Research Article

Outcomes of Different Pre-procedural Loading Doses of Atorvastatin in Patients Undergoing Elective Percutaneous Coronary Intervention

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ABSTRACT

Peri-procedural myocardial injury (PMI) and contrast-induced nephropathy (CIN) are common complications of percutaneous coronary intervention (PCI) and associated with unfavorable procedural outcomes. Treatment with statins has become a cornerstone for the reduction of PCI complications. Our study aimed to investigate the safety, efficacy and clinical outcomes of different pre-procedural atorvastatin loading doses in patients with chronic stable angina (CSA) undergoing elective PCI as well as its impact on PMI and CIN. Sixty CSA patients on statin received 80 mg/day atorvastatin for seven days. At the day before PCI they were randomized to three groups: standard treatment (didn't receive any loading dose of atorvastatin), low load (received 80 mg atorvastatin 12 hours before PCI), and high load(received 80 mg atorvastatin 12 hours before PCI plus 40 mg atorvastatin two hours before PCI), n=20 per group. Patients continued to receive 80 mg/day for additional three months after PCI. The primary end points were assessment of PMI and CIN. The secondary endpoints were assessment of major adverse cardiac events (MACE) and drug safety. The incidence of PMI was significantly lower in low and high load groups compared with standard treatment. The incidence of CIN was significantly lower in high load. The number of the stent was an independent predictor of PMI and the amount of dye was an independent predictor of CIN. In conclusion, the use of pre-procedural high loading dose atorvastatin in patients undergoing elective PCI leads to decrease the incidence of both PMI and CIN compared with standard treatment.

Keywords: High dose atorvastatin; percutaneous coronary intervention; stable angina; peri-procedural myocardial injury; contrast-induced nephropathy.

INTRODUCTION

Coronary artery disease (CAD) is the most common cause of death globally, raised from 5.74 million deaths (12%) in 1990 to 8.14 million deaths (16.8%). [1] CAD will be responsible for a total of 11.1 million deaths globally in 2020. [2]

Ischemic heart diseases include stable angina, unstable angina, myocardial infarction (MI), and sudden coronary death.[3] Angina is the initial manifestation in around half of all patients who present with CAD. The presence of chronic angina nearly doubles the risk of major adverse cardiac events (MACE). [4, 5]

Percutaneous coronary intervention (PCI) represents a treatment strategy for patients with CSA. Advances in PCI resulted in increasing the numbers of patients undergoing such procedure. Although PCI is an evidence-based procedure, peri-procedural myocardial injury (PMI), contrast-induced nephropathy (CIN), and MACE still occur. [6-11]

Pre-procedural treatment with stain considered as one of the several suggested strategies aiming to reduce the risk of PMI, CIN and, MACE after PCI. Many studies and several meta-analyses of randomized controlled trials were supporting this approach. [6,9,10,12-21]Atorvastatin, the most widely used statin, in addition to its beneficial lipid modulation, it exerts a pleiotropic effect and is associated with a significant reduction in cardiovascular morbidity and mortality both in primary and secondary prevention. [22-28]

The current study aimed to compare the protective effect of different loading doses of atorvastatin in Egyptian patients with CSA undergo elective PCI on PMI, CIN, MACE and drug safety.

SUBJECTS AND METHODS

Study design and patients' populations

This is a single-center, prospective, open-label, randomized and parallel study involved patients with CSA scheduled for PCI recruited between December 2015 and May 2016 from the Cardiology Department, Tanta University Hospital. A total of 123 patients were screened for eligibility. Eligible patients were 18 to 65 years of age; have a left ventricular ejection fraction more than 30%, and a glomerular filtration rate (eGFR) >60 ml/min/1.73m^2. Patients were excluded if they present with acute coronary syndromes (ACS); had a left ventricular ejection fraction below 30%; had a history of hemorrhage; major surgery within the past two months; severe renal/hepatic insufficiency; muscular disorders or other contraindications to statin therapy, or unable to give informed consent. Angiographic exclusion criteria were: treatment of restenotic lesions, saphenous vein or

left internal mammary artery graft and treatment of chronic total occlusions.

Study protocol

All Eligible patients withheld nephrotoxic drugs 48 hours before contrast exposure. All patients received 80 mg atorvastatin each night for seven days before the procedure and the day before coronary intervention were randomized to 1:1:1 ratio using a table of random numbers into three groups: group I (standard treatment group, didn't received loading dose of atorvastatin before PCI); group II (low load arm, received 80 mg atorvastatin every 12 hours before PCI); and group III (high load arm, received 80 mg atorvastatin every 12 hours in addition to 40 mg atorvastatin two hours before PCI). Only 60 patients were included. Patients instructed to continue on atorvastatin 80 mg/day for three months after coronary intervention as shown in Figure 1.

