Original Article | Colorectal Surgery

Perioperative statin therapy and long-term outcomes following major colorectal surgery: a retrospective cohort study

Praharsh Bahl[1]^, James Jin[1], Andrew Hill[1,2], Primal (Parry) Singh[1,2]

[1]South Auckland Clinical Campus, The University of Auckland, Middlemore Hospital, Auckland, New Zealand; [2]General and Colorectal Surgeon, Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand

Contributions: (I) Conception and design: A Hill, PP Singh; (II) Administrative support: A Hill, PP Singh; (III) Provision of study materials or patients: PP Singh; (IV) Collection and assembly of data: P Bahl; (V) Data analysis and interpretation: P Bahl, J Jin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Primal (Parry) Singh, MBChB. South Auckland Clinical Campus, The University of Auckland, Middlemore Hospital, Level 2, Esme Green Bldg, Private Bag 93311, Auckland 1025, New Zealand; General and Colorectal Surgeon, Middlemore Hospital, Counties Manukau District Health Board, Auckland, New Zealand. Email: parry.singh@auckland.ac.nz.

Background: Statins exhibit beneficial effects on inflammatory and fibrinolytic pathways that may improve long-term outcomes following major colorectal surgery. A previous randomised controlled trial that compared a perioperative short-term statin (STS) regimen to placebo showed a significant reduction in early postoperative inflammatory markers in the statin group. The present study follows up the participants of this trial and a group of patients on long-term statin (LTS) therapy that underwent surgery during a similar period to investigate whether there was a difference in long-term outcomes.

Methods: This retrospective cohort study analyses data for participants of the original trial, and patients that were initially assessed for eligibility for the randomized controlled trial (RCT) but were on pre-existing statin therapy of any duration (LTS group), that underwent surgery between October 2011 and August 2013. Patients older than 16 years that underwent elective major colorectal surgery were eligible and exclusion criteria included previous adverse reaction to statins, myopathy, rhabdomyolysis, renal or hepatic impairment, and insufficient time between preadmission clinic and surgery. Data was collected from electronic clinical records in February 2022. Outcomes evaluated included complications, small bowel obstruction (SBO), cancer recurrence, and polyp incidence.

Results: Data was collected for patients that received STS (n=65), placebo (n=67), and LTS therapy (n=137) with a median follow-up of 9.5 years. The LTS group was older with more comorbidities. Fewer patients in the STS group required operative intervention for SBO in comparison to the LTS group [SBO overall: 0% *vs.* 50%, P=0.014; adhesive SBO (ASBO): 0% *vs.* 53%, P=0.048]. This difference was similar when compared to the placebo group but was not statistically significant. There was no difference in SBO incidence, polyp incidence, and cancer recurrence.

Conclusions: A short perioperative regimen of simvastatin during major colorectal surgery was associated with a lower operative rate for SBO. This difference may be related to a reduced inflammatory response to surgery and/or formation of postoperative adhesions.

Keywords: Colorectal; perioperative; obstruction; statin

Received: 18 July 2023; Accepted: 26 February 2024; Published online: 20 March 2024.
doi: 10.21037/asj-23-32
View this article at: https://dx.doi.org/10.21037/asj-23-32

^ ORCID: 0000-0003-4304-7805.

Introduction

Major colorectal surgery is associated with considerable short- and long-term morbidity, with approximately one-third of patients experiencing complications (1,2). Postoperative intraperitoneal adhesions, which are bands of fibrin that adhere usually-separated peritoneal surfaces together, form to some degree in almost all patients following abdominal surgery (3). Adhesions are the most common cause of small bowel obstruction (SBO), which is associated with significant morbidity and requires operating management in 20–30% of cases (4,5). Additionally, oncological recurrence is a significant issue amongst patients that undergo resection for colorectal cancer (CRC), with an estimated recurrence rate of 25–45% at five years after surgery (6,7). Hence, there is an ongoing need for interventions to alleviate the life-long burden of complications and disease recurrence in patients that undergo major colorectal surgery.

Statins, a class of drugs commonly used in the setting of hypercholesterolemia (8), may play a role in improving outcomes following major colorectal surgery due to their pleiotropic effects (9,10). In the murine model, statins have been shown to decrease acute peritoneal inflammation (11) and reduce the release of pro-inflammatory cytokines in abdominal sepsis (12,13). Observational clinical studies have found lower rates of anastomotic leakage, sepsis, and short-term mortality amongst statin users following colorectal surgery (14-16). Statins have also been shown to exert pro-fibrinolytic activity in human mesothelial cells *in-vitro* and decrease adhesion formation in animal studies (17,18). This effect may have clinical implications on adhesion-related complications, with statin users experiencing a decrease in the incidence of adhesive SBO (ASBO) and a decreased operative rate for ASBO (19,20). Furthermore, there are potential oncological benefits of statin use in CRC, with retrospective studies reporting lower cancer-specific mortality and reduced incidence of colorectal adenomas amongst these patients (21-23).

A previous randomized controlled trial (RCT) compared a perioperative regimen of simvastatin to placebo in the setting of major colorectal surgery (24). Post-operatively, the simvastatin group experienced lower C-reactive protein levels and concentrations of some pro-inflammatory cytokines in both plasma and peritoneal fluid; however, there was no difference in short-term complications. It is unknown whether the initial biochemical attenuation of the post-surgical inflammatory response observed in the statin-arm of this study is associated with decreased long-term adhesive complications and oncological recurrence. The aim of this study was to follow up the participants of the previous RCT, with the addition of a group that was on pre-existing statin therapy that also underwent major colorectal surgery during the same period, in order to investigate the long-term outcomes of short- (STS) and long-term statin (LTS) therapy on ASBO, cancer recurrence, polyp incidence, and mortality. We present this article in accordance with the STROBE reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-23-32/rc).

