AIM OF THE WORK

To determine the effect of oral statin therapy in patients undergoing coronary artery bypass surgery on:

a) Perioperative myocardial infarction (Fatal and Non fatal MI)

b) Associated perioperative major adverse cardiac events (MACES) which include: heart failure, post operative angina, arrythymias and cerebrovascular stroke.

PATIENTS AND METHODS

Patients

The present study was carried out in MAADI armed forced hospital on 175 adult patients of both sex undergoing coronary artery bypass graft between march 2012 and march 2014 . The study will be approved from the ethical committee of the Alex faculty of medicine.

Exclusion criteria:

- Patients with history of recent myocardial infarction (within 6 weeks of surgery).
- Patients with preoperative serum creatinine > 2.0 mg/dl or on dialysis.
- Known hypersensivity to statins.
- Acute liver diseases.
- Uncontrolled heart failure.

Classification:

Patients will be randomly categorized in three groups:

Control group: 75 patients will be collected retrospective from records from MAADI armed hospital without pre or post operative statin therapy.

Group 1 (statin low dose): 50 patients will receive preoperative oral 10 mg atorvastatin (tablets) before CABG for 7 days once daily at 10 p.m.The same dose of atorvastatin will be given 12 hours post operatively and then daily till discharge from the hospital.

Group 2 (statin high dose): 50 patients will receive preoperative oral 80 mg atorvastatin (tablets) before CABG for 7 days once daily at 10 p.m.The same dose of atorvastatin will be given 12 hours post operatively and then daily till discharge from the hospital.

Methods

All patients will be subjected to the following:

Preoperative evaluation and preparation:

1. Proper history taking and clinical examination to exclude history of recent MI, AF, CVS and renal impairment.
2. ECG preoperative.
3. Laboratory investigations include:

a) Complete blood count.

b) Fasting blood sugar
c) Renal function (serum urea and creatinine)
d) Liver enzymes (SGOT and SGPT)
e) Coagulation profile: bleeding time, clotting time, prothrombin time, partial thromplastin time and INR
f) Serum Na, k, Ca
g) Arterial blood gases (ABG)
h) Preoperative lipid profile e.g. cholesterol, HDL, LDL, TG.

4. The second and third groups will receive atorvastatin (10-80mg) as described previously.

Postoperative evaluation will include the following:

1. Daily ECG assessment till discharge from the hospital for the detection of different types of cardiac ischemia and dyshythmia.
2. Laboratory investigations include:
   a) Complete blood count
   b) Fasting blood sugar
   c) Renal function (serum urea and creatinine)
   d) Liver functions (SGOT, SGPT)
   e) Coagulation profile: bleeding time, clotting time, prothrombin time, partial thromplastin time and INR.
   f) Post operative lipid profile e.g. cholesterol, HDL, LDL, TG.

All preceding investigations will be done daily during the ICU stay and then every 3 days in the ward till discharge.

3. Cardiac markers include:
   a) Troponin I level using Siemens dimensions EXL 200 apparatus.
   b) LDH, CKMB using Siemens dimensions EXL 200 apparatus.
   c) Fibrinogen level using sysmexCA1500 (will be done for the second and third group)

These markers will be measured daily inside the ICU and in the ward till the discharge from the hospital.

4. Type and number of grafts used in revascularization will be recorded.
5. Follow up for major adverse cardiac events for one month after discharge

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. Qualitative data were described using number and percent. Quantitative data were described using Range (minimum and maximum), mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. When more than 20% of the cells have expected count less than 5, correction for chi-square was conducted using Fisher's Exact test or Monte Carlo correction. The distributions of quantitative variables were tested for normality using Kolmogorov-Smirnov test, Shapiro-Wilk test and D'Agstino test, also Histogram and QQ plot were used for vision test. If it reveals normal data distribution, parametric tests was applied. If the data were abnormally distributed, non-parametric tests were used. For normally distributed data, comparison between two independent populations was done using independent t-test while more than two population were analyzed F-test (ANOVA) to be used and Post Hoc test (LSD). Significance of the obtained results was judged at the 5% level.

