Risk of thrombosis and bleeding in gynecologic cancer surgery: systematic review and meta-analysis

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OBJECTIVE: This study aimed to provide procedure-specific estimates of the risk of symptomatic venous thromboembolism and major bleeding in the absence of thromboprophylaxis, following gynecologic cancer surgery.

DATA SOURCES: We conducted comprehensive searches on Embase, MEDLINE, Web of Science, and Google Scholar for observational studies. We also reviewed reference lists of eligible studies and review articles. We performed separate searches for randomized trials addressing effects of thromboprophylaxis and conducted a web-based survey on thromboprophylaxis practice.

STUDY ELIGIBILITY CRITERIA: Observational studies enrolling ≥50 adult patients undergoing gynecologic cancer surgery procedures reporting absolute incidence for at least 1 of the following were included: symptomatic pulmonary embolism, symptomatic deep vein thrombosis, symptomatic venous thromboembolism, bleeding requiring reintervention (including reexploration and angioembolization), bleeding leading to transfusion, or postoperative hemoglobin <70 g/L.

METHODS: Two reviewers independently assessed eligibility, performed data extraction, and evaluated risk of bias of eligible articles. We adjusted the reported estimates for thromboprophylaxis and length of follow-up and used the median value from studies to determine cumulative incidence at 4 weeks postsurgery stratified by patient venous thromboembolism risk factors. The GRADE approach was applied to rate evidence certainty.

RESULTS: We included 188 studies (398,167 patients) reporting on 37 gynecologic cancer surgery procedures. The evidence certainty was generally low to very low. Median symptomatic venous thromboembolism risk (in the absence of prophylaxis) was <1% in 13 of 37 (35%) procedures, 1% to 2% in 11 of 37 (30%), and >2.0% in 13 of 37 (35%). The risks of venous thromboembolism varied from 0.1% in low venous thromboembolism risk patients undergoing cervical conization to 33.5% in high venous thromboembolism risk patients undergoing pelvic exenteration. Estimates of bleeding requiring reintervention varied from <0.1% to 1.3%. Median risks of bleeding requiring reintervention were <1% in 22 of 29 (76%) and 1% to 2% in 7 of 29 (24%) procedures.

CONCLUSION: Venous thromboembolism reduction with thromboprophylaxis likely outweighs the increase in bleeding requiring reintervention in many gynecologic cancer procedures (eg, open surgery for ovarian cancer and pelvic exenteration). In some procedures (eg, laparoscopic total hysterectomy without lymphadenectomy), thromboembolism and bleeding risks are similar, and decisions depend on individual risk prediction and values and preferences regarding venous thromboembolism and bleeding.

Key words: baseline risk, bleeding, gynecologic surgery, modeling, reporting, risk of bias, thromboprophylaxis, venous thromboembolism

Introduction

Millions of gynecologic cancer procedures are performed worldwide every year.[1] Although the safety of surgery has improved, complications remain an important concern.[2–5] These complications include venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and nonfatal or fatal pulmonary embolism (PE), and major bleeding that can lead to transfusion, reintervention, or death.

Pharmacologic thromboprophylaxis reduces the risk of VTE but increases the risk of bleeding.[6] Prophylaxis, therefore, represents a trade-off between a reduction in VTE risk and an increase in bleeding risk. Considering the baseline VTE and bleeding risks is crucial.[7] High VTE risk and low bleeding risk favor pharmacologic prophylaxis. Conversely, when the bleeding risk is high and VTE risk low, pharmacologic prophylaxis likely results in net harm. When the risks are similar, the decision depends on individual risk prediction and patients' values and preferences.

The baseline risk for VTE in patients depends on multiple factors, including personal history of VTE, family history of VTE, hypercoagulable states, obesity, and age.[8,9] Although baseline risks vary also according to procedure, given that comprehensive systematic reviews on procedure-specific risks of VTE and bleeding in gynecologic surgeries have not been conducted, their magnitude remains uncertain.[10–13] At least in part because of uncertainty regarding baseline risk,

AJOG at a Glance

Why was this study conducted?

Postoperative pharmacologic thromboprophylaxis presents a trade-off that critically depends on venous thromboembolism (VTE) and bleeding risks. These risks vary between gynecologic cancer surgery procedures, but their magnitude remains uncertain.

Key findings

We established procedure-specific estimates of symptomatic VTE for 37 and bleeding requiring reintervention for 29 gynecologic cancer procedures. The risks of symptomatic VTE varied from 0.1% in low-VTE-risk patients undergoing cervical conization to 33.5% in high-VTE-risk patients undergoing pelvic exenteration. The bleeding requiring reintervention estimates varied between <0.1% and 1.3% across procedures. Evidence was typically of low or very low certainty.

What does this add to what is known?

The risk of symptomatic VTE varies substantially between gynecologic cancer procedures.

VTE risks are likely higher than those of bleeding requiring reintervention for most, but not all, gynecologic cancer procedures. Procedure-specific guidelines should rationalize thromboprophylaxis in gynecologic cancer surgery worldwide.

gynecologic surgery guidelines have not provided procedure-specific guidance for clinicians,[10,14–16] and practices vary substantially within and between countries.[17–20] We summarized the evidence regarding baseline risks of symptomatic VTE and major bleeding in gynecologic cancer surgery.

Objectives

This study aimed to provide procedure-specific risk estimates of VTE and major bleeding for gynecologic cancer surgery procedures.

Methods

We followed a previously registered (PROSPERO: CRD42021234119) and published study protocol[10] and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis Of Obser-

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vational Studies in Epidemiology) reporting guidance.[21−23] The Appendix, available online, presents more details on the methods.

Eligibility criteria

Through discussion and consensus building, experienced gynecologic surgeons and clinician-methodologists selected the most relevant gynecologic procedures for this study.[10] We included observational studies that enrolled a minimum of 50 adult patients undergoing a procedure for gynecologic cancer. Eligible studies reported the exact procedure/indication for the procedure and an absolute estimate of risk for at least 1 of the patient-important outcomes of interest: fatal PE, symptomatic PE, symptomatic DVT, symptomatic VTE, fatal bleeding, bleeding requiring reintervention, bleeding leading to transfusion, or postoperative hemoglobin <70 g/L. The Appendix and protocol[10] provide more details.

