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Is HMG-Co A Reductase Inhibitor Use Associated with Improved Outcomes in Patients Undergoing Colorectal Cancer Resection?

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Abstract

Purpose: HMG-CoA reductase inhibitors (statins) modulate the immune system and have anti-inflammatory effects. It has been proposed that their use in the peri-operative period may reduce surgical complications by modulating the post-operative pro-inflammatory response. This study aims to evaluate the effect of statins on surgical outcomes following colorectal cancer resection.

Methods: A retrospective analysis of all colorectal cancer resections performed at University Hospital Birmingham, between June 2008 and July 2013, was conducted. Patients were divided into 'Statin Users' and 'Non-statin Users'. Their outcomes and survival were evaluated using univariate, multivariate and cox-regression analysis.

Results: 246/703 patients (35.0%) were statin users. There were no differences in disease stage between the groups. Statin users were found to have a higher proportion of colonic, compared to rectal, cancers than non-statin users (60.2% *vs*. 48.1%, p=0.0023) and a reduced incidence of stoma formation (OR 0.65, 95% CI 0.45-0.95, p=0.0280). Despite significant increases in age, BMI and co-morbidity, statin users had equivalent rates of complications, re-operations, re-admissions and mortality than non-statin users. Statin users were however more likely to be admitted to Critical Care (OR=1.83, 95% CI=1.16-2.87, p=0.0090) and have a prolonged hospital stay (12% increase in LOS, 95% CI=0.002-0.10, p=0.0420). No significant dose related differences were identified in patient outcomes and mortality were observed, although an overall risk reduction in mortality with increasing dose of statin remains possible (HR=0.67, 95% CI=0.41-1.09, p=0.1100).

Conclusions: Statin users achieved equivalent short-term and long-term outcomes to non-statin users despite an increased operative risk and their use in the peri-operative period, particularly at high doses, merits further investigation.

Keywords: Colorectal cancer; HMG-CoA Reductase Inhibitors; Patient outcomes; Statins; Surgery

Introduction

HMG-CoA reductase inhibitors (statins) have been extensively studied and have proven efficacy in the primary and secondary prevention of cardiovascular morbidity and mortality in a variety of populations [1-6]. Their main mechanism of action is reduction of serum cholesterol by means of competitive inhibition of hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is the rate limiting enzyme in the mevalonate synthesis pathway. Consequently, statins reduce the intermediate products of cholesterol synthesis, namely mevalonate and the down-stream isoprenoid intermediaries, which play a vital role in several intracellular signalling pathways leading to a reduction in endogenous cholesterol biosynthesis and a reduction in low-density lipoprotein which is a major risk factor for cardiovascular disease [7-12].

The cholesterol independent effects of HMG-CoA reductase inhibition are known as 'pleiotropic' effects. These pleiotropic effects (anti-inflammatory, immune-modulatory, anti-platelet, anti-thrombotic, protective against oxidative stress, anti-microbial [12-21]) are thought to counteract the detrimental effects of inflammation. In fact, statins have been demonstrated to reduce the release of pro-inflammatory mediators (C-reactive protein [CRP], Tumour Necrosis Factor-α [TNF-α], Interleukin-6 [IL-6], Interleukin-8 [IL-8] in both animal and *in-vitro* studies [12-14]. Evidence from human trials has demonstrated improved outcomes in subjects with hypercholesterolaemia, cardiovascular disease and bacterial infections with statin induced CRP reduction [15-18] and a reduced incidence of major cardiovascular events in healthy individuals without hypercholesterolaemia but with elevated CRP levels [6,19]. Interestingly, a dose dependent anti-inflammatory response has been observed where patients taking high-dose statins were found to have reduced levels of CRP following Acute Coronary Syndrome [20] and reduced periodontal and carotid inflammation in periodontal disease [21].

It has been suggested that statins may influence cancer risk by means of cancer chemoprevention. Statins, in pre-clinical studies, have been demonstrated to exert anti-neoplastic effects (pro-apoptotic, anti-angiogenic, immune-modulatory) which may prevent cancer growth [22,23]. Observational studies and meta-analyses have demonstrated a reduced risk of prostate, hepatocellular, gastric and oesophageal cancer associated with statin use [24-27]. Statins have also been investigated in the context of a potential role in the modification of cancer outcomes and mortality and it is has been demonstrated that patients who take statins prior to their cancer diagnosis are less likely to die from any cause or specifically from cancer [28].

