Postoperative Cardiac Surgery Outcomes in a Statin-Native Population

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Abstract

Background: Statin utilization had been associated with improved survival after cardiac surgery. We aim to study whether perioperative treatment with statin could be associated with increased postoperative complications. Design: This was a retrospective, descriptive, single-center study. Settings: We analyzed morbidity after cardiac surgery as well as the outcome related to statin therapy in a tertiary cardiac center. Patients: A total of 202 consecutive patients were enrolled over 1 year after cardiac surgery. Intervention: Patients were divided into two groups; Group I – statin users and Group II – nonusers. Measurements: Measurements were baseline and follow-up laboratory markers for muscular injury including cardiac muscle and hepatic injuries and renal injuries. Results: The incidence of rhabdomyolysis and elevation of liver enzymes did not differ between both groups. Postoperative atrial fibrillation was significantly lower in the statin group (P = 0.02). In addition, peak cardiac troponin and creatine kinase-MB did not differ significantly in the statin group. Statin-treated group had significant lower length of mechanical ventilation, and length of stay in the Intensive Care Unit and hospital (P = 0.036, 0.04, and 0.027, respectively). Conclusions: Therapy with statin before cardiac surgeries was not associated with high incidence of adverse events.

Keywords: Cardiac surgery, outcome, statins

Introduction

In modern societies and developed countries, cardiovascular diseases and diabetes mellitus are the two leading causes of death and major morbidity. This obligates continuous research efforts tackling these two diseases. Hyperlipidemia is one of the major risk factors for coronary artery disease that requires an effective treatment strategy to reduce cardiovascular morbidity and mortality. Statins will competitively inhibit 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase enzyme to prevent the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in cholesterol biosynthesis.[1]

The reduction of cholesterol biosynthesis synthesis by statins will enhance the expression of the low-density lipoprotein (LDL) receptor gene, and hence raise the number of LDL receptors on the hepatocyte surface to amplify the elimination of the dangerous LDL-cholesterol from the blood. Other suggested theories, similar to the effect of niacin, are that statins could work through the removal of LDL precursors including apolipoprotein B-100, which is a component of VLDL and IDL cholesterol. This will reduce LDL cholesterol. Reduction of LDL cholesterol level is strongly related to a significant prevention of cardiovascular disease.[2]

Statins have pleiotropic effects irrespective of the LDL-cholesterol reduction with a poor correlation to cholesterol changes. This reduces the inflammatory responses by variable mechanisms such as improving endothelial function and reducing neutrophil-endothelial adhesion, adhesion molecules (e.g., intercellular adhesion molecule 1), and cytokine release (e.g., tumor necrosis factor alpha).[3] Pleiotropic effects occur rapidly and are rapidly reversible on discontinuation of the drug. Direct effects in the absence of LDL or total cholesterol modification have been shown both in vitro and in vivo.[2]
Mediated by its lipid-dependent and nonlipid-related mechanisms, statins are widely used in the perioperative settings of cardiac surgery targeting better outcomes. The current evidence suggests that preoperative statin therapy offers substantial clinical benefit to early postoperative outcomes in cardiac surgery patients.[4] Statins enhance graft patency in coronary artery bypass surgery (CABG) through possible beneficial molecular effects on graft biology that affect short- and long-term human graft patency.[4] Cardiovascular events include death from cardiac causes, nonfatal acute myocardial infarction, unstable angina, and ischemic stroke. These could be reduced with perioperative use of a statin independent of the serum cholesterol level.[4] There is evidence that statin utilization is associated with reduced postoperative morbidity and death in valvular cardiac surgery through an independent lipid-lowering mechanism.[5]

Additional possible beneficial effects that supports statin utilization in cardiac surgery – whether on-pump or off-pump – include a reduction in the odds of postoperative atrial fibrillation (POAF) and shortened Intensive Care Unit (ICU) and hospital stay,[5] possible improvement in cardiac and renal function by reducing inflammation and myocardial injury, and a protective effect against postsurgery infections.[6] Moreover, it is associated with a reduced risk of postoperative acute kidney injury (AKI).[7]

The most reported serious adverse effects include drug-induced liver injury and rhabdomyolysis (RML) with or without AKI. Thus, the uncertain safety of statin in cardiac surgery settings remains a major concern. Statins have been shown to have little hepatotoxicity as shown in many studies. However, these mostly focus on transaminitis. Thus, it is strongly recommended to monitor hepatic enzymes in patients with chronic liver disease, especially alanine aminotransferase (ALT), which is elevated in hepatitis or other hepatotoxicity.[8]

The incidence of RML-associated cardiac surgery is extremely variable. In a more recent report, the incidence was 8.41%.[9] RML is a clinical and biochemical syndrome that varies from benign increase of muscle enzymes, especially creatine kinase (CK) and myoglobin as well as AKI. We hypothesize that statin utilization could influence the postoperative complications including elevation of liver enzymes and RML. We aim to study the relationship between statins and morbidity after cardiac surgery. There have been many claims that statin use is associated with multiple morbidity events.

