $p = ns$. Cox regression model demonstrated that the treatment assigned is an independent predictor for no reflow occurrence (HR 0.34 95%, CI 0.18−0.61, $p \leq 0.001$).

Conclusion. The administration of a loading dose of 80 mg atorvastatin before primary PCI is an effective strategy for prevention of no reflow improving also clinical outcomes and free survival rate for the presentation of major adverse cardiovascular events at 30 d. Published by Elsevier Inc. on behalf of IMSS.

Key Words: Acute ST elevation myocardial infarction, No Reflow, Percutaneous coronary intervention, Reperfusion injury, Statins, Biomarkers.

Introduction

Sudden restoration of blood flow in ischemic myocardium can result in a deleterious effect caused by paradoxical reperfusion mechanisms. The prevalence of reperfusion damage, specifically no reflow amounts to 20−50 percent in the context of acute ST elevation myocardial infarction (1,2). The pathophysiology is related to several factors such as coronary spasm, distal embolization of atheroma or thrombus plaques, oxidative stress, microvascular entrapment of platelets and leukocytes, interleukin-6, C- reactive protein and other adhesion molecules. These factors favor endothelial and tissue edema, with compression of the microvasculature and alteration of myocardial perfusion leading to no reflow. This phenomenon is considered and independent predictor of major cardiovascular events such as arrhythmias, heart failure, blockages, cardiogenic shock, and increased ventricular remodeling and mortality (3−6).

The multifactorial nature of this event, makes it unlikely that a single agent will be completely effective in treating it. To date numerous pharmacological interventions have been tested: vasodilators, glycoproteins IIb/IIIa inhibitors, nitric oxide, antibodies against cellular and intracellular adhesion molecules, inhibitors of complement activation, aprotinin, agents that reduce intracellular calcium, cyclosporine, metabolic modulation, glucose potassium solutions, intravenous magnesium, moderate hypothermia, atrial natriuretic peptides, pre and post conditioning maneuvers; all of which are focused on reducing post-reperfusion myocardial damage without showing conclusive results (7,8).

The administration of statins at an experimental level before reperfusion therapy has shown a decrease in the presentation of no reflow from 20−25 percent (9,10). Some clinical trials have also shown a reduction in peri-procedure incidence of this event with the use of a loading dose with these agents prior to percutaneous coronary intervention in patients with stable angina and myocardial infarction without ST Elevation even in patients under chronic treatment of statins (11−15).

Based on the previous argument we proposed to carry out a randomized controlled clinical trial to test the hypothesis of whether the administration of a loading dose of statins prior to primary percutaneous coronary intervention reduces the occurrence of no reflow in patients with ST elevation myocardial infarction.

Material and Methods

We performed a two parallel arms randomized controlled clinical trial. The inclusion criteria were: age from 18−85 years, diagnosis of acute myocardial infarction with ST elevation less than 12 h of evolution (symptoms, electrocardiographic criteria such as ST-segment elevation of 0.2 mV in V1−V3 leads or 0.1 mV in the rest of leads or the apparition of *novo* left bundle branch block, and elevation of cardiac biomarkers: troponin I above the 99th percentile in relation to the reference limit, and/or elevation of MB-fraction creatinephosphokinase of 10 percent with respect to total creatinephosphokinase level). Patients with preexcitation syndromes, myopathies, pericarditis, myocarditis, hepatopathy, medications associated with statins interaction, connective tissue diseases and known allergy to the use of statins were excluded. The clinical trial was approved by the Scientific and Ethics Research Committees. All participants provided written informed consent.

Simple random assignment was made in blocks of variable size according to a random numbers generated by computer. A medical assistant of the emergency cardiovascular department, different from the physician in charge of the patient care, knew the assigned treatment and gave the specific order to the nursing staff for treatment administration. There was blinding of the attending medical staff as well as the team that evaluated the outcomes and those who performed the statistical analysis.

Patients were allocated to a single loading-dose of 80 mg of atorvastatin plus standard treatment (AST group) or to standard treatment (ST group). The standard treatment consisted in antiplatelet adjuvant therapy with a loading dose of 300 mg of aspirin and 300 or 600 mg of clopidogrel prior to primary PCI, antithrombin therapy with intravenous heparin or low molecular weight heparin adjusted to the patient's weight, and according to the operator's criteria glycoprotein IIb/ /IIIa inhibitors. The administration of loading dose of statins prior to primary PCI is not considered part of standard treatment. All patients received, independently of the randomization group, a maintenance dose of 40 mg of atorvastatin daily until 30 d.

At the admission peripheral blood samples were collected to determine levels of creatinephosphokinase, MB-fraction, myoglobin, troponin I which were analyzed by immunological UV test with COBAS 501 module, immunofluorescence of murine monoclonal antibodies against troponin I and myoglobin triage.

Prior to the intervention, intracoronary samples from the culprit vessel were taken for determination of interleukin-6 and hs-CRP levels which were subsequently analyzed using sequential solid-phase immunometric assay by chemiluminescence for in vitro diagnosis with IMMULITE 2000 and 1000 analyzer.