Highlight box

Key findings

- Patients that received a short course of perioperative simvastatin therapy were less likely than patients on pre-existing long-term statin therapy to require operation for small bowel obstruction after undergoing major colorectal surgery.

What is known and what is new?

- Statins exhibit beneficial effects on inflammatory and fibrinolytic pathways that may improve postoperative outcomes.
- This retrospective cohort study follows-up a previous randomized controlled trial that compared a short-term perioperative simvastatin course versus placebo, in addition to patients on long-term pre-existing statin therapy undergoing surgery, investigating differences in outcomes over 9.5 years.

What is the implication, and what should change now?

- Difference in outcomes between the short- and long-term statin therapy groups may be related to a lesser inflammatory profile in the short-term statin group as they were less co-morbid, which may influence the density of adhesions formed and subsequent severity of bowel obstructions.

Methods

This study retrospectively reviewed the long-term clinical and oncological outcomes for patients included in a previous double-blind RCT (24) which was conducted in four hospitals across three district health boards in Auckland, New Zealand, between October 2011 and August 2013. Adults that underwent an elective colorectal resection or a reversal of Hartmann's procedure were eligible and the exclusion criteria were: age under 16 years, already being on a statin or other lipid-lowering therapy, history of adverse reaction to a statin, myopathy, rhabdomyolysis, renal impairment with estimated glomerular filtration rate <30 mL/min, significant hepatic dysfunction, and preadmission clinic appointment

less than three days before surgery. Participants of the initial RCT that were randomized to receive a course of 40 mg oral simvastatin once daily for 3 to 7 days preoperatively till 14 days post operatively formed the 'short-term statin (STS) therapy' group of the present study. The other participants received a placebo for the same duration. A third group of consecutive patients that also underwent elective colorectal resection or reversal of Hartmann's operation and were assessed for eligibility for the original trial during the same October 2011 to August 2013 period but were excluded due to being on pre-existing statin therapy (irrespective of duration of intake), were introduced into the present study as a comparison group representing LTS use.

Follow-up data was collected using Clinical Portal 8 (Orion Health, Auckland, New Zealand) which is an electronic patient information database used across the three district health boards in Auckland, New Zealand. This included patient demographics, co-morbidities, operative details, admissions with SBO, treatment for SBO, follow up colonoscopies, polyps detected, recurrence of CRC, and death. Data was collected during February 2022, which marked the end of the follow up period. This study received institutional ethical approval from the Auckland Health Research Ethics Committee (Reference: AH23365). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and individual consent for this retrospective analysis was waived.

Outcomes of interest

SBO

SBO was defined using clinical, radiological, and operative criteria. Clinical features included nausea, vomiting, abdominal pain and constipation; while radiological evidence included dilated small bowel loops on plain abdominal radiographs or water-soluble contrast study, transition point on computed tomography; and for those undergoing operative management this required the findings of small-bowel entrapment within adhesions or another mechanical cause. SBO was considered to have an adhesive cause in the absence of another cause for obstruction on imaging, or if intra-operative findings showed adhesions to be responsible for the SBO. The time between the index operation to the date of presentation to hospital for SBO was used for survival analysis. Duration of hospitalization for SBO was defined as the number of days between admission and discharge. If SBO developed during admission for another illness, the time between the date of onset to date of discharge was recorded. Treatment was divided into 'operative' if surgery was performed for SBO and 'non-operative' if the SBO resolved without an operation. Non operative management involved nasogastric decompression with or without gastrografin administration, with the decision to escalate to operative management made by the surgical team depending on failure to resolve with conservative management and the patients' clinical disposition.

Cancer recurrence

CRC recurrence was analysed for patients with adenocarcinoma and no known metastases at the time of the index operation and had a complete resection of CRC with curative intent. CRC recurrence was based on radiological, endoscopic, histological or intraoperative evidence of recurrent malignancy and categorised as distant or locoregional based on site of detection. Disease-free survival was calculated from the date of index operation to the date of recurrence or death (from any cause). Patients without evidence of recurrence at death were censored at the date of death while patients alive at the time of follow-up were censored at the date of follow-up analysis.

Incidence of colonic polyps

The incidence of colonic polyps after surgery was derived from surveillance colonoscopy/sigmoidoscopy reports for the subgroup of patients that had a histological diagnosis of adenocarcinoma or a high-grade dysplastic polyp following their colorectal resection. Histological reports were used to determine the incidence of adenomas. Patients were excluded from this analysis if they were diagnosed with a hereditary syndrome that predisposed them to a high number of polyps on colonoscopy, such as familial adenomatous polyposis (FAP), hereditary non-polyposis colorectal cancer (HNPCC) or serrated polyposis syndrome (SPS). Endoscopic investigations that were aborted due to poor bowel preparation were excluded.