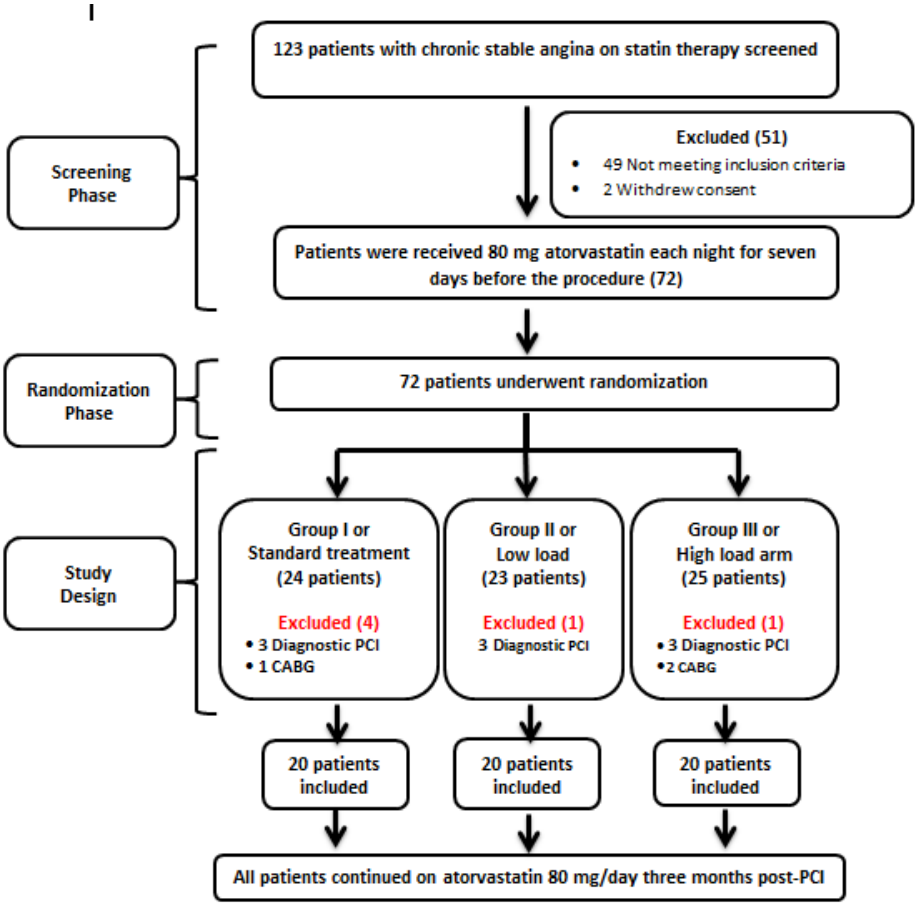

Figure 1: Flow chart of study design

PCI was performed via femoral approach. The operators were blind to assignment group. The same nonionic low osmolar (Ioversol [optray 350] 741mg/mL, Mallinckrodt, Inc, USA) contrast media was used. After PCI, patients were treated with optimal medical treatment according to guidelines. All clinical and angiographic data including adverse events during PCI were recorded by the attending physician.

Venous blood samples were collected from each patient at five-time points: before PCI; six hours, 12 hours, 48 hours, and three months after PCI. Serum cardiac troponin I (cTnI) was assayed before PCI, six and 12 hours post PCI; SCr was assayed before PCI, and 48 hours post PCI. Serum lipid profile (total cholesterol, HDL and TG) and ALT were assayed before and three months after PCI.

Definitions and end points

Angiographic success was defined by final residual restenosis < 20% and TIMI III flow grade. PMI defined by elevation in cTn ≤5x99th percentile upper reference limit (URL) after PCI if cTn value was normal before the PCI—or when the cTn value is >5x99th percentile URL in the absence of ischemic findings. [29] CIN defined by increase in serum creatinine (SCr) of 25% above baseline within 48 hours after PCI.[12, 30, 31]

The primary end point was a composite assessment of PMI and CIN. The secondary endpoint was a composite assessment of major adverse cardiac events (MACE) and drug safety. Clinical follow-up for MACE in term of cardiac death, MI, stroke, and target vessel revascularization were scheduled by direct visit or phone call and patients' interview at 30 days and three months follow-up after PCI. Safety, tolerability, and atorvastatin-related adverse events were assessed and recorded at three months after PCI during clinic visits and patients' interview.

