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Association between statin intensity and adherence, and MACE in post- STEMI patients: A cohort study

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Abstract

BACKGROUND: Statins are among secondary preventive cardiovascular medications that adherence is critical to their effectiveness. Although, the management of cardiovascular diseases emphasize both intensity and patient adherence, observations show that statin adherence and intensity is not adequate. This study aimed to measure statin adherence and intensity in post-ST elevated myocardial infarction patients and its association with major adverse cardiovascular events (MACE).

METHODS: Of 867 patients in the ST-elevated myocardial infarction cohort study in Isfahan, 549 individuals had data on the intensity of statin therapy. 455 of these patients tended to fill out the adherence questionnaire. Morisky Medication Adherence questionnaire and a checklist consisting potential adherence, and intensity-associated factors were filled out.

RESULTS: In the age group of 50-70 years, increasing age (P = 0.014), receiving physician's support on the consequences of statin discontinuation (P = 0.019), taking lower number of medications (P = 0.045) were significantly associated with statin adherence. Besides, the experience of side effects (P = 0.028) and depressed mood (P ≤ 0.0001) were negatively associated with adherence. None of the measured factors were associated with statin intensity. Statin adherence and statin intensity independently affect MACE, such that even after full adjustment, the chance of experiencing MACE increases 8% (95% CI = 1.02, 1.20) for low-statin adherents and 12% (1.04, 1.28) for patients on non-high statin intensity.

CONCLUSION: Statins have a significant role in the prediction of MACE, based on their intensity and adherence. Educational support from the physician, considering patients' mood and number of medications could improve patients' adherence.

Keywords: Statins; Adherence; Statin Intensity; Myocardial Infarction; Major Adverse Cardiovascular Events

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Introduction

Adherence to treatment is defined as a voluntary collaboration of the patient in a list of recommended behaviors to achieve a therapeutic result. Better adherence helps reduce mortality, morbidity, and health care costs[1]. Adherence in chronic diseases such as diabetes mellitus (DM), hyperlipoproteinemia (HLP), cardiovascular diseases (CVDs), hypertension (HTN) is highly valued due to the long-term nature of these diseases and their management[2].

One of the classes of medication that is used in the management of chronic diseases is statin. Statins are lipid-lowering agents that adherence plays a critical role in their effectiveness. Poor adherence to statin treatment is associated with increased mortality and worse clinical outcome such as CVDs[3].

However, statin therapy is associated with some side effects and many patients may discontinue the consumption of the appropriate dosage of the statin during their therapy, the reason could be the symptoms they experience like myalgia, DM, and central nervous system complaints[3]. However, side effects are the main reason, but not the only reason for statin discontinuation; the fatigue of long-term consumption and depression reduced the possibility of statin adherence. Another reason for low adherent could be the asymptomatic nature of high LDL-C that causes the patient not to perceive the benefits of the medications they consume. The effect of some other factors such as age and number of daily consumed medications has not been well identified[1,4,5]. The influence of the physician cannot be neglected as the studies show the more intervention and education the physicians provide the more adherent the patient gets. but identifying the type of intervention that is needed is difficult and varied with different patients[6].

In addition to statin adherence, its intensity is also important in the management of CVDs[7]. The 2018 American Heart Association (AHA)/ American College of Cardiology (ACC) multi-society guideline on the management of blood cholesterol strongly suggests that long-term intensive statin therapy should start immediately in high-risk patients such as patients with confirmed atherosclerotic cardiovascular disease[8]. Despite the guideline suggestion, the utilization of high-intensity statin is suboptimal. Statin underutilization is more common in females, elderly patients, patients with confirmed liver disease and musculoskeletal pain and, DM[9,10]. Also, some studies show there is no difference between clinical outcome of a patient prescribed with high-intensity statin and non-high intensity and in addition to that high-intensity statin is associated with more side effects in patients so the prescription of the right dosage for the right patient is still unclear[6,10,11].