Statistical analysis

Statistical analysis was performed using R (R Core Team, 2021). The two-tailed Fisher's Exact test was used to compare categorical data. *Post-hoc* testing with pairwise Fisher's Exact testing using the Benjamini-Hochberg correction for multiple hypothesis testing was used to determine which specific groups had significant differences. Visualization of the data using histograms and the Shapiro-

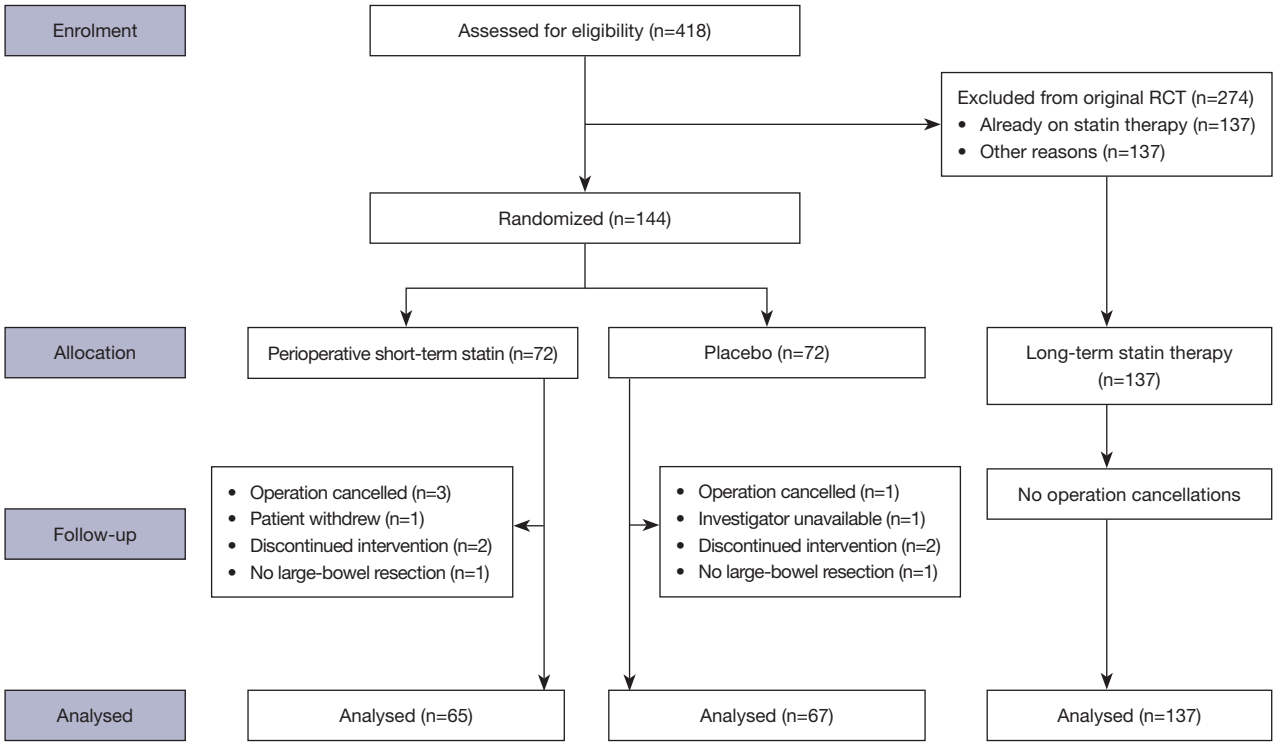

Figure 1 Participant flow diagram. RCT, randomized controlled trial.

Wilks test was used to determine the normality of the distribution of data. The Kruskal-Wallis Rank Sum test was used to compare medians of non-normally distributed data. *Post-hoc* testing was performed using the Wilcoxon Rank Sum Test with the Benjamini-Hochberg correction for non-normally distributed data. Median time-to-follow-up was determined using the reverse Kaplan-Meier method, and survival analysis was performed using a Kaplan-Meier graph for the time to the first presentation with SBO, cancer recurrence, all-cause mortality, and cancer-specific mortality. The log-rank test was used to determine difference in survival between the groups. A P value of <0.05 was considered statistically significant. Body mass index (BMI) was the only identified missing baseline characteristic data, and was handled using mean imputation. As this study followed up the participants of a previous trial, no separate power calculation was performed.

Results

Sixty-five patients that received a perioperative course of simvastatin (STS group) in the original trial, 67 patients that received placebo, and 137 patients that were initially excluded from the original trial due to already being on pre-existing statin therapy (LTS group) were analysed in this study (*Figure 1*). The median time to follow up was 9.5 years [interquartile range (IQR), 9.1–9.9 years].

Baseline characteristics

Table 1 shows the baseline characteristics for patients in the three groups. There were no significant differences between the STS and placebo groups, however, there were significant differences between both these groups and the LTS group with respect to age, BMI, American Society of Anesthesiologists (ASA) score and co-morbidities which were all significantly higher in the LTS group. Data was complete for the STS and placebo groups as this was recorded in detail for the purposes of the original RCT, however BMI data for 26 (19%) participants in the LTS group was missing, which was handled with mean imputation.

