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Full Length Article



The incidence of venous thromboembolism after curative colon cancer surgery within an enhanced recovery after surgery programme

Niklas Nygaard Baastrup^{a,*}, Astrid Kerstine Buch^a, Anders Kierkegaard Gundestrup^a, Anna Sofie Friis Olsen^a, Jakob Kleif^{a,b}, Issam Al-Najami^{c,d}, Ulrik Deding^{c,d}, Claus Anders Bertelsen^{a,b}, on behalf of the COMES II - Copenhagen cOMplete Mesocolic Excision Study II study group, the Danish Colorectal Cancer Group

^a Department of Surgery, Copenhagen University Hospital – North Zealand, 3400 Hillerød, Denmark

^b Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, 2200 Copenhagen N, Denmark

^c Department of Surgery, Odense University Hospital, 5000 Odense, Denmark

^d Department of Clinical Research, University of Southern Denmark, 5000 Odense, Denmark

ABSTRACT

Aim: Based on three randomised controlled trials performed more than a decade ago, several national guidelines recommend prolonged venous thromboprophylaxis for 28 days following elective surgery for colon cancer. None of these studies were conducted within enhanced recovery after surgery setting. Newer studies indicate that prolonged prophylaxis might not be necessary with enhanced recovery after surgery. We aimed to provide further evidence to this unresolved discussion.

Method: Retrospective study of patients undergoing elective surgery for colon cancer stage I-III with enhanced recovery after surgery in the Capital Region of Denmark from 2014 to 2017. Patients were excluded if discharged on postoperative day 28 or later, dying before discharge, undergoing concomitant rectum resection, or discharged with vitamin K antagonists, direct-oral anticoagulants, or low molecular weight heparin treatment. All patients received only low-dose low molecular weight heparin as prophylaxis during their admission.

The primary endpoint was symptomatic lower limb deep venous thrombosis or pulmonary embolism diagnosed within 60 days postoperatively.

Results: Out of the included population of 1806 patients, only three experienced a symptomatic venous thromboembolic event; none was fatal. Two had pulmonary embolism associated with pneumonia, while one patient was diagnosed with lower limb deep venous thrombosis at postoperative day 15 after an uncomplicated course with first discharge at postoperative day 2.

Conclusion: The risk of symptomatic venous thromboembolism after elective surgery for colon cancer with enhanced recovery after surgery seems negligible even without prolonged prophylaxis. The current guidelines need to be reconsidered.

1. Introduction

Active cancer and major abdominal surgery are risk factors for venous thromboembolic events (VTE) [1], i.e., deep vein thrombosis (DVT) and pulmonary embolism (PE). Thus, the English National Institute for Health and Care Excellence [2] and the Danish guidelines [3] advocate for prolonged low molecular weight heparin (LMWH) VTE prophylaxis for four weeks after colorectal cancer surgery without any considerations regarding other risk factors.

These recommendations pertain to three randomised clinical trials on patients undergoing surgery for both benign and malignant colorectal disorders [4], abdominal and pelvic malignancies [5], or laparoscopic colorectal cancer resections [6]. The first two randomised trials were conducted before laparoscopic surgery, and enhanced recovery after

surgery (ERAS) was implemented. The third study did not make any reference to ERAS. ERAS and, in most cases, minimally invasive techniques are now the gold standard. The principles of ERAS in colon surgery were first described in 1995 in a report from one of the participating hospitals [7]. It included appropriate analgesia, early mobilisation and early oral intake, eventually leading to the current ERAS regime being standard in all Danish hospitals for over 15 years.

A recent randomised trial compared 56-day prolonged VTE prophylaxis with in-hospital use only [8]. As a secondary outcome, they showed no causal reduction of risk of VTE after prolonged prophylaxis. Others have reported low incidences of VTE with very poor cost-effectiveness of prolonged prophylaxis in patients undergoing colon cancer resection with ERAS [9,10]. An English population-based study showed a yearly VTE risk reduction associated with minimally invasive

* Corresponding author at: Department of Surgery, Copenhagen University Hospital – North Zealand, Dyrehavevej 29, 3400 Hillerød, Denmark.

E-mail address: niklas.baastrup@gmail.com (N.N. Baastrup).

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surgeries in the elective setting but not associated with the implementation of prolonged prophylaxis [11].

This study aims to examine the risk of VTE after contemporary resection for colorectal cancer with ERAS in a population only receiving in-hospital VTE prophylaxis.

