Effects of high dose atorvastatin before elective percutaneous coronary intervention on highly sensitive troponin T and one year major cardiovascular events; a randomized clinical trial☆

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A B S T R A C T

Introduction: Some studies have demonstrated that post-PCI elevated cardiac enzymes are associated with worse outcomes. In this study, we aimed to determine if high-dose treatment with atorvastatin before planned elective PCI reduces PMI or MACE at 1-year median follow-up.

Material and methods: Eligible participants were randomly allocated to group A (80 mg atorvastatin 12 h and 40 mg 2 h before PCI) and group B (40 mg atorvastatin daily). Blood samples were obtained before and at 24 h after PCI to measure hsTnT. All patients were followed regarding MACE (combination of death, re-hospitalizations for ACS, and unplanned coronary revascularization) during one year after PCI.

Results: 207 patients randomly assigned to Group A (n = 97) or group B (n = 110). The rate of PMI was lower in group A (5.2%) compared to group B (10.9%); despite near to 50% lower rate of PMI in group A, binary logistic regression showed no significant association between atorvastatin recapture and PMI. The occurrence of MACE in 97 patients of group A was 11 (11.3%), higher than 11 (10%) cases of 110 patients in group B. Cox proportional hazards regression model shows no significant difference in MACE of study groups.

Conclusion: Pretreatment of patients with stable angina who were planned to undergo an elective PCI with 120 mg of atorvastatin before the procedure confer them the same benefit in terms of PMI and MACE as 40 mg routine daily dosage of this statin does.

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1. Introduction

Percutaneous coronary intervention (PCI) is a therapeutic approach with a wide range of indications from acute coronary syndromes (ACSs) to elective revascularizations [1]. However, it is not a risk-free procedure and may lead to peri-procedural increase of cardiac enzymes in up to 48% of patients [2–8]. Post-PCI elevation of troponin has been shown to be directly correlated with the extent of myocardial injury on cardiac magnetic resonance imaging [9]. Moreover, studies and meta-analyses demonstrated that elevated cardiac enzymes are associated, both clinically and statistically, with worse outcomes [2–8]. Therefore, it necessitates proper interventions for minimizing the risk.

Efficacy of several strategies for reducing peri-procedural myocardial infarction (PMI) including peri-procedural administration of ticlopidine [10], eptifibatide [11], clopidogrel [12], and beta-blockers [13,14] has been investigated previously. Furthermore, a growing body of evidence demonstrated promising role of pretreatment with statins, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, in patients with either stable angina (SA) or ACS for this purpose [15,16]. Intriguingly, this benefit arises from immediate actions of statins named pleotropic effects rather than their lipid-lowering effects [17–25].

Investigators assessed efficacy of statins in diminishing PMI and major adverse cardiovascular events (MACEs) in patients with SA who are planned to undergo elective PCI previously [26–42]. Although some trials supported statin pretreatment [27,30–32,34,36–41], others demonstrated that it does not provide clinical benefits in terms of PMI [26,28,29,33,35,42] or MACE [26,29,33,39]. Moreover, there are very few studies which reported long-term outcomes [26,30,31,33]. Meanwhile, recent studies on Chinese population raised the concern...
that if effects of statins are influenced by inter-racial differences [26,43,44]. Hence, further studies are needed for addressing these issues.

In this single-blind randomized clinical trial, we aimed to determine if high-dose treatment with atorvastatin before planned elective PCI reduces PMI or MACE at 1-year median follow-up.

2. Materials and methods

2.1. Study design and population

This study was a randomized single-blind trial conducted at Tehran heart center (a large tertiary hospital specializing in cardiovascular disease) in Iran to test the hypothesis that acute high-dose atorvastatin reoad may be protective against MACE and PMI in patients undergoing elective PCI. Eligible participants were all stable coronary artery disease (CAD) patients with refractory angina despite full medical treatment including 40 to 80 mg of atorvastatin daily, aged 18 and over with planned PCI after a diagnostic angiography. The exclusion criteria were acute coronary syndrome settings, the high sensitive troponin T (hsTnT) >24 ng/ml before PCI, liver enzymes more than three times of normal range, creatinine clearance <30 mL/min, ejection fraction <20%. After initial evaluation of included patients, 43 patients were excluded based on exclusion criteria. All of the participants were Asian in ethnicity. Eligible Patients were randomly allocated to undergo either intervention group, as atorvastatin loading group, or control group, who received routine protocol. The flowchart of all stages is shown in Supplemental figure. Data related to sociodemographic status and medical histories were collected from standardized medical records. In all cases, participants’ consent was obtained and the study protocol was approved by the research ethics committee of Tehran University of medical sciences. This study was designed in agreement with the principles of Declaration of Helsinki.