Factors that have an effect on statin adherence or the intensity that a patient consumes have not been fully found or there are a lot of controversies on them such as the effect of age, physician direct support and explanation and the number of daily consumed medication by patients, therefore in this study, we tried to find some of these possible factors. Also, studies in the field of statin adherence suggest that non-adherence to statin treatment is related to worse clinical outcomes; however, further investigations are needed on the subject due to the paucity in the number of studies that were conducted so in a three-year cohort, we checked the hypothesis that changes in the level of statin adherence or statin intensity is associated with major adverse cardiovascular events (MACE).

Materials and Methods

This study was conducted to assess patients' adherence to one of the secondary treatments, statin, and checked whether non-adherence increases MACE. In addition, potential factors contributing to statin non-adherence in post-MI patients were investigated.

Our study was nurtured by data from third year of ST-elevated myocardial infarction (Semi-Ci) study; a 5-year cohort study affiliated with Isfahan University of Medical Science. This study populated on all post-MI patients who were registered to Chamran referral cardiology center started from September 2015, in Isfahan in Iran.

Patients, who developed STEMI before they had been discharged from the hospital due to percutaneous coronary angioplasty or coronary bypass, were excluded from the study. The details of this study have been published elsewhere[12].

Setting and participants

A number of 867 patients participated in Semi-Ci study. During the first and second years of follow-up, 156 patients died and 47 patients dropped out of the study. About 664 patients entered the third-year follow-up; however, 115 of them were excluded because data regarding the intensity of consumed statin was not available for them. From 549 patients who went through intensity analysis, 94 cases were unwilling to fill the adherence questionnaire (response-rate = 82.88%) and therefore only 455 patients were qualified for inclusion in the adherence analysis (Figure 1).

Procedure

In this study, a trained nurse explained the reason of the study for participants and completed Morisky Medication Adherence questionnaire for them through a telephone call. In addition, a checklist was filled for each patient consisting of number of daily-consumed medications, physician support about statin, self-willed dosage refill and its reason. In the next step, data on statin dosage, demographic and clinical characteristics, risk factors and comorbidities were collected from baseline data of Semi-Ci study.

