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

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OBJECTIVE: This study aimed to provide procedure-specific estimates of the risk for symptomatic venous thromboembolism and major bleeding in noncancer gynecologic surgeries.

DATA SOURCES: We conducted comprehensive searches on Embase, MEDLINE, Web of Science, and Google Scholar. Furthermore, we performed separate searches for randomized trials that addressed the effects of thromboprophylaxis.

STUDY ELIGIBILITY CRITERIA: Eligible studies were observational studies that enrolled ≥50 adult patients who underwent noncancer gynecologic surgery procedures and that reported the absolute incidence of at least 1 of the following: symptomatic pulmonary embolism, symptomatic deep vein thrombosis, symptomatic venous thromboembolism, bleeding that required reintervention (including re-exploration and angioembolization), bleeding that led to transfusion, or postoperative hemoglobin level <70 g/L.

METHODS: A teams of 2 reviewers independently assessed eligibility, performed data extraction, and evaluated the risk of bias of the eligible articles. We adjusted the reported estimates for thromboprophylaxis and length of follow-up and used the median value from studies to determine the cumulative incidence at 4 weeks postsurgery stratified by patient venous thromboembolism risk factors and used the Grading of Recommendations Assessment, Development and Evaluation approach to rate the evidence certainty.

RESULTS: We included 131 studies (1,741,519 patients) that reported venous thromboembolism risk estimates for 50 gynecologic noncancer procedures and bleeding requiring reintervention estimates for 35 procedures. The evidence certainty was generally moderate or low for venous thromboembolism and low or very low for bleeding requiring reintervention. The risk for symptomatic venous thromboembolism varied from a median of <0.1% for several procedures (eg, transvaginal oocyte retrieval) to 1.5% for others (eg, minimally invasive sacrocolpopexy with hysterectomy, 1.2%−4.6% across patient venous thromboembolism risk groups). Venous thromboembolism risk was <0.5% for 30 (60%) of the procedures; 0.5% to 1.0% for 10 (20%) procedures; and >1.0% for 10 (20%) procedures. The risk for bleeding the require reintervention varied from <0.1% (transvaginal oocyte retrieval) to 4.0% (open myomectomy). The bleeding requiring reintervention risk was <0.5% in 17 (49%) procedures, 0.5% to 1.0% for 12 (34%) procedures, and >1.0% in 6 (17%) procedures.

CONCLUSION: The risk for venous thromboembolism in gynecologic noncancer surgery varied between procedures and patients. Venous thromboembolism risks exceeded the bleeding risks only among selected patients and procedures. Although most of the evidence is of low certainty, the results nevertheless provide a compelling rationale for restricting pharmacologic thromboprophylaxis to a minority of patients who undergo gynecologic noncancer procedures.

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

Introduction

The volume of noncancer gynecologic surgery is substantial. Each year, surgeons perform approximately 450,000 hysterectomies for benign reasons in the United States alone.[1] Although surgery has evolved and patient safety has improved,[2−4] complications—including venous thromboembolism (VTE) and major bleeding—remain an important concern.[5,6] VTE encompasses deep vein thrombosis (DVT) and nonfatal or fatal pulmonary embolism (PE).[7] Major bleeding can lead to transfusion, reintervention, or even death.[8]

Pharmacologic thromboprophylaxis decreases the risk for symptomatic VTE by approximately 50% but, at the same time, increases the risk for bleeding by a similar percentage.[9−12] The decision to use pharmacologic prophylaxis therefore represents a tradeoff between a reduction in the risk for VTE and an increase in the risk for bleeding. The risks for VTE and bleeding among patients who do not receive prophylaxis (baseline risk) represent crucial information when making

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Why was this study conducted?

Postoperative pharmacologic thromboprophylaxis presents a trade-off that depends on both the risk for a venous thromboembolism (VTE) and the risk for bleeding. These risks vary among procedures, but the magnitude remains uncertain in noncancer gynecologic surgery.

Key findings

We established procedure-specific estimates of symptomatic VTE for 50 noncancer gynecologic procedures and of bleeding requiring reintervention for 35 procedures. The risks for symptomatic VTE varied from <0.1% in transvaginal oocyte retrieval to 4.6% for high-risk patients who underwent minimally-invasive sacrocolpopexy with hysterectomy. The estimates for bleeding that required reintervention varied from <0.1% to 4.0% among procedures. Evidence was typically moderate or low for VTE with low or very low certainty for major bleeding.

What does this add to what is known?

The symptomatic VTE risk varied substantially among noncancer gynecologic procedures. The risk for VTE was generally low for noncancer gynecologic surgery but varied among approaches, procedures, and patients. Procedure-specific guidelines would rationalize thromboprophylaxis in noncancer gynecologic surgery worldwide.

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this tradeoff decision.[13] When the baseline risk for VTE is high and the risk for bleeding low, pharmacologic prophylaxis offers net benefit. However, when bleeding risk is high and VTE risk low, pharmacologic prophylaxis likely leads to net harm. When the risks are similar, the decision depends on individual risk prediction and the importance patients place on avoiding VTE vs avoiding bleeding (values and preferences).[13]

Guidelines have not provided patient- and procedure-specific guidance on thromboprophylaxis in noncancer gynecology procedures[9,14] at least in part because of the uncertainty in the procedure-specific baseline risks for VTE and bleeding. The absence of procedure-specific recommendations (tailored to the particular procedure) contributes to substantial practice variation within and between centers and countries.[15,16] To provide procedure-specific baseline risk estimates of VTE and major bleeding for gynecologic surgery procedures and to thus fill this knowledge gap, we conducted a series of systematic reviews and meta-analyses.[14] In this article, we focused on noncancer gynecologic surgery procedures. Another article will focus on surgical procedures in gynecologic cancer.[17]

Objectives

We conducted a systematic review to provide procedure-specific risk estimates of symptomatic VTE and major bleeding for gynecologic surgery procedures for benign conditions.

Materials and Methods

We followed our previously registered (International Prospective Register of Systematic Reviews identifier, CRD42 021234119) and published study protocol[14] and the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) reporting guidance.[18−20] The Cochrane Handbook provided guidance on methods for conducting our systematic review.[21] A protocol article[14] and the Appendix provide more information about the study methodology; in this section, we briefly summarize the methods.

