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Beyond prophylaxis: Extended risk of venous thromboembolism following primary debulking surgery for ovarian cancer☆

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HIGHLIGHTS

- Overall, 1 in 7 women who underwent primary surgery for ovarian cancer developed a VTE within 6 months.
- Risk of VTE extends well beyond the recommended 28 day course of postoperative VTE prophylaxis.
- Developing an Accordion Grade ≥ 3 postop complication portended the highest 6 month risk of VTE (24%).

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ABSTRACT

Objective. To determine the incidence and risk factors for venous thromboembolism (VTE) within six months after primary debulking surgery (PDS) for epithelial ovarian cancer (EOC).

Methods. In a historical cohort, we estimated the cumulative incidence of clinically diagnosed VTE within 6 months among consecutive women who underwent PDS for EOC at a single institution from 1/1/2003 to 12/31/2011. We evaluated perioperative variables as potential risk factors of VTE within 6 months during the postoperative period using univariate and multivariable Cox proportional hazards models.

Results. Among 860 women without an immediate history (past 30 days) of a VTE, the cumulative incidence of VTE was 7.5% (95% CI, 5.7–9.3) by 30 days and 13.8% (95% CI, 11.4–16.2) by 6 months following surgery. Macroscopic residual disease (adjusted HR 1.99 [95% CI 1.35–2.94] vs microscopic), increasing estimated blood loss (1.25 [1.05–1.49] per doubling), longer hospital length of stay (3.00 [1.57–5.75]), and experiencing a cardiac event within 30 postoperative days (2.72 [1.55–4.80]) were independently associated with subsequent VTE within 6 months. In-hospital VTE prophylaxis included heterogeneous approaches; dual prophylaxis did not impact 30-day or 6-month VTE rates.

Conclusions. VTE occurred in 1 in 7 women with EOC within 6 months of PDS—a substantial risk of VTE that extends into the adjuvant chemotherapy period. Novel prophylactic measures should be explored in these women at high risk for VTE.

1. Introduction

Active cancer increases the risk of venous thromboembolism (VTE), which is associated with an increased risk of death. VTE ranks second only to the cancer itself as cause of death in cancer patients [1,2] and, among all solid tumors, ovarian cancer ranks within the top 3 malignancies associated with increased risk of pulmonary embolism (PE) [3]. Among gynecologic cancers, epithelial ovarian cancer (EOC) has been shown to be an independent predictor of VTE [4] with cumulative incidence of VTE ranging from 3.2% to 15% at 30 days and from 5.2% to 23% at 2 years following the cancer diagnosis [5–7]. Risk factors of VTE common in EOC include longer length of hospital stay, older age, higher body mass index (BMI), and higher surgical complexity [8–11]; however, most studies addressing VTE risk in women with EOC limit to advanced stage disease [8,10] or include patients with heterogeneous approaches to primary EOC treatment [12]. As such, the rate and risk factors for VTE in the setting of EOC vary within the published literature.

VTE risk assessment tools in the setting of cancer surgery as well as outpatient chemotherapy exist and have, in part, helped guide VTE

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prophylaxis. Based on the current American College of Chest Physicians (ACCP) guidelines, women who undergo surgery for EOC meet high-risk VTE criteria and are recommended to receive 28 days of low molecular weight heparin (LMWH) postoperatively [13]. Schmeler et al. demonstrated that administration of 28 days of prophylactic dose LMWH successfully resulted in a 78% reduction in the VTE rate within 30 days after gynecologic cancer surgery; however, the VTE rate at 90 days equalized between the group that received prophylaxis and the control group [14], suggesting the risk of VTE in gynecologic cancers extends beyond the duration of currently recommended postoperative prophylaxis. In the ambulatory chemotherapy setting, there is Level 1 evidence supporting the efficacy and safety of prophylactic dose LMWH [15,16]; however, given the heterogeneous population of solid tumors and low baseline rates of VTE, VTE prophylaxis during ambulatory chemotherapy for solid tumors is not supported by national guidelines. Nevertheless, retrospective data continues to emerge that the diagnosis and treatment of EOC carries with it a remarkable risk of VTE [8,17] and prospective trials of prophylactic LMWH during solid tumor chemotherapy have included only a fraction of women with EOC [15,16]. As such, we aimed to describe the risk of and risk factors for VTE throughout the 6-month postoperative period among women undergoing primary surgery (PS), including staging and/or debulking, for EOC.