The angiographic success of the procedure was considered when the residual stenosis after angioplasty and stenting was less than 20 percent of the diameter of the culprit vessel, in addition to TIMI and Blush grade 3 post interventionism.

After the intervention, all patients continued to be treated with 150 mg of acetylsalicylic acid and 75 mg of clopidogrel daily.

All patients underwent scintigraphy of myocardial perfusion SPECT (Single Photon Emission Computed Tomography) tetrofosmin marked with technetium 99 metastable with dipyridamole using a 1 d protocol, initially in the first week of the infarction and repeated subsequently at 8 weeks. The details for the realization of this technique were the following: after the administration of dipiridamol at a dose of 0.142 mg/kg *per* minute and under electrocardiographic and vital signs monitoring, 10 millicuries of Tetrofosmin-Tc-99m were applied at the time of maximum vasodilation. After 30 min, we proceeded to acquire with 2 range of specific cardiology use Ventri General Electric model with 2 detectors at a fixed angle of 90°. The study was synchronized to the electrocardiogram to obtain data about global and segmental ventricular function. The information was stored for further processing. After the administration of 20 millicuries of radiotracer, under conditions of rest, images with the same parameters were acquired. The Emmory Tool Box program was used for processing and obtaining tomograms in longitudinal and transverse axes. The regional perfusion of the left ventricle and its mobility was analyzed in polar analogous and parametric maps. A second scintigraphy of myocardial perfusion SPECT was performed at 8 weeks hence at this time there is not possibility of confusion of results due at lethal damage for reperfusion or early myocardial stunning.

The primary end point was the presence of no reflow determined by the following:

a) Decrease of less than 50 percent of the basal elevation of ST segment, measured at 90 min after reperfusion with primary PCI.
b) "Angiographic no reflow" determined by a TIMI flow ≤ 2 in the absence of severe coronary dissection, spasm or significant residual stenosis, as well as myocardial Blush flow ≥ 2 at the end of interventional procedure.
c) no reflow by SPECT images when the initial and subsequent study showed no capture of the radiotracer in the reperfused area of the culprit vessel.

The intracoronary levels of interleukin-6 and high sensitive C reactive protein of the culprit vessel of infarction were also determined as a primary outcome.

The secondary endpoint consisted in the single or combined presentation of (major adeverse cardiovascular events) MACE at 30 d (postinfarction angina, reinfarction, need for urgent revascularization, heart failure, arrythmias, cardiogenic shock and cardiovascular death).

Statistical Analysis

We performed descriptive statistics of the data with measures of central tendency and dispersion according to their distribution. For the comparison of categoric variables, χ^2 test was performed. For quantitative variables Student's T test for independent groups was used in case of normal distribution or Mann Whitney test as a non-parametric alternative. Relative risk was calculated with 95% confidence interval (CI), relative risk reduction, absolute risk reduction, as well as need-to-treat number for the presentation of no reflow and the combined end point of MACE at 30 d. The treatment analysis was made under the principle of intention to treat. Free no reflow survival analysis was performed with Kaplan-Meier method. Due to differences in the analysis found in the baseline characteristics despite the randomization, a stratified analysis of Mantel & Haenszel was carried out to determine the presence of potential confounders. Cox's multivariate regression analysis was realized.

An intermediate analysis was planned to be performed at the moment of reaching 50 percent of the initially estimated sample size and according to the results obtained, the suspension of the study was planned. A p value <0.05 was considered significative. The statistical package SPSS 18 and STATA 8 were used to process the data.

Results

A total of 121 patients were admitted from March 15th 2010—August 10th 2011. Thirteen patients were excluded and 108 patients were randomized to one of 2 treatment arms. Figure 1.

Fifty-two patients were allocated to the AST group and 56 in ST group.

The baseline clinical and demographic characteristics are described in Table 1.

Forty-six male patients (85%) received standard treatment against 39 (89%) who received treatment with a loading dose of 80 mg of atorvastatin plus standard treatment before primary PCI, $p \leq 0.05$.

The rest of variables showed not statistical difference between groups.

Angiographic and Procedural Characteristics

Angiographic and percutaneous coronary intervention findings are summarized in Table 2. No significant differences were found according to the assigned treatment group respect to the artery related to the infarction and number