RESULTS

A total of 175 patients undergoing CABG surgery were included in the study, 75 patients without statin therapy (control group), 50 patients who received perioperative statin therapy in low dose of 10 mg (group 1), another 50 patients received perioperative atorvastatin therapy in high doses of 80 mg (group 2)

The results of this work has been tabulated and compared with each other

Preoperative history

Table (1): Preoperative history among studied groups

	Control (n = 75)		10 mg (group1) (n = 50)		P1	80 mg (group2) (n = 50)		P2	P3
	No.	%	No.	%		No.	%		
Risk factors									
DM	29	38.7	18	36.0	0.76	12	24.0	0.08	0.217
HTN	58	77.3	34	68.0	0.24	24	48.0	0.007	0.003*
Smoker	39	52.0	26	52.0	1.00	20	40.0	0.18	0.357
Previous CV Accidents									
CVS	4	5.3	2	4.0	0.73	1	2.0	0.35	0.887
MI	20	26.7	8	16.0	0.16	6	12.0	0.04	0.098
Co-morbid diseases									
Pulmonary	6	8.0	3	6.0	0.67	2	4.0	0.37	0.680
Renal	5	6.7	3	6.0	0.88	1	2.0	0.23	0.569
Preoperative medications									
B Blocker	50	66.7	38	76.0	0.26	32	64.0	0.75	0.388
ACE	29	38.7	19	38.0	0.94	13	26.0	0.14	0.298

p_1: p value for comparing between control and 10 mg
p_2: p value for comparing between control and 80 mg
p_3: p value for comparing between control and10 mg and 80 mg
*: Statistically significant at $p \leq 0.05$

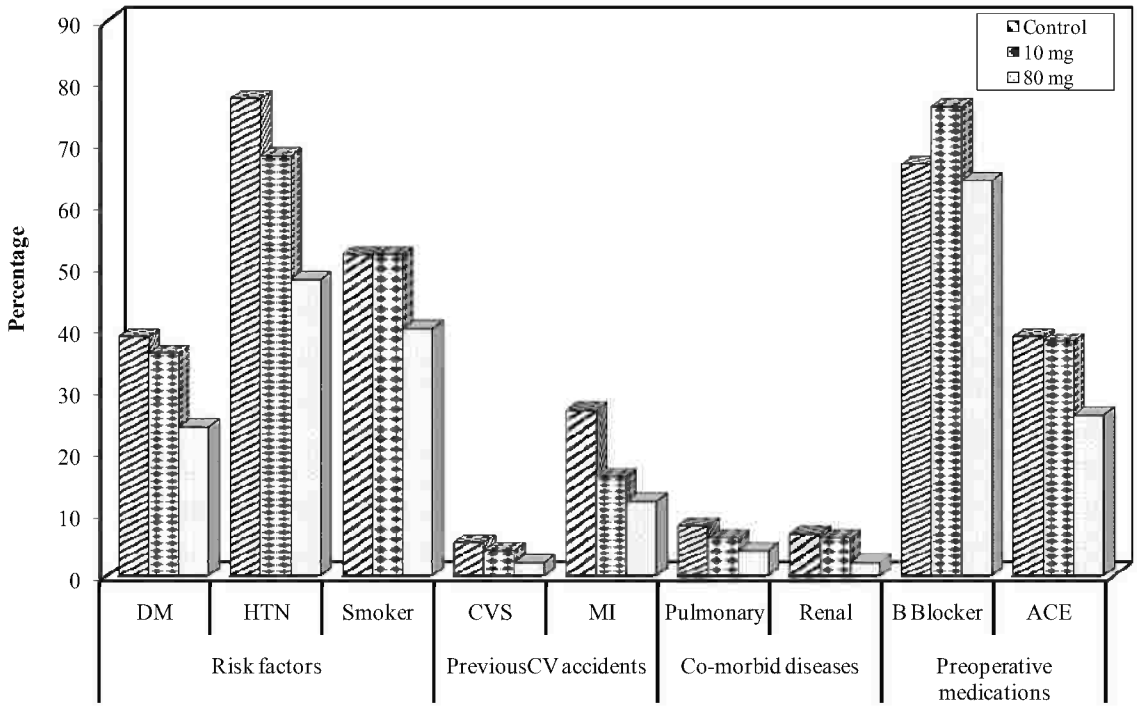

Figure (6): Comparison between the different studied groups according to preoperative history

- No statistically significant difference was found between patients without statin therapy and those who received statin therapy (low and high doses) regarding preoperative DM, smoking. (p=0.217, 0.357 respectively) (Table 1).
- There was a significant difference in the incidence of hypertension p value 0.003* which is due to its prevalence or due to more association with coronary artery disease.
- No statistically significant difference was found between control and treatment groups regarding previous CVS accidents. (p=0.88, 0.09 respectively) (Table 1)
- As regard the Co- morbid diseases, the history of pulmonary diseases and the history of renal disease did not differ between the three groups. (p =0.680, 0.56 respectively) (Table 1)
- Our present findings indicate that the history of B blocker intake (p value =0.388) (Table 1) and ACE inhibitor intake (p value =0.298) (Table 1) didn't differ between patients who didn't received atorvastatin and the patients who received atorvastatin in low and high doses.