The relationship between statins and colorectal cancer has been investigated, but the results are inconclusive both with regard to cancer risk, cancer outcomes and mortality. Epidemiology studies have examined the risk of colorectal cancer with conflicting results from very protective [29] to moderately harmful [30]. A recent meta-analysis of 40 published studies, involving more than eight million subjects, concluded that statins did not strongly reduce the overall risk of colorectal cancer in the general population at low doses used for managing hypercholesterolaemia and cardiovascular disease. There was, however, evidence to suggest an overall risk reduction with statin use although this was not significant [31].

Following major cardio-vascular surgery a reduction in post-operative cardiac complications and a reduction in post-operative infective complications has been documented in patients taking statins pre-operatively [32-36]. Interestingly a dose dependent modulation of inflammation has been observed in coronary artery surgery where high-dose statins, in combination with high-dose ACE-inhibitors, almost completely prevented the systemic inflammatory response associated with surgery and virtually entirely suppressed surgery related changes in plasma concentrations of TNF-α and IL-6 from 10 minutes up to 24 hours after aortic clamping [37].

In the context of general surgery, pre-operative statin use has been independently associated with a decreased risk of major, non-cardiac complications, respiratory complications, venous thrombo-embolic events and infective complications [38-40]. Overall, the pre-operative use of statins appears to be associated with a reduction in major complications [38,39].

Specifically in the context of colorectal surgery, statin use is associated with a significantly lower incidence of systemic inflammatory response syndrome and a lower incidence of surgical site infection [40]. There appears to be no difference however in overall mortality, total complications or median hospital length of stay between statin users and non-statin users undergoing major colorectal resection [38,39]. Studies have demonstrated contradictory results regarding the association of peri-operative statin therapy and anastomotic leak and a beneficial effect of peri-operative statin therapy on the incidence of anastomotic leak cannot be ruled out [41,42]. Patient's taking peri-operative statins appear to have a greater baseline peri-operative risk compared to non-statin users, but they achieve equivalent outcomes overall suggesting that peri-operative statin therapy may indeed be of benefit and reduce morbidity after elective colorectal resection [40,42].

It is well established that infectious complications in patients with cancer are associated with adverse oncological outcomes independent of the morbidity associated with the infectious insult [43-46] and they are associated with an increased mortality as a consequence of metastatic disease [46-50]. It has been proposed that the use of statins in the peri-operative period may reduce surgical complications by modulating the post-operative pro-inflammatory response.

It seems logical to think that statins could be advantageous in the setting of cancer surgery where they might reduce systemic inflammation and post-operative complications with a consequent improvement in oncological outcomes. It was therefore decided to investigate whether statin use is associated with reduced post-operative complications and improved clinical outcomes in patients undergoing elective colorectal cancer resection and whether a dose dependent effect on clinical outcomes could be demonstrated.

Methods

A retrospective review of prospectively collected data was conducted for all elective colorectal cancer resections performed at a single institution (University Hospital Birmingham, Birmingham, United Kingdom) within an established enhanced recovery programme, between June 2008 and July 2013.

The study was registered with and approved by the Clinical Governance Support Unit of the University Hospital Birmingham on 11th October 2013 and conducted in accordance with the ethical principles (CAO-05482-13).

Data acquisition

Data was extracted from existing robust electronic patient databases (Prescribing Information and Communication System and Clinical Portal) by the Bio-informatics Department at University Hospital Birmingham to produce a working dataset. All data was independently controlled for accuracy. Data was manually extracted from the electronic patient databases for 10% of patients which were randomly sampled from the working dataset. Any data field from the sample that was less than 100% accurate was then manually extracted from the electronic databases for all patients in the working dataset.

Patients were divided into statin users and non-statin users. Statin users were defined as patients who were prescribed statins at admission and who were prescribed statins within a five day post-operative period. Statin dose was classified as low-dose, moderate-dose or high-dose and defined as; low-dose ≤20 mg simvastatin, moderate-dose=40 mg simvastatin, high-dose >40 mg simvastatin (or equivalent doses of other statins). All statins currently available for use in the United Kingdom were included (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin).