Operation, disease and postoperative recovery

Table 2 shows the characteristics of the participant's index operation, disease, and post-operative recovery. Operation

Table 1 Patient characteristics

Characteristic	Perioperative short-term statin (n=65)	Placebo (n=67)	Long-term statin (n=137)	P value*
Age, years, median [IQR]	63 [50–70]	64 [50–71]	72 [65–79]	<0.001†
Sex, n [%]				
Male	38 [58]	38 [57]	73 [53]	0.762
Female	27 [42]	29 [43]	64 [47]	
Ethnicity, n [%]				0.823
European	49 [75]	53 [79]	102 [74]	
Māori	4 [6]	6 [9]	12 [9]	
Pacific	7 [11]	4 [6]	7 [5]	
Indian/Asian	4 [6]	3 [4]	10 [7]	
Other	1 [2]	1 [1]	6 [4]	
BMI, kg/m^2, median [IQR]	26.1 [23.1–29.4]	26.6 [23.6–30.4]	30.5 [25.6–35.6]	0.001†
ASA score, n [%]				
I	9 [14]	8 [12]	3 [2]	0.002
II	46 [71]	47 [70]	76 [55]	0.043
III	10 [15]	12 [18]	52 [38]	<0.001
IV	0	0	6 [4]	0.088
Type II diabetes mellitus, n [%]	4 [6]	1 [1]	44 [32]	<0.001
Ischaemic heart disease, n [%]	0	0	37 [27]	<0.001
Cerebrovascular accident/transient ischaemic attack, n [%]	0	1 [1]	21 [15]	<0.001
Smoker, n [%]	11 [17]	11 [16]	13 [9]	0.200
Previous abdominal operation, n [%]	14 [22]	15 [22]	37 [27]	0.648
Pre-operative chemotherapy, n [%]	5 [8]	10 [15]	13 [9]	0.343
Pre-operative radiotherapy, n [%]	6 [9]	11 [16]	16 [12]	0.474
Adjuvant chemotherapy, n [%]	18 [28]	18 [27]	35 [26]	0.934
Adjuvant radiotherapy, n [%]	1 [2]	3 [4]	1 [1]	0.187

*, Fisher's Exact test unless stated otherwise; †, Kruskal-Wallis test. IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists.

type and approach was similar across the three groups except for a lower proportion of patients in the LTS group having a total/subtotal colectomy or reversal of Hartmann's procedure. A significantly greater proportion of patients in the LTS group underwent surgery for colorectal adenocarcinoma compared to the other two groups. Amongst these patients with CRC, a significantly higher proportion in the LTS group had American Joint Committee on Cancer (AJCC) stage III disease compared to the placebo group (31% *vs.* 18%, P=0.045), but this difference was not significant when compared to the perioperative statin group. Fewer patients in the LTS group underwent surgery for inflammatory bowel disease and other benign conditions compared to the other two groups. There were no significant differences between the three groups in overall short-term complications up to 30 days postoperatively and the Clavien-Dindo grade of the worst complication. For types of complications, the only

Table 2 Operation, disease and recovery

Characteristic	Perioperative short-term statin (n=65)	Placebo (n=67)	Long-term statin (n=137)	P value*
Operation type, n [%]				
Ileocolic resection/right hemicolectomy	17 [26]	16 [24]	43 [31]	0.508
Left hemicolectomy/sigmoid colectomy	3 [5]	3 [4]	7 [5]	>0.99
Total/subtotal colectomy	5 [8]	8 [12]	1 [1]	0.001
Anterior resection	19 [29]	18 [27]	53 [39]	0.181
Abdominoperineal resection	4 [6]	6 [9]	13 [9]	0.810
Panproctocolectomy	3 [5]	2 [3]	1 [1]	0.114
Hartmann's procedure	2 [3]	4 [6]	6 [4]	0.797
Reversal of Hartmann's	9 [14]	7 [10]	5 [4]	0.020
Other	3** [5]	3† [4]	8†† [6]	>0.99
Operative approach, n [%]				
Open	46 [71]	51 [76]	97 [71]	0.7164
Laparoscopic	19 [29]	16 [24]	40 [29]	0.7164
Anastomosis	56 [86]	52 [78]	117 [85]	0.3247
Stoma	25 [38]	25 [37]	50 [36]	0.9719
Postoperative histology/diagnosis, n [%]				
Adenocarcinoma	38 [58]	39 [58]	105 [77]	0.006
High grade dysplastic polyp	1 [2]	1 [1]	5 [4]	0.684
No residual malignancy	3 [5]	1 [1]	6 [4]	0.640
Inflammatory bowel disease	7 [11]	3 [4]	3 [2]	0.029
Diverticulitis	6 [9]	5 [7]	6 [4]	0.344
Other benign	10 [15]	18 [27]	12 [9]	0.004
AJCC stage, n [%]				
I	8 [12]	10 [15]	25 [18]	0.580
II	12 [18]	16 [24]	31 [23]	0.746
III	16 [25]	12 [18]	43 [31]	0.116
IV	2 [3]	1 [1]	4 [3]	0.892
Post-operative recovery				
Patients with complications, n [%]	44 [68]	50 [75]	89 [65]	0.379
Clavien-Dindo grade of worst complication, n [%]				
I	1 [2]	2 [3]	6 [4]	0.748
II	36 [55]	36 [54]	59 [43]	0.172
III	3 [5]	9 [13]	11 [8]	0.203
IV	3 [5]	2 [3]	10 [7]	0.441
V	1 [2]	1 [1]	3 [2]	>0.99
Minor complication, grades I–II	37 [57]	38 [57]	65 [47]	0.314
Major complication, grades III–V	7 [11]	12 [18]	24 [18]	0.4399

