CHEST Supplement

ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: ACCP GUIDELINES

Prevention of VTE in Nonorthopedic Surgical Patients

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **VTE is a common cause of preventable death in surgical patients.**
Methods: **We developed recommendations for thromboprophylaxis in nonorthopedic surgical patients by using systematic methods as described in Methodology for the Development of Antithrombotic Therapy and Prevention of Thrombosis Guidelines. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines in this supplement.**
Results: **We describe several alternatives for stratifying the risk of VTE in general and abdominal-pelvic surgical patients. When the risk for VTE is very low (< 0.5%), we recommend that no specific pharmacologic (Grade 1B) or mechanical (Grade 2C) prophylaxis be used other than early ambulation. For patients at low risk for VTE (~1.5%), we suggest mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C). For patients at moderate risk for VTE (~3%) who are not at high risk for major bleeding complications, we suggest low-molecular-weight heparin (LMWH) (Grade 2B), low-dose unfractionated heparin (Grade 2B), or mechanical prophylaxis with IPC (Grade 2C) over no prophylaxis. For patients at high risk for VTE (~6%) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 1B) or low-dose unfractionated heparin (Grade 1B) over no prophylaxis. In these patients, we suggest adding mechanical prophylaxis with elastic stockings or IPC to pharmacologic prophylaxis (Grade 2C). For patients at high risk for VTE undergoing abdominal or pelvic surgery for cancer, we recommend extended-duration, postoperative, pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B). For patients at moderate to high risk for VTE who are at high risk for major bleeding complications or those in whom the consequences of bleeding are believed to be particularly severe, we suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C). For patients in all risk groups, we suggest that an inferior vena cava filter not be used for primary VTE prevention (Grade 2C) and that surveillance with venous compression ultrasonography should not be performed (Grade 2C). We developed similar recommendations for other nonorthopedic surgical populations.**
Conclusions: **Optimal thromboprophylaxis in nonorthopedic surgical patients will consider the risks of VTE and bleeding complications as well as the values and preferences of individual patients.**
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Abbreviations: CABG = coronary artery bypass graft; ES = elastic stockings; ICH = intracranial hemorrhage; IPC = intermittent pneumatic compression; IVC = inferior vena cava; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; QALY = quality-adjusted life year; RR = risk ratio; VCU = venous compression ultrasonography

Summary of Recommendations

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

3.6.1. For general and abdominal-pelvic surgery patients at very low risk for VTE (< 0.5%; Rogers score, < 7; Caprini score, 0), we recommend that no specific pharmaclogic (Grade 1B) **or mechanical** (Grade 2C) **prophylaxis be used other than early ambulation.**

3.6.2. For general and abdominal-pelvic surgery patients at low risk for VTE (~1.5%; Rogers score, 7-10; Caprini score, 1-2), we suggest mechanical prophylaxis, preferably with intermittent pneumatic compression (IPC), over no prophylaxis (Grade 2C)**.**

3.6.3. For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score, > 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest low-molecular-weight heparin (LMWH) (Grade 2B)**, low-dose unfractionated heparin (LDUH)** (Grade 2B)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

3.6.4. For general and abdominal-pelvic surgery patients at moderate risk for VTE (3.0%; Rogers score, > 10; Caprini score, 3-4) who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)**.**

3.6.5. For general and abdominal-pelvic surgery patients at high risk for VTE (~6.0%; Caprini score, ≥ 5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 1B) **or LDUH** (Grade 1B) **over no prophylaxis. We suggest that mechanical prophylaxis with elastic stockings (ES) or IPC should be added to pharmacologic prophylaxis** (Grade 2C)**.**

3.6.6. For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B)**.**

Remarks: Patients who place a high value on minimizing out-of-pocket health-care costs might prefer limited-duration over extended-duration prophylaxis in settings where the cost of extended-duration prophylaxis is borne by the patient.

3.6.7. For high-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)**.**

3.6.8. For general and abdominal-pelvic surgery patients at high risk for VTE (6%; Caprini score, ≥ 5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major

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bleeding complications, we suggest low-dose aspirin (Grade 2C)**, fondaparinux** (Grade 2C)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

3.6.9. For general and abdominal-pelvic surgery patients, we suggest that an inferior vena cava (IVC) filter should not be used for primary VTE prevention (Grade 2C)**.**

3.6.10. For general and abdominal-pelvic surgery patients, we suggest that periodic surveillance with venous compression ultrasound (VCU) should not be performed (Grade 2C)**.**

4.4.1. For cardiac surgery patients with an uncomplicated postoperative course, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over either no prophylaxis (Grade 2C) **or pharmacologic prophylaxis** (Grade 2C)**.**

4.4.2. For cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications, we suggest adding pharmacologic prophylaxis with LDUH or LMWH to mechanical prophylaxis (Grade 2C)**.**

5.4.1. For thoracic surgery patients at moderate risk for VTE who are not at high risk for perioperative bleeding, we suggest LDUH (Grade 2B), **LMWH** (Grade 2B)**, or mechanical prophylaxis with optimally applied IPC** (Grade 2C) **over no prophylaxis.**

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

5.4.2. For thoracic surgery patients at high risk for VTE who are not at high risk for perioperative bleeding, we suggest LDUH (Grade 1B) **or LMWH** (Grade 1B) **over no prophylaxis. In addition, we suggest that mechanical prophylaxis with ES or IPC should be added to pharmacologic prophylaxis** (Grade 2C)**.**

5.4.3. For thoracic surgery patients who are at high risk for major bleeding, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)**.**

6.4.1. For craniotomy patients, we suggest that mechanical prophylaxis, preferably with IPC, be used over no prophylaxis (Grade 2C) **or pharmacologic prophylaxis** (Grade 2C)**.**

6.4.2. For craniotomy patients at very high risk for VTE (eg, those undergoing craniotomy for malignant disease), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)**.**

7.4.1. For patients undergoing spinal surgery, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)**, unfractionated heparin** (Grade 2C)**, or LMWH** (Grade 2C)**.**

7.4.2. For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease or those undergoing surgery with a combined anterior-posterior approach), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)**.**

8.4.1. For major trauma patients, we suggest use of LDUH (Grade 2C)**, LMWH** (Grade 2C)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

8.4.2. For major trauma patients at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), we suggest adding mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury.**

8.4.3. For major trauma patients in whom LMWH and LDUH are contraindicated, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury. We suggest adding pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves** (Grade 2C)**.**

8.4.4. For major trauma patients, we suggest that an IVC filter should not be used for primary VTE prevention (Grade 2C)**.**

8.4.5. For major trauma patients, we suggest that periodic surveillance with VCU should not be performed (Grade 2C)**.**

VTE is a common cause of preventable death in hospitalized patients. Approximately one-third of the 150,000 to 200,000 VTE-related deaths per year in the United States occur following surgery.[1] The

high incidence of postoperative VTE and the availability of effective methods of prevention mandate that thromboprophylaxis should be considered in every surgical patient. In this article, we review the literature pertaining to thromboprophylaxis in nonorthopedic surgical patients and make recommendations for VTE prevention after explicitly weighing the trade-offs between the potential benefits and harms of alternative strategies for prophylaxis.

1.0 Methods

To develop recommendations for thromboprophylaxis among patients undergoing nonorthopedic surgery, we first used the population, intervention, comparator, outcome format to generate a list of questions (Table 1). Through the evidence review, we attempted to identify all relevant studies that compared one or more interventions for thromboprophylaxis with any alternative (including placebo or no treatment) among nonorthopedic surgical patients. We favored studies or systematic reviews that limited inclusion to the target populations and considered indirect evidence from other populations when direct evidence was limited in quantity or quality.

Preferred outcomes included death from any cause, fatal pulmonary embolism (PE); objectively confirmed, nonfatal, symptomatic PE and DVT; fatal bleeding; bleeding requiring reoperation; and other major bleeding. We accepted the definition of major bleeding used in each study, recognizing that there would be substantial heterogeneity in definitions across studies. When symptomatic VTE events were few in number or not reported, we used information about asymptomatic, proximal DVT, preferably when detected or confirmed by ultrasonography or venography. In some cases in which better-quality evidence was not available, we used information about asymptomatic DVT detected by radioactive fibrinogen uptake, recognizing that the sensitivity and specificity of this test are poor.

The Oregon Evidence-Based Practice Center updated the literature review from the prior edition of these guidelines by searching Medline, the Cochrane Controlled Trials Register, and the Cochrane Database of Systematic Reviews for all randomized trials, observational studies, and systematic reviews of thromboprophylaxis in surgical patients published between January 1, 2005, and November 4, 2009 (Table S1). (Tables and figures that contain an "S" before the number and any appendices denote supplementary information not contained in the body of the article and available instead in an online data supplement. See the "Acknowledgments" for more information.) We performed additional searches through December 31, 2010. In addition, we searched other online resources, including Trial Results Center[2]; retrieved original reports from articles that were included in prior systematic reviews, scanned reference lists of retrieved articles, and shared articles from our personal files with one another and with authors of other prevention topic articles in this supplement.

We abstracted relevant information from each study regarding study characteristics, risk of bias, and results. When available, we collected this information from published systematic reviews. When desired information was not available in a published systematic review, we used data from individual studies or pooled data across studies using random-effects models and RevMan statistical software (Cochrane Information Management System), as appropriate.

When formulating recommendations, we considered trade-offs between desirable and undesirable patient-important outcomes by comparing the absolute numbers of expected events. To estimate absolute numbers of expected events, we used relative risk estimates from randomized trials or systematic reviews of randomized trials. We applied these estimates of relative risk to estimates of the baseline risk of symptomatic events that we obtained from observational studies.[3] For example, if prophylaxis reduces the risk of VTE by 50%, and the baseline risk of symptomatic VTE in the absence of prophylaxis in a given population is 20 per 1,000 (2%), then the absolute number of VTE events prevented is 10 per 1,000 patients treated.

When weighing absolute numbers of desirable and undesirable events, we used explicit information about values and preferences for specific outcomes based on results of a survey of Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines panel members.[3] To facilitate weighing trade-offs between thrombotic events and bleeding complications, we frequently elected to combine estimates of nonfatal PE and symptomatic DVT when estimating baseline and relative risks.

To estimate baseline risks of VTE and bleeding events, we sought large, population-based, observational studies with few exclusions or losses to follow-up that measured objectively confirmed, patient-important outcomes over a sufficiently long time horizon (1-3 months). Many studies of baseline VTE risk were limited by small samples, referral center bias, retrospective design, short time horizons, and missing or incomplete information about prophylaxis received. To estimate the expected baseline risk of VTE in the absence of prophylaxis, we adjusted for prophylaxis received by dividing the observed risk of VTE by the relative risk of VTE associated with prophylaxis. For example, in a retrospective study of 1,126 plastic and reconstructive surgery patients, the observed that the risk of symptomatic VTE within 60 days of surgery was 1.27% among patients at moderate risk for VTE, all of whom received mechanical prophylaxis with intermittent pneumatic compression (IPC).[4] Assuming that the relative risk of VTE in patients who receive IPC compared with no prophylaxis is 0.48, the estimated baseline risk of VTE in the absence of prophylaxis is 2.6%.

Studies of bleeding risk were few in number and limited by small samples and heterogeneous definitions of major bleeding. When necessary, we used pooled estimates of bleeding risk from the control groups of randomized controlled trials.

Like other topic articles in these guidelines, we used the Grades of Recommendations, Assessment, Development, and Evaluation system to assess the quality of evidence and describe the strength of recommendations.[5-7] Accordingly, we noted when randomized trials were limited by unclear allocation concealment, incomplete blinding (especially for "subjective" outcomes), measurement of surrogate outcomes (eg, asymptomatic DVT), large (or differential) losses to follow-up, failure to adhere to an intention-to-treat analysis, stopping early for benefit, and failure to report outcomes.

2.0 Safety and Effectiveness of Interventions for Thromboprophylaxis

Alternative interventions for thromboprophylaxis that have been evaluated in studies of nonorthopedic surgical patients include elastic stockings (ES), IPC devices, low-dose unfractionated heparin (LDUH), low-molecular-weight heparin (LMWH), fondaparinux, aspirin, inferior vena cava (IVC) filters, and surveillance with venous compression ultrasonography (VCU) as summarized in Tables 2-4. Characteristics and risk of bias in individual trials are summarized in Tables S2 and S3. Additional details are provided in Appendix S1.

Table 1—*Structured Clinical Questions*

Sections	PICO Question					Methods
	Informal Questions	Population	Intervention	Comparator	Outcome	
3.1. General and abdominal-pelvic surgery, including GI, GU, and Gyn surgery 3.2. Bariatric surgery 3.3. Vascular surgery 3.4. Plastic and reconstructive surgery 4. Cardiac surgery 5. Thoracic surgery 6. Craniotomy 7. Spinal surgery 8. Trauma	Type, timing, dose, frequency, and duration of prophylaxis	Specific surgical population, stratified by risk of VTE	Mechanical prophylaxis (ES, IPC, IVC filter) and pharmacologic prophylaxis (LDUH, LMWH, fondaparinux, aspirin)	No treatment, mechanical prophylaxis and pharmacologic prophylaxis	Asymptomatic proximal DVT, symptomatic DVT, symptomatic PE, fatal PE, bleeding requiring reoperation, fatal bleeding, intracranial bleeding, death	RCTs
All nonorthopedic surgery	Prognostic factors associated with risk of VTE	All	Any or none		Asymptomatic proximal DVT, symptomatic DVT, PE, fatal PE	Case control, retrospective and prospective cohort studies, RCTs
All nonorthopedic surgery	Prognostic factors associated with risk of bleeding complications	All	Any pharmacologic prophylaxis (LDUH, LMWH, fondaparinux, aspirin)		Major bleeding, bleeding requiring reoperation, fatal bleeding, intracranial bleeding	Case control, retrospective and prospective cohort studies, RCTs
All nonorthopedic surgery	Screening with ultrasonography for asymptomatic VTE	All	Any or none		Asymptomatic DVT, symptomatic DVT, PE, fatal PE	Case control, retrospective and prospective cohort studies, RCTs

ES = elastic stockings; GU = urological; Gyn = gynecologic; IPC = intermittent pneumatic compression; IVC = inferior vena cava; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; PE = pulmonary embolism; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial.

Table 2—*Relative Risk Estimates From Published Systematic Reviews and Selected Randomized Trials of Pharmacologic Prophylaxis*

Study/Year and Population	Death From Any Cause	Fatal PE	Nonfatal PE	Symptomatic DVT or VTE	Any DVT or VTE (Including Asymptomatic)	Proximal DVT (Including Asymptomatic)	Fatal Bleeding	Nonfatal Major Bleeding	Bleeding Requiring Reoperation
LDUH vs no prophylaxis									
IMT[8]/1975 General surgery[a]	0.81 (0.61-1.10)	0.13 (0.02-0.55)	NA	0.35 (0.18-0.69)	0.31 (0.23-0.42)	0.11(0.04-0.27)	0.81 (0.21-3.0)	1.37[b] (1.09-1.73)	NA
Collins et al[9]/1988 Mixed surgery[c]	0.82 (0.69-0.99)	0.53 (0.31-0.91)	0.59 (0.41-0.84)	NA	NA	NA	1.14 (0.41-3.15)	1.57 (1.32-1.87)	NA
Collins et al[9]/1988 General surgery[c]	0.82 (0.68-0.99)	0.50 (0.20-1.30)	0.44 (0.31-0.63)	NA	NA	NA	1.01 (0.35-2.97)	1.56 (1.29-1.88)	NA
Collen et al[10]/2008 Neurosurgery	NA	NA	0.96 (0.10-9.06)	NA	0.50 (0.11-2.38)	NA	NA	NA	NA
LMWH vs no prophylaxis									
Pezzuoli et al[11]/1989 Abdominal surgery[a]	0.44 (0.22-0.89)	0.50 (0.12-2.08)	NA	0.33 (0.09-1.23)	NA	NA	None	3.11[d] (1.84-5.28)	2.24 (1.46-3.43)
Iorio and Agnelli[12]/2000 Neurosurgery	1.74 (0.94-3.22)	NA	NA	NA	0.54 (0.38-0.77)	0.48 (0.28-0.83)	NA	1.68 (0.62-4.52)	NA
Mismetti et al[13]/2001 General surgery	0.54 (0.27-1.10)	NA	0.25 (0.08-0.79)	0.29 (0.11-0.73) 0.31[e] (0.12-0.81)	0.28 (0.14-0.54)	NA	NA	2.03 (1.37-3.01)	NA
LMWH vs LDUH									
Geerts et al[14]/1996 Major trauma[a]	NA	None	1 (LMWH)	2 DVT with HIT (LDUH)	0.70 (0.50-0.96)	0.42 (0.13-0.88)	None	5.27 (0.62-44.5)	1 (LMWH)
Mismetti et al[13]/2001 General surgery	1.04 (0.89-1.20)	NA	0.88 (0.64-1.20)	0.71 (0.51-0.99)	0.90 (0.79-1.02)	NA	NA	0.89 (0.75-1.05)	NA
Akl et al[15]/2008 Cancer surgery	0.88 (0.65-1.19)	NA	0.60 (0.22-1.64)	0.73 (0.23-2.28)	NA	NA	NA	0.95 (0.51-1.77)	NA
Collen et al[10]/2008 Neurosurgery	NA	NA	0.43 (0.08-2.41)	NA	1.46 (0.61-3.51)	NA	1.78[f] (0.37-8.50)	1.00 (0.18-5.74)	NA
Extended- vs limited-duration LMWH									
Akl et al[15]/2008 Cancer surgery	1.23 (0.70-2.15) (1 y)	NA	NA	NA	0.21 (0.05-0.94)	NA	NA	2.94 (0.12-71.8)	NA
Bottaro et al[16]/2008 Abdominal surgery	NA	NA	NA	NA	0.46 (0.29-0.74)	0.24 (0.09-0.67)	NA	0.83 (0.22-3.12)	NA
Rasmussen et al[17]/2009 Abdominal/pelvic surgery	1.12 (0.65-1.93)	NA	NA	0.22 (0.06-0.80)	0.41 (0.26-0.63)	0.27 (0.13-0.57)	NA	1.11 (0.62-1.97)	NA
Kakkar et al[18]/2010 Abdominal and pelvic cancer surgery[a]	1.29 (0.45-3.66)	0.32[g] (0.03-3.07)	None	NA	0.63 (0.37-1.10)	0.12 (0.02-0.96)	None	1.97 (0.18-21.6)	NA
Fondaparinux plus IPC vs IPC alone									
Turpie et al[19]/2007 Abdominal surgery[a]	1.64 (0.54-4.98)	1.02 (0.06-16.3)	1.01 (0.06-16.2)	1.01 (0.06-16.2)	0.31 (0.14-0.73)	0.14 (0.02-1.14)	None	10.2 (1.31-79.7)	4/635 vs0/650
Fondapariunx vs LMWH									
Agnelli et al[20]/2005 Abdominal surgery[a]	0.75 (0.38-1.45)	1.0 (0.20-4.94)	2/1,465 vs 0/1,462	1.20 (0.37-3.92)	0.75 (0.52-1.09)	1.00 (0.29-3.45)	0.99 (0.14-7.05)	1.43 (0.93-2.21)	1.57 (0.77-3.23)