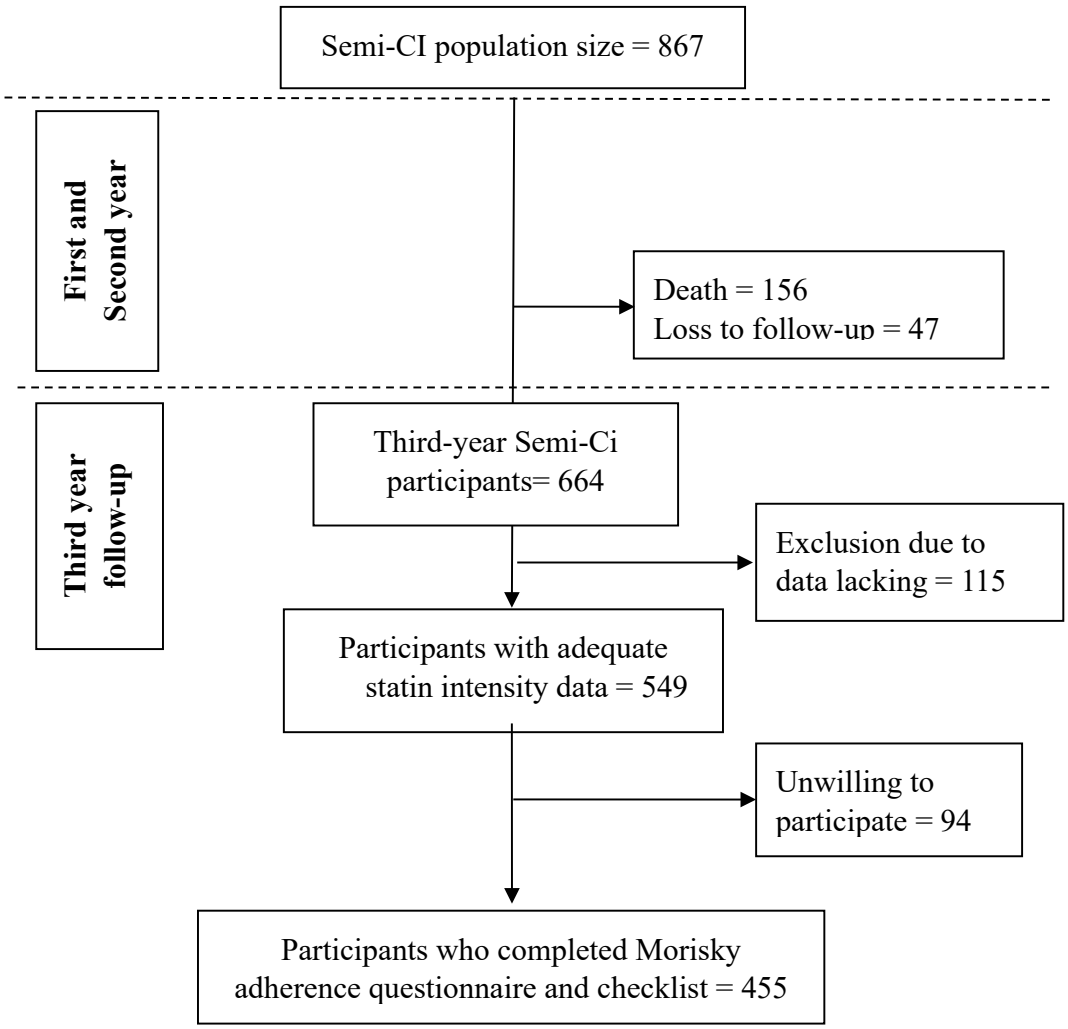


Figure 1. The flowchart of the study population

Ethics

All the patients had written consent and were assured that their information would remain confidential with the executive staff. Due to the data collection method, there was no economic, psychological, and life cost for the participants. This study was affiliated with the Isfahan University of Medical Science with the ethical code of IR.MUI.MED.REC.1399.134.

Measurements

Statin adherence

Adherence was measured based on the Morisky Medication Adherence scale which is an eight-item questionnaire that divides patients into three highly adherent (score 8), moderately adherent (scores 6-7), and low adherent (scores < 6) groups. The first seven items need dichotomous yes-no answers to find the reasons for missing the medication, while the last question is a 5-point Likert scale assessing how often the patient has difficulty remembering medication[12]. The Persian version of this questionnaire was used with internal consistency of $\alpha = 0.80$[13].

Statin intensity

Persistent consumption of guideline-recommended 40-80 mg atorvastatin during the years of follow-up was labeled as high intensity. If the patients refused these doses for personal reasons, intolerance, initial physician nonprescription or contraindication, they were considered non-high intensity group.

Potential adherence-associated factors

a) Number of daily-consumed medications b) Prescription status, which was measured as the doctor has made any changes to the intensity of the statin. c) Physician support and explanation about statin administration, whether it was clarified how and why to use this drug, side effects of statins, and consequences in the case of refusal. d) Any patient-centered dosage refill and its underlying reasons including patient's mood and self-report admission of depression, experience of statin-related side effects after the initiation of the treatment, affordability for providing statin and its accessibility for patients.

Cardiovascular-related variables

Clinical characteristics of MI including its type (anterior versus non-anterior), ejection fraction and number of involved epicardial territories; baseline LDL-C; presence of previous statin administration; comorbidities including chronic kidney disease, thyroid disease, and heart failure; CVD risk factors of hypertension, hyperlipidemia, obesity, diabetes mellitus and smoking; clinical procedures in the follow-up period (Coronary artery bypass graft surgery, Percutaneous coronary intervention, bypass surgery); and re-hospitalization and its reason were extracted from Semi-Ci data and patients' medical records.

Captured demographic factors were as follows: age, gender, educational level based on the duration of their education; 0-5 years, 6-12 years, more than 12 years, region of residence defined as urban or rural, and marital status.

The term "MACE" which is the abbreviated form of major adverse cardiac event refers to atherosclerosis cardiovascular diseases (ASCVD) in coronary and cerebral vessels including non-fatal MI, non-fatal stroke, unstable angina, stent thrombosis, and heart failure. Data on MACE was extracted from Semi-Ci study in which for each patient a telephone call was made to obtain data followed by holding a cardiology panel to confirm the diagnosis of MACE.