**Methods**

We performed a retrospective, descriptive, single-center study with purposive sampling that examined the occurrence of multiple complications after cardiac surgery. This study was conducted from October 2012 to December 2013 over 14 months in the cardiothoracic ICU (12 beds), Heart Hospital, Hamad Medical Corporation. The approval for the study was obtained from the research and ethical committee (reference number 14283/14). Informed consent was obtained from all the patients.

Baseline laboratory markers for muscular injury include cardiac muscle and hepatic injuries and renal injury includes CK, myoglobin, CK-MB isofrom, high-sensitivity troponin T, aspartate aminotransferase, ALT, serum creatinine, and blood urea nitrogen. The CK-MB isofrom and high-sensitivity troponin T were measured to quantify myocardial injury. Serum myoglobin levels were assessed by immunoassay from Beckman Coulter (Analis, Suerlée, Belgium). These laboratory markers were measured at the same time points by the accredited hospital laboratory.

We also collected laboratory data that were routinely obtained in the ICU on admission as well as demographic and clinical information including age, sex, race, medical comorbidities, drugs (statin therapy), type of surgery, anesthesia time, cardiopulmonary bypass (CPB) time, aortic cross-clamp time, use of inotropes and vasopressors, European System for Cardiac Operative Risk Evaluation (Euro-SCORE), length of mechanical ventilation, and length of stay in the ICU and hospital. Complications and outcomes (AKI, arrhythmia, infection, stroke, and death) were recorded for each patient. Patients with preexisting renal failure on dialysis or high liver enzymes as well as patients who already used statins for <4 weeks were excluded from the study.

**Study definitions**

We defined statin users as patients who are treated with a statin for at least 4 weeks and that used the maximum drug effects.[9] We used CK reference levels of 2500 U/ml or higher to define RML.[9] The AKI was defined in this study as an acute (within 48 h) deterioration in kidney parameters with absolute increase in serum creatinine concentration of 0.3 mg/dL (26.4 µmol/L) or greater or a percentage increase of 50% or greater (1.5-fold from baseline).[11] The Euro-SCORE was used to assess differences in patients’ risk profiles. While the American Society of Anesthesiologists (ASA) classification was used to categorize the surgical risk.

**Statistical analysis**

The results are presented as mean ± standard deviation (SD) for quantitative data and frequency and proportion for qualitative data. The groups were compared by *t*-test or Mann–Whitney U-test as appropriate for interval variables. Chi-squared tests were used for categorical variables. The data were expressed as mean ± SD or proportions/percentages for interval and categorical variables, respectively. *P* ≤ 0.05 (two-tailed) was considered to be statistically significant. The primary outcome was association of high liver enzymes or RML in the study population whether statin users or nonusers. The secondary outcomes measure the postoperative complications and length of mechanical ventilation and length of stay in the ICU and hospital. Clinical and laboratory data were entered into a database (Microsoft Excel 2010; Microsoft Corporation, Redmond, WA, USA), and statistical analyses were performed using statistical software (SPSS, version 20; SPSS, Inc., Chicago, IL, USA).
RESULTS

Clinical variables in the groups
There were 202 patients enrolled in our study with a mean age of 54.3 ± 10.8 years [Table 1]. Patients were divided into two groups: Group I included statin users (144 patients) and Group II included nonstatin users (58 patients). Both groups were matched regarding the age, diabetes mellitus (insulin and noninsulin dependent), hypertension, body mass index, ethnicity (Arab or Asian), Euro-Score, left ventricular ejection fraction (LVEF), basal serum creatinine, surgery type (elective or urgent), surgical procedure (CABG), and utilization of inotropes [Table 2].

Laboratory and prognostic variables in the group
The main intraoperative and postoperative parameters were recorded [Table 3]. The postoperative complication did not differ between both groups in terms of elevated liver enzymes, perioperative myocardial infarction (PMI), wound infection, RML, AKI, ventilator-associated pneumonia (VAP), early wound infection (within the hospital), hypoglycemia, early stroke, and in-hospital mortality. Laboratory variables are summarized in Table 4.