2. Methods

We evaluated a historical cohort of women who underwent PDS for epithelial ovarian cancer, fallopian tube cancer (FTC), or primary peritoneal cancer (PPC) (all considered under the umbrella of EOC for this study) at Mayo Clinic, Rochester, MN, between January 1, 2003, and December 31, 2011. Cases were excluded if they received neoadjuvant chemotherapy, had a VTE within 30 days prior to surgery, had surgery for recurrent disease, and those whose primary cancer was not EOC. This study was approved by the Institutional Review Board.

Baseline patient demographics and risk factors for VTE identified in previous studies [8–11] were abstracted. These variables included patient age and BMI at the time of surgery, American Society of Anesthesiologists (ASA) score, personal history of non-ovarian cancer, smoking history (current/past vs. never), ascites, operative time, histology, International Federation of Gynecology and Obstetrics (FIGO) stage, operative complexity [18], residual disease, estimated blood loss, perioperative VTE prophylaxis type, hospital length of stay, preoperative comorbidities including previous VTE > 30 days before EOC diagnosis, and receipt of chemotherapy. In addition, postoperative complications within 30 days of surgery were also abstracted and graded according to the revised Accordion grading scale [19]. Non-VTE postoperative complications had to have occurred before the VTE to be considered as a potential risk factor in the analysis. Postoperative cardiac events were defined as any of the following: myocardial infarction, congestive heart failure, atrial fibrillation, atrial flutter, premature supraventricular tachycardia, or cardiopulmonary arrest.

Venous thromboembolism was defined as a clinically diagnosed DVT or PE. VTEs diagnosed within the Mayo system were verified by imaging (CT for pulmonary emboli and ultrasound for DVT) or autopsy. In addition to medical record review for VTE development, surveys were mailed to women or next of kin, if the woman was deceased, in an attempt to ensure at least 6 months of follow-up. Surveys collected information on VTE development, including timing and location of the VTE, if known. Outside medical summaries were used to confirm VTEs diagnosed at non-Mayo facilities when available. Screening for subclinical VTEs was not performed.

During the years of study, VTE prophylaxis was administered largely according to surgeon preference. Retrospectively, the in-hospital prophylaxis regimens were classified into 4 groups: (1) graduated compression stocking (GCSs) alone or no prophylaxis, (2) sequential compression devices (SCDs) ± GCSs, (3) SCDs ± GCSs + perioperative unfractionated heparin or LMWH and 4) other, which included in-hospital prophylaxis combinations that did not fit groups 1–3. GCSs and SCDs were placed before surgery and continued throughout the length of hospital stay. Among those who received prophylactic unfractionated heparin or LMWH, it was continued throughout the hospital stay. Dismissal on extended duration (28 days) prophylactic LMWH was at the discretion of the primary surgeon during the study period.

The primary outcome of interest was the development of clinically evident VTE within 6 months following PS for EOC. Data were summarized using standard descriptive statistics. Duration of follow-up was calculated from the date of surgery to the date of first VTE within six months; otherwise, for the patients without a VTE within six months, the patients' follow-up was censored at the date of their last relevant clinical follow-up or death if within six months or at six months and 1 day if the patient had more than six months of follow-up. The Kaplan-Meier method was used to estimate the cumulative incidence of VTE within six months. In addition, we estimated the cumulative incidence of VTE taking into account death as a competing risk using the methods outlined by Gooley et al. [20]. Baseline patient characteristics were evaluated for an association with VTE by fitting separate Cox proportional hazard regression models to model the cause-specific hazard. Associations were summarized using hazard ratios (HRs) and corresponding 95% confidence intervals (CIs). Non-linearity of age, body mass index, operative time, and estimated blood loss were evaluated in the univariate Cox models using penalized smoothing splines and the functional forms were graphically assessed; the assumption of a linear relationship was determined to be appropriate for each. Length of initial hospitalization was evaluated as a binary time-dependent covariate that denoted whether the patient was still in the hospital as part of the initial hospitalization. For the absence/presence of each type of postoperative complication within 30 days of surgery, the 0/1 indicator variable was coded as 0 if the postoperative complication occurred after the VTE diagnosis. Factors with a P value of <0.20 based on the univariate Cox regression models were considered in the multivariate model building using backwards and stepwise modeling; variables with a P value < 0.05 were retained in the final model. Because the timing of the receipt of chemotherapy could be altered if the patient was too ill or developed an early VTE, the association between receipt of chemotherapy (within 30 days vs. after 30 days) and subsequent VTE was evaluated using a landmark analysis. The landmark analysis was conditional on the subset of patients without VTE within the first 30 days following surgery and who had >30 days of follow-up. Analyses were performed using the SAS version 9.4 software package (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Patient characteristics and VTE events

