Efficacy and safety of extended duration to perioperative thromboprophylaxis with low molecular weight heparin on disease-free survival after surgical resection of colorectal cancer (PERIOP-01): multicentre, open label, randomised controlled trial

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ABSTRACT

OBJECTIVE
To determine the efficacy and safety of extended duration perioperative thromboprophylaxis by low molecular weight heparin when assessing disease-free survival in patients undergoing resection for colorectal cancer.

DESIGN
Multicentre, open label, randomised controlled trial.

SETTINGS
12 hospitals in Quebec and Ontario, Canada, between 25 October 2011 and 31 December 2020.

PARTICIPANTS
614 adults (age ≥18 years) were eligible with pathologically confirmed invasive adenocarcinoma of the colon or rectum, no evidence of metastatic disease, a haemoglobin concentration of ≥8 g/dL, and were scheduled to undergo surgical resection.

INTERVENTIONS
Random assignment to extended duration thromboprophylaxis using daily subcutaneous tinzaparin at 4500 IU, beginning at decision to operate and continuing for 56 days postoperatively, compared with in-patient postoperative thromboprophylaxis only.

MAIN OUTCOME MEASURES
Primary outcome was disease-free survival at three years, defined as survival without locoregional recurrence, distant metastases, second primary (same cancer), second primary (other cancer), or death. Secondary outcomes included venous thromboembolism, postoperative major bleeding complications, and five year overall survival. Analyses were done in the intention-to-treat population.

RESULTS
The trial stopped recruitment prematurely after the interim analysis for futility. The primary outcome occurred in 235 (77%) of 307 patients in the extended duration group and in 243 (79%) of 307 patients in the in-hospital thromboprophylaxis group (hazard ratio 1.12; 95% confidence interval 0.91 to 1.33; P=0.1). No difference was noted for overall survival at five years in 272 (89%) patients in the extended duration group and 280 (91%) patients in the in-hospital thromboprophylaxis group (hazard ratio 1.12; 95% confidence interval 0.72 to 1.76; P=0.1).

CONCLUSIONS
Extended duration to perioperative anticoagulation with tinzaparin did not improve disease-free survival or overall survival in patients with colorectal cancer undergoing surgical resection compared with in-patient postoperative thromboprophylaxis alone. The incidences of venous thromboembolism and postoperative major bleeding were low and similar between groups.

TRIAL REGISTRATION
ClinicalTrials.gov NCT01455831.

Introduction
Since the establishment of a link between anticoagulants and cancer survival,1 investigators have been evaluating the use of anticoagulation...
to improve cancer outcomes. Warfarin has been reported to decrease cancer recurrence in patients with melanoma.\(^1\) Heparins, in particular, low molecular weight heparin, tinzaparin,\(^2\) have shown antimitastatic properties in preclinical models by potentially inhibiting tumour cell invasion of the extracellular matrix, hindering protection of tumour cells in the circulation from immune mediated destruction, and impairing neovascularisation of micrometastases due to an antiangiogenic effect.\(^3\) An initial meta-analysis assessing the effect of low molecular weight heparin on cancer outcomes reported that the use of low molecular weight heparin improved overall survival.\(^4\) However, more recent analyses including all published studies to date have been unable to support an overall survival benefit for cancer patients.\(^5\) Nonetheless, most of these studies included patients with advanced malignancies or combined multiple tumour types, which can hinder the evaluation of the effect of low molecular weight heparin in preventing metastatic disease.

The perioperative period might be the ideal setting to study the antimitastatic effects of low molecular weight heparin.\(^6\) Surgery results in a hypercoagulable postoperative state and an inability to clear micrometastasis when the disease is present after surgical resection, leading to potential cancer recurrence and worse survival.\(^7\) In preclinical studies, perioperative administration of low molecular weight attenuated postoperative metastatic disease by preventing platelet and fibrin binding and thereby facilitating immune-mediated destruction of tumour cell microemboli by natural killer cells.\(^8\)

Colorectal cancer is the third most common cause of cancer and about 35% of patients recur after surgical resection. The PERIOP-01 study was designed to investigate whether perioperative extended duration low molecular weight heparin (tinzaparin) could improve disease-free survival, when compared with postoperative administration in hospital of tinzaparin in patients with colorectal cancer without evidence of metastatic disease and who were scheduled to undergo surgical resection.