DISCUSSION
The main findings in our study were as follows: (1) the absence of significant incidence of adverse events in patients receiving statins before cardiac surgery and (2) favorable outcome regarding the POAF events and lengths of ventilation as well as the time in ICU and overall hospitalization time in the statins-treated group.

Multiple beneficial effects could be associated with the utilization of statin in cardiac surgery settings either on-pump or off-pump coronary artery surgery, valvular, or vascular surgery. An array of potential adverse effects have been attributed to prolonged utilization of statins. The most common is muscle effects with potential RML. Other additional statin-associated adverse effects included hepatic and pancreatic dysfunction, neuropathy, cognitive loss, and sexual dysfunction.

Both statin and nonstatin users were matched in our study regarding the age, gender, hypertension, diabetes mellitus, body mass index, ethnicity, Euro-Score, serum creatinine, preoperative liver enzymes, LVEF, inotropes, and surgical procedure [Table 2]. The relation of statin and liver enzymes warrants special attention, and the possible interactions through CYP3A4 inhibition deserves increased awareness – when statin therapy is required, the lowest effective dose should be given, especially for patients at jeopardy of having liver problems. Statin users in our study did not show significant liver enzyme elevation versus nonstatin users. Only 3 patients showed elevation after surgery. According to McSweeney et al., a history of MI, previous revascularization, and low EF <40% were independent factors that influence gastrointestinal complications in the postoperative period.

Liver ischemia following cardiac surgery could be attributed to a history of diabetes mellitus and coincidental heart failure. Murphy et al. reported that hepatocellular and visceral vascular perfusion could be affected by prolonged CPB time.

Prolonged surgery is a direct cause for the clinical syndrome of RML with an estimated incidence of 8.1% and 5.9% in vascular and cardiac surgeries, respectively. The outcome of RML varies according to the clinical circumstances where kidney injury and mortality remain the major concerns. In our study, we reported RML incidence of 8.9%, and statin users had slightly higher incidence but without statistical significance (P = 0.41). Lagandré et al., mentioned the precipitating risk factors of RML after surgery include obesity, prolonged surgery duration, prolonged supine posture, and diabetes associated with microangiopathy. Possible risk factors include metabolic derangement including hypernatremia, hypokalemia, hypocalcemia, and hypophosphatemia. Patients with ASA III and IV physical status are also at higher risk of developing RML. Only 3 patients showed elevation after surgery. According to McSweeney et al., a history of MI, previous revascularization, and low EF <40% were independent factors that influence gastrointestinal complications in the postoperative period.

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Muscle injury in statin users is described in <0.5% of cases. It is usually associated with high doses of statin. Statin therapy may potentiate undesirable effects when there is association of underlying neuromuscular disorders. In such cases, the development of clinically apparent disease happens in patients who likely had preclinical disease before statin use was initiated.

Close to RML, the AKI association in statin users in our study did not show any statistical significance (P = 0.316). In an observational study in cardiac surgery settings, Mithani

Table 1: Baseline characteristics of the studied group

| Variable                  | Minimum | Maximum | Mean±SD     |
|---------------------------|---------|---------|-------------|
| Age (years)               | 15      | 78      | 54.3±10.8   |
| BMI (kg/m²)               | 14.5    | 44.8    | 27.4±5.1    |
| Creatinine (µmol/L)       | 14.4    | 74.6    | 92.4±53.1   |
| LVEF (%)                  | 22      | 65      | 49±6.9      |
| HbA1c (%)                 | 5       | 16.6    | 7.4±4.5     |
| Additive Euro-SCORE       | 0       | 17      | 3.6±2.9     |
| CPB time (min)            | 0       | 304     | 110.2±46.3  |
| ACC time (min)            | 0       | 164     | 71.6±35.8   |
| WBCs (white blood cells)  | 5       | 30      | 12.1±4.4    |
| Hb (mg/dL)                | 7       | 16      | 10.2±1.5    |
| Anesthesia time (min)     | 180     | 700     | 323±90      |
| LOV (min)                 | 180     | 4800    | 532±501     |
| LOS_hospital (h)          | 26      | 111     |             |
| LOS ICU (days)            | 4       | 499     | 31.7±29.9   |

