Original Article

Statin Reload before Off-pump Coronary Artery Bypass Graft: Effect on Biomarker Release Kinetics

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Abstract

Objectives: Statins confer protection from ischemia/reperfusion through various pathways including pleiotropic mechanisms. Following chronic administration, activation of intrinsic cellular mechanisms causes attenuation of these pleiotropic effects. **Methods:** Since coronary artery bypass surgery (CABG) represents a reversible ischemia-reperfusion sequence, we assessed if statin reload is effective in patients undergoing off-pump CABG (n = 100) in limiting myocardial injury. Patients received loading dose of rosuvastatin (40 mg initiated 7 days before surgery) while nonloaded patients continued whatever statin dose they were receiving and served as controls. Cardiac biomarkers (Troponin-I, creatine kinase muscle/brain [CK-MB], and B-type natriuretic peptide [BNP]) were measured at 8, 24, and 48 h postoperatively. The primary end-point was the extent of perioperative myocardial injury (area under the curve [AUC]: AUC of each biomarker). **Results:** Despite similar baseline levels, all biomarkers at 8, 24, and 48 h were significantly lower in the loaded group. The AUC for each biomarker was also significantly lower in the loaded group (cTnI 37.96 vs. 70.12 ng. hr/ml, CK-MB 229.64 vs. 347.04 ng. hr/ml, and BNP 5257.56 vs. 15606.68 pg. hr/ml, all $P < 0.001$). Delta cTnI (change from baseline to peak level) (1.00 ± 1.34 vs. 2.25 ± 2.59), delta CK-MB (4.54 ± 5.89 vs. 10.68 ± 9.95), and delta BNP (120.41 ± 172.48 vs. 449.23 ± 790.95) all $P < 0.001$ were also significantly lower in the loaded group. Those loaded with rosuvastatin had lower inotrope duration (22.9 ± 23.33 vs. 31.26 ± 25.39 h, $P = 0.04$) and ventilator support time (16.94 ± 6.78 vs. 23.8 ± 20.53 h, $P = 0.03$). **Conclusion:** In patients undergoing off-pump CABG, statin reload can "recapture" cardioprotection in patients already on statins with favorable effect on release kinetics of biomarkers and postoperative outcomes.

Keywords: *Biomarkers, coronary artery bypass, off-pump, statin reload*

Introduction

The current European Society of Cardiology, American College of Cardiology, and American Heart Association guidelines recommend statins for all patients undergoing coronary artery bypass graft (CABG) unless contraindicated and early reinitiation postoperatively.[1,2] Lower incidence of postoperative atrial fibrillation (AF), stroke, shortened intensive care unit (ICU), in-hospital stay as well as lower mortality is reported in cardiac surgery patients receiving statin therapy when compared with controls.[1,3-5] Apart from plaque stabilization, statins have pleiotropic effects such as anti-inflammatory actions, reduction of oxidative stress, anti-platelet effects, and vasorelaxation due to actions on endothelial nitric oxide. However, despite evidence related to benefits of pre- and peri-operative statins in patients undergoing cardiac surgical procedures, other studies have failed to demonstrate consistent benefit on myocardial infarction (MI), strokes, or mortality.[6-8]

The concept of statin reload

Pleiotropic effects of statins that offer protection from ischemia/reperfusion are mediated through acute activation of the PI3K/Akt pathway that promotes cell survival and has antiapoptotic effects.[9] When this pathway is chronically activated, intrinsic cellular mechanisms (phosphatase and tensin homolog deleted on chromosome ten) inactivate PI3K, leading to attenuation of these pleiotropic effects. Evidence from animal models suggested that statin reload given just before ischemia/reperfusion restores this protection by improving myocardial ischemia-reperfusion injury.[10] An extra dose of statin recaptures or potentiates the

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favorable effects of statins on infarct size when compared with chronic statin therapy alone and has formed the basis of statin reload in patients undergoing percutaneous coronary intervention (PCI). Improved clinical outcomes in patients undergoing PCI have not only been reported in statin-naïve patients but also in patients on chronic statin therapy following an acute statin reload.[11-13]

Since patients undergoing cardiac surgery are also at significant risk for postoperative major adverse cardiovascular events and CABG represents a reversible ischemia/reperfusion sequence, it is important to study if statin reload is potentially effective in these patients. Data on statin loading in patients on chronic statin therapy, especially in the setting of off-pump CABG (OPCAB, which is known to avoid the systemic inflammatory response that may result from cardiopulmonary bypass) are scant.[14,15] Due to differences among ethnic populations in safety, efficacy, and response to statins, it is important to assess if statin reload is applicable to Asian Indians, who have a high prevalence of CAD.