(Continued)

Table 2—*Continued*

Study/Year and Population	Death From Any Cause	Fatal PE	Nonfatal PE	Symptomatic DVT or VTE	Any DVT or VTE (Including Asymptomatic)	Proximal DVT (Including Asymptomatic)	Fatal Bleeding	Nonfatal Major Bleeding	Bleeding Requiring Reoperation
Low-dose aspirin vs no prophylaxis									
PEP trial[21]/2000 Hip fracture, hip or knee replacement[a]	0.96 (0.85-1.09)	0.42 (0.25-0.72)	0.78 (0.51-1.21)	0.72 (0.53-0.96)	NA	NA	0.87 (0.41-1.82)	1.12 (0.94-1.34)	0.97 (0.63-1.51)
Higher-dose aspirin vs no prophylaxis									
APT[22]/1994 Mixed surgery	NA	NA	0.33 (0.03-0.63)	NA	0.77 (0.57-0.97)	NA	NA	1.87 (1.00-3.50)	NA
APT[22]/1994 General surgery	NA	NA	0.29 (0.01-0.57)	NA	0.63 (0.47-0.79)	NA	NA	1.39 (1.12-1.74)	NA

Data are presented as relative risks or OR (95% CI). APT = Antiplatelet Trialists' Collaboration; HIT = heparin-induced thrombocytopenia; IMT = International Multicenter Trial, IPC = intermittent pneumatic compression; NA = not available; PEP = Pulmonary Embolism Prevention; SCITI = Spinal Cord Injury Thromboprophylaxis Investigators. See Table 1 legend for expansion of other abbreviations.

[a]RCTs.

[b]Wound hematoma.

[c]Reanalysis of data using random-effects models.

[d]Postoperative bleeding requiring treatment discontinuation.

[e]Reanalysis of data to reflect reclassification of miscoded events from study by Pezzuoli et al.[11]

[f]Intracranial bleeding.

[g]VTE-related death.

Table 3—*Relative Risk Estimates From Published Systematic Reviews and Selected Randomized Trials of Mechanical Prophylaxis*

Study/Year and Population	PE	Symptomatic DVT	Asymptomatic DVT (Any)	Asymptomatic Proximal DVT
IPC vs no prophylaxis				
Vanek[23]/1998 Mixed surgery	0.89 ($P = .82$)	NA	0.38 ($P < .001$)	0.43 ($P < .001$)
Roderick et al[24]/2005 Mixed medicine/surgery	NS	NA	0.34 (0.20-0.48)	0.48 (0.22-0.74)
Urbankova et al[25]/2005 Mixed surgery	1.12 (0.53-2.35)	NA	0.40 (0.29-0.56)	NA
Collen et al[10]/2008 Neurosurgery	0.37 (0.03-4.06)	NA	0.41 (0.21-0.78)	NA
ES vs no prophylaxis				
Roderick et al[24]/2005 Mixed medicine/surgery	NS	NA	0.34 (0.14-0.54)	0.36 (0-1.30)
CLOTS1[26]/2009 Acute stroke	0.65 (0.32-1.31)	0.90 (0.62-1.31)	0.90 (0.73-1.11)	1.01 (0.74-1.36)
Sachdeva et al[27]/2010 Mixed surgical	0.13 (0-6.68)	NA	0.35 (0.26-0.47)	NA
IPC vs ES				
Vanek[23]/1998 Mixed surgery	1.47 ($P = .71$)	NA	0.53 ($P = .04$)	0.74 ($P = .56$)
Collen et al[10]/2008 Neurosurgery	0.49 (0.08-2.85)	NA	0.81 (0.32-1.78)	NA
Add ES to pharmacologic prophylaxis				
Sachdeva et al[27]/2010 Mixed medicine and surgery	0.36 (0.13-0.99)	NA	0.25 (0.17-0.36)	NA
Reanalysis of data from Roderick, Sachdeva, Kakkar et al[18]	0.43 (0.16-1.18)	NA	0.40 (0.25-0.65)	0.28 (0.09-0.87)
Add IPC to pharmacologic prophylaxis				
Reanalysis of data from Roderick, Sachdeva, Kakkar	0.57 (0.16-2.0)	NA	0.45 (0.20-1.03)	1.04 (0.29-3.79)
Add any mechanical prophylaxis to pharmacologic prophylaxis				
Reanalysis of data from Roderick, Sachdeva, Kakkar	0.48 (0.22-1.05)	NA	0.41 (0.27-0.62)	0.50 (0.21-1.16)

Data are presented as relative risk (95% CI), unless otherwise indicated. CLOTS1 = Clots in Legs or Stockings after Stroke; NS = not significant. See Table 1 and 2 legends for expansion of other abbreviations.

2.1 ES vs No Prophylaxis

A Cochrane review summarized results of eight older trials of ES vs no prophylaxis, including four trials in general surgery and one trial each in orthopedic, cardiac, gynecologic, and neurosurgery.[27] The studies had many limitations, including small samples, incomplete blinding, uncertain concealment of treatment allocation, and use of fibrinogen leg scanning to identify asymptomatic DVT. Across all trials, ES reduced the odds of DVT (including distal and asymptomatic DVT) by 65%. A previous meta-analysis reported similar results for all DVT, but reductions in proximal DVT and PE were neither confirmed nor excluded.[24]

More recently, a large, multicenter, randomized controlled trial in patients with acute stroke provided additional, indirect evidence by comparing thigh-length ES plus routine care with routine care alone (including the use of heparin, warfarin, or alteplase in 12% of participants). Reductions in the risk of fatal or nonfatal PE (OR, 0.65; 95% CI, 0.32-1.31) and symptomatic proximal DVT (OR, 0.84; 95% CI, 0.53-1.31) were neither confirmed nor excluded, but use of ES was associated with a fourfold increase in the risk of skin complications (5.1% vs 1.3%), including breaks, ulcers, blisters, and necrosis.[26] A subsequently published trial of thigh-length stockings vs calf-length stockings found that thigh-length stockings reduced the risk of symptomatic or asymptomatic proximal DVT by 31%, an absolute difference of 2.5 percentage points.[29] In this study, skin complications were observed in 3.9% of patients in the thigh-length ES group. The incidence of skin complications with ES in nonorthopedic surgical patients is likely to be lower than that observed in these trials of elderly patients with stroke who wore stockings for up to 30 days.

2.2 IPC vs No Prophylaxis

Several meta-analyses have compared IPC and no prophylaxis in mixed surgical populations.[23-25]

Table 4—*Relative Risk Estimates From Published Systematic Reviews of Studies Comparing Pharmacologic and Mechanical Prophylaxis*

Study/Year and Population	PE	Asymptomatic DVT (Any)	Asymptomatic Proximal DVT	Nonfatal Major Bleeding	ICH	Death From Any Cause
LDUH vs nonpharmacologic						
Collen et al[10]/2008 Neurosurgery	NA	NA	NA	0.85 (0.12-5.99)	2.11 (0.39-11.3)	0.97 (0.13-7.37)
LMWH vs nonpharmacologic						
Collen et al[10]/2008 Neurosurgery	NA	NA	NA	0.95 (0.18-5.09)	1.97 (0.64-6.09)	0.96 (0.47-1.96)
LMWH vs IPC						
Collen et al[10]/2008 Neurosurgery	1.62 (0.35-7.46)	0.79 (0.30-2.12)	NA	NA	NA	NA
LMWH vs ES						
Collen et al[10]/2008 Neurosurgery	0.29 (0.05-1.85)	0.60 (0.44-0.81)	NA	NA	NA	NA
Any mechanical vs LDUH or LMWH						
Eppsteiner et al[28]/2010 Mixed surgery	1.03 (0.48-2.22)	1.07 (0.72-1.61)	NA	0.43 (0.19-0.98)	NA	NA
Any mechanical vs LDUH						
Eppsteiner et al[28]/2010 Mixed surgery	NA	0.71 (0.42-1.19)	NA	NA	NA	NA
Any mechanical vs LMWH						
Eppsteiner et al[28]/2010 Mixed surgery	NA	1.80 (1.16-2.79)	NA	NA	NA	NA
IPC vs heparin						
Vanek[23]/1998 Mixed surgery	1.04 ($P = 1.0$)	0.52 ($P = .01$)	0.43 ($P = .06$)	NA	NA	NA

ICH = intracranial hemorrhage. See Table 1 and 2 legends for expansion of other abbreviations.

Urbankova et al[25] identified 15 trials, including five in orthopedics, four in general surgery, three in oncologic surgery, three in neurosurgery, and one in urology. Roderick et al[24] identified 19 trials, including five in general surgery, five in orthopedics, five in neurosurgery, two in gynecology, one in urology, and one in trauma. Many studies were limited by small samples, lack of blinding, unclear concealment of allocation sequence, and use of fibrinogen leg scanning (or less commonly, ultrasound or venography) to identify asymptomatic DVT, although DVT was subsequently confirmed by venography in most of the studies that used fibrinogen scanning. Both analyses found that compared with no prophylaxis, IPC reduced the risk of DVT (including asymptomatic and distal DVT) by 60%. In the analysis that examined proximal DVT, IPC reduced the odds by 50%.[24] Results failed to demonstrate or to exclude an effect on PE.[25] Other outcomes (fatal PE, skin complications) were not reported.

Adherence with IPC often is less than optimal. However, in one randomized trial of patients with acute spinal cord injury, 90% of participants were noted to use IPC for at least 75% of the recommended 22 h per day.[30] In another study, adherence with IPC was assessed at six times over a 24-h period in 227 nonambulatory trauma patients.[31] Although full adherence was noted in only 19% of patients, overall adherence across all six measurements was 53%.

2.3 Unfractionated Heparin vs No Prophylaxis

Low doses (10,000-15,000 units/d) of subcutaneously administered unfractionated heparin have been evaluated in numerous randomized controlled studies in heterogeneous surgical populations. Moderate- to high-quality evidence comes from a meta-analysis that analyzed data from 69 studies of LDUH prophylaxis in general surgery, urological surgery, and orthopedic surgery.[9] Many of the studies were limited by lack of blinding, unclear concealment of treatment allocation, and use of fibrinogen leg scanning to identify asymptomatic DVT. However, results were consistent with those from the International Multicenter Trial, a large randomized controlled trial with a low risk of bias.[8] In our reanalysis of data from this meta-analysis, we found that LDUH was associated with an 18% reduction in the odds of death from any cause, a 47% reduction in the odds of fatal PE, and a 41% reduction in the odds of nonfatal PE, along with a 57% increase in the odds of nonfatal major bleeding (Figs S1-S5).

2.4 LMWH vs No Prophylaxis

A meta-analysis summarized data from eight trials of five different preparations of LMWH vs no prophylaxis in general or abdominal surgery.[13] Two of eight studies were open label, and of three studies that reported symptomatic VTE, only one was potentially biased by the routine use of fibrinogen leg scanning to identify asymptomatic DVT. In the control groups, the pooled (baseline) risks of clinical PE, clinical VTE, and death were 0.5%, 0.9%, and 0.9%, respectively. Compared with no prophylaxis, LMWH reduced the risk of clinical PE and clinical VTE by ~70%. In addition, LMWH was associated with a possible reduction in the risk of death from any cause (risk ratio [RR], 0.54; 95% CI, 0.27-1.10). LMWH led to an approximate doubling of the risks of major bleeding (RR, 2.03; 95% CI, 1.37-3.01) and wound hematoma (RR, 1.88; 95% CI, 1.54-2.28). Similar results were reported in the more recent meta-analysis by the British National Collaborating Centre for Acute Care, which included studies of GI, gynecologic, urological, and thoracic surgery.[32]

2.5 LMWH vs LDUH

A meta-analysis of 51 randomized controlled trials compared LMWH and LDUH in >48,000 general and abdominal surgery patients.[13] About one-third of the studies were open label, and a majority used fibrinogen uptake scanning (with or without confirmatory venography) to identify asymptomatic DVT. In most studies, follow-up was for either 7 days or 1 month. Across all studies that reported clinical VTE events, the risk was ~30% lower in the LMWH groups. However, this difference was not apparent when the analysis was restricted to blinded, placebo-controlled trials. In addition, results failed to demonstrate or to exclude a beneficial effect of LMWH vs LDUH on clinical PE, death from any cause, major bleeding, and wound hematoma. Similar results were reported in the meta-analysis by the British National Collaborating Centre for Acute Care.[32]

2.6 Extended- vs Limited-Duration LMWH

The risk of VTE remains elevated for at least 12 weeks following surgery. A population-based, prospective study from the United Kingdom reported that compared with no surgery, the risk of VTE remained 10 to 50 times higher in weeks 7 to 12 following inpatient surgery.[33] In another study, the median time to postoperative VTE was 65 days.[34] Several studies compared extended-duration prophylaxis with LMWH (typically for 4 weeks) with limited-duration prophylaxis. Three systematic reviews summarized the results of these studies.[15-17] Study limitations include an open-label design in two studies and measurement of asymptomatic DVT by venography as a surrogate outcome. All three analyses concluded that extended-duration prophylaxis reduced

the risk of symptomatic or asymptomatic DVT by at least 50%, and two reported that proximal DVT was reduced by 75%. Results failed to demonstrate or exclude differences between groups in other outcomes, including major bleeding and death.

More recently, a multicenter, randomized, blinded, placebo-controlled trial compared an additional 3 weeks of pharmacoprophylaxis with bemiparin with no additional prophylaxis in 626 patients who underwent abdominal or pelvic surgery for cancer, all of whom received ~1 week of prophylaxis with once-daily bemiparin.[18] Surveillance venography was performed after 3 weeks, and patients were followed for clinical events for as long as 3 months. Approximately 20% of patients were excluded from assessment of the primary end point because venography was inadequate or not performed. The primary outcome was a composite of any DVT (including asymptomatic and distal events), nonfatal PE, and death from any cause. Although the risk of the composite outcome was 24% lower and the risk of proximal DVT was 88% lower in the extended-duration prophylaxis group, there were no symptomatic, nonfatal VTE events in either group. Although results failed to demonstrate or exclude a difference in bleeding, major bleeding was very uncommon, suggesting that any true underlying absolute differences will be small.

2.7 Fondaparinux vs LMWH

Fondaparinux was compared with the LMWH dalteparin in a blinded, randomized controlled trial of 2,927 patients at high risk for VTE who underwent abdominal (primarily GI) surgery.[20] Fondaparinux was associated with a possible reduction in asymptomatic or symptomatic DVT (RR, 0.75; 95% CI, 0.52-1.09), but results failed to demonstrate or exclude differences in the risks of fatal PE and nonfatal symptomatic VTE. There was a possible increase in the risk of nonfatal major bleeding with fondaparinux (RR, 1.43; 95% CI, 0.93-2.21), but differences in the risks of fatal bleeding and bleeding requiring reoperation were neither confirmed nor excluded.