Statistical method: Mean±SD for quantitative data and frequency and proportion for qualitative data. BMI=Body mass index, LVEF=Left ventricular ejection fraction, CPB=Cardiopulmonary bypass, ACC=Aortic cross-clamp, WBCs=White blood cells, Hb=Hemoglobin, LOV=Length of mechanical ventilation, LOS_hospital=Length of stay in the hospital, LOS ICU=Length of stay in the ICU, HbA1c=Glycated hemoglobin, SD=Standard deviation, ICU=Intensive Care Unit, Euro-SCORE=European System for Cardiac Operative Risk Evaluation
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et al. found that pretreatment with statin was not associated with lower AKI.\(^19\) Similarly, Bolesa et al. did not find lower or higher AKI association with preoperative statin utilization following cardiac surgery using CPB.\(^20\)

In our study, we analyzed statin association with nosocomial infections, particularly VAP and early wound infections. We did not find any significant reduction in infections in the statin users. In addition, our VAP incidence was low (0.5%). Statins are claimed

### Table 2: Clinical and laboratory variables in both groups

| Variable                        | Group I (statin users) \(n=144\); 71.3\%, \(n\) (%) | Group II (nonstatin users) \(n=58\); 28.7\%, \(n\) (%) | \(P\)  |
|---------------------------------|--------------------------------------------------|--------------------------------------------------|-------|
| Age                             | 55.89±8.25                                       | 52.4±9.72                                       | 0.9   |
| Gender                          |                                                  |                                                  |       |
| Male                            | 134 (93.7)                                       | 51 (87.9)                                       | 0.1   |
| Hypertension                    | 111 (78.2)                                       | 26 (44.8)                                       | 0.001 |
| IDDM                            | 15 (12.0)                                        | 1 (1.9)                                         | 0.021 |
| NIDDM                           | 72 (52.2)                                        | 11 (19.3)                                       | 0.001 |
| BMI                             | 27.9±4.7                                        | 26.5±5.3                                        | 0.4   |
| Ethnicity                       |                                                  |                                                  |       |
| Arab                            | 37 (25.9)                                        | 23 (39.7)                                       | 0.162 |
| Asian                           | 103 (72.0)                                       | 34 (58.6)                                       | 0.154 |
| Euro-SCORE                      | 2.4±2.09                                         | 2.9±2.9                                         | 0.216 |
| Basal creatinine (µmol/L)       | 92.9±58.1                                        | 93.0±63.1                                       | 0.994 |
| LVEF (%)                        | 46.3±10.20                                       | 48.5±8.27                                       | 0.119 |
| Surgery (elective)              | 114 (79.2)                                       | 42 (72.4)                                       | 0.197 |
| Surgery (urgent)                | 30 (20.8)                                        | 16 (27.6)                                       |       |
| Inotropes                       |                                                  |                                                  |       |
| Dopamine                        | 41 (28.5)                                        | 16 (28.1)                                       | 0.551 |
| Adrenaline                      | 17 (11.8)                                        | 10 (17.2)                                       | 0.210 |
| Noradrenline                    | 42 (29.4)                                        | 16 (28.4)                                       | 0.500 |
| Left atrial mass                | 1 (0.7)                                          | 1 (1.8)                                         |       |

Statistical method: \(t\)-test, or Mann-Whitney \(U\)-test as appropriate for interval variables. \(P\leq0.05\) (two-tailed) was considered to be statistically significant.

BMI=Body mass index, LVEF=Left ventricular ejection fraction, IDDM=Insulin-dependent diabetes mellitus, NIDDM=Noninsulin-dependent diabetes mellitus, Euro-SCORE=European System for Cardiac Operative Risk Evaluation