2. Methods

2.1. Design

The study adheres to the STROBE statement [12]. The study was a retrospective analysis, utilising data from the Copenhagen cOMplete Mesocolic Excision Study (COMES). The database contains data on patients undergoing elective macroradical resection for UICC Stage I–III colonic adenocarcinoma in the Capital Region of Denmark between June 1, 2008, and December 31, 2017 [13,14]. These data include complications, e.g. VTE, diagnosed in public hospitals during the first 60 days after surgery. The follow-up period was 60 days rather than 28 days, which would have marked the end of the recommended period of prolonged VTE prophylaxis. During the study period, none of the four colorectal centres in the Capital Region had implemented prolonged VTE prophylaxis as standard care. In-hospital, low-dose LMWH until discharge after the resection was standard VTE prophylaxis.

The primary aim of COMES was oncological outcomes based on prospectively collected data from the patients' electronic health records (EHR). Data had been registered by double data entry in 2020–2021. Due to emerging evidence questioning the effect of prolonged VTE prophylaxis, we decided in 2023 to perform a detailed re-review of the EHRs for all patients undergoing resection during 2014–17, focusing on VTE prophylaxis, preoperative and postoperative anticoagulant treatment, the length of hospital stay, i.e., duration of VTE prophylaxis, and readmission. This aimed to perform double data entry for subsequent audits in case of discrepancy.

Patients with concomitant rectum resection were excluded. As we only intended to assess the risk of VTE in patients without prolonged VTE prophylaxis, patients were excluded if they were on a drug post-discharge considered a more effective than or equivalent anticoagulant to the low-dose LMWH used as prolonged VTE prophylaxis. Thus, we excluded patients discharged with vitamin K antagonists, any dose of LMWH, or direct oral anticoagulants for, e.g. postoperative PE or DVT before discharge or atrial fibrillation. Others were excluded on the following criteria: dying before discharge or discharged on postoperative day 28 or later, and patients diagnosed with VTE less than three months before surgery, as it was assumed these were treated with anticoagulants. Platelet aggregation inhibitors, i.e. clopidogrel and aspirin, were not considered an exclusion criterion since VTE prophylaxis is not within their intended indications.

Table 1

The basic elements of enhanced recovery after surgery.

Preadmission information about what to expect during hospitalisation.
Phosphate enema is the sole bowel preparation in patients with a planned colorectal anastomosis. No bowel preparations in patients scheduled for ileo-colonic or colo-colonic anastomosis, or stoma.
Preoperative carbohydrate loading. Two hours fasting for liquids and 6 h for solids preoperatively.
No use of long-lasting sedation.
Intraoperative single-dose antibiotic prophylaxis
Preferable total intravenous anaesthesia, preoperative mid-thoracic epidural after open resections (optional), peripheral nerve block after laparoscopic resections (optional), no long-lasting opioids during surgery, and long-lasting local anaesthetics at the site of incision.
Surgical incisions are kept at a minimal length at either the midline or transverse.
The patient is kept normothermic by active warming during surgery.
Intraoperative fluid restriction to avoid dehydration or overhydration.
No surgical drains after routine surgery.
Avoidance of nasogastric tube unless postoperative ileus.
Bladder catheter being removed within 24 h.
Low dose magnesium oxide to prevent postoperative ileus.
Postoperative analgesia with 4 g/day acetaminophen, nonsteroidal anti-inflammatory drugs or gabapentin. Epidural bolus when needed. Opioids are to be avoided if possible.
Food intake from postoperative day 0. Oral energy-dense nutritional supplements are given until normal intake.
Early mobilisation with at least 2 h out of bed on the day of surgery and 6 h from the first postoperative day.

Resections were performed at four public university hospitals providing all colorectal cancer treatment for the 1.9 million residents of the Capital Region of Denmark. ERAS had been implemented as standard care at the four hospitals almost a decade before 2014, and they adhered to the general principles outlined by the ERAS Group consensus [15]. The elements of the ERAS protocol are described in detail in Table 1.

2.2. Trial outcomes

The primary outcome was the incidence of symptomatic VTE, i.e. pulmonary embolism or DVT in the lower limb after discharge, within 60 days following surgery. Secondary outcomes were VTE stratified as PE or DVT, and the severity was according to Clavien-Dindo [16].

Doppler ultrasonography and CT pulmonary angiography were the standard diagnostic procedures to verify suspicion of symptomatic lower limb DVT and PE, respectively. All acute patients in Denmark with symptomatic postoperative VTE are referred to, diagnosed at, and treated in public hospitals which share electronic health records.

