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Effects of beta-blocker therapy on mortality after elective colon cancer surgery: a Swedish nationwide cohort study

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ABSTRACT

Objective Colon cancer surgery remains associated with substantial postoperative morbidity and mortality despite advances in surgical techniques and care. The trauma of surgery triggers adrenergic hyperactivation which drives adverse stress responses. We hypothesised that outcome benefits are gained by reducing the effects of hyperadrenergic activity with beta-blocker therapy in patients undergoing colon cancer surgery. This study aims to test this hypothesis.

Design Retrospective cohort study.

Setting and participants This is a nationwide study which includes all adult patients undergoing elective colon cancer surgery in Sweden over 10 years. Patient data were collected from the Swedish Colorectal Cancer Registry. The national drugs registry was used to obtain information about beta-blocker use. Patients were subdivided into exposed and unexposed groups. The association between beta-blockade, short-term and long-term mortality was evaluated using Poisson regression, Kaplan-Meier curves and Cox regression.

Primary and secondary outcomes Primary outcome of interest was 1-year all-cause mortality. Secondary outcomes included 90-day all-cause and 5-year cancer-specific mortality.

Results The study included 22 337 patients of whom 36.1% were prescribed preoperative beta-blockers. Survival was higher in patients on beta-blockers up to 1 year after surgery despite this group being significantly older and of higher comorbidity. Regression analysis demonstrated significant reductions in 90-day deaths (IRR 0.29, 95% CI 0.24 to 0.35, p<0.001) and a 43% risk reduction in 1-year all-cause mortality (adjusted HR 0.57, 95% CI 0.52 to 0.63, p<0.001) in beta-blocked patients. In addition, cancer-specific mortality up to 5 years after surgery was reduced in beta-blocked patients (adjusted HR 0.80, 95% CI 0.73 to 0.88, p<0.001).

Conclusion Preoperative beta-blockade is associated with significant reductions in postoperative short-term and long-term mortality following elective colon cancer surgery. Its potential prophylactic effect warrants further interventional studies to determine whether beta-blockade can be used as a way of improving outcomes for this patient group.

Strengths and limitations of this study

► This cohort study used a prospectively collected database comprising a 99.5% national inclusion coverage of all adult patients undergoing elective surgery for colon cancer.
► It is the first beta-blocker study to evaluate a homogeneous surgical patient group with patient selection limited to planned, standardised major abdominal surgery, a diagnosis of colon cancer mainly affecting the elderly and a healthcare system that provides universal care free at the point of use.
► Multivariate regression analysis was carried out to evaluate the association between beta-blocker use and survival following surgery.
► Given the retrospective design, the current study is unable to determine whether the apparent effect of beta-blocker therapy is due to preoperative or postoperative administration or a required combination of the two.

BACKGROUND

Colon cancer surgery has long been associated with substantial postoperative morbidity and mortality.[1–3] Figures published by the American College of Surgeons National Surgical Quality Improvement Programme demonstrate that one in four patients suffer complications following colorectal surgery while fatalities run at up to four per cent. Ten per cent of the complications are classified as serious and are of both cardiac and non-cardiac nature.[4] Despite a fall in morbidity, as a result of advancements in perioperative and postoperative colorectal cancer care, the incidence of postoperative deaths has not demonstrated the same change during the past decade.[1 5–7]

One contributory factor may be the difficulty in controlling postoperative stress-related events that have been closely linked to the surgery-induced hyperadrenergic state.[8–10] Few effective cardiovascular

preventative measures are established in non-cardiac surgery and patients with pre-existing coronary artery disease are at particular risk.[11–14] In addition, the hyper-adrenergic state has been linked to insulin resistance, inflammatory responses and immunosuppression leading to an increased risk for postoperative complications and death.[15–19] Immunosuppression has not only been linked to worsened outcomes in the context of surgery but there is a close relationship between immunosuppression, chronic inflammation and subsequent cancer development.[20] By reducing adrenergic receptor activation, beta-blockers may decrease physiological stress caused by the insult of major abdominal surgery. Previous studies investigating the relationship between beta-blockade and non-cardiac surgery have tended to lump together several surgical fields.[10] This methodological approach may affect results and it makes it difficult to draw conclusions about abdominal surgery specifically. Reductions in several severe postoperative complications has been measured in patients on preoperative beta-blockers undergoing surgery for rectal cancer as well as increased survival up to 1 year in the same population.[21] The authors have previously published results demonstrating a positive effect of preoperative beta-blocker therapy on short-term survival in patients undergoing emergency surgery for colon cancer.[22] This study investigates whether this effect extends to patients undergoing elective colon cancer resection and whether the effect remains long-term. This may not simply be assumed from previous results since, unlike patients who are forced to undergo emergency intervention, the patient group in this study has already been optimised for surgery. The authors hypothesise that beta-blocker exposure reduces the risk of both short- and long-term postoperative mortality following elective colon cancer surgery.