### Table 3: Clinical outcome in Group I (statin users) and Group II (nonstatin users)

| Variable                        | Group I (statin users) \(n=144\) | Group II (nonstatin users) \(n=58\) | \(P\)  |
|---------------------------------|----------------------------------|----------------------------------|-------|
| Intraoperative parameters       |                                  |                                  |       |
| CPB time (min)                  | 127.3±42.05                      | 135.89±58.1                      | 0.15  |
| ACC time (min)                  | 76.0±29.1                        | 84.48±11.2                       | 0.13  |
| Anesthesia time (min)           | 372.9±292.7                      | 371.81±123.09                    | 0.971 |
| Postoperative parameters        |                                  |                                  |       |
| LOV median (range), min         | 470.5±341.3 (200-1440)           | 586.7±529.8 (180-4800)           | 0.036 |
| LOS\(_{\text{ICU}}\) median (range), h | 56.0±203.9 (83-540)           | 82.14±284.3 (46-2140)           | 0.04  |
| LOS\(_{\text{hosp}}\) median (range), days | 7.35±3.2 (3.6-22)           | 9.7±7.7 (3.9-73)                 | 0.027 |
| Postoperative complication, \(n\) (%) |                                  |                                  |       |
| Elevated liver enzymes          | 2 (1.4)                          | 1 (1.7)                          | 0.640 |
| PMI                             | 7 (4.9)                           | 2 (3.4)                           | 0.492 |
| Wound infection                 | 1 (0.7)                           | 2 (3.4)                           | 0.202 |
| POAF                            | 3 (2.1)                           | 4 (6.9)                           | 0.021 |
| RML                             | 14 (9.7)                          | 4 (6.8)                           | 0.41  |
| AKI                             | 31 (21.5)                         | 10 (17.2)                         | 0.316 |
| VAP                             | 0                                 | 1 (1.2)                           |       |
| Hypoglycemia                    | 2 (1.3)                           | 2 (2.4)                           |       |
| Early stroke                    | 0                                 | 1 (1.7)                           |       |
| In-hospital mortality           | 2 (1.3)                           | 3 (3.7)                           | 0.287 |

Statistical method: \(t\)-test, or Mann-Whitney \(U\)-test as appropriate for interval variables. \(P\leq0.05\) (two-tailed) was considered to be statistically significant.

ICU=Intensive Care Unit, ACC=Aortic cross-clamp, AKI=Acute kidney injury, CPB=Cardiopulmonary bypass, LOV=Length of mechanical ventilation, LOS\(_{\text{ICU}}\)=Length of stay in the ICU, LOS\(_{\text{hosp}}\)=Length of stay in the hospital, PMI=Perioperative myocardial infarction, POAF=Postoperative atrial fibrillation, RML=Rhabdomyolysis, VAP=Ventilator-associated pneumonia
to be associated with a lower rate of postoperative infections because they are anti-inflammatory and immunomodulatory.[6] However, a recent randomized clinical trial showed that statins failed to have preventive effects in postoperative infections.[21]

We followed our patients for the development of POAF within the hospital, and the incidence of POAF was significantly lower in the statin users (P = 0.02) similar to Rezaei et al. who did a meta-analysis of randomized clinical trials. They found that statin native patients were associated with a decreased incidence of POAF.[22] In another meta-analysis of unpublished and published evidence from randomized controlled trials, Rahimi et al. found a beneficial effect from statins on POAF through short-term published trials, which were not supported in longer follow-up trials.[23]

The secondary outcome variables were compared; we found that the length of mechanical ventilation, intensive care, and hospital stay were significantly lower in the statin users (P = 0.036, 0.04, and 0.027, respectively). Liakopoulos et al. similarly found that the statin-treated population had a lower rate of POAF as well as a reduced length of intensive care and hospitalization.[24]

Association of PMI and mortality was not significantly different between the groups in our study population [Table 3]. In a meta-analysis of randomized controlled trials, statin pretreatment had no influence on perioperative mortality, stroke, myocardial infarction, or renal failure. In another systematic review, the duration of ICU as well as hospital stay was reduced after pretreatment with statins in cardiac surgery. This warranted statin utilization in these situations.[25]

Changes in laboratory markers were compared [Table 4], and there is no significant difference in the statin users and controls in terms of cardiac biomarkers (plasma troponin T and isoenzyme of CK), postoperatively. Almansob et al. mentioned possible improvement in cardiac and renal functions by statin utilization perioperatively through the reduction of inflammation and myocardial injury. The inflammatory response is reduced by Akt-eNOS activation and alleviation of p38 signaling pathways in cardiac surgery patients.[6] However, a more recent meta-analysis of statin pretreatment showed no influence on perioperative mortality, stroke, and myocardial infarction.[3] Finally, the working guidelines recommend the use of statins as a secondary prevention in this context.[26,27]

### Study limitations

Our study sheds new light on the value of statin in perioperative cardiac surgery settings, where we could identify possible beneficial effects and exclude other possible early postoperative complications. The study population was predominantly males, the study was single center and the sample volume was relatively low when it comes to certain comparisons.

### Conclusions

Therapy with statins before cardiac surgery was not associated with a high incidence of adverse events; moreover, the statin-treated group had a favorable outcome regarding the POAF events and lengths of ventilation as well as the time in ICU and overall hospitalization time.

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### Conflicts of interest

There are no conflicts of interest.

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