Preoperative laboratory results

Table (2): Preoperative laboratory results among groups

	Control (n = 75)	10 mg (n = 50)	P1	80 mg (n = 50)	P2	P3
CBC						
Hb (g/dl)	13.3±1.88	13.32±2.1	0.95	13.122±1.8	0.59	0.802
Platelet(million /cmm)	224.7±41	216.4±39.9	0.26	215±42.25	0.20	0.398
Wbc (/cmm)	7.8 ±2.41	7.84±2.31	0.92	8.022±2.40	0.61	0.892
Renal profile						
Urea (mg/dl)	43±16.8	42.4±18.11	0.84	40.23±11.05	0.30	0.625
Creatinine(mg/dl)	0.95±0.19	0.95±0.17	1	0.934±0.19	0.64	0.887
Liver profile						
- AST(U/L)	26.24 ±32.51	30.94±53.57	0.54	34.68±67.4	0.35	0.654
- ALT(U/L)	24.45±45.26	30.7 ± 68.60	0.54	34.12 ±82.5	0.40	0.697
Fbs (mg/dl)	148±75.3	155.94±100.2	0.61	170.94±97.97	0.14	0.385
Coagulation profile						
- PTT(sec)	35.8±5.79	36.11±5.94	0.77	35.85±5.8	0.96	0.900
- INR	1.03±0.14	1.029±0.18	0.97	1.0316±0.135	0.95	0.981

p_1: p value for comparing between control and 10 mg
p_2: p value for comparing between control and 80 mg
p_3: p value for comparing between control and10 mg and 80 mg
*: Statistically significant at $p \leq 0.05$

No significant difference was found as regards the complete blood count, the blood sugar level, the renal functions including urea and creatinine, the liver enzymes and the coagulation profile between the studied groups.

Preoperative lipid profile among the three groups

Table 3: Preoperative lipid profile

	Control (n = 75)	10 MG (n = 50)	80 MG (n = 50)
TG	200±15.05	145±14.27	125±19.96
CHOLESTEROL	255±27.25	195±26.16	175±37.7
LDL	170±32.9	110±34.93	95±33.91
HDL	36±10.54	55±9.33	60±10.22

- Among the preoperative lipid profile (cholesterol, TG, LDL), the patient who did not receive atorvastatin had a higher lipid profile in comparison to patients who received atorvastatin 10 mg 7 days preoperative and 80 mg atorvastatin 7 days pre operative.
- The level of triglyceride, cholesterol, LDL was higher in the control group than group 1 and lowest in group 2 before the operation while HDL was lower in the control group than group 1 and highest in group 2.This means that statin had an effect in triglyceride, cholesterol and LDL during this short period and apparently did not reduce HDL even with high dose.

Post operative laboratory results

Table 4: Post operative laboratory results

	Control (n = 75)	10 mg (n = 50)	P1	80 mg (n = 50)	P2	P3
CBC						
Hb (g/dl)	10.09±2.18	10.002+-2.07	0.82	10.2±2.44	0.79	0.889
Platelet(million /cmm)	194.63±62.8	196.46±68.14	0.87	168.5±63.3	0.07	0.048*
Wbc (/cmm)	13.62±3.206	13.54+-3.48	0.89	12.17±3.65	0.06	0.047*
Renal profile						
Urea (mg/dl)	45.83+-16.94	59.39±59.33	0.063	54.01±45.1	0.15	0.190
Creatinine(mg/dl)	1.0333±0.196	1.01+-0.33	0.62	0.94±0.347	0.057	0.250
Liver profile						
- AST(U/L)	42.09± 17.41	44.22± 16.12	**0.49**	48.64± 25.9	0.093	0.199
- ALT(U/L)	58.46±42.2	69.48±49.11	0.18	73.64±53.8	0.080	0.185
Fbs (mg/dl)	200.25±91.04	195.1±88.13	0.75	192.48±87.4	0.63	0.884
Coagulation profile						
- PTT(sec)	39.46±7.161	40.06±7.9	0.66	41.85±8.37	0.09	0.235
- INR	1.19±0.275	1.208±0.23	0.70	1.2±0.234	0.83	0.981
Cardiac enzymes						
Troponin I (ng/ml)	2.32±3.5	1.716±3.03	0.32	1.358±2.55704	0.09	0.223
LDH (Iu/l)	661.05±361.80	640.46±373.46	0.75	591.28±353.97	0.097	0.571
Fibrinogen (g/l)		2.44±1.13		2.15±0.96		0.178

p_1: p value for comparing between control and 10 mg
p_2: p value for comparing between control and 80 mg
p_3: p value for comparing between control and10 mg and 80 mg
*: Statistically significant at $p \leq 0.05$

Our present findings indicate that statins group (low and high doses) and the control groups were similar as regard the post operative laboratory investigations such as the complete blood count, the blood sugar level, the renal functions including urea and creatinine, the liver enzymes, the coagulation profile and the cardiac enzymes.