METHOD
Study design
In this retrospective cohort study patients were identified using the Swedish Colorectal Cancer Registry (SCRCR).[23] The SCRCR is a prospectively collected national quality registry including both surgical and oncological treatments for colorectal cancers. Clinical information, outcomes and demographics are collected from the date of diagnosis and for a period of three years. The registry has a 99.5% nationwide coverage.[24] In the current study, data for all adults (≥18 years) who underwent elective surgery for colon cancer were obtained from the SCRCR. The inclusion period ran from January 2007 to October 2016. Patients who underwent local tumour resection or laparotomy without bowel resection were excluded. Sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, tumour location, TNM (tumour, node, metastases) classification, surgical approach (open or laparoscopic), hospital length of stay, 90-day and 1-year mortality along with the cause of death were obtained from the registry. The SCRCR does not

record comorbidity data. Therefore, comorbidity data was obtained from the National Patient Registry which records diagnoses made both in primary and secondary care. Data on 5-year mortality and cause of death were obtained from the Swedish Causes of Death Registry maintained by the Swedish National Board of Health and Welfare. Death certificates allow for more than one cause of death to be listed with decreasing importance. Colon cancer listed as the first cause of death were classified as cancer-specific deaths.

The study was registered on 7 July 2017 with the Open Database for Research in Sweden.[25] It received funding from the Örebro University Research Committee (grant number OLL-676701). The principles of the Declaration of Helsinki and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines were adhered to. The authors have no conflicts of interest to disclose. No additional data than that included in this manuscript is available.

Patient and public involvement
There was no patient or public involvement in this study. Due to time and funding limitations neither patients nor the public were invited to comment on the design or analysis of this research.

Beta-blocker exposure
Issued beta-blocker prescriptions (ACT codes C07AA, C07AB and C07AG) within a 12-month preoperative period were obtained from the national drugs registry of the Swedish National Board of Health and Welfare, allowing the subdivision of patients according to beta-blocker exposure. A 12-month inclusion period was chosen since beta-blockers are rarely discontinued once initiated (most commonly for a cardiovascular indication) and therefore commonly issued on a long-term basis covering up to a 12-month period with a single prescription. The drugs registry is a population-based database containing all prescriptions issued in Sweden. Unique personal identity numbers were used to link electronic prescriptions in the drugs registry to individual patients in the SCRCR. Inclusion criteria for the beta-blocker exposed group was set to patients with collected prescriptions for regular beta-blocker administration that were in active use at the time of surgery. Information regarding dose and generic drug name were also collected. Patients with physician-issued prescriptions that were not collected by the patient were excluded from the beta-blocker exposed group. According to national guidelines set by the Swedish Society of Anesthesiology and Intensive Care, a patient on regular beta-blocker therapy should always receive this on the morning of surgery and if no absolute contraindications exist the medication will be reinstated as soon as possible postoperatively.

Statistical analysis
Patients' demographic characteristics were presented using descriptive statistical methods and subsequently

compared between subgroups. Continuous variables were portrayed as means and standard deviations (SD) while categorical and ordinal variables were outlined as counts and percentages or medians and quartiles where suitable. χ^2 or Fisher's exact tests were used for comparison between categorical variables and Student's t-test was used for continuous variables with normal distribution. The Mann-Whitney U test was used for variables with ordinal or asymmetrically distributed continuous data. The primary outcome of interest was 1-year all-cause mortality. Secondary outcomes included 90-day all-cause and 5-year cancer-specific mortality.

The association between beta-blocker use and 90-day all-cause mortality was analysed using Poisson regression with robust standard errors (SE).[26] Multiple imputation method was used for handling missing values. Potential confounding was adjusted for in the models by including the following covariates: age, sex, ASA classification, cancer stage, Charlson Comorbidity Index, chemotherapy, type of surgical resection and method. One-year all-cause and 5-year cancer-specific mortality was illustrated using Kaplan-Meier curves and assessed with Cox proportional hazards regression. The Cox models were adjusted for the same covariates as in the Poisson regression model. In the 1-year all-cause mortality analysis, the event was defined as death of any cause within the specified time and censoring was defined as alive at the end of the specified time period. For 5-year cancer-specific survival analysis, the event was defined as death from colon cancer within five years and the censoring was defined as alive at last follow-up or death from any other cause. Results are reported as incidence rate ratio (IRR) for 90-day mortality and as hazard ratio (HR) for 1-year and 5-year mortality with corresponding 95% confidence intervals (CI). Tests were considered statistically significant at a two-sided p value of <0.05. Analyses were carried out using the SPSS Windows V.25.0 (IBM, Armonk, New York).

