Effectiveness of Lower Range of High-intensity Statin Therapy in Lowering LDL-C among STEMI Patients

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ABSTRACT

Background: Lipid-lowering is an important intervention to reduce cardiovascular morbidity and mortality after ST-Elevation myocardial infarction. This study aimed to assess the proportion of such patients achieving guideline-directed therapeutic low-density lipoprotein cholesterol targets while on lower-range high-intensity statin treatment.

Methods: This is a cross-sectional study conducted in Shahid Gangalal National Heart Centre, a tertiary cardiac center in Kathmandu, Nepal, from November 2021 to July 2022 among admitted acute ST-Elevation myocardial infarction patients who were prescribed a lower range of high-intensity statin therapy, Atorvastatin 40mg and Rosuvastatin 20 mg. Clinical characteristics were collected, including lipid parameters at baseline during admission and three months after the treatment. The proportion attaining the guideline-recommended levels was calculated and compared between each statin group.

Results: A total of 240 patients were included in this study. The target low-density lipoprotein cholesterol level of less than 1.4mmol/L was noted only in 16.3% and the target reduction by ≥50% from baseline only in 7.1%. Just 3.3 % achieved a target of <1.4 mmol/L and ≥50% reduction from baseline. However, 40.8% of the participants in our study met the 2012 European Society of Cardiology guidelines' target achievement of less than 1.8 mmol/L.

Conclusions: The overall proportion of patients attaining recommended low-density lipoprotein cholesterol levels after recent ST-Elevation myocardial infarction was low when patients were prescribed with a lower range of high-intensity statin, reflecting the need for rigorous follow up including monitoring of lipid levels and intensification of statin dose and type as recommended by international guidelines.

Keywords: Low-Density Lipoprotein Cholesterol; secondary prevention; statin; statin intensity; ST-Elevation myocardial infarction.

INTRODUCTION

Globally, South Asians have the highest burden of cardiovascular diseases.[1] ST-elevation myocardial infarction (STEMI) has the highest in-hospital mortality and increased risk of cardiovascular events.[2-4] High-intensity statin therapy (Atorvastatin 40mg/80mg and Rosuvastatin 20mg/40mg) is more effective than standard doses in reducing low-density lipoprotein cholesterol (LDL-C) and cardiovascular events after Acute Coronary Syndrome(ACS). [5-8] The current guidelines also recommend a lower range of high-intensity statin of 40mg Atorvastatin or 20 mg Rosuvastatin in secondary prevention of STEMI and are used.[9-10] There's a belief that these lower doses suffice for South Asians due to differences in body mass and side effects. However, research on their efficacy in this population is limited. This study aims to evaluate if STEMI patients at Shahid Gangalal National Heart Center (SGNHC) achieve LDL-C targets on lower-range high-dose statins after three months. Findings could influence treatment guidelines and improve outcomes for South Asian patients.

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METHODS

This study is a cross-sectional study conducted at Shahid Gangalal National Heart Centre, a tertiary cardiac center in Kathmandu, Nepal, from November 2021 to July 2022. The patients admitted to the inpatient department with the diagnosis of acute STEMI and who have been prescribed a lower range of high-intensity statin therapy that is Atorvastatin 40mg and Rosuvastatin 20 mg were enrolled in the study. One hundred and twenty-five patients were enrolled in both groups to estimate the proportion of target LDL-C achievement. A simple convenient, consecutive non-probability sampling technique was used for patient recruitment. Recruitment was stopped once the desired number of patients were enrolled in each group. Inclusion criteria included both sexes aged 18 years of age or older, hospitalized with a primary diagnosis of STEMI and lipid profile drawn within 24h after hospitalization who were prescribed a low-range high-intensity statin. Fasting LDL-C levels were assessed using the Friedewald formula. Exclusion criteria included patients who did not survive until hospital discharge or did not provide consent, patients with any cognitive impairment at discharge and Triglyceride level of more than 400mg/dl or 4.52mmol/L. The patients who succumbed to death on 3 months follow-up and also those who changed the dosage and type of statin that were prescribed during the follow-up period were excluded from the study.

