HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Gynecol Oncol. 2016 June ; 141(3): 531–537. doi:10.1016/j.ygyno.2016.03.023.

Prescription of Extended-Duration Thromboprophylaxis after High-Risk, Abdominopelvic Cancer Surgery

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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 2009–2013 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

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The authors have no conflicts of interest or disclosures.

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.

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 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.

Methods

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.

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.

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 measures of comorbid medical conditions that has been validated and used extensively in health services research.[21]

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 χ^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.

Results

A total of 63,280 procedures patients were identified, including 40,068 who underwent colectomy, 10,260 who underwent ovarian cancer-directed surgery, and 14,518 who underwent hysterectomy for endometrial cancer. The rate of extended prophylaxis increased for each procedure from 2009 to 2013: 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 (Figure 1). The clinical characteristics of the cohort are displayed in Table 1.

Among patients who underwent colectomy, those >54 years of age and patients with ≥2 comorbidities were less likely to receive extended-duration prophylaxis while patients operated on in 2010 and patients in the North Central U.S. more frequently received prophylaxis (Table 2). Compared to open colectomy, the odds ratio for receipt of extended-duration prophylaxis was 0.77 (95% CI, 0.63–0.93) after laparoscopic colectomy. For both hysterectomy and oophorectomy, performance of the procedure in more recent years was associated with receipt of prophylaxis. For oophorectomy, patients residing outside of the Northeast and those undergoing cytoreduction more commonly received prophylaxis. Women who underwent abdominal hysterectomy were more likely to receive prophylaxis than women who underwent either vaginal or minimally invasive hysterectomy.

The VTE rate associated with colectomy was 1.3% during hospitalization and 2.9% during the 3-month postoperative period (Table 3). Similar trends were noted for ovarian cancer; the in-hospital VTE rate was 1.9% while 3.7% of women were diagnosed with VTE postoperatively. The corresponding VTE rates after hysterectomy for endometrial cancer were 0.8% during hospitalization and 2.1% postoperatively. VTE rates were lower for patients who underwent minimally invasive compared to open procedures.

After propensity score balancing, there was not a statistically significant association between use of extended-duration LMWH prophylaxis and reduction in the rate of VTE for any of the 3 procedures: colectomy (2.4% 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), or hysterectomy (2.1% vs. 2.1%; OR=0.96; 95% CI, 0.67-1.38) (Table 4, Supplemental Table 2). Similar findings were noted when the analysis was limited to patients who underwent laparotomy after exclusion of minimally invasive procedures (colectomy and hysterectomy) or in those who underwent cytoreduction (Supplemental Table 3).

Extended-duration prophylaxis was associated with an increased risk of adverse postoperative events for colectomy (Table 4). The odds ratio for the composite endpoint (transfusion, or hemorrhage) associated with extended-duration prophylaxis was 2.20 (95% CI, 1.51-3.19) after colectomy, 1.24 (95% CI, 0.92-1.68) after ovarian cancer-directed surgery and 0.99 (95% CI, 0.66-1.48) after hysterectomy.

Discussion

Our findings suggest that the use of extended-duration thromboprophylaxis is low among cancer patients undergoing surgery. The use of extended-duration prophylaxis has increased slightly over time. In contrast to randomized controlled trials, we found no association between use of extended-duration prophylaxis and reduction in the risk of VTE but noted a small increased risk of adverse events.

A large number of randomized studies have examined the efficacy of VTE prophylaxis during the immediate postoperative period.[1,8] These studies have demonstrated the efficacy of prophylaxis in reducing thromboembolic events and recommendations for perioperative VTE prophylaxis have long been in place to help guide clinicians.[1,8] Despite the strength of

these recommendations, compliance with in-hospital prophylaxis guidelines is highly variable.[27–30] A worldwide analysis of over 18,000 surgical patients found that only 62% received some form of prophylaxis.[28] Similarly, even among high-risk surgical oncology patients, prophylaxis is often omitted.[29]

Additionally, randomized trials as well as systematic reviews have suggested that extended-duration LMWH is efficacious in reducing the risk of nonfatal VTE after surgery.[11–17] One analysis predicted that use of extended-duration prophylaxis among high-risk patients would result in 13 fewer events per 1000 patients without an increased risk of hemorrhagic complications.[8] However, these studies have not demonstrated a statistically significant reduction in mortality and furthermore, the benefits of extended-duration prophylaxis are smaller in lower risk patients.[8] Based on the abundance of data, extended-duration prophylaxis has been recommended in the American College of Chest Physicians (ACCP) guidelines for VTE prophylaxis since 2004.[8,18,19] Despite these guidelines, we noted a surprisingly low rate of extended-duration prophylaxis for patients with colon, ovarian, and uterine cancer undergoing cancer-directed surgery. Over the course of the study the rates of extended-duration prophylaxis rose and then declined by 2013.