RESULTS

Comparison of group characteristics

During the 10-year study period 22 805 patients underwent elective resection surgery for colon cancer in Sweden. Two per cent (n=468) of patients were excluded due to missing data in several of the collected variables, leaving a total of 22 337 patients available for analysis. Out of this cohort, 36.1% (n=8072) of patients were prescribed regular preoperative beta-blocker therapy. An overwhelming majority of patients (85%) were prescribed a beta-1 receptor selective agent, with the most commonly prescribed beta-blocker agent being metoprolol (48.6%) followed by bisoprolol (19.7%) and atenolol (17.0%). There were statistically significant differences between the groups, with beta-blocker exposed patients demonstrating a higher mean age (75 (SD 9) vs 70 (SD 12) years), a higher mean BMI (26.7 (SD 4.9) vs 25.5 (SD

4.5)) and a larger proportion of male patients (50.0% vs 47.6%) (table 1).

The beta-blocked group was deemed less fit for surgery, as suggested by a larger proportion having an ASA score of 3 (44.6% vs 20.4%) or 4 (4.1% vs 1.3%) and more patients with a Charlson Comorbidity Index of 5 and above (87.3% vs 66.3%). Over 70% of patients in the beta-blocker exposed group had diagnosed cardiovascular disease. The equivalent number in the beta-blocker unexposed group was 27.5%. In both groups, a right-sided hemicolectomy was the most common procedure performed occurring in more than 50% in each group (table 1). Additionally, patients unexposed to beta-blocker therapy underwent open surgery to a larger extent (86.0% vs 83.8%) and had a higher incidence of stage IV cancer (13.4% vs 10.1%) (table 1).

Mortality outcomes

Seven-hundred and sixteen (3.21%) out of the total cohort of 22 337 patients died during the 90-day postoperative period. There was a statistically significant difference in mortality rates between the two groups. The beta-blocker unexposed group suffered 316 postoperative deaths (2.2%) in the first 30 days compared with the beta-blocker exposed group with only 70 deaths (0.9%). This difference remained significant at 90 days (3.9% vs 1.9%, p=0.001) and at 1 year (9.6% vs 8.3%, p=0.001) after surgery with numbers needed to treat to benefit of 50 and 77, respectively (table 2). The incidence of cardiac-related deaths was 0.8% in the total cohort. All causes of death at 90 days, with the exception of cerebrovascular insults, demonstrated lower incidences in the beta-blocker exposed group (table 2).

Patients exposed to beta-blockers had a 90-day mortality risk less than one-third of those who were unexposed (adjusted IRR 0.29, 95% CI: 0.24 to 0.35, p<0.001). Both ASA class 3 and 4 as well as cancer stage IV demonstrated major increases in the risk of death within the immediate postoperative period (table 3).

The protective effect of beta-blockade appeared to remain at one year after surgery with a risk reduction of 43% (adjusted HR 0.57, 95% CI 0.52 to 0.63, p<0.001) (table 4, figure 1). Adjuvant chemotherapy and a laparoscopically carried out procedure were also linked to increased chance of survival at one year after elective cancer resection surgery. Following a Cox regression analysis, beta-blocked patients also showed reduced cancer-specific mortality up to five years after surgery with a 20% risk reduction (adjusted HR 0.80, 95% CI 0.73 to 0.88, p<0.001) (figure 2).

DISCUSSION

The results of this large, nationwide cohort study demonstrate that beta-blocker therapy in elective surgery for colon cancer is strongly associated with reduced incidences of death not only in the immediate postoperative period but also long-term. Ninety-day all-cause mortality in