Statistical analysis

The collected data was tabulated using Microsoft® Office Excel 2013, Microsoft Corporation. All statistical analyses were conducted using SPSS statistical package version 22.0, August 2013, IBM corporation software group, USA. Continuous variables were presented as mean (±SD) and were analyzed using ANOVA test. A post hoc analysis using Fisher's least significant difference (LCD) test was conducted. The Student unpaired t-test was used to compare parametrical continuous variables between two groups. Categorical variables were compared using the Chi-square test. Pearson r correlation was used to assess the strengths of association between any two tested variables. The level of significance was set at P <0.05.

RESULTS

Baseline demographic and clinical characteristics

Among the 60 included patients, male were found to be 37(61.7%); the mean (±SD) of age was 52.28 years (±6.63);and BMI was 29.33 kg/m^2 (±5.438). CAD risk factors were relatively frequent in the studied population. Family history of coronary artery disease found in 35 patients (58.3%), 55 patients (91.7%) were hypertensive, 54 patients were hyperlipidemic (90%), 29 patients were diabetic (48.3%), and 22 patients were smokers (36.7%). Baseline characteristics, medical therapy and CAD risk factors weren't statistically significant different among studied groups.

Procedural characteristics and PMI results

Procedural success was achieved in all patients in the three studied groups; no patient had slow or no-reflow phenomenon or coronary artery dissection or coronary perforation or significant side-branch (≥2 mm) closure during the procedure. There were no in-hospital major complications (death or need for urgent revascularization).

Table 1 showed non-statistical significant differences as regard angiographic and procedural characteristics among the three studied groups; the number of patients complained of ischemic symptoms during PCI was 5(25%) in group I, 0(0%) in group II and 1(5%) in group III; in addition, the number of patients that developed transient ST elevation during PCI was 5(25%) in group I, 1(5%) in group II and 0(0%) in group III; similarly, the number of patients that developed ST elevation during PCI was 1(5%) in group I, 0(0%) in group II and 0(0%) in group III and there were statistically significant differences in term of ischemic symptoms and new ECG changes among studied groups(P=0.020 and P=0.038 respectively).

Among the three studied groups in whom stent implanted cTnI before PCI didn't differ significantly. However, cTnI six and 12 hours post-PCI was significantly higher in group I (P=0.000, P=0.001 respectively) Table 1. Post hoc analysis using Fisher's least significant difference (LSD) test showed there were highly statistical significant differences between group I, group II (P=0.002) as well as between group I, group III (P= 0.000) but, there was no statistical significant difference between group II and group III (P=0.167). PMI was significantly higher in group I (7(35%) vs. 1(5%) vs. 0(0%), P=0.002, respectively). Compared with group I, the proportion of patients with PMI was significantly lower in group II (P=0.044) and group III (P=0.008) Figure 2. There was a significant positive correlation between the number of stent and occurrence of PMI (r=0.258, P=0.023).

