Indian Heart Journal 69 (2017) 453–457

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Original article

High versus low dose statin therapy in Indian patients with acute ST-segment elevation myocardial infarction undergoing thrombolysis

K. Priti*, Anand Agrawal, Bhanwar L. Ranwa

Dept of cardiology, JLN hospital, Ajmer, Rajasthan, 305001, India

ARTICLE INFO

Article history:
Received 29 December 2016
Accepted 28 May 2017
Available online 30 May 2017

Keywords:
Statin
ST elevation myocardial infarction
Myalgia
Thrombolysis

ABSTRACT

Objectives: This study sought to compare high dose versus low dose statin therapy in Indian patients with ST-segment elevation myocardial infarction (STEMI) undergoing thrombolysis.
Background: Randomized trials have demonstrated that statin treatment reduced major adverse cardiac events (MACEs) in patients with stable angina pectoris and acute coronary syndrome. However, randomized studies of statin therapy in Indian patients with STEMI are scarce.
Methods: Of 1859 patients with acute STEMI, 1027 eligible patients were randomized to 80-mg (n = 512) or 10-mg (n = 515) atorvastatin. Primary end point was 30-day incidence of MACE (death from any cause, myocardial infarction, NSTE-ACS requiring readmission, ischemia driven revascularization, and stroke). Secondary end points included individual components of primary end point and ST-segment resolution at 90 min after thrombolysis.
Results: Two groups did not differ in primary endpoints of MACEs (8.79% in high dose vs 9.32% in low dose atorvastatin group, OR = 0.938, 95% CI = 0.612–1.436, P = 0.764). With 80 mg atorvastatin, there was insignificant reduction in rate of reinfarction, revascularization and death. Stroke and readmission for NSTE-ACS increased in 80 mg atrovastatin group, but was not statistically significant. ST-segment resolution was significantly higher in 80-mg atorvastatin arm (45.90% vs. 37.67%; p = 0.008). Myalgia was more in 80 mg statin group (18.06% vs 7.57%, p = 0.0001).
Conclusions: High-dose atorvastatin did not show significant difference of MACEs in STEMI patients undergoing thrombolysis but showed significant improvement in immediate coronary flow depicted by ST-segment resolution. This benefit of high dose statin is to be weighed against greater myalgia, drug discontinuation and cost in Indian patients.

1. Introduction

CAD burden in India is likely to increase exponentially due to changing lifestyle and urbanization of villages.1 Angiographic studies show that aggressive cholesterol reduction by a variety of methods, as opposed to dietary modifications alone, results in increased rates of plaque regression and stabilization.2 The results of the TNT and IDEAL trials established the important role for intensive statin therapy in the management of patients with stable CAD, and extend the observations from PROVE IT TIMI 22 in ACS patients to patients with stable disease.3–5 Atorvastatin 80 mg has been extensively used in management of ACS and stable CHD patients in the western world. Such patients benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels. In the Indian context, there is limited data about usage of atorvastatin 80 mg either in ACS patients or stable CHD patients. This may be due to safety concerns of usage of higher dosage of statins in Indian patients.

2. Methods

2.1. Study population

It was a prospective double blind single centre study which included patients (18 years-70 years) admitted in coronary care unit from January 2014 to February 2015 with diagnosis of acute ST elevation myocardial infarction (STEMI) undergoing thrombolysis using fibrinolytic therapy after meticulous screening in the emergency department (ED). Patients with previous (within 3 months) or current treatment with statins; known allergy to heparin, aspirin, clopidogrel, active severe bleeding; pregnancy; history of major surgery or trauma; significant gastrointestinal or genitourinary bleeding (<6 weeks); history of cerebrovascular

* Corresponding author.
E-mail addresses: priti30jan@gmail.com (K. Priti), dranand74@rediffmail.com (A. Agrawal), bhanwar.ranwa@gmail.com (B.L. Ranwa).