Moderate-quality evidence from studies of patients undergoing elective hip replacement, elective knee replacement, and hip fracture surgery, when pooled with results of the previous study[20] in abdominal surgery, suggests that when compared with LMWH, fondaparinux does not reduce patient-important VTE events but leads to more major bleeding events.[35]

2.8 Fondaparinux Plus IPC vs IPC Alone

Another placebo-controlled study compared fondaparinux plus IPC with IPC alone in 1,309 patients who underwent major GI, gynecologic, urological, or other abdominal surgery.[19] In this study, the risk of any VTE (including asymptomatic DVT) was 69% lower in the fondaparinux group, and fondaparinux was associated with a possible reduction in the risk of proximal DVT (RR, 0.14; 95% CI, 0.02-1.14), but there was only one case of symptomatic VTE in each of the treatment groups. Major bleeding was more common among those who received fondaparinux (RR, 10.2; 95% CI, 1.31-79.7), but differences between the groups in fatal bleeding and bleeding requiring reoperation were neither confirmed nor excluded.

2.9 Low-Dose Aspirin (160 mg) vs No Prophylaxis

Perioperative use of low-dose aspirin was studied in orthopedic surgical patients in the PEP (Pulmonary Embolism Prevention) trial, a blinded, placebo-controlled study of > 13,000 patients undergoing hip fracture surgery and almost 4,100 patients undergoing elective arthoplasty.[21] The treatment group received aspirin 160 mg/d for 35 days, with the first dose chewed prior to surgery. In our reanalysis of data from both hip fracture and elective arthroscopy patients (Figs S6-S11), benefits included a 28% reduction in the risk of nonfatal symptomatic DVT (RR, 0.72; 95% CI, 0.53-0.96) and a 58% reduction in the risk of fatal PE (RR, 0.42; 95% CI, 0.25-0.72), whereas harms included a possible increase in the risk of nonfatal myocardial infarction (RR, 1.59; 95% CI, 0.98-2.57). Differences between aspirin and placebo were neither confirmed nor excluded for other outcomes.

Strengths of the PEP trial include the very large sample, adequate blinding of patients and outcome adjudicators, adequate concealment of the allocation sequence, complete follow-up, and reporting of well-defined clinically important outcomes. However, although several types of nonfatal bleeding complications were reported, it is somewhat difficult to assess their severity. A potentially more important limitation is uncertainty about whether the results are applicable to nonorthopedic surgical patients. There have been no studies of low-dose aspirin in nonorthopedic surgical patients, and we consider higher doses of aspirin to be a distinct intervention with uncertain risks and benefits (Figs S12-S23). Because of concerns about indirectness, attendees at the AT9 final conference voted that low-dose aspirin should not be an alternative for pharmacologic prophylaxis in most nonorthopedic surgical patients. Our recommendations for low-dose aspirin, therefore, apply only in circumstances in which LDUH and LMWH are contraindicated or not available.

2.10 Mechanical vs Pharmacologic Prophylaxis

A meta-analysis identified 16 studies that compared mechanical prophylaxis with either LDUH or

LMWH, including seven studies in general or abdominal-pelvic surgery, six in orthopedics, and three in trauma.[28] Studies compared heparin with IPC (nine studies), foot pump (four studies), or ES (three studies). Sample sizes ranged from 51 to >2,000 participants. Patients and treating physicians were not blinded to treatment assignment, and radiologists were blinded in only six studies. Follow-up ranged between 3 and 6 weeks in most studies. When results from all studies were pooled, a difference in the risk of DVT (including asymptomatic and distal DVT) was neither confirmed nor excluded (RR, 1.07; 95% CI, 0.72-1.61). However, when the analysis was restricted to eight studies that compared mechanical prophylaxis with LMWH, the risk of DVT was 80% higher in the mechanical prophylaxis group (RR, 1.80; 95% CI, 1.16-2.79). The risk of major bleeding complications was 57% lower in those who received mechanical prophylaxis, with no difference in the relative risk of bleeding between studies of LDUH and LMWH.

2.11 Mechanical Prophylaxis Plus Pharmacologic Prophylaxis vs Pharmacologic Prophylaxis Alone

Ten studies compared ES plus pharmacologic prophylaxis with pharmacologic prophylaxis alone, including six in general or abdominal surgery[36-41] and four in orthopedics.[42-45] Background (pharmacologic) prophylaxis included LDUH in five studies, dextran in three studies, LMWH in one study, and aspirin in one study. Many of the studies were limited by small samples, incomplete blinding, uncertain concealment of the allocation sequence, and measurement of surrogate outcomes (Table S4). Pooling the results of these studies, we found that the addition of ES resulted in a 60% reduction in DVT (including asymptomatic and distal DVT) and a 72% reduction in proximal DVT, but a difference in the risk of PE was neither confirmed nor excluded (OR, 0.43; 95% CI, 0.16-1.18) (Figs S24-S27).

Five studies compared IPC plus pharmacologic prophylaxis with pharmacologic prophylaxis alone, including four studies in orthopedics and one study in general surgery.[46-50] Background prophylaxis included LMWH (two studies), LDUH (one study), dextran (one study), and aspirin (one study). Once again, most studies were limited by small samples, incomplete blinding, unclear concealment of the allocation sequence, and measurement of surrogate outcomes. Pooled results across all five studies revealed a possible reduction in symptomatic or asymptomatic DVT (OR, 0.45; 95% CI, 0.20-1.03), but differences in proximal DVT or PE were neither confirmed nor excluded (Figs S24-S27).

For studies of both ES and IPC, reductions in symptomatic or asymptomatic DVT were similar across subgroups defined by surgical population (general and abdominal vs orthopedic), background agent used for pharmacoprophylaxis, whether the allocation sequence was adequately concealed, and whether there was blinded assessment of outcomes. Reductions in symptomatic or asymptomatic DVT differed depending on the test or tests used to identify and confirm DVT, with greater magnitudes of benefit observed in studies that used ultrasound (with or without confirmatory venography) or fibrinogen uptake with confirmatory venography than in those that used fibrinogen uptake or venography alone (Figs S28-S47).

2.12 IVC Filter vs No IVC Filter

The highest-quality evidence regarding the effectiveness of IVC filters is indirect, coming from a randomized controlled trial that compared IVC filter placement to no filter placement in patients with objectively confirmed, symptomatic, proximal DVT. In this study, filter placement was associated with a 78% reduction in the odds of symptomatic or asymptomatic PE at day 12, but after 2 years, there was an 87% increase in the odds of DVT, and a difference in PE was neither confirmed nor excluded.[51] After 8 years of follow-up, a 9% absolute reduction in the risk of PE was offset by a 10% absolute increase in the risk of DVT.[52]

More direct, but lower-quality evidence comes from a large, prospective cohort study that used propensity scoring methods to compare VTE outcomes among bariatric surgery patients with and without IVC filters.[53] Before propensity adjustment, patients with IVC filters had higher rates of postoperative VTE and death or serious disability. Following propensity adjustment, the difference in postoperative VTE was no longer statistically significant, but the risk of death or serious disability remained 2.5 times higher in the filter group.

A systematic review of seven nonrandomized studies in trauma reported that the pooled odds of PE were 79% lower (OR, 0.21; 95% CI, 0.09-0.49) among patients who received an IVC filter compared with historical control subjects who were variably matched for type of injury, age, sex, injury severity, and VTE risk.[54] A previous systematic review of 16 case series reported the following pooled risks after IVC filter placement: PE, 0.6%; DVT, 9.3%; insertion site thrombosis, 2%; IVC occlusion or thrombosis, 1.6%; placement complications, 1.4%; and filter migration, 0.4%.[55] Thus, although placement of an IVC filter probably reduces the risk of PE over the short term, complications appear to be frequent, and long-term benefits are unclear. Although retrievable filters have the potential to reduce long-term complications, they often are not removed.

2.13 VCU vs No VCU

Most studies of surveillance VCU have been performed in trauma patients. These patients often have contraindications to pharmacologic and mechanical prophylaxis, and the risk of VTE may be high even when prophylaxis is used.[56-59] However, it is not clear that using VCU to detect and treat asymptomatic DVT reduces the risk of PE or fatal PE. Some studies have demonstrated that PE can occur even when VCU is negative.[60,61] A large retrospective study from a single center reported that over a 6-year period ending in 2000, the frequency of surveillance VCU decreased from 32% to 3.4%, with no increase in the incidence of PE.[61] Furthermore, compared with venography, >50% of the apparently positive findings on surveillance VCU may be false positives,[30] and the potential risks associated with treating false-positive findings are substantial.

2.14 Economic Evaluations of Interventions for Thromboprophylaxis

At least seven studies have examined economic outcomes associated with thromboprophylaxis in nonorthopedic surgical patients (Tables S5, S6). Most used a decision analysis approach and assumed a societal perspective in which all costs were considered. None of the results met prespecified criteria for upgrading or downgrading recommendations on the basis of resource use considerations.[3]

One study compared ES, IPC, LDUH, and no prophylaxis. Compared with no prophylaxis, ES saved 28 lives and reduced costs by $335,000 per 10,000 patients treated. Compared with ES, IPC saved six additional lives and cost an additional $413,000 per 10,000 patients treated, whereas LDUH saved seven additional lives and cost an additional $568,000 per 10,000 patients treated.[62]

Four studies compared LMWH with LDUH in different surgical populations (colorectal, general, gynecologic, and abdominal surgery) within different health-care systems (Ontario, Canada; Germany; US Medicare).[63-66] In two of these studies,[63,65] total costs associated with LMWH treatment were marginally higher than those for LDUH. In contrast, in a study of general surgical patients in Germany,[64] LMWH was more effective than LDUH by 0.01 quality-adjusted life years (QALYs) and was less expensive by $160 per patient treated. In another study in abdominal surgery patients that used Medicare reimbursement as a proxy for costs,[66] LMWH prophylaxis with dalteparin 5,000 units/d cost $21,800 per QALY gained relative to LDUH. One study compared LMWH plus IPC with IPC alone in gynecologic surgery patients and found that LMWH plus IPC cost between $7,200 and $20,000 per QALY gained.[67] Finally, one study compared enoxaparin and fondaparinux and reported that total hospital charges were higher for patients treated with enoxaparin.[68]

3.0 Risk Stratification, Rationale for Prophylaxis, and Recommendations in General, Abdominal-Pelvic, Bariatric, Vascular, and Plastic and Reconstructive Surgery

We divide the remainder of the article into sections based on surgical specialty and body region. We discuss relevant information about risk factors and risk stratification for thrombosis and bleeding, provide recommendations, and explain their rationale. Additional details are provided in the Appendix S1 and Tables S7 and S8.

3.1 Target Population: General and Abdominal-Pelvic Surgery, Including GI Surgery, Gynecologic Surgery, and Urological Surgery

This section covers general and abdominal-pelvic surgery. This group includes patients undergoing GI, urological, and gynecologic surgery as well as other general surgery patients (including those having operations on the breast and thyroid and parathyroid glands).

3.1.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE: In patients undergoing general and abdominal-pelvic surgery, the risk of VTE varies depending on both patient-specific and procedure-specific factors. Examples of relatively low-risk procedures include laparoscopic cholecystectomy, appendectomy, transurethral prostatectomy, inguinal herniorrhaphy, and unilateral or bilateral mastectomy.[69-76] Open-abdominal and open-pelvic procedures are associated with a higher risk of VTE.[75,77] VTE risk appears to be highest for patients undergoing abdominal or pelvic surgery for cancer.[71,75,78,79] A comprehensive list of population-based, procedure-specific estimates of the 91-day risk of clinically diagnosed VTE has been compiled from the California Patient Discharge Data Set.[76]

Patient-specific factors also determine the risk of VTE, as demonstrated in several relatively large studies of VTE in mixed surgical populations. Independent risk factors in these studies include age >60 years, prior VTE, and cancer[80]; age ≥60 years, prior VTE, anesthesia ≥2 h, and bed rest ≥4 days[78]; older age, male sex, longer length of hospital stay, and higher Charlson comorbidity score[34]; and sepsis, pregnancy or postpartum state, central venous access, malignancy, prior VTE, and inpatient hospital stay >2 days.[81] In another study, most of the moderate to strong

independent risk factors for VTE were surgical complications, including urinary tract infection, acute renal insufficiency, postoperative transfusion, perioperative myocardial infarction, and pneumonia.[77]

Risk stratification for VTE is challenging but essential and requires consideration of both patient- and procedure-specific risk factors. Although several models for risk stratification exist, all have important limitations. In the absence of rigorously developed and extensively validated risk assessment models, clinicians should consider the following options as a guide for decision making that should be adapted to individual patient circumstances. Table 5 summarizes the findings of two risk assessment models in three different surgical populations and provides rough estimates for the baseline risk of VTE (in the absence of prophylaxis) in very-low-, low-, moderate-, and high-risk patients.

One rigorously developed model used data from 183,069 patients in the Patient Safety in Surgery Study who underwent general, vascular, and thoracic procedures at one of 128 Veterans Administration medical centers or 14 private sector hospitals between 2002 and 2004.[82] This model assigned points (the Rogers score) to variables that were found to be independent predictors of VTE risk, including type of operation, work relative value units, patient characteristics, and laboratory values (Table 6). Using this model, the risk of symptomatic VTE varied from very low (0.1%) to low (~0.5%) to moderate (~1.5%) in both development and validation samples (Table 5). Unfortunately, this model is somewhat cumbersome to use and has not been externally validated. In addition, information was not provided about how many patients received prophylaxis. It is likely that at least some patients received mechanical prophylaxis, pharmacologic prophylaxis, or both, which may help to explain the relatively low observed risk of VTE.

Another model (the Caprini score) estimates VTE risk by adding points for various VTE risk factors, as shown in Table 7.[83,84] In our adaptation of this model, VTE risk is categorized as being very low (0-1 point), low (2 points), moderate (3-4 points), or high (≥5 points). Although this model was not developed using rigorous statistical methods, and includes some variables that were later found not to be associated with VTE risk,[81] it is relatively easy to use and appears to discriminate reasonably well among patients at low, moderate, and high risk for VTE.

The Caprini score was validated in a large retrospective study in a sample of general, vascular, and urological surgery patients.[81] This study included a representative sample of surgical patients, avoided exclusions, minimized losses to follow-up and was therefore judged to have a low risk of bias. In addition, the investigators collected information about prophylaxis received, which enabled us to adjust for this and estimate what the baseline risk of VTE would have been in the absence of prophylaxis (Table 5). The Caprini score has also been validated in a sample of plastic and reconstructive surgery patients.[4] Although neither the Caprini score nor the Rogers score has yet been validated specifically in gynecologic surgery patients, we believe that these patients are sufficiently similar to other abdominal and pelvic surgery patients to permit generalization.

To derive estimates of the baseline risk of VTE across risk groups, we used the observed risks of VTE reported in the validation study by Bahl et al[81] and adjusted for prophylaxis received. As shown in Table 5, the estimated baseline risks of VTE were < 0.5%, 1.5%, 3.0%, and 6.0% in patients at very low, low, moderate, and high risk for VTE, respectively (after adjusting for prophylaxis received). To estimate the baseline risk of fatal PE, we assumed that the ratio of fatal PE to nonfatal PE was ~20%[9] and further assumed that this ratio did not vary across low-, moderate-, and high-VTE risk categories.

3.1.2 Baseline Risk, Risk Factors, and Risk Stratification for Major Bleeding Complications: Relatively little research has attempted to identify risk factors for thromboprophylaxis-related bleeding in general or abdominal-pelvic surgery, although a few studies have identified risk factors in patients undergoing gastric cancer surgery,[85] pancreaticoduodenectomy,[86] partial hepatic resection,[87] and mixed abdominal surgery (Table 8).[88]

In the absence of data from large, prospective, population-based observational studies, the baseline risk of bleeding can be derived from the control (placebo or no pharmacologic prophylaxis) groups in randomized trials. However, most randomized controlled trials of pharmacoprophylaxis exclude patients who are believed to be at increased risk for bleeding. With that limitation in mind, we estimated the average baseline risk of major bleeding in the absence of prophylaxis by using the pooled risk from the control groups in seven randomized trials of LMWH as reported in a meta-analysis.[13] In our reanalysis of these data, the pooled (random effects) risk of major bleeding in the control groups was 1.2% (95% CI, 0.9%-1.7%). Another meta-analysis reported that the mean risk of wound hematoma and bleeding requiring reoperation in the control groups of randomized trials of thromboprophyaxis with LDUH or LMWH were 0.8% and 0.7%, respectively.[95] When making trade-offs between benefits and harms of pharmacologic prophylaxis, we estimated that the baseline risk of major bleeding is 1.8 times greater in high-risk patients based on data from Cohen et al.[96]

Table 5—*Risk Stratification for VTE in General, Abdominal-Pelvic, Bariatric, Vascular, and Plastic and Reconstructive Surgery*

	Patient Population							
	Patients Undergoing Major General, Thoracic, or Vascular Surgery		Patients Undergoing General Surgery, Including GI, Urological, Vascular, Breast, and Thyroid Procedures		Patients Undergoing Plastic and Reconstructive Surgery			
AT9 VTE Risk Category	Rogers Score	Observed Risk of Symptomatic VTE, %	Caprini Score	Observed Risk of Symptomatic VTE, %	Caprini Score	Observed Risk of VTE, %	Other Surgical Populations in Risk Category	Estimated Baseline Risk in the Absence of Pharmacologic or Mechanical Prophylaxis, %
Very low	< 7	0.1	0	0	0-2	NA	Most outpatient or same-day surgery	< 0.5
Low	7-10	0.4	1-2	0.7	3-4	0.6	Spinal surgery for nonmalignant disease	1.5
Moderate	> 10	1.5	3-4	1.0	5-6	1.3	Gynecologic noncancer surgery Cardiac surgery Most thoracic surgery Spinal surgery for malignant disease	3.0
High	NA	NA	≥ 5	1.9	7-8	2.7	Bariatric surgery Gynecologic cancer surgery Pneumonectomy Craniotomy Traumatic brain injury Spinal cord injury Other major trauma	6.0

AT9 = Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.