The ethical approval for this study was obtained from the Institutional Review Committee of SGNHC (proposal approval number: 40-2021), and written informed consent was obtained from all the participants. All patients admitted with the diagnosis of acute STEMI fulfilling the inclusion criteria were enrolled. All the participants who gave consent were included in the study and were interviewed by trained research assistants. Baseline characteristics included age, sex, and cardiovascular disease (CVD) risk factors such as smoking, hypertension, diabetes mellitus, family history of coronary artery disease (CAD), history of CAD, and obesity. Data was collected with a face-to-face interview with patients at bedside and hospital records using a preformed structured questionnaire. Data collection at baseline was conducted during the admission on the type and dose of the statin used from patient interviews and medical records. All patients were invited to attend a visit at the study clinics at the end of the third month after discharge and repeat lipid profiles were obtained during the 3-month follow-up in the Out-Patient Department (OPD). Adherence to the prescribed statin and its dose was confirmed in the questionnaire during the follow-up after three months of treatment with statin.

STEMI was defined according to the standard guideline as "a clinical syndrome defined by characteristic symptoms of MI in association with persistent electrocardiographic (ECG) ST elevation and subsequent release of biomarkers of myocardial necrosis".[11]

Hypertension (HTN) was defined as a previously diagnosed case of HTN or chronic use of antihypertensive drugs.[12]

Diabetes Mellitus (DM) was defined as a patient previously diagnosed with DM or newly diagnosed DM or on oral hypoglycemic drugs or Insulin.[13]

Family History of CAD was defined as a history of premature coronary artery disease (< 55 years in first-degree male relatives and < 65 years in female relatives).[11]

Obesity was defined as BMI >25 as per the Western Pacific Regional Office of World Health Organization (WHO) definition for Asian people.[14]

Smoking was defined as "an adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes" as per the National Health Interview survey by the Centre for Disease Control (CDC) and Prevention.[15]

Physical inactivity was defined as any activity less than "at least 150 min of moderate-intensity physical activity per week".[16]

The outcome variables were the target achievement of LDL-C level in a three-month follow-up period and were categorized into four groups that included those achieving LDL-C less than 1.4mmol/L; less than 1.8mmol/L; a decline of LDL-C by more than or equal to 50% from baseline; and achieving both LDL-C target of less than 1.4mmol/L and decline of LDL-C by more than or equal to 50% from baseline. Less than 1.8mmol/L of LDL-C was measured to assess the target achievement of target LDL-C according to the 2012 ESC guidelines of STEMI.[17]

All data were entered into an electronic spreadsheet (Microsoft Excel, Redmond), and the statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20 (IBM Armonk, NY, USA). Categorical data were expressed as frequency and percentages. Continuous data were expressed as mean ± standard deviation (SD), while skewed data were expressed as the median and interquartile range (IQR). Results were analyzed using the chi-square test to compare the categorical variables. The odds ratio was calculated with a predetermined level of significance (0.05) and a confidence interval (CI) of 95%.

RESULTS

The flow chart of the selection of the study participants is shown in Figure 1. We selected a total of 250 patients admitted to the cardiac care unit of SGNHC during the study period. In each group, 125 patients were included. Out of these patients, four patients in each group had mortality during the follow-up period. One patient from the Rosuvastatin group was excluded due to a high Triglyceride level (more than 400mg/dl or 4.52mmol/L) resulting in an inappropriate calculation of LDL-C using the Friedewald formula. One patient in the Atorvastatin group was excluded due to a change in statin dosage after two months of treatment. A total of 240 patients were included in our analysis and the mean age was 58.53±11.9years with 178 (74.2%) male and 62 (25.8%) female.