Statistics

Statistical Package for Social Science (SPSS) Version 16 (SPSS, Inc., Chicago, IL) was the analysis software in this study.

Statin adherence and intensity were considered independent variables, while MACE was dependent variable. Mean±standard deviation was used for continuous variables and frequency and percentage for categorical ones. Analysis of variance (ANOVA) and independent t-test was used to analyze continuous variables. All the categorical variables were analyzed by Chi-square method. To find the association

between intensity and MACE we used logistic regression and odds ratio. Ordinal regression was used to find the association between the level of adherence and MACE, which was adjusted for demographic characteristics, risk factors, the severity of disease, and the number of drug consumption in four models. Each model consisted of the variables of the previous model added by a new factor, the last model consisting of all (fully adjusted).

Results

In total, 549 patients entered our intensity analysis with mean age of 60.59±12.89. Female were 17.9 percent of population. On alarming importance, in the third year of follow up only 42.4% (233/549) of the patients were on high intensity regimen. Of these cases, 455 patients were included in the adherence analysis with the mean age and gender distribution of 58.09±11.81 and 13.2%. Most of the patients were moderately adherent and Atorvastatin was the most consumed statin.

As shown in Table 1, older patients are more likely to adhere to statin treatment (P = 0.01). A marginal significance was found between adherence and the patients' region of residence (P = 0.062). No association was found between intensity and other measured factors including demographics, clinical characteristics, comorbidities and cardiovascular risk factors.

We also evaluated some factors that possibly motivated statin non-adherence (Table 2). Predictably, number daily-consumed medication was significant with P = 0.04, patients who take more medication are less adherent to statin treatment. Whether the physician provided the patient with explanation on the consequences of statin discontinuation (P = 0.019) is significantly and rationale for statin administration (P = 0.071) and side effects of the drug (P = 0.071) is marginally associated with how much the patients adhered to the medication regimen. As patient-based adjustments of consuming dosage can affect the patients' adherence level, we evaluated how patients' explanation for dosage refill was associated with adherence; Experiencing side effects and feeling down about taking the medication (depression) were associated the most (P-values of 0.028 and ≤ 0.0001, respectively). Although lack of affordability was the most reported reason for dosage refill, we failed to find significant association for it. Based on the data, statin was accessible to almost all patients. Apparently, intensity did not associate with any of the evaluated factors.

As depicted in Table 3, 84 of the patients included in intensity analysis and 63 of the patients in adherence analysis experienced MACE. How the patient adhered to the statin regimen and what intensity had been consumed significantly associated with total MACE (P = 0.03). An association was found between adherence level and, MI, unstable angina, and heart failure. The same pattern held for intensity except for the last one.

Lower levels of adherence and intensity could increase the MACE odds by 10 (95% CI = 1.05, 1.21) and 22 percent (95% CI = 1.11, 1.43). These associations remained after adjustment with adherence or intensity-related factors. Adding demographic characteristics of age, sex, education, region of residence, marital status in the first model did not change the association strength of adherence and intensity. In the second model, we added cardiovascular risk factors (Hypertension, Hyperlipidemia, Smoking, Diabetes mellitus, Obesity), and the OR kept decreasing for both associations. The severity of the disease defined as the number of involved epicardial territories and ejection fraction rate increased the association strength in model 3 compared to the previous model. In our final model, we involved the number of daily-consumed medication, which reduced the unadjusted association rate. However, even after all of these adjustments and irrespective of all the factors, the chance for experiencing MACE increased 8 (95% CI = 1.02, 1.20) and 12 percent (95% CI = 1.04, 1.28) when the adherence level and intensity of the therapy decreased (Table 4).