2.2. Interventions and measurements

Eligible participants were randomly allocated to group A (atorvastatin loading/recapture), who received 80 mg atorvastatin 12 h before the PCI and 40 mg 2 h before PCI, and group B (routine protocol), who received 40 mg atorvastatin daily as routine protocol, as shown in the flowchart. It should be noted that administration of 120 mg of atorvastatin 24 h prior to PCI in our study is supported by several studies [37,45,46]. Randomization was performed with a permuted block randomization method to decrease the chance of imbalance rate. PCI was performed according to current guidelines and standard protocols of Tehran heart center. After intervention, all patients received 40 mg atorvastatin daily, regardless of the initial randomization. Blood samples were obtained before and at 24 h after PCI to measure hsTnT, lipid profiles, fasting blood sugar (FBS), HbA1c, hemoglobin and creatinine using enzymatic methods. They were drawn into ethylenediamine tetraacetic acid (EDTA)-containing tubes and immediately placed on ice and sent to the laboratory. The Level of hsTnT was detected using Roche Elecsys kit. Protocol-based follow-up of PCI patients was done in 1, 6, and 12 months post-procedural then annually. The follow-up was carried out through direct office visit (the PCI clinic which is dedicated to post-PCI patients) by cardiologist and any admission or events during follow up period were registered. When the clinical visit was not possible, a telephone call was used by the trained nurses. In each visit, detailed history, physical examination, electrocardiogram and routine laboratory tests including liver function tests were investigated. All data were registered in our hospital data base. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters. Diabetes mellitus (DM) was characterized by FBS ≥126 mg/dl [7.0 mmol/L] or HbA1c ≥6.5% [47]. Hypertension (HTN) was defined as blood pressure of at least 140/90 mm Hg or taking antihypertensive agents [48]. Hyperlipidemia (HLP) was defined as fasting triglyceride levels >150 mg/dL (1.7 mmol/L) or total cholesterol >200 mg/dL (5.2 mmol/L) or taking lipid lowering treatment [49].

2.3. Endpoints

The main endpoints were occurrence of MACE, at a 12-month period, and PMI following PCI, which assessed in the intention-to-treat population. MACE was defined as combination of death, re-hospitalizations for ACS, and unplanned coronary revascularization during 12 months. Troponin was measured before and 24 h after PCI to assess PMI. According to the fourth universal definition of MI [50] and for conferring more clinical relevance to the outcomes [51], PMI following PCI was defined as an elevation of troponin level to 5 or more times the upper reference limit for (URL) inferring.

2.4. Statistical analysis

We calculated sample size based on the study of Nafasi et al. in which the last universal definition of MI was employed, as in this study [27]. The incidence of PMI was expected to be 10.5% in the placebo group and 3.1% in the Atorvastatin group. Therefore, a total sample size of 182 (91 in each group) with an alpha level of 0.05, confer our study a power of 80%. By assuming 15% sample loss, sample size increased to 110 in each group. Normality of distribution was evaluated using Kolmogorov-Smirnov test. Continuous normally distributed variables were reported as mean ± standard deviation and compared by t-test. On the other hand, continuous non-normally distributed variables were expressed as median and interquartile range (IQR) and compared with Mann-Whitney U test. Categorical variables were shown as frequencies and percentages and compared by the chi-square test. Univariate analysis was done to assess the association of independent variables with endpoints. Binary logistic regression model was used to determine the independent association of atorvastatin recapture with PMI in two models and expressed by odds ratio (OR) and 95% confidence intervals (CI). In model 1, no variables were added to atorvastatin recapture due to non-significant results in univariate analysis in model 2 (adjusted model), several known variables which have been shown to be effective on clinical outcome following PCI including age, sex, smoking, BMI, history of DM, HTN and HLP, and prior history of ACS [45–50], were added to the multivariable logistic regression model. The event-free survival at 12 month follow up in both group were presented using Kaplan-Meier survival curves. The treatment effects and MACE hazard were compared between study groups using Cox proportional hazards regression model in two mentioned models and shown by hazard ratios (HRs) and 95% CI. All endpoint analysis was according to intention-to-treat method. P values ≤0.05 were considered statistically significant. Data were analyses were conducted using IBM SPSS Statistics for Windows, version 23.0.