Methods
Study design and oversight
The PERIOP-01 trial was a multicentre, open label, randomised controlled trial comparing extended duration to in-hospital thromboprophylaxis using low molecular weight heparin. The members of the steering committee (see appendix) had final responsibility for the trial design, clinical protocol, and study oversight. The institutional review boards at each of the 12 participating sites in Quebec and Ontario in Canada approved the protocol, which is available online with the full text of this article. Data were collected at the sites and entered in an online database managed by the Methods Centre of the Ottawa Hospital Research Institute. A central adjudication committee, whose members were unaware of treatment assignment, reviewed all suspected outcome events. An independent data safety monitoring board periodically reviewed trial outcomes.

Study participants and setting
Patients with colorectal cancer, no evidence of metastatic disease, and scheduled to undergo surgical resection were potentially eligible. The inclusion criteria required a diagnosis of pathologically confirmed invasive adenocarcinoma of the colon or rectum, preoperative investigations that showed potential resectability without evidence of metastatic disease, a haemoglobin concentration of 8 g/dL or more, patients aged 18 years or older, and the capacity to provide written informed consent. Neoadjuvant treatment (chemotherapy or radiation or both) was allowed. Patients were excluded if they had carcinoma only present in a completely excised polyp; previous venous thromboembolism, including deep vein thrombosis or pulmonary embolism; a need for continuous anticoagulation; contraindication to heparin treatment (eg, previous history of heparin induced thrombocytopenia, thrombocytopenia (ie, platelet count <100×10^9/L), renal insufficiency with glomerular filtration rate <30 mL/min); and history of other cancers (except for adequately treated basal or squamous cell carcinoma or carcinoma in situ) within five years of the colorectal cancer diagnosis. Other exclusion criteria included pregnancy, breastfeeding, and unwillingness or inability to provide informed consent.

Randomisation and intervention
Eligible patients were randomly assigned in a 1:1 ratio at the time of decision for surgery, by use of a centralised, web based randomisation system, to extended duration thromboprophylaxis, within 24 h of randomisation (required a minimum of one preoperative dose to maximum of six weeks) and continuing for 56 days postoperatively, or in-hospital thromboprophylaxis, beginning on postoperative day 1 and continuing for the duration of stay in hospital. Tinzaparin (4500 IU, subcutaneously, daily) was used for thromboprophylaxis in both groups (extended duration and in-hospital thromboprophylaxis). Randomisation was permuted in blocks of two and four, prepared using random number tables by the trial’s statistician (RM). Randomisation was stratified by participating centre and tumour type (rectal or colon cancer). Patients were followed up for up to five years or to death, regardless of the duration of study drug.

Outcomes
The primary outcome was disease-free survival at three years in the intention to treat population. Disease-free survival at three years has been shown to be an excellent predictor of overall survival at five years.\(^9\)\(^-\)\(^11\) Disease-free survival events were defined as survival without locoregional recurrence, distant metastases, second primary (same cancer), second primary (other cancer), or death.\(^12\) Secondary outcome measures

BMJ: first published as 10.1136/bmj-2022-071375 on 13 September 2022. Downloaded from http://www.bmj.com/ on 1 December 2022 by guest. Protected by copyright.
were venous thromboembolism, major surgery related bleeding events, major bleeding events, clinically relevant non-major bleeding events, postoperative complications,\textsuperscript{13,\textsuperscript{14}} transfusion requirements, overall survival at five years, wound infection, and anastomotic leakage. Venous thromboembolism was defined as objectively confirmed; symptomatic or incidental; proximal, lower, or upper extremity deep vein thrombosis; unusual site thrombosis (ie, cerebral, splanchnic, or renal vein thrombosis); or pulmonary embolism; occurring between the day of the surgery and postoperative day 56 (coincident with discontinuation of tinzaparin in the extended duration group). Major surgery related bleeding was defined as overt bleeding that was associated with a decrease in the haemoglobin level of 4 g/dL or more, led to transfusion of four or more units of packed red blood cells, required reoperation, or contributed to death during the initial seven days after surgery.\textsuperscript{15}