The present study, therefore, assessed if high-dose statin therapy given shortly before OPCAB graft (OPCABG) can "recapture" cardioprotection in patients already on chronic statin therapy, with focus on release kinetics of various biomarkers and postoperative outcomes.

Methods

Patients scheduled to undergo OPCABG (n = 100 on chronic, i.e., >30 days of statin therapy) were included in the study; all study participants gave informed consent and the study conformed to the institutional ethical guidelines. Patients with renal failure creatinine >3 mg/active liver disease or increased liver enzyme levels, left ventricular ejection fraction (LVEF) <35%, history of muscle disease, nonconsenting patients, other comorbid illnesses (previous cerebrovascular stroke with a significant residual neurological deficit and cardiogenic shock) and known intolerance to statins were excluded from the study. Patients' inclusion was irrespective of type and doses of chronic statin therapy. Eligible patients received loading dose of rosuvastatin (40 mg once a day initiated 7 days before surgery, group RL) while the nonloaded patients continued whatever statin dose they were receiving and served as controls (nonloaded, group NL). Patients were assigned to the study or control arm in a 1:1 ratio using a computer-generated sequence. The assigned therapy was fully blinded; surgeons and investigators performing postoperative assessment were not aware of the assignment. Levels of the biomarkers (Troponin I, creatine kinase muscle/brain [CK-MB] and B-type natriuretic peptide [BNP]) were measured 24 h before surgery and serially at 6, 24, and 48 h, after surgery. The measurements were carried out by fluorescence immunoassay using a commercially available kit (Alere Triage Cardio3 Panel; Alere San Diego, Inc., San Diego, CA, USA). Normal limits of CK-MB and troponin T were defined as ≤5 ng/mL and <0.1 μg/L, respectively.

Coronary artery bypass graft procedure

Patients underwent OPCAB using standard techniques with an octopus tissue stabilization system (Medtronic, Inc., Minneapolis, MN, USA) and intracoronary shunts (Flo-Thru Intraluminal Shunt; Synovis Life Technologies, Inc., St. Paul, MN, USA). The anastomosis was performed using 8/0 Prolene (Ethicon, Somerville, NJ, USA) for arterial grafts and 7/0 Prolene for venous grafts, according to the standard protocol at our institute. All patients received at least one left internal mammary artery graft to the left anterior descending artery; radial artery and/or saphenous vein grafts were used for other lesions. Stabilization of the heart was achieved with pericardial hitch stitches and a stabilizer, as we described previously.

Statistical analysis

The primary end-point was the extent of perioperative myocardial injury assessed according to the area under the curve (AUC) of Troponin-I and CK-MB release as derived from blood samples obtained 8, 24, and 48 h after surgery. Secondary end-points included the prevalence of (a) mean delta change in biomarker (change from baseline to peak), (b) >10 times rise in troponin I and CK-MB, (c) >5 times rise in troponin-I and CK-MB, and (c and d) 30-day incidence of major adverse cardiac events (MACE) including cardiac death, fatal or nonfatal MI, and stroke or repeat revascularization by percutaneous intervention or redo bypass surgery. Approximately 50%–60% of patients undergoing CABG can have high postoperative cardiac enzyme levels[16] do you have a reference for this, please?; hypothesizing that ~35% of patients may have cardiac biomarker elevation following OPCABG and statin reload will be expected to produce a 70% reduction in events with statin reload (based on Atorvastatin for Reduction of Myocardial Damage during Angioplasty [ARMYDA] and ARMYDA-acute coronary syndrome (ARMYDA-ACS) trials,[15,17] a total sample size of 90 patients (45 in each group) would provide 80% power to detect difference with an alpha level of 0.05.