Between January 1, 2003, and December 31, 2011, a total of 888 women underwent PS for EOC. Patient characteristics are summarized in Table 1. Among the 888, we excluded the 28 (3.2%) patients who were diagnosed with a pre-operative VTE within 30 days of surgery. Among the remaining 860 patients, 112 (13.0%) were diagnosed with a clinically evident VTE within 6 months from the date of surgery; 100 cases of VTE were confirmed via medical record review, while an additional 12 were identified via survey. Among the 112 VTEs, 44 (39.3%) were PEs, 51 (45.5%) were DVTs, 12 (10.7%) were both DVT and PE, and 5 (4.5%) reported via patient survey were unknown as to DVT, PE, or both. Regarding the time of events, 63 (56.3%) were diagnosed within 30 days after surgery and 49 (43.8%) after 30 days. Of the remaining 748 patients, 57 patients died within the first 6 months after their surgery and an additional 53 patients had <6 months of relevant clinical follow-up. Overall, the cumulative incidence of clinically evident VTE

Table 1
Patient characteristics.

Characteristic[a]	N = 860
Age (years), mean (SD)	63.4 (12.0)
BMI (kg/m^2), mean (SD)	28.3 (6.5)
ASA score, N (%)	
≤2	503 (58.5)
>2	357 (41.5)
Past medical history/comorbidities, N (%)	
Cardiac event[b]	64 (7.4)
Cardiovascular risk factor[c]	508 (59.1)
Diabetes	83 (9.7)
Anemia	162 (18.8)
Stroke	40 (4.7)
DVT/PE[e]	38 (4.4)
Asthma/COPD	87 (10.1)
Personal history of non-ovarian cancer, N (%)	108 (12.6)
Smoking history, N (%)	
Never	526 (61.2)
Ever (past/current)	334 (38.8)
FIGO stage, N (%)	
I/II	222 (25.8)
III/IV	638 (74.2)
Ascites, N (%)	448 (52.1)
Operative complexity, N (%)	
Low	147 (17.1)
Intermediate	502 (58.4)
High	211 (24.5)
Operative time (minutes), mean (SD)	257 (101)
Estimated blood loss (mL), mean (SD)	966 (802)
Residual disease, N (%)	
Microscopic	515 (59.9)
Yes, measurable (≤1 cm)	246 (28.6)
Yes, suboptimal or extensive (>1 cm)	99 (11.5)
Histology, N (%)	
Non-serous	237 (27.6)
Serous	623 (72.4)
Hospital length of stay (days), mean (SD)	8 (7)
In-hospital VTE prophylaxis, N (%)	
GCSs alone or no prophylaxis	101 (11.7)
Intraoperative and postoperative prophylaxis with SCDs ± GCSs	428 (49.8)
Perioperative dual prophylaxis with heparin and SCDs ± GCSs	308 (35.8)
Other	23 (2.7)
30-day postoperative complications, N (%)[f]	
Ileus	191 (22.2)
Bowel obstruction	23 (2.7)
Bowel leak	30 (3.5)
Surgical site infection	63 (7.3)
Intra-abdominal abscess	26 (3.0)
Upper respiratory infection	14 (1.6)
Urinary tract infection	63 (7.3)
Cardiac event[d]	43 (5.0)
CNS event	4 (0.5)
Return to operating room	68 (7.9)
Blood transfusion	416 (48.4)
Highest Accordion graded 30-day postoperative complication, N (%)[f]	
Grade ≤ 1	338 (39.3)
Grade 2	366 (42.6)
Grade ≥ 3	156 (18.1)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DVT/PE, deep vein thrombosis/pulmonary embolism; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; GCS, graduated compression stocking; SCD, sequential compression devices; VTE, venous thromboembolism.

[a] Complete data was available on all patient characteristics with the exception that BMI was missing for one patient.

[b] Cardiac event represents patients with a history of coronary artery disease, myocardial infarction, or other cardiac event.

[c] Cardiovascular risk factors represent patients with a history of hypertension, hyperlipidemia, or peripheral vascular disease.