Information sources and search strategy

In collaboration with an experienced information specialist (R.J.C.), we conducted comprehensive searches without language restrictions in Embase, MEDLINE, Web of Science, and Google Scholar to identify contemporary articles from January 1, 2000 to November 25, 2020. After completing the screening for articles identified from the search, we searched for relevant articles from reference lists of eligible studies and relevant review articles.

We performed separate searches for randomized trials addressing the effects of pharmacologic and mechanical prophylaxis on risks of VTE and bleeding after surgery. The Appendix (pages 205−222) provides details of the search strategies. We also conducted a web-based survey of practicing abdominal surgeons to gather information on current (2010−present) and earlier (2000−2010) thromboprophylaxis practices (Appendix, pages 171−178).

Study selection and data extraction

We developed standardized forms with detailed instructions for screening of abstracts and full texts, assessment of risk of bias and evidence certainty, and data extraction. Independently and in duplicate, 2 methodologically trained screeners applied the forms to screen study reports for eligibility and extracted data. In the full-text screening, at least 1 of the screeners was a gynecologic surgeon. Because of the large number of studies, we conducted our data extraction in 2 phases. First, we extracted data regarding procedure characteristics (procedure name, number of patients for this procedure, outcomes reported) and assessed the risk of bias. When, for a target procedure, we identified ≥5 articles at low risk of bias with a total of ≥1000 patients, we excluded studies with moderate or high risk of bias. When this was not the case, but ≥10 articles with ≥2000 patients from studies proved at very low, low, or moderate risk of bias, we excluded studies with high risk of bias. In other situations, we used all studies irrespective of their risk of bias (details are included in the Appendix, pages 6−43). In the second phase (after exclusions based on risk of bias assessments), we collected information on patient characteristics and detailed data on outcomes reported. An adjudicator (lead author or clinician-methodologist) resolved disagreements on judgments at each stage. We contacted the original authors of each primary article for confirmation or correction of our consensus data extraction and asked for clarification regarding missing or unclear information.

Assessment of risk of bias

We developed an instrument to categorize the risk of bias of the studies (Appendix, pages 72−100).[8,10,24−28] For the risk of bias assessments, we evaluated each study according to 6 criteria: sampling of the study population, reporting of thromboprophylaxis, source of information, whether most patient recruitment years were earlier or later than 2010, clear specification of the duration of follow-up, and study type. For each domain, we judged studies to have either a high or low risk of bias. We classified studies according to risk of bias domains as follows: studies with no high risk of bias domains as very low, 1 high risk of bias domain as low, 2 high risk of bias domains as moderate, and ≥3 high risk of bias domains as high overall risk of bias.[10]

Data synthesis

Outcome measures

The primary outcomes were procedure-specific cumulative incidence of symptomatic VTE and major bleeding at 4 weeks (28 days) after surgery (in the absence of thromboprophylaxis). We used 3 separate major bleeding definitions[10,29]: (1) bleeding requiring reintervention (including reexploration and angioembolization), (2) bleeding leading to the transfusion of at least 1 unit of red blood cells, and (3) bleeding leading to postoperative hemoglobin <70 g/L (all analyzed separately). VTE included symptomatic PE, symptomatic DVT, or both in the same patient. We separately recorded symptomatic splanchnic vein thrombosis, including thrombosis of the portal, splenic, mesenteric, or suprahepatic veins (not included in the VTE estimate), and the incidence of fatal PE and fatal bleeding.

In addition to stratifying VTE and bleeding risk by procedure, we also classified the risk estimates by approach (such as open, laparoscopic, or robotic).

Calculating the risk of venous thromboembolism and bleeding for individual studies

Because our goal was to provide procedure-specific VTE and bleeding estimates in the absence of thromboprophylaxis, we adjusted the reported incidence of VTE and bleeding when patients received thromboprophylaxis, accounting for both pharmacologic and mechanical thromboprophylaxis. For patients who received prophylaxis, we multiplied the reported incidence (of VTE/bleeding) by the relative risk (RR) of thromboprophylaxis for the duration of prophylaxis use (Appendix, pages 176−179). Our updated meta-analyses informed the RR estimates of thromboprophylaxis (forest plots included in the Appendix, pages 190−204).[8,24,25,30−32] As suggested by the best available evidence, we adjusted as follows: (1) for unfractionated heparin and low-

molecular-weight heparin (LMWH) RR of 0.46 for VTE and 1.51 for bleeding; (2) for aspirin RR of 0.76 for VTE and 1.20 for bleeding; (3) for any mechanical prophylaxis RR 0.43 for VTE (no adjustment for bleeding); and (4) for combination therapy of pharmacologic plus mechanical (vs pharmacologic alone) RR of 0.59 for VTE (no adjustment for bleeding). We considered the effects of direct oral anticoagulants and of LMWH identical given that a recent systematic review and network meta-analysis of 68 randomized controlled trials (RCTs) (>45,000 patients) in noncardiac surgery reported that direct oral anticoagulants had similar effects on both VTE and bleeding as LMWH.[6] We had high certainty in estimates of the effects of pharmacologic prophylaxis but low certainty for mechanical prophylaxis (surrogate outcomes, very few patient-important events, unblinded patients and assessors). Finally, we inferred that preoperative thromboprophylaxis did not provide meaningful extra benefit or harm.[33] For studies that provided the number of DVT or PE events but not of VTE events, we modeled the number of VTE events using studies that had reported all DVT, PE, and VTE events (Appendix, page 179).

