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# Prescription of extended-duration thromboprophylaxis after high-risk, abdominopelvic cancer surgery

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## HIGHLIGHTS

- Use of extended-duration thromboprophylaxis is low among high-risk cancer patients undergoing surgery
- The use of extended-duration prophylaxis has increased slightly over time.
- Further study to determine the comparative effectiveness of extended-duration thromboprophylaxis is warranted.

## ARTICLE INFO

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## ABSTRACT

*Objective.* Extended-duration thromboprophylaxis for 4 weeks after discharge has been demonstrated to reduce venous thromboembolic events (VTE) in cancer patients undergoing abdominopelvic surgery and is recommended in national guidelines. We examined the utilization and effectiveness of extended-duration low molecular weight heparin prophylaxis in high-risk cancer patients.

*Methods.* We analyzed patients with colon, ovarian, and uterine cancer who underwent surgery from 2009 to 2013 and who were recorded in the MarketScan database. Multivariable models and propensity score analysis with inverse probability of treatment weight were developed to examine uptake and predictors of use of post-discharge low molecular weight heparin (LMWH), as well as associated adverse events (transfusion, and hemorrhage).

*Results.* A total of 63,280 patients were identified. Use of extended-duration prophylaxis increased from 2009 to 2013 from 1.4% to 1.7% ($P = 0.67$) for colectomy, 5.9% to 18.3% for ovarian cancer surgery ($P < 0.001$), and 6.3% to 12.2% ($P < 0.001$) for hysterectomy for endometrial cancer. There was no association between use of extended-duration prophylaxis and reductions in VTE for any of the procedures: colectomy (2.4% with extended-duration prophylaxis vs. 2.9% without prophylaxis, OR = 0.84; 95% CI, 0.54–1.31), ovarian cancer-directed surgery (3.7% vs. 3.6%, OR = 1.01; 95% CI, 0.76–1.33), hysterectomy (2.1% vs. 2.1%; OR = 0.96; 95% CI, 0.67–1.38). Extended-duration prophylaxis was associated with an increased risk of adverse postoperative events: 2.20 (95% CI, 1.51–3.19) after colectomy, 1.24 (95% CI, 0.92–1.68) following ovarian cancer-directed surgery and 0.99 (95% CI, 0.66–1.48) for hysterectomy for endometrial cancer.

*Conclusion.* Use of extended-duration thromboprophylaxis is low among high-risk cancer patients undergoing surgery.



## 1. Introduction

Venous thromboembolism is a major cause of morbidity and mortality for surgical patients [1]. Among surgical patients not receiving prophylaxis, 15–20% will develop an asymptomatic deep venous thrombosis (DVT) while up to 0.9% will develop a fatal pulmonary embolism (PE) [1–4]. Certain sub-groups of patients, such as those undergoing orthopedic or oncologic surgery, are at particularly high-risk [1,5,6]. The risk of venous thromboembolic events (VTE) among patients undergoing cancer-directed surgery is two to three-fold higher than in non-cancer patients [6]. Given the high-risk of VTE, strategies using

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pharmacologic prophylaxis have been tested in numerous prospective trials and recommended in national guidelines for more than two decades [1,5,6].

Even after hospital discharge, the risk of venous thromboembolic disease remains elevated for several weeks to months following surgery [7–10]. A study of nearly one million women from the United Kingdom found that, compared to patients who had not undergone surgery, the relative risk for VTE 7–12 weeks postoperatively was 19.6, while patients 4–6 months after surgery were 9-fold more likely to develop a VTE [7]. To reduce the risk of VTE during the postoperative, post-discharge period, several randomized trials have investigated extended-duration VTE prophylaxis with low molecular weight heparin (LMWH) in high-risk patients who underwent abdominal or pelvic surgery [11–13]. These studies have demonstrated that extended-duration prophylaxis, typically for 4 weeks, reduces the risk of DVT by at least 50% [8,14–17]. Importantly, extended prophylaxis was not associated with an increased risk of bleeding complications in these studies [8,14–17].

Based on the efficacy of extended prophylaxis, national consensus guidelines have recommended extended-duration prophylaxis with LMWH for 4 weeks after hospital discharge in cancer patients who undergo abdominal or pelvic surgery [6,8,18,19]. Despite these recommendations, little is known about the patterns of extended-duration prophylaxis use in actual clinical practice. We examined the utilization and effectiveness of extended-duration low molecular weight heparin VTE prophylaxis in high-risk cancer patients who underwent abdominal and pelvic surgery.

## 2. Methods

### 2.1. Data source

The Truven Health MarketScan database was used for analysis [20]. The database contains a sample of patients enrolled in commercial health plans sponsored by approximately 100 payers. The database captures claims on over 50 million covered lives, includes all inpatient and outpatient medical claims and prescription drug data.[20] The database collects detailed information on monthly enrollment and allows longitudinal data capture on patients. Data was de-identified and deemed exempt by the Columbia University Institutional Review Board.

