Available online at www.ijpcr.com
International Journal of Pharmaceutical and Clinical Research 2015; 7(1): 52-60

ISSN- 0975 1556

Research Article

Evaluation of Statin Effect on Low-Density Lipoprotein Cholesterol Goal Attainment In Patients With Myocardial Infarction

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Available Online: 1st January, 2015

ABSTRACT

According to *NCEP ATP III update* 2004, patients with myocardial infarction have been classified as very high-risk patient. The panel then recommends an optional LDL-C goal <70 mg/dL for this patients. This study evaluated the extent to which this recommendation can be attained by the use of currently available statin therapies. The study was a descriptive analytical observational study conducted retrospectively through medical records and laboratory data of myocardial infarction patients aged ≥18 years who received statin therapies. The patients were monitored within 6 month since diagnosed with acute myocardial infarction at cardiac clinic of a hospital in Yogyakarta Indonesia between 1 January 2009 and 30 September 2013. Statistical analysis was done to determine whether statin therapy within 6 months can attain a significant reduction in LDL-C level and bivariate analysis to determine some factors associated with LDL-C goal attainment. A total of 141 patients diagnosed with acute myocardial infarction were included in this study. The statin prescribed was mostly simvastatin (50.4%). Most patients experienced much change in their treatment regimen (62.4%) with an average change in the treatment regimens per patient was 1.5 ± 0.8 times. The most change in treatment regimen was atorvastatin 40 mg/day to simvastatin 10 mg/day (18.4%). Regimen for patients who their treatment remain unchanged within six months was simvastatin 20 mg/day (23.4%) followed by atorvastatin 40 mg/day (7.1%). Overall, statin therapy within 6 months after the patients diagnosed with AMI, exhibited significant reduction in LDL-C levels by 19.5% ($p<0.0001$) with final LDL-C level was 109.24±37.18 mg/dL, while initial LDL-C level was 132.22±40.61 mg/dL. However, the reduction did not occur in all patients, only 109 patients (77.3%) experienced reduction in their LDL-C levels while 32 patients (22.7%) experienced an increase in their LDL-C levels. Only 18 patients (12.7%) can attain LDL-C goal <70 mg/dL and a factor associated with the attainment adherence in taking statin drug consistently.

Keywords: myocardial infarction, statin, LDL-C attainment

INTRODUCTION

Coronary Heart Disease (CHD) remains a major cause of death worldwide.[1] Each year an estimated 17 million people worldwide die from heart disease and as many as seven million of the deaths were due to heart attack.[2, 3] One of the clinical manifestations of CHD is Myocardial Infarction.[4] The main cause of myocardial infarction is coronary atherosclerosis.[4, 5] Various important step in the management of myocardial infarction therapy has been carried out based on existing evidence-based, one of which is the provision of statin therapy.[6] A meta-analysis suggests that any reduction in Low-Density Lipoprotein Cholesterol (LDL-C) level by 1 mmol/L (≈39 mg/dL) provides a major reduction in vascular events by 21%, non-fatal myocardial infarction 27%, coronary death 20%, ischemic stroke 16%, and mortality 10%.[7]

National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) up-date of 2004 has set LDL cholesterol as the primary target of therapy and myocardial infarction patients classified as very high-risk patients so that they recommends an optional LDL-C goal <70 mg/dL.[8] European Society of Cardiologist (ESC) also recommends attainment of LDL-C levels <70 mg/dL as a target of lipid-lowering drug therapy in patients with Acute Myocardial Infarction (AMI) and re-evaluate the lipid level 4-6 weeks after infarction.[9]

Based on the foregoing, statin therapy benefits patients in reducing recurrence and death. These benefits can be obtained if a given statin therapy can be directed to attain LDL-C goal that is recommended for patients with AMI, ie <70 mg/dL. However, it is still unknown presently to what extent these recommendations can be attained with statin therapy so that we intend to conduct this study to evaluate the effect of statins therapy on the attainment of LDL-C goal in patients with AMI and also to determine factors that may associated with the attainment of this goal.

METHODS

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Table 1. Baseline characteristics of patients