Data extracted from the electronic patient databases is outlined in Table 1.

The following definitions were applied to the extracted data.

- Post-operative complications ≤30 days after surgery were recorded for all patients and were defined as follows:
  - Abdominal Collection was defined as a radiologically diagnosed collection of the abdominal cavity or pelvis that required intervention or prolonged hospital stay.
  - Acute Kidney Injury was defined as a percentage increase in serum creatinine ≥50% from baseline.
  - Anastomotic Dehiscence was defined as surgically confirmed dehiscence and/or radiologically diagnosed dehiscence (fluid collection in close proximity to an anastomosis that was drained yielding purulent fluid or gas and/or evidence of contrast leak).
  - Bacteraemia was defined as the presence of a positive microbiology culture from a central or peripheral blood sample.
  - Cardio-respiratory Events included a confirmed diagnosis of myocardial infarction, pulmonary embolism and/or cardiac dysrhythmia (which was not as a consequence of infection) that required appropriate treatment.
  - Intestinal Obstruction was defined as a confirmed radiological diagnosis of mechanical or functional intestinal obstruction which resulted in a prolonged hospital stay.
  - Lower Respiratory Tract Infection was defined as a confirmed diagnosis of pneumonia that required antibiotic therapy.
- Re-operations were defined as a return to theatre ≤30 days of the index procedure.
- Re-admissions were defined as a return to hospital ≤30 days of the index procedure requiring a hospital stay ≥24 hours.
- Critical Care LOS was defined by the number of days on critical care requiring level-2 or level-3 care.

- Total LOS was defined by the number of days in hospital including the day of surgery.
- Post-operative Antibiotic Use was defined as a prescription for co-amoxiclav, piperacillin-tazobactam, meropenem or vancomycin ≤30 days after surgery and was used as a surrogate marker for post-operative infective complication.
- Mortality was recorded and categorised into 30-day, 90-day, 12-month, 24-month and 60-month mortality.

Pre-operative inflammatory markers included pre-operative values closest to the day of surgery and not including the day of surgery. Post-operative inflammatory markers included the minimum, maximum and mean values within a 7 day post-operative period.

Statistical analysis

Statistical comparisons between statin and non-statin groups were calculated using Mann-Whitney U test and χ^2 test or Fisher Exact test for continuous and categorical data respectively. Univariate linear and logistic regression analyses were performed for continuous and categorical data respectively. Multivariate analysis was then performed including all variables from the univariate analyses with a p-value <0.4 with 100% complete data. Survival was evaluated using Kaplan-Meier graphs and Tarone-Ware p-values were used as a measure of significance. Multivariate survival analysis was performed using Cox Regression analysis. Statistical analyses were performed by using SPSS version 17 (IBM SPSS Statistics, IBM Corporation, Armonk, NY).Statistical significance was defined a priori as a p-value <0.05.

Results

A total of 703 patients undergoing elective colorectal cancer resection within an established enhanced recovery programme, between June 2008 and July 2013 were reviewed. The median age of the population was 69 years (IQR 60-76 years) with 58.3% of male gender. 53.2% of patients underwent a resection involving the rectum and 31.7% of procedures were completed entirely laparoscopically. Only 2.7% of patients required a re-operation. The median length of stay was 9 days (IQR 6-15 days) and 9.0% of patients were readmitted up to 30 days of the index procedure. 30-day, 90-day, 12-month, 24-month and 60-month mortality was 1.1%, 2.3%, 7.7%, 11.7%, and 20.6% respectively with a median follow-up of 51 months (Range 22-82 months, IQR 35-66 months). Data completeness was generally high for patient variables and was 100% for all patient outcomes.

246 (35.0% [246/703]) patients were statin users. The mean number of statin doses omitted during the index admission was 1.36 doses (95% CI=1.04-1.67 doses). The majority of patients were on simvastatin (76.0% [186/246]) and the remainder were on atorvastatin (18.3% [45/246]), pravastatin (2.85% [7/246]), rosuvastatin (2.44% [6/246]) and fluvastatin (0.41% [1/246]). The majority of patients were on moderate-dose statin (64.6% [159/246]) and the remainder were on low-dose (26.0% [64/246]) and high-dose (9.4% [23/246]) statins.