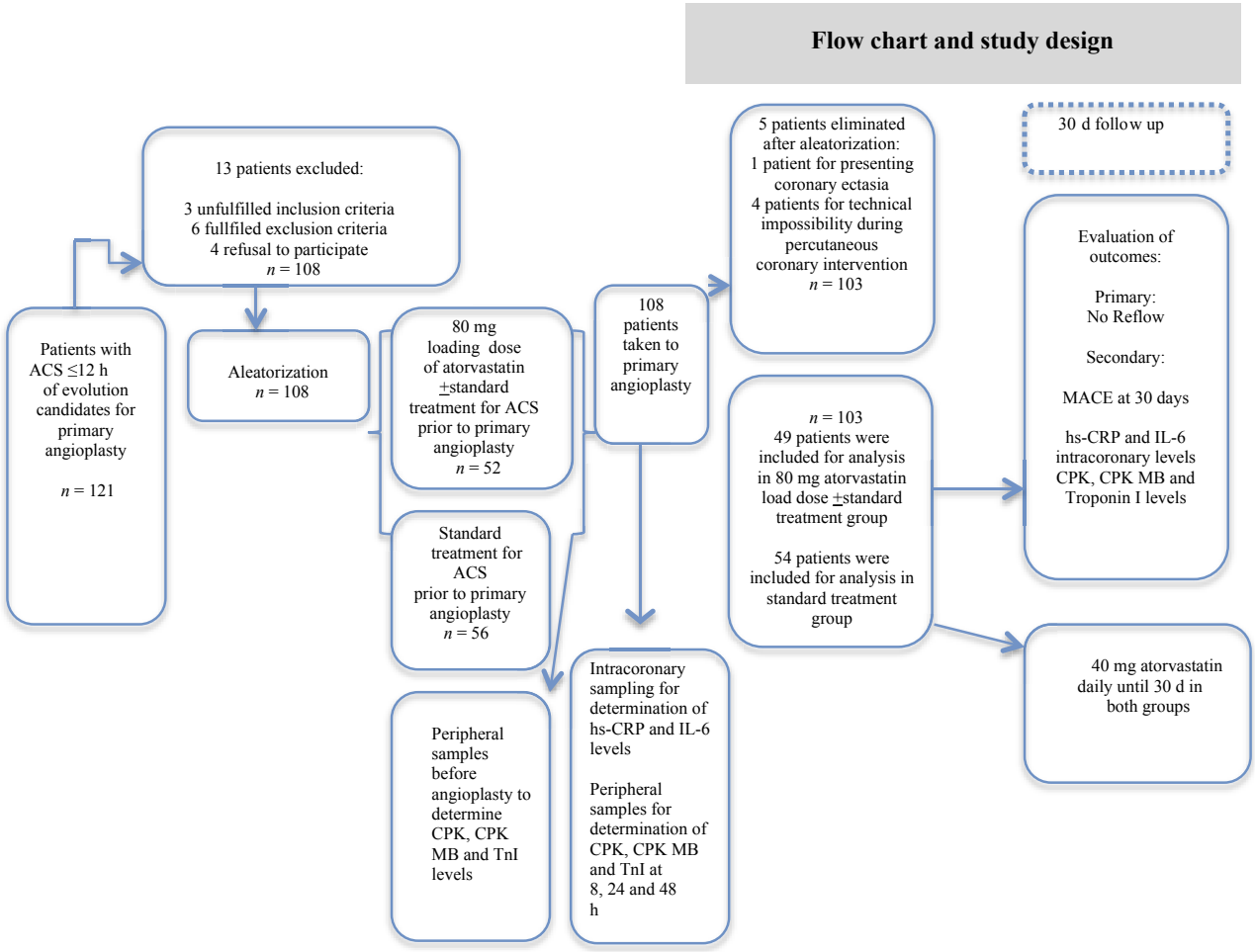

Figure 1. ACS: Acute coronary syndrome. CPK: creatinphosphokinase. CPK MB: creatinphosphokinase fraction MB. TnI: troponin I. MACE: major advanced cardiovascular events. hs-CRP: high sensitive C reactive protein. IL-6: interleukin-6.

of vessels affected. The diameter of the culprit vessel was the same for both groups with a median of 3.5 centimeters (3−3.5 cm), p = *ns*. Regarding to the interventionist technique, 87% of the patients underwent a conventional technique of primary percutaneous coronary intervention and 13% received direct stenting technique. The comparison between groups did not showed statistically significant differences.

The comparative difference in both groups with respect to the presence of intracoronary thrombus, large plaque burden greater than 13.5 mm, presence of calcium and TIMI and myocardial blush flow at the beginning and end of the procedure neither showed statistically significant differences.

Table 3 summarizes concomitant treatment during interventional procedure. Twenty-two patients received a loading dose of 600 mg of clopidogrel before the intervention (41%) in ST group versus 17 (35%) in AST group; and 32 patients received a loading dose of 300 mg of clopidogrel (65 %) in ST group versus 32 (59%) in AST group, without finding significant differences, p = 0.53. The use of glycoproteins IIb/IIIa inhibitors were in 43 patients (80%) in ST group and 29 (59%) in the AST group, p ≤0.02. No statistical difference was reported for the rest of the concomitant therapy in both groups.

The median for hs-CRP levels in the standard treatment group was 2.69 mg/dL (1.1−8.5) vs. 2.2 (0.98−4.9) mg/dL in the AST group, p = 0.72. The interleukin-6 levels were 6.35 pg/mL (3.7−10.1) vs. 5.2 pg/mL (2.6−9.2) for AST and ST group respectively, p = 0.22. No difference was found in peak levels of creatinephosphokinase, MB-fraction and myoglobin between groups. The median for serum levels of troponin I was 30 ng/mL (19.7−30) in the standard treatment group vs. 17.1 ng/mL (1.1−29.5) in the AST group, p ≤0.03.