Characteristics	Category	Values (%)
Gender	Male	116 (82.3)
	Female	25 (17.7)
Age (years)	Mean ± Standar Deviation	58.21 ± 10.15
	Median (minimum-maximum)	57 (37-88)
	18 - 34 years old	0 (0.0)
	35 - 44 years old	7 (5.0)
	45 - 54 years old	47 (33.3)
	55 - 64 years old	52 (36.9)
	≥ 65 years old	35 (24.8)
Body Mass Index (BMI)	≥ 25 kg/m^2	47 (33.3)
	< 25 kg/m^2	94 (66.7)
Smoking status	Smokers	60 (42.6)
	Ex-smokers	31 (22.0)
	Non-smokers	50 (35.5)
Diagnose	STEMI	95 (67.4)
	NSTEMI	46 (32.6)
Reperfusion therapy	PCI	71 (50.4)
	Fibrinolytic	4 (2.8)
	PCI + Fibrinolytic	8 (5.7)
	CABG	1 (0.7)
	Without reperfusion	57 (40.4)
Number of comorbidities	≥ 3 comorbids	82 (58.2)
	2 comorbids	33 (23.4)
	1 comorbids	23 (16.3)
	No comorbids	3 (2.1)
Comorbidities	Dyslipidemia	107 (75.9)
	Hypertension	90 (63.8)
	Diabetes Mellitus	60 (42.6)
	Heart Disease	50 (35.5)
	Renal Impairment	24 (17.0)
Co-medication	Antiplatelets	141 (100.0)
	Anticoagulants	119 (84.4)
	Nitrates	102 (72.3)
	Angiotensin Inhibitor (ACE-ARB)	129 (91.5)
	Beta blockers	104 (73.8)
	Calcium Channel Blockers	21 (14.9)
	Diuretics	44 (31.2)
	Antiarrhythmics	11 (7.8)
	Digoxin	4 (2.8)
	Insulin	49 (34.8)
	Oral hypoglycemic agents	22 (15.6)
	Antigout	26 (18.4)
	Antianxiety	124 (87.9)
	Antiinfective agents	27 (19.1)
Number of co-medication	≥6	96 (68.1)
	1-5	45 (31.9)

Study Design and Subject Recruitment: This study was a descriptive analytical observational study conducted by a retrospective search through medical records and laboratory data of myocardial infarction patients aged ≥ 18 years who received statin therapies within 6 month since the outpatients were diagnosed with acute myocardial infarction (AMI) at cardiac clinic of a hospital in Yogyakarta Indonesia between 1 January 2009 and 30 September 2013. Patients were included if they have complete medical reports, especially the workup results of LDL-C levels. LDL-C assessment was performed at baseline (prior to initiation of statin) and at follow up (within 6 months). Patients who died before the 6-month period, did not have complete data workup LDL-C, obtain combination therapy with other lipid-lowering drugs, and who had LDL-C final results are less than 4 weeks from the date of initial LDL test results were excluded from this study.

Study variables included LDL-C levels (at baseline and follow-up), patients characteristics include sex, age, Body Mass Index (BMI), smoking status, types and numbers of comorbidities, types and number of concomitant medication (co-medication), and types of statin therapy include statin dose regimen, Defined Daily Dose (DDD),

duration on statin, and Medication Possession Ratio (MPR). DDD is the average of daily maintenance dose of a drug used in its main indication in adults set by the World Health Organization[10] where atorvastatin 20 mg, simvastatin 30 mg, pravastatin 30 mg, and rosuvastatin 10 mg. DDD considered <1 when the dose of statin used is less than DDD specified, eg: <20 mg of atorvastatin or <30 mg of simvastatin. DDD considered ≥1 when statin dose used is equal to or more than the specified DDD, eg ≥20 mg for atorvastatin or ≥30 mg for simvastatin. MPR is a formula used to determine the level of patients adherence, calculated as the sum of prescription days supply divided by the total number of days between the date of LDL-C baseline and the date of LDL-C final. Ratios were multiplied by 100 to generate adherence percentage. Adherence was defined as MPR equal to or greater than 80%.

Lipid profile assessment was performed at baseline (prior to initiation of statin) and at follow-up. Data collected from patient's medical records or electronic laboratory data. Goal attainment was evaluated at 6-month period after AMI with the final follow-up laboratory results were obtained. For patients with missing data (not had a LDL-C measurement at 6-month point), the most recent laboratory data were carried forward as the endpoint values. LDL-C goal attainment was defined as less than 70 mg/dL according to NCEP Guidelines[8] as the studied population was considered to be at very high-risk patients. This study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Gadjah, Indonesia.

Statistical Analysis: Descriptive statistics (numbers, frequency distributions, means, medians, and standard deviations) were used to present patients characteristics and profiles of statin therapy. Wilcoxon signed rank test was used to compare means between LDL-C baseline and LDL-C at follow up in the overall patients. Group differences in continuous variable were test by Mann-Whitney-U test (nonparametric analysis). Differences in the proportion of goal attainment across two groups were test by Chi-Square test or Fisher exact test. A two-tailed p-value of <0.05 was considered to be significant.

RESULTS

Patients characteristrics**:** A total of 141 patients were included in this study. The majority of patients were male (82.3%), average age 58.21 years, the youngest age was 37 years old and the oldest 88 years old, smokers (42.6%), have a BMI less than 25 kg/m^2 (66.7%), have comorbid ≥3 (58.2%) mostly dyslipidemia (75.9%), followed by hypertension (63.8%), diabetes mellitus (42.6%), heart disease (35,5%), and renal impairment (17%). Patients generally get co-medication ≥6 drugs (68.1%), mostly antiplatelet (100%), followed by angiotensin inhibitors (91.5%), antianxiety (87.9%), anticoagulants (84.4%), beta blockers (73.8%), nitrates (72.3%), insulin (34.8%), diuretics (31.2%), anti-infective (19.1 %), antigout, (18.4%), oral antidiabetic (15.6%) calcium channel blockers (14,9%), antiarrhythmics (7.8 %), and digoxin (2.8%), as presented in Table 1.