Table 1. Baseline characteristics on the basis of statin adherence and statin intensity category

	Low adherence (N=115)	Medium adherence (N=206)	High adherence (N=134)	P value	High-intensity (N=233)	Low-intensity (N=316)	P value
Demographic characteristics							
Age (mean±SD)	56.92±11.49	57.13±11.47	60.58±12.28	0.014	58.64±11.81	59.99±12.20	0.196
Sex, N(%)							
Male	102(25.3)	180(45.6)	113(28.6)	0.567	200(43.3)	262(56.7)	0.354
Female	13(21.7)	26(43.3)	21(35.5)		33(37.9)	54(62.1)	
Education, N(%)							
0-5y	46(28.9)	66(41.5)	47(29.5)	0.389	75(39.9)	113(60.1)	0.731
6-12y	31(30.7)	32(31.8)	38(37.6)		56(42.7)	75(57.3)	
>12y	6(14.6)	24(58.5)	11(26.8)		15(32.6)	31(67.4)	
Region of residence, N (%)							
Urban	59(17.3)	179(52.5)	103(30.2)	0.062	135(41.0)	194(59.0)	0.537
Rural	15(21.4)	26(37.1)	29(41.4)		24(36.9)	21(63.1)	
Marital status, N(%)							
Single	2(33.3)	4(66.7)	0(0.0)	0.279	5(55.6)	4(44.4)	0.268
Married	113(25.3)	201(45.0)	133(29.8)		228(42.2)	312(57.8)	
Clinical characteristics							
Type of AMI, N (%)							
Anterior myocardial infarction	62(25.6)	101(41.7)	79(32.6)	0.197	131(43.8)	168(56.2)	0.371
Non-anterior myocardial infarction	53(24.9)	105(49.3)	55(25.8)		102(40.6)	148(59.4)	
EF (mean±SD)	39.60±11.89	38.86±11.35	38.11±11.89	0.644	36.85±11.56	38.12±11.78	0.069
Number of involved epicardial territories							
1	54(27.4)	92(46.7)	59(25.9)	0.492	89(38.4)	143(61.6)	0.106
2	34(23.4)	66(45.5)	45(31.0)		78(43.1)	103(56.9)	
3	20(20.6)	43(44.3)	34(35.1)		62(50)	62(50)	
Baseline LDL (mean±SD)	110.85±38.60	111.96±43.24	107.74±33.48	0.777	111.49±43.06	108.65±39.03	0.543
Previous use of statin (n%)	28(26.1)	56(27.2)	36(24.3)	0.848	58(24.9)	94(29.7)	0.209
Underlying conditions							
Chronic kidney disease N (%)	3(4.1)	4(1.9)	4(3.0)	0.600	5(3.1)	6(2.5)	0.711
Thyroid disease N (%)	2(2.5)	9(4.4)	3(2.2)	0.534	5(3.1)	9(2.8)	0.736
Heart failure N (%)	14(26.9)	28(53.8)	10(19.2)	0.447	30(44.8)	37(55.2)	0.491
Risk factors							
Hypertension N (%)	37(32.2)	69(33.5)	45(33.6)	0.965	83(41.3)	118(58.2)	0.648
Hyperlipidemia N (%)	32(27.8)	70(36.6)	46(34.3)	0.679	79(44.6)	98(55.4)	0.772
Smoking N (%)	53(28.3)	82(43.8)	52(27.8)	0.561	103(47.2)	115(52.8)	0.063
Diabetes mellitus N (%)	31(24.6)	59(46.8)	36(28.5)	0.919	70(44.6)	87(66.4)	0.503
Obesity	68(26.0)	115(43.9)	79(30.2)	0.615	122(41.6)	171(58.4)	0.964

Discussion

The present study demonstrated that statin intensity and statin adherence is an important factor that affects MACE directly and independently. Furthermore, older patients, patients consuming a lower number of medications and receiving physician support are more likely to adhere to statin treatment.

Table 2. Interplay between number of daily-consumed medication, physician support, patient-centered dosage refill and statin adherence and statin intensity