[d] Cardiac event represents patients with a postoperative premature supraventricular tachycardia, atrial fibrillation, atrial flutter, myocardial infarction, congestive heart failure, or cardiopulmonary arrest.

[e] History of DVT/PE > 30 days prior to surgery.

[f] 30-day postoperative complications includes complications during initial hospitalization, complications during 30-day readmission, and postoperative blood transfusions; for those with a VTE following surgery, only complications that occurred prior to the VTE are considered.

at 30 days was 7.5% (95% CI, 5.7–9.3) and the incidence rose to 13.8% (95% CI, 11.4–16.2) by six months (Fig. 1). Taking into consideration the competing risk of death did not result in an appreciable difference in the cumulative incidence (7.4% at 30 days and 13.5% at 180 days). Of the 112 women diagnosed with a VTE after PS, four (3.6%) died as a result of PE, including two with a PE first diagnosed on autopsy.

3.2. Risk factors for diagnosis of VTE within 6 months of primary surgery

Perioperative factors associated with an increased risk in VTE identified using univariate analysis included increasing age, remote history of VTE, advanced FIGO stage, preoperative ascites, serous histology, the presence of residual disease, increasing operative time, high surgical complexity, higher estimated blood loss, and longer length of initial hospitalization (Table 2). Body mass index, ASA score, smoking status, and other past medical comorbidities were not identified as significantly associated with postoperative VTE on univariate analyses.

Among our cohort, 101 (11.7%) received graduated compression stocking (GCSs) alone or no prophylaxis, 428 (49.8%) received sequential compression devices (SCDs) ± GCSs, 308 (35.8%) received perioperative dual prophylaxis with heparin and SCDs ± GCSs, and 23 (2.7%) received in-hospital VTE prophylaxis that did not fit one of those three categories. There were no differences in the risk of VTE within the first 30 days (intraoperative and postoperative prophylaxis with SCDs ± GCSs [unadjusted HR 1.28 (95% CI 0.57, 2.86)]; perioperative dual prophylaxis with heparin and SCDs ± GCSs [0.77 (0.32, 1.85)]; other [0.60 (0.07, 4.85)] v. GCSs alone or no prophylaxis (reference), $P = 0.33$) or first six months ($P = 0.87$) (Table 2) among the different methods of in-hospital VTE prophylaxis.

There were 23 patients (2.7%) with stage IA or IB and grade 1 or 2 histology in which adjuvant chemotherapy was not indicated for cancer treatment and, as such, not administered. Chemotherapy was indicated but not received by 59 (6.9%) (12 patients too ill, 13 patients declined, 10 patients no plan for chemotherapy, and 24 patients died before chemotherapy), initiated within 30 days of surgery for 261 (30.3%), initiated >30 days after surgery for 331 (38.5%), received but timing not available for 74 (8.6%), and unknown if received for 112 (13.0%). Based on a landmark analysis of patients without VTE within the first 30 days after surgery, the cumulative incidence of having a VTE by 6 months after surgery was 8.4% (95% CI, 4.8–11.8%) and 7.4% (95% CI, 4.4–10.3%) among those who had chemotherapy initiated either within 30 days of surgery or after 30 days, respectively ($P = 0.67$).

Postoperative complications (within 30 days) identified via univariate analyses as associated with subsequent VTE diagnosis included bowel leak, occurrence of a cardiac event, urinary tract infection, return to the operating room (OR), and receipt of a blood transfusion (Table 1). Increasing severity of postoperative complication was associated with an increasing risk of subsequent VTE within 6 months (HR 1.80 [95% CI 1.14–2.85] for Grade 2, 2.90 [HR 95% CI 1.75–4.82] for Grade ≥ 3, $P < 0.001$, vs Grade ≤ 1) (Table 1). Furthermore, those with Grade ≤ 1 postoperative complications had a 30-day VTE rate of 4.3% (95% CI, 2.1–6.4) and 6-month VTE rate of 8.8% (95% CI, 5.6–11.8), those with a Grade 2 postoperative complication had a 30-day VTE rate of 8.3% (95% CI, 5.4–11.1) and a 6-month VTE rate of 14.8% (95% CI, 11.0–18.4), while those who had a Grade ≥ 3 postoperative complication had a 30-day VTE rate of 12.8% (95% CI, 7.3–18.1) and 6-month VTE rate of 23.7% (95% CI, 16.1–30.7) (Fig. 2).