Profile of statin therapy: Most patients were prescribed simvastatin (50.4%) and atorvastatin (14.2%). In addition, many patients experience a change in treatment regimen (35.4%) both in terms of the type and dose of statins, with an average change treatment regimens per patient of 1.5±0.8 times (1-5 times). The most change in regimens was atorvastatin 40 mg/day to simvastatin 10 mg/day (18.4%). For patients with regimen unchanged during the period of six months, simvastatin 20 mg/day is the most widely prescribed (23.4%) followed by atorvastatin 40 mg/day (7.1%). Most of the patients (48.2%) were given statin therapy in average daily doses below the WHO recommended dose (DDD <1) and others (36.2%) experienced a reduction in the dose, 2.8% patients experienced increasing dose, and only 18 patients (12.8%) who received statin therapy in appropriate doses and above the average of the daily dose recommended by the WHO. Almost all of patients (96.5%) used statins in less than 6 months duration and only a small proportion (3.5%) was using statins in the duration of 6 months. Overall, 55.3% patients had MPR ≥80%.

LDL-C measurement results: The majority of patients (77.3%) experienced a decrease in LDL-C levels after statin therapy given over a period of 6 months. The median value of LDL-C final was 103 (39-276) mg/dL (mean: 109.24 ± 37.18 mg/dL), while the median value of LDL-C baseline was 128 (48-293) mg/dL (average: 132.22 ± 40.61 mg/dL). Overall, the percentage reduction in LDL-C was 19.1% and this is statistically significant (p<0.0001). However, this reduction in LDL levels did not occur in all patients, only 109 patients (77.3%) that declined while 32 patients (22.7%) experienced an increase in levels of LDL-C final.

Attainment of LDL-C goal <70 mg/dL.: Only 18 patients (12.7%) of 141 patients attained LDL-C goal <70 mg/dL after receiving statin monotherapy within 6 months period of follow up. Based on the results of bivariate analysis (Table 2.), patient adherence (defined by MPR) being the only factor significantly associated with LDL-C goal attainment <70 mg/dL (p=0.040).

DISCUSSION

This study has showed that there is a significant reduction in LDL-C levels after monitoring for statin therapy in patients within 6-month period since AMI. However, the decrease did not occur in all patients because there was a small proportion of patients had an increase in LDL-C levels. These patients generally are those who are no longer visit the doctor for treatment (23 patients) or those visited a doctor but not prescribed statins (9 patients). The reason of not prescribing are unknown but there was one patient who complained of side effects of the drugs such as stiff neck, upper left arm ache, pain, and pain when moved, and pain on the left shoulder joint. Another patient had LDL-C 67 mg/dL but uncontrolled hypertension that physicians discontinue statin therapy and focus on antihipertensive treatment. After hypertension can be controlled, LDL-C levels have increased. In addition, there are also two other patients with uncontrolled hypertension and continued to receive statin therapy but the dose

lowered. Overall, in addition to increased levels of LDL-C, patients who do not respond to statin therapy also experienced an increase in total cholesterol levels (18 patients), triglycerides (11 patients), decreased HDL (11 patients), uncontrolled hypertension (3 patients), uncontrolled blood sugar (7 patients) and underwent a change to less effective treatment regimens (22 patients). To note that, not all final LDL-C levels obtained in this study was LDL-C levels at month 6. The final LDL-C levels that can be obtained was the last owned by the patient within a period of 6 months since diagnosed with AMI. This led to the acquisition of the final LDL levels in a non-uniform time. These inconsistencies were due to the irregularity measurement of LDL-C or because the patients visit irregularly in the regular time intervals as recommended in the treatment guidelines. Because this is a retrospective study, we can only retrieve data based on what is available in the medical records and then analyzed them according to the actual conditions in the clinical practice.

Table 2. The results of bivariate analysis on patient's characteristics based on LDL-C goal attainment

