DISCUSSION

Despite progress in surgical techniques, cardiac surgical morbidity and mortality is still a problem of medical and socioeconomic significance. [71] As statin therapy has been shown to have an early beneficial effect in patients with acute coronary syndromes and in patients undergoing percutaneous coronary interventions, studies investigate the role of atorvastatin therapy in patients undergoing coronary artery bypass graft. [72]

Elevated cholesterol and TG levels have been shown to increase the risk of atherosclerotic heart disease and its complications, while lipid lowering has been shown to reduce adverse cardiovascular events. Hyperlipedemia has been shown to be a risk factor for major cardiac events.

Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase and are the most effective lipid-lowering agents available to clinicians. They exert their action by inhibiting the conversion of 3-hydroxy-3-methylglutaryl coenzyme A into mevalonate, which is the rate-limiting step in cholesterol synthesis. In addition to inhibition of mevalonic acid synthesis, statins also decrease the synthesis of other isoprenoid intermediates involved in the cholesterol pathways. When a cell is exposed to one of the statins, the function of this enzyme is inhibited and therefore mevalonate and the isoprenoids are not produced. Mevalonic acid (MVA) depletion induces the up-regulation of the low-density lipoprotein (LDL) receptor expression, mainly in liver cells, which explains most of the LDL cholesterol lowering effect of statins. [73]

Statins up regulate endothelial nitric oxide synthase, leading to coronary artery vasodilatation and improved flow in patients with occlusive coronary artery disease. [74] Statin has a role in improvement of endothelial function, dilatation of coronary micro vessels and has anti-thrombotic effects and anti-inflammatory action. [75, 76]

As regard risk factors and previous cardiovascular accidents, our study found that history of diabetes was 18 (36%) in patients receiving low doses of atorvastatin (group 1) versus 12 (24%) in patients receiving high doses (group 2).The history of hypertension was statically significant between both groups (p= 0.040 .History of myocardial infarction was reported in 6 patients who received 80 mg atorvastatin 6 (12.0%) versus 20 (26%) in patients who does not receive atorvastatin. While Kulik et al. found that the history of prior MI was 14.2 % for statin users versus 15.8 % for non statin users group. No difference was observed between the low and high doses as regards the co morbid diseases and preoperative medications. [77]

Hyperlipidemia is known as one of the major risk factors associated with vascular endothelial injury, causing atherosclerotic plaque formation and coronary artery disease (CAD) that result in recurrent ischemic cardiovascular events. We speculate that differences in the ability to lower LDL and cholesterol levels lead to significant differences

in the anti-atherosclerotic effect. Moreover, there were significant positive correlations between percent LDL, cholesterol and triglyceride reduction and percent change in the occurrence of major adverse cardiac events.

Our present findings indicate that statins group (low and high doses) and the control groups were similar as regard the pre and post operative laboratory investigations such as the complete blood count, the renal functions including urea and creatinine, the liver enzymes, the coagulation profile .Cardiac enzymes after the operation were higher in control group than in group 1 and lowest in group 2 which is related to myocardial injury.

By comparison, the incidence of complications in patients taking atorvastatin 10 mg and 80 mg in relation to TG, it was found that the incidence of complications was 10%, 0% in low TG group and was 48%, 0% in high TG group in patients taking 10mg and 80 mg respectively which was lower than the incidence of complications in control group which was 83%in low TG and 58% in high TG. In accordance that the mean of triglyceride was lower in atorvastatin group 135±13.27, 115±18.96 in patients taking 10 mg and 80 mg respectively which was lower than the control group 170±14.05. This means that the incidence of complications has decreased in patients taking 10 mg and 80 mg in relation to TG and this reduction was dose dependant .Patients with high TG had more complications than patients with low TG.

Numerous clinical trials have demonstrated that decreasing LDL, TG and cholesterol levels is highly effective in primary and secondary prevention of CAD by substantially reducing the risk of adverse cardiovascular events, particularly in selected groups of patients with hyperlipidemia, familial atherosclerosis, a previous history of CABG or acute coronary syndromes. In our study, when compare the incidence of complications in patients taking atorvastatin 10 mg and 80 mg in relation to cholesterol, it was found that the incidence of complications was 26%, 0% in low cholesterol group and was 60%, 0% in high cholesterol group in patients taking 10mg and 80 mg respectively which was lower than the incidence of complications in control group which was 47% in low cholesterol and 91% in high cholesterol. In accordance that the mean of cholesterol was lower in atorvastatin group180±26.16, 150±36.7 in patients taking 10 mg and 80 mg respectively which was lower than the control group 240±27.25. This means that the incidence of complications has decreased in patients taking 10 mg and 80 mg in relation to cholesterol level, this reduction was dose dependant and the complications were high among patients with high cholesterol level.