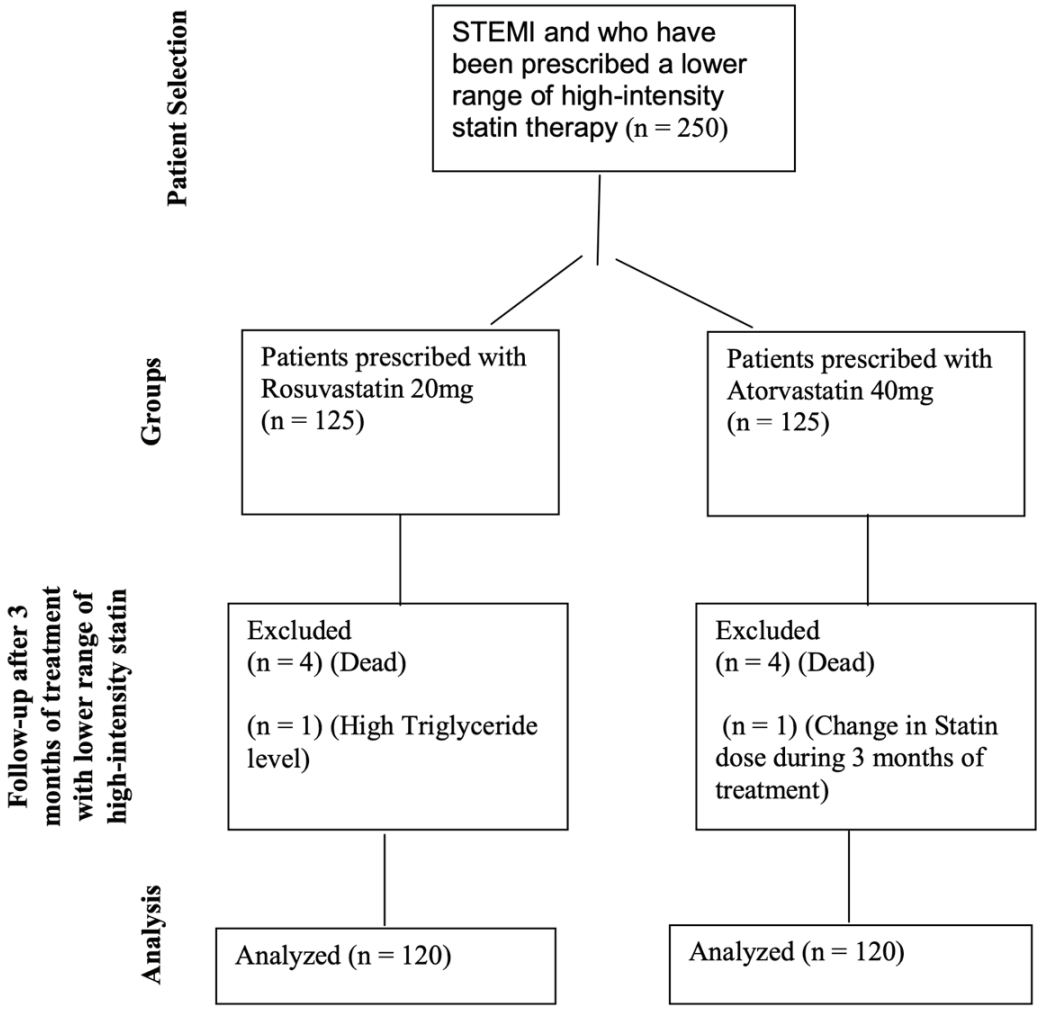

Figure 1. Selection of study participants.

The baseline characteristics of the patients enrolled in our study are presented in Table 1. There was no significant difference between age, gender, and type of MI between the Atorvastatin and Rosuvastatin groups. Among CVD risk factors, hypertension, current smoking status, past history of CAD and physical inactivity were not significantly different between the two groups. However, patients with diabetes mellitus were more in the Rosuvastatin group (p= 0.039) whereas patients with a family history of CAD (p= 0.030) and obesity were more in the atorvastatin group (p= 0.028). In addition, the baseline total cholesterol level, HDL and LDL-C levels were higher in the Rosuvastatin group compared to the Atorvastatin group.

Table 1. Baseline characteristics of the study population.