Characteristics		Patient's groups				p	Odds Ratio (OR)	Confidence Interval (CI) 95%
		LDL-C ≥ 70 mg/dL (n = 123)		LDL-C < 70 mg/dL (n = 18)				
		n	%	n	%			
Gender								
Female		22	17.9	3	16.7	1.000	1.089	0.290-4.088
Male		101	82.1	15	83.3		ref	
Age group								
≥ 65 years		31	26.0	3	16.7	0.188	4.267	0.565-32.236
55 - 64 years		48	39.0	4	22.2	0.144	4.800	0.696-33.108
45 - 54 years		38	30.9	9	50.0	0.621	1.689	0.281-10.152
35 - 44 years		5	4.1	2	11.1		ref	
Body Mass Index (BMI)								
≥ 25 kg/m^2		43	35.0	4	22.2	0.284	0.532	0.165-1.715
< 25 kg/m^2		80	65.0	14	77.8		ref	
Smoking Status								
Smoker		49	39.8	11	61.1	0.217	2.020	0.651-6.267
Ex-smoker		29	23.6	2	11.1	0.702	0.621	0.113-3.414
Non-Smoker		45	36.6	5	27.8		ref	
No. of comorbidities								
≥ 3 comorbid		75	61.0	7	38.9	0.259	5.357	0.430-66.738
2 comorbid		27	22.0	6	33.3	0.488	2.250	0.174-29.055
1 comorbid		19	15.4	4	22.2	0.488	2.375	0.171-32.999
0 comorbid		2	1.6	1	5.6		ref	
Comorbidities								
Dyslipidemia	yes	94	76.4	13	72.2	0.769	1.247	0.410-3.791
	no	29	23.6	5	27.8		ref	
Hypertension	yes	80	65.0	10	55.6	0.434	1.488	0.547-4.049
	no	43	35.0	8	44.4		ref	
Diabetes Mellitus	yes	52	42.3	8	44.4	1.000	0.915	0.338-2.479
	no	71	57.7	10	55.6		ref	
Heart Disease	yes	42	34.1	8	44.4	0.394	0.648	0.238-1.765
	no	81	65.9	10	55.6		ref	
Renal Disorders	yes	22	17.9	2	11.1	0.738	1.743	0.373-8.133
	no	101	82.1	16	88.9		ref	
Concurrent medication								
Antiplatelets	yes	123	100.0	18	100.0	-	-	-
	no	0	0.0	0	0.0			
Anticoagulants	yes	103	83.7	16	88.9	0.739	0.644	0.137-3.021
	no	20	16.3	2	11.1		ref	
Nitrates	yes	90	73.2	12	66.7	0.579	1.364	0.473-3.928
	no	33	26.8	6	33.3		ref	
ACEI-ARB	yes	114	92.7	15	83.3	0.183	2.533	0.617-10.410
	no	9	7.3	3	16.7		ref	
Beta blockers	yes	93	75.6	11	61.1	0.250	1.973	0.702-5.543
	no	30	24.4	7	38.9		ref	
CCB	yes	19	15.4	3	16.7	1.000	0.913	0.241-3.463

	no	104	84.6	15	83.3		ref	
Diuretics	yes	37	30.1	7	38.9	0.451	0.676	0.243-1.881
	no	86	69.9	11	61.1		ref	
Antiarrhytmics	yes	8	6.5	3	16.7	0.149	0.348	0.083-1.456
	no	115	93.5	15	83.3		ref	
Digoxin	yes	2	1.6	2	11.1	0.079	0.132	0.017-1.005
	no	121	98.4	16	88.9		ref	
Insulin	yes	43	35.0	6	33.3	1.000	1.075	0.377-3.065
	no	80	65.0	12	66.7		ref	
Oral hypoglycemic	yes	19	15.4	3	16.7	1.000	0.913	0.241-3.463
	no	104	84.6	15	83.3		ref	
Antigout	yes	24	19.5	2	11.1	0.527	1.939	0.417-9.012
	no	99	80.5	16	88.9		ref	
Antianxiety	yes	108	87.8	16	88.9	1.000	0.900	0.188-4.309
	no	15	12.2	2	11.1		ref	
Antiinfections	yes	23	18.7	4	22.2	0.750	0.805	0.242-2.673
	no	100	81.3	14	77.8		ref	
Number of co-medication		87	70.7	9	50.0	0.078	2.417	0.887 – 6.584
≥ 6		36	29.3	9	50.0		ref	
1-5								

Notes: AMI=Acute Myocardial Infarction; LDL-C=Low-Density Lipoprotein Cholesterol; ACEI=Angiotensin-Converting Enzyme Inhibitor; ARB=Angiotensin II Receptor Blockers, CCB=Calcium Channel Blockers; ref=referency.

Table 3. The results of bivariate analysis on statin therapy based on LDL-C goal attainment

Variables	Patient's Groups				p	OR	Confidence Interval (95%)
	LDL ≥ 70 mg/dL (n = 123)		LDL < 70 mg/dL (n = 18)				
	n	%	n	%			
Statin Regimen							
Change to less effective regimens	73	59.3	9	50.0	0,481	1,442	0.519-4.008
Change to more effective regimens	5	4.1	1	5.6	1,000	0,889	0.091-8.646
Unchange	45	36.6	8	44.4		ref	
Defined Daily Dose (DDD)							
≥ 1 to < 1 (decreased-dose)	45	36.6	6	33.3	0.667	0.357	0.040-3.158
< 1 to ≥ 1 (increased-dose)	3	2.4	1	5.6	0.289	0.143	0.007-2.940
< 1	54	43.9	10	55.6	0.276	0.257	0.031-2.135
≥ 1	21	17.1	1	5.6		ref	
Duration on Statin							
1 month	38	30.9	5	27.7	0.503	1.900	0.176-20.559
2 months	20	16.3	4	22.2	1.000	1.250	0.109-14.343
3 months	22	17.9	3	16.7	0.538	1.833	0.150-22.366
4 months	23	18.7	3	16.7	0.525	1.917	0.157-23.347
5 months	16	13.0	2	11.1	0.539	2.000	0.143-27.990
6 months	4	3.2	1	5.6		ref	
Medication Possesion Ratio (MPR)							
< 80%	59	48.0	4	22.2	0.040	3.227	1.005-10.356
≥ 80%	64	52.0	14	77.8		ref	