Statin users were significantly older (71 *vs.* 67, p<0.0001), had a higher BMI (27.5 *vs.* 26.0, p=0.0005), had a higher incidence of medical co-morbidities including diabetes mellitus, heart failure, hypertension and ischaemic heart disease (All p<0.0001). Interestingly, statin users were significantly more likely to have a colonic cancer than a rectal cancer (60.2% *vs.* 48.1%, p=0.0023) and this is reflected in significantly fewer rectal resections, a reduced requirement for neo-adjuvant therapy and fewer stomas formed.

No statistical differences were identified in post-operative complications, post-operative antibiotic use, re-operations and re-admissions. Statin users appeared to have an increased rate of Critical Care admission, Critical Care length of stay and total length of stay. It also appeared that statin users had a greater mortality at 12-months, 24-months and 60-months. The population characteristics and outcomes according to statin use are shown in Table 2 and Table 3 respectively.

Patient Demographics	Age
	BMI
	Gender
	Smoking Status
Patient Co-morbidities	Chronic Kidney Disease
	Diabetes Mellitus
	Heart Failure
	Hypertension
	Ischaemic Heart Disease
	Lung Disease
Tumour Characteristics	Cancer Location
	T-stage
	N-stage
	M-stage
	Neo-adjuvant Therapy
Operative Characteristics	Operation Type
	Operation Technique
	Stoma Formation
Post-operative Complications	Abdominal Collection
	Acute Kidney Injury
	Anastomotic Dehiscence
	Bacteraemia
	Cardio-respiratory Event
	Intestinal Obstruction
	Lower Respiratory Tract Infection
Re-operations	Re-operation (any cause)
Post-operative Antibiotic Use	Co-amoxiclav
	Piperacillin-tazobactam
	Meropenem
	Vancomycin
Length of Stay (LOS)	Critical Care LOS
	Total LOS
Re-admissions	30-day readmission
Mortality	30-day mortality
	90-day mortality
	12-month mortality
	24-month mortality
	60-month mortality
Pre- and Post-operative Blood Tests	Absolute White Cell Count
	Neutrophil Count
	Lymphocyte Count
	Platelet Count
	Neutrophil-Lymphocyte Ratio
	C-reactive Protein (Post-operative only)

Table 1: Data extracted from the electronic databases.

There were no statistically significant differences in pre-operative inflammatory markers between statin and non-statin users. In particular there was no difference in pre-operative neutrophil-lymphocyte ratio. Post-operatively, statin users had a higher maximum absolute white cell count (13.1 *vs.* 12.4, p=0.0418) but a lower minimal platelet count (198.0 *vs.* 208.5, p=0.0217) and minimal CRP level (32.0 *vs.* 42.0, p=0.0188).

Univariate analysis

Univariate analysis demonstrated significant increases in the rate of admission to Critical Care (OR=1.91, 95% CI=1.23-2.97, p=0.0040) and in the total length of stay (14% increase in LOS, 95% CI=0.012-0.10,

Variable	Statin User (n=246)	Non-statin User (n=457)	p-value
Age, median (IQR)	71 (65-78)	67 (58-76)	**<0.0001**
Gender, n (%), M/F	146/100 (59.3/40.7)	264/193 (57.8/42.2)	0.6894
BMI, median (IQR), kg/m²	27.5 (24.8-31.7)	26.0 (22.9-29.6)	**0.0005**
Smoking Status, n (%), 1/2/3[a]	28/87/112 (11.4/35.4/45.5)	53/147/234 (11.6/32.2/51.2)	0.4882
Chronic Kidney Disease, n (%), y	14 (5.7)	13 (2.8)	0.2000
Diabetes Mellitus, n (%), y	76 (30.9)	35 (7.6)	**<0.0001**
Heart Failure, n (%), y	12 (4.8)	2 (0.4)	**<0.0001**
Hypertension, n (%), y	163 (66.3)	153 (33.5)	**<0.0001**
Ischaemic Heart Disease, n (%) y	71 (28.8)	17 (3.7)	**<0.0001**
Lung Disease, n (%), y	39 (15.9)	67 (14.7)	0.6734
Cancer Location, n (%), 1/2[b]	148/98 (60.2/39.8)	220/237 (48.1/51.9)	**0.0023**
T-Stage, n (%), 0/1/2/3/4	18/33/136/56 (7.3/13.4/55.2/22.7)	37/54/229/117 (8.1/ 11.8/50.1/25.6)	0.6544
N-Stage, n (%), 0/1/2	145/60/39 (58.9/24.4/15.9)	252/139/62 (55.1/30.4/13.6)	0.2185
M-Stage, n (%), 0/1	210/35 (85.4/14.2)	377/76 (82.5/16.7)	0.4480
Neo-adjuvant Therapy, n (%), y	38 (15.4)	102 (22.3)	**0.0298**
Operation Type, n (%), 1/2[c]	142/104 (57.7/42.3)	224/233 (49.0/51.0)	**0.0275**
Operation Technique, n (%), 1/2[d]	163/83 (66.3/33.7)	317/140 (69.4/30.6)	0.3988