3. Results

3.1. Study population

As shown in Fig. 1, of the 250 stable CAD patients who were candidate for elective PCI, 43 patients were excluded according to exclusion criteria, and other eligible 207 patients randomly assigned to Group A, as atorvastatin loading group (n = 97) or group B, as routine protocol (n = 110). Patients were followed for median of 12 months (8–14 months). Demographic and baseline characteristics of both groups are shown in Table 1. The mean age of all participants was 59.41 ± 10.05 years and the majority of them were men (69.6%). The most common type of prior history of ACS in eligible participants was non-ST elevation MI (46.4%), followed by ST elevation MI (14.5%) and unstable angina (6.3%). The baseline features including smoking, BMI, DM, HLP, HTN, hemoglobin, and creatinine did not differ significantly in both groups. The serum level of FBS, high density
lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), and triglyceride (TG) were lower in group A, without statistically significant difference (Table 1). The mean serum level of hsTnT before and after PCI and difference between them showed no significant alteration between both groups (P = 0.590).

3.2. Endpoints analysis

In univariate analysis, there were no significant association between independent variables and endpoints (P > 0.05). The atorvastatin recapture (loading) also shows no significant correlation with PMI and MACE (Table 2). Despite the non-significant results in univariate analysis, we added several known factors in literature, affecting clinical outcomes following PCI, to multivariable regression models to assess the independent association of atorvastatin recapture and our endpoints. As shown in Fig. 1, the rate of PMI was lower in group A (5.2%) compared to group B (10.9%); despite near to 50% lower rate of PMI in group A, binary logistic regression showed no significant association between atorvastatin recapture and PMI in model 1 (OR: 0.44, 95% CI: 0.015–1.31; P = 0.14) and 2 (OR:0.45, 95% CI: 0.14–1.43; P = 0.18).

The occurrence of MACE in 97 patients of group A was 11 (11.3%), higher than 11 (10%) cases of 110 patients in group B. Cox proportional hazards regression model shows no significant difference in MACE of study groups in model 1 (HR = 1.20; 95% CI: 0.52–2.76; P = 0.67) and 2 (HR = 0.67, 95% CI:0.25–1.80, P = 0.43). In model 1, the hazard for MACE in group B was 1.20 fold higher than that in group A in adjusted model 2, those receiving routine protocol (group B) have a hazard that is only 0.67 that for somebody getting atorvastatin recapture (group A). However, all results were statistically non-significant. Fig. 2 compares the probability of remaining free of MACE in both groups in the intention-to-treat population at 12-month median follow-up.

The Kaplan-Meier curves show group B outperforming group A in terms of MACE-free survival.

4. Discussion

In this study, we found that high-dose atorvastatin pretreatment of statin-treated patients who underwent elective PCI does not reduce PMI or MACE at 1-year median follow-up in comparison with routine use of atorvastatin.

There are evidences showing that statins may exert their effects not only through decreasing serum lipid levels but also by their pleiotropic effects [17–25]. Indeed, administration of statins, immediately, result in such effects including reduction of inflammation [17,21–25], inhibition of platelet aggregation [17,18,24,25], improvement of endothelial function [17–21,24,25], and plaque stabilization [17–19,22–25]. It is suggested that these consequences are mediated by inhibition of 3-hydroxy-methylglutaryl coenzyme A which in turn reduces serum isoprenoids [24,25]. Thus, it seems rational to hypothese that high-dose statin pretreatment may improve clinical outcomes after PCI.

Recent meta-analyses indicated that high-dose pretreatment with statins reduces PMI in patients with ACS and SA by near to 60% based on evidences with moderate quality [15,16]. It should be noted that this difference remained significant after adjustment for prior history of statin use [15,16]. These findings are concordant with some of the previous studies [27,30–32,34,36–41]; however, contradict our results and several other trials [26,28,29,33,35,42]. Similar to Fujii et al. [35], we employed the most recent and accepted definition of PMI (cardiac troponin > 5 URL) [50,51], and concluded the same; however, Nafasi et al. [27] and Briguori et al. (creatine kinase-MB > 5URL) [41] with the same criteria found statistically significant decrease of PMI. It is noteworthy to mention that there are studies on both statin-naïve [29,31,33–36,38–42] and statin-treated [26–30,37] patients with SA.
which resulted in both positive [27,29–31,34,36–41] and neutral [26,28,29,33,35,42] effects on MACE. Noticeably, all of the neutral trials [26,28,29,33,35,42], including our study, are at high risk of performance and detection biases based on the GRADE system and have lower quality of evidence in comparison with positive trials [16].