This study also showed that only a few number of patients can attain recommended LDL-C goal <70 mg/dL (12.7%). This result is similar to other research conducted by Munawar *et al* who found that only 12.1% of patients at very high-risk that were capable of attainning LDL-C goal <70 mg/dL.[11] The results of bivariate analysis showed that factor gender, age, BMI, smoking, and even statin therapy did not show a statistically significant association with the attainment of LDL-C goal <70 mg/dL.

Gender factor did not show a statistically significant association with attainment of LDL-C goal <70 mg/dL (p=1.000). The proportion of men who do not attained LDL-C goal is slightly lower than that of men who attained LDL-C goal (82.1% vs. 83.3%), whereas in women, women who did not attained LDL-C goal is slightly higher

Table 4. The results of nonparametric analysis on statin dose at the beginning and end of monitoring statin therapy

Categori	*n*	*Median (minimum-maximum)*	*Means ± SB*	*p*[*]
Atorvastatin doses at the beginning				
Group ≥ 70 mg/dL	58	40 (10-80)	41.90 ± 13.17	0.544
Group < 70 mg/dL	5	40 (40-80)	48.00 ± 17.89	
Atorvastatin doses at the end of monitoring				
Group ≥ 70 mg/dL	22	40 (10-40)	31.82 ± 11.40	0.464
Group < 70 mg/dL	2	40 (40-40)	40.00 ± 00.00	
Simvastatin doses at the beginning				
Group ≥ 70 mg/dL	64	20 (10-40)	19.53 ± 5.75	0.963
Group < 70 mg/dL	13	20 (10-40)	20.77 ± 9.54	
Simvastatin doses at the end of monitoring				
Group ≥ 70 mg/dL	100	10 (10-40)	14.10 ± 5.52	0.138
Group < 70 mg/dL	15	20 (10-20)	16.00 ± 5.07	

[*]Tested with *Mann-Whitney U test* because not distributed normally. SD: standard deviation

than the proportion of women who attained LDL-C goal (17.9% vs. 16.7%). However, this difference did not give a statistically significant association. These results are consistent with those of another study.[12] Research conducted by Vonbank *et al* showed different results that gender affects the attainment of LDL-C goal <70 mg/dL because the study found differences in LDL-C baseline between men and women.[13] In our study, there was no difference in LDL-C baseline between men and women (132.16±38 vs. 132.48±53 mg/dL, p=0.701) so there was no significant difference between men and women to attain LDL-C goal <70 mg/dL.

Age factor did not show a statistically significant association with attainment of LDL-C goal <70 mg/dL (p> 0.05). However, the risk of not attainning LDL-C goal is greater. This is indicated by the increased value of OR in the higher age groups, particularly in the older age (≥55 years). Older patients (≥55 years) had a higher OR (OR> 4) than the younger patients (<55 years, OR=1.689) so that older patients have more risk of not attainning LDL-C goal by 4 times compared to the younger ones. More comorbid in older age, a complex drug regimen, low patient compliance rate due to polypharmacy, given the lower dose of the drug because fear of side effects, are all factors that make older patients difficult to continue treatment and so attain LDL-C goal.[14, 15]

Patients with BMI <25 kg/m^2 attain much more LDL-C goal compared with patients who can not attain LDL-C goal (77.8% vs. 65.0%), whereas patients with a BMI ≥ 25 kg/m^2 less to attain LDL-C goal compared with those not attain LDL-C goal (22.2% vs. 35.0%). However, this difference is not enough to give a statistically significant association with attainment of LDL-C goal (p=0.284). Cone *et al* also found no association between LDL-C attainment with BMI, both BMI as a continuous variable and BMI as a categorical variable that Cone *et al* suggested that each health care system started using abdominal obesity as a measure of obesity in the patient medical record.[16]

Smoking status also showed no significant association with LDL-C goal attainment. However, smoker patients less attained the LDL-C goal than patients who ex-smokers and non-smokers (39.8% vs. 23.6% vs. 36.6%). This smoking status data are taken from the patient's anamnesis when patients on admission to the hospital instead of smoking status data after patients undergoing outpatients treatment. Smoking status data after a patient undergoing outpatients treatment is not available in the medical record. Based on data from the time of admission this statistical analysis is done and the results give a non-significant value (p=0.217) when compared smokers with ex-smokers and non-smokers. However, factors of smoking had an OR>1 (OR=2.020 95% CI:0.651-6.267), meaning that smoking increases the risk for patients not to attain LDL-C goal <70 mg/dL by 2.02 times.