All data were analyzed using SPSS version 20 statistical software (SPSS, Inc., Chicago, IL, USA). All data are expressed as mean ± standard deviation. Student's t-test was used to compare means between groups, and the Chi-square test was used to compare proportions between groups. The Pearson correlation was used to analyze the correlations between BNP at baseline and each postoperative time point with the other variables included in the study. Logistic regression analysis was used to assess the various factors predicting ventilation time, pleural drainage time, inotropic support time, ICU stay, and total hospital stay. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

Of the 118 patients, initially evaluated, five were excluded due to baseline serum creatinine >3 mg/dl, 4 due to altered LFT's, 4 due to low LVEF, and 5 due to concomitant valve procedures (3 MVR, 2 AVR). The mean age of the study population (n = 100) was 60.6 ± 7.41 years (38–76) and 86% were males. Diabetes was present in 39%, hypertension in 31%, and history of smoking in 30%. Clinical presentation included chronic stable angina in 54% and ACS in 46%, while the mean EuroScore was 2.3 ± 1.41.

Prior statin doses

Out of 50 patients in the rosuvastatin loaded group, 36 were already on atorvastatin, while in the control group 35 were on atorvastatin. Rosuvastatin was being taken by 14 and 15, respectively [doses mentioned in Table 1].

The demographics and baseline characteristics of the rosuvastatin group (Group RL, n = 50) and control group (Group NL, n = 50) are summarized in Table 1. There was no significant difference in baseline characteristics in terms of age, gender distribution, body mass index, recent history of ACS/chronic stable angina, duration of symptoms, prevalence of diabetes or hypertension, history of smoking, baseline LVEF, biochemical profile, and mean EuroScore. While overall LVEF (on echocardiography) was normal and similar in both groups, impaired LV function (LVEF <50%) was noted in 17/50 (34%) in groups RL and 15/50 (30%) and NL, respectively, P = 0.49.

Table 1: Baseline characteristics of patients

Parameter	Loaded group (n=50)	Control group (n=50)	P
Male	43	43	
Age (years)	59.78±6.90	61.60±7.85	0.3
BMI (kg/m^2)	27.13±1.46	27.29±1.55	0.7
ACS	24	22	0.8
Stable angina	26	28	0.8
Baseline statin dose			
Atorvastatin 10	5	7	
Atorvastatin 20	18	16	
Atorvastatin 40	7	5	
Atorvastatin 80	6	7	
Rosuvastatin 5	6	7	
Rosuvastatin 10	8	8	
Rosuvastatin 20	0	0	
Duration of symptoms (months)	20.74±24.57	26.94±18.65	0.159
Diabetes	20	19	1.0
Hypertension	16	15	1.0
Smoking	26	28	0.84
Hb (g/dl)	13.18±0.69	12.79±0.90	0.01
Serum creatinine (mg/dl)	0.99±0.22	1.04±0.22	0.234
Serum cholesterol (mg/dl)	129.6±42.86	132.64±49.16	0.742
Serum TG (mg/dl)	143.70±67.08	118.8±28.92	0.02
Serum LDL (mg/dl)	67.53±33.05	73.79±67.08	0.42
Serum HDL (mg/dl)	36.38±9.48	40.12±11.19	0.08
Serum VLDL (mg/dl)	28.82±13.26	24.18±6.09	0.03
SBP (mmHg)	123.82±12.81	129.48±10.45	0.02
DBP (mmHg)	78.44±7.254	80.36±5.98	0.15
LVEF (%)	54.36±10.99	55.88±10.87	0.49
EuroScore	2.1±1.22	2.5±1.60	0.89

BMI: *Body mass index*, ACS: Acute coronary syndromes, LVEF: Left ventricular ejection fraction, TG: *Triglycerides*, LDL: Low-density lipoprotein, VLDL: Very LDL, HDL: High-density lipoprotein, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, Hb: *Hemoglobin*

Biomarker change following off-pump coronary artery bypass graft

Baseline values for cardiac biomarkers are depicted in Table 2. There was no significant difference in the baseline troponin-I values (0.70 ± 2.63 vs. 0.57 ± 0.64 ng/ml, P = 0.71), baseline CK-MB values (4.29 ± 11.98 vs. 4.39 ± 7.7 ng/ml, P = 0.95), and baseline BNP values (125.57 ± 110.08 vs. 102.39 ± 63.6 pg/ml, P = 0.2) in NL versus RL groups, respectively. Although all three cardiac biomarkers increased within 8 h following OPCABG in both groups and peaked at 24–48 h, the levels at all times of assessment (8 h, 24 h, and 48 h) were significantly higher in the NL group [Table 2 and Figures 1-3].