Table 2: Population characteristics according to statin use.
y=yes, 1/2/3[a] =active/former/never
1/2[b]=colon/recto-sigmoid junction and rectum.
1/2[c]=segmental/rectal.
1/2[d]=open and laparoscopic converted to open/laparoscopic.

Outcomes	Statin User (n=246)	Non-statin User (n=457)	p-value
Abdominal Collection, n (%), y	7 (2.9)	18 (3.9)	0.3829
Acute Kidney Injury, n (%), y	7 (2.9)	7 (1.5)	0.5274
Anastomotic Dehiscence, n (%), y	13 (5.3)	15 (3.3)	0.7003
Bacteraemia, n (%), y	3 (1.2)	4 (0.2)	0.3273
Cardio-respiratory Event, n (%), y	11 (4.5)	20 (4.4)	1.0000
Intestinal Obstruction, n (%), y	18 (7.3)	25 (5.4)	0.2631
Lower Respiratory Tract Infection, n (%), y	16 (6.5)	22 (4.8)	0.2258
Re-operation, n (%), y	7 (2.9)	12 (2.6)	0.8640
Stoma, n (%), y	52 (21.1)	134 (29.3)	**0.0199**
Post-operative Antibiotic Use, n(%), y	156 (63.4)	268 (58.6)	0.2175
Critical Care Admission, n (%), y	51 (20.7)	60 (13.1)	**0.0094**
Critical Care LOS, median (range, IQR), days	0.0 (0.0-72.4, 0.0-0.0)	0.0 (0.0-35.1, 0.0-0.0)	**0.0049**
Critical Care LOS, mean (95% CI), days	1.57 (0.70-2.45)	0.56 (0.31-0.82)	**0.0049**
Total LOS, median (range, IQR), days	9.87 (2.0-277.4, 6.8-17.1)	8.94 (1.2-246.1, 6.1-13.5)	**0.0160**
Total LOS, mean (95% CI), days	16.57 (13.66-19.48)	13.79 (11.95-15.63)	**0.0160**
Readmission, n (%), y	25 (10.2)	38 (8.3)	0.8414
Mortality, n (%), y			
30-day	5 (2.0)	3 (0.7)	0.1359
90-day	9 (3.6)	7 (1.5)	0.1081
12-month	32 (13.0)	22 (4.8)	**0.0002**
24-month	46 (18.7)	36 (7.8)	**<0.0001**
60-month	74 (30.0)	71 (15.5)	**<0.0001**

Table 3: Population outcomes according to statin use.
y=yes

p=0.0130) in statin users. Statin users were significantly less likely to require a stoma after elective colorectal cancer resection (OR 0.65, 95% CI 0.45-0.93, p=0.0190). The results of univariate analysis are displayed in Table 4.

Multivariate analysis

The criteria for inclusion into multivariate analysis was p<0.4000, event incidence ≥28 and data completeness of 100% (marked **). After adjustment for age and gender differences, multivariate analysis demonstrated significant increases in rate of admission to Critical Care (OR=1.83, 95% CI=1.16-2.87, p=0.0090) and in the total length of stay (12% increase in LOS, 95% CI=0.002-0.10, p=0.0420) in statin users. Statin users were significantly less likely to require a stoma after elective colorectal cancer resection (OR 0.65, 95% CI 0.45-0.95, p=0.0280) than non-statin users. The results of multivariate analysis are displayed in Table 5.