Table 6—*Risk Assessment Model From the Patient Safety in Surgery Study*

Risk Factor	Risk Score Points
Operation type other than endocrine	
Respiratory and hernic	9
Thoracoabdominal aneurysm, embolectomy/thrombectomy, venous reconstruction, and endovascular repair	7
Aneurysm	4
Mouth, palate	4
Stomach, intestines	4
Integument	3
Hernia	2
ASA physical status classification	
3, 4, or 5	2
2	1
Female sex	1
Work RVU	
> 17	3
10-17	2
Two points for each of these conditions	2
Disseminated cancer	
Chemotherapy for malignancy within 30 d of operation	
Preoperative serum sodium > 145 mmol/L	
Transfusion > 4 units packed RBCs in 72 h before operation	
Ventilator dependant	
One point for each of the conditions	1
Wound class (clean/contaminated)	
Preoperative hematocrit level ≤ 38%	
Preoperative bilirubin level > 1.0 mg/dL	
Dyspnea	
Albumin level ≤ 3.5 mg/dL	
Emergency	
Zero points for each of these conditions	0
ASA physical status class 1	
Work RVU < 10	
Male sex	

ASA = American Society of Anesthesiologists; RVU = relative value unit. Republished with permission from Rogers et al.[82]

3.2 *Target Population: Bariatric Surgery*

Despite the explosion in the number of bariatric surgical procedures over the past 2 decades, few randomized controlled trials have evaluated interventions for VTE prophylaxis in these patients. Low-quality evidence comes from a number of uncontrolled and nonrandomized controlled studies (Table S9). We elected to apply higher-quality evidence about relative risks from randomized controlled trials in patients undergoing abdominal and pelvic surgery (section 3.1.2) when making recommendations for bariatric surgery patients, most of whom are at high risk for VTE.

3.2.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE and Major Bleeding Complications: Obesity and perioperative stasis and hypercoagulability place most bariatric surgery patients at high risk for VTE. A systematic review of 37 studies of varying design concluded that obesity is a risk factor for VTE in both medical and bariatric surgical patients.[89] Across 11 studies of bariatric surgery patients, the median incidence of symptomatic VTE and fatal PE were 2.4% and 0.3%, respectively. In most studies, patients received some form of prophylaxis, most often a combination of mechanical and pharmacologic methods, so the baseline risk is almost certainly higher. In the International Bariatric Surgery Registry, PE was the most common cause of postoperative death, accounting for 30% of all mortal events.[97] Reported risk factors for postoperative VTE following bariatric surgery include higher BMI,[97-104] older age,[53,105,106] male sex,[98,103,104] obstructive sleep apnea or obesity hypoventilation syndrome,[98,102,103,107] and a history of VTE.[100,102,103,108] Although these characteristics may help to identify bariatric surgery patients who are at especially high risk, virtually all bariatric surgery patients will have a Caprini score of at least 4 and, therefore, be at least at moderate risk for VTE, and many will have an even higher score that places them in the high-risk category. Although we did not identify studies that specifically addressed the risk of bleeding complications following bariatric surgery, we provide a list of potential risk factors as a guide (Table 8).

3.3 *Target Population: Vascular Surgery*

Eight small randomized controlled trials of thromboprophylaxis have been performed in vascular surgery (Tables S2, S3).[109-116] Most enrolled patients undergoing diverse vascular procedures, but two studied patients undergoing aortic surgery,[109,115] and one enrolled patients undergoing lower-extremity amputation.[116] Three studies compared LDUH (with or without IPC) to no prophylaxis, one compared aspirin to no prophylaxis, and three compared LDUH to LMWH. One study compared LDUH, LDUH plus ergotamine, and dextran.[112] Studies were limited by small samples, incomplete blinding, unclear concealment of treatment allocation, and inconclusive results (Figs S48-S51). Because of these limitations, we apply more-precise estimates of relative risk from higher-quality studies in general and abdominal-pelvic surgery when making recommendations for vascular surgery patients.

3.3.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE: In vascular surgery, inflammation, stasis, and hypercoagulability are at least partially mitigated by intraoperative anticoagulation and early postoperative mobilization. Other unique considerations include a relative contraindication to mechanical prophylaxis in some vascular patients who undergo lower-limb bypass procedures. Although numerous observational studies have examined VTE risk in

Table 7—*Caprini Risk Assessment Model*

1 Point	2 Points	3 Points	5 Points
Age 41-60 y	Age 61-74 y	Age ≥ 75 y	Stroke (< 1 mo)
Minor surgery	Arthroscopic surgery	History of VTE	Elective arthroplasty
BMI > 25 kg/m^2	Major open surgery (> 45 min)	Family history of VTE	Hip, pelvis, or leg fracture
Swollen legs	Laparoscopic surgery (> 45 min)	Factor V Leiden	Acute spinal cord injury (< 1 mo)
Varicose veins	Malignancy	Prothrombin 20210A	
Pregnancy or postpartum	Confined to bed (> 72 h)	Lupus anticoagulant	
History of unexplained or recurrent spontaneous abortion	Immobilizing plaster cast	Anticardiolipin antibodies	
Oral contraceptives or hormone replacement	Central venous access	Elevated serum homocysteine	
Sepsis (< 1 mo)		Heparin-induced thrombocytopenia	
Serious lung disease, including pneumonia (< 1 mo)		Other congenital or acquired thrombophilia	
Abnormal pulmonary function			
Acute myocardial infarction			
Congestive heart failure (< 1 mo)			
History of inflammatory bowel disease			
Medical patient at bed rest			

vascular surgery patients (Appendix S1), most were limited by small samples, incomplete information about use of prophylaxis, and measurement of surrogate outcomes (asymptomatic DVT).

Data from the British Million Women Study showed that the risk of symptomatic VTE in the 12 weeks following inpatient surgery is almost as high in vascular surgery patients (one in 115) as it is in those who have surgery for cancer (one in 85).[33] Another study that used data from the California Discharge Data Set reported that the risk of symptomatic VTE within 91 days of vascular surgery was ~1.7% for all the following vascular procedures: peripheral vascular shunt or bypass, resection and replacement of abdominal aorta, above-knee amputation, aortoilliofemoral bypass or femoral-popliteal aneurysm resection with graft, and ligation and stripping of varicose veins.[75] The risk was slightly lower for patients who underwent below-knee amputation and arteriovenous fistula placement (0.5%-0.9%), and it was lowest for carotid endarterectomy (0.2%). Use of prophylaxis was not described in either of these studies, so the risk of symptomatic VTE in the absence of prophylaxis is likely to be higher.

Risk factors for VTE in vascular surgery are not well established, although several studies have attempted to identify risk factors in this population, with little success.[117-119] However, vascular surgery patients comprised 16% of the retrospective cohort in a validation study of the Caprini model (V. Bahl, DMD, MPP, personal communication, November 29, 2010). Likewise, vascular patients comprised 18% of the sample in the Patient Safety in Surgery Study,[82] supporting the generalizability of both models to vascular surgery patients.

3.3.2 Baseline Risk, Risk Factors, and Risk Stratification for Major Bleeding Complications: Few studies have examined the risk of bleeding in vascular surgery. Across three randomized trials of thromboprophylaxis,[109,111,115] the pooled weighted risk of major bleeding in the control (no prophylaxis) groups was 0.3% (95% CI, 0.2%-2.4%). However, an observational study reported that the incidence of life-threatening hemorrhage among 973 patients undergoing complex major vascular procedures was 1.8%, with most episodes of bleeding occurring intraoperatively and only 0.4% of patients experiencing severe bleeding postoperatively.[120] Because the baseline risk of bleeding is difficult to pinpoint in vascular surgery, we use the baseline risk from studies of general and abdominal-pelvic surgery (1.2%) and provide a list of risk factors as a guide (Table 8).

3.4 Target Population: Plastic and Reconstructive Surgery

Because there have been no randomized controlled trials of thromboprophylaxis in plastic and reconstructive surgery, we applied indirect evidence about relative risks from trials in general and mixed surgical patients when making recommendations.

3.4.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE: A retrospective study examined the 60-day risk of postoperative VTE in 1,126 patients who were at least at moderate risk for VTE (Caprini score, 3-4) and underwent plastic and reconstructive surgery at one of five tertiary-care facilities in the United States between 2006 and 2009.[4] All patients received mechanical prophylaxis with IPC.

Table 8—*Risk Factors for Major Bleeding Complications*

General risk factors
Active bleeding
Previous major bleeding
Known, untreated bleeding disorder
Severe renal or hepatic failure
Thrombocytopenia
Acute stroke
Uncontrolled systemic hypertension
Lumbar puncture, epidural, or spinal anesthesia within previous 4 h or next 12 h
Concomitant use of anticoagulants, antiplatelet therapy, or thrombolytic drugs
Procedure-specific risk factors
Abdominal surgery
Male sex, preoperative hemoglobin level < 13 g/dL, malignancy, and complex surgery defined as two or more procedures, difficult dissection, or more than one anastamosis[89]
Pancreaticoduodenectomy
Sepsis, pancreatic leak, sentinel bleed[87]
Hepatic resection
Number of segments, concomitant extrahepatic organ resection, primary liver malignancy, lower preoperative hemoglobin level, and platelet counts[88]
Cardiac surgery
Use of aspirin[90]
Use of clopidogrel within 3 d before surgery[91]
BMI > 25 kg/m^2, nonelective surgery, placement of five or more grafts, older age[92]
Older age, renal insufficiency, operation other than CABG, longer bypass time[93]
Thoracic surgery
Pneumonectomy or extended resection[94]
Procedures in which bleeding complications may have especially severe consequences
Craniotomy
Spinal surgery
Spinal trauma
Reconstructive procedures involving free flap

CABG = coronary artery bypass graft.

The observed risks of symptomatic VTE, stratified by Caprini score, were 0.6% among those with a score of 3 to 4, 1.3% among those with a score of 5 to 6, 2.7% among those with a score of 7 to 8, and 11.3% among those with a score > 8 (Table 5). Of note, these scores in plastic and reconstructive surgery patients correspond to lower risks of VTE than would be expected in patients undergoing general or abdominal-pelvic surgery.

3.4.2 Baseline Risk, Risk Factors, and Risk Stratification for Major Bleeding Complications: Across three observational studies of patients who underwent plastic and reconstructive procedures, the baseline risk of wound hematoma (in the absence of pharmacologic prophylaxis) ranged from 0.5% to 1.8%.[121-123] Based on this limited evidence, we consider most plastic and reconstructive surgery patients to be at average risk for bleeding complications, recognizing that the consequences of wound hematoma in patients with free flaps can be dire.

3.5 Explanation of Evidence Profiles and Rationale for Recommendations

We believe that the risk stratification scheme described in Table 5 is appropriate for use in general, GI, urological, gynecologic, bariatric, and vascular surgery patients. In addition, the Caprini score can be used in plastic and reconstructive surgery patients, although the baseline risk of VTE appears to be lower among these patients with any given Caprini score (Table 5). For example, although a Caprini score of 3 to 4 is associated with a moderate risk of VTE (~3.0%) in general or abdominal-pelvic surgery, this same score is associated with a low risk of VTE (~1.5%) in plastic and reconstructive surgery.

Information presented in the Table 8 can be used as a guide to help to identify patients in whom the risk of bleeding is high or the consequences of bleeding are especially severe. Statements about the quality of evidence refer to recommendations for patients undergoing general or abdominal-pelvic surgery. Because of indirectness, the quality of evidence should be rated down in other surgical populations.

Among patients with a very low risk of symptomatic VTE (< 0.5%), there is moderate-quality evidence that the harms of pharmacologic prophylaxis with LDUH or LMWH outweigh the benefits. Compared with no prophylaxis, one can expect zero to three fewer nonfatal VTE events and four to 10 more nonfatal major bleeding complications per 1,000 patients treated with LDUH. Trade-offs are similar for LMWH and no prophylaxis. There is low-quality evidence that compared with no prophylaxis, mechanical prophylaxis with IPC or ES can also be expected to prevent zero to three nonfatal VTE events at the expense of inconvenience, cost, and an uncertain number of skin complications, including breaks, blisters, ulcers, and necrosis, suggesting that the harms of mechanical prophylaxis probably outweigh the benefits in this very-low-risk group.

Among patients with a low risk of VTE (~1.5%), moderate-quality evidence suggests that, compared with no prophylaxis, pharmacologic prophylaxis with either LDUH (Table 9) or LMWH (Table 10) can be expected to result in similar numbers of nonfatal VTE events prevented and nonfatal major bleeding events caused, and there is no important reduction in fatal PE. Low-quality evidence suggests that mechanical prophylaxis with either IPC (Table 11) or ES (Table 12) can be expected to prevent about eight to 10 nonfatal VTE events per 1,000 patients treated at the expense of an uncertain number of skin complications. Although direct high-quality evidence

Table 9—*Summary of Findings: Unfractionated Heparin Compared With No Prophylaxis for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: unfractionated heparin
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk Unfractionated Heparin			
Fatal PE (autopsy)	Low-risk population[b]		OR 0.53 (0.31-0.91)	13,492 (20 studies[c])	High[d]
	3 per 1,000	2 per 1,000 (1-3)			
	Medium-risk population[b]				
	6 per 1,000	3 per 1,000 (2-5)			
	High-risk population[b]				
	12 per 1,000	6 per 1,000 (4-11)			
Fatal bleeding (autopsy)	Study population[e]		OR 1.14 (0.41-3.15)	13,280 (7 studies[c])	Moderate[f]
	1 per 1,000	1 per 1,000 (0-3)			
	Low-risk population[e]				
	1 per 1,000	1 per 1,000 (0-3)			
	Medium-risk population[e]				
	2 per 1,000	2 per 1,000 (1-6)			
Nonfatal symptomatic VTE inferred from nonfatal PE (clinical diagnosis)	Low-risk population[g]		OR 0.44 (0.31-0.63)	12,698 (22 studies[c])	Moderate[h,i,j]
	15 per 1,000	7 per 1,000 (5-10)[k]			
	Medium-risk population[g]				
	30 per 1,000	13 per 1,000 (9-19)[k]			
	High-risk population[g]				
	60 per 1,000	27 per 1,000 (19-39)[k]			

(Continued)

Table 9—*Continued*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: unfractionated heparin
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk Unfractionated Heparin			
Nonfatal major bleeding inferred from excessive intraoperative bleeding or need for transfusion (clinical diagnosis)	Low-risk population[l]		OR 1.57 (1.32-1.87)	12,929 (44 studies)	Moderate[h,m]
	12 per 1,000	19 per 1,000 (16-22)[n]			
	Medium-risk population[l]				
	22 per 1,000	34 per 1,000 (29-40)[n]			

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. GRADE = Grades of Recommendations, Assessment, Development, and Evaluation. See Table 1 legend for expansion of other abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Pooled risk of fatal PE was 55 of 6,683 (0.8%) in the control groups. Risk of fatal PE in low-, moderate-, and high-risk groups calculated under the assumption that the ratio of PE to fatal PE did not vary across risk categories.

[c]Relative risk estimates based on reanalysis of data reported in meta-analysis by Collins et al,[9] using a random-effects statistical model. Duration of follow-up varied, but usually to hospital discharge.

[d]Mild to moderate unexplained heterogeneity across 10 studies of general surgery; no significant heterogeneity between surgical populations or across all 20 studies.

[e]Pooled risk of fatal bleeding was six of 6,577 (0.1%) in the control groups. Risk of fatal bleeding in low- and high-risk groups calculated under the assumption that the ratio of clinically important bleeding to fatal bleeding did not vary across risk categories.

[f]Pooled effect includes possibility of both substantial benefit and serious harm.

[g]Baseline risk of VTE in moderate-, high-, and very-high-risk patients, after adjustment for prophylaxis received. Data from Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%.

[h]Many studies were not blinded, and allocation concealment was not adequately described.

[i]There was mild heterogeneity across surgical specialties. OR for nonfatal PE was 0.44 (95% CI, 0.31-0.63) in 22 trials of general surgery, 0.29 (95% CI, 0.03-2.24) in two trials of urological surgery and 4.66 (95% CI, 0.53-40.8) in two trials of orthopedic trauma.