3.3. Independent risk factors for VTE development

On multivariate analysis the same four variables were identified separately from both stepwise and backward variable selection methods. Macroscopic residual disease (adjusted HR 1.99 [95% CI 1.35–2.94] vs microscopic), increasing estimated blood loss (1.25 [1.05–1.49] per doubling), longer hospital length of stay (3.00 [1.57–5.75]), and

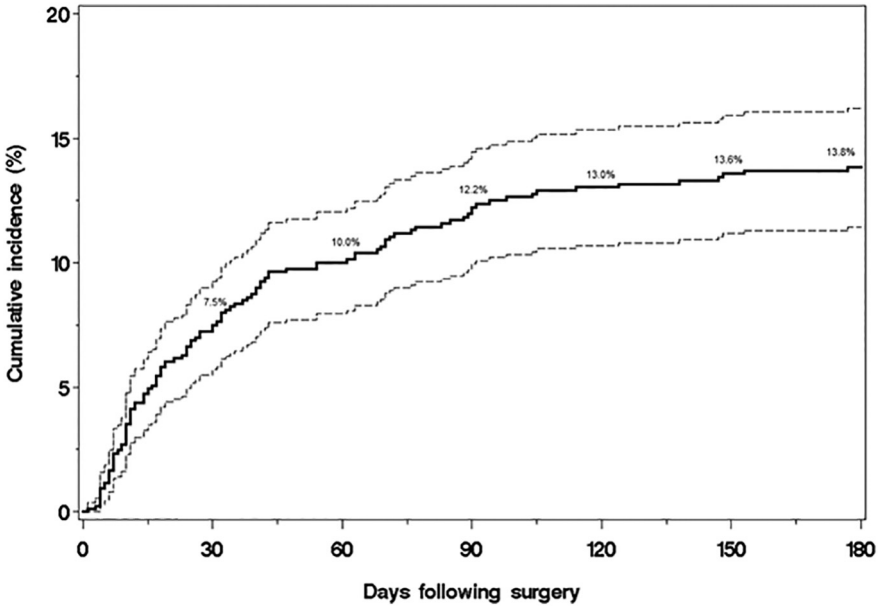

Fig. 1. Six-month cumulative incidence of VTE following primary surgery for ovarian cancer, estimated using the Kaplan-Meir method ignoring the competing risk of death. The dashed lines denote the 95% confidence limits.

experiencing a cardiac event within 30 days following surgery (2.75 [1.56–4.80]) were independently associated with diagnosis of VTE within six months after surgery (Table 3). Given that only 2 of the 222 patients with FIGO stage I/II disease had macroscopic residual disease and the median estimated blood loss was significant less in early versus advanced stage patients (median, 500 vs. 600 mL), we fit additional multivariable models stratified by stage which are presented in Table 3. Among the 222 patients with early stage disease there were just 13 diagnosed with a clinically evident VTE within 6 months from the date of surgery and therefore the 95% CIs for the adjusted hazard ratios are wide.

4. Discussion

VTE is a life-threatening complication and EOC ranks among the highest risk solid tumor cancers for VTE [3]. We found that 1 in 7 women with a new diagnosis of EOC who underwent primary surgery developed a VTE within their initial surgical and adjuvant chemotherapy course, a rate similar to the 12.5% VTE rate during adjuvant chemotherapy describe by Pant, et al. [8]. Notably, in our study nearly 4% of VTE events were fatal PEs. Among those who developed a severe (Grade ≥ 3) postoperative complication within 30 days, nearly 1 in 4 were subsequently diagnosed with a clinically evident VTE within 6 months of EOC diagnosis. This rate is similar to the findings of Greco, et al. in which the cumulative VTE incidence spanning the full course of primary EOC cancer care in women treated with neoadjuvant chemotherapy (NACT) was nearly 27% [17]. Additionally, the elevated risk is not relegated to patients with other complications. Even among patients who experienced a Grade 1 or no postoperative complication, 1 in 11 women developed a VTE within 6 months. Taken together, it is apparent that i) VTE risk is substantial in this exceptionally high-risk cancer, ii) VTE risk is not restricted to just the surgical episode, and iii) further interventions to reduce the risk of VTE over the course of active treatment are urgently needed. These considerations should also be factored into the management of patients receiving neoadjuvant chemotherapy or chemotherapy alone.