Wang et al. [15] in a meta-analysis of randomized clinical trials demonstrated that patients with SA receive no benefit in terms of MACE with exclusion of PMI (OR = 0.71, P = 0.12), in contrary to the patients presented with ACS (OR = 0.52, P = 0.003). Again there is a similar scenario for MACE as with PMI. High-dose statin pretreatment in statin-naïve [31,33,38–40] and statin-treated [26,30,32,37] patients with SA may have either modifying [30,32,37,38,40] or non-modifying [26,33,39] effects on MACE. In all of the trials which found modifying effects, notably, the incremental value of MACE has been derived mainly from PMI, not from reduced death, stroke, or target vessel revascularization [31,37,38,40], except for the study of Li et al. [32] and the ROMA trial [30]. Therefore, our results, regarding MACE, are consistent with the latest meta-analysis [15] and previous trials [26,31,33,37–40], and in contrast with 2 aforementioned studies [30,32].

Recently, in SECURE-PCI trial [52] periprocedural loading doses of atorvastatin did not reduce the rate of MACE at 30 days. Results are congruent with our study. Although the sample size of this study is interesting, inclusion of the patients who were candidate for elective PCI and long term follow up (one year) make our study different. Despite several strengths including employing the most recent criteria for definition of PMI, determining long-term outcomes of patients, and considering Asian population, our study has number of limitations. First, this is a single-blind randomized clinical trial without placebo arm that may render it susceptible to biases. Second, we did not evaluate possible complications of high-dose statin treatment including elevation of liver transaminases in plasma. Although some studies have shown none [37] or minimal [45] adverse effects with pretreatment with 120 mg of atorvastatin, it should be encouraged to study such effects on PMI. Noticeably, all of the neutral trials [26,28,29,33,35,42] effects on PMI. Noticeably, all of the neutral trials [26,28,29,33,35,42] effects on PMI. Noticeably, all of the neutral trials [26,28,29,33,35,42] effects on PMI. Noticeably, all of the neutral trials [26,28,29,33,35,42] effects on PMI. Noticeably, all of the neutral trials [26,28,29,33,35,42] effects on PMI. Noticeably, all of the neutral trials [26,28,29,33,35,42] effects on MACE.

### Table 1
Demographic and baseline characteristics.

| Characteristics         | Group A (atorvastatin recapture) | Group B (routine protocol) | Total (n = 207) | P value |
|-------------------------|----------------------------------|-----------------------------|-----------------|---------|
| Age (y)                 | 58.73 ± 9.65                     | 60.00 ± 10.41               | 59.41 ± 10.05   | 0.366   |
| Gender (%)              |                                  |                             |                 | 0.885   |
| Male                    | 67 (69.1)                        | 77 (70)                     | 144 (69.6)      |         |
| Female                  | 30 (30.9)                        | 33 (30)                     | 63 (30.4)       |         |
| Cigarette smoking (%)   | 16 (16.5)                        | 24 (21.8)                   | 40 (19.3)       | 0.333   |
| BMI (kg/m²)             | 28.14 ± 4.07                     | 28.20 ± 3.94                | 28.17 ± 3.99    | 0.90    |
| DM (%)                  | 40 (41.2)                        | 47 (42.7)                   | 87 (42)         | 0.828   |
| HLP (%)                 | 66 (68)                          | 72 (65.5)                   | 138 (66.7)      | 0.694   |
| HTN (%)                 | 54 (55.7)                        | 60 (54.5)                   | 114 (55.1)      | 0.871   |
| FBS (mg/dL)             | 119.59 ± 36.41                   | 122.36 ± 45.23              | 221.27 ± 38.43  | 0.63    |
| LDL-cholesterol (mg/dL) | 7.91 ± 1.53                      | 7.02 ± 2.04                 | 7.32 ± 1.01     | 0.13    |
| TG (mg/dL)              | 150.14 ± 70.50                   | 157.66 ± 79.28              | 154.14 ± 75.21  | 0.48    |
| HbA1c (%)               | 14.29 ± 1.75                     | 14.68 ± 1.72                | 14.49 ± 1.74    | 0.116   |
| Cr (mg/dL)              | 0.92 ± 0.26                      | 0.97 ± 0.26                 | 0.95 ± 0.26     | 0.172   |
| Ejection fraction (%)   | 48.00 ± 9.00                     | 50.00 ± 8.00                | 49.4 ± 7.8      | 0.9     |
| Family history of CAD (%) | 19 (19.5)                      | 25 (22.7)                   | 44 (21.2)       | 0.16    |
| History of CABG (%)     | 9 (9.2)                          | 12 (10.9)                   | 21 (10.1)       | 0.4     |
| History of ACS (%)      |                                  |                             |                 |         |
| UA (%)                  | 7 (7.2)                          | 6 (5.5)                     | 13 (6.3)        | 0.272   |
| NSTEMI                  | 42 (43.3)                        | 54 (49.1)                   | 96 (46.4)       | 0.404   |
| STEMI                   | 14 (14.4)                        | 16 (14.5)                   | 30 (14.5)       | 0.982   |
| Angiography results     |                                  |                             |                 | 0.37    |
| SVD (%)                 | 29 (28.8)                        | 32 (29)                     | 61 (29.4)       |         |
| 2VD (%)                 | 39 (40.2)                        | 48 (43.6)                   | 87 (42)         |         |
| 3VD (%)                 | 28 (28.8)                        | 29 (26.3)                   | 57 (27.5)       |         |
| LM (%)                  | 1 (1)                            | 1 (0.9)                     | 2 (0.9)         |         |
| hsTnT                   |                                  |                             |                 |         |
| Before PCI              | 12.31 (8.44–15.42)               | 12.40 (9.64–16.62)          | 12.38 (9.07–16.46) | 0.520   |
| After PCI               | 16.15 (11.09–23.19)              | 17.48 (12.53–26.85)         | 17.27 (12–25.46) | 0.312   |
| Difference              | 4.06 (0.51–9.56)                 | 3.49 (0.75–13.33)           | 3.76 (0.57–11.07) | 0.590   |