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	Perioperative short-term statin (n=65)	Placebo (n=67)	Long-term statin (n=137)	P value*
Worst complication type, n [%]				
Wound infection	9 [14]	14 [21]	10 [7]	0.020
Pulmonary infection	7 [11]	2 [3]	9 [7]	0.207
Ileus	12 [18]	15 [22]	18 [13]	0.218
Anastomotic leak	2 [3]	3 [4]	8 [6]	0.813
Abdominal/pelvic collection	3 [5]	3 [4]	6 [4]	>0.99
Urinary tract infection	3 [5]	3 [4]	9 [7]	0.830
Other	8[§] [12]	10[‖] [15]	29[§§] [21]	0.284

*, Fisher's Exact test unless stated otherwise; **, proctectomy (n=2), completion colectomy and end ileostomy (n=1); [†], anterior resection and ileocolic resection (n=2), completion colectomy and abdominoperineal resection (n=1); [††], caecectomy (n=3), small bowel resection and reversal of Hartmann's (n=1), abdominoperineal resection, small bowel resection and pelvic reconstruction (n=1), sigmoid diverticulum repair and appendicectomy (n=1), low anterior resection and right hemicolectomy (n=1), wedge resection of splenic flexure and cholecystectomy (n=1); [§], small bowel obstruction, confirmed on radiology (n=2), bile leak requiring reoperation (n=1), epidural hematoma requiring blood patch (n=1), fast atrial fibrillation (n=1), small bowel enterocutaneous fistula (n=1), small bowel perforation (n=1), splenic bleed requiring splenectomy (n=1); [‖], bleeding esophageal ulcer (n=1), ischemic colitis (n=1), bleeding from anastomosis requiring blood transfusion (n=1), parastomal abscess (n=1), mesenteric bleed requiring reoperation (n=1), symptomatic bradycardia requiring pacemaker (n=1), upper respiratory tract infection (n=1), high stoma output requiring readmission and electrolyte replacement (n=1), wound hematoma (n=1), urinary retention (n=1); [§§], hypotension requiring vasopressor or inotrope (n=4), anaemia requiring blood transfusion (n=3), pressure ulcers (n=2), high stoma output requiring electrolyte replacement and/or total parenteral nutrition (n=2), severe nausea and vomiting (n=2), asphyxia due to aspiration of vomit (n=1), urinary retention (n=1), fast atrial fibrillation (n=1), incarcerated incisional hernia (n=1), type II myocardial infarction (n=1), acute on chronic renal failure (n=1), intraperitoneal sepsis (n=1), dehydration (n=1), atelectasis (n=1), ventricular fibrillation cardiac arrest (n=1), respiratory arrest (n=1), gastric pneumatosis (n=1), ischaemic colitis (n=1), small bowel perforation (n=1), small bowel obstruction confirmed on radiology (n=1), constipation (n=1). AJCC, American Joint Committee on Cancer.

significant difference observed was fewer wound infections in the LTS group compared to the placebo group (7% *vs.* 21%, P=0.009).

SBO

There was no difference between all groups in the incidence of SBO due to any cause, ASBO specifically, median length of hospital stay, number of patients with multiple admissions for SBO and SBO-free survival (*Table 3* and *Figure 2*). No patients in the STS group required operative intervention for SBO which was statically significant when compared to the LTS group for SBO overall (0% *vs.* 50%, P=0.014) and ASBO specifically (0% *vs.* 53%, P=0.048). This difference was similar when compared to the placebo group but did not reach statistical significance for SBO overall (0% *vs.* 42%, P=0.055) or ASBO (0% *vs.* 50%, P=0.085). Non-operative management was standard across all three groups with a trial of nasogastric decompression initially, and there was no difference in gastrografin administration during admission for SBO or ASBO between the groups.

Oncological outcomes

Polyps

Post-operative surveillance colonoscopy data was analysed for 37 patients in the STS group, 38 in the placebo group and 110 in the LTS group that were diagnosed with adenocarcinoma or high-grade dysplastic polyps following their index operation. Colonoscopy rates were similar across the three groups (*Table 4*). There was no significant difference in the number of patients that developed polyps of any kind or adenomas specifically between the groups. The median number of polyps and adenomas detected per patient was also similar.

Recurrence

No significant difference in CRC recurrence and disease-free survival was found between the groups (*Table 4* and *Figure 3*). Cancer-related mortality was compared between

Table 3 Small bowel obstruction

Variables	Perioperative short-term statin (n=65)	Placebo (n=67)	Long-term statin (n=137)	P value*
Patients admitted with SBO, n [%]	8 [12]	12 [18]	22 [16]	0.685
Operative treatment required	0	5 [42]	11 [50]	0.030
Gastrografin administered	3 [38]	7 [58]	13 [59]	0.648
Patients with adhesive SBO, n [%]§	6 [9]	8 [12]	17 [12]	0.893
Operative treatment required	0	4 [50]	9 [53]	0.058
Gastrografin administered	2 [33]	6 [75]	9 [53]	0.346
Median length of hospital stay, days [IQR]	4 [3–7]	7 [3–10]	3 [2–8]	0.357†
Patients with multiple admissions for SBO, n [%]	1 [2]	3 [4]	5 [4]	0.748

*, Fisher's Exact test unless stated otherwise; †, Kruskal Wallis test; §, non-adhesive causes for SBO were ileostomy stricture (n=1) and small bowel tumour (n=1) in the perioperative statin group; small bowel tumour (n=1), large retroperitoneal liposarcoma (n=1), parastomal hernia (n=1) and related to intraabdominal metastases (n=1) in the Placebo group; and parastomal hernia (n=1), anastomotic stricture (n=1), small bowel tumour (n=1), and incarcerated anterior abdominal wall hernia (n=2) in the long-term statin group. SBO, small bowel obstruction; IQR, interquartile range.