The majority of patients had various comorbidities. Patients with ≥3 comorbids totaling 82 patients (58.16%). More comorbidities increase the complexity of therapy, especially in the selection and use of drugs. Polypharmacy becomes an inevitable and is likely to increase the occurrence of modification of therapy, drug interactions and side effects so may influence LDL-C goal attainment. The results of bivariate analysis showed no significant association between the number of comorbid with LDL-C goal attainment (p>0.05). However, the results also showed that OR values increase as the number of comorbid increased. Patients who had ≥3 comorbid have the highest OR value (OR=5.357 95% CI: 0.430-66.738). This suggests that the greater the number of comorbid the greater the risk for patients not to attain LDL-C goal.

Five major comorbids found in patients with AMI in this study were dyslipidemia, hypertension, diabetes mellitus (DM), heart disease, and renal impairment. The fifth disease is thought to affect the attainment of LDL-C goal due to its contribution to disease progression. The results of the bivariate analysis showed that patients with renal disorders have the highest risk for not attainning the LDL-C goal compared with others (OR=1.743 95% CI: 0.373-8.133), meaning that renal disorders increases the risk for patients not to attain LDL-C goal <70 mg/dL by 1.743 times.

Comorbid brings about many consequences on the increase of the type of drug used to treat it. Polypharmacy is inevitable and this increases the risk of side effects and potential drug interactions that lead to modification of therapy is sometimes necessary to prevent it. This situation might affect the attainment of LDL-C goal so that statin can not be used in maximum doses to attain therapeutic

targets. The results of bivariate analysis showed that there was no significant difference between the two groups of patients in terms of type of co-medication. Although the results of statistical tests indicate there are some medications that have a value of OR>1 but it does not give a statistically significant association to the outcome of therapy (p>0.05). This is probably due to no significant effects occur as a result of drug interaction between the two groups of patients who use these co-medication because statins have been used in a range of safe doses so as to prevent the onset of the interaction.

Number of co-medication also allegedly affect the achievement of therapeutic targets for the amount of LDL that many drugs can reduce patient compliance in the treatment of patients so it is possible not to take medication was consequently difficult to achieve therapeutic targets. Bivariate analysis had been conducted to determine association between the number of co-medication with LDL-C goal attainment. Figure five cutpoint used in categorizing co-medication amount due based treatment guidelines that patients with AMI will receive five different drugs as a secondary preventive therapy, ie aspirin, clopidogrel, ACE inhibitors/ARBs, beta blockers, and nitrates. The results of bivariate analysis showed that the proportion of patients with ≥6 co-medication number more in the group of patients who did not attained the LDL-C goal compared with the group of patients who attained the LDL-C goal (70.7% vs. 50.0). However, this difference is still not enough to provide a statistically significant difference. It can be caused due to these drugs is necessary for the specific conditions of the patients where the drug if it can properly control the patient's condition will also helped contribute to the improvement of primary disease.[17] The result also shows the value of OR>1 for the number of co-medication ≥6 (OR=2.417 95% CI: 0.887-6.584). This means that the number of co-medication that many (≥6) increases the risk of patients with AMI to not attain LDL-C <70 mg/dL for 2.417 times. Thus, it is important to always choose the drug that is really fit the patient's condition (exact indications) and to prevent the use of unnecessary drug therapy regimen in order to keep it simple making it easier for patients to undergo treatment and attain the goal.

Initial (baseline) LDL-C level alleged effect on LDL-C goal attainment. High baseline LDL-C levels require statin with high dose in order to attain LDL-C <70 mg/dL. National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) in the treatment guidelines update 2004 mentions that LDL levels ≥100 mg/dL as a cutpoint to initiate lipid-lowering drug therapy in high risk patients (including IMA). The results of bivariate analysis shows that the proportion of patients with initial LDL levels ≥100 mg/dL is greater in the group that did not attain the goal compared to the group who attain the goal (82.1% vs. 61.1 %). Although not statistically significant, the initial LDL levels had an OR>1 (p=0.058 OR=2.921 95% CI: 1.018-8.381) which means that the initial LDL levels ≥100 mg/dL may increase the risk of not attainning LDL-C goal by 2.921 times. Initial LDL levels ≥100 mg/dL require statin dose that can lower LDL by ≥30%. The larger the initial LDL levels need more intensive statin dosage.

Statin therapy is thought to be the main factors that influence LDL-C goal attainment. As the drug of choice for lipid therapy, statins can lower LDL by 22-60%. The ability of statins is dose-dependent and linear. Low doses produce a substantial reduction in LDL-C level and any increase in dose of twice the daily dose will provide additional LDL-C lowering effect on average by 6-7%.[18] The results of the analysis in Table 3 shows that the change in treatment regimen to the less effective regimens are more experienced by the group of patients who did not attain the LDL-C goal compared with those who attained the LDL-C goal (59.3% vs. 50.0%). In contrast, change regimens to more effective regimens, less experienced by the group of patients who did not attain LDL-C goal compared with those who attained the LDL-C goal (4.1% vs. 5.6%). But, this difference did not give significant p values (p>0.05). However, change therapy regimens to the less effective regimens have a value of OR>1 (OR=1.442 95% CI: 0.519-4.008) so that it can be interpreted that change regimens to less effective treatment regimens increases the risk of patients to not attain LDL-C goal <70 mg/dL by 1.442 times.