	Low adherent 115(29.5)	Medium adherent 206(45.3)	High adherent 134(25.3)	P Value	High-intensity 233(42.4)	Low-intensity 316(57.6)	P Value
number of daily consumed medication(mean)	4.92±2.19	4.30±2.39	4.17±2.24	0.045	4.62±2.35	4.33±2.29	0.223
Physicians support and explanation about statin (n%)							
Reason	31(41.9)	69 (33.5)	61(45.5)	0.071	62(39.0)	97(40.8)	0.725
How to use	73(98.6)	203(98.5)	133(99.1)	0.836	159(100)	223(97.9)	0.066
Side effects	7(9.5)	25(12.1)	26(19.4)	0.078	21(13.6)	35(14.7)	0.674
Consequences of statin discontinuation	11(24.9)	54(26.2)	44(32.1)	0.019	38(23.9)	68(28.6)	0.303
Patient-centered dosage refill (n%)							
Side effects	21(28.4)	37(18.0)	18(13.4)	0.028	35(22.0)	39(16.4)	0.158
Depression	31(41.9)	47(22.8)	19(14.1)	0.0001	36(22.6)	58(24.4)	0.691
Low Accessibility	2(2.5)	1(0.5)	0(0.0)	0.852	3(2.5)	3(1.2)	0.720
Lack of Affordability	36(18.6)	76(36.9)	59(44.0)	0.105	67(42.1)	49(41.6)	0.915

Table 3. Relationship between MACE and statin adherence and statin intensity

Major clinical event, (n%)	Low adherence	Medium adherence	High adherence	P value	High intensity	Low intensity	P value
Total mace	36(31.3)	15(7.3)	12(8.9)	0.03	24(10.3)	60(19.0)	0.03
MI	11(9.6)	4(1.9)	3(2.2)	0.02	4(1.7)	17(5.4)	0.04
Unstable Angina	15(13.4)	8(3.8)	5(2.6)	0.04	5(2.1)	27(8.5)	0.04
Stent Thrombosis	0(0.0)	2(1.0)	2(1.5)	0.44	2(0.9)	3(0.9)	0.91
Stroke	0(0.0)	1(0.5)	2(1.5)	0.32	4(1.7)	2(0.6)	0.22
Heart Failure	10(8.7)	4(1.9)	2(1.5)	0.08	9(3.9)	19(6.0)	0.25

Also experiencing side effects and feeling down about taking medication is associated with a lower level of adherence.

Reaching to a better adherence is a worldwide challenge because adherence is under the influence of many different factors. in this study we tried to find some of these factors, one of them is age. Other studies that investigated the association between adherence and age did not find a consistent manner on the subject, in different studies they found that patients younger than 50 years and older than 70 are less adherent or in a systematic review, adherence was better with increasing age. However, we notice that the mean age of our patients in all

Table 4. Relationship between MACE and statin adherence and statin intensity after adjusting with relevant factors

	Drug adherent	Intensity
Crude	1.10(1.05, 1.21)	1.22(1.11, 1.43)
Model 1	1.10(1.02, 1.15)	1.17(1.08, 1.31)
Model 2	1.09(1.01, 1.13)	1.15(1.05, 1.29)
Model3	1.11(1.02, 1.17)	1.16(1.07, 1.32)
Model 4	1.08 (1.02, 1.20)	1.12(1.04, 1.28)

Model 1: Adjust demographic characteristics (age, sex, Education, Region of residence, Marital status)

Model 2: Adjust demographic characteristics and risk factors (Hypertension, Hyperlipidemia, Smoking, Diabetes mellitus, Obesity)

Model 3: Adjust demographic characteristics, risk factors and severity of disease (number of involved epicardial territories and ejection fraction)

Model 4: Adjust demographic characteristics, risk factors, severity of disease and number of daily-consumed medication

of the regimens is between 50-70 years so we could get to a conclusion about the adherence of patients between 50-70 years old that the older the patients are the more adherent to statin treatment they will be[4,5].

The number of medications CVD patients have to take has a significant impact on how they adhere to the drug regimen in a negative way[5]. Our results further support this idea. Patients with CVD often have other chronic comorbidities including hypertension and diabetes for which they need to consume plenty of pills[14]. That is where the idea of combining these pills into a polypill comes across[15].

Physicians support and explanation about statin treatment also have an effect on adherence. Nowadays, people can get the information about statin almost everywhere, media, a place that they can get the most of the information from, is full of negative stories about statins, and patients who are under the influence of these negative sights have poor long-term adherence. Therefore, the role of physicians to explain the benefits of statin treatment and give the right information is very important[16]. Previous studies considered patient-health care providers relation in increase adherence[6]. However, no study investigated the detailed explanation that results in higher adherence. We found that physician explanation on consequences of discontinuation has the most effect on statin adherence and explanation on side effect the patients may experience and the reason they are using this drug is marginally associated with better adherence. Therefore, physicians should consider that how much effect they have on patients and use it properly to achieve a higher adherence.