Other laboratory data, such as total platelet count at admission showed no differences between groups.

The total leukocyte count at admission was 10600/µl (8600−12400) in the standard treatment group vs. 9700/µL (7500−11900) in the AST group, p = 0.13. Hence

Table 1. Demographic & clinical baseline characteristics by allocation group

Variable	Loading dose of 80 mg of atorvastatin + ST (AST) (n = 49)	Standard treatment (ST) (n = 54)	p
Age	64 ±11	64 ±11	0.36
Male gender	36 (89)	46 (85)	0.05
Smoking	27 (55)	33 (61)	0.53
Systemic Hypertension	26 (53)	34 (63)	0.30
Type 2 Diabetes	22 (45)	16 (30)	0.11
Dyslipidemia	23 (47)	21 (39)	0.40
Chronic use of statins	11 (22)	9 (17)	0.48
Previous angina	17 (35)	16 (30)	0.58
Previous infarction	13 (26)	14 (26)	0.94
Previous coronary intervention	8 (16)	9 (17)	0.96
Previous stent	6 (12)	8 (15)	0.70
Previous revascularization	2 (4)	2 (4)	0.92
Symptom <48 hrs	42 (86)	44 (81)	0.56
Infarction localization			
Diafragmatic	4 (8)	7 (13)	
Anterior	7 (14)	11 (20)	
Post-inferior	8 (16)	5 (9)	
Post-inferior & lateral	6 (12)	10 (19)	0.64
Post-inferior and RV extension	9 (18)	8 (15)	
Extensive anterior	15 (31)	13 (24)	
Pain evolution time (minutes)	257 ±154	289±124	0.24
Time of pain-onset to primary PCI (min)	292±157	327±126	0.21
Killip-Kimbal			
I	45 (92)	48 (89)	0.62
II	4 (8)	5 (9)	
IV	-	1 (2)	

Values reported: number of patients (% percentage) mean ± standard deviation ST: standard treatment.

Table 2. Angiographic and interventional procedure characteristics by allocation group

Variable	Loading dose of 80 mg of atorvastatin + ST (AST) (n = 49)	Standard treatment (ST) (n = 54)	p
Infarct related artery			
Left descending anterior artery	24 (49)	26 (48)	
Circumflex artery	7 (14)	6 (11)	0.57
Right coronary artery	18 (37)	20 (37)	
Bypass graft	17 (35)	2 (4)	
Diameter of the culprit vessel	3.5 (3-3.5)	3.5 (3-3.5)	0.08
Type of percutaneous coronary intervention			
Primary conventional	45 (85)	42 (85)	0.50
Direct stenting	8 (15)	5 (10)	
Number of affected vessels	13 (27)	15 (28)	
1	8 (16)	13 (24)	0.56
2	28 (57)	26 (48)	
3			
Thrombus	45 (92)	48 (89)	0.61
Large plaque burden >13.5 mm	44 (90)	50 (93)	0.61
Calcium	20 (41)	15 (28)	0.16
Eccentric coronary lesion	20 (41)	20 (37)	0.70
Type of Lesion			
A	5 (10)	3 (6)	0.18
B	-	8 (15)	
C	44 (90)	43 (80)	
Time to lesion <3 months	32 (65)	38 (70)	0.58
>3 months	17 (35)	16 (30)	
Initial TIMI grade			
0	33 (67)	40 (75)	
1	10 (20)	9 (17)	0.46
2	6 (12)	3 (6)	
3	-	1 (2)	
Thrombus aspiration	20 (41)	26 (48)	0.45
Final TIMI grade	3 (6)	2 (4)	
0	4 (8)	4 (7)	
1	8 (16)	17 (31)	0.34
2	34 (69)	31 (57)	
3			
Final Blush grade			
0	2 (4)	5 (9)	
1	5 (10)	6 (11)	0.44
2	7 (14)	12 (22)	
3	35 (71)	31 (57)	
Stent	45 (94)	50 (93)	0.81
DES	30 (64)	31 (58)	0.59
BMS	17 (36)	22 (42)	0.59

DES, Drug Eluting Stent; BMS, bare metal stent.
Values reported: number of patients (% percentage), ST: standard treatment.

leukocyte count could be associated with no reflow, we compared it between patients with and without no reflow showing slightly tendency to association (10700/μL 9200−14900 vs. 9600/μL 7500−12000 p = 0.05).

Other variables of importance such as the glucose level at admission, as well as the glomerular filtration rate did not show significant difference when comparing both treatment groups and neither in relation to the development of no reflow.

The left ventricular fraction according to the assigned treatment was subclassified into 4 groups: >50 percent, 40−50 percent, 30−40 percent and less than 30% without showing significant differences.

