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Efficacy and safety of extended duration postoperative thromboprophylaxis with low molecular weight heparin among subgroups of patients undergoing surgical resection of colorectal cancer: A post-hoc analysis of the PERIOP-01 trial

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ABSTRACT

Background: Extended duration postoperative thromboprophylaxis is suggested by clinical practice guidelines after any cancer-related major abdominal surgeries. However, recent evidence reported relatively low rates of symptomatic venous thromboembolism (VTE) after colorectal cancer surgeries, suggesting the need of a careful risk-benefit assessment in this setting.

Methods: This is a pre-planned post-hoc analysis of the PERIOP-01 trial which compared extended to standard thromboprophylaxis in patients undergoing surgical resection of localized colorectal cancer. Subgroup analyses were performed based on different baseline characteristics. The primary efficacy and safety outcomes were major VTE and clinically relevant bleeding events, respectively.

Results: A total of 614 patients were included in the modified intention-to-treat analysis (307 patients in each group). Major VTE events occurred in 2 % and 1 % of the extended and standard-duration thromboprophylaxis groups, respectively. Clinically relevant bleeding events occurred in 3 % of each group. No specific characteristics were found to be associated with a decreased incidence of major VTE among patients receiving extended thromboprophylaxis. Patients with colon cancer resection receiving extended thromboprophylaxis were at an increased risk of clinically relevant bleeding (HR 2.57, 95%CI 1.25–5.30). Other characteristics that may be associated with an increased incidence of bleeding included age (≥75) (HR 2.37, 95%CI 0.47–11.98) and sex (HR 2.13, 95%CI 0.20–23.17).

Conclusions: In the PERIOP-01 trial, extended thromboprophylaxis did not reduce the incidence of major VTE in any subgroups of patients. However, this strategy may be associated with an increased incidence of bleeding among patients with colon cancer, and perhaps among male and elderly patients.

1. Article summary

- Venous thromboembolism is a known common life-threatening complication of cancer and major surgery is one of the strongest additional transient risk factors among cancer patients.
- Extended thromboprophylaxis after major cancer-related surgeries might not be needed for all patients and selection of patients at higher risk might provide better tailored management, reducing possible associated complications.

AC	Anticoagulation

(*continued on next page*)

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(*continued*)

CI	Confidence Interval
CRNMB	Clinically Relevant Non-Major Bleeding
DVT	Deep Vein Thrombosis
ECOG	Eastern Cooperative Oncology Group
HR	Hazard Ratio
ISTH	International Society on Thrombosis and Haemostasis
LMWHs	Low Molecular Weight Heparins
MB	Major Bleeding
PE	Pulmonary Embolism
VTE	Venous Thromboembolism

2. Background

It is estimated that up to 20 % of all new cases of venous thromboembolism (VTE) have recent surgery as a provoking factor [1]. The risk of developing deep vein thrombosis (DVT) and pulmonary embolism (PE) remains substantially higher in the first 12 weeks after surgery and varies considerably by type of procedure [2].

Compared with non-cancer patients, those with malignancy have a 2- to 3-fold increased risk for VTE during the perioperative period [2,3]. Postoperative venous thromboembolic complications are not only frequent but may also represent significant cause of morbidity and mortality among patients with cancer [4]. In fact, VTE has previously been reported as the most common cause of 30-day mortality following cancer surgery, with a six-fold increase in overall mortality in this patient population [5].

Postoperative thromboprophylaxis administered until hospital discharge has been previously reported to reduce the risk of symptomatic VTE [6,7]. However, the majority of VTE occur beyond hospitalization (only 35 % occur while patients are still in the hospital [8]) and extended duration thromboprophylaxis was previously shown to decrease the risk of postoperative VTE [9–11]. Hence, clinical practice guidelines suggest the use of extended duration postoperative low molecular weight heparin (LMWH) thromboprophylaxis for up to 28 days after a major abdominal cancer-related surgery (very low certainty evidence of effect) [12,13].