http://dx.doi.org/10.1016/j.ihj.2017.05.026

attack; and cardiogenic shock with mechanical ventilation, other contraindication to fibrinolytic therapy, suspected pulmonary thromboembolism, creatinine level of more than 2.0 mg per deciliter, obstructive hepatobiliary disease or other serious hepatic disease, known hypersensitivity to statin, chronic liver or muscle disease, history of treatment with drugs that are strong inhibitors of cytochrome P-450 3A4 within the month before randomization and those undergoing primary PCI were excluded from the study. Diagnosis was confirmed on the basis of ECG, serial CK-MB/troponin T measurements and echocardiography as per universal definition of myocardial infarction. STEMI was defined as a clinical syndrome with characteristic symptoms of myocardial ischemia in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis. Diagnostic ST elevation in the absence of left ventricular (LV) hypertrophy or left bundle-branch block (LBBB) was defined as new ST elevation at the J point in at least 2 contiguous leads of $\geq$2 mm (0.2 mV) in men or $\geq$1.5 mm (0.15 mV) in women in leads V2–V3 and/or of $\geq$1 mm (0.1 mV) in other contiguous chest leads or the limb leads. New or presumably new LBBB at presentation, ST depression in $\geq$2 precordial leads (V1–V4) diagnostic of posterior wall STEMI; multilead ST depression with coexistent ST elevation in lead aVR were also included in STEMI group.[6]

2.2. Study protocol

All the patients received standard treatment for STEMI according to guidelines: thrombolytic therapy, heparin, nitrates, aspirin, clopidogrel, beta blockers, angiotensin converting enzyme inhibitor. Drugs with known or suspected interactions with statin were prohibited within five half-lives prior to inclusion and during the study.

2.3. Randomization

They were randomized in 1:1 manner using a table of randomized numbers containing double digits randomization codes (from 11 to 50) generated using computer program. Randomization codes were allotted to the enrolled patients by starting at random point in the table. Patients receiving code from 11 to 30 received low dose 10 mg atorvastatin (group A) and those with code from 31 to 50 received high dose 80 mg atorvastatin (group B). Randomization was performed at entry before starting any treatment. Adverse events were collected during the study period from selection to the end of follow-up at 30 days.

2.4. Endpoints

The primary end point was 30-day incidence of MACEs (death from any cause, myocardial infarction, documented Non ST elevation acute coronary syndrome [NSTE-ACS] requiring readmission, ischemia driven revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting, and stroke). Reinfarction within 18 h after initiation of fibrinolytic therapy should be based on recurrence of severe ischemic-type chest discomfort that lasts at least 30 min, usually but not always accompanied by recurrent ST-segment elevation of at least 0.1 mV in at least 2 contiguous ECG leads and re-elevation of CK-MB to more than the upper limit of normal or increased by at least 50% over the previous value and reaching at least >3 times the normal value, in association with ischemic symptoms. After 18 h, reinfarction was defined as new pathological Q waves or re-elevation of CK-MB to >3 times the normal value (24 h to discharge) or >2 times the normal value (after hospital discharge).[7] NSTE-ACS was defined as ischemic discomfort at rest for at least 10 min prompting rehospitalization, combined with one of the following: ST-segment or T-wave changes, cardiac-marker elevations that were above the upper limit of normal but did not meet the criteria for myocardial infarction, or a second episode of ischemic chest discomfort lasting more than 10 min and that was distinct from the episode that had prompted hospitalization. Secondary end points included individual components of the primary end point and ST-segment resolution at 90 min after thrombolysis.

2.5. Follow-up

A 30 days clinical follow-up was performed for all patients to evaluate MACEs (death from any cause, myocardial infarction, documented NSTE-ACS requiring readmission, ischemia driven revascularization and stroke.)