Table 1 Patient demographics

	BB⁻ n=14 265	BB⁺ n=8072	P value
Male sex, n (%)	6794 (47.6)	4039 (50.0)	0.001
Age in years, mean (SD)	70 (12)	75 (9)	<0.001
Age in years, median (Q1, Q3)	72 (63, 79)	76 (70, 82)	
BMI, mean (SD)	25.5 (4.5)	26.7 (4.9)	<0.001
BMI, median (Q1, Q3)	24.9 (22.6, 27.8)	26.1 (23.5, 29.4)	
ASA classification, n (%)			<0.001
1	2932 (20.6)	162 (2.0)	
2	7962 (55.8)	3851 (47.7)	
3	2913 (20.4)	3597 (44.6)	
4	182 (1.3)	333 (4.1)	
Missing	276 (1.9)	127 (1.6)	
Type of beta-blocker, n (%)	–		n/a
Atenolol	–	1370 (17.0)	
Bisoprolol	–	1591 (19.7)	
Metoprolol	–	3926 (48.6)	
Other	–	1185 (14.7)	
Surgical resection n (%)			<0.001
Ileocecal resection	139 (1.0)	77 (1.0)	
Right hemicolectomy	7733 (54.2)	4672 (57.9)	
Resection of transverse colon	265 (1.9)	182 (2.3)	
Left hemicolectomy	1695 (11.9)	843 (10.4)	
Resection of sigmoid colon	3612 (25.3)	1847 (22.9)	
Total colectomy	569 (4.0)	239 (3.0)	
Hartmann's	252 (1.8)	212 (2.6)	
Surgical approach, n (%)			<0.001
Open	12 271 (86.0)	6764 (83.8)	
Laparoscopic	1994 (14.0)	1308 (16.2)	
Adjuvant chemotherapy, n (%)	3517 (24.6)	1155 (14.3)	<0.001
Cancer stage n (%)			<0.001
I	2191 (15.4)	1493 (18.5)	
II	5475 (38.4)	3195 (39.6)	
III	4691 (32.9)	2571 (31.9)	
IV	1908 (13.4)	813 (10.1)	
T, N and M classification, n (%)			<0.001

Continued

Table 1 Continued

	BB⁻ n=14 265	BB⁺ n=8072	P value
T1-2	2700 (18.9)	1796 (22.2)	
T3	8664 (60.7)	4815 (59.7)	
T4	2869 (20.1)	1457 (18.1)	
N1-2	6117 (42.9)	3166 (39.2)	
M1	1907 (13.4)	813 (10.1)	
Charlson Comorbidity Index			<0.001
≤2	701 (4.9)	33 (0.4)	
3-4	4111 (28.8)	996 (12.3)	
≥5	9453 (66.3)	7043 (87.3)	
Cardiovascular disease, n (%)*	3926 (27.5)	5880 (72.8)	<0.001
CHF	342 (2.4)	1226 (15.2)	
Arrhythmia	862 (6.0)	2400 (29.7)	
MI	313 (2.2)	1349 (16.7)	
Hypertension	2878 (20.2)	4411 (54.6)	
Other	425 (3.0)	251 (3.1)	
Coagulopathic disease, n (%)	103 (0.7)	162 (2.0)	<0.001
Respiratory disease, n (%)	1120 (7.9)	847 (10.5)	<0.001
Cerebrovascular disease, n (%)	616 (4.3)	723 (9.0)	<0.001
Renal failure, n (%)	1677 (11.8)	1502 (18.6)	<0.001
Diabetes mellitus, n (%)	1327 (9.3)	1659 (20.6)	<0.001

* Represents the total number of patients with cardiovascular disease. The total is lower than the listed cardiovascular conditions combined due to some patients having more than one cardiovascular condition.

ASA, American Society of Anesthesiologists; BB⁺, beta-blocker positive; BB⁻, beta-blocker negative; BMI, body mass index; CHF, congestive heart failure; MI, myocardial infarction; n/a, not applicable; Q1, first quartile; Q3, third quartile; T, N and M, tumour, node and metastases.

beta-blocker unexposed patients was 3.9% and the equivalent figure in beta-blocker exposed patients was 1.9% (p=0.001). After adjustment for confounding factors, patients on preoperative beta-blocker therapy showed a 70% relative risk reduction in 90-day mortality compared with patients who did not receive beta-blockers. In the context of long-term survival, beta-blocker use was associated with a 43% risk reduction in 1-year overall mortality (HR 0.57, 95% CI 0.52 to 0.63, p<0.001). The protective effect of beta-blockade on mortality was also seen for 5-year cancer-specific mortality (HR 0.80, 95% CI 0.73 to 0.88, p<0.001).

The physical trauma of surgery triggers hypothalamic activation of the sympathetic autonomic nervous system with subsequent surges in catecholamine secretion, leading to stress responses causing activation of multiple