Post operative lipid profile

Table 5: Post operative lipid profile

	control (n = 75)	10 MG (n = 50)	80 MG (n = 50)
TG	170±14.05	135±13.27	115±18.96
CHOLESTEROL	240±27.25	180±26.16	150±36.7
LDL	160±31.9	110±33.9	80±32.91
HDL	40±10.54	57±9.33	62±10.22

- In comparison to the three groups we found that the lipid profile (cholesterol, TG, LDL) of the patients who received 80 mg was less than the patients who received atorvastatin 10 mg which was less than the patient who did not receive atorvastatin postoperative .
- Among our study we found that the lipid profile of the post operative of the three group patients was less than the lipid profile of the preoperative patients
- The level of triglyceride, cholesterol, LDL was higher in the control group than group 1 and lowest in group 2 after the operation while HDL was lower in the control group than group 1 and highest in group 2.This means that statin had an effect in triglyceride, cholesterol and LDL during this short period and apparently did not reduce HDL even with high dose.

Postoperative complications

Table 6: Postoperative complications

Complications	Control (n = 75)		10 mg (n = 50)		P1	80 mg (n = 50)		P2	P3
	No.	%	No.	%		No.	%		
MI	10	13.3	4	8.0	0.35	2	4.0	0.08	0.195
CVS	4	5.3	2	4.0	0.39	1	2.0	0.35	0.887
MOR	6	8.0	2	4.0	0.14	0	0.0	0.04	0.097
AF	25	33.3	14	28.0	0.52	3	6.0	0.003	0.002*
HF	8	10.7	3	6.0	0.36	1	2.0	0.06	0.180

p_1: p value for comparing between control and 10 mg
p_2: p value for comparing between control and 80 mg
p_3: p value for comparing between control and10 mg and 80 mg
*: Statistically significant at $p \leq 0.05$

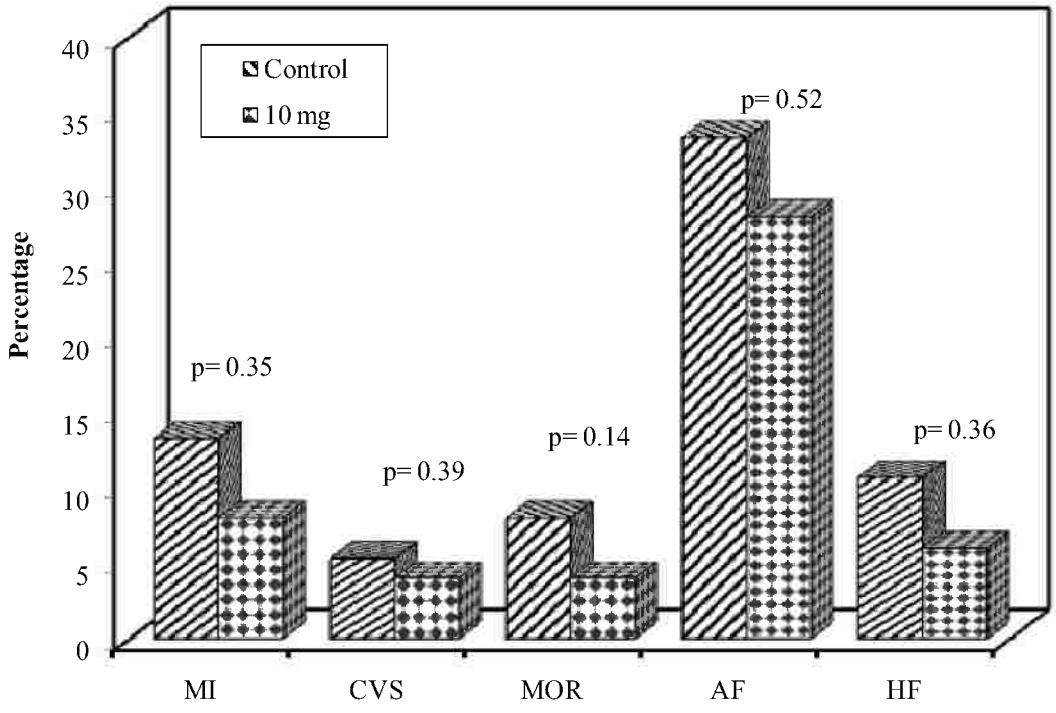

Figure (7): Comparison between the control group and group 1 according to postoperative complications