More recent studies have reported a lower than previously described incidence of VTE among these patients [14–18], potentially related to less invasive interventions (e.g., laparoscopic, minimally invasive, etc.), decreased operating room times, enhanced recovery after surgery (ERAS) protocols and early mobilization. As such, to optimize the risk-benefit ratio of extended duration thromboprophylaxis following major cancer-related abdominal surgery, it is important to identify the subsets of cancer patients that would most benefit without increasing the underlying high risk of bleeding. We sought to determine the impact of extended perioperative thromboprophylaxis with tinzaparin on VTE and major bleeding among different subgroups of patients with localized colorectal cancer undergoing resection included in the PERIOP-01 trial.

3. Methods

3.1. Study design and population

This is a pre-planned post-hoc analysis of the PERIOP-01 trial, a multicentre, open label, randomised controlled trial, involving 12 Canadian hospitals, which compared two strategies of perioperative thromboprophylaxis in patients undergoing surgical resection of localized colorectal cancer [15] (SeeSupplemental Appendix 1). Eligible participants were randomized to receive either thromboprophylaxis with tinzaparin (4500 IU, subcutaneously, daily) beginning on postoperative day 1 and continuing for the duration of the hospital stay (standard strategy), or extended duration of same thromboprophylaxis, beginning within 24 h of randomization (a minimum of one preoperative dose to maximum of six weeks) and continuing for 56 days postoperatively. Patients receiving extended duration thromboprophylaxis were taught to self-administer subcutaneous injections. Compliance with tinzaparin injections 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.

The primary outcome of the PERIOP-01 was disease-free survival at three years in the modified intention to treat population, defined as survival without locoregional recurrence, distant metastases, second primary (same cancer or other cancer), or death. Secondary outcome measures included VTE, major bleeding (MB), clinically relevant non-major bleeding (CRNMB), postoperative major bleeding complications, and five-year overall survival [15].

The primary outcomes of this subgroup analysis included efficacy and safety outcomes, represented by major VTE and clinically relevant bleeding combining both MB and CRNMB events, respectively. Major VTE event was defined as objectively confirmed; symptomatic or incidental; proximal, lower, or upper extremity DVT; unusual site thrombosis (i.e., cerebral, splanchnic, or renal vein thrombosis); or PE; occurring between the day of the surgery and postoperative day 56. Major bleeding and CRNMB were defined by the International Society on Thrombosis and Haemostasis (ISTH) [19,20]. For this study, bleeding events were captured between postoperative day 7 and 56. Major surgery related bleeding events (occurring between day of surgery and day 7) were not included in this analysis as the aim was to determine the impact of extended thromboprophylaxis on the primary and secondary outcomes.

For this subgroup analysis, the incidences of outcomes among patients receiving standard or extended postoperative thromboprophylaxis were evaluated within pre-defined subgroups of patients. These subgroups were determined based on patient demographics, concurrent treatments, and cancer characteristics, and were defined as follows: age (<65, ≥ 65 years; <75, ≥ 75 years), sex (male, female), race (white, other than white), weight (<60, 60 to 90, >90 kg), body mass index (BMI; <35, ≥ 35 kg/m^2), creatinine clearance (30–50, >50 mL/min), antiplatelet drug use, type of primary cancer (rectal, colon) and tumor stage (T1-2, T3-4), use of neoadjuvant and/or adjuvant treatments, type of surgery (open, laparoscopic) and baseline Eastern Cooperative Oncology Group (ECOG) status (0–1, 2).