2.6. Statistical analysis

The statistical analysis was performed using IBM SPSS statistics version 20 (Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ SD, and categorical variables were presented as absolute number and proportion (%). Comparisons of categorical variables were made using the chi-square test and Fisher exact test, as indicated. Data were analyzed using the 2-tailed test to identify differences between groups and analysis of variance for repeated measures with Bonferroni correction for intragroup data. Nominal data were analyzed by the chi-square test. All efficacy analyses are based on the intention-to-treat principle. Event-free survival analysis was be analyzed by the Kaplan-Meier method with log-rank test group comparison. We considered 95% confidence intervals (CIs) that excluded unity, or, equivalently, $p < 0.05$, as statistically significant. Calculation of sample size was based on a 2-sample and 2-sided test. We assumed the incidence of MACEs might be similar between patients with STEMI treated with primary PCI or fibrinolytic therapy. Therefore, we calculated a sample size by analogy with the STATIN STEMI (Efficacy of High-Dose Atorvastatin Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction) study.[8] MACE in the STATIN STEMI study was 5.8% for high-dose (80-mg) atorvastatin arm versus 10.6% for conventional dose (10-mg) arm. Using a 2-sided alpha level of 0.05 and statistical power of 80%, we estimated the need for 511 patients in high-dose atorvastatin arm and 511patients in low dose arm, or a total of 1022 patients.

3. Results

Of 1859 patients with acute STEMI, 832 patients were excluded. Eligible patients (n = 1027) were randomized in 1:1 manner to 80-mg atorvastatin (n = 512) or 10-mg atorvastatin (n = 515) arms for pre-treatment before thrombolytic therapy and continued on the respective statin dose post thrombolysis (Fig. 1).

3.1. Baseline characteristics

Baseline demographic and clinical characteristics are displayed in Table 1. Mean age was 57.01 $\pm$10.65 years and 74.2% of the patients were men. Demographic characteristics did not differ significantly between the 2 groups. Mean left ventricular ejection fraction was 46 $\pm$ 8% in all patients and did not differ between the 2 groups. The pain-to-needle time and door-to-needle time were also not different between the 2 groups (4.9 $\pm$ 1.77 vs. 4.98 $\pm$ 1.88 h, P = 0.483 and 13.6 $\pm$ 4.76 min vs. 4.98 $\pm$ 1.88 min, P = 0.665, respectively). The proportion of patients taking medications after fibrinolysis was also similar between the 2 groups (Table 1). Peak CK-MB level was 243 $\pm$156 ng/dl in group A vs 253 $\pm$ 162 ng/dl in group B (P = 0.314).

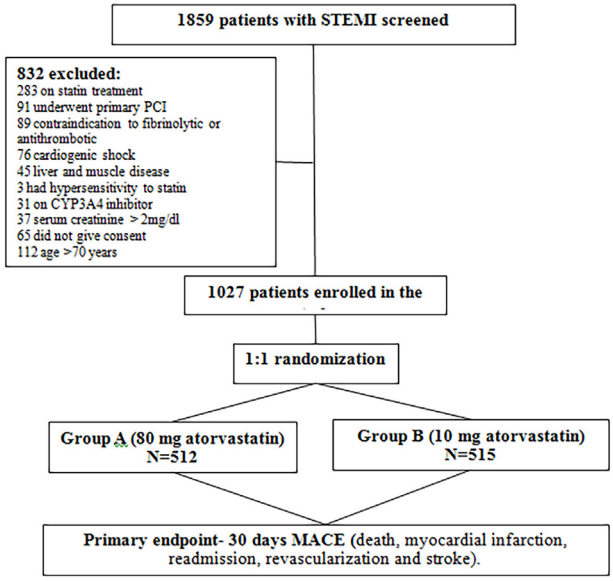

Fig. 1. Study Protocol of the trial.
Between Januray 2014 and February 2015, a total of 1859 STEMI patients were admitted to the ER. Eligible patients were randomized to receive 80 or 10 mg of atorvastatin. MI-myocardial infarction; STEMI- ST segment elevation myocardial infarction; PCI- Percutaneous coronary intervention; MACE-major adverse cardiac event.

3.2. Primary end point

For all randomized patients, the Kaplan–Meier event rates of the primary end point at 30 days were 8.79% in the high dose atorvastatin group and 9.32% in the low dose atorvastatin group (p = 0.75) (Fig. 2).No significant difference in major adverse cardiac event (MACE)-free survival at 30 days was observed between the 2 groups (OR = 0.938, 95% CI = 0.612–1.436, P = 0.764).