Substitution therapy regimens experienced by many patients will make the patients receiving different doses at the beginning and end of therapy monitoring. This situation could give effect to the patient's ability to attain LDL-C goal <70 mg/dL. To determine whether the differences in the dose giving a significant difference, then performed a statistical analysis of various doses of statins are ever given to patients with AMI in this study. The results of the analysis are listed in Table 4. The results showed that none of the statin dose provides a meaningful difference to the attainment of LDL-C goal between the two groups of patients. However, the results also showed that the average dose of statins in the group of patients who did not attain LDL-C goal were lower than those who attained the LDL-C goal <70 mg/dL, although not statistically significant p>0.05).

STELLAR Study measuring the efficacy of LDL-C reduction of each statin therapy in a 6-week period, suggests that rosuvastatin 40 mg/day provides the greatest LDL-C lowering effect (55.0%), followed by atorvastatin 80 mg/day (51.1%), atorvastatin 40 mg/day (47.8%), simvastatin 80 mg/day (45.8%), atorvastatin 20 mg/day (42.6%), simvastatin 40 mg/day (38.8%), atorvastatin 20 mg/day (36.8%), simvastatin 20 mg/day (35.0%), pravastatin 40 mg/day (29.7%), simvastatin 10 mg/day (28.3%), pravastatin 20 mg/day (24.4%), and pravastatin 10 mg/day (20.1%) (19). Some literatures also suggest that change in therapy regimens performed 4-6 weeks after starting statin therapy (9,20,21). Therefore, no significant differences in terms of treatment regimens and doses of statins in this study is likely due to the changes is done in a short duration (<1 month). At the beginning of therapy, most patients with AMI receiving statin in high-intensity dose (30% reduction in LDL-C efficacy - ≥ 50%, such as atorvastatin 40-80 mg/day or simvastatin 40 mg/day), but then this regimen experienced turnover time <1 month and

carried to the type and/or a dose of statin with lower efficacy in reducing LDL-C concentration (eg from atorvastatin 40 mg/day to simvastatin 10 mg/day or from atorvastatin 40 mg/day to atorvastatin 20 mg/day). This is likely due to doctors tailor therapy based on the patient's insurance system where patients do not warrant the cost of treatment outside the provisions of the enactment.[11] Another cause was the fear of side effects due to the use of statin dose with a higher intensity. Although large-scale clinical studies have proven the efficacy and safety of statins for a diverse population, the study was limited to Asian populations. In addition, the more potent statins have a higher price and not yet available in generic form so it is not covered by the patient.[22] These conditions would complicate the attainment of LDL-C goal <70 mg/dL, especially if the patient has a very high baseline LDL levels which should be given a more potent statin to attain a LDL-C goal but this can not be done because of insurance policy.

Duration on statin use was also expected to affect the attainment of LDL-C goal <70 mg/dL. Because not all patients taking statin drugs on a regular basis (some patients ever had dropped out drug), category for the duration on statin factor is divided into per month. To determine whether the duration on statin is associated with the attainment of LDL-C goal <70 mg/dL, then performed statistical analysis. The results are presented in Table 3. The results showed that there was no significant association between factor of duration on statin towards the attainment of LDL-C goal <70 mg / dL (p> 0.05). This is likely due to the use of statins is not continuous so that the effect of statins could be decreased and targeted therapy becomes difficult to attain. However, the statistics also show the value of OR>1 for the duration of statin use <6 months. This means that the use of statins <6 months may increase the risk for patients with AMI not attaining the LDL-C goal of <70 mg/dL.

Other risk factor thought to influence the attainment of LDL-C goal is patients adherence. Patient adherence rate was calculated using MPR (Medication Possession Ratio) formula. MPR is a widely used method to estimate patient adherence to medication taking for research data derived from administrative data and figures 80% is the most commonly used cutpoint.[23] The results of the analysis are listed in Table 3. The results showed that MPR factor provide a significant association to the attainment of LDL-C goal <70 mg/dL. The proportion of patients who had MPR <80% was more in the group of patients who did not attain the LDL-C goal compared with those who attained the LDL-C goal (48.0% vs. 22.2%). These results indicate that the degree of adherence have a significant association on the attainment of LDL-C goal <70 mg/dL.

Based on a statistical analysis of the factors that can affect LDL-C goal attainment, MPR is the only factor associated with the attainment of LDL-C goal <70 mg/dL so that multivariate analysis is not necessary performed again.

CONCLUSION

This study shows that LDL-C <70 mg/dL goal attainment is still very low at very high risk patients suffering from AMI due to low levels of patient adherence in taking statin drugs on a regular basis. This will be a challenge for healthcare professional (especially pharmacist) to find the best therapeutic approach strategy in treating the patients using the currently available statin therapies for the good outcomes can be achieved.