The defined primary end-point of the study (AUC of postprocedural total cTnI/CK-MB and BNP release in each group) was calculated and found to be significantly affected by the study drug. The AUC of cTnI, CK-MB, and BNP was significantly higher in the control group than in the not loaded group (Troponin 37.96 vs. 70.12 ng. hr/ml, CK-MB 229.64 ng. hr/ml vs. 347.04 ng/ml, and BNP 5257.56 vs. 15606.68 pg. hr/ml, all P < 0.001) [Figures 4-6].

The mean delta troponin-I (change from baseline to peak level) was significantly lower in the RL group (1.00 ± 1.34 vs. 2.25 ± 2.59 in control group, P = 0.003). The corresponding values for delta CK-MB (4.54 ± 5.89 vs. 10.68 ± 9.95, P < 0.001) and delta BNP (120.41 ± 172.48 vs. 449.23 ± 790.95, P = 0.006) were also significantly lower in the loaded group as compared to controls.

Periprocedural post-CABG MI (as defined by rise in troponin-I >10 times baseline you have later described perioperative MI as Trop I >5 or 10 times baseline……) developed in 5 (1% incorrect figure?) in the loaded arm versus 7 (1.4% incorrect figure?) in the control arm. Elevations of troponin-I >5 and <10 times baseline developed in 7 (1.4% incorrect figure?) versus 17 (34%) in control arm, P < 0.001. None of the patients developed new electrocardiographic changes or echocardiographic signs suggestive of a new postoperative MI.

Table 2: Parameters in controls and loaded group

	Loaded group	Control group	*P*
Pre-LVEF	54.36±10.93	55.88±10.87	0.49
Post-LVEF	55.54±10.93	57.3±10.357	0.48
Inotrope time (h)	22.9±23.33	31.26±25.39	0.05
Ventilator time (h)	16.94±6.78	23.8±20.53	0.03
ICU stay (days)	3.14±0.12	3.18±0.18	0.58
Hospital stay (days)	5.24±0.18	5.86±0.24	0.69
Troponin baseline	0.57±0.64	0.70±2.63	0.714
Troponin (8 h)	0.91±1.19	1.74±2.19	0.02
Troponin (24 h)	1.01±1.31	1.72±1.47	0.01
Troponin (48 h)	1.09±1.07	2.13±3.40	0.04
Baseline CK-MB	4.39±7.7	4.29±11.98	0.95
CK-MB (8 h)	5.19±6.27	9.9±14.61	0.04
CK-MB (24 h)	5.89±3.59	8.87±7.9	0.01
CK-MB (48 h)	6.91±7.15	10.05±5.79	0.02
Baseline BNP	102.39±63.6	125.57±110.08	0.2
BNP (8 h)	109.9±120.71	250.7±306.18	0.003
BNP (24 h)	141.83±154.14	477.29±752.39	0.003
BNP (48 h)	155.8±174.29	443.82±509.97	<0.001
Δ Trop (peak-baseline)	1.00±1.34	2.25±2.59	0.003
Δ CK-MB (peak-baseline)	4.54±5.89	10.68±9.95	<0.001
Δ BNP (peak-baseline)	120.41±172.48	449.23±790.95	0.006
48 h serum creatinine	1.25±0.14	1.26±0.09	0.851

LVEF: Left ventricular ejection fraction, ICU: Intensive care unit, CK-MB: Creatine kinase-MB, BNP: Brain natriuretic peptide

Operative variables

Various operative variables were analyzed in the two groups [Table 2]. The inotrope duration (22.9 ± 23.33 vs. 31.26 ± 25.39 h, $P = 0.04$) and ventilator support time (16.94 ± 6.78 vs. 23.8 ± 20.53 h, $P = 0.03$) were significantly lesser in RL group as compared to the NL arm. There was no significant difference in postsurgery LVEF (55.54 ± 10.93 vs. 57.3 ± 10.35%, $P = 0.48$), mean ICU (3.14 ± 0.12 vs. 3.18 ± 0.18 days, $P = 0.58$), and mean hospital stay (5.24 ± 0.18 vs. 5.86 ± 0.24 days, $P = 0.69$) in the loaded versus control groups, respectively.