Eligibility criteria

We included observational studies that involved ≥50 patients who underwent noncancer gynecologic surgery procedures[14] and that reported absolute estimates of risk for one or more outcomes of interest, including fatal PE, symptomatic PE, symptomatic DVT, symptomatic VTE, symptomatic splanchnic vein thrombosis (thrombosis of the portal, splenic, mesenteric, and/or suprahepatic veins), fatal bleeding, bleeding requiring reintervention (including exploration and angioembolization), bleeding leading to transfusion, and bleeding leading to postoperative hemoglobin level of <70 g/L.

Observational studies of unselected patients are likely the best sources of estimates for baseline risks of VTE and bleeding.[14] We did not include randomized trials because although these provide the most trustworthy evidence when evaluating treatment efficacy, they often feature selected patient demographics that may not be representative of routine practice and therefore may not accurately reflect baseline risks.

Information sources and search strategy

We conducted comprehensive searches, developed with the aid of an information specialist (R.J.C.), on Embase, MEDLINE, Web of Science, and Google Scholar from January 1, 2000, to November 25, 2020, without language restrictions. We also reviewed the reference lists of the eligible studies and review articles. In addition, this review included separate searches for randomized trials that addressed the effects of pharmacologic and mechanical prophylaxis on the risks for VTE and bleeding after surgery,[14,17] and to gather information on the current (years 2010−present) and earlier (years 2000−2010) thromboprophylaxis practices, a web-based survey of practicing gynecologic surgeons was conducted.

Study selection and data extraction

Pairs of reviewers independently assessed the eligibility and risk of bias and extracted the data on the procedure and patient characteristics and outcomes. We developed an instrument to categorize studies as having a very low, low, moderate, or high risk of bias.[14] When we identified a sufficient number of patients and articles with low or moderate risk of bias for a given procedure, we used risk of bias as an eligibility criterion.[17] Finally, we sent our consensus data extraction to the authors of all the original articles for confirmation or correction and asked for clarification regarding unclear or missing information.

Assessment of risk of bias and evidence certainty

Because the criteria for risk of bias are still poorly established for studies on the baseline risks in comparison with studies on therapeutic interventions, through iterative discussion and consensus-building and informed by the previous literature,[22−26] we developed an instrument to assess the risk of bias.[14] The tool evaluated each study according to 6 domains, namely (1) sampling of the study population, (2) reporting of thromboprophylaxis, (3) source of information, (4) whether most patient recruitment years were earlier or later than 2010, (5) clear specification on the duration of follow-up, and (6) study type (Appendix, page 75). For each individual domain, we determined if studies had a high or low risk of bias and then classified studies as follows: studies with no high-risk domains were classified as having a very low risk of bias; studies with 1 high-risk domain were classified as being at low risk of bias; studies with 2 high-risk domains were classified as having moderate risk of bias; and studies with ≥3 high-risk domains were classified as having a high risk of bias.[14]

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the evidence certainty (quality of evidence; Appendix, page 143).[27,28] The evidence certainty from observational studies that addressed a question of prognosis (such as risk for VTE or bleeding after surgery) was classified as high. We always rated down the classification to moderate certainty because of underlying uncertainty in our modeling

(thromboprophylaxis use, adjusting follow-up time, patient risk strata). When identified, we further rated down the classification for risk of bias, inconsistency, indirectness, or imprecision (details in the Appendix, page 143).[17]

Data synthesis

Outcome measures

The primary outcomes were the cumulative incidence, in the absence of thromboprophylaxis, of symptomatic VTE and major bleeding within 4 weeks (28 days) of the surgery. Symptomatic VTE included symptomatic PE, symptomatic DVT, or both in the same patient. We used 3 major bleeding definitions, namely (1) bleeding that required reintervention (including exploration and angioembolization), (2) bleeding that led to transfusion of red blood cells, and (3) bleeding that led to a postoperative hemoglobin level below 70 g/L. We also separately measured the incidence of symptomatic splanchnic vein thrombosis and recorded the incidence of fatal PE and fatal bleeding. We analyzed all outcomes separately for each type of procedure and approach.

Calculating the risk of venous thromboembolism and bleeding

As described in an accompanying paper,[17] in calculating the VTE and bleeding risk, we adjusted the analyses for the use of mechanical and pharmacologic thromboprophylaxis (Appendix, pages 145–148). For studies that did not report on the use of thromboprophylaxis, we estimated the thromboprophylaxis use (Appendix, pages 149–156). For each study, to arrive at cumulative risk estimates at 4 weeks postsurgery, we adjusted the VTE and major bleeding risks for the duration of follow-up (Appendix, page 161–169)[29] using the median value of estimates from eligible studies for the procedure as the best single estimate.[14,17] We used median values from eligible studies instead of pooled estimates because of the potential of larger studies' idiosyncratic factors and methodologic quality to substantially influence the estimates.[14] After assessing the procedure-specific baseline risk for VTE, we stratified the risk based on patient-related risk factors[30–38] using a method previously described (Table 1).[9–11]

Results

Study selection

For the baseline risk estimation, we identified 6926 titles and abstracts from the search, 179 from reviews found in the search, and 451 from the reference list of eligible studies, totaling 7556 titles and abstracts (flow chart in the Appendix, page 206). We reviewed the full text of 1608 article of which 131 (including 1,741,519 patients) that reported on 50 gynecologic noncancer surgery procedures proved to be eligible. Table 2 and the Appendix (pages 7-75) provide details, including the number of articles and patients per procedure. Of the 131 studies, 19 (15%) authors provided additional information, corrected errors, or confirmed the accuracy of the data (Appendix, pages 7–57 and 217).

Study and patient characteristics

Table 2 presents the characteristics of the studies for each procedure (additional details are provided in the Appendix, pages 58–75). For the baseline risk of VTE and bleeding, the median of the mean or median ages was 37 years for myomectomy, 24 years for management of adnexal torsion, 59 years for sacrocolpopexy, and 49 years for total hysterectomy. The median size of the study population across the procedures was 7011 patients.