Primary and secondary endpoints. The comparison of primary and secondary endpoints are summarized in Table 4. Angiographic no reflow was reported in 34 (63%) patients in standard group and in 13 (27%) patients in the AST and ST groups respectively, p ≤0.0001. Non statistical difference was reported regarding to the decrease less than 50 percent of ST segment and no reflow evaluated by perfusion scintigraphy in both groups. The ''combined no reflow'' evaluation was reported in 38 patients (70%) and

Table 3. Concomitant treatment during interventional procedure by allocation group

Variable	Loading dose of 80 mg atorvastatin +ST (AST) (n = 49)	Standard treatment (ST) (n = 54)	p
Loading dose of clopidogrel before primary PCI			
300 mg	17 (35)	22 (41)	0.53
600 mg	32 (59)	32 (65)	0.53
GP IIb/IIIa inhibitors	29 (59)	43 (80)	0.02
Unfractioned heparin	44 (90)	45 (83)	0.33
Molecular low weight heparin	5 (10)	9 (16)	0.33
Intravenous nitroglycerin	10 (20)	15 (28)	0.38
Intracoronary nitroglycerin	27 (55)	31 (57)	0.81
Intracoronary adenosine	20 (41)	29 (54)	0.19
Intravenous verapamil	2 (4)	2 (4)	0.92
Intracoronary epinephrine	3 (6)	4 (7)	0.80
Dopamine	11 (22)	10 (19)	0.62
Dobutamine	3 (6)	-	0.06

Values reported: number of patients (% percentage) ST: standard treatment.

Table 4. Primary and Secondary endpoints by allocation group

Variable	Loading dose of 80 mg atorvastatin + ST (AST) (n = 49)	Standard treatment (ST) (n = 54)	p
Decline of ST segment ≤50 percent	18 (38)	27 (50)	0.17
Angiographic no reflow	13 (27)	34 (63)	<0.001
SPECT no reflow	25 (58)	27 (70)	0.30
Combined no reflow	15 (31)	38 (70)	<0.001
Postinfarction angor	5 (10)	6 (11)	0.89
Reinfarction	2 (4)	2 (4)	0.90
Acute Heart failure	10 (20)	9 (17)	0.62
Arrythmias	11 (22)	24 (44)	0.02
Need for revascularizatio	5 (10)	9 (17)	0.34
Cardiogenic shock	10 (20)	10 (19)	0.81
Death	3 (6)	6 (11)	0.37
MACE	23 (47)	31 (57)	0.28

15 patients (31%) respectively, $p \leq 0.0001$. With respect to the presentation of isolated cardiovascular outcomes at 30 d: arrhythmias were present in 24 patients (44%) in the standard group vs. 11 patients (22%) in the loading dose of 80 mg of atorvastatin plus standard treatment group, $p \leq 0.02$. The primary combined endpoint for MACE at 30 d was present in 31 patients (57%) vs. 23 patients (47%), $p = 0.28$ respectively.

Clinical outcomes. Figure 2 shows the relative risk for outcomes at 30 d according to allocation treatment. The loading dose of 80 mg of atorvastatin with standard treatment was a protective factor for the presentation of arrhythmias with a relative risk (RR) 0.50 95% CI (0.27−0.92), $p \leq 0.02$, as well as for the prevention of angiographic no reflow, RR 0.42, 95% CI 0.25−0.7, $p \leq 0.0001$ and for the ''combined no reflow'' RR 0.43 95% CI 0.27−0.68, $p \leq 0.0001$. With respect to the presentation of major adverse cardiovascular events for the group with additional use of a loading dose of 80 mg of atorvastatin shows RR 0.81, 95% CI 0.56−1.1, $p = 0.28$.

The results of the multivariate analysis (Cox proportional hazard model) is shown in Figure 3. The only independent factor for the development of ''combined no reflow'' was the loading dose of 80 mg of atorvastatin added to the standard treatment prior to primary percutaneous intervention with hazard ratio (HR) 0.34 95% CI 0.18−0.61, $p \leq 0.0001$.

The relative risk reduction (RRR) for presentation of ''angiographic no reflow'' was 0.57, which means that a loading dose of 80 mg of atorvastatin additional to standard treatment showed a 57% reduction with respect to standard treatment alone. Absolute risk reduction (ARR) was 0.36, which means that with 100 patients treated with a loading dose of 80 mg of atorvastatin additional to standard treatment we could avoid 36 cases of ''angiographic no reflow''. The need to treat number was calculated in 2.7, which means that are needed 3 patients with the treatment proposed to prevent 1 case of ''angiographic no reflow''.

Relative risk reduction (RRR) for presentation of ''combined no reflow'' was 0.56 which means that the new treatment showed a 56% reduction with respect to standard treatment. Absolute risk reduction (ARR) was 0.39 which means that for every 100 patients treated with a loading dose of 80 mg of atorvastatin additional to standard treatment we could avoid 39 cases of ''combined no reflow''. The number needed is calculated to be 2.5, which means that are needed 3 patients with the treatment proposed to prevent 1 case of ''combined no reflow''.