A number of patient, physician, and hospital-related factors influence utilization of VTE prophylaxis.[28,30–33] The type of procedure performed appears to be one of the most important predictors of use of VTE prophylaxis.[28,33] The rates of in-hospital VTE prophylaxis are highest for colorectal and gastrointestinal procedures and lower for gynecologic and urologic procedures.[28,33] To date, there has been little data specifically evaluating use and predictors of extended-duration VTE prophylaxis. While we noted an overall low rate of use of extended-duration prophylaxis, use was highest for women undergoing surgery for ovarian cancer and appeared to be increasing over time.

A multitude of factors likely contribute to the low use of extended-duration prophylaxis. Administration of extended-duration prophylaxis is complex and requires a subcutaneous injection that must be taught to patients prior to discharge. LMWH is expensive, and for most patients, requires insurance coverage to offset out-of-pocket expense. Lastly, physician factors including lack of awareness about the potential value of extended-duration prophylaxis may also contribute to the low use of the intervention.

Our data raise important questions about the comparative effectiveness of extended-duration LMWH after cancer-directed surgery. Not only was the use of extended-duration prophylaxis not associated with a lower rate of VTE, treatment was also associated with an increased risk of adverse events in some sub-groups. For a number of interventions, efficacy in highly selected patients enrolled in clinical trials has not translated into effectiveness when applied to the general population.[34,35] There are a number of possible explanations for our findings. Given the low overall rate of use of extended-duration prophylaxis in our cohort, those at higher risk may have preferentially received extended-duration prophylaxis. Alternatively, patients in the general population may be at lower risk than those enrolled in clinical trials, particularly as the use of lower risk minimally invasive surgery has increased, and as such, the risk-benefit ratio of extended prophylaxis is skewed. Lastly, utilization of

LMWH in those prescribed the drug may have been suboptimal. Regardless of the etiology, these findings clearly warrant further investigation.

While our study benefits from the inclusion of a large cohort of patients treated across the U.S., we recognize a number of important limitations. First, use of prophylactic low molecular weight heparin may have been under captured in a small number of patients. To mitigate this bias, we performed a series of sensitivity analyses attempting to capture not only LMWH, but also other anticoagulants, similarly, we used a variety of windows of time and our findings were largely unchanged. Additionally, given the cost associated with the drug, it is unlikely that many patients received LMWH without a claim. Second, we are unable to perform complete risk adjustment as data is lacking for several factors such as surgical complexity, tumor characteristics, preoperative laboratory values, and estimated blood loss that may have influenced the decision to prescribe extended-duration prophylaxis. As such, both measured and unmeasured confounding factors may have biased our estimates of the efficacy of extended-duration LMWH. Third, our data is limited to patients who are commercially insured and may not be generalizable to other surgical populations within the U.S. A further intrinsic limitation of the MarketScan dataset is the limited demographic data available for the cohort. Fourth, we relied on administrative data and thus could only capture billed services and outcomes. We cannot exclude the possibility of undercapture of some outcomes and we are unable to capture asymptomatic DVTs. Lastly, our analysis focused on prescription of LMWH, however, we cannot confirm the patients who filled the prescription were compliant with use of the drug.

Going forward, further prospective, comparative effectiveness studies of the safety and efficacy of extended-duration LMWH in real world populations would be of great value. Given the potential benefits of extended-duration prophylaxis, efforts to raise awareness may increase compliance. Further, pragmatic interventions aimed at promoting utilization of extended-duration prophylaxis may be of benefit to cancer patients undergoing surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Dr. Wright (NCI R01CA169121-01A1) and Dr. Hershman (NCI R01 CA166084) are recipients of grants) from the National Cancer Institute.

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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.