Risk of bias of included studies and evidence certainty

Of the 131 studies, we determined that none was at very low risk of bias, 12 (9%) were at low risk of bias, 29 (22%) were at moderate risk, and 90 (69%) were at high risk of bias (Appendix, pages 76–94). The evidence certainty was generally moderate or low for VTE and low or very low for bleeding that require reintervention and bleeding that lead to transfusion (Tables 3–5 and the Appendix, pages 7–57).

Thromboprophylaxis use

Of the 131 studies, 10 (8%) reported both the use and duration of pharmacologic thromboprophylaxis, 10 (8%) reported only the proportion of patients who received pharmacologic prophylaxis, and 111 (85%) studies did not report on pharmacologic prophylaxis. The reported duration of pharmacologic thromboprophylaxis varied. The median was 0 days after vaginal sling surgery for incontinence, surgical abortion, and uterine artery embolization; 3 days after vaginal pelvic organ prolapse surgery with hysterectomy and vaginal total hysterectomy; 4 days after open total hysterectomy; 10 days after minimally invasive deep endometriosis surgery; and 21 days after minimally invasive sacrocolpopexy. Authors reported the use of mechanical prophylaxis in 14 (11%) studies, 3 of which also reported the duration. Table 2 and the Appendix (pages 95–112 and 149–156) provide details on prophylaxis, survey results on

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 one of the following: Age ≥75 y Body mass index ≥35 VTE in 1st degree relative (parent, full sibling, or child)	2×
High risk	Previous VTE or Patients with any combination of 2 or more risk factors	4×

VTE, venous thromboembolism.

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TABLE 2
Summary of studies included by procedure

Procedure	Studies (patients)	Recruitment period	Median patient age (y)	Median length of stay (d)	Number of studies reporting pharmacologic TPX, n (%)[a]	Pharmacologic TPX (%)[b]
Deep endometriosis surgery, with or without bowel surgery, minimally invasive[c]	14 (2915)	1987–2019	33	5	3 (21)	100
Deep endometriosis surgery, with bowel surgery, minimally invasive	8 (1686)	2000–2017	32	7	2 (25)	100
Deep endometriosis surgery, without bowel surgery, minimally invasive	3 (1113)	2004–2019	37	NR	0	—
Myomectomy, minimally invasive	9 (7055)	1995–2016	37	1	0	—
Myomectomy, open	6 (5064)	1995–2016	37	3	0	—
Management of adnexal torsion, laparoscopic	3 (20,722)	1987–2015	24	2	0	—
Management of adnexal torsion, open	1 (68,580)	2001–2015	31	2	0	—
Oophorectomy, minimally invasive	1 (52,599)	2009–2012	NR	NR	0	—
Salpingo-oophorectomy, minimally invasive	3 (464)	2000–2009	49	1	0	—
Ovarian cystectomy, minimally invasive	1 (34,915)	2009–2012	NR	2	0	—
Sacrocolpopexy, laparoscopic	13 (24,714)	1994–2017	58	2	2 (15)	100
Sacrocolpopexy, robotic	6 (994)	1999–2018	60	1	1 (17)	0
Sacrocolpopexy, open	15 (7422)	1988–2017	59	3	3 (20)	17
Sacrocolpopexy, with hysterectomy, minimally invasive	3 (1234)	1996–2015	61	1	1 (33)	100
Sacrocolpopexy, without hysterectomy, minimally invasive	6 (3028)	1994–2016	60	2	2 (33)	50
Vaginal pelvic organ prolapse surgery, without mesh, with or without hysterectomy	19 (74,972)	1985–2017	61	3	4 (21)	92
Vaginal pelvic organ prolapse surgery, without mesh, with hysterectomy	10 (5576)	1985–2013	60	4	2 (20)	79
Vaginal pelvic organ prolapse surgery, without mesh, without hysterectomy	9 (4786)	1988–2016	66	2	2 (22)	100
Transvaginal mesh	10 (4567)	1999–2014	65	3	1 (10)	100
Vaginal sling surgery for urinary incontinence	7 (55,472)	1999–2016	NR	0	1 (14)	0
Urethral bulking, vaginal	1 (973)	2007–2016	59	NR	0	
Transvaginal oocyte retrieval	8 (60,045)	1987–2014	33	3	1 (13)	4
Sterilization by means of tubal occlusion, minimally invasive	1 (105,357)	2010–2014	41	0	0	
Uterine artery embolization, minimally invasive	2 (267)	1997–2000	44	1	1 (50)	0
First-trimester surgical abortion	4 (60,804)	1980–2011	30	NR	2 (50)	0
Second-trimester surgical abortion	6 (15,517)	1980–2010	24	0	2 (33)	0
Supracervical hysterectomy, laparoscopic	3 (7450)	1999–2012	44	2	0	
Supracervical hysterectomy, open	1 (2332)	2008–2012	48	NR	0	

Lavikainen. Procedure-specific thrombosis and bleeding risks in noncancer gynecologic surgery. Am J Obstet Gynecol 2024.

(continued)

TABLE 2
Summary of studies included by procedure *(continued)*

Procedure	Studies (patients)	Recruitment period	Median patient age (y)	Median length of stay (d)	Number of studies reporting pharmacologic TPX, n (%)[a]	Pharmacologic TPX (%)[b]
Total hysterectomy, laparoscopic	11 (60,727)	1993–2017	48	3	9	59
Total hysterectomy, robotic	2 (10,812)	2008–2012	45	1	0	
Total hysterectomy, vaginal	11 (16,915)	1987–2013	54	5	2 (18)	68
Total hysterectomy, open	3 (6967)	1997–2009	50	7	1 (33)	72

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 medians lengths reported in the individual studies.

NR, not reported; *tpx*, thromboprophylaxis.

[a] Studies included that reported the number of patients receiving pharmacologic thromboprophylaxis; [b] The median proportion of patients who received pharmacologic thromboprophylaxis in the individual studies that reported the use is reported; [c] Includes studies regardless of whether they involved bowel resection. Not all procedures were included in this table (the Appendix contains complete characteristics for all procedures).

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prophylaxis practices, and estimated prophylaxis durations for procedures.