Major bleeding was defined by the International Society of Thrombosis and Haemostasis as overt bleeding that was associated with a decrease in the haemoglobin level of 2 g/dL or more, led to transfusion of two or more units of packed red blood cells, occurred in a critical site (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome), or contributed to death.\textsuperscript{15} Major bleeding events were captured between the day of randomisation to the day of the surgery and between postoperative day 7 and 56. All study outcomes were blindly adjudicated by an independent adjudication committee, consisting of oncology or thrombosis specialists. Compliance with study drugs was estimated using syringes counted by patients in a medication diary and reviewed by the study coordinator. Compliance was defined as high if 80% or more of the study drug was taken.

Statistical analysis
We expected a disease-free survival of 66% at three years in patients receiving in-hospital thromboprophylaxis. The trial hypothesis was that extended duration thromboprophylaxis with tinzaparin is superior to in-hospital thromboprophylaxis in providing at least an absolute reduction of 8.5% (hazard ratio of 0.75) in the primary outcome (disease-free survival at three years). To detect this hazard ratio using a significance level of two sided α=0.05 and a power of 80%, a total of 380 events needed to be observed before the final analysis. Based on the projected event rate for disease-free survival, we estimated that 1075 patients with colorectal cancer undergoing surgical resection would be sufficient to show this reduction.

The primary analysis was done in the intention-to-treat population that included all patients who had been randomly assigned to a group. The hazard ratios for the primary outcome were estimated using a Cox proportional hazard model controlling for age, sex, and centre. We also did a time-to-event analysis on overall survival at five years. Proportions of the other secondary outcomes were compared using $\chi^2$. The hazard ratios for the primary outcomes in prespecified subgroups were estimated using a Cox proportional hazard model controlled for age, sex, and centre. One sensitivity analysis including compliant patients (>80% of study drug) was planned for the primary outcome.

Two interim analyses for futility were planned. These analyses were expected to be done once 30% and 60% of enrolled participants have completed three year follow-up. The first interim analysis was done on 23 July 2020 using data from 591 patients, which constituted 55% of the total target sample size of 1075. The median follow-up was 2.2 years (interquartile range 1.0-3.6). Recurrent cancers, new cancers, or deaths occurred in 59 events in 298 patients receiving in-hospital thromboprophylaxis and 59 events in 293 patients receiving extended duration thromboprophylaxis. Based on these event rates, and the assumptions made in the original power calculation (380 events), the conditional power to detect a hazard ratio of 0.75 was determined to be 48%. On 6 November 2020, the data safety and monitoring board recommended to stop enrolment based on a low conditional power and difficulty in recruitment due to the covid pandemic. The final sample size was 614.

Patient and public involvement
Patient partners were not involved in the design or conduct of this study that began in 2011. Patient partners in the CanVECTOR network (www.canvector.ca) will be involved in dissemination/knowledge translation activities.