3.2. Statistical analysis

The analyses were performed in the modified intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of tinzaparin. The baseline characteristics of the patients who had the event by the treatment arm were summarized using mean (standard deviation (SD)) and number (%) as appropriate. Any episodes of VTE or clinically relevant bleeding that happened up until day 56 following surgery were included in the analysis and described using frequency and percentages. Hazard ratios (HR) with 95 % confidence intervals (CI) were calculated using the Cox proportional hazards model to compare the treatment effect, accounting for clustering at study center level. For all statistical tests, two-tailed test was used to determine significance at the 5 % level. A forest plot was created to demonstrate the treatment effect across subgroups. All statistical analyses were performed using SAS, Version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

4. Results

A total of 614 patients were included in the modified intention-to-treat analysis PERIOP-01 trial (307 in the extended and 307 in the standard duration thromboprophylaxis groups). Overall, the mean age of the participants was 61 years, 41 % of them were women, and a large majority of patients were Caucasian/white (90 %). Overall, 311 (51 %) and 303 (49 %) patients had rectal and colon cancer, respectively.

Compliance was 93 % and 97 % in the extended and standard duration thromboprophylaxis groups, respectively. During the study period, major VTE events occurred in five patients (2 %) and four patients (1 %) of the extended- and standard-duration prophylaxis groups, respectively (P = 0.8). Major VTE included 3 PEs, one lower extremity DVT and one portal vein thrombosis among patients receiving extended-duration thromboprophylaxis, and 2 PEs and 2 lower limb DVTs among patients receiving standard-duration thromboprophylaxis. Clinically relevant bleeding (i.e., MB and CRNMB events) occurred in 8 patients (3 %) of each group (including 4 anastomotic bleeding events). Of the 16 clinically bleeding events, 5 (3 and 2 in the extended and standard duration, respectively) were beyond 28 days following the surgery. Baseline characteristics of patients who developed either VTE or clinically relevant bleeding events are depicted in Tables 1 and 2, respectively.

No specific characteristics were found to be associated with a decreased incidence of major VTE among patients receiving extended duration thromboprophylaxis (Fig. 1). Patients with colon cancer receiving extended thromboprophylaxis were at an increased incidence of clinically relevant bleeding complications compared to the same population receiving standard treatment (HR 2.57, 95%CI 1.25–5.30, P = 0.01) (Fig. 2). Other characteristics that may be associated with an increased incidence of clinically relevant bleeding among patient receiving extended thromboprophylaxis included age≥75 (HR 2.37, 95%CI 0.47–11.98) and male sex (HR 2.13, 95%CI 0.20–23.17), although these characteristics were not statistically significant (Fig. 2).

5. Discussion

This pre-planned post-hoc analysis of the PERIOP-01 trial demonstrated that the assessment of individual risks for developing postoperative VTE following colorectal cancer resection is still challenging. We could not identify any specific characteristics that were associated with a decreased incidence of major VTE among patients receiving extended duration of postoperative thromboprophylaxis. However, a higher incidence of clinically relevant bleeding was found among patients with colon cancer and a potentially higher risk among elderly and male patients, though not significant. These findings outline some variables that should be considered when making decisions on the duration of postoperative thromboprophylaxis in cancer patients undergoing colorectal cancer resection.

The optimal regimen and duration of antithrombotic prophylaxis in patients undergoing cancer-related major abdominal surgery is still controversial. Although a recent Cochrane review assessing the efficacy of extended duration thromboprophylaxis utilizing LMWH after major abdominopelvic surgery reported a significant reduction in the overall incidence of VTE (encompassing both asymptomatic and symptomatic events) (Odds Ratio (OR) 0.38, 95%CI 0.28–0.54) [21], clinical equipoise remains on the use of extended duration thromboprophylaxis in this patient population and its adoption in clinical practice is low [22]. This might be related to the lack of data about extended duration thromboprophylaxis in patients managed according to the ERAS protocols, which by themselves could mitigate the risk of VTE in the postoperative period, and the relatively low absolute rates of symptomatic events in this patient population. The rate of symptomatic major VTE was low in the PERIOP-01 trial (9 out of 614 patients (1.5 %)) without significant differences between the two treatment groups, consistent with recent literature including patients undergoing colon cancer resection following ERAS protocols. An observational study including 1806 patients that did not receive extended duration thromboprophylaxis following colon cancer resection reported a low rate of symptomatic VTE of only 0.17 % (95%CI 0.04–0.52) over a 60-day follow-up period [18]. Furthermore, our study showed that patients undergoing colon cancer resection might be at higher risk of clinically relevant bleeding when receiving extended duration thromboprophylaxis. The colon is more vascularized than the rectum potentially leading to higher risk of anastomotic leaks and bleeding complications. These findings are questioning the need for extended duration thromboprophylaxis for all patients undergoing colorectal resection and highlight the need to carefully assess the risk (e.g., clinically relevant bleeding) and benefits (e.g., decreasing symptomatic VTE) on an individual basis for these patients. Our subgroup analysis may help clinicians identify subgroups of patients undergoing colorectal cancer resection at higher incidence of clinically relevant bleeding complications.