[j]Relative risk of symptomatic VTE assumed to be identical to that for nonfatal PE.

[k]Overall incidence of VTE within 30 d of surgery in a large prospective study of patients undergoing general, urological, or vascular surgery (Bahl et al[81]) prior to adjustment for prophylaxis.

[l]In seven studies of LMWH vs no prophylaxis in abdominal surgery (Mismetti et al[13]), the weighted pooled (random-effects model) risk of major bleeding in the control groups was 1.2%. In 36 studies of LMWH vs unfractionated heparin in abdominal surgery, the pooled risk of major bleeding in the unfractionated heparain groups was 3.2%, including 2.7% of patients without cancer and 8.1% of patients with cancer. After adjustment for prophylaxis, the risks for noncancer and cancer surgery were 1.7% and 5.1%, respectively. In a more-recent comparison of LMWH vs fondaparinux, the risk of bleeding requiring reoperation or intervention was 1.0% in the LMWH group (Agnelli et al[20]). In a secondary analysis of RCT data (Cohen et al[90]), the odds of major bleeding were 1.8 times greater in patients with cancer.

[m]Surrogate outcome: major bleeding defined as excessive intraoperative bleeding or need for transfusion.

[n]Pooled observed risk of clinically important bleeding in unfractionated heparin groups, not adjusted for prophylaxis.

Table 10—*Summary of Findings: LMWH Compared With No Prophylaxis for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: LMWH
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk LMWH			
Fatal PE inferred from all-cause mortality Follow-up: 7-270 d	Low-risk population[b]		RR 0.54 (0.27-1.1)	5,142 (5 studies)	Moderate[c]
	3 per 1,000	2 per 1,000 (1-3)			
	Medium-risk population[b]				
	6 per 1,000	3 per 1,000 (2-7)			
	High-risk population[b]				
	12 per 1,000	6 per 1,000 (3-13)			
Fatal bleeding Follow-up: 21-270 d	Study population		No events reported	5,078 (4 studies)	Moderate
	See comment	See comment			
	Low-risk population				
	1 per 1,000	0 per 1,000 (0-0)			
	Medium-risk population				
	2 per 1,000	0 per 1,000 (0-0)			
Nonfatal symptomatic VTE Follow-up: 21-270 d	Low-risk population[d]		RR 0.31 (0.12-0.81)	4,890 (3 studies)	Moderate[e]
	15 per 1,000	5 per 1,000 (2-12)			
	Medium-risk population[d]				
	30 per 1000	9 per 1000 (4-24)			
	High-risk population[d]				
	60 per 1,000	19 per 1,000 (7-49)			
Nonfatal major bleeding (clinical diagnosis) Follow-up: 7-270 d	Low-risk population[f]		RR 2.03 (1.37-3.01)	5,457 (7 studies)	High[g]
	12 per 1,000	24 per 1,000 (16 to 36)			
	Medium-risk population[f]				
	22 per 1,000	45 per 1,000 (30 to 66)			

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. RR = risk ratio. See Table 1 and 9 legends for expansion of other abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Pooled risk of death from any cause was 24 of 2,589 (0.9%) in the control groups. Risk of fatal PE in low-, moderate-, and high-VTE risk groups was calculated under the assumption that the ratio of death from any cause to symptomatic VTE did not vary across risk categories.

[c]The 95% CI includes the possibility of both no effect and substantial benefit.

[d]Baseline risk of VTE in moderate-, high-, and very-high-risk patients after adjustment for prophylaxis received. Data from Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%.

[e]One study was not blinded, and one study had unclear concealment of allocation sequence; nonfatal symptomatic VTE was not objectively confirmed in one large study.

[f]In seven studies of LMWH vs no prophylaxis in abdominal surgery (Mismetti et al[13]), the weighted pooled (random-effects model) risk of major bleeding in the control groups was 1.2%. In 36 studies of LMWH vs unfractionated heparin in abdominal surgery, the pooled risk of major bleeding in the unfractionated heparin groups was 3.2% but was only 2.7% in noncancer surgery and 8.1% in cancer surgery. After adjustment for prophylaxis, the risks for noncancer and cancer surgery were 1.7% and 5.1%, respectively. In a more-recent comparison of LMWH vs fondaparinux, the risk of bleeding requiring reoperation or intervention was 1.0% in the LMWH group. In a secondary analysis of RCT data (Cohen et al[90]), the odds of major bleeding were 1.8 times greater in patients with cancer.

[g]Variable definition of major bleeding across studies.

Table 11—*Summary of Findings: IPC Compared With No Prophylaxis for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: IPC
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk IPC			
Symptomatic VTE, inferred from proximal DVT (FUT ± IPG ± venography or DUS + venography)	Low-risk population		OR 0.48 (0.22-0.74)	1,534 (9 studies)	Low
	15 per 1,000	7 per 1,000 (3-11)			
	Medium-risk population				
	30 per 1,000	15 per 1,000 (7-22)			
	High-risk population				
	60 per 1,000	30 per 1,000 (14-45)			
Skin breaks, blisters, ulcers, necrosis	No evidence				

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. DUS = Doppler ultrasound; FUT = fibrinogen uptake test; IPG = impedence plethysmography. See Table 1 and 9 legends for expansion of other abbreviations.

[a]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

is lacking, we favor IPC over ES primarily on basis of indirect evidence from the Clots in Legs or Stockings after Stroke (CLOTS1) trial in patients with stroke that ES increased the risk of skin complications without reducing the risk of VTE.[26] Low-quality evidence favors mechanical prophylaxis over pharmacologic prophylaxis with either LMWH (Table 13) or LDUH (Table 14) in this group of patients.

Among patients with a moderate risk of VTE (~3.0%) who are not at high risk for major bleeding complications, moderate-quality evidence indicates that compared with no prophylaxis, pharmacologic prophylaxis with either LDUH (Table 9) or LMWH (Table 10) will result in approximately twice as many nonfatal VTE events prevented as nonfatal major bleeding events caused. In addition, one can expect zero to three fewer deaths from PE per 1,000 patients treated. Low-quality evidence suggests that mechanical prophylaxis with either IPC (Table 11) or ES (Table 12) can be expected to prevent 13 to 17 nonfatal VTE events per 1,000 patients treated at the expense of an uncertain number of skin complications. Although low-quality evidence for the direct comparisons between mechanical prophylaxis and LMWH (Table 13) or LDUH (Table 14) seems to favor mechanical prophylaxis in this group of patients, three of the seven authors of this article placed more value on the higher-quality evidence favoring pharmacologic prophylaxis and, therefore, preferred pharmacologic prophylaxis over mechanical prophylaxis in this group. There is moderate-quality evidence that LMWH is at least as safe and effective as LDUH (Table 15).

Among patients with a moderate risk of VTE (~3.0%) who are at high risk for major bleeding complications, moderate-quality evidence indicates that compared with no prophylaxis, pharmacologic prophylaxis with either LDUH (Table 9) or LMWH (Table 10) can be expected to result in similar numbers of nonfatal bleeding events caused and nonfatal VTE events averted. Although the quality of the evidence is low, the balance between desirable and undesirable outcomes appears to be more favorable with mechanical prophylaxis (Tables 11, 12), particularly IPC, which is expected to result in seven to 20 fewer nonfatal VTE events per 1,000 patients at the expense of an uncertain number of skin complications.

Among patients who are at high risk for VTE (~6.0%) but not at high risk for major bleeding complications, there is high-quality evidence that compared with no prophylaxis, LDUH will result in one to eight fewer deaths from PE (Table 9), and there is moderate-quality evidence that LMWH prophylaxis may result in six fewer (95% CI, nine fewer to one more) deaths from PE (Table 10). In addition, there

Table 12—*Summary of Findings: ES Compared With No Prophylaxis for VTE Prevention in Surgical Patients*

Patient or population: for VTE prevention in surgical patients
Settings: hospital
Intervention: ES
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk ES			
Symptomatic VTE inferred from distal or proximal DVT (venography or FUT or IPG ± venography) Follow-up: usually to hospital discharge[b]	Low-risk population[c]		OR 0.35 (0.26-0.47)[d]	1,239 (8 studies[e,f])	Low[g,h]
	15 per 1,000	5 per 1,000 (4-7)[i]			
	Medium-risk population[c]				
	30 per 1,000	11 per 1,000 (8-14)[i]			
	High-risk population[c]				
	60 per 1,000	22 per 1,000 (16-29)[i]			
Skin breaks, blisters, ulcers, necrosis case note review Follow-up: 1-30 d	13 per 1,000	52 per 1,000 (31-87)	OR 4.18 (2.4-7.27)	2,518 (1 study)	Low[j,k]

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 3, 9, and 11 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Duration of follow-up varied, but usually to hospital discharge.

[c]Baseline risk of VTE in moderate-, high-, and very-high-risk patients after adjustment for prophylaxis received. Data from large, retrospective, observational study by Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%.

[d]The OR for PE (one study) was 0.13 (95% CI, 0-6.7). In a separate meta-analysis by Roderick et al,[24] the pooled OR for proximal DVT was 0.36 (95% CI, 0-1.30).

[e]Data for other critical outcomes (eg, fatal PE) not available; bleeding complications not relevant.

[f]Meta-analysis by Sachdeva et al[27] included eight studies of ES in mixed surgical populations.

[g]Unblinded assessment of outcomes and unclear concealment of allocation sequence in many studies.

[h]Relative risk of symptomatic VTE inferred from surrogate outcome (proximal or distal DVT).

[i]Pooled observed risk of proximal or distal DVT in ES groups across eight studies.

[j]Unblinded ascertainment based on case note review.

[k]Based on data from the CLOTS1 study in patients with stroke.

Table 13—*Summary of Findings: Mechanical Prophylaxis Compared With LMWH for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: mechanical prophylaxis
Comparison: LMWH

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk LMWH	Corresponding Risk Mechanical Prophylaxis			
Symptomatic VTE inferred from proximal or distal DVT	Low-risk population		RR 1.80 (1.16-2.79)	3,134 (8 studies[c])	Low
	5 per 1,000	9 per 1,000 (6-14)[b]			
	Medium-risk population				
	9 per 1,000	16 per 1,000 (10-25)[b]			
	High-risk population				
	19 per 1,000	34 per 1,000 (22-53)[b]			
Major bleeding	Low-risk population[d]		RR 0.51 (0.4-0.64)	5,457 (7 studies)	High
	24 per 1,000	12 per 1,000 (10-15)			
	Medium-risk population[d]				
	45 per 1,000	23 per 1,000 (18-29)			
Skin breaks, ulcers, blisters, necrosis	51 per 1,000	13 per 1,000 (7-22)	RR 0.25 (0.14-0.43)	2,518 (1 study)	Low[e,f]

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 3, 9, and 10 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Numbers of events in control group were not reported. Estimated number at risk, assuming equal numbers in intervention and control groups.

[c]Data for other critical outcomes (eg, fatal PE) were not available.

[d]Baseline risk of bleeding estimated from control groups in trials of LMWH vs no prophylaxis adjusted to reflect use of LMWH in all patients.

[e]Unblinded assessment based on case note review.

[f]Data from CLOTS1 study in patients with stroke; applies specifically to prophylaxis with graduated compression stockings and not IPC.

Table 14—*Summary of Findings: Mechanical Prophylaxis Compared With Unfractionated Heparin for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Intervention: mechanical prophylaxis
Comparison: unfractionated heparin

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Unfractionated Heparin	Corresponding Risk Mechanical Prophylaxis			
Symptomatic VTE inferred from any DVT Follow-up: variable	Low-risk population[b]		RR 0.71 (0.42-1.19)[c]	1,269 (8 studies[d])	Low[e]
	7 per 1,000	5 per 1,000 (3-8)[f]			
	Medium-risk population[b]				
	13 per 1,000	9 per 1,000 (5-15)[f]			
	High-risk population[b]				
	26 per 1,000	18 per 1,000 (11-31)[f]			
Major bleeding, defined as excessive intraoperative bleeding or need for transfusion	Low-risk population[g]		OR 0.47 (0.32-0.7)	12,929 (44 studies)	Low[h,i]
	19 per 1,000	9 per 1,000 (6-13)			
	Medium-risk population[f]				
	35 per 1,000	17 per 1,000 (11-25)			
Skin breaks, ulcers, blisters, necrosis	51 per 1,000	13 per 1,000 (7-22)	RR 0.25 (0.14-0.43)	2,518 (1 study)	Low[j,k]

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 3, 9, and 10 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Baseline risk of VTE in moderate-, high-, and very-high-risk patients after adjustment for prophylaxis received. Data from Bahl et al.[S1] In low-risk patients, rate of symptomatic VTE was 0%.

[c]Pooled OR for PE across 15 studies was 1.03 (95% CI, 0.48-2.22). Pooled OR for any DVT for comparison of LMWH vs mechanical across eight studies was 0.71 (95% CI, 0.42-1.19), and pooled OR for any DVT for comparison of unfractionated heparin vs mechanical across eight studies was 1.80 (95% CI, 1.16-2.79).

[d]Data for other critical outcomes (eg, fatal PE) not available.

[e]95% CI includes possibility of both substantial benefit and no effect.

[f]Numbers of events in control group were not reported. Estimated number at risk, assuming equal numbers in intervention and control groups.

[g]Baseline risk of bleeding estimated from control groups in trials of LMWH vs no prophylaxis, adjusted to reflect use of unfractionated heparin in all patients.

[h]Lack of blinding, incomplete details about concealment of allocation sequence, measurement of surrogate outcome.

[i]Data from studies of general, urological, and elective orthopedic surgery and trauma (Collins et al[9]).

[j]Unblinded assessment based on case note review.

[k]Data from CLOTS1 study in stroke patients; applies specifically to prophylaxis with graduated compression stockings and not IPC.

Table 15—*Summary of Findings: LMWH Compared With LDUH for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: LMWH
Comparison: LDUH

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk LDUH	Corresponding Risk LMWH			
Fatal PE inferred from all-cause mortality	Low-risk population[b]		RR 1.04 (0.89-1.2)	41,386 (30 studies)	High
Follow-up: 7-10 d in most studies	3 per 1,000	3 per 1,000 (3-4)[c]			
	Medium-risk population[b]				
	6 per 1,000	6 per 1,000 (5-7)[c]			
	High-risk population[b]				
	12 per 1,000	12 per 1,000 (11-14)[c]			
Symptomatic VTE (objectively confirmed)	Low-risk population[d]		RR 0.71 (0.51-0.99)[e]	13,776 (23 studies)	Moderate[f]
Follow-up: 7-10 d in most studies	7 per 1,000	5 per 1,000 (4-7)[c]			
	Medium-risk population[d]				
	13 per 1,000	9 per 1,000 (7-13)[c]			
	High-risk population[d]				
	26 per 1,000	18 per 1,000 (13-26)[c]			
Major bleeding clinical diagnosis	Medium-risk population[g]		RR 0.89 (0.75-1.05)	18,555 (36 studies)	Moderate[f,h]
Follow-up: 7-10 d in most studies	19 per 1,000	17 per 1,000 (14-20)[c]			
	High-risk population[g]				
	35 per 1,000	31 per 1,000 (26-37)[c]			

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 9, and 10 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Pooled risk of death in unfractionated heparin groups was higher in patients with cancer (4.8% ± 0.8%) than in patients without cancer (1.5% ± 0.1%).

[c]Estimated number of events and patients at risk, assuming equal numbers of patients at risk in unfractionated heparin and LMWH groups.

[d]Baseline risk of symptomatic VTE was higher in patients with cancer (1.8%) than in patients without cancer (1.2%). High-risk estimate from Bahl et al,[81] adjusted to control for prophylaxis given.

[e]Indirect OR is 0.52 (95% CI, 0.18-1.45) based on indirect comparison of LMWH vs unfractionated heparin from studies of LMWH vs placebo and unfractionated heparin vs placebo or no prophylaxis.

[f]About one-half of studies were unblinded; allocation procedures were not described; and, most importantly, trends favoring LMWH for all outcomes disappeared when only double-blinded studies were analyzed.

[g]Baseline risk of major bleeding was higher in patients with cancer (8.1% ± 1.0%) vs patients without cancer (2.7% ± 0.2%).

[h]Definition of major bleeding varied across studies.

is moderate-quality evidence that both LDUH and LMWH will result in substantially more nonfatal VTE events prevented than nonfatal major bleeding events caused. Only low-quality evidence supports the use of mechanical prophylaxis with IPC or ES, which can be expected to result in 30 to 40 fewer nonfatal VTE events per 1,000 patients and an uncertain number of skin complications (Tables 11, 12). However, there is low-quality evidence that in this group of patients, use of mechanical prophylaxis compared with LMWH results in a similar number of major bleeding events averted and VTE events not prevented (Table 13). Nevertheless, we favor LDUH or LMWH over mechanical methods in this group because of the higher quality of evidence and the expected reductions in fatal PE.