In-hospital course

One patient died in each group (1 in the RL group due to progressive pump failure on the 8th postoperative day and 1 in the NL group due renal failure and acute tubular necrosis on the 6th day following surgery). Postoperative AF occurred in 4 patients (8%) in the RL group and in 14 patients (28%) in the NL group, $P = 0.001$. All patients reverted to sinus rhythm with pharmacological management.

Follow-up

No additional death or MI or repeat revascularization was observed in either of the two groups at 30 days. There were three readmissions (1 each in RL and NL group due to chest infection and 1 in the NL group due to accelerated hypertension, all managed conservatively with satisfactory recovery).

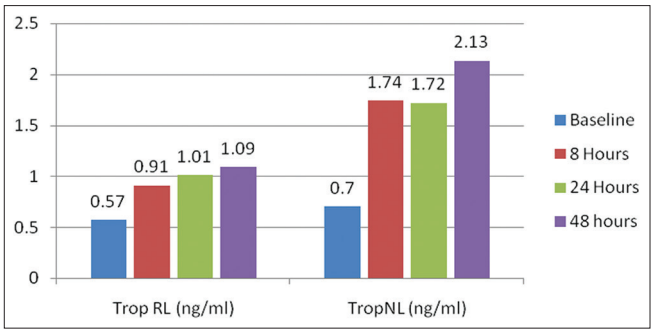

Figure 1: Serial troponin in loaded and control groups

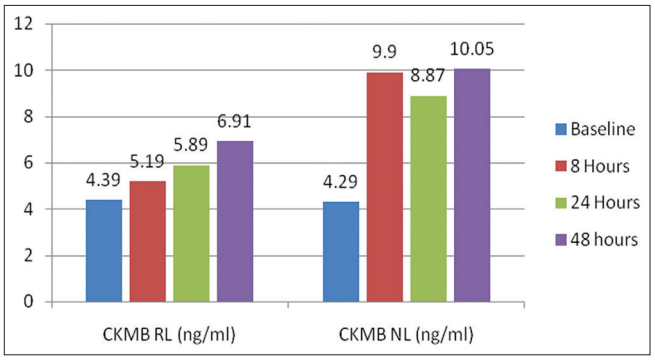

Figure 2: Serial creatine kinase muscle/brain in loaded and control groups

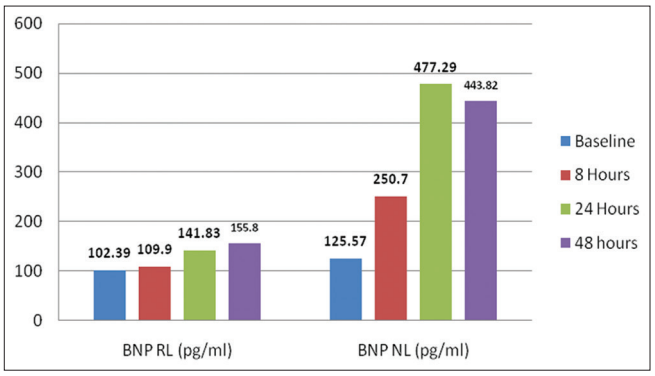

Figure 3: Serial B-type natriuretic peptide in loaded and control groups

Discussion

Among 100 patients of CAD on chronic statin therapy undergoing OPCABG, rosuvastatin reload (40 mg initiated 7 days before surgery) resulted in significantly lower levels of all three cardiac biomarkers (troponin-I, CK-MB, and BNP) at 8, 24, and 48 h following surgery. The absolute change in all biomarkers (peak to baseline) was also significantly lower in those receiving loading dose of rosuvastatin. Periprocedural MI (troponin-I >10 times normal) and postoperative AF were more frequently seen in the control group. High-dose statin (40 mg rosuvastatin 7 days before surgery) was well tolerated and did not lead to any significant change in postprocedure creatinine spell check please levels.