Survival analysis

Univariate survival analysis revealed an increased mortality rate associated with statin use (Tarone-Ware p-value=0.0450), however, when adjusted for age and gender, multivariate Cox Regression analysis revealed no significant difference in mortality associated with statin use (HR=1.21, 95% CI=0.90-1.62, p=0.2120) over a median follow-up of 51 months (Range 22-82 months, IQR 35-66 months).

Dose dependent effect of Statin therapy

The number of statin users on low-dose, moderate-dose and high-dose statins were 64/246 (26.0%), 159/246 (64.6%) and 23/246 (9.4%) respectively. There were no statistical differences in patient characteristics according to statin dose. Univariate analysis demonstrated a significant increase in the total length of stay (4% increase in LOS, 95% CI=1.00-1.22, p<0.0001) with increasing dose of statin. The results of univariate analysis for increasing dose of statin are displayed in Table 6.

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Univariate Logistic Regression			
Abdominal Collection	0.71	0.29-1.73	0.457
Acute Kidney Injury	1.88	0.65- 5.43	0.242
Anastomotic Dehiscence**	1.64	0.77-3.51	0.199
Bacteraemia	1.40	0.31-6.30	0.663
Cardio-respiratory Event	1.02	0.48-2.17	0.953
Intestinal Obstruction**	1.36	0.73-2.55	0.331
Lower Respiratory Tract Infection**	1.38	0.71-2.67	0.346
Re-operation	1.09	0.59-1.98	0.791
Stoma**	0.65	0.45-0.93	**0.019**
Post-operative Antibiotic Use**	1.17	0.84-1.64	0.347
Critical Care Admission**	1.91	1.23-2.97	**0.004**
Readmission	1.25	0.73-2.12	0.414
Outcomes	**Change in Risk (%)**	**95% Confidence Interval**	**p-value**
Univariate Linear Regression			
Critical Care LOS**	43	0.67-7.31	0.102
Total LOS**	14	0.01-0.10	**0.013**

Table 4: Univariate Logistic Regression Analysis and Univariate Linear Regression Analysis (indicating 'Odds Ratio' and 'Change in Risk' for ***statin use***).

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Multivariate Logistic Regression			
Anastomotic Dehiscence	1.40	0.65-3.05	0.394
Intestinal Obstruction	1.50	0.78-2.89	0.221
Lower Respiratory Tract Infection	1.24	0.63-2.43	0.536
Stoma	0.65	0.45-0.95	**0.028**
Post-operative Antibiotic Use	1.36	0.96-1.92	0.087
Critical Care Admission	1.83	1.16-2.87	**0.009**
Outcomes	**Change in Risk (%)**	**95% Confidence Interval**	**p-value**
Multivariate Linear Regression			
Critical Care LOS	36	-0.01-0.28	0.065
Total LOS	12	0.002-0.10	**0.042**

Table 5: Multivariate Logistic Regression Analysis and Multivariate Linear Regression Analysis (indicating 'Odds Ratio' and 'Change in Risk' for ***statin use***).

The criteria for inclusion into multivariate analysis was p<0.4000 and data completeness of 100% (marked **). After adjustment for age and gender, multivariate analysis demonstrated no significant differences in rates of abdominal collection, acute kidney injury, re-operation or total length of hospital stay with increasing dose of statin. The results of multivariate analysis are displayed in Table 7.

Univariate survival analysis revealed a reduction in mortality associated with high-dose statin (Tarone-Ware p-value=0.0490). When adjusted for age and gender, multivariate Cox Regression analysis revealed no significant reduction in mortality when comparing high-dose and low-dose statin therapy (HR=0.67, 95% CI=0.41-1.09, p=0.1100)over a median follow-up of 51 months (Range 22-82 months, IQR 35-66 months).

Discussion

35.0% of patients undergoing elective colorectal cancer resection were on statins. The published literature documents the incidence of statin use in a general surgical population ranges from 10.5–32.0% [38,41,42]. The largest colorectal cancer patient cohort, form Denmark, revealed 18.8% (518/2755) of patients received statins in the peri-operative period [38]. This discrepancy may reflect differences in prescribing policy between different nations and/or true differences in levels of health in the patient populations as statins are principally used for primary and secondary prevention of cardiovascular morbidity and mortality in a variety of populations [1-6]. The mean percentage of statin doses omitted during the index admission was 8.5%,which equates to one missed dose per statin user, indicating that patients resumed statin therapy as they resumed enteral nutrition and their regular medications.