Among patients with a high risk of VTE (~6.0%) who are at high risk for major bleeding complications, moderate-quality evidence indicates that the trade-offs still favor pharmacologic prophylaxis with either LDUH (six fewer fatal PE, 33 fewer nonfatal VTE events, and 12 more nonfatal major bleeding events per 1,000 patients) or LMWH (six fewer deaths from any cause, 41 fewer nonfatal VTE events, and 23 more nonfatal major bleeding events per 1,000 patients) over no prophylaxis (Tables 9, 10). However, as the baseline risk of major bleeding approaches 4%, the harms of pharmacologic prophylaxis begin to outweigh the benefits, suggesting that mechanical prophylaxis with IPC (Table 11) or ES (Table 13) should be chosen when the risk of bleeding is judged to be very high or the consequences of major bleeding are believed to be particularly severe.

Among high-VTE risk patients, there is low-quality evidence (Tables 16, 17) that the absolute number of nonfatal VTE events can be further reduced by the addition of either IPC (10 fewer events per 1,000) or ES (11 fewer events per 1,000) to pharmacologic prophylaxis at the expense of an uncertain number of skin complications. The additional reduction in VTE applies to lower-risk groups as well, but the absolute number of events prevented is fewer.

Among patients at high risk for VTE undergoing abdominal surgery for cancer, there is moderate-quality evidence that compared with limited-duration prophylaxis (1 week), extended-duration prophylaxis (4 weeks) with LMWH provides additional protection from nonfatal VTE (13 fewer events per 1,000), without an important increase in the risk of nonfatal major bleeding complications (Table 18). The additional reduction in VTE applies to lower-risk groups as well, but the absolute number of events prevented is smaller. In addition, the quality of evidence is lower in noncancer surgery patients and patients at lower risk for VTE because of indirectness.

Some patients who would otherwise benefit from anticoagulant prophylaxis are not eligible to receive LDUH or LMWH primarily because of heparin allergy or a history of heparin-induced thrombocytopenia. Among such patients who are at high risk for VTE but not at increased risk for perioperative bleeding complications, low-quality evidence supports the use of either fondaparinux (Table 19), low-dose aspirin (Table 20), or mechanical prophylaxis (Tables 11, 12) over no prophylaxis. Among such patients at high risk for VTE who are at high risk for major bleeding, trade-offs favor mechanical prophylaxis. Because of the very low quality of the evidence and the availability of preferable alternatives, we do not recommend the use of high-dose aspirin for VTE prevention in any group of patients (Table 21).

For patients at high risk for VTE who are not candidates for either mechanical or pharmacologic prophylaxis, very-low-quality evidence suggests that IVC filter placement will probably cause at least as many DVT events as PE events prevented and that additional serious complications may occur in as many as 5% of patients (Table 22). Likewise, it is not clear that using VCU to detect and treat asymptomatic DVT reduces the risk of PE or fatal PE in patients at high risk for VTE. Furthermore, false-positive findings are common, and the potential risks associated with treating false-positive findings are substantial.

3.6 Recommendations

The following recommendations apply to patients undergoing general surgery, GI surgery, urological surgery, gynecologic surgery, bariatric surgery, vascular surgery, and plastic and reconstructive surgery (Table 23).

3.6.1. For general and abdominal-pelvic surgery patients at very low risk for VTE (< 0.5%; Rogers score, < 7; Caprini score, 0), we recommend that no specific pharmacologic (Grade 1B) **or mechanical** (Grade 2C) **prophylaxis be used other than early ambulation.**

3.6.2. For general and abdominal-pelvic surgery patients at low risk for VTE (~1.5%; Rogers score, 7-10; Caprini score, 1-2), we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)**.**

3.6.3. For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score, > 10; Caprini score, 3-4) who are not at high risk for major bleeding complications, we suggest LMWH (Grade 2B)**, LDUH** (Grade 2B)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

Table 16—*Summary of Findings: Combined Therapy With IPC and Pharmacologic Prophylaxis Compared With Pharmacologic Prophylaxis Alone for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: combined therapy with IPC and pharmacologic prophylaxis
Comparison: pharmacologic prophylaxis alone

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Pharmacologic Prophylaxis Alone	Corresponding Risk Combined Therapy With IPC and Pharmacologic Prophylaxis			
Symptomatic VTE inferred from any DVT (Venography [2], ultrasound [2], and FUT [1]) Follow-up: usually to hospital discharge	Low-risk population[b]		OR 0.45 (0.2-1.03)[c]	2,429 (5 studies[d])	Very low[e,f,g]
	5 per 1,000	2 per 1,000 (1-5)			
	Medium-risk population[b]				
	9 per 1,000	4 per 1,000 (2-9)			
	High-risk population[b]				
	19 per 1,000	9 per 1,000 (4-20)			
Skin breaks, blisters, ulcers, necrosis	No evidence				

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 9, and 11 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Baseline risk of VTE in moderate-, high-, and very-high-risk patients was adjusted to assume that all patients received background prophylaxis with LMWH. Data from Bahl et al.[91] In low-risk patients, the rate of symptomatic VTE was 0%.

[c]Reanalysis of data from Roderick et al[24] and Kakkar et al.[18] Pooled risks of proximal DVT and PE were 1.04 (95% CI, 0.29-3.79) and 0.57 (95% CI, 0.16-2.00), respectively.

[d]Data for other critical outcomes (eg, fatal PE) not available; bleeding complications were not relevant.

[e]Unblinded assessment of VTE, unclear concealment of allocation sequence, and measurement of surrogate outcome (asymptomatic DVT).

[f]Data from studies of orthopedic surgery (four) and general surgery (one). Background agents included dextran, unfractionated heparin, LMWH, LMWH plus ES, and aspirin plus ES plus hypotensive epidural anesthesia.

[g]The 95% CI includes the possibility of both substantial benefit and no effect.

Table 17—*Summary of Findings: Combined Therapy With ES and Pharmacologic Prophylaxis Compared With Pharmacologic Prophylaxis Alone for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: combined therapy with ES and pharmacologic prophylaxis
Comparison: pharmacologic prophylaxis alone

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Pharmacologic Prophylaxis Alone	Corresponding Risk Combined Therapy With ES and Pharmacologic Prophylaxis			
Symptomatic VTE inferred from any DVT Follow-up: to hospital discharge	Low-risk population[b]		OR 0.40 (0.25-0.65)[c]	1,089 (10 studies[d])	Low[e,f,g]
	5 per 1,000	2 per 1,000 (1-3)[h]			
	Medium-risk population[b]				
	9 per 1,000	4 per 1,000 (2-6)[h]			
	High-risk population[b]				
	19 per 1,000	8 per 1,000 (5-12)[h]			
Skin breaks, blisters, ulcers, necrosis (Case note review) Follow-up: 1-30 d	13 per 1,000	54 per 1,000 (31-95)	RR 4.18 (2.4-7.27)	2,518 (1 study)	Low[i,j]

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 3, 9, and 10 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Baseline risk of VTE in moderate-, high-, and very-high-risk patients was adjusted to assume that all patients received background prophylaxis with LMWH. Data from Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%.

[c]OR for proximal DVT and PE were 0.28 (95% CI, 0.09-0.87) and 0.43 (95% CI, 0.16-1.18), respectively.

[d]Data for other critical outcomes (eg, fatal PE) not available; bleeding complications not relevant.

[e]Unclear concealment of allocation sequence and unclear blinding and measurement of surrogate otucomes in most or all studies.

[f]Mild to moderate unexplained heterogeneity across studies.

[g]Data from studies of general and abdominal (six) and orthopedic (four) surgery. Background prophylaxis included unfractionated heparin (five), dextran (three), LMWH (one), and aspirin (one).

[h]Pooled risk of any DVT in the combined therapy treatment groups.

[i]Unblinded ascertainment based on case note review.

[j]Based on data from CLOTS1 study in patients with stroke.

Table 18—*Summary of Findings: Extended-Duration Prophylaxis Compared With Limited-Duration Prophylaxis for VTE Prevention in Surgical Patients at High Risk for VTE*

Patient or population: patients with VTE, prevention in high-VTE risk surgical patients
Settings: hospital and postdischarge
Intervention: extended-duration prophylaxis
Comparison: limited-duration prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk Limited-Duration Prophylaxis	Corresponding Risk Extended-Duration Prophylaxis			
All-cause mortality Follow-up: 3 mo	54 per 1,000	60 per 1,000 (36-99)	OR 1.12 (0.65-1.93)	1,021 (4 studies)	Moderate[b]
Nonfatal symptomatic VTE Follow-up: 3 mo	Low-risk population		OR 0.22 (0.06-0.8)	901 (4 studies)	Low[c,d]
	5 per 1,000	1 per 1,000 (0-4)			
	Medium-risk population				
	8 per 1,000	2 per 1,000 (0-6)			
	High-risk population				
	17 per 1,000	4 per 1,000 (1-14)			
Major bleeding Follow-up: 3 mo	Low-risk population		OR 1.11 (0.62-1.97)	1,242 (4 studies)	Low[b,c]
	12 per 1,000	13 per 1,000 (7-23)			

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1 and 9 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]The 95% CI around the estimate includes the possibility of both substantial benefit and serious harm.

[c]Incomplete blinding and incomplete details about concealment of allocation sequence.

[d]Bias introduced by measurement of surrogate outcome (venographic assessment of asymptomatic DVT).

Table 19—*Summary of Findings: Fondaparinux Compared With No Prophylaxis for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: fondaparinux
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk Fondaparinux			
Fatal PE inferred from death from any cause	Low-risk population[b]		RR 0.41 (0.15-1.07)	1,433 (6 studies)	Low[c,d]
	3 per 1,000[e]	1 per 1,000 (0-3)[f]			
	Medium-risk population[b]				
	6 per 1,000[e]	2 per 1,000 (1-6)[f]			
	High-risk population[b]				
	12 per 1,000[e]	5 per 1,000 (2-13)[f]			
Nonfatal symptomatic VTE	Low-risk population[g]		RR 0.39 (0.13-1.18)	1,465 (4 studies)	Very low[c,d,h]
	15 per 1,000	6 per 1,000 (2-18)[f]			
	Medium-risk population[g]				
	30 per 1,000	12 per 1,000 (4-35)[f]			
	High-risk population[g]				
	60 per 1,000	23 per 1,000 (8-71)[f]			
Nonfatal major bleeding	Low-risk population[i]		RR 2.92 (1.62-5.25)	1,433 (8 studies)	Low[c,h]
	12 per 1,000	35 per 1,000 (19-63)[f]			
	High-risk population[i]				
	22 per 1,000	64 per 1,000 (36-116)[f]			

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 9, and 10 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Risk of death from any cause was 20 of 1,429 (1.4%) in the LMWH (control) group, which was higher than the risk of death in treatment groups in studies of LMWH vs no prophylaxis (0.4%). For overall baseline risk, we used pooled risk from control groups in studies of LMWH vs no prophylaxis (0.9%). Risk of death from any cause in low-, moderate-, and high-risk groups was calculated under the assumption that ratio of death from any cause to symptomatic VTE did not vary across risk categories.

[c]ORs calculated based on indirect comparison from large RCT of fondaparinux vs LMWH and meta-analysis of five studies of LMWH vs placebo, all in patients undergoing abdominal surgery.

[d]The 95% CI includes the possibility of both substantial benefit and no effect.

[e]Pooled risk of death in control groups from studies of LMWH vs placebo or no prophylaxis (Mismetti et al[13]).

[f]Absolute risks in fondaparinux group taken from Agnelli et al.[20]

[g]Baseline risk of VTE in moderate-, high-, and very-high-risk patients after adjustment for prophylaxis received. Data from Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%.

[h]In a large RCT comparing fondaparinux and LMWH, generation and concealment of allocation sequence were not described; measurement of patient-important outcomes (symptomatic VTE) was potentially confounded by surveillance for asymptomatic events.

[i]In seven studies of LMWH vs no prophylaxis in abdominal surgery (Mismetti et al[13]), the weighted pooled (random-effects model) risk of major bleeding in the control groups was 1.2%. In a more-recent comparison of LMWH vs fondaparinux, the risk of bleeding requiring reoperation or intervention was 1.0% in the LMWH group. After adjustment for prophylaxis, the risk was 0.5%. In a secondary analysis of RCT data (Cohen et al[90]), the odds of major bleeding were 1.8 times greater in patients with cancer.

Table 20—*Summary of Findings: Low-Dose Aspirin Compared With No Prophylaxis for VTE Prevention in Nonorthopedic Surgical Patients*

Patient or population: patients with VTE, prevention in nonorthopedic surgical patients
Settings: hospital
Intervention: low-dose aspirin
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk Low-Dose Aspirin			
Fatal PE inferred from death from any cause Follow-up: 35 d	Low-risk population[b]		RR 0.97 (0.85-1.1)	13,356 (1 study)	Moderate[c]
	3 per 1,000	3 per 1,000 (3-3)			
	Medium-risk population[b]				
	6 per 1,000	6 per 1,000 (5-7)			
	High-risk population[b]				
	12 per 1,000	12 per 1,000 (10-13)			
Nonfatal symptomatic VTE (objectively confirmed with venography, ultrasound, lung scan, or pulmonary angiogram) Follow-up: 35 d	Low-risk population[d]		RR 0.71 (0.54-0.94)	13,356 (1 study)	Low[c,e]
	15 per 1,000	11 per 1,000 (8-14)			
	Medium-risk population[d]				
	30 per 1,000	21 per 1,000 (16-28)			
	High-risk population[d]				
	60 per 1,000	43 per 1,000 (32-56)			
Nonfatal major bleeding inferred from all reported nonfatal bleeding complications, including hematemesis, melena, hematoma, bleeding from wound, and other bleeding requiring transfusion Follow-up: 35 d	Low-risk population[f]		RR 1.32 (1.17-1.48)[g]	13,356 (1 study)	Moderate[c]
	12 per 1,000	16 per 1,000 (14-18)			
	Medium-risk population[f]				
	22 per 1,000	29 per 1,000 (26-33)			
	High-risk population[f]				
	40 per 1,000	53 per 1,000 (47-59)			
Nonfatal myocardial infarction (Two or more of the following: typical chest pain, ECG changes, or enzyme changes) Follow-up: 35 d	3 per 1,000	5 per 1,000 (3-8)	RR 1.57 (0.93-2.65)	13,356 (1 study)	Low[e,h]

(Continued)

Table 20—*Continued*

Patient or population: patients with VTE, prevention in nonorthopedic surgical patients
Settings: hospital
Intervention: low-dose aspirin
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk Low-Dose Aspirin			
Nonfatal stroke (Rapid development of cerebral dysfunction lasting at least 24 h) Follow-up: 35 d	4 per 1,000	5 per 1,000 (3-7)	RR 1.13 (0.69-1.85)	13,356 (1 study)	Moderate[c]

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 2, 9, and 10 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Pooled risk of death from any cause was 24/2,589 (0.9%) in the control groups in studies of LMWH vs no prophylaxis. Risk of death in low-, moderate-, and high-VTE risk groups was calculated under the assumption that the ratio of death from any cause to symptomatic VTE did not vary across risk categories.

[c]PEP study performed in orthopedic surgery patients; results were taken from patients with hip fractures. Approximately 44% of patients also received prophylaxis with LMWH or unfractionated heparin and ~30% received mechanical prophylaxis with ES, evenly distributed between the treatment groups.

[d]Baseline risk of VTE in moderate-, high-, and very-high-risk patients after adjustment for prophylaxis received. Data from Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%.

[e]Among patients at high risk for VTE , the lower limit of the 95% CI for absolute number of events overlaps with the upper limit for absolute number of major bleeding complications.

[f]In seven studies of LMWH vs no prophylaxis in abdominal surgery (Mismetti et al[13]), the weighted pooled (random-effects model) risk of major bleeding in the control groups was 1.2%. In 36 studies of LMWH vs unfractionated heparin in abdominal surgery, the pooled risk of major bleeding in the unfractionated heparin group was 3.2% but was only 2.7% in noncancer surgery and 8.1% in cancer surgery groups. After adjustment for prophylaxis, the risks for the noncancer and cancer surgery groups were 1.7% and 5.1%, respectively. In a secondary analysis of RCT data (Cohen et al[90]), the odds of major bleeding were 1.8 times greater in patients with cancer.

[g]In PEP, risk of hematoma requiring evacuation was 24 of 6,679 (0.4%) in the aspirin group and 33 of 6,677 in the control group (0.5%). The relative risk was 0.73 (95% CI, 0.43-1.23).

[h]The 95% CI includes the possibility of both serious harm and no effect.