Results
From 25 October 2011 to 31 December 2020, 614 patients underwent randomisation at 12 hospitals in Canada and were included in the primary and secondary analyses (fig 1). The baseline characteristics of the patients were well balanced between groups (table 1). Overall, the mean age was 61 years, fewer than half of participants were women (41%), and most people were white (90%). Three hundred and eleven patients (51%) had primary rectal cancer whereas 303 (49%) had primary colon cancer. Two hundred and twenty nine (38%) patients received neoadjuvant treatment for rectal cancer and 287 (48%) patients with colon or rectal cancer received adjuvant treatment; these results were similar between groups. A total of 201 (67%) patients in the extended duration group and 203 (76%) patients in the in-hospital thromboprophylaxis group had laparoscopic surgery, respectively. Overall, 201 (33%) patients had node positive disease; 105 (34%) in the extended duration group and 96 (31%) in the in-hospital thromboprophylaxis group. The median duration of study drug, preoperatively, was four days (interquartile range two to nine) in the extended duration group; and postoperatively, 55 days (53-56) in the extended duration group and five days (three to seven) in the in-hospital thromboprophylaxis group. The study drug...
was discontinued as per participants’ wish in eight patients in each of the extended duration and standard thromboprophylaxis groups. Compliance was high in both groups at 93% and 97% in the extended duration and in-hospital thromboprophylaxis groups, respectively. The median duration of follow-up was 35 months (interquartile range 17-53) in the extended duration group and 35 months in the in-hospital thromboprophylaxis group (18-49).

**Primary and secondary outcomes**

The primary outcome occurred in 235 (77%) of 307 patients in the extended duration group and in 243 (79%) of 307 patients in the in-hospital thromboprophylaxis group (hazard ratio 1.1, 95% confidence interval 0.90 to 1.33; P=0.4; table 2, fig 2).

Table 2 shows the secondary outcomes. Venous thromboembolism occurred in five patients (2%) receiving extended duration and in four patients (1%) in the in-hospital thromboprophylaxis groups (P=0.8). Similarly, bleeding related to major surgery occurred in one patient (<1%) receiving extended duration group and in six patients (2%) in the in-hospital thromboprophylaxis group (P=0.1), and additional major bleeding events were reported in no (0%) patient and two (0.7%) patients in the extended duration and in-hospital thromboprophylaxis groups, respectively. Nine (3%) patients in the extended duration group and six (2%) patients in the in-hospital thromboprophylaxis group had a clinically relevant non-major bleeding event (P=0.5). Postoperative complications occurred in 136 (22%) of 614 patients and were similar in both groups, including 76 wound infections, 19 anastomotic leaks, and 41 Clavien grade III-V postoperative complications. Twenty three patients required transfusion of packed red blood cells: 12 (median 1; range 1-2) in the extended group and 11 (2; 2-4) in the in-hospital thromboprophylaxis group. Adverse events, unrelated to surgery, were reported in 102 patients in the extended duration group and 101 patients in the in-hospital thromboprophylaxis group, of which seven and two events were classified as being possibly related to study drug.

Overall survival at five years after randomisation was 272 (89%) patients in the extended duration and 280 (91%) patients in the in-hospital thromboprophylaxis group (hazard ratio 1.12, 95% confidence interval 0.72 to 1.76; P=0.1; table 2).

In the sensitivity analysis of compliant patients (>80% compliance), the primary outcome could be evaluated in 216 (78%) of 276 patients in the extended duration group and in 235 (80%) of 292 patients in the in-hospital thromboprophylaxis group (hazard ratio 1.13, 95% confidence interval 0.90 to 1.42; P=0.3).

Subgroup analyses for the primary outcome are shown in supplementary figure S1 in the appendix. The hazard ratios were not significant for the primary outcome in patients with colon cancer at 1.42 (95% confidence interval 0.88 to 2.30) and with rectal cancer at 0.88 (0.62 to 1.24). Patients who underwent surgery also had non-significant hazard ratios for laparoscopic surgery (0.96 (0.72 to 1.29)) and for open surgery (1.34 (0.96 to 1.87)). Similarly, no difference was reported for disease-free survival in patients who received pain controlled intravenous anaesthesia (1.15 (0.89 to 1.49) or epidural anaesthesia (1.13 (0.73 to 1.74)). No significant interactions between
### Table 1 | Baseline clinical characteristics. Data are number (%) of participants unless stated otherwise