	Atorvastatin Group n (%)	**Rosuvastatin Group** n (%)	**N=240**
Characteristics			**P value**
Age (Mean ± Standard Deviation) in years	58.5±11.4	58.5±12.4	0.974
Male	92 (76.7)	86 (71.7)	0.395
Female	28 (23.3)	34 (28.3)	
CAD Risk Factors			
Hypertension	65 (54.2)	56 (46.7)	0.302
Diabetes Mellitus (DM)	31 (25.8)	**47 (39.2)**	**0.039**
Current Smoker	64 (53.3)	61 (50.8)	0.796
Family History of CAD	**5 (4.2)**	0 (0)	**0.030**
Past History of CAD	1 (0.8)	2 (1.7)	0.500
Physical Inactivity	7 (5.8)	4 (3.3)	0.539
Obesity	**24 (20.0)**	11(9.2)	**0.028**
Type of Myocardial Infarction			
Anterior Wall MI	29 (24.2)	34 (28.3)	0.734
Antero-septal Wall MI	11 (9.2)	13 (10.8)	
Extensive Anterior Wall MI	10 (8.3)	12 (10.0)	
High Lateral Wall MI	2 (1.7)	0 (0)	
Inferior Wall MI	43 (35.8)	38 (31.7)	
Inferior Posterior Wall MI	18 (15.0)	18 (15.0)	
Inferior Wall MI with RV Infarction	1 (0.8)	2 (1.7)	
Lateral Wall MI	6 (5.0)	3 (2.5)	
Baseline lipid parameters (Mean ± Standard Deviation)			
Total Cholesterol (TC) (mmol/L)	4.0±0.9	4.4±1.4	**0.021**
Low-Density Lipoprotein (LDL) (mmol/L)	2.4±0.9	2.7±1.2	**0.038**
Triglyceride (TG) (mmol/L)	1.6±0.9	1.6±1.2	**0.707**
High-Density Lipoprotein (HDL) (mmol/L)	1.0±0.3	1.1±0.4	**0.033**

Table 2 shows the change in lipid parameters after 3 months of treatment with the lower-range high-intensity statin. There was a decrease in total cholesterol and LDL levels and a significant increase in HDL levels after treatment with a statin (p= <0.001). However, there was a slight increase in Triglyceride levels after statin treatment in this study which was not significant (p= 0.300).

Table 2. Change in various lipid parameters before and after the treatment with statin.

	Before Treatment N=240			After Treatment N=240			Change in Parameters*	
	Mean ±SD (mmol/L)	Min	Max	Mean ± SD (mmol/L)	Min	Max	Mean ± SD (mmol/L)	p-value
Total Cholesterol (TC) (mmol/L)	4.2±1.2	1.5	13.7	3.3±0.8	1.3	7.6	0.9±0.9	<0.001
Triglyceride (TG) (mmol/L)	1.6±1.1	0.7	4.0	1.7±1.2	0.5	3.6	-0.1±0.1	0.300
High-Density Lipoprotein (HDL) (mmol/L)	1.1±0.4	0.4	3.8	1.4±0.5	0.3	4.2	-0.4±0.03	<0.001
Low-Density Lipoprotein (LDL) (mmol/L)	2.5±1.03	0.6	8.7	2.01±0.8	0.1	5.8	0.5±0.6	<0.001

Table 3 demonstrates the comparison of mean levels of various lipid parameters between the Atorvastatin and Rosuvastatin groups. There was a substantial reduction in total cholesterol and LDL levels and an increase in HDL levels in the Rosuvastatin group compared to the Atorvastatin group when comparing the mean change in lipid parameters between the two treatment groups. The difference in triglyceride levels between the two groups, however, was not significant.

Table 3. Comparison of the mean level of various lipid parameters in the Atorvastatin and Rosuvastatin groups.

	Atorvastatin Group	Rosuvastatin Group	p-value
Total Cholesterol (TC) Mean ± SD (mmol/L)	0.7±0.7	1.1±1.01	<0.001
Triglyceride (TG) Mean ± SD (mmol/L)	-0.1±1.2	-0.04±1.1	0.315
High-Density Lipoprotein (HDL) Mean ± SD (mmol/L)	-0.2±0.4	-0.5±0.5	<0.001
Low-Density Lipoprotein (HDL) Mean ± SD (mmol/L)	0.4±0.6	0.6±0.7	<0.001

The change in LDL-C before and after treatment with a statin is shown in Figure 2. At 3 months follow-up, an LDL-C level of less than 1.8mmol/L was observed in 98 (40.8%) patients whereas only 39 (16.3%) patients achieved the target of less than 1.4mmol/L. A decline of LDL of more than 50% was observed in 17(7.1%) patients while target achievement of both less than 1.4mmol/L and decline of LDL of more than or equal to 50% was noted in only 8(3.3%) patients.