Occurrence of side effects is a cause of non-adherence and statin discontinuation. Myalgia, muscle weakness and pain are common types of side effects[4]. Although these side effects do not contradict the patients for statin administration, they are one of the principal reasons for not taking appropriate statins[17]. Our results go in line with previous studies as experiencing side effects was a noticeable factor preventing patients from statin administration. However, some recent studies suggest that experienced side effects may be due to negative expectations about side effects as these studies were unable to show increase of side effects in placebo-controlled trials[18]. Further studies should look for the existence of causality between statins and side effects in our population.

In our study, self-report admission of depression was a significant factor decreasing adherence, previous studies have shown that depression has a negative impact on patients' adherence to not only statins, but also other chronic disease medications like hypertension and diabetes[14]. In a study by Katzmann et al. highly adherent patients were less depressed[19]. This relationship may be partly explained by lack of motivation, which is prominent in depressed patients.

MACE is the composite endpoint of many cardiovascular conditions. Numerous studies were conducted to find the factors that aggregate, improve and predict MACE. Adherence has been proven as one of these predictors. Various studies have shown the independent effect of statin adherence on long-term cardiovascular outcomes and our results further support this evidence[20–22]. According to Morisky questionnaire items, patients who adhere to drug regimen take their medication with appropriate dosage and in accurate time. In addition, they do not cut back the drug without consulting the physician or when feeling that drug fails to work. All of which have positive impact on how much statin can improve the outcomes. In addition, adherence can be a surrogate of healthy behavior. Besides the effect that taking the medications in the recommended manner can have on long-term outcomes, highly adherent patients are more likely to adopt healthy behaviors including smoking cessation and healthy diet that can positively increase patient's survival[23].

Intensity is also an important factor when talking about statin. Our study showed consuming high intensity statin affects MACE substantially. However, statins are under dosed

and underutilized as our study revealed that only 42.4% percent of patients were on high-intensity regimens. This finding is of alarming importance as recent meta-analysis has shown the necessity of high statin in reducing MACE in post-MI patients[11]. Contrary to the expectations, this study did not find any factor that significantly affects statin intensity. Previous studies have shown that some factors determine with what intensity statins are prescribed and consumed. Sex, age, comorbidities such as diabetes and administration of some other medications are among those factors[24–26]. As deciding about statin dosage needs medical expertise and is based on physicians' opinion, this discrepancy can be attributed to physicians in our study population being concerned with beneficences of high intensity statin reported in guidelines.

Our study comes with some limitations that can shed light on future research. first, we mentioned that statin side effects are reasons for non-adherence; however, these side effects were patient-reported and we did not investigate whether they were clinically relevant to statin or not. second, depression was labeled subjectively by asking patients about their mood, it is important to bear in mind the possible bias in these responses. Third, existence of recall bias associated to the use of questionnaires and checklists is inevitable. Forth, overestimation of adherence due to participants feeling pressured to provide positive response to the questioner. Fifth, we did not find affordability as a factor affecting adherence. However, this result should be interpreted with caution as many factors can contribute to this result including socioeconomic status, income and health insurance coverage of statin. Further studies, which take these variables into account, will need to be undertaken.

Conclusions

This study set out to find statin adherence effect on MACE and its associated factors in a post-MI population. This research has identified that adherence has an independent and strong association with MACE. Educational support from the physician improved patients' adherence and therefore could decrease MACE. Considering patients' mood and how many medications other than statin they used is important in clinical setting as they had an impact on statin adherence. Intensity of statin was also a prominent factor affecting MACE and adhering to guideline-recommended dosage is suggested both for prescribers and patients.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: MS; ZT; HR
Data Acquisition: -
Data Analysis or Interpretation: HR
Manuscript Drafting: MA; ER; AE; KK
Critical Manuscript Revision: MA; ER; AE; KK

All authors have approved the final manuscript and are responsible for all aspects of the work.

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