To estimate thromboprophylaxis use in studies with missing thromboprophylaxis information, we used previously published studies as follows: (1) if we had identified a study that reported the use of thromboprophylaxis from the same country/region, time period, and procedure, we used data from this study; and (2) if information for the same procedure from a similar time and place was unavailable, we used information from a large survey or population-based study on thromboprophylaxis practice. If there were no previously published articles, we used data from a web-based survey on the use of thromboprophylaxis to inform our decisions (Appendix, pages 171−178).

Modeling the risk of venous thromboembolism and bleeding over time

We used cumulative incidence estimates at postoperative day 28 for the procedure-stratified estimates of the incidence of VTE and major bleeding. For the studies that did not report VTE estimates using this interval, we used the model developed in a separate systematic review to adjust the absolute VTE risk from the day of surgery until 28 days after operation.[34] For the timing of VTE from 28 to 90 days postoperatively, we modeled estimates, as previously conducted,[8] using large-scale population-based studies.[35,36] Using information from the recent systematic review[34] and the older approach,[8] we developed an updated model for the time course of VTE from the day of surgery to 90 days after surgery (Appendix, pages 183−185). This model shows that for symptomatic VTEs occurring within 90 days after surgery, 31% occur by the first, 48% by the second, 65% by the fourth, and 86% by the eighth week after surgery.

For the studies that did not report bleeding estimates using this interval, to adjust the absolute bleeding risk by postoperative day, using data from the placebo arm of a large RCT,[30] we created a new model (Appendix, pages 186−187). This model of bleeding risk over time shows that 86% of the 30-day bleeding events happen during the first week after surgery.

Choosing the best estimates

We used the median value of incidence from studies to estimate the baseline risk of VTE and major bleeding.[10] Given that an incidence of 0.00% for VTE or major bleeding is implausible in gynecologic surgery, when the median estimate was 0.00% and the mean was not 0.00%, we used the mean rather than the median. If no studies reported on the incidence for a particular procedure, we sometimes used an estimate from the most similar procedure (Appendix, pages 6−43). Finally, we estimated the case fatality rates by dividing the number of fatal PE events by the number of symptomatic VTE events using studies that provided both estimates (Appendix, page 182). We used a similar approach to estimate the case fatality for major bleeding. We estimated the fatal VTE and fatal major bleeding risks for procedures by taking case fatality rates of the overall reported risk of symptomatic events for the procedure.

Risk stratification

Stratifying the risk estimates according to patient risk factors

After assessing the procedure-specific baseline risk of VTE, we used a method described earlier to stratify the risk by patient-related risk factors into 3 groups[8,10,24,25] (Table 1). Eligible studies and the previous literature provided the estimates of the proportion of patients with each of these risk factors, allowing estimates of the extent of overlap and thus calculation of estimates for each VTE patient risk group (Appendix, pages 180−181). Our search did not reveal studies demonstrating convincing and replicable risk factors for bleeding.[10] Therefore, we did not stratify bleeding risk by patient-specific factors.

Assessment of evidence certainty

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to rate the evidence certainty (also known as quality of evidence) (Table 2).[37,38] The

TABLE 1
Model for risk of venous thromboembolism according to patient risk factors

Risk group	Risk factors	Risk
Low risk	No risk factors	1×
Medium risk	Any of the following: Age ≥75 y Body mass index ≥35 VTE in first-degree relative (parent, full sibling, or child)	2×
High risk	Previous VTE Patients with any combination of ≥2 risk factors	4×

VTE, venous thromboembolism.

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TABLE 2
Principles for the use of GRADE for assessment of evidence of risk of complications, and examples of GRADE use for estimating evidence of the risk of venous thromboembolism and bleeding requiring reintervention after gynecologic surgery

Domain	General principles in GRADE	Criteria for judgment in our study	Examples
Risk of bias	The risk of misleading results is higher if studies are fiawed in their design or conduct	If we had at least 1000 patients and 5 articles for a target procedure in studies with very low or low risk of bias, we excluded studies with moderate and high risk of bias. If we had at least 2000 patients and 10 articles for a certain target procedure in studies with very low, low, or moderate risk of bias, we excluded studies with high risk of bias. In other situations, we used all studies irrespective of their risk of bias. We always rated down for risk of bias if most patients (>50%) came from studies at high risk of bias. We did not rate down for risk of bias if most patients (>50%) came from studies at low or very low risk of bias.	For risk of VTE after open surgery for ovarian cancer, we identified 4 low risk of bias and 14 moderate risk of bias studies with 101,238 patients. We used only low and moderate risk of bias studies in our analysis. For risk of bleeding requiring reintervention after open surgery for ovarian cancer, we identified 1 low (298 patients), 2 moderate (673 patients), and 9 high (1355 patients) risk of bias studies. We used all studies in the analysis. We did not rate down VTE estimates for risk of bias (all studies low or moderate risk of bias). We rated down bleeding requiring reintervention estimates for risk of bias (>50% of patients from high risk of bias studies).
Inconsistency	Widely differing estimates (heterogeneity or variability in results) across studies is called inconsistency. If point estimates vary substantially across studies, or confidence intervals show little or no overlap, certainty is likely to be rated down for inconsistency. Variability may arise from differences in populations or methodology.	We rated down for inconsistency if >10% of the studies had at least a 3% difference from the median value of the VTE and the study with either the highest or lowest rate of VTE, or at least a 1.5% difference from the median value of bleeding requiring reintervention. However, if removing outliers did not materially change the median estimate, we considered not rating down for inconsistency.	18 studies for open surgery for ovarian cancer had median VTE of 7.2%; the highest reported incidence was 18.2%, and the lowest 2.3%. Because >10% of the studies differed >3% from the median value, we rated down for inconsistency.
Indirectness	Evidence can be indirect in several ways. Indirectness may arise from differences in the population or outcome of interest between included studies.	We did not usually rate down for indirectness, as the eligible studies measured relevant outcomes in representative populations.	We did not have any studies providing estimates for bleeding requiring reintervention after laparoscopic supracervical hysterectomy for malignant disease. To estimate the risk, our expert panel considered the bleeding risk to be similar to that in minimally invasive total hysterectomy for malignant disease (0.2%). We considered the risk of bleeding requiring reintervention to be 0.2% after laparoscopic supracervical hysterectomy and rated down twice for indirectness.
Imprecision	When studies have wide confidence intervals, typically because of relatively few patients or events, imprecision occurs.	We rated down by 1 level if studies included <1000 patients and by 2 levels if they included <200 patients.	Open pelvic exenteration had 2 studies with 154 patients for bleeding requiring reintervention. We rated down twice for imprecision.