| Baseline characteristics                           | In-hospital thromboprophylaxis (n=307) | Extended thromboprophylaxis (n=307) |
|---------------------------------------------------|----------------------------------------|-------------------------------------|
| **Personal**                                      |                                        |                                     |
| Mean (SD) age (year)                              | 60.8 (12.6)                            | 61.4 (13.2)                         |
| Women                                             | 121 (39)                               | 128 (42)                            |
| Race or ethnicity:                                |                                        |                                     |
| White                                             | 273 (89)                               | 278 (90)                            |
| Black or African American                         | 6 (2)                                  | 4 (1)                               |
| Hispanic                                          | 3 (1)                                  | 3 (1)                               |
| Asian                                             | 11 (4)                                 | 15 (5)                              |
| Native American                                   | 9 (3)                                  | 5 (2)                               |
| Other                                             | 3 (1)                                  | 2 (1)                               |
| **Mean (SD) body mass index**                     | 5.5 (28.4)                             | 5.7 (28.3)                          |
| **Mean (SD) creatinine clearance (mL/min)**       | 17.4 (74.8)                            | 17.5 (76.7)                         |
| **Tumour type**                                   |                                        |                                     |
| Colon                                             | 151 (49)                               | 152 (49)                            |
| Rectum                                            | 156 (51)                               | 155 (51)                            |
| **Positive family history of colorectal cancer†** | 50 (17)                                | 52 (18)                             |
| **ECOG performance status**                       |                                        |                                     |
| 0 or 1                                            | 244 (80)                               | 251 (82)                            |
| 2                                                 | 63 (20)                                | 56 (18)                             |
| **Concomitant antiplatelet drug treatments**      |                                        |                                     |
| Acetylsalicylic acid                              | 42 (14)                                | 46 (15)                             |
| Non-steroidal anti-inflammatory drugs             | 20 (7)                                 | 26 (9)                              |
| **Neoadjuvant or adjuvant treatment‡**            |                                        |                                     |
| Neoadjuvant treatment (before surgical resection):| 113 (37)                               | 116 (39)                            |
| Pelvic radiation: short course (25 Gy in 5 fractions) | 45 (15)                           | 58 (20)                             |
| Pelvic radiation: long course (55 Gy in 25 fractions) | 68 (22)                           | 57 (19)                             |
| Adjuvant treatment §                               | 143 (53)                               | 144 (54)                            |
| Capecitabine or fluorouracil                      | 72 (27)                                | 77 (29)                             |
| Oxaliplatin                                       | 63 (24)                                | 61 (23)                             |
| Other                                             | 14 (5)                                 | 14 (5)                              |
| **Operative data**                                |                                        |                                     |
| Type of surgery:                                  |                                        |                                     |
| Laparoscopy                                       | 203 (67)                               | 227 (76)                            |
| Open                                              | 100 (33)                               | 72 (24)                             |
| **Procedure**                                     |                                        |                                     |
| Right hemicolecoty                                | 48 (16)                                | 55 (18)                             |
| Left hemicolecoty                                 | 23 (8)                                 | 21 (7)                              |
| Transverse colectomy                              | 7 (2)                                  | 8 (3)                               |
| Sigmoid colectomy                                 | 30 (10)                                | 30 (10)                             |
| Low anterior resection                            | 146 (48)                               | 139 (47)                            |
| Abdominal perineal resection                      | 31 (10)                                | 29 (10)                             |
| Subtotal colectomy                                | 3 (1)                                  | 4 (1)                               |
| Unknown or multiple procedures                    | 15 (5)                                 | 13 (4)                              |
| Heparin administration in the operating room:     |                                        |                                     |
| Given just before surgery                         | 287 (95)                               | 290 (97)                            |
| Given in the operating room                       | 108 (36)                               | 103 (35)                            |
| **Estimated blood loss:**                         |                                        |                                     |
| <200 mL                                           | 188 (63)                               | 198 (68)                            |
| ≥200-499 mL                                       | 91 (30)                                | 75 (25)                             |
| 500-999 mL                                        | 18 (6)                                 | 15 (5)                              |
| 1000-2000 mL                                      | 3 (1)                                  | 5 (2)                               |
| >2000 mL                                          | 0                                     | 0                                   |
| **Cancer staging**                                |                                        |                                     |
| Pathological T stage**                            |                                        |                                     |
| 0                                                 | 27 (9)                                 | 22 (7)                              |
| 1                                                 | 25 (8)                                 | 23 (8)                              |
| 2                                                 | 76 (26)                                | 81 (28)                             |
| 3                                                 | 149 (50)                               | 145 (49)                            |
| 4                                                 | 22 (7)                                 | 23 (8)                              |
| Node positive††                                   | 96 (32)                                | 105 (36)                            |
| Positive margins††                                | 9 (3)                                  | 5 (2)                               |
| Intraoperative metastatic disease                 | 2 (1)                                  | 4 (1)                               |