Relative risk reduction (RRR) for MACE presentation at 30 d was 0.18, it means that new treatment showed a MACE reduction in 18% with respect to standard treatment. Absolute risk reduction (ARR) was 0.10, it means that for every 100 patients treated with a loading dose of 80 mg of atorvastatin additional to standard treatment we could prevent 10 cases of MACE. The number needed to treat was calculated in 10, it means that we need to treat 10 patients with the treatment proposed to prevent 1 case of MACE at 30 d. Figure 4 shows the Kaplan Meier curve in relation to the free event survival rate for MACE to 30 d. With the loading dose of 80 mg of atorvastatin plus standard treatment there were a 73.5% of free event rate for MACE vs. 37% with standard treatment alone, log rank $p < 0.0001$.

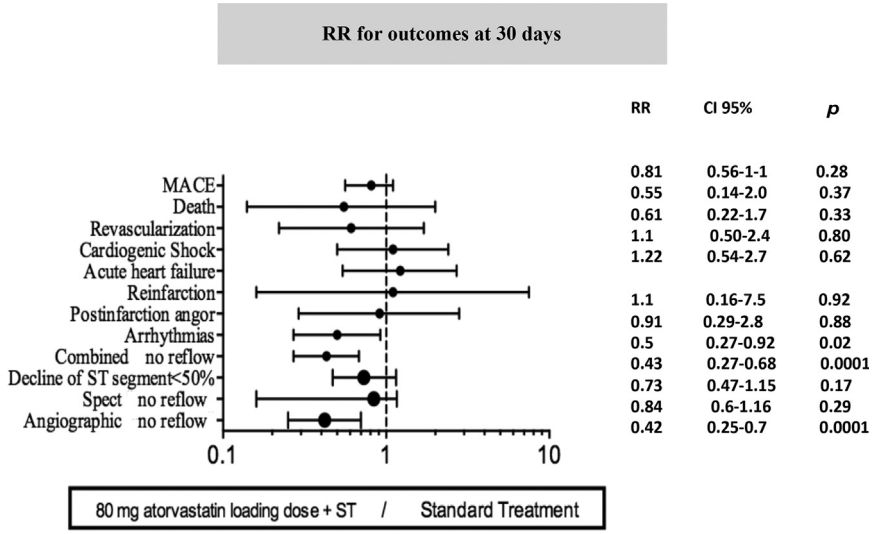

Figure 2. MACE: major adverse cardiovascular events. RR: relative risk. CI 95%: 95% Confidence Interval. *p* value.

There were not adverse events related to experimental maneuver.

Discussion

The study is the first national clinical controlled randomized trial that assesses the effectiveness of the use of a loading dose of statins in patients with acute myocardial infarction with elevated ST-segment prior to performing primary percutaneous coronary intervention. The occurrence of cardiovascular events at 30 d did not show significant differences between the treatment groups when they were evaluated as isolated events. However, our study suggests that the use of high dose of statin load prior to primary PCI can improve microvascular perfusion evaluated with the combined point of decline of ST $<50\%$, ''angiographic no reflow'' and no reflow by SPECT. Also reporting improvement in the event free rate survival for the combined point of major advanced cardiovascular events (MACE) at 30 d with a difference of 36.5 percent in favor of the loading dose of 80 mg of atorvastin plus standard treatment when comparing the survival curves analyzed for the two treatments.

The benefit of using of statins in the context of primary and secondary prevention is well established (16,17). These agents are considered to have a variety of favorable effects on the vascular system not directly related to their lipid lowering function known as pleiotropic effects. Retrospective studies have shown favorable effects in short and medium-term survival, and the development of post-

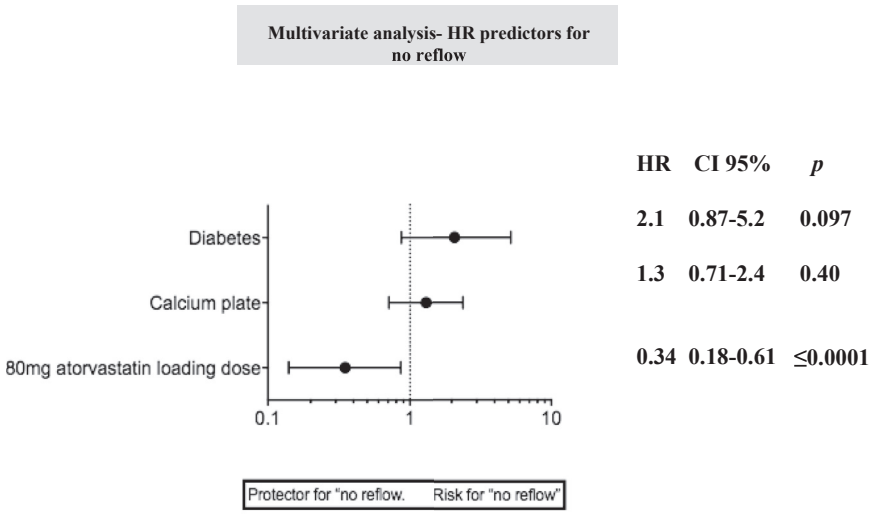

Figure 3. HR: hazard ratio. CI 95%: 95% Confidence Interval. *p* value.