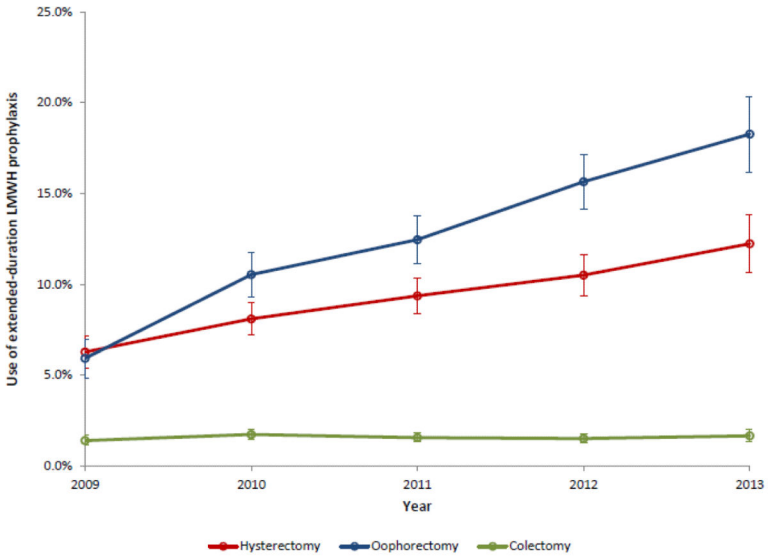

Figure 1.

Use of extended-duration low molecular weight heparin prophylaxis stratified by type of primary surgery performed.

Table 1

Clinical and demographic characteristics of the cohort stratified by extended-duration low molecular weight heparin.

	Colectomy[1,4]					Oophorectomy[2,4]					Hysterectomy[3,4]				
	No LMWH		Extended-Duration LMWH		*P-value*	No LMWH		Extended-Duration LMWH		*P-value*	No LMWH		Extended-Duration LMWH		*P-value*
	N	(%)	N	(%)		N	(%)	N	(%)		N	(%)	N	(%)	
	39,437	(98.4)	631	(1.6)		9,001	(87.7)	1,259	(12.3)		13,213	(91.0)	1,305	(9.0)	
Age					<0.001					0.002					0.36
≤34	710	(1.8)	22	(3.5)		532	(5.9)	47	(3.7)		198	(1.5)	25	(1.9)	
35–44	2,643	(6.7)	50	(7.9)		985	(10.9)	114	(9.1)		892	(6.8)	79	(6.1)	
45–54	9,063	(23.0)	199	(31.5)		2,446	(27.2)	352	(28.0)		2,958	(22.4)	290	(22.2)	
55–64	13,037	(33.1)	223	(35.3)		3,250	(36.1)	500	(39.7)		6,092	(46.1)	627	(48.1)	
≥65	13,984	(35.5)	137	(21.7)		1,788	(19.9)	246	(19.5)		3,073	(23.3)	284	(21.8)	
Sex					0.04					—					—
Female	19,031	(48.3)	330	(52.3)		—	—	—	—		—	—	—	—	
Male	20,406	(51.7)	301	(47.7)		—	—	—	—		—	—	—	—	
Year					0.52					<0.001					<0.001
2009	7,024	(17.8)	100	(15.9)		1,731	(19.2)	109	(8.7)		2,618	(19.8)	175	(13.4)	
2010	8,968	(22.7)	158	(25.0)		2,166	(24.1)	255	(20.3)		3,353	(25.4)	295	(22.6)	
2011	9,573	(24.3)	152	(24.1)		2,144	(23.8)	305	(24.2)		3,236	(24.5)	334	(25.6)	
2012	8,533	(21.6)	131	(20.8)		1,872	(20.8)	347	(27.6)		2,600	(19.7)	305	(23.4)	
2013	5,339	(13.5)	90	(14.3)		1,088	(12.1)	243	(19.3)		1,406	(10.6)	196	(15.0)	
Region					<0.001					<0.001					<0.001
Northeast	7,444	(18.9)	92	(14.6)		2,026	(22.5)	220	(17.5)		3,313	(25.1)	275	(21.1)	
North central	10,441	(26.5)	206	(32.7)		2,063	(22.9)	447	(35.5)		3,678	(27.8)	560	(42.9)	
South	14,331	(36.3)	233	(36.9)		2,928	(32.5)	331	(26.3)		3,444	(26.1)	251	(19.2)	
West	6,738	(17.1)	88	(14.0)		1,870	(20.8)	240	(19.1)		2,666	(20.2)	197	(15.1)	
Unknown	483	(1.2)	12	(1.9)		114	(1.3)	21	(1.7)		112	(0.9)	22	(1.7)	
Comorbidity[5]					<0.001					0.35					0.56
0	26,787	(67.9)	476	(75.4)		7,219	(80.2)	1,030	(81.8)		9,340	(70.7)	935	(71.7)	