*SD=standard deviation.

**Missing 37 values (18 in standard and 19 in extended duration).

†Family history is defined as a diagnosis in one or more first degree relatives; missing 23 values (11 in standard and 12 in extended duration).

‡Excludes 12 patients who were randomly assigned but were withdrawn before surgery (four in standard and eight in extended duration groups).

§Received within 12 months of surgery; missing 65 values (35 in standard and 30 in extended duration groups).

¶Missing nine values (three in standard and six in extended duration).

**Missing nine values (four in standard and five in extended duration).

††Missing eight values (four in standard and four in extended duration).
invasive colorectal cancer without evidence of metastatic disease who were eligible to undergo surgical resection. Furthermore, the rates of venous thromboembolism and postoperative major bleeding complications were low in this patient population, and similar between groups.

To our knowledge, this study is the largest randomised controlled trial assessing the role of low molecular weight heparin and disease-free survival in patients with cancer undergoing surgical resection. Recruitment was stopped prematurely because the predefined interim analysis reported a low power (48%) to reject the null hypothesis and difﬁculties in recruitment. The results of our study are consistent with the Tinzaparin in Lung Tumors (TILT)16 and the Adjuvant Chemotherapy with or without Nadroparin in Patients with Completely Resected Non- Small-Cell Lung Cancer (NVALT-8) trials,17 evaluating the effect of adjuvant tinzaparin and nadroparin in patients with resected stage II-III lung cancer where low molecular weight heparin had no effect on overall or disease-free survival. Prophylactic dosing of tinzaparin was used in the PERIOP-01 trial because therapeutic dosing could have a higher risk of bleeding complications in the perioperative setting. A substantial number of patients with colorectal cancer are already bleeding from the underlying tumour before surgery, and major bleeding complications might increase after major abdominal surgery in patients receiving therapeutic dosing of an anticoagulant.18 Furthermore, other dosing regimens have already been assessed by TILT (intermediate dosing of tinzaparin 100 IU/kg, once a day for 12 weeks) and NVALT-8 (two weeks of therapeutic dosing then 14 weeks on intermediate dosing) and showed no benefit.16 17 The PERIOP-01 trial used tinzaparin as an early adjuvant treatment starting from the day of surgery until day 56. At day 56, patients with indications for adjuvant chemotherapy started treatment.

About 53% of patients in our trial received adjuvant chemotherapy (table 1). Although low molecular weight heparins have consistently shown antimetastatic properties in preclinical studies, this effect has not been translated into clinical benefit. The metastatic cascade and subsequent development of clinically detected recurrence is a complex process with a multitude of mechanistic interactions, and modifying one mechanism could simply be insufficient in any clinical setting. Nonetheless, the immediate postoperative period remains an important window to prevent the development of metastatic disease and an area to explore novel treatments. Importantly, the PERIOP-01 trial also assessed the role of preoperative thromboprophylaxis because the tinzaparin was initiated before the resection for four days (interquartile range two to nine) to ensure that if antimetastatic properties required preoperative administration, these could be abrogated before surgery and potential metastatic spread. Hence, the PERIOP-01 provides evidence that both preoperative and postoperative extended duration thromboprophylaxis with other subgroups and type of thromboprophylaxis were reported (supplementary figure S1).