### 2.2. Patients and procedures

We selected patients with high-risk abdominopelvic malignancies, including gynecologic cancers and colorectal tumors, in which extended-duration VTE prophylaxis has previously been evaluated. Specifically, our cohort consisted of patients with colorectal (ICD9 153.x, 154.x), ovarian (ICD9 183.x), or uterine (ICD9 182.x) cancer who underwent colectomy, oophorectomy and/or hysterectomy or cytoreduction, or hysterectomy, respectively, from 2009 through 2013 (Supplemental Table 1). Patients who underwent colectomy were further classified as having undergone either a minimally invasive (laparoscopic or robotic-assisted) procedure or an open colectomy. Women in the ovarian cancer cohort were stratified based on whether concurrent cytoreduction was performed. Hysterectomy for uterine cancer was classified as open, vaginal, or minimally invasive (laparoscopic or robotic-assisted).

Patients with incomplete coverage for 3 months prior or 3 months after the primary procedure and those without pharmacy benefits were excluded. Similarly, patients with a preoperative diagnosis of either a deep vein thrombosis or pulmonary embolism and those receiving anticoagulation (oral or injectable) prior to the admission for the surgical procedure were excluded from the analysis. We recorded the diagnosis of venous thromboembolism (both DVT and PE) both during and after discharge from the hospital.

### 2.3. Outcomes and covariates

The primary outcome was the provision of extended-duration thromboprophylaxis. We chose a permissive definition of extended-duration prophylaxis, defined as prescription and receipt of low molecular weight heparin (enoxaparin, dalteparin, tinzaparin, parnaparin, certoparin, reviparin, nadroparin, bemiparin) within one week of discharge from the admission for the surgical procedure of interest. Patients who developed a venous thromboembolic event during the index hospitalization were excluded from this portion of the analysis as they would have received therapeutic anticoagulation. Similarly, those patients who received a therapeutic dose of LMWH or who had a diagnosis of a DVT or PE after discharge but prior to receipt of LMWH were categorized as not having received extended-duration prophylaxis. Patients who received prophylaxis but subsequently developed a VTE were retained in the analysis.

Bleeding complications including transfusion and hemorrhage were examined. These events were measured both during the index hospitalization as well as within 3 months after discharge. A composite measure for adverse events was developed and included the occurrence of either of these events. Patients who had a code for a complication both during the hospitalization and after discharge were only coded as having had a complication during hospitalization since it is impossible to determine if the postoperative code represented a separate occurrence of the event.

Clinical and demographic characteristics analyzed included age (≤34, 35–44, 45–54, 55–64 and ≥65 years), gender (male or female), year of surgery (2009–2013), and region (northeast, north central, south, west, unknown). Comorbidity was measured using the Charlson comorbidity score and classified as 0, 1, or ≥2 [21]. The Charlson index is a weighted measure of comorbid medical conditions that has been validated and used extensively in health services research [21].

### 2.4. Statistical analysis

Utilization of extended-duration prophylaxis as well as rates of VTE, both in-hospital and after discharge, are reported descriptively. Frequency distributions between categorical variables were compared using $\chi^2$ tests. Multivariable logistic regression models were developed to determine the association between clinical and demographic characteristics and receipt of extended-duration prophylaxis. Results are reported as odds ratios with 95% confidence intervals.

To account for imbalances in the cohort, a propensity score (PS) analysis was utilized to analyze the association between receipt of extended-duration prophylaxis and the occurrence of VTE and the adverse events. A propensity score is the predicted probability of receipt of a treatment, extended-duration prophylaxis in this analysis [22–24]. To estimate the PS, a logistic regression model was fit to determine predictors of use of extended-duration prophylaxis. The model included age, sex, year, region, comorbidity, hysterectomy, oophorectomy, colectomy, and hospital complications (any instance of transfusion, or hemorrhage) and all possible two-way interaction terms. The inverse probability of treatment weight (IPTW) was then calculated from the PS. To reduce the bias introduced by influential weights, the variance of the IPTW was decreased by stabilization and trimming at cutoffs of 0.1 and 10 [25,26].

To verify the robustness of our findings, a number of sensitivity analyses were performed. We altered the definition of extended-duration prophylaxis and defined prophylaxis as use of LMWH within 6 weeks after surgery. Further, sub-group analyses after exclusion of patients who underwent minimally invasive surgery (colectomy or hysterectomy) or ovarian cancer surgery that did not require cytoreduction were performed. All analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). All statistical tests were two-sided. A $P$-value of $<0.05$ was considered statistically significant.