2.3. Statistical analysis

Continuous data are presented as median and interquartile range (IQR), and categorical data as frequencies and proportions. The primary outcomes were presented as incidences with 95 % confidence intervals (CI). Worst-case scenario sensitive analysis was performed based on the assumption that all deaths with an unknown cause within 60 days postoperatively were caused by PE. Statistical analysis was performed using R statistical software, version 4.3 (R Foundation for Statistical Computing, Vienna, Austria) [17].

2.4. Ethical considerations

All participating departments approved the study. Data collection was approved by the Danish Data Protection Agency and the Danish Patient Safety Authority. Local Ethics Committee approval was not required under Danish legislation. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT06009484) (NCT06009484).

3. Results

During the period 2014–2017, of the 2141 patients undergoing elective resection for stage I–III colon cancer in the Capital Region, 335 patients were excluded (Fig. 1). Nine of these patients had PE before discharge and three DVT. The demographic and tumour characteristics of the 1806 patients in the study group are presented in Table 2. The postoperative length of stay is shown in Fig. 2. Readmission within 28 days postoperatively occurred in 100 (5.5 %) of the 1806 patients.

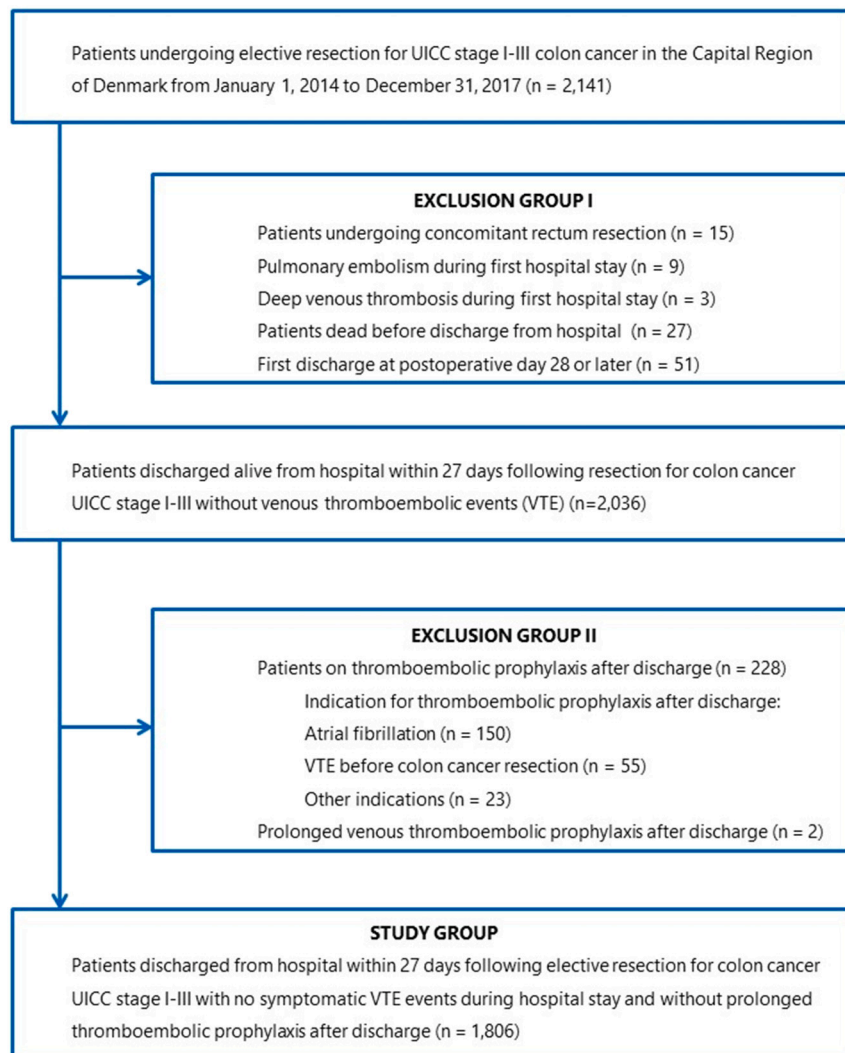


Fig. 1. Flowchart showing the selection of the study group.

Three out of the 1806 patients (0.17 %; 95 % CI 0.04–0.52) discharged within 28 days following surgery without prolonged VTE prophylaxis were diagnosed with symptomatic VTE during the first 60 days postoperatively. Table 3 shows the patient characteristics of these three patients.