- The incidence of myocardial infarction was lower in patient receiving 10 mg atorvastatin 4 (8%) as compared with control group 10 (13%) (p value= 0.35) but it did not reach the significance level.
- The present study indicate that the incidence of atrial fibrillation was less in patients receiving 10 mg atorvastatin 14 (28%) than in comparison with patients who did not receive 25 (33%) (p value= 0.5)
- The incidence of heart failure was 8 (10%) in control group and was 3 (6%) among patients receiving 10 mg atorvastatin (p value= 0.36)
- The post operative cerebrovascular stroke did not differ between both groups (p value= 0.39)
- The mortality rate was 6 (8%) in the control group versus 2 (4%) in patients receiving 10 mg atorvastatin (p value= 0.14) (Table 6) (Figure 7)

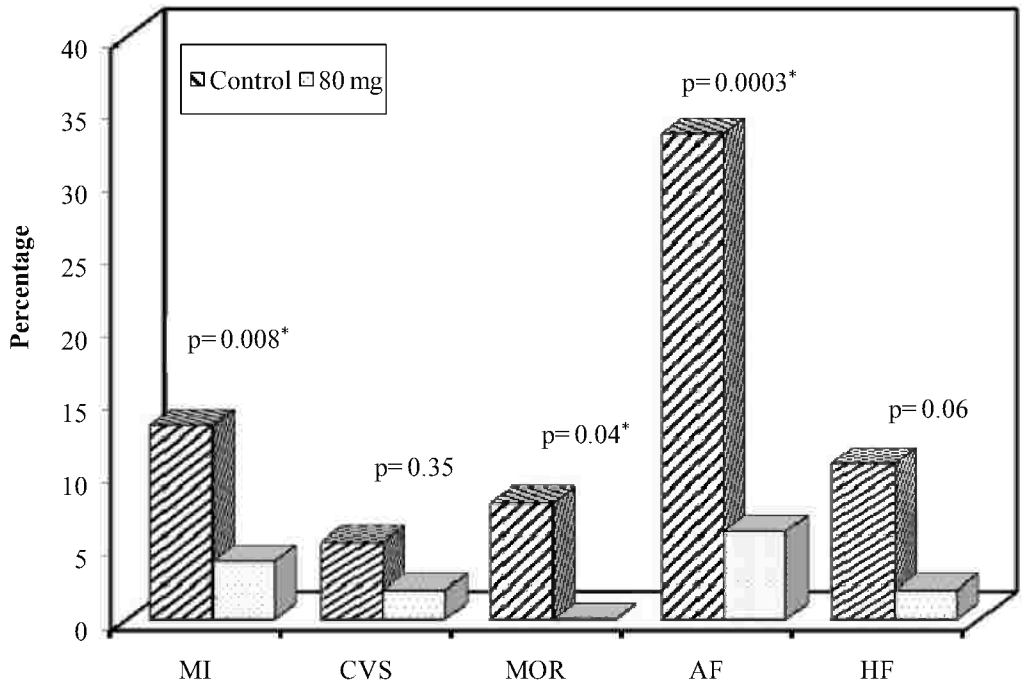

Figure (8): Comparison between the control group and group 2 according to postoperative complications

- Although we found a clinically relevant trend toward reduction in myocardial infarction , it did not meet the threshold for statistical significance so patient without atorvastatin therapy had more incidence for myocardial infarction 10 (13%) in comparison to patients who received atorvastatin therapy 80 mg 2 (4.0%) (p=value 0.08)

- Our study confirmed the clinical benefit of statins in terms of reducing atrial fibrillation among patients who received atorvastatin in high doses 3(6%) in comparison to patients who does not receive atorvastatin 25 (33%) which show a significant stastical finding (p value = 0.0003)

- As regard heart failure, analysis showed that there was no difference between both control groups 8 (10%) and patients receiving 80mg atorvastatin 1(2%) (p value= 0.06) but the incidence of heart failure was much lower in patients treated with high dose atorvastatin 80mg.