REFERENCES

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Abayans V. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;(380):2095–128.
2. Delima D, Mihardja L, Siswoyo H. Prevalensi dan Faktor Determinan Penyakit Jantung di Indonesia. Bul Penelit Kesehat. 2009;37(3):142–59.
3. Ndindjock R, Gedeon J, Mendis S, Paccaud F, Bovet P. Potential impact of single-risk factor versus total risk management for the prevention of cardiovascular events in Seychelles. Bull World Health Organ. 2011;89(4):286–95.
4. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mahonen M, Blackett KN. World Health Organization Definition of Myocardial Infarction: 2008-2009 revision. Int J Epidemiol. 2011;40(1):139–46.
5. Antman EM. ST-Segment Elevation Myocardial Infarction: Pathology, Pathophysiology, and Clinical Features. In: Braunwald E, editor. Braunwald's Heart Disease A Textbook of Cardiovascular Medicine. 9th ed. Philadelphia: Elsevier Saunders; 2012. p. 1088.
6. Nakatani D, Sakata Y, Suna S, Usami M, Matsumoto S, Shimizu M. Incidence, Predictors, and Subsequent Mortality Risk of Recurrent Myocardial Infarction in Patients Following Discharge for Acute Myocardial Infarction. Circ J. 2013;77(2):439–46.
7. CTT (Cholesterol Treatment Trialists') Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670–81.
8. Grundy SM, Cleeman JI, Merz NB, Brewer Jr HB, Clark LT, Hunning Hake DB, et al. NCEP Report Implication of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004;110(2):227–39.
9. Steg PG, James SK, Atar D, Badano LP, Blömstrom-Lundqvist C, Borger MA. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2012;33(20):2569–619.
10. WHO. WHOCC - ATC/DDD Index [Internet]. 2013 [cited 2014 Jun 3]. Available from: http://www.whocc.no/atc_ddd_index/?code=C10AA
11. Munawar M, Hartono B, Rifqi S. LDL Cholesterol Goal Attainment in Hypercholesterolemia: CEPHEUS Indonesian Survey. Acta Cardiol Sin. 2013;(29):71–81.
12. Xanthopoulou I, Davlourus P, Siahos S, Perperis A, Zaharioglou E, Alexopoulos D. First-line treatment

patterns and lipid target levels attainment in very high cardiovascular risk outpatients. Lipids Health Dis. 2013;12(170):1–9.
13. Vonbank A, Saely CH, Rein P, Sturn D, Drexel H. Current cholesterol guidelines and clinical reality: a comparison of two cohorts of coronary artery disease patients. Swiss Med Wkly. 2013;143(w13828):1–8.
14. Cook K, Tisdale JE. Cardiovascular. In: Hutchison LC, Sleeper RB, editors. Fundamentals of Geriatric Pharmacotherapy An Evidence-Based Approach. Bethesda Maryland: American Society of Health-System Pharmacist, Inc.; 2010. p. 121–57.
15. Hilmer S, Gnjldlc D. Statins in older adults. Aust Prescr. 2013;36(3):79–82.
16. Cone C, Murata G, Myers O. Demographic determinants of response to statin medications. Am J Health Syst Pharm. 2011;68(6):511–7.
17. Hajjar ER, Hanlon JT. Polypharmacy and Other Forms of Suboptimal Drug Use in Older Patients. In: Hutchison LC, Sleeper RB, editors. Fundamentals of Geriatric Pharmacotherapy An Evidence-Based Approach. Bethesda Maryland: American Society of Health-System Pharmacist, Inc.; 2006. p. 110.
18. Page RL, Nappi JM. Acute Coronary Syndrome. In: Alldredge B., Corelli RL, Ernst ME, Guiglielmo BJ, Jacobson PA, Kradjan WA, et al., editors. Koda-Kimble and Young's Applied Therapeutics The Clinical Use of Drugs. 10th ed. Philadelphia: Lippincott Williams and Wilkins Wolters Kluwer Health; 2013. p. 408.
19. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, et al. Comparison of the Efficacy and Safety of Rosuvastatin Versus Atorvastatin, Simvastatin, and Pravastatin Across Doses (STELLAR* Trial). Am J Cardiol. 2003;92(2):152–60.
20. American Pharmacist Association. Drug Information Handbook. 22nd ed. Ohio: Lexi-com Inc.; 2013.
21. Grundy SM, Becker D, Clark LT, Cooper RS, Denke MA, Howard WJ. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)-Executive Summary. JAMA J Am Med Assoc. 2001;285(19):2486–97.
22. Chin CW, Gao F, Le TT, Tan RS. Lipid Goal Attainment and Prescription Behaviour in Asian Patients with Acute Coronary SyndromeL Experience from a Tertiary Hospital. Clin Med Insights Cardiol. 2013;(7):51–7.
23. Chi MD, Vansomphone SS, Liu IA, Cheetham TC, Green KR, Scott RD, et al. Adherence to Statins and LDL-Cholesterol Goal Attainment. Am J Manag Care. 2014;20(4):e105–e112.