Table 21—*Summary of Findings: High-Dose Aspirin (600-1,500 mg/d) Compared With No Prophylaxis for VTE Prevention in Nonorthopedic Surgical Patients*

Patient or population: patients with VTE, prevention in nonorthopedic surgical patients
Settings: hospital
Intervention: high-dose aspirin (600-1,500 mg/d)
Comparison: no prophylaxis

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Prophylaxis	Corresponding Risk High-Dose Aspirin (600-1,500 mg/d)			
Fatal PE inferred from all-cause mortality Follow-up: hospital discharge	Low-risk population[b]		OR 0.45 (0.14-1.49)	1,102 (2 studies)	Low[c,d]
	3 per 1,000	1 per 1,000 (0-4)			
	Medium-risk population[b]				
	6 per 1,000	3 per 1,000 (1-9)			
	High-risk population[b]				
	12 per 1,000	5 per 1,000 (2-18)			
Nonfatal symptomatic VTE inferred from any DVT (FUT ± venography or venography) Follow-up: usually to hospital discharge	Low-risk population[e]		RR 0.52 (0.32-0.83)[f]	3,173 (8 studies)	Low[g,h]
	15 per 1,000	8 per 1,000 (5-12)			
	Medium-risk population[e]				
	30 per 1,000	16 per 1,000 (10-25)			
	High-risk population[e]				
	60 per 1,000	31 per 1,000 (19-50)			
Major bleeding inferred from excessive intraoperative or other bleeding Follow-up: to hospital discharge	Low-risk population[i]		OR 1.61 (1-2.6)	1,645 (2 studies)	Low[j,k]
	12 per 1,000	19 per 1,000 (12-31)			
	High-risk population[i]				
	22 per 1,000	35 per 1,000 (22-55)			

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 9, and 11 legends for expansion of abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Pooled risk of death from any cause was 24 of 2,589 (0.9%) in the control groups in studies of LMWH vs no prophylaxis. Risk of death in low-, moderate-, and high-VTE risk groups was calculated under the assumption that ratio of death from any cause to symptomatic VTE did not vary across risk categories.

[c]Exclusion of patients after randomization (two of eight).

[d]The 95% CI includes the possibility of both substantial benefit and no effect.

[e]Baseline risk of VTE in moderate-, high-, and very-high-risk patients after adjustment for prophylaxis received. Data from Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%.

[f]Relative risk of proximal DVT in four trials was 0.41 (95% CI, 0.10-1.68), and relative risk of any PE in six trials (with mild heterogeneity across trials) was 0.43 (95% CI, 0.20-0.92), whereas the risk of symptomatic DVT in three trials was 0.90 (95% CI, 0.46-1.75).

[g]Unclear concealment of allocation sequence (seven of eight); measurement of surrogate outcomes (six of eight); exclusion of patients after randomization (two of eight); unclear or absent blinding (two of eight).

[h]Moderate unexplained heterogeneity across trials.

[i]In seven studies of LMWH vs no prophylaxis in abdominal surgery (Mismetti et al[13]), the weighted pooled (random-effects model) risk of major bleeding in the control groups was 1.2%. In 36 studies of LMWH vs unfractionated heparin in abdominal surgery, the pooled risk of major bleeding in the unfractionate heparin group was 3.2% but was only 2.7% in noncancer surgery and 8.1% in cancer surgery groups. After adjustment for prophylaxis, the risks for noncancer and cancer surgery were 1.7% and 5.1%, respectively. In a secondary analysis of RCT data (Cohen et al[90]), the odds of major bleeding were 1.8 times greater in patients with cancer.

[j]Unclear concealment of allocation sequence (seven of eight); measurement of surrogate outcomes (six of eight); exclusion of patients after randomization (two of eight); unclear or absent blinding (two of eight).

[k]The 95% CI includes the possibity of both serious harm and no effect.

Table 22—*Summary of Findings: IVC Filters Compared With No Filter for VTE Prevention in High-VTE Risk Patients With Trauma*

Patient or population: patients with VTE, prevention in high VTE-risk trauma patients
Settings: hospital
Intervention: IVC filters
Comparison: no filter

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (Studies)	Quality of the Evidence (GRADE)
	Assumed Risk No Filter	Corresponding Risk IVC Filters			
Fatal or nonfatal PE	Low-risk population[b]		OR 0.21 (0.09-0.49)	1,900 (7 studies)	Low[c]
	5 per 1,000	1 per 1,000 (0-2)			
	Medium-risk population[b]				
	10 per 1,000	2 per 1,000 (1-5)			
	High-risk population[b]				
	20 per 1,000	4 per 1,000 (2-10)			
Symptomatic DVT	Low-risk population[b]		RR 1.60 (0.76-3.37)	232 (2 studies)	Very low[c,d,e]
	10 per 1,000	16 per 1,000 (8-34)			
	Medium-risk population[b]				
	20 per 1,000	32 per 1,000 (15-67)			
	High-risk population[b]				
	40 per 1,000	64 per 1,000 (30-135)			
Complications, including insertion site thrombosis (5), IVC thrombosis (8), hematoma (1), tilting filter (1), and migration to RV (1)			RR 0 (0 to 0)	375 (5 studies)	Low

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. RV = right ventricle. See Table 1, 9, 10 legends for expansion of other abbreviations.

[a]The basis for the assumed risk (eg, the median control group risk across studies) is provided in the following footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Baseline risk of VTE in moderate-, high-, and very-high-risk patients after adjustment for prophylaxis received. Data from Bahl et al.[81] In low-risk patients, rate of symptomatic VTE was 0%. Distribution of PE and DVT assumes that roughly one-third of all VTE events are PE.

[c]Comparison with historical control subjects, variably matched for age, severity, and diagnosis.

[d]Severe unexplained heterogeneity in study results.

[e]The 95% CI includes the possibility of both serious harm and no effect.

Table 23—*Recommendations for Thromboprophylaxis in Various Risk Groups*

Risk of Symptomatic VTE	Risk and Consequences of Major Bleeding Complications: Average Risk (~1%)	Risk and Consequences of Major Bleeding Complications: High Risk (~2%) or Severe Consequences
Very low (< 0.5%)	No specific prophylaxis	
Low (~1.5%)	Mechanical prophylaxis, preferably with IPC	
Moderate (~3.0%)	LDUH, LMWH, *or* mechanical prophylaxis, preferably with IPC	Mechanical prophylaxis, preferably with IPC
High (~6.0%)	LDUH *or* LMWH *plus* mechanical prophylaxis with ES *or* IPC	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High-risk cancer surgery	LDUH *or* LMWH *plus* mechanical prophylaxis with ES *or* IPC *and* extended-duration prophylaxis with LMWH postdischarge	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added
High risk, LDUH and LMWH contraindicated or not available	Fondaparinux *or* low-dose aspirin (160 mg); mechanical prophylaxis, preferably with IPC; or both	Mechanical prophylaxis, preferably with IPC, until risk of bleeding diminishes and pharmacologic prophylaxis can be added

See Table 1 for expansion of abbreviations. See Table 5 for details about risk stratification for VTE; see Table 8 for information about risk factors for major bleeding.

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

3.6.4. For general and abdominal-pelvic surgery patients at moderate risk for VTE (~3.0%; Rogers score, > 10; Caprini score, 3-4) who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)**.**

3.6.5. For general and abdominal-pelvic surgery patients at high risk for VTE (~6.0%; Caprini score, ≥ 5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 1B) **or LDUH** (Grade 1B) **over no prophylaxis. We suggest that mechanical prophylaxis with ES or IPC should be added to pharmacologic prophylaxis** (Grade 2C)**.**

3.6.6. For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended-duration pharmacologic prophylaxis (4 weeks) with LMWH over limited-duration prophylaxis (Grade 1B)**.**

Remarks: Patients who place a high value on minimizing out-of-pocket health-care costs might prefer limited-duration over extended-duration prophylaxis in settings where the cost of extended-duration prophylaxis is borne by the patient.

3.6.7. For high-VTE-risk general and abdominal-pelvic surgery patients who are at high risk for major bleeding complications or those in whom the consequences of bleeding are thought to be particularly severe, we suggest use of mechanical prophylaxis, preferably with IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)**.**

3.6.8. For general and abdominal-pelvic surgery patients at high risk for VTE (~6%; Caprini score, ≥ 5) in whom both LMWH and unfractionated heparin are contraindicated or unavailable and who are not at high risk for major bleeding complications, we suggest low-dose aspirin (Grade 2C)**, fondaparinux** (Grade 2C)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

3.6.9. For general and abdominal-pelvic surgery patients, we suggest that an IVC filter should not be used for primary VTE prevention (Grade 2C)**.**

3.6.10. For general and abdominal-pelvic surgery patients, we suggest that periodic surveillance with VCU should not be performed (Grade 2C)**.**

4.0 Target Population: Cardiac Surgery

Of two randomized controlled trials of VTE prophylaxis in cardiac surgery patients (Appendix S1), one compared ES alone with ES plus IPC,[124] and the other compared LDUH plus IPC with LDUH alone in patients who underwent cardiac surgery at a single center over a period of 10 years.[125] Because direct evidence about the safety and effectiveness of prophylaxis in patients undergoing cardiac surgery is limited, we applied indirect evidence about relative risks from studies of mixed surgical patients when making recommendations. Risk stratification is discussed next.

4.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE

The risk of VTE following cardiac surgery is uncertain. Predisposing factors include perioperative stasis, inflammation, and activation of the coagulation system, but these are mitigated by early mobilization and use of anticoagulants, aspirin, and other antiplatelet drugs.

Relatively precise, but possibly dated estimates of the risk of VTE following cardiac surgery come from the California Patient Discharge Data Set for the years 1992 to 1996.[75] In this large data set, the risks of VTE in the 91 days after coronary artery bypass graft (CABG) and valve replacement surgery were 1.1% and 0.5%, respectively. Similarly, in an analysis of registry data from New York State in 1999, 133 of 16,325 (0.8%) patients were readmitted for VTE within 30 days after CABG.[126] Unfortunately, information about the use of prophylaxis was not reported in either study.

Based on results of these and other studies, we believe that most cardiac surgery patients are at moderate risk for VTE.[127-131] Possible factors that increase the risk of VTE in cardiac surgery include older age,[130] postoperative complications,[127,130] prolonged preoperative hospitalization or postoperative recovery,[128,129] CABG surgery compared with valve surgery,[129] and off-pump CABG compared with cardiopulmonary bypass.[132]

4.2 Baseline Risk, Risk Factors, and Risk Stratification for Major Bleeding Complications

A systematic review of English-language studies of surgical bleeding complications published between 1997 and 2007 identified six studies in cardiac surgery patients, including four retrospective cohort studies and two randomized trials.[133] In five studies, major bleeding was defined as bleeding requiring reexploration[90-92,134]; across these studies, the risk of major bleeding was remarkably consistent, with a median risk of 4.7% (range, 3.1%-5.9%). Thus, we classify most cardiac surgery patients as being at high risk for anticoagulant prophylaxis-related bleeding.

Risk factors for bleeding following cardiac surgery varied across studies (Table 8). One study found that the risk of bleeding was similar for on-pump compared with off-pump CABG.[135] Two others reported that the risk of bleeding was approximately twice as high in patients treated with aspirin[90] or clopidogrel, at least when given within 3 days of surgery.[91] In one series of 2,898 consecutive patients undergoing CABG, independent risk factors for bleeding requiring reexploration included BMI ≥ 25 kg/m^2, nonelective surgery, placement of five or more grafts, and older age.[92] In an earlier study of 6,015 patients undergoing cardiopulmonary bypass between 1986 and 1993, independent risk factors for bleeding included older age, renal insufficiency, operation other than CABG, and longer bypass time.[93]

4.3 Explanation of Evidence Profiles and Rationale for Recommendations in Cardiac Surgery

We classify most patients undergoing cardiac surgery as being at moderate risk for VTE and at high risk for major bleeding complications. In these patients, low-quality evidence (moderate-quality evidence downgraded for indirectness) suggests that the benefits of pharmacologic prophylaxis with either LDUH (Table 9) or LMWH (Table 10) are probably outweighed by the potential harms. In contrast, low-quality evidence suggests that the balance between desirable and undesirable outcomes is more favorable with mechanical prophylaxis (Tables 11, 12), which is expected to result in 15 to 20 fewer nonfatal VTE events at the expense of an uncertain number of skin complications.

When additional risk factors for VTE are present and the baseline risk of VTE is high, the trade-offs still appear to favor mechanical prophylaxis over both no prophylaxis (Tables 11, 12) and pharmacologic prophylaxis (Tables 13, 14). However, the relatively high risk of postoperative bleeding almost surely decreases over time in patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications. We classify such patients as being at high risk for VTE and low (or average) risk for bleeding, and these patients may benefit from the addition of pharmacologic prophylaxis to mechanical prophylaxis, although the trade-offs only slightly favor combined prophylaxis over mechanical prophylaxis alone (Table 24).

4.4 Recommendations for Cardiac Surgery

4.4.1. For cardiac surgery patients with an uncomplicated postoperative course, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over either no prophylaxis (Grade 2C) **or pharmacologic prophylaxis** (Grade 2C)**.**

4.4.2. For cardiac surgery patients whose hospital course is prolonged by one or more nonhemorrhagic surgical complications, we suggest adding pharmacologic prophylaxis with LDUH or LMWH to mechanical prophylaxis (Grade 2C)**.**

5.0 Target Population: Thoracic Surgery

Of two small trials in thoracic surgery, one compared LDUH 5,000 bid with LDUH 7,500 bid,[136]

Table 24—*Summary of Findings: Combined Therapy With Pharmacologic Plus Mechanical Prophylaxis Compared With Mechanical Prophylaxis Alone for VTE Prevention in Surgical Patients*

Patient or population: patients with VTE, prevention in surgical patients
Settings: hospital
Intervention: combined therapy with pharmacologic plus mechanical prophylaxis
Comparison: mechanical prophylaxis alone

Outcomes	Illustrative Comparative Risks[a] (95% CI)		Relative Effect (95% CI)	No. of Participants (studies)	Quality of the Evidence (GRADE)
	Assumed Risk Mechanical Prophylaxis Alone	Corresponding Risk Combined Therapy With Pharmacologic Plus Mechanical Prophylaxis			
Symptomatic VTE inferred from PE (objectively confirmed events) Follow-up: until hospital discharge or 30 d after discharge	Low-risk population		RR 0.39 (0.24-0.64)	3,978 (3 studies)	Moderate
	7 per 1,000	3 per 1,000 (2-4)			
	Medium-risk population				
	14 per 1,000	5 per 1,000 (3-9)			
	High-risk population				
	29 per 1,000	11 per 1,000 (7-19)			
Major bleeding (clinical diagnosis) Follow-up: 7 to 270 d	Low-risk population		RR 2.03 (1.37-3.01)	5,457 (7 studies)	Moderate
	12 per 1,000	24 per 1,000 (16-36)			
	High-risk population				
	22 per 1,000	45 per 1,000 (30-66)			

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality, we are very uncertain about the estimate. See Table 1, 9, and 10 legends for expansion of abbreviations.
[a]The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

whereas the other compared fixed-dose with weight-adjusted-dose nadroparin (Appendix S1).[137] Although direct evidence about the safety and effectiveness of prophylaxis in patients undergoing thoracic surgery is limited, we believe that evidence about relative risks from studies of patients undergoing general or abdominal-pelvic surgery can be applied to thoracic surgery patients without downgrading for indirectness. Baseline risk and risk stratification is discussed next.

5.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE

Based on results of observational studies and our clinical judgment, we consider most thoracic surgery patients to be at least at moderate risk for VTE. Three relatively large retrospective studies reported the risk of symptomatic VTE events. In one study of 693 thoracotomies for lung cancer, symptomatic VTE was observed in 1.7% of patients, including PE in 1.3%, despite routine use of prophylaxis with LDUH or LMWH. In another analysis of 1,735 lung resections for malignancy, autopsy-confirmed fatal PE occurred in 1.2% of patients, despite ongoing heparin prophylaxis in most of them.[138] Another study of 706 thoracic surgery patients reported objectively confirmed PE in 20 of 344 (7%) patients who did not receive prophylaxis, but there were no episodes of PE among 362 patients who wore IPC.[139] Finally, the 91-day risk of clinically detected VTE for almost 13,000 patients undergoing major lung resection for malignant disease was 1.6% in the California Patient Discharge Data Set.[75]

Thoracic surgery patients undergoing extended pulmonary resection, pneumonectomy, extrapleural pneumonectomy, or esophagectomy are probably at higher risk for VTE. In a prospective study of 336 patients undergoing pneumonectomy for malignancy, the risk of symptomatic VTE was 7.4%.[140] Similarly, in a study of 496 patients undergoing extrapleural pneumonectomy for malignant mesothelioma, DVT occurred in 6.4% of patients, and fatal PE was observed in 1.2%.[141] Other risk factors for VTE in thoracic surgery have not been rigorously evaluated, although individual studies have implicated malignancy, larger tumors, and pack-years of smoking as possible risk factors.[140,142-144] In another study, age, sex, BMI, operation time, time to ambulation, operative method, and malignancy were not associated with VTE.[139]

5.2 Baseline Risk, Risk Factors, and Risk Stratification for Major Bleeding Complications

A review of complication rates from 14 studies of patients undergoing major lung resections for cancer distinguished between standard resection and pneumonectomy or extended resection.[94] Across nine studies of almost 17,000 patients who underwent standard resection, bleeding requiring reoperation was reported in 1%. However, in five studies of 1,223 patients who underwent pneumonectomy or extended resection, ~5% of patients required reexploration for bleeding. In a more-recent retrospective analysis of 1,100 patients who underwent video-assisted thoroscopic lobectomy at a single center, intraoperative bleeding required conversion to thoracotomy in six (0.55%) patients, and 45 (4.5%) patients required postoperative red cell transfusion, but there were no episodes of fatal bleeding or bleeding requiring reoperation.[145]

5.3 Explanation of Evidence Profiles and Rationale for Recommendations in Thoracic Surgery

Most thoracic surgery patients are at moderate risk for VTE. In these patients, moderate-quality evidence suggests that compared with no prophylaxis, pharmacologic prophylaxis with either LDUH or LMWH will result in more cases of VTE events prevented than bleeding episodes caused (Tables 9, 10). Low-quality evidence supports the use of mechanical prophylaxis over no prophylaxis, preferably with IPC (Tables 11, 12). The addition of mechanical prophylaxis with either ES (Table 16) or IPC (Table 17) to pharmacologic prophylaxis will prevent a few additional VTE events at the expense of skin complications, added cost, comfort, and convenience.