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TABLE 2
Principles for the use of GRADE for assessment of evidence of risk of complications, and examples of GRADE use for estimating evidence of the risk of venous thromboembolism and bleeding requiring reintervention after gynecologic surgery *(continued)*

Domain	General principles in GRADE	Criteria for judgment in our study	Examples
Evidence certainty/quality of evidence	In studies of the risk of prognosis (including complications), a body of observational evidence begins as high certainty. However, several categories of limitations may reduce evidence certainty, including risk of bias, imprecision, inconsistency, and indirectness. Evidence certainty options include high, moderate, low, and very low.	Although certainty in a body of evidence from observational studies addressing a question of prognosis begins as high certainty, we rated down to moderate owing to uncertainties in our models of the risk of VTE and bleeding over time and in our model of patient risk strata. We then further rated down as described for the other 4 categories.	For open surgery for ovarian cancer, for VTE estimation, we rated down for uncertainty in our models and inconsistency, resulting in low evidence certainty. For bleeding requiring reintervention, we rated down for uncertainty in our models, risk of bias, and inconsistency, resulting in very low evidence certainty.

GRADE, Grading of Recommendations Assessment, Development and Evaluation; *VTE*, venous thromboembolism.

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certainty of a body of evidence from observational studies addressing a question of prognosis begins as high certainty[25,39]; for all procedures and all outcomes, we rated down to moderate certainty owing to uncertainties in our modeling of risk of VTE and bleeding over time, patient risk strata, and the relative effect of thromboprophylaxis regimens.[10,34] When identified, we further rated down the evidence certainty for risk of bias, inconsistency of results, indirectness of evidence, or imprecision. In the case of very low risk of VTE, even multiplying the risk by 5 times would lead to low (or very low) risk of VTE and would not change decisions on pharmacologic thromboprophylaxis. Therefore, we considered rating up the evidence certainty, if: (1) risk of VTE was ≤0.1% for all VTE risk strata, and (2) evidence certainty was low or moderate.

Results

Study selection

For estimation of baseline risks for VTE and major bleeding, the search found 6926 titles and abstracts, reviews from the search identified an additional 179, and reference lists of the eligible studies identified an additional 451, totaling 7556 titles and abstracts. After screening titles and abstracts, we judged 1608 as warranting a full-text review (flowchart in the Appendix, page 225) and screened 1190 full texts (135 were not retrieved and 283 were not journal articles). After excluding ineligible studies, evaluating the risk of bias, and evaluating the number of articles and patients for a procedure, we included 188 studies including 398,167 patients (Appendix, page 225). These studies informed on 37 gynecologic cancer surgery procedures. Of the 188 studies, authors from 20 of them (11%) provided the additional information requested, corrected errors, or confirmed the accuracy of our data extraction (Appendix, pages 44–166, 237).

Study and patient characteristics

Table 3 presents the characteristics of the studies for each procedure (details in the Appendix, pages 44–82). The median age of the study population was 62 years for total hysterectomy, 48 years for radical hysterectomy, 31 years for trachelectomy, 61 years for surgery for ovarian cancer, and 55 years for pelvic exenteration. The median size of the study population (across the procedures) was 3347 patients. Out of the 188 studies, 5 (3%) were multinational, 52 (28%) multicenter in 1 country, 124 (66%) single-center, and 7 (4%) were single-surgeon. The sources of information for the studies were prospective data collection in 32 (17%), retrospective chart review in 135 (72%), and administrative databases in 21 (11%).

Risk of bias of included studies and quality of evidence

Of the included 188 studies, 19 had low, 36 moderate, and 133 high risk of bias. The evidence certainty was moderate for VTE estimates in laparoscopic total hysterectomy with or without lymphadenectomy, estimates of bleeding requiring reintervention in robotic total hysterectomy with lymphadenectomy, and estimates of bleeding leading to transfusion in laparoscopic total hysterectomy without lymphadenectomy. For other procedures, evidence certainty was low or very low for all outcomes. (Tables 4 and 5; Appendix).

Thromboprophylaxis use

Of the 188 included studies, only 27 (14%) reported both the use and duration of pharmacologic thromboprophylaxis (Table 3). Among studies that provided this information, thromboprophylaxis use was longest for laparoscopic total hysterectomy and pelvic exenteration (both median, 21 days; 3 studies for laparoscopic total hysterectomy and 1 for pelvic exenteration providing information), and shortest for primary surgery for ovarian cancer and open radical hysterectomy with lymphadenectomy (for both: 5 studies reporting a median of 8 days). Seventeen (9%) of the studies reported the use of pharmacologic