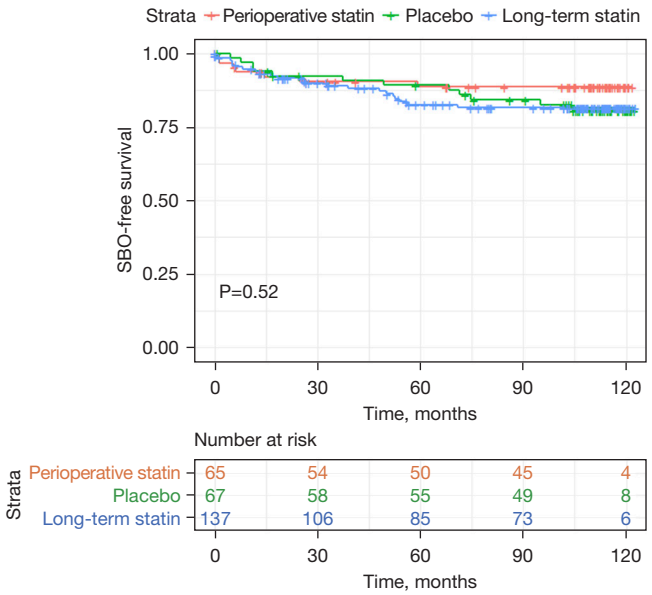

Figure 2 Small bowel obstruction-free survival for patients that had short-term perioperative simvastatin (red line), placebo (green line), and long-term statin therapy (blue line), P=0.52 (log rank test). SBO, small bowel obstruction.

the STS and placebo groups, and no significant difference was found (6 *vs.* 6, P>0.99).

Discussion

This study of patients with different periods of statin exposure when undergoing major colorectal surgery found a similar incidence of SBO and ASBO after a median follow-up period of 9.5 years. However, significantly fewer patients who received short-term perioperative statin therapy needed to undergo operative treatment for SBO overall and ASBO specifically compared to the long-term preoperative statin group. A similar trend was seen when comparing operative rates between the STS and placebo group for SBO overall and ASBO; however, this did not reach statistical significance. Patients on LTS therapy were significantly older, had more medical comorbidities, and a higher proportion undergoing surgery for malignancy, but there were no significant differences between groups in overall complications, cancer recurrence, or development of polyps.

The findings of this study align with a previous retrospective study that reported an association between statin therapy and decreased operative rates for ASBO (20). This may indicate a decreased severity of ASBO amongst the perioperative simvastatin group allowing successful non-operative management (25). Obstructions may have been less severe in this group due to a decreased density of post-operative adhesions secondary to an attenuated pro-inflammatory response or the pro-fibrinolytic effects of the simvastatin regimen (17,18). Interestingly, the fibrinolytic activity in peritoneal drain fluid of 95 of the 132 participants from the original RCT was measured and there was no difference between the groups (26). However, this study only looked at fibrinolytic activity up to 24 hours

Table 4 Colonoscopy rate, polyp incidence and cancer recurrence for patients with adenocarcinoma and high-grade dysplastic polyps

Variables	Perioperative short-term statin (n=37)	Placebo (n=38)	Long-term statin (n=110)	P value*
Patients that underwent post-op surveillance colonoscopies, n [%]	24 [65]	26 [68]	58 [53]	0.165
Patients with polyps, n [%]	17 [71]	19 [73]	38 [66]	0.821
Polyps detected per patient, median [IQR]	1 [0–4]	3 [0–6]	2 [0–5]	0.902†
Patients with adenomas, n [%]	11 [46]	10 [38]	29 [50]	0.620
Adenomas detected per patient, median [IQR]	0 [0–1]	0 [0–1]	1 [0–1]	0.574†
Patients with adenocarcinoma recurrence, n [%]	4 [11]	5 [13]	24 [22]	0.27

*, Fisher's Exact test unless stated otherwise; †, Kruskal-Wallis test. IQR, interquartile range.

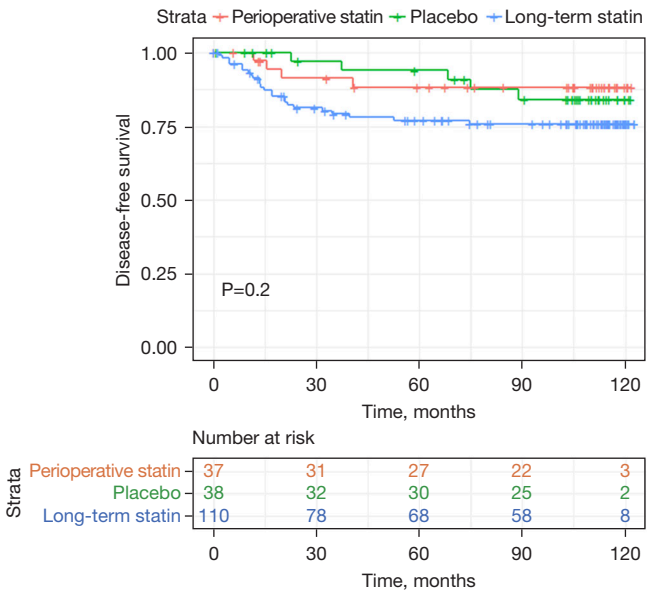

Figure 3 Disease-free survival for patients that had perioperative simvastatin (red line), placebo (green line), and long-term preoperative statin therapy (blue line), P=0.2 (log rank test).

after surgery, so it is unknown whether fibrinolytic activity between these groups diverged after this time.