Women who undergo surgery for EOC are recommended to receive prophylactic dose LMWH for 28 days [13]. This recommendation is based on data from the ENOXACAN-II trial which demonstrated that among patients undergoing abdominal or pelvic cancer surgery, 28 days of prophylactic dose LMWH, compared to 1 week, significantly decreased the rate of VTE at both 31 days and 3 months [21]. However, women undergoing treatment for primary EOC represent a heterogeneous patient population treated with primary surgery followed by adjuvant chemotherapy, NACT and interval debulking, or chemotherapy alone. The ACCP, American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) guidelines all support 28 days of prophylactic LMWH following surgery [22,23,25] and adoption of VTE prophylaxis in gynecologic perioperative care appears to reduce the 30-day rate of VTE [14]. However, ASCO and NCCN do not recommend VTE prophylaxis during outpatient, ambulatory chemotherapy for any patients with solid tumors [23,25] despite Level 1 evidence demonstrating LMWH administered during ambulatory chemotherapy leads to a 50–65% reduction in VTE [15,16]. Unfortunately, the heterogeneity of tumor types and low percentage of women with EOC included in the PROTECHT and SAVE-ONCO trials translated to low baseline rates of VTE (<4% in each study) and a large number needed to treat to prevent each VTE [15,16]. The findings in our study as well as those of Pant, et al. [8] and Greco, et al. [17] suggest the baseline VTE risk among women with EOC receiving primary treatment, which ranges from 12 to 27%, far exceeds that of the mostly low-risk cohorts in PROTECHT and SAVE-ONCO.

Postoperative prophylaxis for 28 days also does not appear to be adequate in reducing the risk of VTE after surgery for gynecologic cancer as 36–83% of VTEs are diagnosed >4 weeks after surgery regardless of whether patients received 28 days of prophylaxis [4,14]. This current study focused specifically on women who underwent primary surgery for EOC and we found that 45% of VTEs occurred after the 28-day timeframe for extended postoperative prophylactic LMWH. Additionally, the cumulative incidence over six months continued to rise, with a slowing, but not plateau, of events before six months (Fig. 1). As such, the risk of VTE extends through the entire course of primary EOC treatment, including adjuvant chemotherapy. These findings further support the need for prospective studies to determine the optimal duration of VTE prophylaxis and optimal prophylactic agent(s) in women diagnosed with EOC.

This current study has several strengths including the large cohort size from a single institution with the same gynecologic oncology surgeons throughout the study period and a standardized surgical approach across surgeons. We also included patients with early stage

Table 2
Univariate analysis of perioperative characteristics as potential predictors of VTE within 6 months following PS for EOC.