In terms of population characteristics, statin users were significantly different from non-statin users. Those patients on statins were significantly older, had a higher BMI and were a more co-morbid population (diabetes mellitus, heart failure, hypertension and ischaemic heart disease). Despite these differences, statin users had equivalent outcomes in frequency of post-operative complications (abdominal collection, acute kidney injury, anastomotic dehiscence, bacteraemia, cardio-respiratory event, lower respiratory tract infection), post-operative antibiotic use (used as a surrogate to indicate post-operative

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Univariate Logistic Regression			
Abdominal Collection**	1.05	0.99-1.12	0.081
Acute Kidney Injury	1.01	0.88-1.16	0.0937
Anastomotic Dehiscence	0.98	0.90-1.06	0.550
Bacteraemia	0.91	0.81-1.02	0.115
Cardio-respiratory Event	0.98	0.91-1.06	0.621
Intestinal Obstruction	0.62	0.91-1.06	0.621
Lower Respiratory Tract Infection	0.99	0.97-1.05	0.760
Re-operation**	0.95	0.89 - 1.00	0.058
Stoma	0.99	0.97-1.02	0.459
Post-operative Antibiotic Use	1.00	0.97-1.02	0.712
Critical Care Admission	1.00	0.96-1.04	0.896
Readmission	1.01	0.97-1.04	0.750
Outcomes	**Change in Risk (%)**	**95% Confidence Interval**	**p-value**
Univariate Linear Regression			
Critical Care LOS	-10	-0.69-0.85	0.836
Total LOS**	4	1.00-1.22	<0.0001

Table 6: Univariate Logistic Regression Analysis and Univariate Linear Regression Analysis (indicating 'Odds Ratio' and 'Change in Risk' for ***increasing dose of statin***).

Outcomes	Odds Ratio	95% Confidence Interval	p-value
Multivariate Logistic Regression			
Abdominal Collection	0.97	0.94-1.06	0.096
Acute Kidney Injury	0.96	0.90-1.03	0.250
Re-operation	0.95	0.90-1.06	0.550
Outcomes	**Change in Risk (%)**	**95% Confidence Interval**	**p-value**
Multivariate Linear Regression			
Total LOS	3	-0.004-0.001	0.270

Table 7: Multivariate Logistic Regression Analysis and Multivariate Linear Regression Analysis (indicating 'Odds Ratio' and 'Change in Risk' for ***increasing dose of statin***).

infective complication), re-operations and re-admissions and there was no statistically significant difference in mortality after appropriate age and gender adjustments with a median follow-up of 51 months (Range 22-82 months, IQR 35-66 months).

It is known that patients with pre-existing co-morbidities are at an increased peri-operative risk of developing complications as the surgical insult increases the demand on organs with already compromised function [51]. It has also been demonstrated that elevated BMI, in conjunction with advanced age, is predictive of morbidity and mortality following general surgery [52]. Despite a greater base-line peri-operative risk, evidenced by an older more co-morbid population, statin users had analogous outcomes and complication profiles to non-statin users.

Univariate analysis, however, demonstrated significant increases in the rate of admission to Critical Care and in the total length of stay in statin users compared to non-statin-users and these findings remained statistically significant, after adjustment for age and gender differences, in multivariate analysis. Statin users were 1.83 times more likely to need Critical Care support and had a hospital length of stay 12% longer than non-statin users. This is not only a reflection of an increased co-morbidity but a sign of a prolonged functional recovery and it may also represent an additional patient need for assistance with physiotherapy, occupational therapy and stoma therapy in this specific patient group.

There were no differences in pre-operative markers of inflammation between statin and non-statin users. Post-operatively, statin users had a higher maximum absolute white cell count, but conversely, a lower minimum platelet count and CRP levels than non-statin users. It is known that IL-6 is the primary mediator of inflammation following surgery and is responsible for the production of CRP. IL-6 has been demonstrated to predict post-operative complications [53] and it has been shown that IL-6 is suppressed by statin therapy [54,55]. This would therefore explain the significant reduction in post-operative minimum CRP observed in statin users.