- In the present study as regard the post operative cerebrovascular stroke the incidence was 4 (5%) in control group versus 1 (2%) in patients received 80 mg atorvastatin (p value= 0.35)

- The present findings indicate that the more intensive regimen resulted in a lower mortality rate among patients receiving 80 mg of atorvastatin 0(0%) in comparison to patients who did not receive atorvastatin 6 (8%) which shows a statically significant difference (p value= 0.04) (Table 6) (Figure 8)

Comparison between the studied groups according to TG

Table 7: Comparison between the studied groups according to TG

TG level	High		Low		p
	No.	%	No.	%	
Control	**(n=51)**		**(n=24)**		
No Complication	21	41.2	4	16.7	0.036*
Complication	30	58.8	20	83.3	
10 mg	**(n=40)**		**(n=10)**		
No Complication	21	52.5	9	90.0	
Complication	19	47.5	1	10.0	0.037
80 mg	**(n=32)**		**(n=18)**		
No Complication	25	78.1	18	100.0	0.040*
Complication	7	21.9	0	0.0	

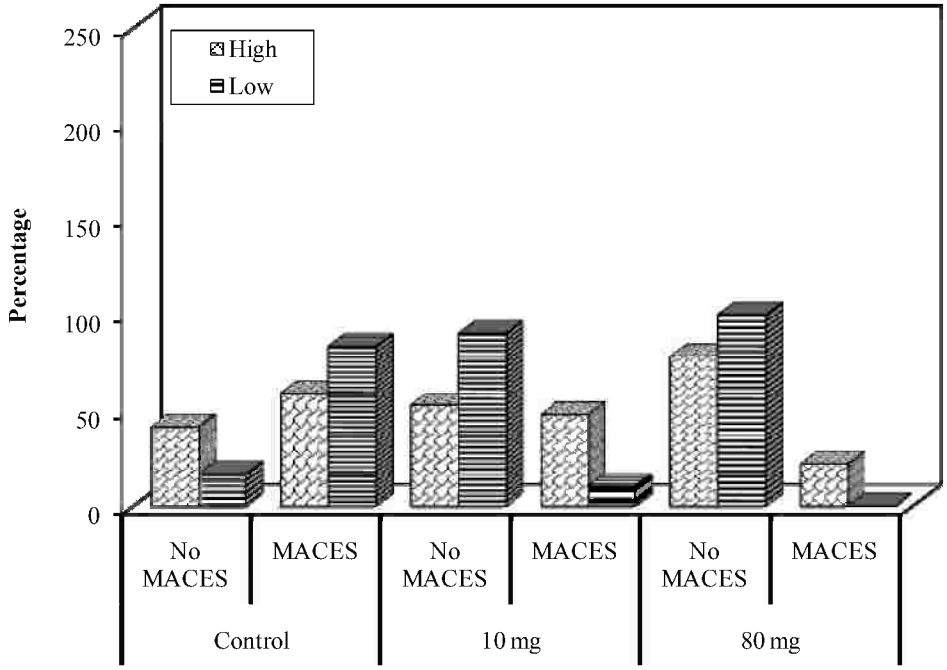

Figure (9): Comparison between studied groups according to TG

- In control group, the incidence of complication was 20 complication (83%) in low TG level versus 30 complication (58.8%) in high TG group which was statistically different (P value =0.036)
- In group 1, the incidence of complication is one complication in low TG (10%) versus 19 complications (48%) in high TG group which was statistically significant (P value= 0.037) this means that high TG are still effective in increasing the incidence of the complication despite drug treatment.
- In group 2, the incidence of complication was no complication (0%) in low TG level versus 7 complications (21%) in high TG group which was statistically different (P value= 0.040) (Table 7)

Comparisonbetween the studied groups according to cholesterol

Table 8: Comparison between the studied groups according to cholesterol

Cholesterol level	High		Low		p
	No.	%	No.	%	
Control	**(n=35)**		**(n=40)**		
No Complication	3	8.6	21	52.5	<0.001*
Complication	32	91.4	19	47.5	
10 mg	**(n=20)**		**(n=30)**		
No Complication	8	40.0	22	73.3	0.018*
Complication	12	60.0	8	26.7	
80 mg	**(n=23)**		**(n=27)**		
No Complication	18	78.3	27	100.0	0.016*
Complication	5	21.7	0	0.0	