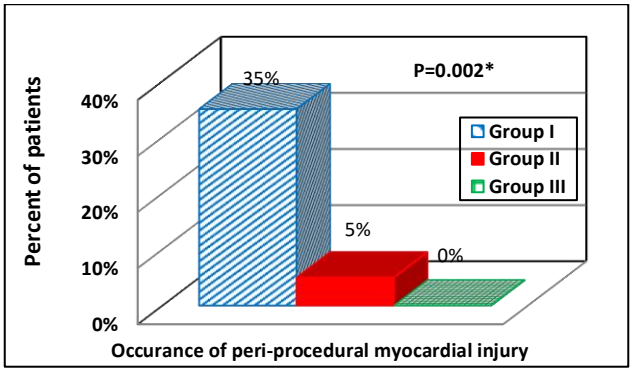

Figure 2: Occurrence of peri-procedural myocardial injury among studied groups

*Statistically significant difference among studied groups

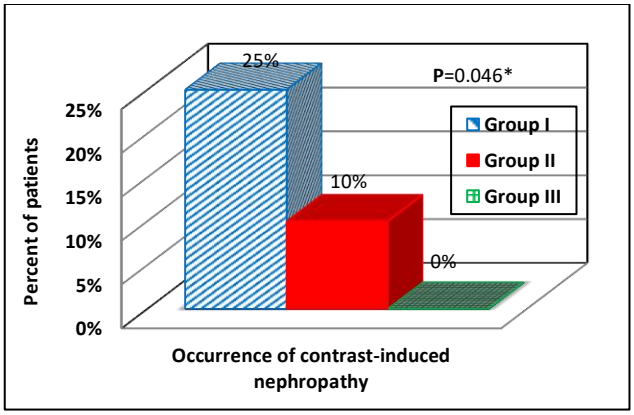

Figure 3: Occurrence of contrast-induced nephropathy among the three groups

*Statistically significant difference among studied groups

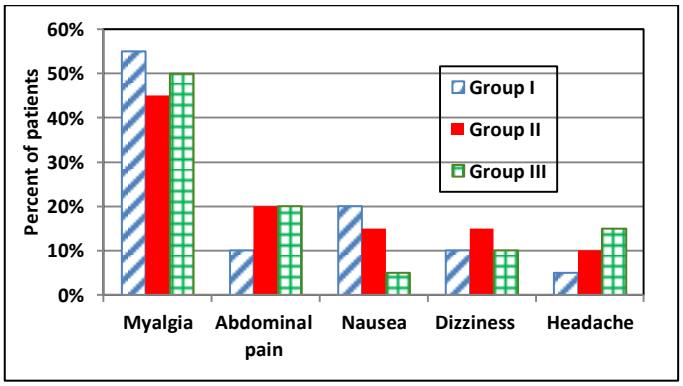

Figure 4: Reported side effects of atorvastatin among studied groups after three months follow-up post-procedure

Table 1: Percutaneous coronary intervention and cardiac troponin I data among studied groups

Variable	Group I (n=20)	Group II (n=20)	Group III (n=20)	P Value
Number of diseased vessels				0.911
Single vessel	4 (20)	6 (30)	5 (25)	
Two vessels	12 (60)	9 (45)	10 (50)	
Three vessels	4 (20)	5 (25)	5 (25)	
Culprit vessel				0.854
LAD	4 (20)	5 (25)	4 (20)	
RCA	2 (10)	2 (10)	1 (5)	
LCx	1 (5)	0 (0)	0 (0)	
LAD, LCx	3 (15)	4 (20)	3 (15)	
LAD, RCA	7 (35)	6 (30)	6 (30)	
RCA, LCx	0 (0)	0 (0)	2 (10)	
LAD, LCx, RCA	3 (15)	3 (15)	4 (20)	
Percutaneous coronary intervention data				
Number of stent	2.35± 0.875	2.10±0.968	2.35±0.875	0.605
Stent length	50.85±25.11	55.337±26.999	60.10±30.201	0.571
Stent diameter	3.02±0.371	2.984±0.31	3.155±0.231	0.193
Direct stenting	15 (75)	12 (60)	16 (80)	0.344
Pre-dilatation	10 (50)	13 (65)	9 (45)	0.419
Post-dilatation	12 (60)	13 (65)	15 (75)	0.592
Dye amount (CC)	237.50±88.667	230±83.351	242.5±87.772	0.900
Bar metal stent	12 (60)	12 (60)	15 (75)	0.517
Drug eluting stent	18 (80)	17 (75)	17 (75)	0.866
Ischemic symptoms	5 (25)	0 (0)	1 (5)	0.020*
New ECG changes				0.038*
° **Transient ST elevation**	5 (25)	1 (5)	0 (0)	
° **ST elevation**	1 (5)	0 (0)	0 (0)	
Serum level of cardiac troponin I pre-PCI, six hours and 12 hours post-PCI				
cTnI level pre-PCI	0.053±0.033	0.049±0.021	0.087±0.171	0.442
cTnI 6 hr post-PCI	1.275±0.767	0.677±0.502	0.424±0.372	0.000*
cTnI 12 hr post-PCI	2.615±1.747	1.559±0.821	1.149±0.503	0.001*

Values presented as n (%) or mean ± SD. **LAD,** left anterior descending artery; **RCA,** right coronary artery; **LCx,** left circumflex artery; **PCI**, percutaneous coronary intervention; **cTnI**, cardiac troponin I.; *Statistically significant difference among studied groups

CIN

There were no statistically significant differences among studied groups in term of pre-procedure SCr (P= 0.330), BUN (P=0.078), GFR (P=0.902) and similarly, post-procedure SCr (P=0.536). CIN occurred in seven patients (11.7 %) and no one underwent dialysis. Figure 3 showed that the number of patients developed CIN was 5(25%) in group I, 2(10%) in group II, 0(0%) in group III, that was statistically significant different among the three studied groups (P=0.046). Compared with group I, the proportion of patients with post-procedural CIN was significantly lower in only high load group (P=0.047). In addition, there was a significant positive correlation between dye amount (CC) and occurrence of CIN (r=0.272, P=0.018).