Two patients died from unknown causes within 60 days following the colon resection. In the sensitivity analysis of the worst-case scenario, in which PE caused these two deaths, the incidence of symptomatic VTE was five (0.27 %; 95 % CI 0.10–0.68) of the 1806 patients.

4. Discussion

In patients receiving in-hospital VTE prophylaxis only, the 60-day incidence of symptomatic VTE was 0.17 % after elective colon cancer surgery with ERAS. None of these events were fatal.

One patient developed a DVT, and two patients developed a PE. All three were treated with direct oral anticoagulants only, and none of the patients was admitted to an intensive care unit, i.e., only Clavien-Dindo grade II complications. Only one of the patients was slightly overweight, with a BMI of 25.3. All three patients underwent laparoscopic resection, and none of them received neoadjuvant chemotherapy. Two patients died from unknown causes within 60 days postoperatively, which in a worst-case scenario corresponds to 0.27 % developing a symptomatic VTE. The 60-day follow-up in the COMES database ensures that the risk of missing cases of symptomatic VTE was considered negligible.

Most symptomatic VTE occurred in-hospital when the patients received VTE prophylaxis. One of the patients was diagnosed with PE on postoperative day 41, subsequently to pneumonia and superficial phlebitis. Whether 28-day prolonged prophylaxis would have prevented PE, in this case, seems questionable.

The latest Cochrane review [18] included all randomised trials, published until 2017, comparing prolonged VTE prophylaxis (defined as ≥ 14 days postoperatively) with in-hospital prophylaxis in patients undergoing malignant and benign abdominal or pelvic surgery. The primary outcome was symptomatic or asymptomatic VTE. The review found a risk of VTE of 5.3 % after prolonged prophylaxis compared with 13.2 % after in-hospital VTE prophylaxis only, with an odds ratio (OR) of 0.38 (95 % CI 0.26–0.54). None of the included studies mentions ERAS, and only one study included patients undergoing laparoscopic resection for colorectal cancer. Patients included in the two other randomised trials were not screened for DVT or PE before randomisation [4,5]. Thus, asymptomatic DVT and PE developed before surgery might contribute to the high proportion of VTE. It is hard to imagine that the generalisability of the Cochrane review is high in contemporary colorectal cancer care settings, as ERAS is now widely implemented and laparoscopic resection is performed in most cases.

Recent population-based and cohort studies report very low rates of VTE in patients undergoing colorectal resection within an ERAS setting without prolonged VTE prophylaxis [9,10]. This is supported by a recently randomised trial by Auer et al. [8], who examined the effect of

Table 2
Patient demography, tumour characteristics and procedures performed.

Variables	Study group (n = 1806)
Age (years), median and [IQR]	71.25 [64.28, 77.24]
Male sex (%)	886 (49.1)
Body mass index (kg/m ²), median and [IQR]	25.35 [22.72, 28.20]
ASA grade	
I	331 (18.3)
II	1085 (60.1)
III–IV	390 (21.6)
WHO performance score	
0–1	1647 (91.2)
2	130 (7.2)
3–4	29 (1.6)
Synchronous tumours	56 (3.1)
Tumour location†	
Caecum	348 (19.3)
Ascending colon	264 (14.6)
Hepatic flexure	92 (5.1)
Transverse colon	175 (9.7)
Splenic flexure	58 (3.2)
Descending colon	99 (5.5)
Sigmoid colon	770 (42.6)
Primary procedure	
Right hemicolectomy (incl. ileocaecal resection)	604 (33.4)
Extended right hemicolectomy	184 (10.2)
Transverse colectomy	8 (0.4)
Right-sided subtotal colectomy	43 (2.4)
Left hemicolectomy	120 (6.6)
Sigmoid resection	732 (40.5)
Other segmental resection, e.g. splenic flexure	91 (5.0)
Total colectomy	24 (1.3)
Supplementary colonic resections‡	18 (1.0)
Laparoscopic resection completed§	1381 (76.5)
Conversion to open surgery	264 of 1645 (16.0)
Neoadjuvant chemotherapy	66 (3.7)
UICC stage	
No residual tumour after neoadjuvant chemotherapy	2 (0.1)
I	476 (26.4)
II	718 (39.8)
III	610 (33.8)

Values in parentheses are percentages unless indicated otherwise; *values are median (IQR). †Colonic tumour with highest pT and subsequent pN category in patients with synchronous adenocarcinomas. ‡Resection of two separate segments; for example, invasion of sigmoid tumour into the caecum resulting in sigmoid resection and supplementary (ileocaecal) resection. §Laparoscopic resection was initially planned in 1645 patients in the study group. ASA: American Society of Anesthesiologists; UICC: International Union Against Cancer Control.