Data are reported as mean ± standard deviation or median (inter-quartile range) or frequency (prevalence rates).

ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; Cr, creatinine; DM, diabetes mellitus; FBS, fasting blood sugar; Hb, hemoglobin; HbA1c, Hemoglobin A1C; HDL, high density lipoprotein; HLP, hyperlipidemia; hsTnT, high sensitive troponin T; HTN, hypertension; LAD, left descending artery; LCA, left circumflex artery; LDL, low density lipoprotein; LM, left main; NSTEMI, non ST elevation myocardial infarction; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST elevation myocardial infarction; SVD, single vessel disease; TC, total cholesterol; TG, triglyceride; UA, unstable angina; 2VD, two vessel disease; 3VD, three vessel disease.

### Table 2
Univariate correlation of independent variables with endpoints.

| PMI | MACE |
|-----|------|
|     | P value | P value |
| Age | 0.17  | 0.84   |
| Sex | 0.92  | 0.73   |
| Smoking | 0.33  | 0.84   |
| BMI | 0.27  | 0.78   |
| DM | 0.94  | 0.86   |
| HLP | 0.21  | 0.75   |
| HTN | 0.85  | 0.39   |
| FBS | 0.66  | 0.80   |
| HbA1c | 0.58  | 0.80   |
| HDL | 0.24  | 0.38   |
| LDL | 0.74  | 0.18   |
| TG | 0.33  | 0.59   |
| Hb | 0.85  | 0.76   |
| Cr | 0.26  | 0.41   |
| History of ACS | NSTEMI | 0.08  | 0.10   |
| STEMI | 0.57  | 0.42   |
| UA | 0.29  | 0.18   |
| Atorvastatin recapture | 0.11  | 0.75   |

Abbreviations: refer to Table 1.
effects especially in Asians due to lack of data in this ethnicity. Third, pre- and post-treatment measurement of inflammatory markers such as C-reactive protein (CRP) and high-sensitive CRP might have implications in ascertaining mechanism of action of statins [27,40] and also possible interaction with treatment strategy [38].

In our opinion, the current discrepancies in the literature regarding the matter necessitates further studies based on the most widely accepted definition of PMI and by addressing the aforementioned concerns in order to introduce more homogenous and high-quality evidence. Consequently, future meta-analyses will define the role of pretreatment with high-dose of statins before PCI for reducing PMI and MACE.

5. Conclusion

In conclusion, we demonstrated that pretreatment of patients with SA who were planned to undergo an elective PCI with 120 mg of atorvastatin before the procedure confer them the same benefits in terms of PMI and MACE as 40 mg routine daily dosage of this statin does. Further randomized controlled clinical trials with consistent definitions and protocols, and future meta-analyses are warranted.

Supplemental data to this article can be found online at https://doi.org/10.1016/j.ijcha.2018.12.003.

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Fig. 2. MACE-free survival in patients who underwent percutaneous coronary intervention (PCI). At 12 months median follow up, the survival benefit for group B was non-significantly higher than group A. MACE, major adverse cardiovascular event.
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