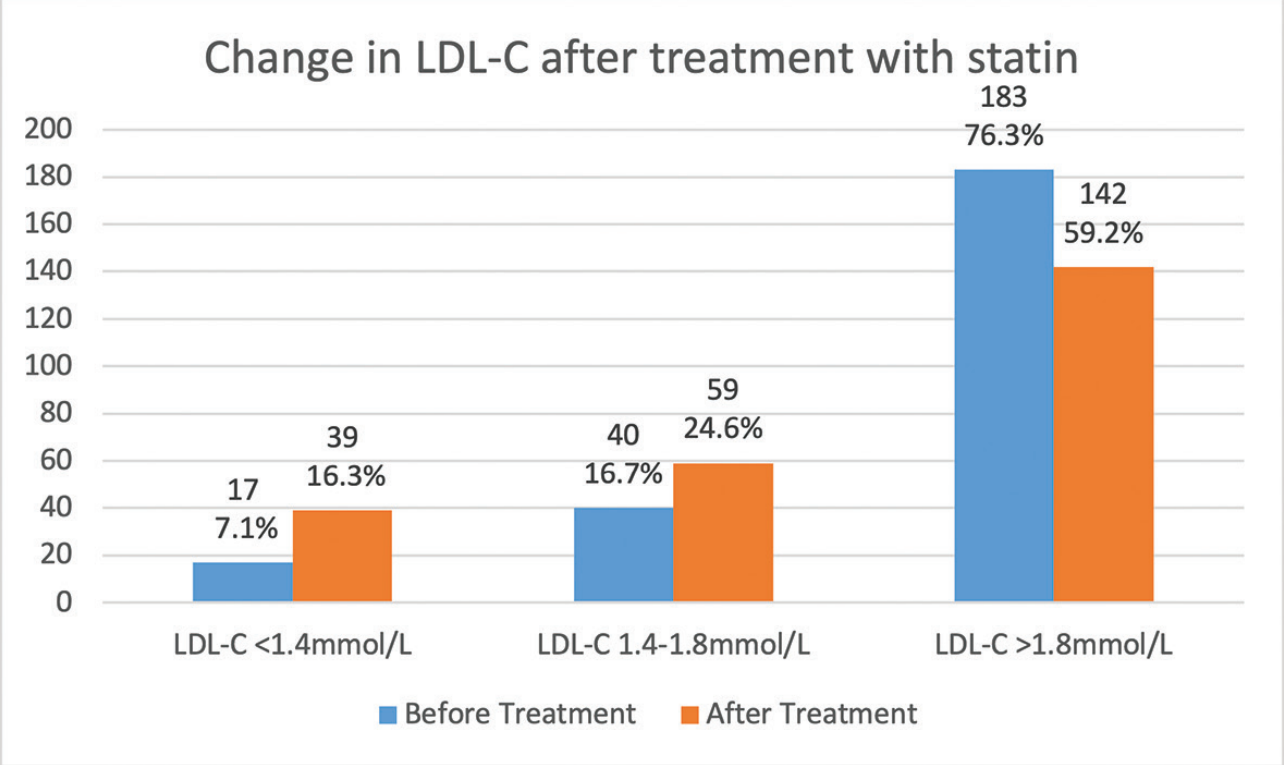

Figure 2. Change in percentage of patients achieving LDL-C targets before and after the statin treatment.

Table 4 shows the comparison of the percentage of patients achieving different LDL-C targets in the Atorvastatin and Rosuvastatin groups. After therapy with Atorvastatin 40 mg and Rosuvastatin 20 mg, there was no significant difference between the two statin groups in terms of reaching various LDL-C goal values. Even though LDL-C significantly decreased in both groups, the proportion of patients achieving target LDL-C levels was well below 50% for all target endpoints as shown in the table.

Table 4: Comparison of percentage of patients achieving different LDL-C targets in the Atorvastatin and Rosuvastatin groups.

	Atorvastatin Group n (%)	Rosuvastatin Group n (%)	p-value
LDL less than 1.4mmol/L	17 (14.2)	22 (18.3)	0.382
LDL less than 1.8mmol/L	48 (40.0)	50 (41.7)	0.793
LDL decline more than 50%	7 (5.8)	10 (8.3)	0.450
Both LDL less than 1.4mmol/L and ≥50% decline	2(1.7)	6(5.0)	0.281

Table 5 demonstrates the association of different LDL-C targets and demographic parameters and cardiovascular risk factors. When the achievement of different LDL-C target levels was analyzed for association with demographic characteristics and cardiovascular risk factors, none of the parameters were significantly associated with the achievement of LDL-C targets.