	Colectomy[1,4]					Oophorectomy[2,4]					Hysterectomy[3,4]				
	No LMWH		Extended-Duration LMWH		*P-value*	No LMWH		Extended-Duration LMWH		*P-value*	No LMWH		Extended-Duration LMWH		*P-value*
1	8,469	(21.5)	123	(19.5)		1,341	(14.9)	176	(14.0)		2,920	(22.1)	286	(21.9)	
≥2	4,181	(10.6)	32	(5.1)		441	(4.9)	53	(4.2)		953	(7.2)	84	(6.4)	
Colectomy type					0.01					—					—
Open	28,726	(72.8)	489	(77.5)		—	—	—	—		—	—	—	—	
Laparoscopic	10,711	(27.2)	142	(22.5)		—	—	—	—		—	—	—	—	
Ooophorectomy type					—					<0.001					—
Cytoreduction	—	—	—	—		5,706	(63.4)	998	(79.3)		—	—	—	—	
No cytoreduction	—	—	—	—		3,295	(36.6)	261	(20.7)		—	—	—	—	
Hysterectomy type					—					—					<0.001
Abdominal	—	—	—	—		—	—	—	—		7,630	(57.8)	886	(67.9)	
Laparoscopic	—	—	—	—		—	—	—	—		3,508	(26.6)	262	(20.1)	
Robotic	—	—	—	—		—	—	—	—		1,847	(14.0)	155	(11.9)	
Vaginal	—	—	—	—		—	—	—	—		228	(1.7)	2	(0.2)	
Hospital complications															
Transfusion	2,231	(5.7)	27	(4.3)	0.14	443	(4.9)	59	(4.7)	0.72	301	(2.3)	39	(3.0)	0.11
Hemorrhage	535	(1.4)	8	(1.3)	0.85	163	(1.8)	15	(1.2)	0.11	198	(1.5)	7	(0.5)	0.005
Composite	2,658	(6.7)	34	(5.4)	0.18	587	(6.5)	73	(5.8)	0.33	469	(3.6)	44	(3.4)	0.74

[1] 511 patients who had VTE during the hospitalization were excluded (N=40,068).

[2] 196 patients who had VTE during the hospitalization were excluded (N=10,260).

[3] 122 patients who had VTE during the hospitalization were excluded (N=14,518).

[4] Postoperative LMWH is defined as daily dose of enoxaparin ≤ 40 mg and/or dalteparin ≤ 5000 IU within 1 week after hospitalization (starting from date of discharge), and no VTE diagnosis before LMWH claims. 171, 147, and 166 patients in the colectomy, oophorectomy and hysterectomy cohort who received therapeutic LMWH (Lovenox > 40 mg and/or Fragmin > 5000 IU) and/or who had diagnosis of VTE before LMWH were grouped as no for postoperative LMWH.

[5] Comorbidity defined as number of comorbid medical conditions as defined by the Charlson index.

Table 2

Multivariable logistic regression models of predictors of use of extended-duration prophylaxis low molecular weight heparin.