The major strength of this study is derived from the robust

Table 1
Baseline characteristics of patients with venous thromboembolism events.

Characteristic	Overall population (n = 614)	Venous thromboembolism	
		In-hospital thromboprophylaxis (n = 4)	Extended thromboprophylaxis (n = 5)
Age (years), mean (SD)	61 (13)	64 (15)	65 (5)
Male sex, n (%)	365 (59)	4 (100)	4 (80)
BMI <35 kg/m^2, n (%)	511 (83)	4 (100)	4 (80)
Creatinine clearance >50 mL/min, n (%)	579 (94)	4 (100)	5 (100)
Tumor type, n (%)			
Colon cancer	303 (49)	1 (25)	2 (40)
Rectal cancer	311 (51)	3 (75)	3 (60)
Concomitant antiplatelet medication, n (%)	88 (14)	1 (25)	0
ECOG performance status score, n/total (%)			
0-1	495 (81)	4 (100)	3 (60)
2	119 (19)	0	2 (40)
Neoadjuvant therapy	229 (38)	3 (75)	2 (40)

Abbreviations: BMI – Body Mass Index. ECOG – Eastern Cooperative Oncology Group.

Table 2
Baseline characteristics of patients with clinically relevant bleeding events.

Characteristic	Overall population (n = 614)	Clinically relevant bleeding	
		In-hospital thromboprophylaxis (n = 8)	Extended thromboprophylaxis (n = 8)
Age (years), mean (SD)	61 (13)	64 (11)	69 (15)
Male sex, n (%)	365 (59)	2 (25)	4 (50)
BMI <35 kg/m^2, n (%)	511 (83)	6 (75)	7[a] (100)
Creatinine clearance >50 mL/min, n (%)	579 (94)	8 (100)	7 (87.5)
Tumor type, n (%)			
Colon cancer	303 (49)	2 (25)	5 (62.5)
Rectal cancer	311 (51)	6 (75)	3 (37.5)
Concomitant antiplatelet medication, n (%)	88 (14)	0	1 (12.5)[b]
ECOG performance status score, n/total (%)			
0-1	495 (81)	6 (75)	5 (62.5)
2	119 (19)	2 (25)	3 (37.5)
Neoadjuvant therapy	229 (38)	5 (62.5)	1 (12.5)

Abbreviations: BMI – Body Mass Index. ECOG – Eastern Cooperative Oncology Group.

[a] Frequency Missing = 1.

[b] Patient with rectal cancer.