prolonged VTE prophylaxis for 56 days compared with in-hospital prophylaxis after colorectal cancer resection. As secondary outcomes, VTE was defined as symptomatic or incidental diagnosed proximal, lower, or upper extremity DVT; PE; or thrombosis in cerebral, splanchnic or renal veins. The incidence of VTE was 2 % after prolonged VTE prophylaxis group versus 1 % after in-hospital prophylaxis ($P = 0.8$). ERAS was not mentioned, but in a personal correspondence, the authors reported that circa 80 % of the patients followed an ERAS regime. Thus, the current evidence regarding prolonged VTE prophylaxis after elective colorectal cancer resection with ERAS does not support the positive treatment effect found in studies before the ERAS era. While this study does not examine the direct effect of the ERAS protocol, we hypothesise that the decrease in post-discharge VTE, when compared with historical data, is caused by the focus on early mobilisation, directly from the post-operative mobilisation of the patient on the day of surgery and indirectly from not tying the patient to the bed with surgical drains, a urinary catheter and nasogastric tubes. Even though prolonged VTE prophylaxis is not associated with an increased risk of bleeding [8], the cost-effectiveness is considered negligible [9]. It seems doubtful whether current national guidelines are justified.

In this study, we excluded patients with a history of VTE and patients receiving VTE prophylaxis on other indications. However, even though

VTE still occurs in small numbers in our cohort, individual risk stratification, such as the Caprini score, might be useful in selecting patients benefiting from prolonged VTE prophylaxis. Further studies regarding this issue are warranted.

The clinical consequences of asymptomatic VTEs remain unknown. After symptomatic DVT, post-thrombotic syndrome (PTS) is reported to develop in 20–50 % of patients, with 5–10 % developing severe PTS, including venous ulcers [19]. Among several risk factors for PTS are extensive DVT, recurrent DVT in the same limb, obesity, and older age. Even with a median age of 71 years in the present study and the proportion of patients with obesity rising, very few colon cancer patients might benefit from prolonged prophylaxis to prevent PTS. Unfortunately, the tools for selecting patients for prolonged VTE prophylaxis have not been described.

Our dataset offers high external validity as a large population-based cohort consisting of all patients undergoing elective curative-intended resection for UICC stage I–III colon cancer in the Capital Region of Denmark.

This study is limited by its partly retrospective design. Patients were included prospectively, but data on previous history of VTE might not always be available, and current medication at the time of surgery was collected retrospectively. However, as part of the standard procedure at admission and discharge, current medication is updated in the patient's electronic health record and the national medication database, which contains data on all prescription medication.

The 60-day follow-up was chosen when the database was designed to ensure all relevant postoperative complications were registered. Chemotherapy-associated thrombosis and random events might bias the outcome, but none of the included patients with VTE received chemotherapy.

Another potential limitation might have been migration to the western half of Denmark during the 60-day follow-up and VTEs diagnosed at private hospitals. We are unaware of any patients migrating during follow-up, and no private hospitals in Denmark provide emergency care. All cases of VTE are diagnosed in public hospitals providing tax-financed free care.

Prospective cohort studies with Doppler ultrasonography before and after surgery might show the true incidence of asymptomatic and symptomatic lower limb DVT occurring after colorectal resections. A randomised trial seems not feasible, as the study population size based on the incidences reported [8] would exceed 4000. Population-based studies with propensity score adjustments, weighting, or matching might shape the future of VTE research. Advanced big data analytics [20] might enable selecting patients benefitting from prolonged prophylaxis.

5. Conclusion

The risk of symptomatic VTE after elective surgery for colon cancer within an enhanced recovery after surgery set-up seems negligible, even without prolonged prophylaxis. This study adds to the growing evidence questioning the indication of prolonged VTE prophylaxis after colon cancer resection. However, further large-scale population studies examining the risk of post-discharge VTE are needed.

Ethical considerations

The study was approved by the Danish Patient Safety Authority and the regional Data Protection Agency. Danish legislation did not require approval from the patient or local ethics committee.