There is also evidence that coronary plaque's inflammatory characteristics strongly influence the likelihood of plaque rupture, which is at highest risk in hyperlipidemic patients. By comparison the incidence of complications in patients taking atorvastatin 10 mg and 80 mg in relation to LDL it was found that the incidence of complications was 26% , 0% in low LDL group and was 60%, 0% in high LDL group in patients taking 10mg and 80 mg respectively which was lower than the incidence of complications in

control group which was 39% in low LDL and 95% in high LDL .In accordance that the mean of LDL was lower in atorvastin group 110±33.9,80±32.91 in patients taking 10 mg and 80 mg respectively which was lower than the control group 160±31.9. This means that the incidence of complications has decreased in patients taking 10 mg and 80 mg in relation to LDL and this reduction was dose dependant. Patients with high LDL had more complications than patients with low LDL.

In the present study, Statins reduce the level of Triglyceride (TG), cholesterol and low density lipoprotein (LDL) and this reduction was dose dependant. .The post operative complications were higher in the control group than in group 1 and lowest in group 2. In the three groups, it was found that patients with high TG or high cholesterol or high LDL or low HDL had more complications than patients with low cholesterol, TG, LDL or with high HDL.

A significant reduction in the composite end point (myocardial infarction, atrial fibrillation, heart failure, CVS and mortality) between the control, low dose (10mg), high dose (80mg) (13% vs10% vs3%) giving p value=0.01. Statins will lead to reduction in the incidence of complications probably through its anti inflammatory effect also the level of the cardiac enzymes which is related to myocardial injury and this was dose dependent.

Since the introduction of statin in 1987, many clinical studies have reported that statin therapy reduces major cardiovascular events by reducing the LDL and cholesterol level, which lead to a revolution in the management of cardiovascular disease. The Scandinavian Simvastatin Survival Study (4S) [78] was the first large-scale study showing that using statins reduced major cardiovascular events, cardiovascular mortality, and total mortality in patients with coronary artery disease and high blood cholesterol levels. Then, the West of Scotland Coronary Prevention Study (WOSCOPS) [79] showed that statins reduce major cardiovascular events and cardiovascular mortality in patients with high blood cholesterol levels but without coronary artery disease.

In the agreement with the present study Sanjiv J. Shah et al show that patients with previous CABG who had their LDL and cholesterol lowered with atorvastatin 80 mg had a significantly better outcome than those with LDL and cholesterol lowered with 10 mg of atorvastatin. Compared with the less-aggressively treated patients, those in the atorvastatin 80 mg group experienced a 27% reduction in major cardiovascular events and a 30% reduction in repeat coronary revascularization (either CABG or percutaneous coronary intervention) during a mean follow-up of 4.9 years. On balance, intensive dosing of statins appears to offer benefits to patients and should be considered in light of patient history and profile and possible adverse consequences so aggressive lipid-lowering with atorvastatin 80 mg decreases major cardiovascular events and the need for repeat revascularization in patients with CABG with the goal of reducing cardiovascular morbidity and mortality and prolonging bypass graft patency.

PROVE IT [80] study has show that 4162 patients with acute coronary syndrome were randomized to intensive statin (atorvastatin 80 mg) versus standard therapy. There was significant 16%reduction in outcome events defined as death from any cardiac cause, myocardial infarction, documented unstable angina, revascularization performed at least 30 days after randomization .

The Treating to New Targets (TNT) [81] trial was the first large-scale randomized trial curried over 4.9 years to investigate the effects of 80 mg of atorvastatin in a population of patients with stable coronary artery disease and moderately elevated LDL and cholesterol. La Rosa et al sought to determine whether aggressive LDL and cholesterol lowering with high-dose therapy would provide incremental benefit over moderate dose therapy. The investigators randomized 10 001 patients with stable coronary artery disease to atorvastatin 80 mg or 10 mg and followed them for a median of 4.9 years. The investigators observed a 22% reduction in the primary end point (composite of coronary death, non-fatal MI, resuscitated cardiac arrest, or stroke) in the atorvastatin 80 mg.

Concerning atrial fibrillation as a type of rhythm disturbance that affects about one-third of patients after cardiac surgery, there is an outstanding evidence for the beneficial actions of statin. [83] In the present study present study indicate that there was a statistically significant difference between patients who did not receive atorvastatin 25 (33%) and patients who received atorvastatin in high doses (80mg) 3 (6%) as regard post operative atrial fibrillation ($p = 0.0003$). Also, the present findings indicate that patients receiving atorvastatin in high doses (80mg) have developed atrial fibrillation 3 (6 %) in a significant reduction in comparison with low doses (10mg) atorvastatin 14 (28%).