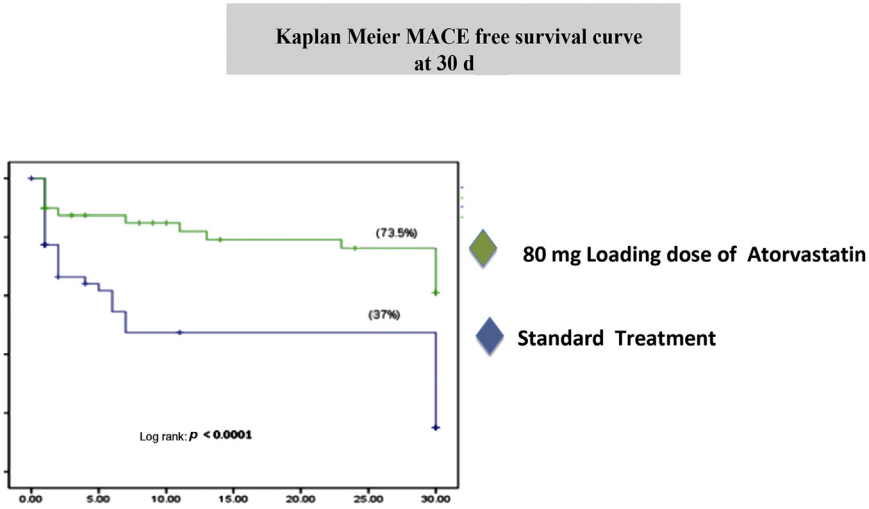

Figure 4. MACE: major adverse cardiovascular events.

procedure myocardial infarction (18−20). Researchers from the ARMYDA group study showed and 81 percent reduction in risk of peri-procedural myocardial infarction using a 7 d pretreatment with 40 mg of atorvastatin versus placebo in the context of stable angina (11). The ARMYDA-ACS study evaluated patients in the context of unstable angina and acute myocardial infarction without ST elevation. Pretreatment with a loading dose of 80 mg of atorvastatin vs. placebo administered in a short period of time prior to elective percutaneous coronary intervention decreased the incidence of periprocedural infarction (5 vs. 15%), $p = 0.04$, showed lower elevation of creatinphosphokinase fraction MB levels (7 vs. 27%), $p < 0.001$ and troponin I levels (41 vs. 58%), $p = 0.039$ comparatively (12).

Although the beneficial effects of the use of high doses of statins prior to reperfusion, cannot be fully explained, experimental animal models have shown to mediate through a protective effect against post- reperfusion myocardial damage, through the activation of the phosphatidyl inositol 3- kinase (PI3K)/AKT pathway which activates the RISK (Reperfusion Injury Salvage Kinase pathway) cascade of kinases activated by cyclic AMP that promotes protection against lethal reperfusion damage avoiding subsequent apoptosis (21).

Statins stimulate nitric oxide synthase (eNOS), which promotes actions on the endothelium, intracytoplasmic sequestration of the NFκB transcription factor and the inflammatory response, vascular effects, decrease in platelet adhesion, decrease in the binding of leukocytes to the endothelium, increase of coronary vasodilation and decrease of no reflow (21,22).

Yellon et al, in their basic research model showed that chronic administration of statins prevents the production of nitric oxide through the RISK cascade and secondary inhibition by overexpression of tensinphosphatase (PTEN) with antagonist action on the 1.3 Phosphatidylinositol kinase (1,3 PK) (23). The protective effect on the myocyte is lost due to the increase in the concentrations of tensinphosphatase (PTEN).

The most important finding of this procedure was the evidence that an additional loading dose reduced the ratio of myocardial necrosis/ischemia in animals treated for 1−2 weeks with atorvastatin with a loading dose recapturing the RISK way which inhibits PTEN expression and increases P1-3 Kinase-Akt- eNOS with consequent nitric oxide production (9).

ARMYDA RECAPTURE trial carried out in context of stable chronic angina and acute coronary syndrome without ST elevation in patients under chronic treatment with statins and a loading dose of 80 mg of atorvastatin given 12 h before interventionism and 40 mg additional given before the procedure vs. placebo showed significant reduction of myocardial damage markers and MACE at 30 d (13). NAPLES II study in elective coronary angiography with patients naïve to statin treatment also demonstrated the utility of the administration of a loading dose of 80 mg of atorvastatin 24 h prior to elective coronary percutaneous intervention (14).

The previously studies were carried out during elective coronary interventional procedures in patients with stable angina or acute coronary syndrome without ST-elevation, being difficult to assume the same behavior and benefit in context of patients with acute coronary syndrome with ST elevation. For this reason, it was attractive for our researchers group to test the hypothesis of whether the administration of a loading dose of 80 mg of atorvastatin was able to reduce no reflow in patients undergoing reperfusion with primary percutaneous coronary intervention. The time between loading dose of atorvastatin and primary PCI ranged from ≤90−150 min in our study. The literature reports detectable levels of the drug at 60 min of its administration.

Our results demonstrate efficacy of the administration of a loading dose of 80 mg of atorvastatin prior to primary PCI on the prevention of ‘‘no reflow’’.