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

Risks for symptomatic VTE and major bleeding at 4 weeks postsurgery among patients who did not receive thromboprophylaxis varied among procedures and patient risk groups (Tables 3–5; the Appendix, pages 7–57). The median symptomatic VTE risk varied from <0.1% for transvaginal oocyte retrieval and vaginal sling surgery for urinary incontinence to 1.5% for minimally invasive sacrocolpopexy with hysterectomy (1.2%–4.6% across patient VTE risk groups; moderate certainty evidence). The risk for VTE was <0.5% for 30 (60%) procedures, 0.5% to 1.0% for 10 (20%) procedures, and 1.0% to 1.5% for 10 (20%) procedures. The median risk for bleeding that led to reintervention varied from <0.1% for uterine artery embolization (very low certainty evidence) and transvaginal oocyte retrieval (low certainty evidence) to 4.0% (open myomectomy; very low certainty evidence). The risk for bleeding that required reintervention was <0.5% for 17 (49%) procedures, 0.5% to 1.0% for 12 (34%) procedures, and >1.0% for 6 (17%) procedures. The evidence did not allow an estimation of the risk for bleeding that require reintervention for 15 (30%) procedures.

The median VTE risk at 4 weeks proved to be at least 1.0% higher than the median risk for bleeding that requires reintervention in open sacrocolpopexy (1.4% vs <0.1%; moderate to very low certainty) (Table 4). When also considering the patient risk factors, the VTE risk was at least 1.0% higher than the risk for bleeding that requires reintervention among the high-risk VTE group of patients who undergo minimally invasive deep endometriosis surgery (with or without bowel surgery; 1.7% VTE risk vs 0.6% bleeding requiring reintervention risk in the high-risk VTE group; low to very low certainty) and minimally invasive sacrocolpopexy (with or without hysterectomy; 1.7% vs. 0.2% in high VTE risk patients; moderate to low certainty) (Tables 3 and 4).

VTE and bleeding requiring reintervention risks proved to be similar for patients who undergo minimally invasive deep endometriosis surgery without bowel surgery (median, 0.7% VTE vs 0.9% bleeding requiring reintervention; low to very low certainty), second-trimester surgical abortion (0.2% vs 0.3%; low certainty), minimally invasive total hysterectomy (0.2% vs 0.5%; moderate certainty), and vaginal total hysterectomy (0.2% vs 0.4%; moderate to low certainty).

The risk for bleeding that requires reintervention was at least 1.0% higher than the VTE risk after an open myomectomy (median 0.5% VTE risk vs 4.0% bleeding requiring reintervention risk; moderate to very low certainty), open supracervical hysterectomy (0.7% vs 2.1%; moderate to very low certainty), and open total hysterectomy (0.8% vs 2.1%; moderate certainty).

The median VTE risk within 4 weeks of the procedure was ≤0.1% for many procedures, including minimally invasive myomectomy (high certainty), minimally invasive sterilization by means of tubal occlusion and transvaginal oocyte retrieval (both moderate certainty), and laparoscopic management of adnexal torsion and first-trimester surgical abortion (both low certainty).

The evidence allowed determining the risk estimates for bleeding that leads to transfusion within 4 weeks of the surgery in the absence of thromboprophylaxis for 47 (94%) procedures. The median risk for bleeding leading to transfusion varied from <0.1% (for minimally invasive salpingo-oophorectomy; very low certainty) to 14.1% (for open myomectomy; low certainty). The risk for bleeding that leads to transfusion was <0.5% in 11 (23%) procedures, 0.5% to 1.0% in 15 (32%) procedures, and

TABLE 3
The 4-week postoperative risk for symptomatic VTE and bleeding requiring reintervention after deep endometriosis surgery, myomectomy, and adnexal surgery

Procedure	Outcome	Patients (studies)	Estimate (%)	Patient VTE risk strata	Evidence certainty
			Median	Low — medium — high (%)	
Deep endometriosis surgery, with or without bowel surgery, minimally invasive	VTE	745 (6)	0.5	0.4 — 0.9 — 1.7	Very low
	Bleeding requiring reintervention	3081 (8)	0.6		Low
Deep endometriosis surgery, with bowel surgery, minimally invasive	VTE	397 (3)	0.6	0.5 — 1.1 — 2.2	Very low
	Bleeding requiring reintervention	1269 (5)	1.3		Low
Deep endometriosis surgery, without bowel surgery, minimally invasive	VTE	189 (2)	0.7	0.6 — 1.2 — 2.3	Very low
	Bleeding requiring reintervention	1036 (2)	0.9		Low
Myomectomy, minimally invasive	VTE	4488 (5)	<0.1	<0.1 — 0.1 — 0.1	High
	Bleeding requiring reintervention	2550 (4)	0.3		Low
Myomectomy, open	VTE	4671 (5)	0.5	0.4 — 0.9 — 1.7	Moderate
	Bleeding requiring reintervention	52 (1)	4.0		Very low
Management of adnexal torsion, laparoscopic	VTE	20,722 (3)	0.1	0.1 — 0.1 — 0.2	Low
	Bleeding requiring reintervention	0 (0)	NR		
Management of adnexal torsion, open	VTE	68,580 (1)	0.3	0.3 — 0.5 — 1.1	Low
	Bleeding requiring reintervention	0 (0)	NR		
Oophorectomy, minimally invasive	VTE	52,599 (1)	0.3	0.1 — 0.3 — 0.6	Moderate
	Bleeding requiring reintervention	0 (0)	NR		
Salpingo-oophorectomy, minimally invasive	VTE	203 (1)	<0.1	<0.1 — <0.1 — <0.1	Very low
	Bleeding requiring reintervention	0 (0)	NR		
Ovarian cystectomy, minimally invasive	VTE	34,915 (1)	0.1	0.1 — 0.1 — 0.2	Low
	Bleeding requiring reintervention	0 (0)	NR		
Sterilization by means of tubal occlusion, minimally invasive	VTE	105,357 (1)	<0.1	<0.1 — <0.1 — 0.1	Moderate
	Bleeding requiring reintervention	0 (0)	NR		
Transvaginal oocyte retrieval	VTE	40,011 (2)	<0.1	<0.1 — <0.1 — 0.1	Moderate
	Bleeding requiring reintervention	18,534 (5)	<0.1		Low

Minimally invasive procedures refer to laparoscopic or robotic procedures.