**Discussion**

**Principal findings**

The PERIOP-01 trial showed that extended duration to perioperative thromboprophylaxis with tinzaparin did not result in an improvement in disease-free survival at three years compared with in-hospital thromboprophylaxis among patients with localised colorectal cancer. The PERIOP-01 trial showed no benefit.16 17 The PERIOP-01 trial used tinzaparin as an early adjuvant treatment starting from the day of surgery until day 56. At day 56, patients with indications for adjuvant chemotherapy started treatment.

About 53% of patients in our trial received adjuvant chemotherapy (table 1). Although low molecular weight heparins have consistently shown antimetastatic properties in preclinical studies, this effect has not been translated into clinical benefit. The metastatic cascade and subsequent development of clinically detected recurrence is a complex process with a multitude of mechanistic interactions, and modifying one mechanism could simply be insufficient in any clinical setting. Nonetheless, the immediate postoperative period remains an important window to prevent the development of metastatic disease and an area to explore novel treatments. Importantly, the PERIOP-01 trial also assessed the role of preoperative thromboprophylaxis because the tinzaparin was initiated before the resection for four days (interquartile range two to nine) to ensure that if antimetastatic properties required preoperative administration, these could be abrogated before surgery and potential metastatic spread. Hence, the PERIOP-01 provides evidence that both preoperative and postoperative extended duration thromboprophylaxis with
tinzaparin does not improve disease-free survival in patients with colorectal cancer undergoing surgical resection.

The rates of venous thromboembolism were low (<2%) without significant differences between the two groups. These low rates of venous thromboembolism are consistent with a recent meta-analysis of randomised trials reporting a 30 day incidence of clinical venous thromboembolism of 1.4% in patients receiving extended duration and 0.3% in patients receiving thromboprophylaxis in hospital after major abdominal or pelvic surgery.19 In our study, no significant reduction in symptomatic venous thromboembolism was reported between the extended duration and in-hospital thromboprophylaxis groups (2% vs 1%). Several explanations might account for this discrepancy. Unlike previous randomised controlled trials, screening ultrasounds of the lower extremities were not done. The use of asymptomatic deep vein thrombosis of the lower extremities diagnosed on screening ultrasound or venography is often used as a surrogate outcome measure; however, its clinical relevance remains unclear. Outcomes important to patients, including symptomatic events, are preferred to establish clinical practice guidelines.20 Furthermore, the definition of venous thromboembolism used in the PERIOP-01 trial included upper extremity and unusual site deep vein thromboses. Finally, venous thromboembolism was reported over a 56 day follow-up period to coincide with discontinuation of tinzaparin in the extended duration group. Nonetheless, the PERIOP-01 trial is the largest randomised trial study of postoperative thromboprophylaxis with low molecular weight heparin at an extended duration in this population and provides additional data that will help clinicians to assess the risk (bleeding) to benefits (venous thromboembolism) ratio of using extended duration thromboprophylaxis in people with colorectal cancer undergoing surgical resection.

Limitations of this study
A limitation of our trial is the open label design, which could be associated with a risk of bias regarding the frequency of the outcomes, as compared with the frequency that might have been observed in a placebo controlled trial. However, the primary outcome measure (disease-free survival) in our trial is an objective outcome that means that bias is unlikely. Furthermore, all primary and secondary outcomes were adjudicated by a blinded, independent committee. The PERIOP-01 trial included patients with both rectal and colon cancers leading to some heterogeneity in the patient population. However, the trial was pragmatic and representative of current clinical practice of general and colorectal surgeons. Furthermore, all participating centres provided comprehensive colorectal cancer care in their respective regions and all patients undergoing a surgical resection were assessed for eligibility and enrolment, so we believe that the results are generalisable. Finally, the trial was stopped early after the recommendations from the data monitoring and safety board. However, given the lower power reported at the interim analysis, completion of the total sample size would be unlikely to change the interpretation and conclusions of the trial.