Table 5. Association of different LDL-C targets and demographic parameters and cardiovascular risk factors.

	<1.4 mmol/L	<1.8 mmol/L	≥50% decline	Both LDL <1.4mmol/L and ≥50% decline
	n (%)	n (%)	n (%)	n (%)
Age<65years	29(74.4)	71(72.4)	15(88.2)	7(87.5)
Male	31 (79.5)	73(74.5)	13 (76.5)	6(75)
Female	8 (20.5)	25(25.5)	4(23.5)	2(25)
HTN	23(59.0)	48(49.0)	8(47.1)	5(62.5)
DM	12(30.8)	34(34.7)	6(35.3)	2(25.0)
Current Smoker	17(43.6)	46(46.9)	7(41.2)	4(50)
Family history of CAD	2(5.1)	4(4.1)	0(0)	0(0)
Past history of CAD	1(2.6)	1(1.0)	0(0)	0(0)
Physical Inactivity	1(2.6)	5(5.1)	0(0)	0(0)
Obesity	6(15.4)	19(19.4)	3(17.6)	1(12.5)
LDL-C <1.4mmol/L	16(41.0)	17(17.3)	2(11.8)	2(25)
LDL-C 1.4-1.8mmol/L	15(38.5)	38(38.8)	0(0)	0(0)
LDL-C >1.8mmol/L	8(20.5)	43(43.9)	15(88.2)	6(75)

DISCUSSION

Our study demonstrated that the LDL-C target achievement among the post-STEMI patients who were prescribed a lower range of high-dose statin was low. The target achievement of LDL-C level less than 1.4mmol/L was noted only in 16.3% of the patients and the target of LDL-C reduction by ≥50% from baseline was noted in 7.1%. Only 3.3 % of the study population achieved the target of both LDL-C goal of <1.4 mmol/L and ≥50% reduction of LDL-C from baseline. However, 40.8% of the participants in our study met the 2012 ESC STEMI guidelines' LDL-C target achievement of less than 1.8 mmol/L.

The 16.3% decline in the percentage of patients achieving the target of LDL-C level to less than 1.4mmol/L was higher than the 7.4% decline noted in a retrospective study conducted in Brazil from 2008 to 2015.[18] However, a decline of ≥50% from baseline was noted in 18.3% of the study population in Brazil which was higher than 7.1% among our study population. The reason for this disparity might be that the mean LDL-C level before the statin treatment was higher in a study conducted in Brazil compared to our study population. Similarly, LDL-C levels were reduced by more than or equal to 50% in 28.5% in a study conducted in Korea among post-acute MI patients who had mean LDL-C level of 3.05mmol/L during presentation[19] and 23.2% among post-MI patients in Thailand.[20] While analyzing the LDL-C target attainment of less than 1.8mmol/L according to the previous guidelines, we noted 40.8% population achieved this target which was similar to the Dyslipidemia International Study-China (DYSIS-China) study[21] but higher than the Dyslipidemia International Study II (DYSIS II) study performed in 18 countries,[22] study in Thailand,[20] and a recent study in China.[23] However, it was less among patients aged 60 years and more in Singapore[24] and among the Korean patients after one year of follow-up.[19] This reflects the need to upgrade our statin therapy to achieve both recent guideline recommendations of LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L.

The decrease in LDL-C with the use of high-dose statin resulted in a decline in clinical event rate which was noticed in a large-scale study.[25] Intensive lipid-lowering therapy in post-STEMI patients has been associated with improved long-term clinical outcomes in many important trials.[26,27] The predictors of LDL-C goal achievement in different studies were age, the potency of statin treatment and baseline LDL-C level, whereas, female sex, obesity or overweight, higher CV risk and lipid-lowering therapy other than statin were associated with less likely LDL-C goal achievement.[28] Also, a history of symptomatic congestive heart failure negatively predicted target LDL-C achievement.[29] However, both previous and current smoking did not show any association with goal achievement in previous studies.[28] In our study, demographic parameters and none of the cardiovascular risk factors were associated with a decline in LDL-C, however, this study was not powered for estimation of predictors.