3.3. Secondary endpoints

Secondary endpoints are displayed in Table 2 (Fig. 3). With high dose atorvastatin, there was insignificant reduction in rate of reinfarction (0.98% vs 1.75%, OR = 0.555, 95%CI = 0.185–1.666, P = 0.286), revascularization (1.17% vs 1.36%, OR = 0.862, 95% CI = 0.287–2.578, P = 0.791) and death (4.49% vs4.66%, OR = 0.962, 95% CI = 0.536–1.728, P = 0.888). Readmission for NSTE-ACS (OR = 1.299, 95% CI = 0.479–3.514, P = 0.603) and stroke rate (OR = 1.392, 95% CI = 0.555–3.488, P = 0.479) increased in the high dose atrovastatin group, but was not statistically significant. Complete STR (70% STR at 90 min) was also higher in the 80-mg atorvastatin arm (45.90% vs.37.67%; OR = p = 0.008).

3.4. Tolerability and safety

At the time of randomization, the mean serum LDL-C concentration was 83.68 ± 17.74 mg/dl in group A vs 83.68 ± 17.74 mg/dl in group B (P = 0.666). Reduction in LDL-C was statistically significant (P = 0.000) at the end of 30 days in atorvastatin 80 mg group (29.16 ± 10.57%) as compared to that of atorvastatin 10 mg (12.51 ± 4.80%) group (Table 3). But this reduction in LDL-C was not related to primary endpoints.

The rates of discontinuation of treatment because of an adverse event or the patient's preference were 15.43 percent in the high dose atorvastatin group and 4.66 percent in the low dose atorvastatin group at 30 days (P = 0.0001). The percentages of patients who had elevations in alanine aminotransferase levels that were more than three times the upper limit of normal were 0.78 percent in the high dose atorvastatin group and 0.58 percent in the low dose atorvastatin group (P = 0.725). 93 patients (18.06%) in high dose atorvastatin group and 39 patients (7.57%) in low dose atorvastatin group experienced myalgia (p = 0.0001). The study medication was discontinued by the investigators because of a report of moderate to severe muscle symptoms including myalgias, muscle aches, tenderness or stiffness with or without elevations in creatine kinase levels in 11.33 percent of high dose atorvastatin-treated patients, as compared with 3.49 percent of low dose

Table 1
Baseline Characteristics:.

	Atorvastatin		
	Group A	Group B	P value
Age	56.64 ± 10.86	57.35 ± 10.44	0.286
Sex (male)	393 (76.76)	369 (71.65)	0.075
Diabetes	124 (24.22)	110 (21.36)	0.298
Hypertension	193 (37.7)	167 (32.43)	0.078
Dyslipidemia	127 (24.8)	139 (26.99)	0.434
Smoker	159 (31.05)	133 (25.83)	0.072
Renal insufficiency	45 (8.79)	36 (6.99)	0.299
Previous MI	12 (2.34)	13 (2.52)	1.000
Previous PCI/CABG	9 (1.76)	7 (1.36)	0.626
LVEF	45 ± 9	46 ± 8	0.06
WBC count ($\times 10^9$ cells/L)	12.9 ± 5.3	13.4 ± 6.1	0.161
Hemoglobin (g/dl)	14.3 ± 4.3	13.9 ± 3.6	0.106
Serum creatinine (mg/dl)	1.17 ± 0.5	1.21 ± 0.6	0.246
Pain to needle time (hours)	4.9 ± 1.77	4.98 ± 1.88	0.483
Door to needle time (minutes)	13.6 ± 4.76	13.73 ± 4.87	0.665
In hospital medications			
Aspirin	512 (100)	515 (100)	1
Clopidogrel	512 (100)	515 (100)	1
Beta blocker	341 (66.60)	329 (63.88)	0.394
ACE inhibitor or ARB	354 (69.14)	366 (71.07)	0.539

Data are presented as mean± SD or n (%). LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker.