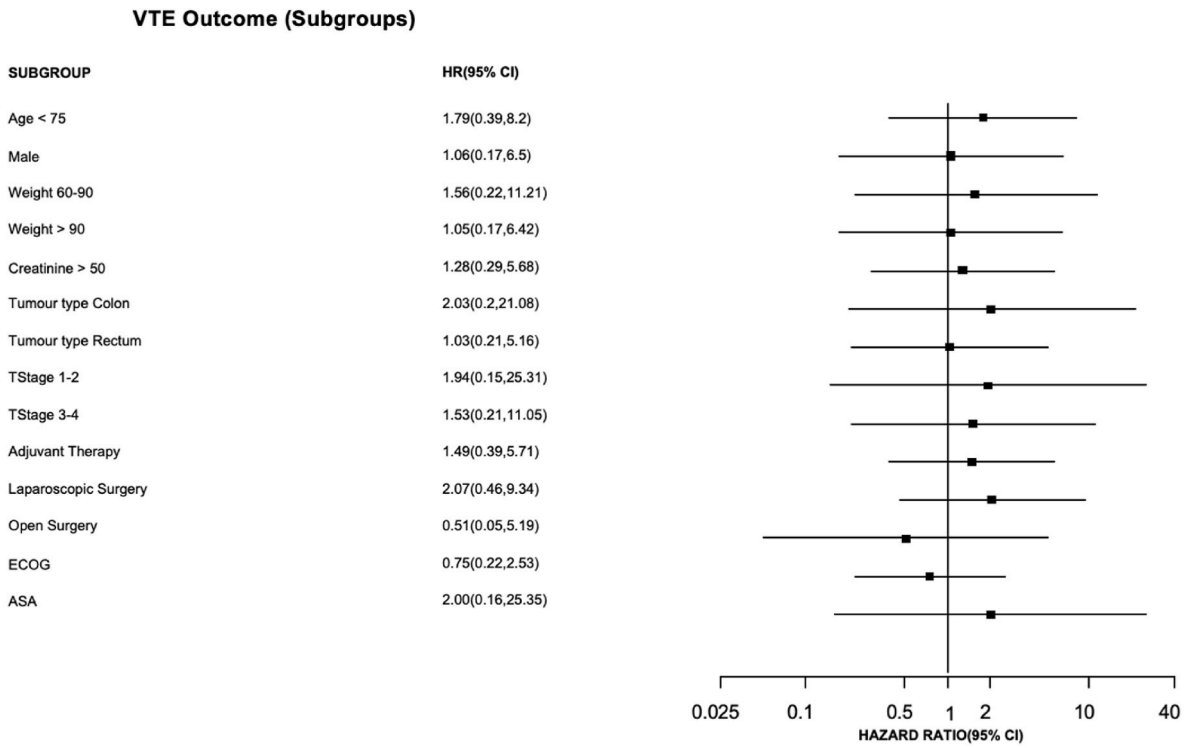

Fig. 1. Incidence of venous thromboembolism (VTE) within the different pre-defined subgroups in patients receiving postoperative extended thromboprophylaxis.