In the patient VTE risk strata column, we present the VTE estimates by patient VTE risk strata. In the VTE risk strata, patients with no VTE risk factor are classified as low VTE risk, patients with 1 VTE risk factor (age ≥75 years; body mass index of ≥35; or history of VTE in parents, full siblings, or children) are classified as medium VTE risk, and patients with 2 risk factors and those with a personal history of VTE are classified as high VTE risk. For more details, see the Appendix pages 7–36.

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

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TABLE 4
The 4-week postoperative risk for symptomatic VTE and bleeding requiring reintervention after sacrocolpopexy, vaginal pelvic organ prolapse surgery, and other gynecologic noncancer surgery

Procedure	Outcome	Patients (studies)	Estimate (%)	Patient VTE risk strata	Evidence certainty
			Median	Low — medium — high (%)	
Sacrocolpopexy, minimally invasive	VTE	22,394 (12)	0.6	0.4 — 0.9 — 1.7	Low
	Bleeding requiring reintervention	1082 (5)	0.2		Moderate
Sacrocolpopexy, laparoscopic	VTE	21,465 (9)	0.6	0.5 — 1.0 - 1.9	Moderate
	Bleeding requiring reintervention	1,017 (4)	0.2		Moderate
Sacrocolpopexy, robotic	VTE	929 (5)	1.6	1.3 — 2.5 — 5.1	Very low
	Bleeding requiring reintervention	65 (1)	<0.1		Very low
Sacrocolpopexy, open	VTE	6411 (12)	1.4	1.1 — 2.1 — 4.3	Low
	Bleeding requiring reintervention	130 (2)	<0.1		Very low
Sacrocolpopexy, with hysterectomy, minimally invasive	VTE	1234 (3)	1.5	1.2 — 2.3 — 4.6	Moderate
	Bleeding requiring reintervention	206 (1)	0.3		Low
Sacrocolpopexy, without hysterectomy, minimally invasive	VTE	430 (4)	1.7	1.2 — 2.5 — 5.0	Very low
	Bleeding requiring reintervention	310 (2)	0.4		Very low
Vaginal pelvic organ prolapse surgery, without mesh, with or without hysterectomy	VTE	73,626 (13)	0.2	0.1 — 0.2 — 0.4	Low
	Bleeding requiring reintervention	1050 (4)	0.9		Low
Vaginal pelvic organ prolapse surgery, without mesh, with hysterectomy	VTE	4485 (6)	0.2	0.1 — 0.3 — 0.6	Very low
	Bleeding requiring reintervention	918 (3)	0.4		Very low
Vaginal pelvic organ prolapse surgery, without mesh, without hysterectomy	VTE	4531 (6)	0.1	<0.1 — 0.1 — 0.1	Low
	Bleeding requiring reintervention	132 (2)	0.8		Very low
Transvaginal mesh	VTE	3136 (5)	0.2	0.2 — 0.3 — 0.7	Very low
	Bleeding requiring reintervention	1383 (4)	0.6		Low
Vaginal sling surgery for urinary incontinence	VTE	55,472 (7)	<0.1	<0.1 — 0.1 — 0.1	Moderate
	Bleeding requiring reintervention	7117 (1)	0.1		Moderate
Urethral bulking, vaginal	VTE	973 (1)	<0.1	<0.1 — <0.1 — <0.1	Very low
	Bleeding requiring reintervention	0 (0)	NR		
Uterine artery embolization, minimally invasive	VTE	267 (2)	0.2	0.2 — 0.4 — 0.8	Very low

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TABLE 4
The 4-week postoperative risk for symptomatic VTE and bleeding requiring reintervention after sacrocolpopexy, vaginal pelvic organ prolapse surgery, and other gynecologic noncancer surgery *(continued)*

Procedure	Outcome	Patients (studies)	Estimate (%) Median	Patient VTE risk strata Low − medium − high (%)	Evidence certainty
	Bleeding requiring reintervention	67 (1)	<0.1		Very low
First-trimester surgical abortion	VTE	56,117 (1)	<0.1	<0.1 − <0.1 − <0.1	Low
	Bleeding requiring reintervention	60,804 (4)	0.5		Low
Second-trimester surgical abortion	VTE	1220 (2)	0.2	0.2 − 0.3 − 0.6	Low
	Bleeding requiring reintervention	14,436 (5)	0.3		Low

Minimally invasive refers to laparoscopic or robotic procedures. In the patient VTE risk strata column, we present the VTE estimates by patient VTE risk strata. In the VTE risk strata, patients with no VTE risk factor are classified as low VTE risk, patients with 1 VTE risk factor (age ≥75 years; body mass index of ≥35; or history of VTE in parents, full siblings, or children) are classified as medium VTE risk, and patients with 2 risk factors and those with a personal history of VTE are classified as high VTE risk. For more details, see the Appendix pages 37−57.

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

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>1.0% in 21 (45%) procedures (Appendix, pages 7−57). In nine (19%) procedures, the risk for VTE was higher than the risk for bleeding leading to transfusion, and in 38 (81%) procedures, the risk for VTE was similar or lower than the risk for bleeding leading to transfusion.

Evidence allowed determining the risk estimates for bleeding leading to postoperative hemoglobin levels <70 g/L for 8 (16%) procedures (all very low certainty). Except for first-trimester surgical abortion (0.5%), the risk for bleeding that leads to postoperative hemoglobin levels <70 g/L was generally <0.1%. Evidence allowed determining the risk estimates for symptomatic splanchnic vein thrombosis for 14 (28%) procedures (10 very low certainty, 4 low certainty). Except for deep endometriosis surgery with bowel surgery (0.3%; very low certainty), symptomatic splanchnic vein thrombosis risk generally proved to be <0.1%. The Appendix provides more information, including all the risk estimates for bleeding leading to transfusion, symptomatic splanchnic vein thrombosis, fatal VTE, and fatal bleeding.