Clinical outcomes

MACE at 30-day post-PCI was 1(5%) in group I, 0(0%) in group II, and III. In addition, MACE at three months' post-PCI was 3(15%) in group I, 1(5%) in group II, 0(0%) in group III. The rate of cumulative MACE at 30 days and three months weren't statistically significant different among studied groups.

Safety outcome

Side effects of atorvastatin weren't statistically significant different and were relatively frequent among the studied population Figure 4. Similarly, there were no statistically significant differences among studied groups in pre-procedure and post-procedure ALT. In addition, there was no evidence of significant increase in (ALT level >3xULN) three months after procedure.

There were no statistically significant differences among studied groups in term of pre-procedure lipid profile. However, post-procedure TC and LDL were statistically higher in group III compared with group I, II (P= 0.001; 0.000respectively).

DISCUSSION

Periprocedural myocardial injury (PMI) occurs in 10–40% of CSA cases and is often characterized by a slight increase of cardiac markers after PCI, sometimes without symptoms, electrocardiographic changes or impairment of cardiac function. PMI may result from thrombosis, dissection, side branches occlusion, no-reflow phenomena, and distal microembolization of plaque components and enhanced inflammatory state. The cardioprotective effect of statin appeared to be greater and faster than that expected from lipid-lowering effect. It may be attributed to its pleiotropic effects (modulation of coronary endothelial function through a rapid improvement in vasoreactivity, increased nitric oxide bioavailability, anti-inflammatory, immuno-modulatory properties, anti-thrombotic activity and anti-oxidant effects). [32] Therefore, in our study low and high loading doses significantly reduced vascular injury and cardiac biomarkers release. In addition, we identified that the number of stent implantation was an independent predictor of PMI as the vascular injury increased by increasing number stents.

In accordance with our study results, the cardio protective efficacy of different pre-procedural atorvastatin loading doses was evaluated by Sun Y, *et al.* Eighty Non–ST-segment elevation acute coronary syndromes (NSTE-ACS) patients were randomized into standard therapy group, low load group (80 mg), mid load group (80 mg plus 40 mg) and high load group (80 mg plus 60 mg). All patients received 40 mg/day one month thereafter. They found that short-term pre-procedural loading doses were well tolerated and could significantly reduce the occurrence of PMI (P<0.007). The beneficial effects augmented with increasing dose and frequency of statin loading. This loading treatment was concomitant with relatively mild and tolerable adverse reactions.[26]

In agreement with our study, Di Sciascio G, et al., in ARMYDA RECAPTURE trial studied patients on statin therapy with stable angina or NSTE-ACS. They found that reloading with high dose atorvastatin (80 mg plus 40 mg) significantly reduce PMI (as shown from lowering CK-MB and cTnI levels, P = 0.017 & P=0.021 respectively).[28]

Different studies[18, 21] performed a head-to-head comparison of the potential cardioprotective effect between various lipid lowering strategies in patients who underwent coronary intervention..In addition, in ROMA II trial, Sardella G, *et al.,*[18] found that statin high loading dose improved procedural outcomes in elective patients on chronic statin therapy. In addition, both atorvastatin and rosuvastatin showed similar beneficial effects on myocardial necrosis. Briguori *et al.,* [21] are performing an ongoing REMEDY trial on elective patients with stable CAD. They are evaluating the occurrence of PMI, CIN, and MACE among various lipid lowering strategies. This trial, when finished will add important information on the cardio protective effects of statins after PCI

In agreement with our results, Pasceri V, *et al.,* supported the cardio protective effect of pre-procedural short-term statin use (seven days) in statin naïve patients who underwent elective PCI.[20] Similarly, Kumar Saha, *et al.,*[22] and Briguori C, *et al.,*[33] found that peri-procedural MI significantly reduced by using a single high loading dose (80 mg) of before PCI compared with control group. Similar findings were observed using pre-procedural rosuvastatin single high loading dose, by Sardella G, *et al.,*[17](ROMA trial) and Cay S, *et al,*[34]on statin-naive patients with stable angina underwent elective PCI, and by Yun KH, *et al.,*[35]on ACS patients underwent urgent PCI.