	Colectomy	Oophorectomy	Hysterectomy
Age			
≤34	Referent	Referent	Referent
35–44	0.61 (0.37–1.01)	1.21 (0.84–1.73)	0.69 (0.42–1.11)
45–54	0.73 (0.46–1.14)	1.43 (1.03–1.97) *	0.76 (0.49–1.17)
55–64	0.58 (0.37–0.91) *	1.47 (1.07–2.03) *	0.77 (0.50–1.18)
≥65	0.34 (0.22–0.54) *	1.29 (0.92–1.80)	0.68 (0.44–1.06)
Sex			
Female	Referent	—	—
Male	0.85 (0.73–1.00) *	—	—
Date			
2009	Referent	Referent	Referent
2010	1.34 (1.04–1.73) *	1.92 (1.52–2.43) *	1.39 (1.15–1.70) *
2011	1.24 (0.96–1.61)	2.37 (1.88–2.98) *	1.72 (1.42–2.08) *
2012	1.19 (0.91–1.56)	3.07 (2.45–3.86) *	1.96 (1.61–2.39) *
2013	1.33 (0.99–1.78)	3.72 (2.92–4.73) *	2.39 (1.92–2.97) *
Region			
Northeast	Referent	Referent	Referent
North central	1.65 (1.28–2.11) *	2.18 (1.83–2.60) *	1.84 (1.58–2.15) *
South	1.23 (0.96–1.57)	1.09 (0.91–1.31)	0.84 (0.70–1.00)
West	1.07 (0.79–1.43)	1.26 (1.03–1.53) *	0.92 (0.76–1.12)
Unknown	1.82 (0.99–3.35)	1.72 (1.04–2.82) *	2.38 (1.47–3.85) *
Comorbidity			
0	Referent	Referent	Referent
1	0.91 (0.74–1.12)	0.89 (0.75–1.06)	0.93 (0.80–1.07)
≥2	0.53 (0.37–0.76) *	0.83 (0.61–1.12)	0.84 (0.66–1.06)

	Colectomy	Oophorectomy	Hysterectomy
Colectomy type			
Open	Referent	—	—
Laparoscopic	0.77 (0.63–0.93)*	—	—
Oophorectomy type			
No cytoreduction	—	Referent	—
Cytoreduction	—	2.14 (1.85–2.48)*	—
Hysterectomy type			
Abdominal	—	—	Referent
Laparoscopic	—	—	0.66 (0.57–0.76)*
Robotic	—	—	0.64 (0.53–0.76)*
Vaginal	—	—	0.08 (0.02–0.31)*
Hospital complications (composite)			
No	Referent	Referent	Referent
Yes	0.86 (0.60–1.21)	0.82 (0.63–1.06)	0.84 (0.61–1.15)

* P<0.05

Table 3

Occurrence of venous thromboembolic disease during and after hospitalization and use of extended-duration low molecular weight heparin prophylaxis.

	In-hospital analysis			Post-discharge analysis				
		VTE in-hospital			VTE post-hospital*		LMWH post hospital*≠	
	N	N	(%)	N*	N	(%)	N	(%)
Colectomy								
Colectomy (all)	40,579	511	(1.3)	40,068	1,160	(2.9)	631	(1.6)
Open	29,647	432	(1.5)	29,215	922	(3.2)	489	(1.7)
Laparoscopic	10,932	79	(0.8)	10,853	238	(2.2)	142	(1.3)
Oophorectomy								
Oophorectomy (all)	10,456	196	(1.9)	10,260	376	(3.7)	1,259	(12.3)
No cytoreduction	6,836	132	(1.9)	6,704	267	(4.0)	998	(14.9)
Cytoreduction	3,620	64	(1.8)	3,556	109	(3.1)	261	(7.3)
Hysterectomy								
Hysterectomy (all)	14,640	122	(0.8)	14,518	307	(2.1)	1,305	(9.0)
Abdominal hysterectomy	8,623	107	(1.2)	8,516	227	(2.7)	886	(10.4)
Laparoscopic hysterectomy	3,779	9	(0.2)	3,770	54	(1.4)	262	(7.0)
Robotic-assisted hysterectomy	2,006	4	(0.2)	2,002	22	(1.1)	155	(7.7)
Vaginal hysterectomy	232	2	(0.9)	230	4	(1.7)	2	(0.9)

*511, 196, 122 patients who had VTE during the hospitalization were excluded from the colectomy (N=40,068), oophorectomy (N=10,260), and hysterectomy (N=14,518) cohorts, respectively.

≠LMWH post-discharge hospital is defined as daily dose of enoxaparin ≤ 40 mg and/or dalteparin ≤ 5000 IU within 1 week after hospitalization (starting from date of discharge), and no VTE diagnosis before LMWH. 171, 147, and 166 patients who received therapeutic LMWH (enoxaparin > 40 mg and/or dalteparin > 5000 IU) and/or who had diagnosis of VTE before LMWH were grouped as no for LMWH post hospital in colectomy, oophorectomy and hysterectomy cohort respectively.