Comment

Principal findings

As summarized in our infographic (Figure), this comprehensive systematic review provides a summary of the current best estimates of the procedure-specific risks for symptomatic VTE and major bleeding in gynecologic noncancer surgery among patients who did not receive thromboprophylaxis.

The evidence certainty proved to be moderate to low for VTE and low to very low for bleeding requiring reintervention and bleeding leading to transfusion. The risks varied between procedures, approaches, and patient risk factors. The median symptomatic VTE risk within 4 weeks after surgery varied from <0.1% to 1.5%, the risk for bleeding requiring reintervention varied from <0.1% to 4.0%, and the risk for bleeding leading to transfusion varied from <0.1% to 14.1%.

For 33 (66%) of 50 noncancer gynecologic procedures, the median risk for symptomatic VTE proved to be ≤0.5%. However, for minimally invasive sacrocolpopexy with hysterectomy, the VTE risk was 1.5% (1.2%−4.6% across patient VTE risk groups, moderate certainty), and for open total hysterectomy, the VTE risk was 0.8% (0.6%−2.4%, moderate certainty). For 17 (49%) of 35 procedures in which we established the bleeding requiring reintervention risk estimates, the median risk proved to be ≤0.5%. After open myomectomy, the bleeding requiring reintervention risk was 4.0% (very low certainty), and after open total hysterectomy, the risk was 2.1% (moderate certainty).

The risk for VTE was high when compared with the risk for bleeding requiring reintervention among patients who underwent an open sacrocolpopexy (1.4% vs <0.1%; moderate to very low certainty evidence). The risk for bleeding requiring reintervention was high when compared with the risk for VTE after an open myomectomy (4.0% vs 0.5%; moderate to very low certainty evidence) or an open total hysterectomy (2.1% vs 0.8%; moderate certainty evidence). For most procedures, the risk for VTE was low or trivial (ie, <0.5%).

Comparison with existing literature

This was a comprehensive systematic summary of the procedure-specific VTE risks in noncancer gynecologic surgery. An earlier systematic review examined the incidence of VTE after mesh sacrocolpopexy in comparison with the incidence after native vaginal tissue repairs.[39] In that review, the authors searched for randomized trials and observational studies until 2012 and included 30 studies (8,693 patients) that addressed the VTE risk. That review found a 0.6% incidence of VTE after mesh sacrocolpopexy and a 0.1% incidence after native vaginal tissue repairs; they did not report the bleeding risks.[39] Our review of 37 eligible studies

TABLE 5
The 4-week postoperative risk for symptomatic VTE and bleeding requiring reintervention after hysterectomy for benign disease

Procedure	Outcome	Patients (studies)	Estimate (%) Median	Patient VTE risk strata Low — medium — high (%)	Evidence certainty
Supracervical hysterectomy, laparoscopic	VTE	7450 (3)	0.1	0.1 — 0.2 — 0.4	Moderate
	Bleeding requiring reintervention	4042 (3)	0.5		Very low
Supracervical hysterectomy, open	VTE	2332 (1)	0.7	0.6 — 1.3 — 2.5	Moderate
	Bleeding requiring reintervention	2248 (2)	2.1		Very low
Total hysterectomy, minimally invasive	VTE	71,404 (11)	0.2	0.1 — 0.2 — 0.5	Moderate
	Bleeding requiring reintervention	4042 (3)	0.5		Moderate
Total hysterectomy, laparoscopic	VTE	60,727 (11)	0.2	0.1 — 0.3 — 0.6	Moderate
	Bleeding requiring reintervention	4042 (3)	0.5		Moderate
Total hysterectomy, robotic	VTE	10,677 (1)	0.3	0.2 — 0.5 — 1	Moderate
	Bleeding requiring reintervention	0 (0)	NR		
Total hysterectomy, open	VTE	6967 (3)	0.8	0.6 — 1.3 — 2.5	Moderate
	Bleeding requiring reintervention	2248 (2)	2.1		Moderate
Total hysterectomy, vaginal	VTE	16,519 (8)	0.2	0.1 — 0.3 — 0.6	Moderate
	Bleeding requiring reintervention	2252 (5)	0.4		Low

Minimally invasive refers to laparoscopic or robotic procedures. 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 low VTE risk, patients with 1 VTE risk factor (age ≥75 years; body mass index of ≥35; or history of VTE in parents, full siblings, or children) are classified as medium VTE risk, and patients with 2 risk factors and those with a personal history of VTE are classified as high VTE risk. For more details, see the Appendix pages 12—21.