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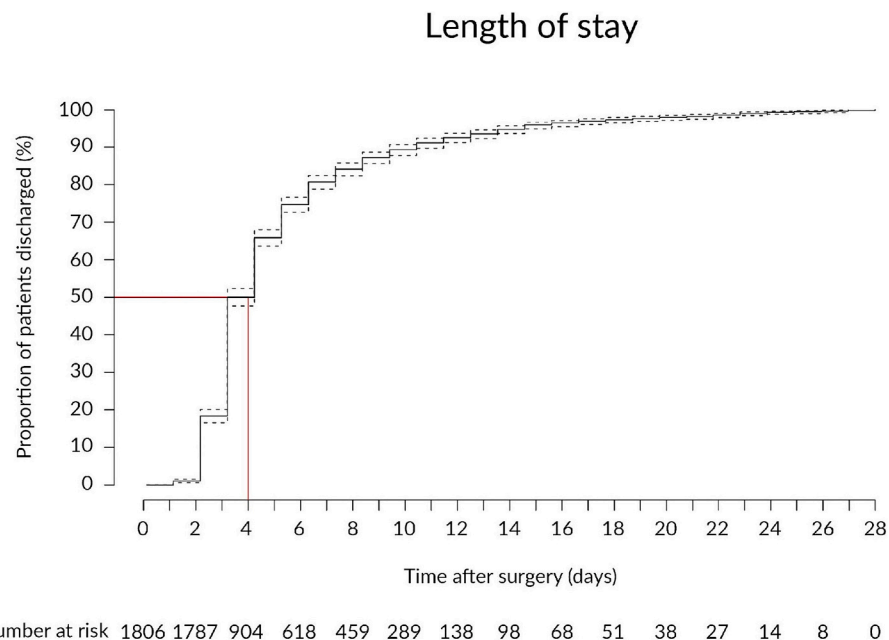


Fig. 2. The cumulative incidence of discharge in the study group. The median length of stay is marked with a red line.

Table 3

Characteristics of patients with VTE diagnosed within the first 60 days following colon resection.

Patient	#1	#2	#3
Age at the time of surgery (years)	88	75	76
Body mass index (kg/m ²)	19.9	24.3	25.3
Sex	Male	Male	Female
ASA* score	3	2	1
WHO performance score	2	0	0
Neoadjuvant chemotherapy	No	No	No
Tumour site(s)	Transverse colon, left third	Ascending colon	Caecum and descending colon
UICC stage	III	II	III
Resection	Right-sided subtotal colectomy with ileosigmoideostomy	Right hemicolectomy	Right-sided subtotal colectomy with ileosigmoideostomy
Laparoscopic resection	Yes	Yes	Yes
POD** discharge	8	2	15
Complications before VTE***	POD 7: Pneumonia	None	POD 35: phlebitis in the greater saphenous vein, DVT not suspected POD 39: Pneumonia
POD readmission	9	15	35
Postoperative day (diagnosis VTE)	13	15	41
Pulmonary embolism (PE) or deep venous thromboembolism (DVT)	PE	DVT	PE
Clavien-Dindo score (VTE)	2	2	2
Comments		Familial predisposition	

*ASA: American Society of Anesthesiologists **POD Postoperative day *** VTE venous thromboembolism.

no role in study design, data collection, analysis, interpretation of data, the manuscript’s writing, or the decision to submit the paper for publication.

Niklas Nygaard Baastrup and Claus Anders Bertelsen had access to all the data, and Niklas Nygaard Baastrup, as the corresponding author, had the final responsibility to submit for publication.

Previous representations

European Society of Coloproctology 18th Scientific Conference on September 29, 2023, Vilnius, Lithuania. Annual meeting of the Danish Surgical Society on November 16, 2023, Copenhagen, Denmark.

Patient consent statement

The study was approved by the Danish Patient Safety Authority and the regional Data Protection Agency. Danish legislation did not require approval from the patient or local ethics committee.

CRedit authorship contribution statement

Niklas Nygaard Baastrup: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Astrid Kerstine Buch:** Writing – review & editing, Validation, Investigation. **Anders Kierkegaard Gundestrup:** Writing – review & editing, Validation, Investigation, Data curation. **Anna Sofie Friis Olsen:** Writing – review & editing, Validation, Investigation, Data curation. **Jakob Kleif:** Writing – review &

editing, Methodology, Formal analysis, Conceptualization. **Issam Al-Najami:** Writing – review & editing, Conceptualization. **Ulrik Deding:** Writing – review & editing, Conceptualization. **Claus Anders Bertelsen:** Writing – review & editing, Validation, Supervision, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

After de-identification, individual participant data will be made available to investigators with a methodologically sound proposal for meta-analyses. Proposals should be directed to Claus Anders Bertelsen (cabertelsen@gmail.com).

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