This is the first study to attempt to determine if a dose dependent effect of statin therapy on patient outcomes following elective colorectal cancer resection exists. There were no observed differences in post-operative complications, post-operative antibiotic use, re-operations, admission to Critical Care, Critical Care length of stay, total length of stay and re-admissions with increasing dose of statin. Univariate analysis demonstrated a significant increase in the total length of stay with increasing dose of statin but this finding did not remain statistically significant after adjustment for age and gender in multivariate analysis. Regarding survival, univariate survival analysis revealed a reduction in mortality associated with high-dose statin, but when adjusted for age and gender, multivariate Cox Regression analysis revealed no significant dose dependent difference in mortality (HR=0.67, 95% CI=0.41-1.09, p=0.1100).

There were no observed differences in operative technique or tumour stage between statin and non-statin users. Interestingly, statin users were significantly more likely to have a colonic cancer than a rectal cancer and consequently significantly fewer rectal resections, a reduced requirement for neo-adjuvant therapy and fewer stomas formed. In multivariate analysis statin users were significantly less likely to require a stoma after elective colorectal cancer resection than non-statin users. It is known that of the 10,000 or so patients undergoing surgery for rectal cancer each year in the United Kingdom (Anterior Resection, Abdominoperineal Resection, Hartmann's Resection) over 80% undergo stoma formation of which the majority are temporary ileostomies used to 'cover' the colorectal anastomosis of an Anterior Resection [56] and so this finding, in the context of fewer rectal cancer incidences, is not surprising.

The finding of relatively fewer rectal cancers compared to colon cancers has been reported in the published literature in cohorts from the USA and the Netherlands which describe a risk reduction for rectal cancer of 30-40% [57-59] in statin users. This finding has not been described in a patient cohort from the United Kingdom to date. It has been proposed that statins may affect cancer genotype [60] and they have been associated with a reduced incidence of KRAS-wild-type mutations which have a tendency to affect the rectum [61], perhaps by their role in prenylation of KRAS [62]. Statins have also been found to inhibit the production of cyclogenoxygenase-2 [63] which is also commonly found to be overexpressed in rectal cancer [64]. These molecular differences may, in part, explain the observed increased incidence of colonic versus rectal cancers in statin users.

This retrospective analysis has several limitations. As with any retrospective analysis, the study is limited by the patient groups not being matched at baseline and consequently this can introduce confounding with the potential for unmeasured factors influencing the observed results. Examples include the use of aspirin and metformin which, conceivably, would have been used more frequently in statin users and have been associated with reduced cancer related mortality [13,65-67]. Although peri-operative care was provided within the setting of an established enhanced recovery programme, which utilises a standardised surgical protocol, confounders in patient management cannot be excluded.

The definition of statin user was dependent upon the prescription of statins at admission and who were prescribed statins within a five day post-operative period. There was an assumption that patients prescribed statins at admission were taking statins regularly pre-operatively prior to their admission and were therefore within the window of potential pleiotropy.

The strengths of this study include prospective data collection, high data completeness (associated with the use of robust electronic patient databases [Prescribing Information and Communication System and Clinical Portal] and vigorous data validation) and the use of multivariate analysis in an attempt to minimise confounding.

Conclusions

This study has explored the impact of peri-operative statin therapy on post-operative outcomes after elective colorectal cancer resection. Despite statin users having a higher peri-operative risk (significant increases in age, BMI and co-morbidity), they had equivalent outcomes in frequency of post-operative complications, post-operative antibiotic use, re-operations, re-admissions and there was no statistically significant difference in mortality after appropriate age and gender adjustments. Statin users were, however, more likely to need Critical Care support and had an increased hospital length of stay than non-statin users. This may reflect a higher peri-operative risk but also an additional need for assistance with physiotherapy, occupational therapy and stoma therapy in this specific patient group. No statistically significant dose related differences were identified in patient outcomes although an overall risk reduction in mortality with increasing dose of statin remains possible. Statin users achieved equivalent short-term and long-term outcomes to non-statin users despite an increased operative risk and their use in the peri-operative period, particularly at high doses, merits further investigation.

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