Table 2 Clinical outcomes

	BB⁻ n=14 265	BB⁺ n=8072	P value
Hospital length of stay			
Days, mean (SD)	9 (10)	10 (10)	<0.001
Days, median (Q1, Q3)	6 (5, 10)	7 (5, 11)	
All-cause mortality, n (%)			
30 days	316 (2.2)	70 (0.9)	<0.001
90 days	559 (3.9)	157 (1.9)	0.001
1 year	1375 (9.6)	674 (8.3)	0.001
Cause-specific mortality at 30 days, n (%)			
Cardiovascular	92 (0.6)	20 (0.2)	<0.001
Respiratory	45 (0.3)	11 (0.1)	0.01
Sepsis	37 (0.3)	7 (0.1)	0.005
Cerebrovascular	3 (0.0)	4 (0.0)	0.247
Multiorgan failure	118 (0.8)	26 (0.3)	<0.001
Unknown	21 (0.1)	2 (0.0)	0.006
Cause-specific mortality at 90 days, n (%)			
Cardiovascular	133 (0.9)	46 (0.6)	0.004
Respiratory	66 (0.5)	18 (0.2)	0.005
Sepsis	41 (0.3)	7 (0.1)	0.002
Cerebrovascular	4 (0.0)	4 (0.0)	0.414
Multiorgan failure	291 (2.0)	80 (1.0)	<0.001
Unknown	22 (0.2)	2 (0.0)	0.005
Colon cancer-specific mortality, n (%)			
Up to 5 years	1586 (11.1)	776 (9.6)	<0.001

BB⁺, beta-blocker positive; BB⁻, beta-blocker negative; Q1, first quartile; Q3, third quartile.

Table 3 Incidence rate ratio (IRR) for 90-day mortality

	IRR (95% CI)	P value
Preoperative BB	0.29 (0.24 to 0.35)	<0.001
Age	1.03 (1.02 to 1.04)	<0.001
Female sex	0.73 (0.63 to 0.84)	<0.001
ASA classification		
1	Ref	–
2	1.99 (1.31 to 3.02)	0.001
3	6.11 (4.04 to 9.23)	<0.001
4	14.36 (9.14 to 22.55)	<0.001
Charlson Comorbidity Index		
≤2	Ref	–
3-4	1.00 (0.35 to 2.84)	0.996
≥5	1.25 (0.44 to 3.57)	0.682
Cancer stage		
I	Ref	–
II	1.31 (1.00 to 1.72)	0.054
III	2.30 (1.74 to 3.03)	<0.001
IV	4.68 (3.56 to 6.15)	<0.001
Surgical approach		
Open	Ref	–
Laparoscopic	0.65 (0.49 to 0.86)	0.002
Surgical resection		
Ileocecal resection	Ref	–
Right hemicolectomy	0.75 (0.48 to 1.18)	0.217
Resection of transverse colon	0.66 (0.35 to 1.22)	0.184
Left hemicolectomy	0.76 (0.46 to 1.23)	0.262
Resection of sigmoid colon	0.55 (0.35 to 0.89)	0.014
Total colectomy	0.93 (0.53 to 1.62)	0.784
Hartmann's	0.71 (0.40 to 1.26)	0.241
Adjuvant chemotherapy	0.10 (0.06 to 0.17)	<0.001

Poisson regression model with robust SEs. Multiple imputation method was used for missing values. All results adjusted for all variables in the table.
ASA, American Society of Anesthesiologists; BB, beta-blocker.

organ systems. Adrenoceptors serve a regulating cardiovascular purpose but also serve other organ systems and metabolic and inflammatory networks.[8] Although a natural response to injury, the activation of adrenoceptors has been linked to an increased risk of death and there is a close relationship between patient epinephrine levels at hospital admission and mortality risk following traumatic injury.[15 27] The complex role of catecholamines contributes to the understanding of the association between physiological trauma and adverse effects such as cardiovascular overload, insulin resistance and increased inflammatory activation and hypercoagulability.[13] A plausible explanation to increased mortality in the drug-naïve patients could lie in the risk of such adverse events. In elective surgery, blocking of epinephrine release by thoracic epidural has shown to reduce insulin resistance by almost half.[18] Insulin resistance and hyperglycaemia in surgery has demonstrated a close relationship to the development of complications especially infections and sepsis.[19] Controlling insulin resistance has been brought forward as a key mechanism behind the success of the Enhanced Recovery After Surgery protocols.[28] In vivo, the rise in

plasma catecholamines during surgery can be linked to surgery-related stress responses and adrenergic activation is maintained beyond the end of the procedure.[29] Such observations lead to the hypothesis that maintained administration of preoperatively prescribed beta-blockers could serve a prophylactic role and improve clinical outcomes for patients undergoing complex operations such as colon cancer surgery. The proposed mechanism of action is blockage and attenuation of catecholamine-mediated stress responses initiated by major surgery.