TABLE 3
Summary of the studies included by procedure

Procedure	Studies (patients)	Recruitment period	Median patient age (y)	Median length of stay (d)	Malignant (%)	Studies reporting pharmacologic TPX, n (%)[a]	Pharmacologic TPX (%)[b]
Cervical conization, vaginal	1 (1359)	2004–2010	39	NR	9	0	
Trachelectomy, any, vaginal	6 (623)	1986–2012	31	4	100	0	
Trachelectomy, any, open	5 (412)	1998–2013	31	11	100	0	
Surgery for ovarian cancer, any, minimally invasive	2 (4885)	2001–2012	56	2	100	0	
Surgery for ovarian cancer, any, open	40 (106,035)	1983–2017	61	9	100	13 (33)	100
Interval surgery for ovarian cancer, open	4 (603)	2000–2015	56	NR	100	1 (25)	100
Primary surgery for ovarian cancer, open	22 (13,472)	1983–2015	61	9	100	5 (23)	100
Pelvic exenteration, any, open	14 (1689)	1982–2018	55	19	100	4 (29)	100
Vulvectomy for cancer, any	2 (618)	1998–2012	68	NR	100	0	
Radical vulvectomy, with lymphadenectomy, open	2 (250)	1974–2000	69	20	100	1 (50)	100
Total hysterectomy, without lymphadenectomy, laparoscopic	1 (2049)	2015–2016	62	NR	100	0	
Total hysterectomy, with lymphadenectomy, minimally invasive	21 (6708)	1990–2016	62	2	100	9 (43)	100
Total hysterectomy, with lymphadenectomy, laparoscopic	15 (4784)	1990–2016	62	2	100	5 (33)	100
Total hysterectomy, with lymphadenectomy, robotic	8 (2001)	1998–2016	62	2	100	5 (63)	100
Total hysterectomy, with lymphadenectomy, open	9 (12,732)	1997–2016	58	8	100	3 (33)	100
Radical hysterectomy, with lymphadenectomy, minimally invasive	29 (7632)	1994–2019	47	8	100	7 (24)	100
Radical hysterectomy, with lymphadenectomy, laparoscopic	20 (3952)	1986–2018	47	10	100	4 (20)	100
Radical hysterectomy, with lymphadenectomy, robotic	15 (2742)	1998–2019	49	2	100	4 (27)	100
Radical hysterectomy, with lymphadenectomy, open	24 (19,846)	1988–2017	47	6	100	4 (17)	100

Age is given as the median of the means or medians reported in the individual studies. The length of stay is given as the median of the means or median lengths reported in the individual studies.

NR, not reported; *TPX*, thromboprophylaxis.

[a] Studies included that reported number of patients receiving pharmacologic TPX; [b] The median proportion of patients receiving pharmacologic TPX in the individual studies reporting the use is reported. Not all procedures are included in this table; the Appendix includes complete characteristics for all procedures.

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thromboprophylaxis without reporting its duration. Use of mechanical prophylaxis was reported in 36 (19%) studies, of which 17 studies also reported duration. The Appendix (pages 101–128 and 171–178) provides details on reported prophylaxis and estimated prophylaxis durations for procedures.

TABLE 4
The 4-week postoperative risk of symptomatic venous thromboembolism and bleeding requiring reintervention after gynecologic cancer surgery except hysterectomy

Procedure	Outcome	Patients (studies)	Estimate (%)	Patient VTE risk strata	
			Median	Low - Medium - High (%)	Evidence certainty
Cervical conization, vaginal	VTE	1359 (1)	0.1	0.1 - 0.2 - 0.3	Low
	Bleeding requiring reintervention	0 (0)	NR		
Trachelectomy, radical, with laparoscopic pelvic lymphadenectomy, vaginal	VTE	226 (2)	2.8	2.5 - 5.0 - 10.1	Very low
	Bleeding requiring reintervention	267 (3)	1.2		Very low
Trachelectomy, radical, with pelvic lymphadenectomy, open	VTE	156 (1)	2.0	1.8 - 3.6 - 7.2	Very low
	Bleeding requiring reintervention	192 (3)	0.4		Very low
Surgery for ovarian cancer, any, minimally invasive	VTE	4885 (2)	2.9	2.1 - 4.3 - 8.6	Low
	Bleeding requiring reintervention	0 (0)	NR		
Surgery for ovarian cancer, any, open	VTE	101,238 (18)	7.2	5.2 - 10.4 - 20.8	Low
	Bleeding requiring reintervention	2326 (12)	1.2		Very low
Interval surgery for ovarian cancer, open	VTE	603 (4)	9.1	7.0 - 14 - 28	Very low
	Bleeding requiring reintervention	56 (1)	<0.1		Very low
Primary surgery for ovarian cancer, open	VTE	12,867 (20)	7.2	5.1 - 10.2 - 20.4	Very low
	Bleeding requiring reintervention	937 (4)	1.1		Very low
Pelvic exenteration, any, open	VTE	1327 (10)	11.1	8.4 - 16.8 - 33.6	Very low
	Bleeding requiring reintervention	154 (2)	0.7		Very low
Vulvectomy for cancer, any[a]	VTE	618 (2)	3.2	1.9 - 3.9 - 7.7	Low
	Bleeding requiring reintervention	0 (0)	NR		
Radical vulvectomy, with lymphadenectomy, open	VTE	250 (2)	12.2	7.2 - 14.3 - 28.6	Very low
	Bleeding requiring reintervention	0 (0)	NR		

In the Estimate column, we present median estimates for VTE and bleeding requiring reintervention by procedure. In the Patient VTE risk strata column, we present VTE estimates by patient VTE risk strata. In the VTE risk strata, patients with no VTE risk factor are classified as having low VTE risk, patients with 1 VTE risk factor (age ≥75 years, body mass index ≥35, or history of VTE in parents, full siblings, or children) as having medium VTE risk, and patients with 2 risk factors and those with personal history of VTE as having high VTE risk. "Minimally invasive" refers to laparoscopic or robotic procedures.

NR, not reported; *VTE*, venous thromboembolism.

[a] Including radical and nonradical vulvectomies. The Appendix includes more details (pages 6–16).