Although the occurrence of major cardiac events was not significantly different between the two groups at 30 days,

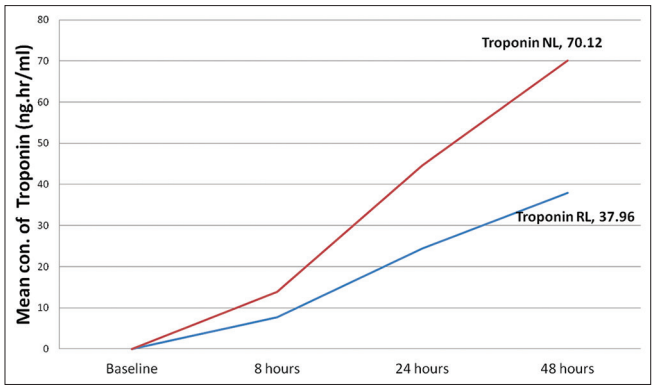

Figure 4: Area under the curve for mean troponin (ng. h/ml) in loaded and control groups

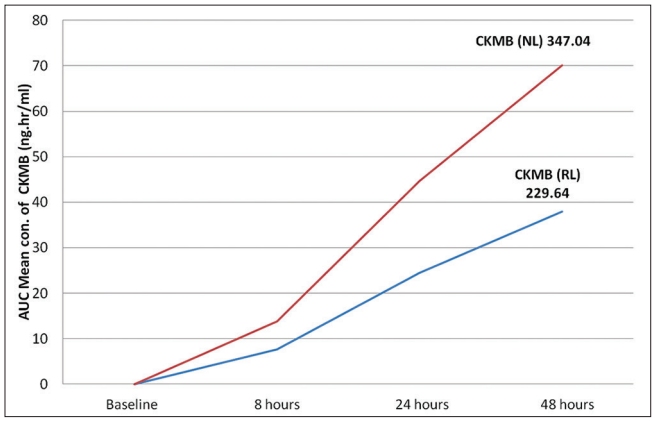

Figure 5: Area under the curve for mean creatine kinase muscle/brain (ng. h/ml) in loaded and control groups

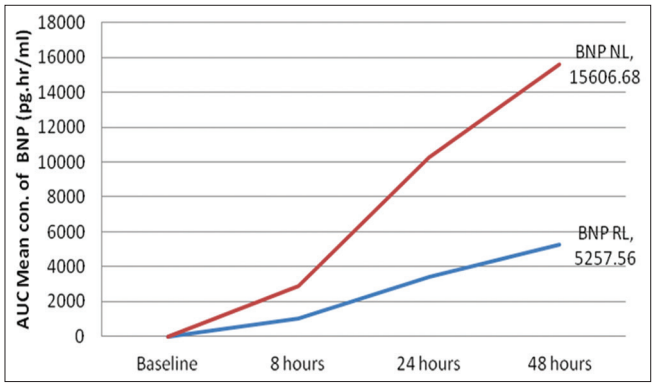

Figure 6: Area under the curve for mean B-type Natriuretic Peptide (pg. h/ml) in loaded and control groups

our study suggests that high-dose rosuvastatin loading before OPCAB significantly reduces myocardial damage as assessed on the basis of increase in biochemical markers. It is well recognized that though global cardiac function may remain unaltered, myocardial damage as indicated by biomarker release is a sensitive predictor of cardiovascular events, both in the short term and long term.