The benefits of beta-blockers have been demonstrated in multiple trials in the context of cardiac surgery.[30] In elective cardiothoracic surgery, the use of perioperative

Table 4 HR for 1-year mortality

	Adjusted HR (95% CI)	P value
Preoperative BB	0.57 (0.52 to 0.63)	<0.001
Age	1.03 (1.02 to 1.04)	<0.001
Female sex	0.91 (0.83 to 1.00)	0.038
ASA Classification		
1	Ref	–
2	1.63 (1.33 to 2.01)	<0.001
3	3.05 (2.47 to 3.76)	<0.001
4	6.85 (5.27 to 8.90)	<0.001
Charlson Comorbidity Index		
≤2	Ref	–
3-4	0.52 (0.34 to 0.79)	0.002
≥5	0.67 (0.43 to 1.04)	0.073
Cancer stage		
I	Ref	–
II	1.40 (1.16 to 1.70)	0.001
III	3.17 (2.63 to 3.83)	<0.001
IV	9.43 (7.83 to 11.35)	<0.001
Surgical approach		
Open	Ref	–
Laparoscopic	0.61 (0.51 to 0.72)	<0.001
Surgical resection		
Ileocecal resection	Ref	–
Right hemicolectomy	0.63 (0.47 to 0.86)	0.003
Resection of transverse colon	0.65 (0.44 to 0.97)	0.033
Left hemicolectomy	0.48 (0.34 to 0.67)	<0.001
Resection of sigmoid colon	0.38 (0.28 to 0.53)	<0.001
Total colectomy	0.74 (0.52 to 1.07)	0.110
Hartmann's	0.69 (0.48 to 1.00)	0.047
Adjuvant chemotherapy	0.37 (0.31 to 0.44)	<0.001

All results adjusted for all variables in the table.
ASA, American Society of Anesthesiologists; BB, beta-blocker.

or early postoperative beta-blockade is accepted as part of standardised care with level B evidence supporting reduced negative cardiac events. Such measures are endorsed by the American College of Cardiology and American Heart Association (ACC/AHA) guidelines.[31] Whether this effect is sustained in non-cardiac surgery is under evaluation. However, the Agency for Healthcare Research and Quality's evidence report summarises the use of perioperative beta-blockers as the second-highest-rated safety practice protecting against surgical morbidity and mortality.[32]

Favourable effects of beta-blockade on postoperative deaths in patients undergoing non-cardiac surgery have been demonstrated. In the randomised, double-blinded, placebo-controlled trial by Mangano *et al* patients treated with perioperative and postoperative atenolol demonstrated significant reductions in overall mortality up to two years following hospital discharge. This study included patients undergoing elective neurosurgical, orthopaedic, major vascular and abdominal surgical procedures.[33] Furthermore, Lindenauer *et al* published their retrospective study with results based on a cohort of over 700 000 patients undergoing non-cardiac surgery. Their study demonstrated a significant reduction in hospital deaths of between 29% to 42% in patients with a raised Revised Cardiac Risk Index (RCRI) and on beta-blockade. The beneficial effect was limited to patients with a RCRI of at least two.[9] Similarly, Kwon and colleagues showed, in a cohort of over 8000 patients undergoing elective abdominal surgery, that failure to continue regular preoperative beta-blocker therapy during and following surgery led to increased adverse events. In patients with an increased cardiac risk (RCRI >2) the rate of adverse events was increased sixfold, compared with the observed twofold increase for patients with a RCRI ≤2.[10]

In the current study, there were significantly fewer cardiovascular-related deaths in those exposed to preoperative beta-blocker therapy (0.6% vs 0.9%, p=0.004) despite a higher prevalence in cardiovascular disease in this group. The current findings do, however, contrast the randomised controlled Perioperative Ischemic Evaluation (POISE) trial by Devereaux, where no effect on mortality could be detected despite a reduction in cardiovascular adverse events in their beta-blocked cohort.[34] Similar non-significant results in mortality to that of the POISE trial have been reproduced by others.[16 35 36] One possible explanation for previous studies demonstrating both significant and non-significant results with regards to mortality could be due to the lack of discrimination between different surgical indications and procedures. For example, the POISE trial included three major surgical fields (orthopaedic, abdominal and vascular procedures) under the umbrella term of 'non-cardiac' surgery. This heterogeneity of different surgical patient populations, diseases within each of these surgical fields and the procedures performed is an important limitation and makes it difficult to draw conclusions about any specific surgical subgroup. For this reason, the current study opted to focus specifically on patients subjected to elective abdominal surgery for colon cancer thus yielding a more homogeneous surgical study population.