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

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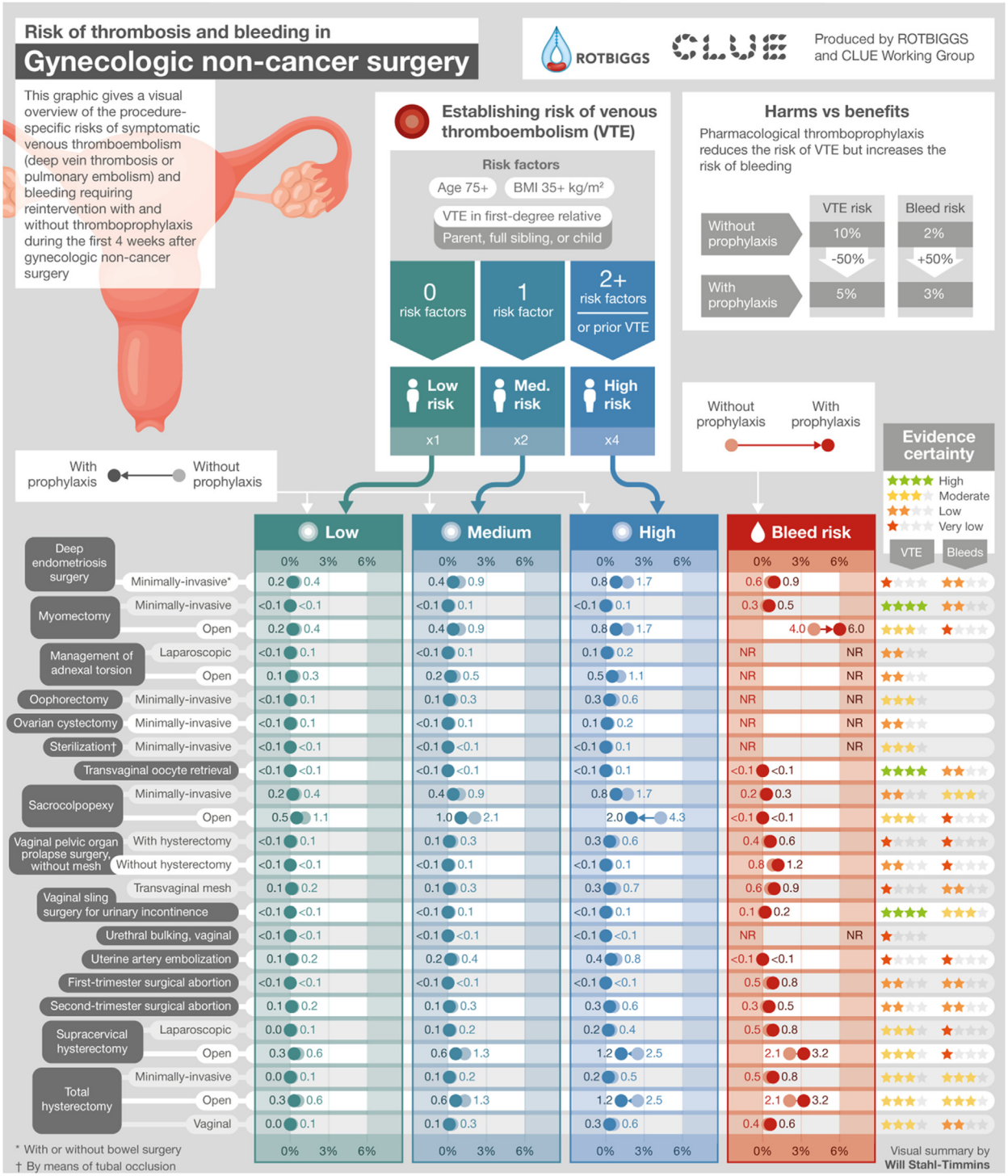
(102,971 patients) provides a risk estimate of 0.6% for symptomatic VTE after minimally invasive sacrocolpopexy (12 studies, 22,934 patients), an estimate of 1.4% after open sacrocolpopexy (12 studies, 6411 patients), and an estimate of 0.2% after vaginal pelvic organ prolapse surgery without mesh (with or without hysterectomy; 13 studies, 73,626 patients). Besides stratifying estimates by procedure, approach, and the extent of resection, we adjusted for thromboprophylaxis use, follow-up time, and stratified the VTE risk by patient risk factors——none of these were performed in the earlier review.[39]

Strengths and limitations

The strengths of our study include a comprehensive and procedure-specific search; comprehensive screening; rigorous adherence to methodologic standards that include duplicate assessment of the eligibility, risk of bias, and data extraction; and assessment of the evidence certainty using the GRADE system.[27,28] We also considered patient risk factors and developed models that considered length of follow-up and the use of thromboprophylaxis.[29] We estimated risks separately for 50 different procedures in gynecologic surgery for benign diseases, including all major VTE and serious bleeding outcomes.

Our review also has limitations. We generally found moderate or high risk of bias studies that often did not provide information regarding the use of thromboprophylaxis or did not report outcomes within 4 weeks after the surgery. Furthermore, we did not adjust for additional interventions like antihemorrhagic prophylaxis that could influence the estimates of bleeding risk. For many procedures, our estimates therefore represent only low-certainty evidence, reflecting uncertainty in the primary evidence and our modeling approaches, including assumptions on thromboprophylaxis use and follow-up time.

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



BMI, body mass index; *ROTBIGGS*, Risk of Thrombosis and Bleeding in General and Gynecologic Surgery; *VTE*, venous thromboembolism.

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Conclusions and implications

Patients who undergo noncancer gynecologic surgeries are mostly at low risk for VTE. Our estimates suggest that pharmacologic thromboprophylaxis may often lead to a minimal reduction in the VTE risk with the potential of increasing the major bleeding risk, which outweighs the potential benefits. The current evidence suggests that VTE prophylaxis has a net benefit for some patients and procedures (eg, high-risk patients undergoing minimally invasive sacrocolpopexy); bleeding harm outweighs the benefit for many others (minimally invasive total hysterectomy, vaginal pelvic organ prolapse surgery). For some procedures and patient risk groups (for instance, medium risk patients undergoing minimally invasive deep endometriosis surgery), the risks are closely balanced and decisions ought to depend on the individual risk prediction and values and preferences related to VTE and bleeding.

Our work highlights that the evidence for symptomatic VTE and especially major bleeding in gynecologic surgery for benign conditions is often of low or very low certainty or completely absent. Procedure-specific research that adheres to standards, such as comprehensive characterization and documentation of patient populations, follow-up times, thromboprophylaxis use, and patient-important VTE and bleeding outcomes, is rare and needed.

These summaries have important implications for the practice of noncancer gynecologic surgery worldwide. Because of an absence of previous procedure-specific systematic summaries of symptomatic VTE and major bleeding risks for noncancer gynecologic procedures, guidelines have been based on the duration of surgery and patient risk factors.[14,40] Our estimates account for procedure- and patient-specific factors and give more specific guidance for practitioners, guideline panels, and patients. These fundamental advances—visually summarized in an infographic (Figure)—inform clinicians, patients, guideline developers, and policymakers in making optimal management decisions and recommendations regarding the use of surgical thromboprophylaxis. ■