Routine preoperative treatment with statins has been assessed in patients scheduled for cardiac surgery, while some studies have reported a decrease in short-term mortality and MACE including MI, AF, stroke, and renal failure in patients receiving preoperative statins, others have failed to demonstrate a beneficial effect.[5-8] Previous studies of periprocedural high-dose statins in patients undergoing CABG have reported benefit. In a retrospective cohort analysis of high-dose statins in patients undergoing CABG, Curtis *et al*. reported that preoperative statin dose of more than 20 mg atorvastatin or equivalent continued till surgery significantly decreased short-term postoperative mortality.[17] Ouattara *et al*. also observed that high-dose statin therapy significantly reduced incidence of adverse in-hospital cardiovascular outcomes following CABG as compared to those who received low-dose statin therapy or no statins.[18]

Readministration of a loading dose of statin in patients already taking statins has the potential to "recapture" the beneficial effects and reduction in adverse clinical outcomes, a hypothesis which was favorably tested in the ARMYDA-RECAPTURE trial of patients undergoing PCI.[13] These benefits are primarily driven by reduction in procedural myocardial injury and periprocedural MI as evidenced by lower levels of cardiac enzymes post-PCI. The mechanisms involved are probably related to the pleiotropic effects of statins including improved endothelial function, reduced inflammation and platelet aggregability, anti-platelet, and decreased thrombotic diathesis.

Studies on statin reload among patients undergoing CABG have used different types of statins, varying doses and dosing schedules with conflicting results. The ARMYDA-3 trial in which patients received atorvastatin 40 mg 7 days before CABG did not find any favorable effect on mortality, although there was a significant reduction in postoperative AF and hospital stay in statin-treated patients.[19] In contrast to our study, all patients in the ARMYDA-3 were statin-naïve and serial biomarker assay was not performed. Reduction in inflammatory response and inducible nitric oxide synthase expression has been demonstrated with the administration of pravastatin (40–80 mg) 2 h before anesthetic induction for on-pump CABG without any effect on biomarker levels.[20] Although some studies have serially assessed biomarker levels as performed in the current study, patient populations, dosing schedules, and outcomes have varied**.** Mannacio *et al*. also reported a benefit with rosuvastatin initiated 7 days prior; however, a dose of 20 mg was used and all patients underwent on-pump CABG.[16] Administration of rosuvastatin before OPCABG was reported to be associated with lower mean CK-MB and Troponin T levels by Youn *et al*.; however, the loading schedule was 40 mg 12 h before surgery and a 2nd 20 mg dose 2 h.[14] In the Statin Therapy in Cardiac Surgery (STICS) trial, Zheng *et al*. reported that perioperative statin therapy did not prevent postoperative AF and had no significant effect on troponin I release as assessed y AUC.[15] In contrast to the STICS study, we observed significant reduction in the extent of

perioperative myocardial injury as assessed by AUC of all three cardiac biomarkers. It is important to note that in the STICS study, any prescribed statin therapy was stopped, and patients were then randomly assigned to receive the study drug or placebo; moreover in ~60% of the patient's rosuvastatin was initiated near the time of surgery (<2 days before the day of surgery). Statins need time to exert their full pleiotropic effects (up to 7–14 days); hence, a sufficient duration of reload needs to be administered to elicit maximum benefits.

As previously reported, we also observed lesser AF burden in those loaded with statin as well as reduction in inotrope duration and ventilator support time; however, no significant reduction in ICU or hospital stay or 30-day mortality possibly because of less patient numbers and a short-term follow-up.

Conclusion

Our study strongly supports the idea that use of high dose of rosuvastatin given shortly before OPCABG can "recapture" cardioprotection in patients already on chronic statin therapy, with favorable effect on release kinetics of various biomarkers and postoperative outcomes. It not only attenuates biomarker release with lower AUC for all measured biomarkers but was also associated with reduced inotrope duration and ventilator support time in the postoperative phase. In patients on chronic statins, there is possible attenuation of the pleiotropic effect of statins that can be potentiated or recaptured by statin reload administered a short time before the surgery.

Limitations

Although we could demonstrate a benefit in the primary endpoint (AUC of the biomarkers), no difference in clinical events or mortality was demonstrable. This was because of the limited number of patients in our study along with an only 30-day outcome analysis. More studies with larger number of patients and longer-term follow-up shall address these issues. Although the pleiotropic benefits of statins appear to be class dependent, some differences might exist reflecting the different pharmacologic profiles of the drugs. Hence, further studies with different statins and using different dosing and timing schedules are important.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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