In addition to their protective role in cardiovascular deaths, beta-blocker use was also associated with a reduced incidence in early deaths caused by respiratory complications, sepsis and multiorgan failure. In line with this is previous evidence demonstrating an association between changes in immune response and physiological stress. In animal models, beta-receptor activation has demonstrated an important immunomodulating role in the context of physiological stress.[37] Beta-blocker administration has shown a down-regulation of proinflammatory factors such as interleukin-6 and tumour necrosis
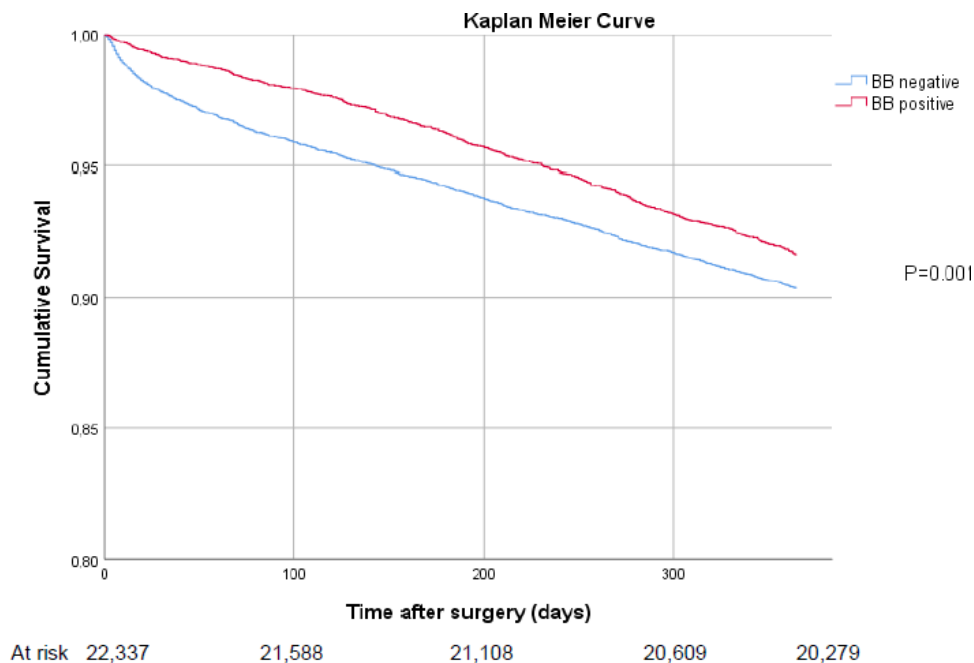
Figure 1 Kaplan-Meier graph of 1-year all-cause mortality.

factor-α.[15][16] The current study provides further support for a possible anti-inflammatory effect of beta-blockade.

Despite the observed difference in cardiovascular events, there was no observed difference in cerebrovascular deaths (p=0.414). The association between beta-blockade and an increased risk of stroke was raised in 2008 in the POISE trial.[34] The lack of such results in the current study is, however, in line with more recent findings. Obeid and colleagues found no link between beta-blocker therapy and stroke risk in patients pre-procedurally treated with beta-blockers for more than

30 days.[38] This might be explained by the beta-blocker dose administered: in the POISE study patients received 200 mg extended-release metoprolol daily,[34] whereas the highest daily dose prescribed for patients in the current study was 125 mg metoprolol with the majority receiving a dose of 50 mg. Additionally, an overwhelming majority of beta-blocker exposed patients in the current study had received the drug for at least 12 months prior to surgery. This contrasts with the POISE trial where beta-blocker treated patients were drug-naïve up until drug-initiation immediately before surgery, suggesting that a period of
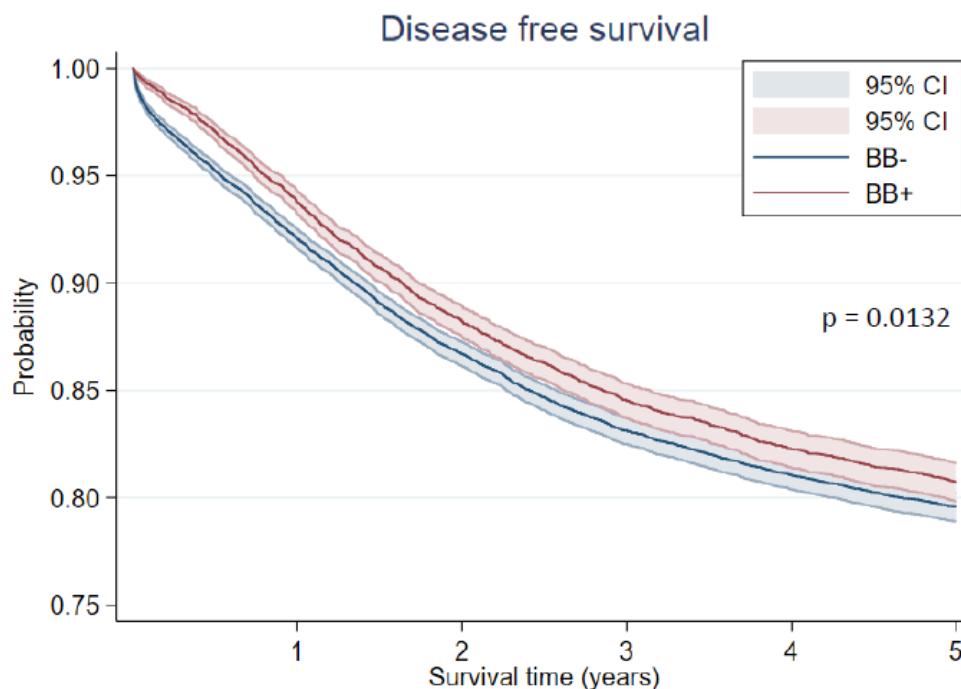
Figure 2 Kaplan-Meier graph of 5-year cancer-specific mortality. BB–, beta-blocker negative; BB+, beta-blocker positive.