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TABLE 5
The 4-week postoperative risk of symptomatic venous thromboembolism and bleeding requiring reintervention after hysterectomy for malignant disease

Procedure	Outcome	Patients (studies)	Estimate (%)	Patient VTE risk strata	Evidence certainty
			Median	Low - Medium - High (%)	
Total hysterectomy, without lymphadenectomy, laparoscopic	VTE	2049 (1)	0.3	0.3 - 0.5 - 1.1	Moderate
	Bleeding requiring reintervention	1793 (8)	0.3		Very low
Total hysterectomy, with lymphadenectomy, minimally invasive	VTE	6708 (21)	1.2	0.9 - 1.8 - 3.5	Moderate
	Bleeding requiring reintervention	2057 (8)	0.1		Low
Total hysterectomy, with lymphadenectomy, laparoscopic	VTE	4734 (14)	1.2	0.9 - 1.8 - 3.6	Moderate
	Bleeding requiring reintervention	588 (3)	0.3		Low
Total hysterectomy, with lymphadenectomy, robotic	VTE	2001 (8)	1.6	1.2 - 2.4 - 4.7	Low
	Bleeding requiring reintervention	1413 (5)	0.2		Moderate
Total hysterectomy, with lymphadenectomy, open	VTE	12,569 (8)	3.2	2.5 - 5.0 - 9.9	Very low
	Bleeding requiring reintervention	106 (1)	<0.1		Very low
Radical hysterectomy, with lymphadenectomy, minimally invasive	VTE	6930 (21)	1.5	1.2 - 2.5 - 4.9	Very low
	Bleeding requiring reintervention	947 (4)	0.5		Very low
Radical hysterectomy, with lymphadenectomy, laparoscopic	VTE	3531 (16)	1.7	1.4 - 2.8 - 5.5	Very low
	Bleeding requiring reintervention	765 (3)	1.3		Very low
Radical hysterectomy, with lymphadenectomy, robotic	VTE	2511 (11)	0.5	0.4 - 0.8 - 1.6	Very low
	Bleeding requiring reintervention	177 (3)	0.3		Very low
Radical hysterectomy, with lymphadenectomy, open	VTE	10,227 (18)	3.2	2.7 - 5.3 - 10.6	Low
	Bleeding requiring reintervention	2888 (6)	0.5		Very low

In the Estimate column, we present median estimates for VTE and bleeding requiring reintervention by procedure. In the Patient VTE risk strata column, we present VTE estimates by patient VTE risk strata. In the VTE risk strata, patients with no VTE risk factor are classified as having low VTE risk, patients with 1 VTE risk factor (age ≥75 years, body mass index ≥35, or history of VTE in parents, full siblings, or children) as having medium VTE risk, and patients with 2 risk factors and those with personal history of VTE as having high VTE risk. The Appendix includes more details (pages 17–43).

NR, not reported; *VTE*, venous thromboembolism.

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The 4-week postoperative risk of symptomatic venous thromboembolism and major bleeding

Tables 4 and 5 and the Appendix (pages 6–43) present symptomatic VTE and major bleeding estimates by procedure, approach, and indication. We established VTE risks for 37, risks of bleeding requiring reintervention for 29, risks of bleeding leading to transfusion for 34, and risks of bleeding leading to hemoglobin <70 g/L for 2 procedures. Median symptomatic VTE risk (in the absence of prophylaxis) was <1% in 13 of 37 (35%) procedures, 1% to 2% in 11 of 37 (30%),

and >2.0% in 13 of 37 (35%). Median risk of bleeding requiring reintervention was <1% in 22 of 29 (76%) and 1% to 2% in 7 of 29 (24%) procedures. Median risk of bleeding leading to transfusion was <2% in 15 of 34 (44%), 2% to 4% in 5 of 34 (15%), and >4% in 14 of 34 (41%) procedures. The risks of VTE varied from a median of 0.1% (across risk groups 0.1%−0.3%; low-certainty evidence) for patients undergoing cervical conization to a median of 11.1% (across risk groups 8.4%−33.6%; very low certainty) for patients undergoing open pelvic exenteration. The risks of bleeding requiring reintervention varied from a median of <0.1% (interval surgery for ovarian cancer; very low certainty) to 1.3% (laparoscopic radical hysterectomy with lymphadenectomy; very low certainty). The median risk of bleeding leading to transfusion varied from 0.9% for robotic radical hysterectomy with lymphadenectomy (very low certainty) to 32.9% for open primary surgery for ovarian cancer (very low certainty) (the Appendix Evidence profiles [pages 6−43] provide all estimates for bleeding leading to transfusion).

Ovarian cancer surgery had 2.9% risk of symptomatic VTE when performed minimally invasively and 7.2% when performed with the open approach (both low certainty) (Table 4). Risk of bleeding requiring reintervention was 1.2% after open surgery for ovarian cancer (very low certainty; we did not find estimates for minimally invasive surgery). Risk of bleeding leading to transfusion was 3.2% with the minimally invasive approach (very low certainty) and 11.9% with the open approach (low certainty) (Appendix, pages 10−13).

Depending on the patient risk group, the incidence of VTE in vulvectomies varied from 1.9% in low-VTE-risk patients undergoing (any) vulvectomy for cancer (low certainty), to 28.6% for high-VTE-risk patients undergoing radical vulvectomy (very low certainty) (Table 4). We could not derive any bleeding estimates for vulvectomies. We identified very-low-certainty evidence suggesting higher incidence of postoperative VTE compared with that of bleeding requiring reintervention in radical trachelectomies (vaginal: 2.8% symptomatic VTE vs 1.2% bleeding requiring reintervention; open: 2.0% vs 0.4%) (Table 4).

The risk of VTE varied in hysterectomies for malignant diseases (Table 5), with laparoscopic total hysterectomy without lymphadenectomy having the lowest VTE risk (median, 0.3%; 0.3%−1.1% across risk groups; moderate certainty; patients with stage I−III endometrial cancer) and open radical hysterectomy with lymphadenectomy having the highest risk (median, 3.2%; 2.7%−10.6% across risk groups; low certainty). The risk of bleeding requiring reintervention varied from <0.1% (open total hysterectomy with lymphadenectomy; very low certainty) to 1.3% (laparoscopic radical hysterectomy with lymphadenectomy; very low certainty).

Reported median symptomatic splanchnic vein thrombosis risk was <0.1% for all the 13 procedures for which we had estimates (ie, laparoscopic, robotic, and open radical hysterectomy with lymphadenectomy). Two studies reported the proportion of patients with postoperative hemoglobin <70 g/L for 2 procedures: minimally invasive hysterectomy (0.6%) and robotic radical hysterectomy with lymphadenectomy (1.2%). The Appendix (pages 6−43) provides more details, including all risk estimates for bleeding leading to transfusion, symptomatic splanchnic vein thrombosis, fatal major bleeding, and fatal VTE.