Opposing to our study, Gordin J, *et al,* [24] assessed 1482 patients who underwent urgent or elective PCI. They found that long-term statin therapy (≥ seven days) didn't decrease the occurrence of PMI in elective PCI. But, in unstable angina patients may be useful, particularly at a high dose. Consequently, these different findings from our study results can be explained in the light of different protocols of treatment.

Post-procedural CIN is a recognized complication in patients with normal baseline serum creatinine (SCr) levels or with pre-existing chronic renal failure and result in 11% of hospital acquired acute kidney injury which is the third leading cause of acute tubular necrosis. However, CIN pathophysiology is not completely elucidated. Some studies have suggested that oxidative stress, inflammation, reduction in renal blood flow and direct tubular cell damage resulted from contrast media administration might play important roles in kidney injury.[10, 12]Statins reduce both local and systemic inflammation in the kidney. In addition, they reduce the receptor-mediated endocytosis in proximal tubule cells and consequently the tubule reabsorption of proteins.

This process of protein reabsorption is locally pro-inflammatory and contributed to tubulointerstitial fibrosis. Blocking protein reabsorption in the tubule cells and reducing protein trafficking across the proximal tubule cells might attenuate the inflammation, endothelial dysfunction and tubulointerstitial disease complicating by administration of iodinated contrast media.[6] In our study, the renoprotective effect was significantly higher with atorvastatin high loading dose. The increased amount of dye was found to be an independent predictor of CIN, as the amount of dye increased, more retained in the kidney leading to increase the incidence of CIN.

In agreement with our study, Zhou X, *et al.,* found that pre-procedural high dose atorvastatin was superior in reducing CIN than low dose atorvastatin in 100 patients who underwent PCI.[36]

An updated network meta-analysis conducted by Fan J, *et al.*,[37] included 9000 patients from 19 trials. In agreement with our study, they found that high pre-procedural statin use effectively reduce the incidence of CIN compared to a placebo or untreated group with a similar safety profile. In addition, there were no significant differences between atorvastatin, rosuvastatin or simvastatin.

In agreement with our results, Acikel S, *et al*., [38] found that both short-term atorvastatin and chronic statin therapy were similar in protecting against CIN development after elective PCI. Furthermore, Zhao J, *et al.,* [39] performed head-to-head comparison of the potential renoprotective effect between various lipid lowering strategies on AMI patients who underwent primary PCI. They found that the renoprotective effect, which is a class specific and not restricted to an individual statin, significantly reduce the incidence CIN (P<0.01) compared with those who didn't receive statin.

In our study, 30 days and three months follow-up of MACE were similar among the studied groups. MACE may be affected more by chronic long-term statin therapy which was the same among studied groups.

In accordance with our study results, Jang Y, *et al,*[40] found that the use of atorvastatin loading doses (80 mg plus 40 mg before PCI) in statin naïve patients with NSTE-ACS scheduled for PCI didn't significantly lower MACE at 30 days' follow-up after PCI compared with standard treatment.

Opposing to our study results, Di Sciascio G, et al., [28] found that pre-procedural reloading with high dose atorvastatin (80 mg plus 40 mg) significantly reduce MACE (P=0.037).

Study limitations/Recommendations

This study was self-funded and the small sample size was the main study limitation, but we considered this study as a pilot one providing preliminary evidence that pre-procedural high loading dose of statin may decrease the incidence of both PMI and CIN. Large-scale trials are needed to confirm the clinical efficacy of this approach. The clinical follow-up of MACE needs further evaluation at 6 and 12 months' periods. We suggest performing future meta-analysis study in order to reach unanimous & clinically relevant conclusion.

CONCLUSION

Our study revealed that the use of pre-procedural high loading dose atorvastatin in patients with chronic stable angina undergoing elective PCI may leads to reduce the incidence of both PMI and CIN compared with standard treatment. In addition, drug safety of high loading dose seems to be the same as standard treatment.

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Compliance with ethical standards

Ethical Approval

All procedures performed in this study involving human participants were approved and in accordance with the ethical standards of ethical committee at College of Pharmacy, Tanta University; and Tanta University Hospital Institutional Review Board research committee. The study was conducted in conformity with the standards of Good Clinical Practices and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Eligible patients were informed of the study's purposes and of anticipated side effects that recipients might experience. A signed informed consent was obtained from all study patients.

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