In agreement with the present study, Giovanni et al. [84] found over a two-year period and in 405 consecutive patients who underwent isolated CABG procedures using univariate analysis in exploring the relationship regarding statin use and AF development that preoperative statins reduce postoperative AF after CABG and patients undergoing elective revascularization may benefit from a preventive statin approach.

Also these results met with Dotani et al.[85] who found a significant difference between both groups regarding postoperative AF. Statin use was associated with decreased occurrence of post-CABG AF which occurred in 12% of patients in the atorvastatin group vs. 26% of patients in the placebo group ($p < 0.001$)

In contrast, Miceli et al. [86] concluded that statin was associated with a significantly higher incidence of postoperative atrial fibrillation compared with no statin treatment in patients undergoing isolated coronary artery bypass grafting. This may be due to variation in the duration of follow up and number of patients and the short period of preoperative atorvastatin intake.

The present study showed a trend toward reduction in myocardial infarction in patients who have received high doses of atorvastatin 80 mg 2 (4%) in comparison to control

group10 (13%) p value 0.08.Mannacio et al. evaluated the effect of 20 mg/d rosuvastatin pretreatment for 1 week before on-pump CABG. Troponin I, myoglobin, and CK-MB mass values were assessed, and all biological markers were significantly lower in the rosuvastatin pretreatment group.

Gurbuz et al. [87] has investigated predictors of symptom recurrence (recurrent angina, MI and congestive heart failure) and adverse cardiac events (MI, coronary reintervention and any cardiac-related mortality including sudden cardiac death) and concluded that postoperative statin use was associated with both decreased symptom recurrence ($p < 0.0001$) and adverse cardiac events ($p < 0.0001$).

The other hand, Florens et al, [88] reported a randomized study in which giving atorvastatin before elective CABG did not result in a post-operative reduction in systemic inflammatory reaction or any improvement in clinical outcome. Dotani et al [85] showed that Myocardial infarction occurred within the first postoperative year in 0% of patients in the atorvastatin group vs. 1.4% of patients in the placebo group ($p =0.6$)

This difference may be attributed to several factors, including the poor standardization in the perioperative statin therapy regimen (e.g. The duration of atorvastatin intake by the patient preoperative. Increasing the number of patients would also probably result in sufficient number of incidence related to postoperative myocardial infarction. Future studies with larger sample size allowing multivariate analysis to adjust for multiple confounding factors would provide strong evidence

In accordance with 2011 ACCF/AHA guideline for coronary artery bypass graft surgery [89] in management of Hyperlipidemia which show that

- All patients undergoing CABG should receive statin therapy, unless contraindicated (class1a)
- For patients undergoing urgent or emergency CABG who are not taking a statin, it is reasonable to initiate high-dose statin therapy immediately (class 2a)

In the present study, as regard the post operative cerebrovascular stroke the incidence was higher 4 (5%) in control group versus 1 (2%) in patients received 80 mg atorvastatin but without statically difference ($p=0.35$). In our study, the post operative cerebrovascular stroke between the two groups was 2 (4%) in patients receiving 10 mg of atorvastatin versus 1 (2%) in patients receiving 80 mg of atorvastatin ($p= 0.55$)

In agreement with the present study, Koenig et [90] al. analyzed data of more than 5000 patients undergoing CABG procedures and failed to detect a decreased incidence of stroke after bypass procedures. In a large patient cohort study, Borger et al [91] could not find any relevant effects of statin therapy on perioperative adverse events including stroke after multivariate analysis. Pan et al [92] showed that statin therapy was independently associated

with a significant reduction in the risk of the composite outcome of 30-day all-cause mortality and stroke compared with non-users (7.1% versus 4.6%, respectively; $p < 0.05$)

The results of the present work do not match with Heart Protection Study (HPS) in which simvastatin significantly reduced the incidence of strokes by 25% due to short period of follow up in our study and the short period of preoperative atorvastatin intake

In Our study, we have studied the relation of low doses and high doses statins and their impact on the mortality rate in patients undergoing CABG. Our present findings indicate that the mortality rate was stastically significant between control group 6 (8%) and patients receiving 80 mg atorvastatin 0 (0%) ($p= 0.04$)

In agreement with our study, fifteen studies with 28 517 patients investigated the association between preoperative statin therapy and early all-cause mortality. Mortality was significantly lower in patients undergoing cardiac surgery who received preoperative statin therapy compared with controls, with an absolute risk reduction of 1.5%. Their meta-analysis revealed a 43% reduction in the odds of short-term mortality in patients receiving statins before cardiac surgery. [93] Also, Clark et al [94] reported a retrospective analysis with findings of lower mortality in patients who received a statin before cardiac surgery.

In contrast to the present study, Ali and buth [95] assessed whether preoperative statin use is associated with decreased mortality, they showed that preoperative statin was not associated with a reduction in hospital mortality in patients undergoing coronary artery bypass graft due to short period of follow up in our study and the short period of preoperative atorvastatin intake.