Comment

Principal findings

This systematic review provides a summary of the relevant literature and estimates of procedure-specific baseline risks of symptomatic VTE and major bleeding outcomes in gynecologic cancer surgery. Risks of VTE vary substantially by procedure. These important findings—visually summarized in an infographic in the Figure—should inform clinicians, patients, guideline panelists, and policymakers in making optimal treatment decisions and guideline recommendations regarding the use of thromboprophylaxis in gynecologic cancer surgery.

We identified moderate-certainty evidence for minimally invasive total hysterectomies, but for other procedures the quality of the studies was often low, and evidence proved particularly scarce for bleeding requiring reintervention. Consequently, we have mostly low or very low certainty in our VTE and major bleeding estimates.

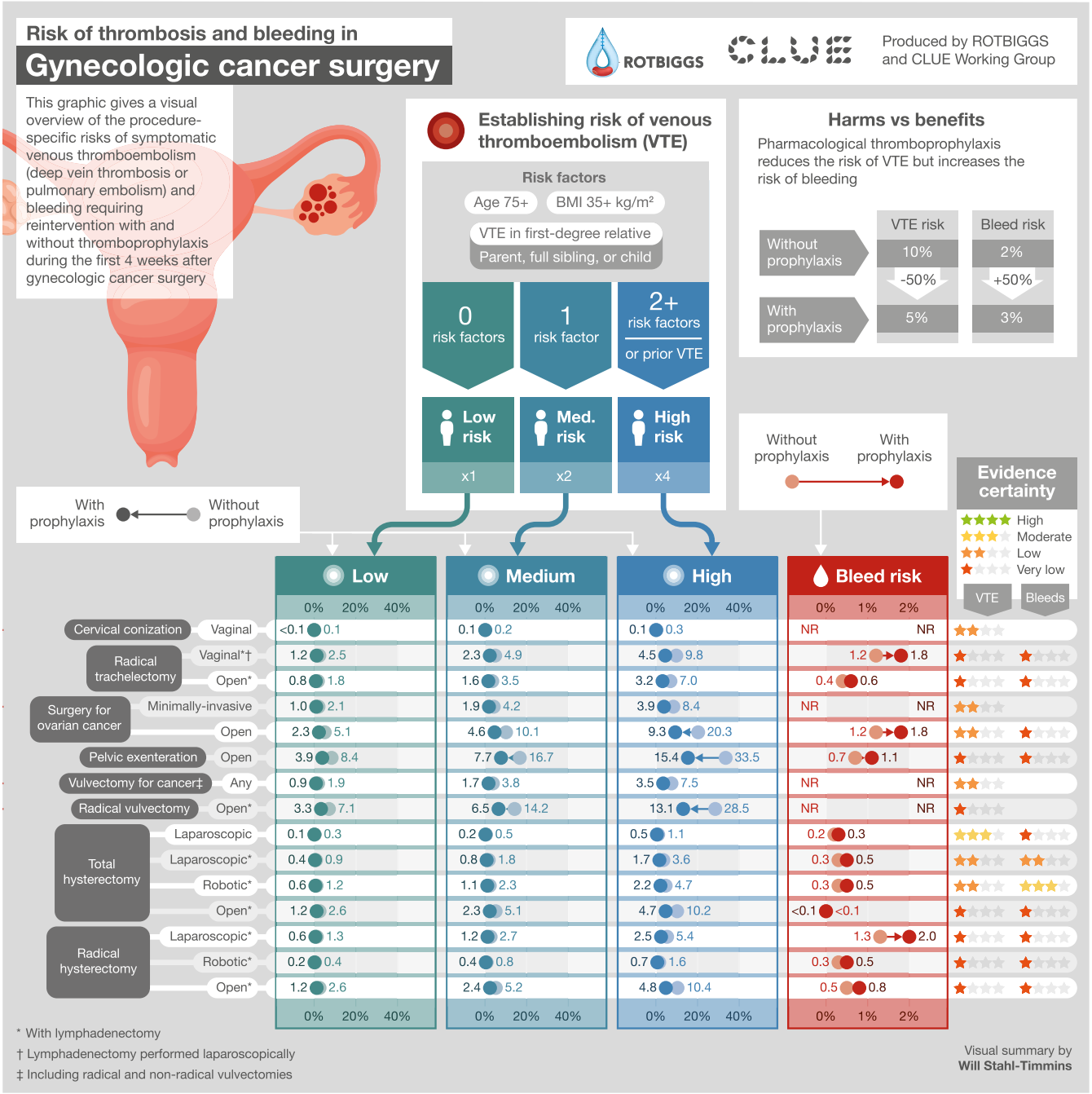
The VTE risks varied by procedure and patient risk factors (age, body mass index, and history of VTE). In all patient risk strata, VTE occurred more frequently than bleeding requiring reintervention in both open ovarian cancer surgery (VTE risk of 5.2% for low-risk patients vs bleeding risk of 1.2%) and total hysterectomies with lymphadenectomy (minimally invasive: 0.9% vs 0.1%; open: 2.5% vs <0.1%). This was also the case for trachelectomies (1.8%−2.5% VTE risk for low-risk patients vs 0.4%−1.2% bleeding risk), pelvic exenteration (8.4% vs 0.7%), and radical hysterectomies (minimally invasive: 1.2% vs 0.5%; open: 2.7% vs 0.5%). For laparoscopic total hysterectomy without lymphadenectomy in low-risk patients, the incidences of VTE and bleeding requiring reintervention were similar and low (0.3% vs 0.3%). For cervical conization, the VTE risk was very low (median, 0.1%; 0.1%−0.3% across risk groups), but authors did not report bleeding estimates.