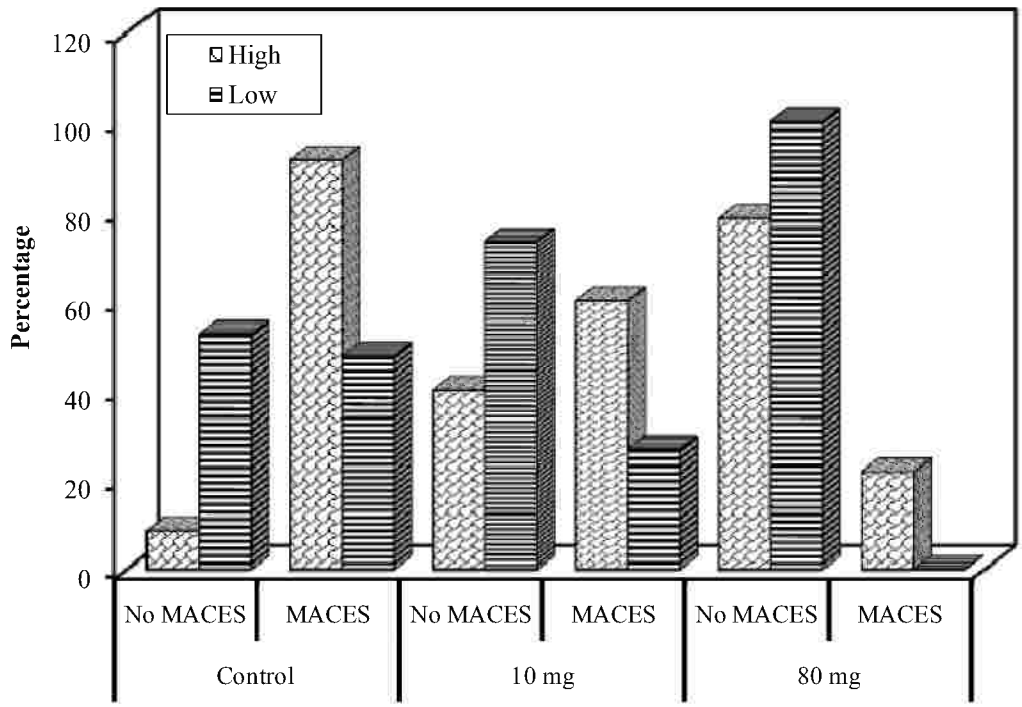

Figure (10): Comparison between studied groups according to cholesterol

- In control group, the incidence of MACES was 19 complications (47%) in low cholesterol group versus 32 (91%) in high cholesterol groups (p value=0.0001)
- In group 1, the incidence of MACES was 8 complications in low cholesterol group (26%) versus 12 in high cholesterol groups (60%) (P value= 0.018)
- In group 2, the incidence of MACES was 0 complications (0%) in low cholesterol group versus 5 (21%) in high cholesterol groups (p value=0.001) (Table 8)

Comparison between the studied groups according to LDL

Table 9: Comparison between the studied groups according to LDL

LDL level	High		Low		p
	No.	%	No.	%	
Control	**(n=42)**		**(n=33)**		
No Complication	2	4.8	20	60.6	<0.001*
Complication	40	95.2	13	39.4	
10 mg	**(n=20)**		**(n=30)**		
No Complication	8	40.0	22	73.3	0.018*
Complication	12	60.0	8	26.7	
80 mg	**(n=23)**		**(n=27)**		
No Complication	18	78.3	27	100.0	0.016*
Complication	5	21.7	0	0.0	