Interestingly, a decreased operative rate for SBO was not observed in the LTS group. Similar outcomes would be expected if these patients were also benefiting from the anti-inflammatory and pro-fibrinolytic actions of statins. This difference between the STS and LTS groups may be related to a difference in inflammatory profiles between these groups given the LTS group was significantly older and had more chronic medical conditions, such as diabetes mellitus, which are associated with a chronic, low-grade inflammatory state and increased levels of anti-fibrinolytic factors such as plasminogen activator inhibitor which may result in an increased density of adhesions (27).

Whilst this study showed no significant difference in the overall incidence of ASBO or mechanical SBO due to any cause, a recent retrospective analysis of two populations found differences in ASBO incidence and other adhesion-related complications amongst statin users (19). This study was much larger with almost 1.3 million participants in total and found a hazard ratio of developing SBO of 0.80 [95% confidence interval (CI): 0.70–0.92] in one population and 0.88 (95% CI: 0.85–0.91) in the other. In comparison, our study may have been limited by its small sample size to find such an effect.

While there is some evidence that statin use may be associated with a decreased incidence of developing colorectal adenomas (22,23), this study did not find a difference in adenoma or polyp development. Statins have also been investigated in the setting of CRC, with a retrospective study finding an increased response to neoadjuvant chemotherapy in statin users with rectal adenocarcinoma, suggesting that statins possess some anti-carcinogenic effects (28). A 2018 meta-analysis found inconclusive results with five studies reporting increased cancer survival and five reporting no difference in survival between statin users and non-users (29). Conversely, there is some indication that pharmacological interventions that dampen the inflammatory response may be associated with an increased risk of CRC metastasis, as shown in a study investigating outcomes for patients that received preoperative dexamethasone (30). This study did not find an increase or decrease in cancer recurrence despite perioperative statin therapy attenuating the early pro-

inflammatory response following surgery.

There are several limitations to this study including its retrospective design and small sample size. Due to the retrospective chart-review method of this study, outcome data may have been incomplete if patients did not present to hospital or if the clinical documentation of diagnosis and treatment of complications was incomplete or inaccurate. For example, fewer patients in the LTS group experienced wound infections, which may reflect a difference in retrospective versus. prospective data collection as minor infections may not have been consistently recorded in the retrospective sources that were examined for this group. The original RCT from which this sample was derived was powered to detect complications up to 30 days post-operatively, so the present study was not powered to detect differences in SBO, polyp incidence, or cancer recurrence. The influence of type I statistical error must also be considered for the outcomes in which we performed subgroup analyses, such as SBO operative rate. The retrospective nature of this study also introduces a risk of confounding with unmatched variables between groups, which is particularly true for patients in the LTS group. While the STS and placebo groups were well-matched at baseline, this becomes less protective over the long follow-up period, such as potential cross-over due to later statin use. We were unable to gather information of the type of statin, dose, duration of use and compliance with statin therapy in the LTS group due to the retrospective design of the study. While the original trial reported no difference in operation time between the STS (median 190 minutes, IQR, 137–236 minutes) and placebo (median 194 minutes, IQR, 136–264 minutes) groups (24), which likely represents similar bowel handling time, no data on operation time was available for the LTS group retrospectively which may be another potential confounding factor. Therefore, the positive findings of this study can only be considered hypothesis-generating. The scope of the study was limited to patients undergoing elective operations only as recruitment of participants to the original RCT would not have been feasible for patients undergoing emergency or nonelective urgent operations. The findings may not be applicable to patients undergoing acute or emergency operations.

Conclusions

Patients undergoing major colorectal surgery that were given a perioperative regimen of 40 mg oral simvastatin and developed SBO were less likely to require operative intervention than those given placebo or on LTS therapy. While this finding needs to be interpreted with caution given the small sample size of this study, the significant morbidity associated with SBO and reoperation warrants further investigation into the role of perioperative statin therapy as a simple and widely available intervention that may help reduce the risk of such a common long-term complication following abdominal surgery.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://asj.amegroups.com/article/view/10.21037/asj-23-32/rc

Data Sharing Statement: Available at https://asj.amegroups.com/article/view/10.21037/asj-23-32/dss

Peer Review File: Available at https://asj.amegroups.com/article/view/10.21037/asj-23-32/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://asj.amegroups.com/article/view/10.21037/asj-23-32/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study received institutional ethical approval from the Auckland Health Research Ethics Committee (Reference: AH23365) and individual consent for this retrospective analysis was waived.