As like other study, our work has several limitations that must be considered. This study was carried in a short duration of pretreatment with atorvastatin to influence on the incidence of the major adverse cardiac events. Future studies with larger sample sizes and longer duration follow up allowing multivariate analysis to adjust for multiple confounding factors would provide strong evidence on potential effect of atorvastatin treatment on major adverse cardiac events. Further study to explain the effect of statin on post operative complications in other cardiac surgery.

This study demonstrates an improvement in early clinical outcome for patients of coronary artery bypass graft treated with perioperative statins. We believe that it is reasonable and in compliance with existing guidelines to advocate high dose statin treatment in a prolonged and reasonable time before the operation followed by a vigorous postoperative re-initiation regimen in all patients with multiple cardiac risks and coronary heart disease scheduled for coronary artery bypass graft. These results support existing practice guidelines and confirm that in the absence of serious contraindications; essentially all patients should be prescribed long-term statin therapy after CABG. [96]

SUMMARY

Coronary artery bypass graft surgery (CABG) is a major advance in the care of patients with coronary disease. Coronary artery bypass grafting (CABG) is associated with several perioperative major cardiovascular events including myocardial infarction (MI), atrial fibrillation, stroke, mortality which may significantly prolong length of stay in Intensive Care Unit (ICU) with increased costs and severe long term complications.

Elevated cholesterol and TG levels have been shown to increase the risk of atherosclerotic heart disease and its complications, while lipid lowering drugs has been shown to reduce adverse cardiovascular events

The aim of our work was to determine the effect of statin therapy in patients undergoing coronary bypass surgery on perioperative myocardial infarction and associated perioperative major adverse cardiac events (MACES) which include arrhythmias, heart failure, mortality and cerobrovascular stroke.

The study was carried out on 175 adult patients of both sex undergoing coronary artery bypass graft in MAADI armed forced hospital. Patients were randomly categorized in three groups: control group: 75 patients were collected retrospective from records from MAADI armed hospital without statin therapy. Group 1 (statin low dose): 50 patients had received preoperative oral 10 mg atorvastatin before CABG for 7 days .The same dose of atorvastatin had be given post operatively till discharge from the hospital. Group 2(statin high dose): 50 patients had received preoperative oral 80 mg atorvastatin before CABG for 7 days .The same dose of atorvastatin had been given post operatively a till discharge from the hospital. A Follow up for one month after discharge for major adverse cardiac events was conducted.

The three groups were compared according to preoperative data which includes proper history and clinical examination (risk factors, previous cardiovascular accidents, Co- morbid diseases and preoperative medications in form of B blockers and ACE inhibitors), ECG changes and laboratory investigations which include blood count, renal, liver , coagulation profile and lipid profile including (TG,cholesterol,LDL,HDL)

Post operative data were evaluated between the three studied groups which included Type and number of grafts used in revascularization, ECG changes laboratory investigations including complete blood count, cardiac markers(troponin I,LDH, fibrinogen), renal, liver, coagulation profile and lipid profile including (TG, cholesterol, LDL, HDL)

The following results were obtained:

- The highest incidence in risk factors in the whole population was hypertension .is it due to its prevalence or due to more association with coronary artery disease.
- The level of triglyceride, cholesterol, LDL was higher in the control group than group 1 and lowest in group 2 before and 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.
- Cardiac enzymes after the operation were higher in the control group than in group 1 and lowest in group 2.
- Perioperative statin therapy reduces the risk of atrial fibrillation and the mortality rate post coronary artery bypass graft. High dose statin therapy reduces the incidence of myocardial infarction versus low doses statins but without stastically significant difference. The incidence of cebrovascular stroke and the development of heart failure did not show any significant difference between the two groups.
- The post operative complications were higher in the control group than group 1 and lowest in group 2.
- More over patients in the control group who did not receive statin with high triglyceride or high cholesterol or high LDL or low HDL had more complications than patients with low cholesterol, triglyceride, LDL or with high HDL.
- The same finding was observed in both groups who received statin .patients with high cholesterol, triglyceride, LDL and low HDL had higher incidence of complications.

CONCLUSION

From this study we can conclude the following:

1) Statins given before CABG reduced the level of cholesterol, LDL, triglyceride and this reduction was dose dependant .At the same time there was no reduction in HDL even with high dose.

2) Statins will lead to reduction in the incidence of complications probably through its anti inflammatory effect also the level of the cardiac enzymes which is related to myocardial injury and this was dose dependent

3) In the three groups it was found that the incidence of complications was higher in patients with higher level of triglyceride, cholesterol, HDL and lower level of HDL. And this was not related to statin because it was also present in the control group and this observation could not be explained in this study.