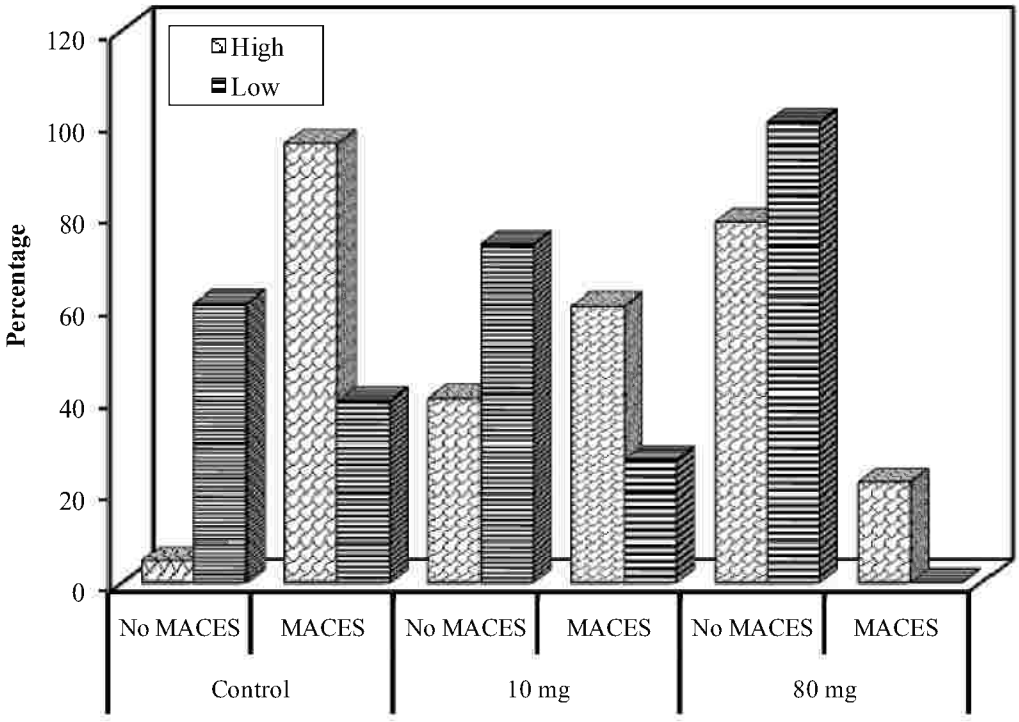

Figure (11): Comparison between studied groups according to LDL

- In control group, the incidence of complication was 13 complications (39.4%) in low LDL level versus 40 complications (95%) in high LDL group which was statistically significant (P value =0.001)
- In group 1,the incidence of complication is 8 complications in low LDL (26%) versus 12 in high LDL group (60%) which was statistically significant (P value= 0.0184)

- In group 2,the incidence of complication was no complication (0%) in low LDL level versus 5 complications (21%) in high LDL group which was statistically different (P = value 0.001) (Table 9)

Comparison between the studied groups according to HDL

Table 10: Comparison between the studied groups according to HDL

HDL level	High		Low		p
	No.	%	No.	%	
Control	**(n=25)**		**(n=50)**		
No Complication	21	84.0	15	30.0	<0.001*
Complication	4	16.0	35	70.0	
10 mg	**(n=35)**		**(n=15)**		
No Complication	27	77.1	5	33.3	0.003*
Complication	8	22.9	10	66.7	
80 mg	**(n=30)**		**(n=20)**		
No Complication	22	73.3	7	35.0	0.007*
Complication	8	26.7	13	65.0	

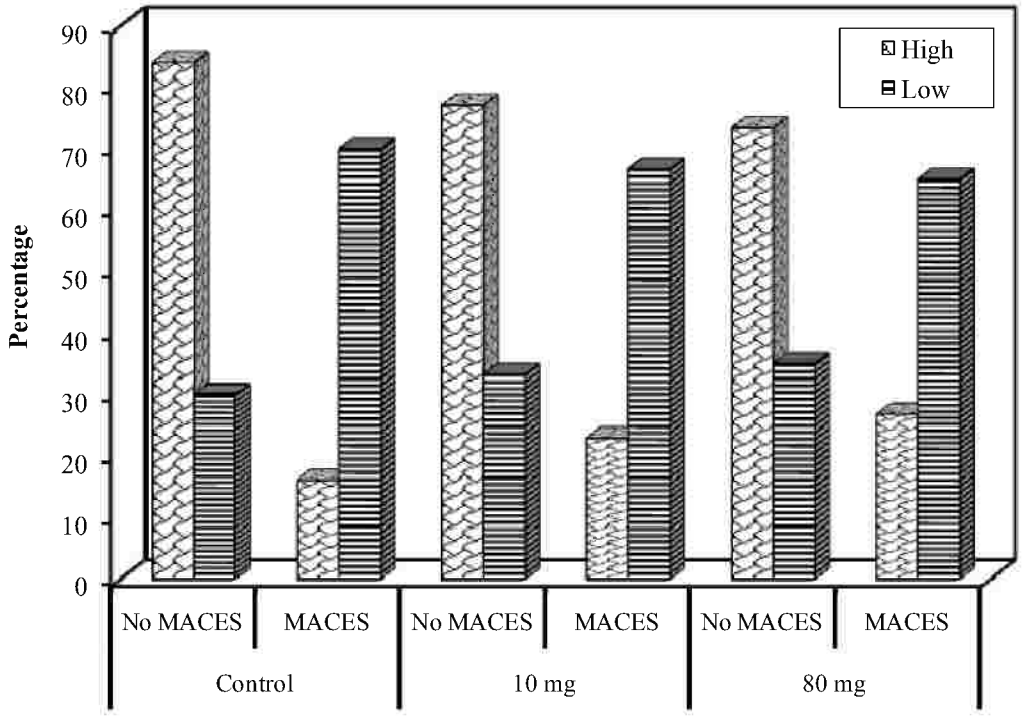

Figure (12): Comparison between studied groups according to HDL

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- In control group, the incidence of complication was 35 complications (70%) in low HDL level versus 4 complications (16%) in high HDL group which was statistically different (P value= 0.0001)
- In group 1, the incidence of complication was 10 complications (66%) in low HDL level versus 8 complications (22%) in high HDL group which was statistically different (P value= 0.003)
- In group 2, the incidence of complication was 13complication (65%) in low HDL level versus 8 complications (26%) in high HDL group which (P value= 0.0071) (Table 10)