References

1. Alves A, Panis Y, Mathieu P, et al. Postoperative mortality and morbidity in French patients undergoing colorectal surgery: results of a prospective multicenter study. Arch Surg 2005;140:278-83, discussion 284.
2. de Silva S, Ma C, Proulx MC, et al. Postoperative complications and mortality following colectomy for ulcerative colitis. Clin Gastroenterol Hepatol 2011;9:972-80.
3. Ouaïssi M, Gaujoux S, Veyrie N, et al. Post-operative adhesions after digestive surgery: their incidence and prevention: review of the literature. J Visc Surg 2012;149:e104-14.
4. ten Broek RP, Issa Y, van Santbrink EJ, et al. Burden of adhesions in abdominal and pelvic surgery: systematic review and met-analysis. BMJ 2013;347:f5588.
5. Behman R, Nathens AB, Haas B, et al. Population-based study of the impact of small bowel obstruction due to adhesions on short- and medium-term mortality. Br J Surg 2019;106:1847-54.
6. Gunawardene A, Desmond B, Shekouh A, et al. Disease recurrence following surgery for colorectal cancer: five-year follow-up. N Z Med J 2018;131:51-8.
7. Farhat W, Azzaza M, Mizouni A, et al. Factors predicting recurrence after curative resection for rectal cancer: a 16-year study. World J Surg Oncol 2019;17:173.
8. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78. Erratum in: Lancet 2005;366:1358.
9. Fang SY, Roan JN, Luo CY, et al. Pleiotropic vascular protective effects of statins in perioperative medicine. Acta Anaesthesiol Taiwan 2013;51:120-6.
10. Skrlin S, Hou V. A review of perioperative statin therapy for noncardiac surgery. Semin Cardiothorac Vasc Anesth 2010;14:283-90.
11. Fischetti F, Carretta R, Borotto G, et al. Fluvastatin treatment inhibits leucocyte adhesion and extravasation in models of complement-mediated acute inflammation. Clin Exp Immunol 2004;135:186-93.
12. Merx MW, Liehn EA, Janssens U, et al. HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. Circulation 2004;109:2560-5.
13. Souza Neto JL, Araújo Filho I, Rego AC, et al. Effects of simvastatin in abdominal sepsis in rats. Acta Cir Bras 2006;21 Suppl 4:8-12.
14. Pourlotfi A, Ahl R, Sjolin G, et al. Statin therapy and postoperative short-term mortality after rectal cancer surgery. Colorectal Dis 2021;23:875-81.
15. Disbrow D, Seelbach CL, Albright J, et al. Statin medications are associated with decreased risk of sepsis and anastomotic leaks after rectal resections. Am J Surg 2018;216:31-6.
16. Fransgaard T, Thygesen LC, Gögenur I. Statin use is not associated with improved 30-day survival in patients undergoing surgery for colorectal cancer. Int J Colorectal Dis 2018;33:199-207.
17. Aarons CB, Cohen PA, Gower A, et al. Statins (HMG-CoA reductase inhibitors) decrease postoperative adhesions by increasing peritoneal fibrinolytic activity. Ann Surg 2007;245:176-84.
18. Choi GJ, Park HK, Kim DS, et al. Effect of statins on experimental postoperative adhesion: a systematic review and meta-analysis. Sci Rep 2018;8:14754.
19. Scott FI, Vajravelu RK, Mamtani R, et al. Association Between Statin Use at the Time of Intra-abdominal Surgery and Postoperative Adhesion-Related Complications and Small-Bowel Obstruction. JAMA Netw Open 2021;4:e2036315.
20. Srinivasa S, Kahokehr AA, Sammour T, et al. Use of statins in adhesive small bowel obstruction. J Surg Res 2010;162:17-21.
21. Li L, Cui N, Hao T, et al. Statins use and the prognosis of colorectal cancer: a meta-analysis. Clin Res Hepatol Gastroenterol 2021;45:101588.
22. Broughton T, Sington J, Beales IL. Statin use is associated with a reduced incidence of colorectal adenomatous polyps. Int J Colorectal Dis 2013;28:469-76.
23. Siddiqui AA, Nazario H, Mahgoub A, et al. The long-term use of statins is associated with a decreased incidence of adenomatous colon polyps. Digestion 2009;79:17-22.
24. Singh PP, Lemanu DP, Soop M, et al. Perioperative Simvastatin Therapy in Major Colorectal Surgery: A Prospective, Double-Blind Randomized Controlled Trial. J Am Coll Surg 2016;223:308-320.e1.
25. Zielinski MD, Bannon MP. Current management of small bowel obstruction. Adv Surg 2011;45:1-29.
26. Alexander ZE, Su'a B, Hill CT, et al. The effect of oral simvastatin on fibrinolytic activity after colorectal surgery-a pilot study. J Surg Res 2016;205:28-32.

27. Esmon CT. The impact of the inflammatory response on coagulation. Thromb Res 2004;114:321-7.
28. Mace AG, Gantt GA, Skacel M, et al. Statin therapy is associated with improved pathologic response to neoadjuvant chemoradiation in rectal cancer. Dis Colon Rectum 2013;56:1217-27.
29. Dobrzycka M, Spychalski P, Łachiński AJ, et al. Statins and Colorectal Cancer - A Systematic Review. Exp Clin Endocrinol Diabetes 2020;128:255-62.
30. Singh PP, Lemanu DP, Taylor MH, et al. Association between preoperative glucocorticoids and long-term survival and cancer recurrence after colectomy: follow-up analysis of a previous randomized controlled trial. Br J Anaesth 2014;113 Suppl 1:i68-73.

doi: 10.21037/asj-23-32
Cite this article as: Bahl P, Jin J, Hill A, Singh PP. Perioperative statin therapy and long-term outcomes following major colorectal surgery: a retrospective cohort study. AME Surg J 2024.