Conclusion
Extended duration to perioperative thromboprophylaxis with tinzaparin (given before surgery and for 56 days after surgery), as compared with in-hospital thromboprophylaxis, does not increase disease-free survival at three years in patients with localised invasive colorectal cancer without evidence of metastatic disease who were eligible to undergo surgical resection. The rates of clinically detected venous thromboembolism were low and extended duration thromboprophylaxis was not associated with a reduction in venous thromboembolism.

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Contributors: RA and MC contributed to the conception and design of the study in collaboration. All authors gathered the data. RA and MC verified the data. RA, TR, RM, and MC analysed the data, and all authors interpreted the data. All authors had access to all the data in the study, participated in developing or reviewing the manuscript, and provided final approval to submit the manuscript for publication. No medical writer was engaged to write any part of this manuscript. PERIOP-01 study investigators were responsible for local implementation of the study; recruited patients; and critically revised and approved the final manuscript. PERIOP-01 study adjudicators reviewed suspected study events. PERIOP-01 study data safety monitoring committee reviewed study safety reports and the interim analyses. MC is the guarantor of the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: Sponsored by the Ottawa Hospital Research Institute with funding from the Canadian Institute for Health Research, The Canada Foundation for Innovation, The Cancer Research Society, The Ottawa Hospital Academic Medical Organisation, and Leo Pharma, as well as
as through generous patient donations through The Ottawa Hospital Foundation. Patient recruitment at the London Health Sciences Center was subsidised through funds provided by the Department of Surgery, University of Western Ontario. MC, VT, TR, and GLG are investigators of the CanVECTOR Network; the Network receives grant funding from the Canadian Institutes of Health Research (funding reference: OTT-142654). RA holds a T1 clinical research chair on Perioperative Cancer Therapeutics from the Department of Surgery, Division of General Surgery, and the University of Ottawa. MC holds a T1 clinical research chair on Cancer and Thrombosis from the Department of Medicine and the University of Ottawa. The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare support from the Canadian Institute of Health Research, Ottawa Hospital Academic Medical Organisation, and Leo Pharma, as well as through generous patient donations through the Ottawa Hospital Foundation for the submitted work. MC has received research funding from BMS, Pfizer, and Leo Pharma, and honorariums from Bayer-Pfizer, BMS, Servier, and Leo Pharma. VT received consulting honorariums from Pfizer-BMS and Daiichi-Sankyo and has received research funding from Sanofi. MB received consulting honorariums from Johnson and Johnson. AOM received consulting honorariums from Johnson and Johnson. MO received consulting honorariums from Johnson and Johnon and Eshcon. All other authors declare no competing interests.

Ethical approval: Institutional research ethics board approval was obtained at Ottawa Hospital Research Ethic Board (OCREB No 10-092) and at all participating centres.

Data sharing: De-annotised patient level data and the full dataset with low risk of identification are available on reasonable request from the corresponding author after approval by the trial steering committee and Ottawa Hospital Research Institute.

The lead author and guarantor (MC) affirms that the manuscript is honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: Disseminating the results to patients will be by each site investigator if possible. This trial was designed and conducted by investigators of the CanVECTOR research network. CanVECTOR (https://www.canvector.ca) has partnered with knowledge translation and venous thrombosis experts from across Canada to identify new, workable, effective strategies to extend the reach of knowledge translation activities. (Specifically, CanVECTOR’s CLOT (https://plus.mcmaster.ca/clothplus) provides a continuously updated collection of high quality and highly relevant clinical research papers to more than 500 subscribers, as well as evidence summaries tailored for frontline physicians. CLOT+ also partners with CanVECTOR patient partners to produce lay summaries targeted at the patient and family audience. The results of this trial will be used to produce evidence summaries directed towards frontline surgeons and patients. Dissemination will also be done through Thrombosis Canada (https://thrombosiscanada.ca/) and the Canadian Association of General Surgeons (https://cagas-acgc.ca/). Social media will also be used for promotion of the study publication; for example, CanVECTOR has an active Twitter account (@canvector) and a growing network of followers and collaborative partners.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix 1: Supplementary tables and text
Web appendix 1: Trial protocol