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REFERENCES

1. Mehta A, Xu T, Hutfless S, et al. Patient, surgeon, and hospital disparities associated with benign hysterectomy approach and perioperative complications. Am J Obstet Gynecol 2017;216:497.e1–10.
2. Aarts JW, Nieboer TE, Johnson N, et al. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database Syst Rev 2015;2015:CD003677.
3. Lin CH, Long CY, Huang KH, Lo TS, Wu MP. Surgical trend and volume effect on the choice of hysterectomy benign gynecologic conditions. Gynecol Minim Invasive Ther 2021;10:1–9.
4. Tyan P, Hawa N, Carey E, et al. Trends and perioperative outcomes across elective benign hysterectomy procedures from the ACS-NSQIP 2007−2017. J Minim Invasive Gynecol 2022;29:365–74.e2.
5. Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) Study Investigators, Spence J, LeManach Y, et al. Association between complications and death within 30 days after noncardiac surgery. CMAJ 2019;191:E830–7.
6. International Surgical Outcomes Study group. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. Br J Anaesth 2016;117:601–9.
7. Hoffman R, Benz EJ, Silberstein LE, et al. Hematology: basic principles and practice. Philadelphia, PA: Elsevier; 2017.
8. Schulman S, Angerås U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. J Thromb Haemost 2010;8:202–4.
9. Tikkinen KA, Agarwal A, Craigie S, et al. Systematic reviews of observational studies of risk of thrombosis and bleeding in urological surgery (ROTBUS): introduction and methodology. Syst Rev 2014;3:150.
10. Tikkinen KAO, Craigie S, Agarwal A, et al. Procedure-specific risks of thrombosis and bleeding in urological cancer surgery: systematic review and meta-analysis. Eur Urol 2018;73:242–51.
11. Tikkinen KAO, Craigie S, Agarwal A, et al. Procedure-specific risks of thrombosis and bleeding in urological non-cancer surgery: systematic review and meta-analysis. Eur Urol 2018;73:236–41.
12. Marcucci M, Etxeandia-Ikobaltzeta I, Yang S, et al. Benefits and harms of direct oral anticoagulation and low molecular weight heparin for thromboprophylaxis in patients undergoing non-cardiac surgery: systematic review and network meta-analysis of randomised trials. BMJ 2022;376:e066785.
13. Tikkinen KAO, Guyatt GH. Baseline risks of venous thromboembolism and major bleeding are crucial in decision-making on thromboprophylaxis. Eur Urol 2020;78:369–70.
14. Lavikainen LI, Guyatt GH, Lee Y, et al. Systematic reviews of observational studies of Risk of Thrombosis and Bleeding in General and Gynecologic Surgery (ROTBIGGS): introduction and methodology. Syst Rev 2021;10:264.
15. Pourjamal N, Lavikainen LI, Halme ALE, et al. Global practice variation in pharmacologic thromboprophylaxis for general and gynaecological surgery: systematic review. BJS Open 2022;6:zrac129.
16. Nambiar D, Thachil J, Yoong W, Balachandran Nair D. Thromboprophylaxis in gynaecology: a review of current evidence. The Obstet Gynaecol 2023;25:59–71.
17. Lavikainen LI, Guyatt GH, Luomaranta AL, et al. Risk of thrombosis and bleeding in gynecologic cancer surgery: systematic review and meta-analysis. Am J Obstet Gynecol 2023 [Epub ahead of print].
18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9.
19. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
20. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
21. Higgins J, Thomas J, Chandler J, et al. Cochrane handbook for systematic reviews of interventions. London, England: The Cochrane Collaboration; 2023.
22. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence—

study limitations (risk of bias). J Clin Epidemiol 2011;64:407–15.
23. Ma LL, Wang YY, Yang ZH, Huang D, Weng H, Zeng XT. Methodological quality (risk of bias) assessment tools for primary and secondary medical studies: what are they and which is better? Mil Med Res 2020;7:7.
24. Page MJ, McKenzie JE, Higgins JPT. Tools for assessing risk of reporting biases in studies and syntheses of studies: a systematic review. BMJ Open 2018;8:e019703.
25. Pesonen JS, Vernooij RWM, Cartwright R, et al. The impact of nocturia on falls and fractures: a systematic review and meta-analysis. J Urol 2020;203:674–83.
26. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280–6.
27. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924–6.
28. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995–8.
29. Singh T, Lavikainen LI, Halme ALE, et al. Timing of symptomatic venous thromboembolism after surgery: meta-analysis. Br J Surg 2023;110:553–61.
30. Caprini JA. Thrombosis risk assessment as a guide to quality patient care. Dis Mon 2005;51:70–8.
31. Edmonds MJ, Crichton TJ, Runciman WB, Pradhan M. Evidence-based risk factors for postoperative deep vein thrombosis. ANZ J Surg 2004;74:1082–97.
32. Hansson PO, Welin L, Tibblin G, Eriksson H. Deep vein thrombosis and pulmonary embolism in the general population. 'The Study of Men Born in 1913'. Arch Intern Med 1997;157:1665–70.
33. Pannucci CJ, Laird S, Dimick JB, Campbell DA, Henke PK. A validated risk model to predict 90-day VTE events in postsurgical patients. Chest 2014;145:567–73.
34. Parkin L, Sweetland S, Balkwill A, et al. Body mass index, surgery, and risk of venous thromboembolism in middle-aged women: a cohort study. Circulation 2012;125:1897–904.
35. Rogers SO Jr, Kilaru RK, Hosokawa P, Henderson WG, Zinner MJ, Khuri SF. Multivariable predictors of postoperative venous thromboembolic events after general and vascular surgery: results from the patient safety in surgery study. J Am Coll Surg 2007;204:1211–21.
36. Stein PD, Hull RD, Kayali F, Ghali WA, Alshab AK, Olson RE. Venous thromboembolism according to age: the impact of an aging population. Arch Intern Med 2004;164:2260–5.
37. Tosetto A, Frezzato M, Rodeghiero F. Prevalence and risk factors of non-fatal venous thromboembolism in the active population of the VITA Project. J Thromb Haemost 2003;1:1724–9.
38. Weill-Engerer S, Meaume S, Lahlou A, et al. Risk factors for deep vein thrombosis in inpatients aged 65 and older: a case-control multicenter study. J Am Geriatr Soc 2004;52:1299–304.
39. Siddiqui NY, Grimes CL, Casiano ER, et al. Mesh sacrocolpopexy compared with native tissue vaginal repair: a systematic review and meta-analysis. Obstet Gynecol 2015;125:44–55.
40. Cantrell LA, Garcia C, Maitland HS. Thrombosis and thromboprophylaxis in gynecology surgery. Clin Obstet Gynecol 2018;61:269–77.