The reduction of markers of myocardial damage as the maximum levels of troponin I in the group with a loading dose of 80 mg of atorvastatin additional to standard treatment compared with standard treatment alone, reflected a smaller enzymatic size of the infarction. It is important to emphasize that this marker has been related to bad forecast associated with mortality (24,25).

Borrayo et al, compared interleukin-6 levels in patients with acute STEMI. Levels in those that developed no reflow were 34.8 ± 11.3 pg/mL vs. 8.73 ± 6.4 pg/mL in whose presented that no reflow, $p = 0.032$ (5). In our study, however, we could not corroborate these differences. The documented values in non parametric ranges were lower and were performed with different laboratory techniques.

In 2005, Turkish researchers demonstrated in a clinical study that hs-CRP levels was an independent predictor associated with poor myocardial perfusion. With adjusted odds ratios of 1.85 for hs-CRP, 95% CI 1.23−2.80, $p = 0.003$. In this study we didn't find these differences (26).

Recognizing that according to scientific literature, decreased glomerular filtration rate on admission in patients with ST elevation myocardial infarction is independently associated with the risk of poor myocardial perfusion following after primary PCI, and corroborated by Celik et al in 2009, with adjusted odds ratio 12.05 for low estimated glomerular filtration rate (eGFR), 95% confidence interval 2.11−68.70, $p = 0.005$, (27) we specifically analyzed the glomerular filtration rate based on the abbreviated Modification of Diet in Renal Disease study equation (MDRD) at hospital admission, without finding significant differences for the development of no reflow.

Some studies based on blood parameters have shown interesting results regarding their relationship with the development of no reflow. In the Huczek stud, mean platelet volume was considered a strong independent predictor of no reflow in patients treated with primary PCI with odds ratio (OR) 4.7, 95% confidence interval (CI) 2.3−9.9, $p \leq 0.0001$ (28) although we did not have in our database the available information data related mean platelet volume, the specific analysis of total platelet count at admission did not show difference in both treatment groups and it was not associated with the development of no reflow.

Other authors have shown that an increase in platelet-leukocyte aggregates levels may predict the development of no reflow phenomenon in patients with STEMI who underwent PCI (29). We could only determine in our analysis that there was a greater increase in leukocyte levels at admission in patients who developed no reflow, however it did not show to be an independent predictor in the multivariate analysis.

Other blood count parameters that have been reported to be independent predictors of impaired angiographic reperfusion and long-term mortality among patients with STEMI undergoing primary PCI are red blood cell distribution width (RDW), platecrit, neutrophil-lymphocyte ratio and RDW-platelet ratio (30). It will be extremely interesting in new clinical studies to evaluate these parameters in a specific way.

Finally returning again the perspective towards the use of statins in acute coronary syndrome, recently the results published in SECURE PCI trial did not show a reduction in MACE at 30 d in the overall heterogenous ACS population analized. However the analysis of the subgroup of patients with STEMI undergoing primary PCI who received a loading-dose of 80 mg of atorvastatin in the short time before the intervention showed a significant reduction in MACE at 30 d (31). Our clinical study definitely is consistent with the results where the treatment with the 80 mg loading dose of atorvastatin plus standard treatment before primary PCI showed a clear reduction in the major adverse cardiovascular events at 30 d which is shown in the Kaplan Meier curve. In the univariate analysis, when the clinical events were evaluated in an isolated manner, the outcome where the greatest reduction was observed in relation to this treatment were arrhythmias.

There is clear evidence according to these results of the benefit of statins in this context. It should be noted that early administration of statins before primary PCI is not currently recommended in Evidence-based cardiovascular Guidelines; so these interesting findings should be analyzed in detail since they could change medical decisions in these critical scenarios.

Study Limitations and Strengths

One of the main limitations was the lack of blinding of patients due to impossibility to carry out the manufacture of the placebo. Although the evaluation of no reflow from the angiographic point of view may have some limitations, the addition in our study of myocardial perfusion images with radiotracers as Tc-99 tetrofosmin, has shown good correlation to detect alterations of microcirculation and it is a hard way to evaluate this outcome variable, being an accessible method in our center. In future studies it would be very interesting to used methods such as fractional reserve flow or even PET, or contrast echocardiography, and cardiac MRI that is now the gold standard test for the diagnosis of no reflow, however the specific utilization of this technological resource could not be used in this trial because it was not available in our center. Despite the low number of patients in this trial and that the results were obtained from an intermediate analysis, we calculated a statistical power of 94 percent for the difference of proportions obtained in both treatment groups for the presentation of primary endpoint of no reflow.

Conclusions

Our study shows that administration of a loading dose of 80 mg of atorvastatin additional to standard treatment

before primary percutaneous intervention in patients with acute myocardial ST-elevation infarction is associated with a protective effect for development of no reflow with higher with higher rate of event-free survival for the presentation of major advanced cardiovascular events at 30 d compared with standard treatment alone.

Acknowledgment

This work was supported by the grant from "Fondo de Investigación en Salud" FIS/IMSS/PROT/G09/777.

Conflict of Interest

The authors have no conflicts of interests to disclose.

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