adjustment to the drug may be beneficial prior to the patient undergoing surgery.

The protective association of preoperative beta-blocker therapy and mortality remained beyond the immediate postoperative period and a significant association could be observed at one year after surgery still. In addition, patients on beta-blockers also showed an 20% reduced risk of colon cancer-specific mortality up to five years following surgery. The link between beta-blockade and cancer has previously been under discussion. In 2015, Childers *et al* published a meta-analysis suggesting that the risk of breast cancer-related deaths could be reduced with the use of beta-blockers.[39] Such results have been further supported by animal models implicating beta-adrenoceptors in the modulation of breast cancer metastasis.[40] The association has been extended from breast cancer to other cancer types including colon cancer where beta-blocker therapy has been associated with longer survival for patients with stage 4 disease.[41] Previous data suggest that stress-related simulation through beta-adrenergic activation might contribute towards cancer growth progression which provides a possible underlying mechanism of action.[42] In addition, there is evidence suggesting that events, such as anti-inflammatory and anti-adrenergic drug administration, occurring during the perioperative period may affect the risk of cancer progression following surgery.[43] For example, the preoperative administration of propranolol has shown to attenuate biomarkers of breast cancer metastasis in a blinded randomised trial.[44] Results have, however, not been unanimous and immortal time bias has been suggested to underlie previously demonstrated beneficial effects of beta-blockade.[45–47] In addition to the risk of immortal time bias, retrospective studies including the current study risk suffering systematic errors from the chosen definition of cancer-specific mortality and survival. The chosen definition of cancer-specific death for the current study was that of a registered death with colon cancer listed as the primary cause of death. This method relies on the accuracy of death certificates which has been shown to vary. Therefore, the outlined results regarding cancer-specific mortality in the current study have to be interpreted with caution. The results of the current study, together with previous results, do however support the need for a prospective interventional design.

The study presented possesses several strengths including the use of information from a prospectively collected database comprising a 99.5% national inclusion coverage of all colon cancer patients from a health system that provides universal care; and the focus on standardised, major abdominal surgery for a single type of cancer mainly affecting the elderly population. The results can, however, only be used to draw conclusions about an associative relationship. An interventional design is required to be able to suggest causality and is strongly encouraged by the authors. There are limitations to this study that require discussion. First, the national drugs registry only collects data on prescribed medications and not the indication for the issued prescription. This could lead to unidentified confounding factors not adjusted for in the current analysis. An additional limitation of the study is the inability to determine whether the apparent survival benefit of beta-blocker treatment is explained by the preoperative administration of beta-blocker therapy or if the effect comes from continued administration of beta-blockade throughout the postoperative period. In line with standard national guidelines, all patients in Sweden are initiated on their regular drug prescriptions on admission to hospital. Therefore, an assumption of the current study is that patients continued to receive their beta-blocker throughout the majority of the duration of their hospital admission. Beta-blocker prescriptions issued following the hospital stay were also checked to ensure that beta-blocker exposed patients were continued on their preoperative beta-blocker regime following discharge. The question of hospital drug administration can, however, not be answered fully due to the retrospective nature of the study and requires an interventional design with the use of a randomised allocation procedure of the intervention studied. Although the majority of patients were prescribed metoprolol as the preferred beta-blocker, the current study does include a certain mix of beta-blocking agents. Its design also allows for a range of time intervals between drug administration and start of surgery. These are variables that would be preferable to control in order to reduce the impact of potential bias.

CONCLUSION

This large cohort study demonstrates a substantial positive effect associated with beta-blocker use on both short- and long-term mortality in patients undergoing elective colon cancer surgery. While awaiting results of future randomised trials, the current study corroborates previous findings that beta-blocker therapy is associated with a significant protective effect on overall outcome after major non-cardiac surgery.

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