Characteristic	Unadjusted HR (95% CI)	*P*
Age (years)[e]	1.20 (1.02, 1.41)	0.028
BMI (kg/m^2)[e]	1.08 (0.94, 1.24)	0.27
ASA score		0.12
≤2 (N = 503)	Reference	
>2 (N = 357)	1.35 (0.93, 1.95)	
Past medical history/comorbidities		
Cardiac event[a] (N = 64)	1.15 (0.58, 2.28)	0.68
Cardiovascular risk factor[b] (N = 508)	1.18 (0.81, 1.73)	0.39
Diabetes (N = 83)	0.75 (0.36, 1.53)	0.43
Anemia (N = 162)	0.92 (0.56, 1.50)	0.72
Stroke (N = 40)	0.57 (0.18, 1.79)	0.34
DVT/PE[d] (N = 38)	2.19 (1.11, 4.34)	0.024
Asthma/COPD (N = 87)	0.58 (0.27, 1.25)	0.17
Personal history of non-ovarian cancer (N = 108)	0.80 (0.44, 1.45)	0.46
Smoking history		0.15
Never (N = 526)	Reference	
Ever (past/current) (N = 334)	1.31 (0.90, 1.90)	
FIGO stage		<0.001
I/II (N = 222)	Reference	
III/IV (N = 638)	2.78 (1.56, 4.95)	
Ascites (N = 448)	1.91 (1.29, 2.82)	0.001
Operative complexity		0.009
Low (N = 147)	Reference	
Intermediate (N = 502)	1.27 (0.70, 2.32)	
High (N = 211)	2.18 (1.17, 4.07)	
Operative time (minutes)[e]	1.17 (1.06, 1.29)	0.003
Estimated blood loss (mL)[e]	1.34 (1.12, 1.59)	0.001
Residual disease		<0.001
Microscopic (N = 515)	Reference	
Yes, measurable (≤1 cm) (N = 246)	2.66 (1.78, 3.97)	
Yes, suboptimal or extensive (>1 cm) (N = 99)	1.94 (1.08, 3.48)	
Histology		0.028
Non-serous (N = 237)	Reference	
Serous (N = 623)	1.70 (1.06, 2.74)	
Hospital length of stay (days)[f]	4.72 (2.51, 8.87)	<0.001
In-hospital VTE prophylaxis		0.87
GCSs alone or no prophylaxis (N = 101)	Reference	
Intraoperative and postoperative prophylaxis with SCDs ± GCSs (N = 428)	0.98 (0.55, 1.77)	
Perioperative dual prophylaxis with heparin and SCDs ± GCSs (N = 308)	0.83 (0.45, 1.54)	
Other (N = 23)	0.90 (0.26, 3.14)	
30-day postoperative complications[g]		
Ileus (N = 191)	1.31 (0.86, 1.99)	0.21
Bowel obstruction (N = 23)	0.33 (0.05, 2.39)	0.27
Bowel leak (N = 30)	3.16 (1.65, 6.05)	<0.001
Surgical site infection (N = 63)	1.61 (0.88, 2.93)	0.12
Intra-abdominal abscess (N = 26)	1.84 (0.81, 4.19)	0.15
Upper respiratory infection (N = 14)	2.12 (0.67, 6.67)	0.20
Urinary tract infection (N = 63)	2.11 (1.23, 3.64)	0.007
Cardiac event[c] (N = 43)	3.71 (2.15, 6.39)	<0.001
CNS event (N = 4)	1.74 (0.24, 12.47)	0.58
Return to operating room (N = 68)	1.88 (1.09, 3.24)	0.02
Blood transfusion (N = 416)	1.85 (1.26, 2.70)	0.002
Highest Accordion graded 30-day postoperative complication[g]		<0.001
Grade ≤ 1 (N = 338)	Reference	
Grade 2 (N = 366)	1.80 (1.14, 2.85)	
Grade ≥ 3 (N = 156)	2.90 (1.75, 4.82)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; DVT/PE, deep vein thrombosis/pulmonary embolism; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; GCS, graduated compression stocking; HR; hazard ratio; PS, primary surgery; SCD, sequential compression devices; VTE, venous thromboembolism.

[a] Cardiac event represents patients with a history of coronary artery disease, myocardial infarction, or other cardiac event.

[b] Cardiovascular risk factors represent patients with a history of hypertension, hyperlipidemia, or peripheral vascular disease.

[c] Cardiac event represents patients with a postoperative premature supraventricular tachycardia, atrial fibrillation, atrial flutter, myocardial infarction, congestive heart failure, or cardiopulmonary arrest.

[d] History of DVT/PE > 30 days prior to surgery.

[e] Hazard ratio is per 10-year increase in age, 5-unit increase in BMI, 60-min increase in operative time, and per a doubling in estimated blood loss upon applying a logbase-2 transformation to the skewed blood loss distribution.

[f] Length of initial hospitalization was evaluated in a univariate Cox regression model as a binary time-dependent covariate that denoted whether or not the patient was still in the hospital as part of the initial hospitalization. The HR of 4.72 suggests that patients still in the hospital are at a 4.7-fold increased risk of a 6-month VTE compared to those no longer in the hospital.

[g] 30-day postoperative complications includes complications during initial hospitalization, complications during 30-day readmission, and postoperative blood transfusions; for those with a VTE following surgery, only complications that occurred prior to the VTE are considered.