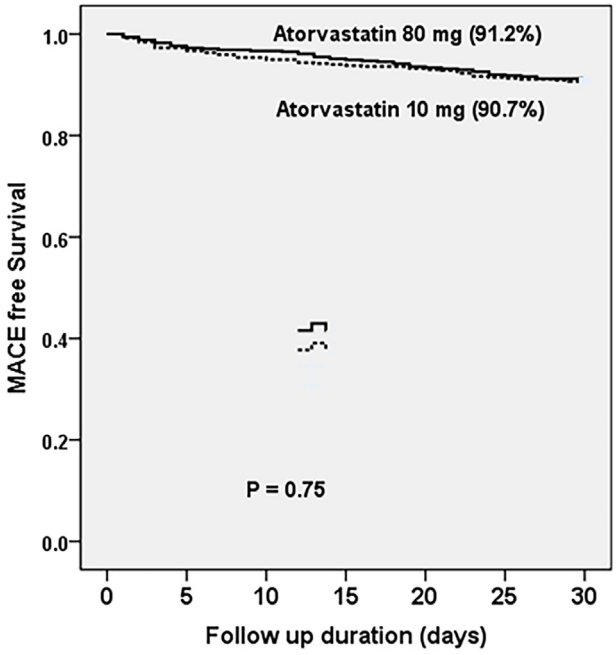

Fig. 2. Kaplan-Meier 30 days MACE-Free Survival.

Table 2
Incidence of MACE at 30-days Follow-Up.

	Atorvastatin			
	80 mg (n = 512)	10 mg (n = 515)	Odds Ratio (95% CI)	P value
Readmission	9 (1.76)	7 (1.36)	1.29 (0.48–3.51)	0.603
Death	23 (4.49)	24 (4.66)	0.96 (0.54–1.73)	0.888
Reinfarction	5 (0.98)	9 (1.75)	0.55 (0.18–1.67)	0.286
Stroke	11 (2.15)	8(1.55)	1.39 (0.56–3.49)	0.479
Revascularization	6 (1.17)	7 (1.36)	0.86 (0.29–2.58)	0.791
MACE	45 (8.79)	48 (9.32)	0.94 (0.61–1.44)	0.764

Data are presented as n (%). Revascularization- ischemia driven revascularization, MACE- major adverse cardiovascular events.

Table 3
Evaluation of LDL-C level at baseline and 30 days follow up:.

LDL-C	10 mg Atorvastatin group	80 mg Atorvastatin group	P value
Baseline (mg/dl)	83.68 ± 17.74	84.16 ± 17.83	0.666
Day 30 (mg/dl)	73.13 ± 15.40	65.19 ± 12.79	0.000
% Reduction of LDL-C from baseline	12.51 ± 4.80	29.16 ± 10.57	0.000

Data are presented as mean ± SD or (%).

atorvastatin-treated patients (P = 0.0001). There were no cases of rhabdomyolysis in either group.

4. Discussion

This study is the first randomized trial to evaluate the efficacy of high-dose atorvastatin (80 mg) in STEMI patients undergoing fibrinolytic therapy. Occurrence of cardiac events was not significantly different between the 10-mg and 80-mg atorvastatin pre-treatment at the 1-month clinical follow-up assessments. However, our study suggested that high-dose atorvastatin loading before fibrinolysis may improve microvascular coronary perfusion as determined by STR after fibrinolysis. Our results are consistent with STATIN STEMI trial, in which high-dose atorvastatin (80 mg) pre-treatment before PCI did not show a significant reduction of MACEs compared with low-dose atorvastatin (10 mg) but did show improved immediate coronary flow after primary PCI.8

The benefit of statins in primary and secondary prevention for coronary artery disease is well established.9–11 But there are limited studies, which have tested efficacy and safety of statins in Indian population. IRIS (Investigation of Rosuvastatin in South Asian Subjects) trial was conducted in patients of South Asian origin with hypercholesterolemia settled in United States and Canada. They were randomized to receive rosuvastatin 10 or 20 mg or Atorvastatin 10 or 20 mg for 6 weeks. LDL-C decreased by 45% with rosuvastatin 10 mg versus 40% with atorvastatin 10 mg ($P = 0.0023$) and by 50% with rosuvastatin 20 mg versus 47% with atorvastatin 20 mg (P = NS). In addition, both drugs were well-tolerated and were without significant side effects.12 CURE-ACS study was an open label study, which compared the reduction in LDL-C levels in patients with acute coronary event presenting within 10 days to seven cardiology centers across India. The patients were randomized to receive either atorvastatin 40 mg or atorvastatin 80 mg. A dose-dependent response was observed with a greater reduction of LDL-C in atorvastatin 80 mg (27.5% vs. 19.04%) than that of atorvastatin 40 mg group at the end of 12 weeks. No significant adverse were observed in both groups.13