Table 4

Perioperative outcomes stratified by receipt of extended-duration low molecular weight heparin prophylaxis.

	Colectomy			Oophorectomy			Hysterectomy		
	Events[5]	**(%)**	**Odds Ratio (95% CI)**	**Events**[5]	**(%)**	**Odds Ratio (95% CI)**	**Events**[5]	**(%)**	**Odds Ratio (95% CI)**
VTE[1]									
Extended-Duration LMWH									
No	1,146	(2.9)	Referent	329	(3.6)	Referent	283	(2.1)	Referent
Yes	20	(2.4)	0.84 (0.54–1.31)	62	(3.7)	1.01 (0.76–1.33)	33	(2.1)	0.96 (0.67–1.38)
Transfusion[2]									
Extended-Duration LMWH									
No	379	(1.0)	Referent	166	(2.0)	Referent	98	(0.8)	Referent
Yes	17	(2.2)	2.18 (1.34–3.56)*	31	(2.0)	1.00 (0.68–1.47)	11	(0.7)	0.90 (0.48–1.70)
Hemorrhage[3]									
Extended-Duration LMWH									
No	367	(1.0)	Referent	87	(1.0)	Referent	149	(1.2)	Referent
Yes	13	(1.6)	1.70 (0.97–2.97)	26	(1.6)	1.59 (1.02–2.46)*	19	(1.2)	1.05 (0.65–1.69)
Composite (transfusion, hemorrhage)[4]									
Extended-Duration LMWH									
No	664	(1.8)	Referent	233	(2.8)	Referent	224	(1.8)	Referent
Yes	30	(3.9)	2.20 (1.51–3.19)*	55	(3.4)	1.24 (0.92–1.68)	27	(1.8)	0.99 (0.66–1.48)

* *p-value* < 0.05. LMWH post hospital is defined as daily dose of enoxaparin ≤ 40 mg and/or dalteparin ≤ 5000 IU within 1 week after hospitalization (starting from date of discharge), and no VTE diagnosis before LMWH. 171, 147, and 166 patients who received therapeutic LMWH (Lovenox > 40 mg and/or Fragmin > 5000 IU) and/or who had diagnosis of VTE before LMWH were grouped as no for LMWH post hospital in the colectomy, oophorectomy, and hysterectomy cohort and included in deriving the propensity score. Age, sex, year, region, comorbidity, hysterectomy, oophorectomy, colectomy, and hospital complications (any of transfusion or hemorrhage) and all possible two-way interactions were included in the models for propensity score.

[1] Number of patients in the pseudocohort after applying IPTW is 40,258, 10,765, and 14,848 for colon, ovarian, and uterine cohort.

[2] 171, 147, and 166 patients who received therapeutic LMWH (enoxaparin > 40 mg and/or dalteparin > 5000 IU) and/or who had diagnosis of VTE before LMWH, and 2,245, 496, and 334 patients who had transfusion in hospital were excluded from the colectomy, oophorectomy, and hysterectomy cohort. Number of patients after applying IPTW is 37,838, 10,083, and 14,334 for the colectomy, oophorectomy, and hysterectomy cohortrespectively.

[3]171, 147, and 166 patients who received therapeutic LMWH (enoxaparin > 40 mg and/or dalteparin > 5000 IU) and/or who had diagnosis of VTE before LMWH, and 539, 175, and 200 patients who had hemorrhage in hospital were excluded from the colectomy, oophorectomy, and hysterectomy cohort. Number of patients after applying IPTW is 39,549, 10,435, and 14,479 for the colectomy, oophorectomy, and hysterectomy cohortrespectively.

[4]171, 147, and 166 patients who received therapeutic LMWH (enoxaparin > 40 mg and/or dalteparin > 5000 IU) and/or who had diagnosis of VTE before LMWH, and 2,677, 651, and 503 patients who had any complications in hospital were excluded from the colectomy, oophorectomy, and hysterectomy cohort. Number of patients after applying IPTW is 37,407, 9,926, and 14,165 for the colectomy, oophorectomy, and hysterectomy cohortrespectively.

[5]Number of events was weighted by the inverse probability of treatment weighting and rounded to integer.