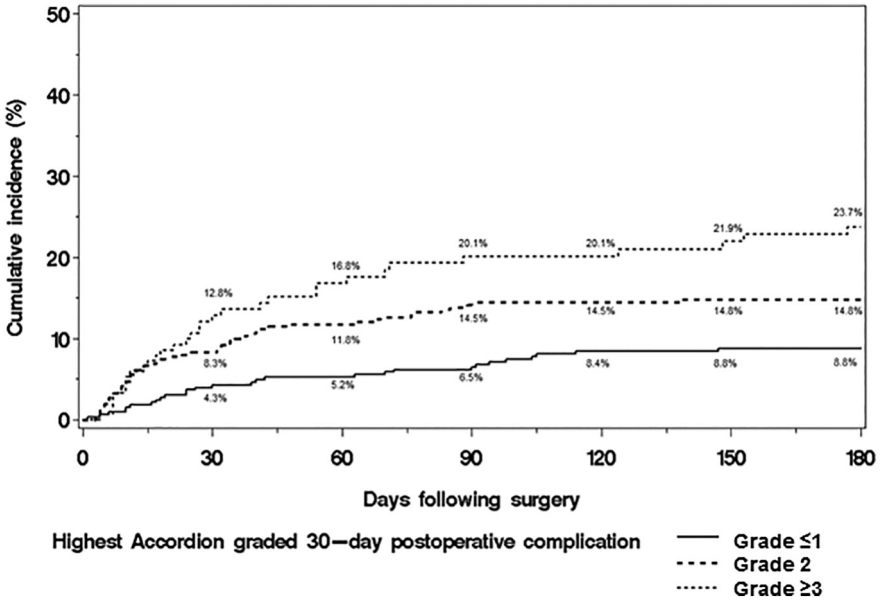

Fig. 2. Six-month cumulative incidence of VTE according to highest Accordion graded 30-day postoperative complication, estimated using the Kaplan-Meir method ignoring the competing risk of death.

Table 3
Multivariate analysis of potential predictors of VTE within 6 months following PS for EOC.

Characteristic	Based on all patients (N = 860)		Among patients with FIGO stage I/II (N = 222)		Among patients with FIGO stage III/IV (N = 638)	
	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Estimated blood loss (mL)[a]	1.25 (1.05, 1.49)	0.01	N/I		1.23 (1.02, 1.49)	0.03
Macroscopic residual disease[b]	1.99 (1.35, 2.94)	<0.001	N/I		1.85 (1.21, 2.82)	0.005
Hospital length of stay (days)[c]	3.00 (1.57, 5.75)	<0.001	21.79 (4.08, 116.37)	<0.001	2.44 (1.20, 4.97)	0.01
Cardiac event within 30 days of surgery[d]	2.72 (1.55, 4.80)	<0.001	7.47 (1.58, 35.31)	0.01	2.60 (1.42, 4.76)	0.002

Abbreviations: CI, confidence interval; EOC, epithelial ovarian cancer; HR, hazard ratio; N/I, not included; PS, primary surgery; VTE, venous thromboembolism.
[a] Hazard ratio is per doubling in estimated blood loss upon applying a logbase-2 transformation to the skewed distribution.
[b] Based on the findings from the univariate analysis in Table 2, the categories of "measurable ≤ 1 cm" and "suboptimal or extensive (>1 cm)" were collapsed into macroscopic and compared versus microscopic.
[c] Length of initial hospitalization was evaluated as a binary time-dependent covariate that denoted whether or not the patient was still in the hospital as part of the initial hospitalization. The HR of 3.00 suggests that patients still in the hospital are at a 3.0-fold increased risk of a 6-month VTE compared to those no longer in the hospital.
[d] Cardiac event represents patients with a postoperative premature supraventricular tachycardia, atrial fibrillation, atrial flutter, myocardial infarction, congestive heart failure, or cardiopulmonary arrest; for those with a VTE following surgery, only cardiac events that occurred prior to the VTE are considered.

disease, which allowed us to assess stage as a risk factor rather than assume that women with early stage EOC are at low risk for VTE development. Our study was limited in that we excluded patients who underwent surgery for recurrent disease as well as those who received NACT. While our findings are not generalizable to those groups of patients, the rate of VTE among those who receive NACT in prior investigations may be higher [17] than the overall rate of VTE in our primary debulking cohort. Our study period also occurred during a time when perioperative inpatient VTE prophylaxis was heterogeneous, although we did not observe differences in VTE rates among the prophylaxis approaches. The study period also occurred prior to our practice standardization of dismissal with 28 days of prophylactic dose LMWH which also added to the heterogeneity of the cohort. Additionally, since the study period, our practice has implemented an enhanced recovery after surgery program as well as bundled approaches to reduce transfusion and surgical site infection [26–28], all of which may impact postoperative VTE risk.

In summary, our findings add to the existing data showing that the high risk time frame for development of VTE in EOC spans the 18-week adjuvant chemotherapy period. With an increasing percent of patients receiving NACT, this implies a need to address this risk irrespective of surgical intervention. Further interventions to try to mitigate the risk of VTE across the spectrum of EOC care are needed.

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Author contributions

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Conflict of interest statement

The authors report that they have no conflicts of interest.

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