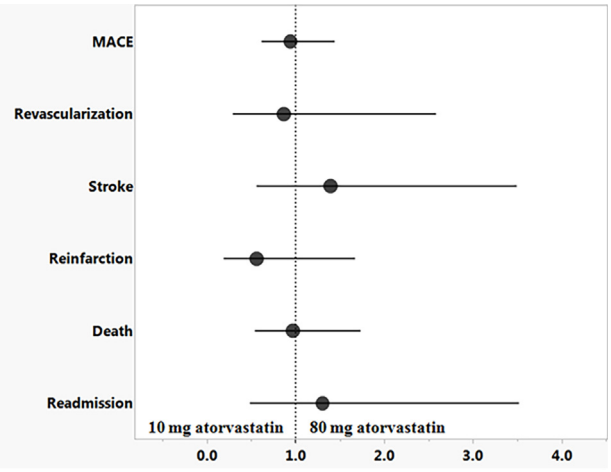

Fig. 3. Odds ratio plot of MACE at 30 days follow up.

Pharmacokinetic studies suggest that Indians achieve higher levels of circulating statins compared to the Caucasian population when administered equivalent doses. A study conducted in Singapore has revealed that Asian Indians achieved 1.68 the plasma levels of rosuvastatin when compared to the Caucasian population when administered single 40 mg dose of rosuvastatin. 14 This pharmacokinetic variation of statins in Indian subgroup might explain similar efficacy of high and low dose statin in our study.

We found that STR was higher in the 80-mg atorvastatin arm. This beneficial effect on myocardial perfusion of acute high-dose statin treatment may be explained by the pleiotropic effects of statin that may be initiated before the lipid-lowering effects.15–17 Previous studies have provided evidence for beneficial effects of acute atorvastatin treatment that may be related to lipid-independent pleiotropic effects such as improvement of endothelial function, dilation of coronary microvessels, and anti-inflammatory and antithrombotic actions.15–17

Interestingly, myalgia was significantly higher in 80 mg atorvasatin arm (18.06% vs 7.57%, p = 0.0001). One of the important determinants for statin induced myopathy is the presence of solute carrier organic anion transporter family member 1B1 (SLCO1B1) variants. SLCO1B1 gene encodes membrane-bound sodium-independent organic anion-transporting polypeptide 1B1 that is involved in an active cellular influx of statin in hepatocytes. The SLCO1B1 (c. 521T > C) C allele causes lower statin uptake in the liver and is a risk factor for simvastatin induced myopathy. The variant, prevalent in 15% of the Caucasian population, is responsible for more than 60% of cases of myopathy.18 A study from Kerala showed the presence of this variant in 15% of population, which

was surveyed.19 We did not evaluate this genetic variant in our population which might explain increased myopathy in our study group.

4.1. Study limitations

First, it was a single centre study. A multicentre study is needed to confirm our findings. Second, the follow up period was short, i.e, 30 days. A longer follow up is needed to see the long term outcomes. Third, we did not evaluate C- reactive protein and followed only the clinical parameters. Fourth, only STR was used as the index for myocardial reperfusion. Other indices were not taken into account. Lastly, even though our group of patients experienced higher rates of myalgia in comparison to other studies, we did not perform the genetic study for SLCO1B1 variants.

5. Conclusions

High-dose atorvastatin treatment did not show a significant difference of MACEs compared with low dose atorvastatin in STEMI patients undergoing thrombolysis but showed significant improvement in immediate coronary flow after thrombolysis as depicted by ST-segment resolution. This benefit of high dose statin is to be weighed against greater myalgia, drug discontinuation and cost in Indian patients.

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