The multi-factorial challenges resulting in decreased LDL-C goal attainment post-ACS were the inadequate intensification of statin therapy, a decrease in the use of combination therapy at the right time and a lack of rigorous follow-up at 4-6 weeks.[21] This is alarming as not achieving the recommended goal may not derive the maximal benefit of post-MI statin treatment and is associated with a very high risk for new cardiovascular events in the short to medium term.[18] The patient and physician-related factors for such lower goal attainment were suboptimal adherence; lower rate of high-intensity prescription; dissatisfaction with treatment; physicians not setting the lipid goals; and guideline non-concordance.[21] Though the adherence in our study was assessed through interviews, the adherence to statin therapy was not confirmed with further tests. The other physician and patient-related factors along with the financial barriers were not probed in our study. Return on Expenditure Achieved for Lipid Therapy in Asia (REALITY ASIA) study also pointed out that there exists statin phobia at the regional, country, physician and patient levels in Asia and also the perception that Asians are intolerant to statins[30] should be negated with appropriate awareness and education.

In our study, it was also noted that the decline in mean total cholesterol level, mean LDL-C and HDL-C levels were significantly lower in the Atorvastatin group compared to the Rosuvastatin group. However, the Atorvastatin group had considerably lower baseline mean levels of total cholesterol, HDL-cholesterol, and LDL-cholesterol before starting statin medication This might have resulted in the difference in levels of the lipid parameters after therapy between the groups. We can also notice the preference for Rosuvastatin among the higher levels of LDL-C among our study population. However, adequately powered studies for comparison between two groups without significant baseline different lipid profile levels are suggested in the future to clarify whether this difference exists in reality.

As this is an observational study, it has an inherent limitation in making causal associations between the measured variables. Also, being a single-center study, the generalization of the findings to the whole population requires further confirmation. Statin adherence was only assessed with a verbal answer to the questionnaire, and the actual intake of the prescribed drugs was not verified. The use of statin before the index cardiac event and the use of combination therapy with other non-statin drugs, most notably Ezetimibe as recommended in the recent guidelines were also not studied. Limited information regarding sociodemographic and medication details that might have influenced the lipid parameters, lifestyle modification therapy, economic status and access to statin were not assessed in this study. Also, common side effects of statins like myopathy, myalgias, muscle weakness, arthropathies and rarely rhabdomyolysis were absent from the analysis in our study.

The findings of this study stress the lower LDL-C goal achievement in post-STEMI patients with the use of a lower range of high-intensity statin which is alarming as lower LDL-C levels are associated with lower clinical event rates in the future. As the Asian region comprises a very heterogeneous population, as seen in differences in Atherosclerotic cardiovascular disease-related mortality across the region,[30] we recommend specific CVD risk assessment tools for Asian countries to accurately predict cardiovascular risk in our diverse population. In addition, specific CVD-related guidelines to minimize the CVD risk for primary and secondary prevention need to be developed based on the data from our population. The myth that a lower range of high-intensity statin is enough in an Asian population due to lower body mass and an increase in side effects of statin needs to be scientifically proven. Until then, rigorous follow-up with improved patient-provider interactions to minimize the myths regarding statin and its side effects and motivate each patient to target LDL-C achievement with appropriate dosing of statin is recommended. The individual after STEMI represents the very high-risk population associated with higher incidence and elevated hazards of recurrent clinical events, therefore, each patient should be regularly monitored clinically and appropriate actions should be taken as recommended to minimize future cardiac events instead of using a lower range of high-intensity statin with the assumption of the requirement of lower range compared to western population.

CONCLUSIONS

This study showed that the overall rate of attainment of recommended LDL-C levels in patients who developed recent STEMI was low among patients prescribed with the lower range of high-dose statin, which predisposes them to a higher residual risk of atherothrombotic events. There is a need for improved current practices for managing LDL-C levels in our settings with rigorous follow up including monitoring of lipid levels and intensification of statin dose and type as necessary.

CONFLICT OF INTEREST

There are no conflicts of interest.

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