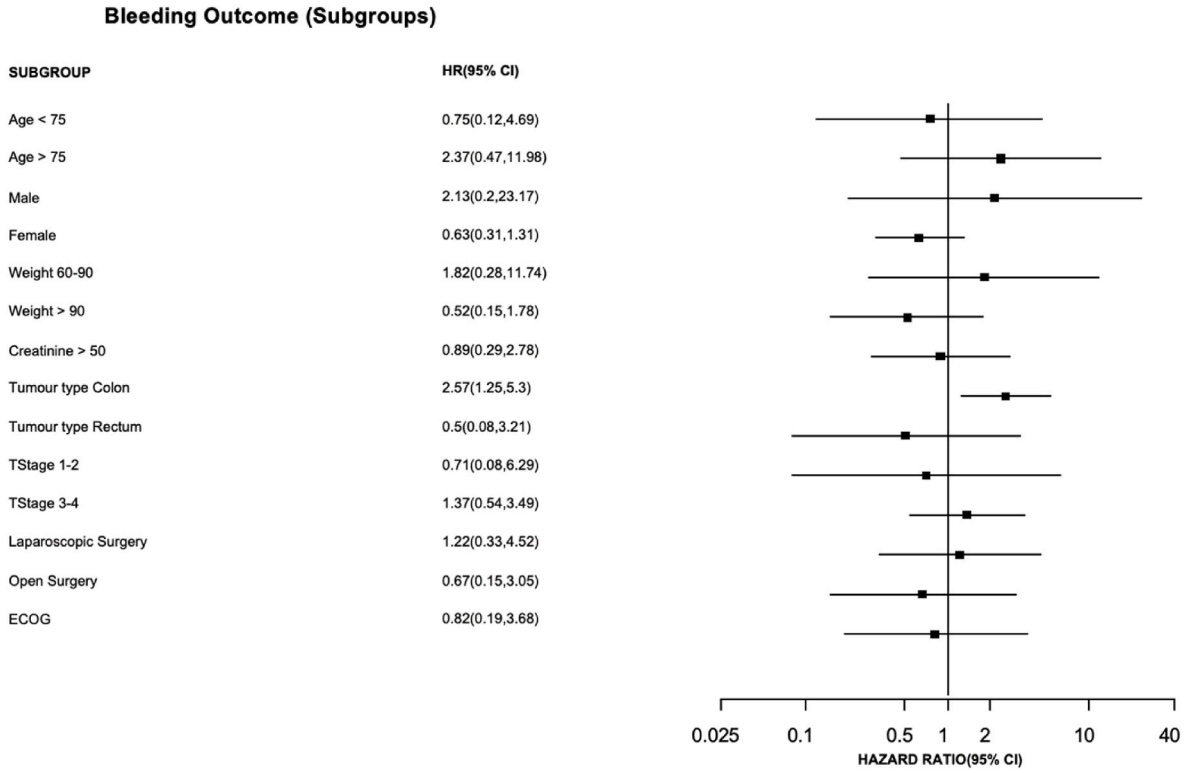

Fig. 2. Incidence of clinically relevant bleeding within the different pre-defined subgroups in patients receiving postoperative extended thromboprophylaxis.

methodology used in the PERIOP-01 trial. This was a multicenter, open label, randomized controlled trial, with few losses to follow up, reducing the potential risk of bias in patient sampling and outcome measurements. Our study also has important limitations to acknowledge. The PERIOP-01 trial was stopped early due to futility. Furthermore, the number of major VTE and clinically relevant bleeding events were relatively small, especially for certain subgroups of patients, leading to wide confidence intervals and imprecision. Moreover, this analysis consists of a limited cancer population (colorectal) receiving thromboprophylaxis with tinzaparin, as such, these findings may not be

generalizable to all cancer types undergoing major abdominal surgeries or other types of low molecular weight heparin. Future large population-based studies or prospective trials with wider, cancer-specific populations are needed to reinforce our results. Surely, our findings confirmed that the safety associated with the use of extended post-operative thromboprophylaxis needs to be combined with efficacy for decision making.

6. Conclusions

In the PERIOP-01 trial, extended thromboprophylaxis did not reduce the incidence of major VTE in any subgroups of patients undergoing surgical resection of localized colorectal cancer. However, extended duration thromboprophylaxis may be associated with an increased incidence of bleeding complications in patients with colon cancer, and perhaps among male and elderly ones. Hence, risk-benefit ratio of extended duration thromboprophylaxis should be carefully evaluated according to patients' specific characteristics.

CRediT authorship contribution statement

Laura Girardi: Methodology, Data curation, Writing – original draft, Visualization. **Ranjeeta Mallick:** Formal analysis, Quality control of data and algorithms. **Tzu-Fei Wang:** Data curation, Writing – review & editing, Visualization. **Marc Carrier:** Conceptualization, Methodology, Data curation, Writing – review & editing, Visualization, Supervision, Project administration. **Rebecca Auer:** Data curation, Writing – review & editing, Visualization.

Ethical approval

Institutional research ethics board approval was obtained at Ottawa Hospital Research Ethic Board (OCREB # 10–092) and at all participating centers.

Declaration of competing interest

L. Girardi, T.-F. Wang, R. Auer and R. Mallick report no conflicts of interests. M. Carrier has received research funding from BMS, Pfizer, and Leo Pharma, and honoraria from Bayer, Pfizer, BMS, Servier, and Leo Pharma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.109701.

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