The major bleeding outcomes of our systematic review included bleeding requiring reintervention, bleeding leading to transfusion, and bleeding leading to postoperative hemoglobin <70 g/L, with the latter two shown to be independently associated with mortality.[29] In our study, risks of bleeding leading to transfusion were generally considerably higher than risks of bleeding requiring reintervention. We found very little evidence on the incidence of postoperative hemoglobin <70 g/L. The Appendix (pages 6−43) includes all of these estimates.

Comparison with existing literature

To the best of our knowledge, there has been no comprehensive systematic summary of procedure-specific VTE risks in gynecologic cancer surgery in

FIGURE
Procedure-specific risks of VTE and bleeding after gynecologic cancer surgery



BMI, body mass index.

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previous literature. One earlier systematic review examined the incidence of VTE in patients with ovarian cancer.[40] The review reported a 3.0% VTE risk in epithelial ovarian cancer surgery. However, they did not adjust for follow-up times or thromboprophylaxis regimens, both of which have important effects on VTE risk and vary substantially between studies. We found low-certainty evidence suggesting that surgery for ovarian cancer has a median symptomatic VTE baseline risk of 7.2% with an open approach and 2.9% with a minimally invasive approach during 28

days after surgery (the earlier review did not separate different approaches). We identified a median duration of pharmacologic prophylaxis of 10 days and of mechanical prophylaxis of 8 days after open ovarian cancer surgery. Taking this estimated use of thromboprophylaxis into account, the earlier unadjusted risk of 3.0% would have led to an actual baseline risk of 5.2%—an estimate between our estimates of 7.2% for the open and 2.9% for the minimally invasive approach. The earlier review did not provide any estimates for major bleeding.[40] In our review, the baseline risk of bleeding requiring reintervention was 1.2% and of bleeding leading to transfusion 11.9%.

Another earlier systematic review and meta-analysis examined complications after minimally invasive total hysterectomies in obese (body mass index $\geq$30) patients with endometrial cancer.[41] Authors found a VTE risk of 0.5% for laparoscopic (14 studies, 1015 patients, 5 events) and 0.5% for robotic hysterectomy (5 studies, 388 patients, 2 events).[41] We provided VTE and bleeding estimates not only for obese, but also for nonobese patients. In our study, for medium-VTE-risk patients (such as obese patients) undergoing hysterectomy for cancer, 28-day symptomatic VTE risk was 0.5% for laparoscopic total hysterectomy without lymphadenectomy (1 study, 2049 patients, 7 events), 1.8% for laparoscopic total hysterectomy with lymphadenectomy (14 studies, 4734 patients, 56 events), and 2.4% for robotic total hysterectomy with lymphadenectomy (8 studies, 2001 patients, 24 events). Explanations for the higher VTE estimates in our study (relative to the earlier study[41]) include that the earlier systematic review did not adjust for the use of thromboprophylaxis or follow-up duration. In addition, we provided VTE estimates separately for hysterectomies with and without lymphadenectomy.

Strengths and limitations

The strengths of our systematic review include the very comprehensive and procedure-specific search and screening of over 7500 abstracts and 1000 full texts; rigorous adherence to methodological standards including duplicate assessment of eligibility, risk of bias, and data extraction; and use of the GRADE approach for the assessment of evidence certainty.[37,38] We also considered patient risk factors and developed models for timing of VTE[34] and bleeding that considered the length of follow-up and the use of thromboprophylaxis (Appendix, pages 176−179, 189−190, 192−199). To guide our estimates of the incidence of VTE and bleeding when information on the use of thromboprophylaxis was not otherwise available, we performed an international survey on thromboprophylaxis use among practicing surgeons (Appendix, pages 180−186).

There are also limitations to this study. Given the lack of established indexing for observational studies, we may have missed some relevant studies (including those not published in English). Many studies failed to provide estimates separately for procedures or approaches. Gynecologic cancer surgery is complex, and therefore the extent of some of our procedures may have varied, and possible concomitant procedures may have affected the risks (eg, in surgery for ovarian cancer). Most studies did not provide information regarding thromboprophylaxis use (type, duration) or follow-up duration, and were therefore considered to have moderate or high risk of bias. Given that there are few randomized trials addressing thromboprophylaxis in gynecologic surgery, our estimates of the relative effect of thromboprophylaxis on risks of VTE and bleeding are mainly based on trials conducted among general surgery patients. Consequently, despite using advanced clinical epidemiologic methods in collaboration with expert gynecology surgeon-scientists, many of our best estimates are based on low or very low evidence certainty, reflecting limitations in the available evidence.

Conclusions and implications

We performed a systematic review to provide estimates of absolute risks of symptomatic VTE and major bleeding in gynecologic surgeries for cancer. Our results suggest that for many gynecologic cancer procedures and patients, thromboprophylaxis results in a substantial reduction in VTE, with only modest increases in bleeding requiring reintervention. For some procedures and patient risk groups, the trade-off between risks and benefits is more balanced (eg, low-risk patients for total laparoscopic hysterectomy with or without lymphadenectomy). In these situations, the decision regarding thromboprophylaxis depends on individual risk prediction and values and preferences regarding VTE and bleeding consequences.

There is no clear consensus regarding the optimal use of thromboprophylaxis in gynecologic cancer surgery, which is reflected in the wide variation in practice.[17−19] When estimates clearly suggest that VTE prevention causes more benefit than harm, or vice versa, such variation is problematic.

We found that risks of VTE and bleeding substantially vary across procedures. We also identified areas in which the evidence is completely absent or of low or very low quality, such as bleeding requiring reintervention estimates for radical hysterectomies and surgery for ovarian cancer. Areas where evidence is missing should therefore be a research priority. Our review outlines methodological standards for such procedure-specific research, including characterization and documentation of patient populations, follow-up times, thromboprophylaxis use (including type and duration), and patient-important VTE and bleeding outcomes.

This systematic review provides estimates of absolute risks of symptomatic VTE and major bleeding in gynecologic cancer surgery. Summaries presented in this article on gynecologic cancer surgery and the accompanying article[42] on gynecologic noncancer surgery have important implications worldwide, and implementation of our findings should reduce problematic variation in practice internationally. ■

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