For thoracic surgery patients at high risk for VTE (including those undergoing extended pulmonary resection, pneumonectomy, extrapleural pneumonectomy, and esophagectomy), moderate-quality evidence suggests that when compared with no prophylaxis, the benefits of pharmacologic prophylaxis with LDUH (Table 9) or LMWH (Table 10) outweigh the harms. Because the risk of bleeding requiring reexploration appears to be elevated in patients who require pneumonectomy or extended-lung resection, prudence dictates that mechanical prophylaxis should be used until adequate hemostasis has been established and the risk of bleeding diminishes.

5.4 Recommendations for Thoracic Surgery

5.4.1. For thoracic surgery patients at moderate risk for VTE who are not at high risk for major bleeding, we suggest LDUH (Grade 2B)**, LMWH** (Grade 2B)**, or mechanical prophylaxis with optimally applied IPC** (Grade 2C) **over no prophylaxis.**

Remarks: Three of the seven authors favored a strong (Grade 1B) recommendation in favor of LMWH or LDUH over no prophylaxis in this group.

5.4.2. For thoracic surgery patients at high risk for VTE who are not at high risk for major bleeding, we suggest LDUH (Grade 1B) **or LMWH** (Grade 1B) **over no prophylaxis. In addition, we suggest that mechanical prophylaxis with ES or IPC should be added to pharmacologic prophylaxis** (Grade 2C)**.**

5.4.3. For thoracic surgery patients who are at high risk for major bleeding, we suggest use of mechanical prophylaxis, preferably with optimally applied IPC, over no prophylaxis until the risk of bleeding diminishes and pharmacologic prophylaxis may be initiated (Grade 2C)**.**

6.0 Target Population: Craniotomy

Two published meta-analyses summarized the results of randomized controlled trials of pharmacologic and mechanical prophylaxis in neurosurgery, including patients undergoing craniotomy and spinal surgery.[12,10] Many of the studies were limited by small samples; open-label design; incomplete follow-up; and use of ultrasound, venography, or fibrinogen uptake scanning to identify asymptomatic DVT.

One meta-analysis summarized the results of three trials in mixed neurosurgical patients that compared LMWH with placebo with or without adjunctive use of ES in both treatment groups.[12] In these studies, LMWH reduced the risk of any VTE (including asympotomatic DVT) by 46% and venographically confirmed proximal DVT by 52%. Consistent with results of studies in general and abdominal surgery, LMWH increased the risk of nonfatal major bleeding complications (mostly intracranial) by 68%. In addition, there was a possible increase in the risk of death from any cause (OR, 1.74; 95% CI, 0.94-3.22).

Another meta-analysis made several comparisons, including IPC vs no prophylaxis, LDUH vs no prophylaxis, LDUH vs LMWH, and IPC vs LMWH.[10] In two trials that compared IPC and no prophylaxis in mixed neurosurgery patients,[146,147] IPC reduced the risk of asymptomatic DVT by 59% and PE by 63%. For the other comparisons, differences in the risk of DVT, PE, or intracranial hemorrhage (ICH) were neither confirmed nor excluded. Accordingly, for these comparisons, we applied indirect but higher-quality evidence about relative risks from studies of general or mixed surgical patients in our evidence profiles.

6.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE

Although no VTE risk stratification scheme has been validated for patients undergoing craniotomy, data from published observational studies suggest that cancer, advanced age, longer duration of surgery, and paresis are associated with an increased risk of VTE.[148-150] To estimate the baseline risks of nonfatal PE and symptomatic VTE in the absence of prophylaxis, we used data from an observational study of almost 2,400 neurosurgical admissions[151] and a structured literature review that pooled results from numerous smaller studies of patients undergoing craniotomy.[152] In the study by Chan et al,[151] the risk of clinically diagnosed VTE within 30 days after discharge was 3.9% among all patients, and it was especially high for patients undergoing craniotomy for primary malignancy (7.5%) or metastasis (19%). In this study, pharmacologic and mechanical prophylaxis was used in 67% of patients with cancer and 84% of patients without cancer. Smaller studies of malignant glioma patients reported risks of symptomatic, postoperative DVT that ranged between 3% and 25%.[153] In the analysis by Danish et al,[152] the pooled risk of symptomatic VTE was 2.1% across 13 studies that included almost 3,000 patients who received prophylaxis with IPC alone, whereas it was 2.2% in five studies that included $>3,500$ patients who received combined prophylaxis with unfractionated heparin and IPC. Accordingly, we classify craniotomy patients as being at high risk for VTE, especially those who undergo craniotomy for malignancy.

6.2 Baseline Risk, Risk Factors, and Risk Stratification for ICH

In craniotomy patients, we focus on ICH rather than on the more generic major bleeding outcome because ICH is a potentially devastating complication of craniotomy and because pharmacologic VTE prophylaxis increases the risk of operative site bleeding. Although the risk of ICH probably varies depending on patient- and procedure-specific factors, we found no validated bleeding risk stratification system for craniotomy patients. Data from a structured literature review that included 20 different studies and $>31,000$ patients who underwent craniotomy without pharmacologic prophylaxis indicate that the baseline risk of ICH is $\sim$1.1% (95% CI, 0.9%-1.4%).[152] We favor this relatively precise estimate of baseline risk, although we recognize that it is higher than those reported in the meta-analysis by Collen et al,[10] in which the pooled risks of intracranial hemorrhage were 0.04% (95% CI, 0%-3.7%) among those who did not receive pharmacologic prophylaxis, 0.35% (95% CI, 0%-7.4%) among those who received LDUH, and 1.5% (95% CI, 1.1%-1.9%) among those who received LMWH.

6.3 Explanation of Evidence Profiles

We classify patients undergoing craniotomy for nonmalignant disease as being at high risk for VTE

(~5%) and those with malignant disease as being at very high risk (≥ 10%). Although the baseline risk of bleeding (ICH) is probably ~1%, the consequences of ICH are likely to be very severe.

For craniotomy patients at high risk for VTE (~5%), such as those undergoing craniotomy for vascular disease, there is low-quality evidence that mechanical prophylaxis with IPC is beneficial. Compared with no prophylaxis, one can expect 11 to 40 fewer symptomatic VTE events per 1,000 patients treated with IPC (Table S10). As mentioned previously (Table S11), we favor IPC over ES primarily on the basis of indirect evidence from the CLOTS1 trial in stroke patients that ES increased the risk of skin complications without reducing the risk of VTE,[29] although differences between IPC and ES were neither demonstrated nor excluded in the meta-analysis of studies in neurosurgery.

In this group, there is moderate-quality evidence that compared with no prophylaxis, the benefits of pharmacologic prophylaxis with low-dose LMWH are probably outweighed by the harms (Table S12). First of all, LMWH was associated with a possible increase in the risk of death from any cause. In addition, although LMWH can be expected to prevent between eight and 36 VTE events, this comes at a cost of four to 22 additional intracranial bleeds. Based on the assumption that the disutility of intracranial hemorrhage is approximately two to three times greater than that associated with an average VTE event, the trade-offs favor no prophylaxis over LMWH. Although the trade-offs appear to be somewhat more favorable for LDUH compared with no prophylaxis (Table S13), the evidence is low in quality and sufficiently indirect to cast doubt on its relevance to craniotomy patients. Low-quality evidence for the comparison between LMWH and IPC suggests that the trade-offs favor IPC over pharmacologic prophylaxis in this group (Table S14).

For craniotomy patients at very high risk for symptomatic VTE (~10%), such as those with cancer, low-quality evidence favors IPC, LDUH, and (possibly) LMWH over no prophylaxis (Tables S10, S12, S13). Trade-offs for the comparison between LMWH and IPC probably favor IPC, with six to 26 more nonfatal VTE events per 1,000 patients treated but four to 22 fewer episodes of nonfatal ICH (Table S14).

A more difficult question is whether and when to add pharmacologic prophylaxis to mechanical prophylaxis in the very-high-risk craniotomy patient. Indirect evidence from studies in patients undergoing abdominal or elective orthopedic surgery suggests that the addition of fondaparinux or warfarin to mechanical prophylaxis further reduces DVT or PE by ~60%. Assuming that the risk of symptomatic VTE is 4.1% in those who receive IPC alone, low-quality evidence suggests that adding pharmacologic prophylaxis to IPC will prevent 23 additional VTE events per 1,000 patients treated (95% CI, 34 fewer to three more) at the expense of 11 more intracranial bleeds (95% CI, four more to 22 more) (Table S15). Because most ICH occur in the first 12 to 24 h after craniotomy, whereas approximately one-half of VTE events occur after the first week,[150] it is advisable to delay adding LMWH or LDUH until adequate hemostasis is established and the risk of bleeding is judged not to be excessively high.

6.4 Recommendations for Craniotomy

6.4.1. For craniotomy patients, we suggest that mechanical prophylaxis, preferably with IPC, be used over no prophylaxis (Grade 2C) **or pharmacologic prophylaxis** (Grade 2C)**.**

6.4.2. For craniotomy patients at very high risk for VTE (eg, those undergoing craniotomy for malignant disease), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)**.**

7.0 Target Population: Spinal Surgery

Six randomized trials examined interventions to prevent VTE in spinal surgery patients, most limited by small samples, unclear concealment of treatment allocation, incomplete blinding, and measurement of asymptomatic DVT (Tables S2-S4). One compared pharmacologic prophylaxis with placebo,[154] one compared unfractionated heparin with LMWH,[155] and three compared different methods of mechanical prophylaxis with or without pharmacologic prophylaxis.[156-158] A meta-analysis summarized results of these and several other trials that enrolled mixed neurosurgical patients.[10] The authors found that IPC reduced the risk of DVT by 59% compared with no prophylaxis (RR, 0.41; 95% CI, 0.21-0.78). However, for comparisons of IPC with ES (RR, 0.81; 95% CI, 0.32-1.78) and LMWH with IPC (RR, 0.79; 95% CI, 0.30-2.12), differences in the risk of DVT were neither confirmed nor excluded. Because studies of mixed surgical patients provide higher-quality evidence and more-precise estimates of treatment effect, we used indirect evidence from these studies to estimate the relative risk of symptomatic VTE for these comparisons.

7.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE

Three systematic reviews described in Appendix S1 have examined the baseline risk of VTE in spinal

surgery.[159-161] Most of the studies were limited by small sample sizes and the measurement of asymptomatic DVT, although one large retrospective study reported a very low risk of symptomatic DVT (0.05%) among 1,919 patients who received heparin prophylaxis and did not undergo routine surveillance for DVT.[162]

Risk factors for VTE in spinal surgery patients likely include a combined anterior-posterior approach; multiple operative levels; and patient-related factors, such as older age, prior VTE, and malignancy.[163,164] In a population-based retrospective analysis of discharges from California hospitals in 1992 to 1996, the risk of symptomatic VTE within 91 days of surgery was 0.5% (95% CI, 0.4%-0.5%) among 34,355 patients who underwent spinal surgery for nonmalignant disease, whereas the risk of VTE was 2.0% (95% CI, 1.4%-2.6%) among 1,545 who underwent spinal surgery for malignant disease.[75] Accordingly, we classify the baseline risk of VTE in spinal surgery as low for most patients with nonmalignant disease and moderate for those with malignancy.

7.2 Baseline Risk, Risk Factors, and Risk Stratification for Major Bleeding Complications

In a large retrospective study of spinal surgery patients treated with nadroparin,[162] major bleeding (defined as hemorrhage associated with a mass effect on postoperative spinal MRI and neurologic deterioration or a large-wound hematoma with intractable pain) was observed in 13 of 1,954 (0.7%) patients. In another observational study, 720 noncranial neurosurgical patients who were not at high risk for bleeding received twice-daily prophylaxis with LDUH. Two patients (0.3%) developed epidural hematomas that required reoperation.[165] In a small randomized trial of LDUH vs placebo, deep hematomas were noted in two patients in the placebo group and no patients in the heparin group.[154] In another trial comparing LMWH plus dihydroergotamine vs LDUH plus dihydroergotamine, there were no hematomas in either group, although increased intraoperative bleeding was noted to be more common in the LDUH group.[155] Based on these data, we believe that the baseline risk of major bleeding in spinal surgery is probably $< 0.5\%$, but the consequences are potentially very severe.

7.3 Explanation of Evidence Profiles

Among spinal surgery patients at low risk for VTE, including those with nonmalignant disease, we estimate that compared with no prophylaxis, there will be similar reductions in the numbers of symptomatic VTE events when prophylaxis is given with IPC (five per 1,000), ES (six per 1,000), LDUH (five per 1,000), and LMWH (six per 1,000) (Tables S16-S19). These modest reductions are offset by similar increases in the absolute numbers of major bleeding complications with LDUH (three per 1,000) and LMWH (five per 1,000). Likewise, the benefits of IPC and ES are offset by an uncertain number of skin complications. Comparisons of IPC vs ES (Table S20), IPC vs LDUH (Table S21), and IPC vs LMWH (Table S22) suggest that the balance of desirable and undesirable outcomes favors IPC in these patients.

Among spinal surgery patients at moderate risk for VTE, including those with malignant disease and those undergoing surgery with a combined anterior-posterior approach, even greater reductions in symptomatic VTE events are anticipated with IPC (29 per 1,000), ES (31 per 1,000), LDUH (27 per 1,000), and LMWH (33 per 1,000), all compared with no prophylaxis (Tables S16-S19). Although the balance between benefits and harms favors either pharmacologic or mechanical methods over no prophylaxis, the tradeoffs involved in the comparison between pharmacologic prophylaxis and mechanical prophylaxis with IPC are not as clear cut (Tables S21, S22). IPC may still be preferred over LMWH if the consequences of a nonfatal major bleeding event are believed to be at least two times more severe than those of nonfatal VTE.

7.4 Recommendations for Spinal Surgery

7.4.1. For patients undergoing spinal surgery, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C)**, unfractionated heparin** (Grade 2C)**, or LMWH** (Grade 2C)**.**

7.4.2. For patients undergoing spinal surgery at high risk for VTE (including those with malignant disease and those undergoing surgery with a combined anterior-posterior approach), we suggest adding pharmacologic prophylaxis to mechanical prophylaxis once adequate hemostasis is established and the risk of bleeding decreases (Grade 2C)**.**

8.0 Target Population: Major Trauma, Including Traumatic Brain Injury, Acute Spinal Cord Injury, and Traumatic Spine Surgery

Decision making about thromboprophylaxis in trauma patients poses numerous challenges. Although traumatic inflammation, fractures, immobilization, and surgical intervention contribute to the high risk of VTE, both the risk and, potentially, the dire consequences of bleeding complications weigh heavily, especially in cases of visceral, spinal, and head injury.

Seven randomized controlled trials of LMWH thromboprophylaxis in trauma limited enrollment to patients with isolated lower-extremity injuries; results of these trials and accompanying recommendations are described by Falck-Ytter et al[35] in this supplement. Nineteen other trials enrolled diverse groups of moderately to severely injured patients, including eight trials in patients with spinal cord injury[30,166-172] and four studies in patients with orthopedic injuries.[173-176] Studies evaluated both mechanical (eg, IPC, myostimulation, continuous passive motion) and pharmacologic (eg, LDUH, LMWH) interventions, but no randomized trials examined IVC filter placement or use of surveillance ultrasound. Study limitations included small samples, incomplete or absent blinding, unclear concealment of treatment allocation, use of surrogate outcomes, exclusion of large numbers of randomized patients from primary outcome assessment, and imprecise results (Appendix S1). Accordingly, there is little moderate- or high-quality direct evidence to support the use of one or more interventions for thromboprophylaxis in trauma. Therefore, when making recommendations, we used estimates of relative risk from studies in other populations that suffered from less risk of bias and that were more precise.

8.1 Baseline Risk, Risk Factors, and Risk Stratification for VTE

Numerous studies have examined the risk of VTE in trauma (Appendix S1). Across four studies of patients with mixed trauma, the risk of symptomatic VTE ranged from > 1% to 7.6%.[61,177-179] The risk is probably highest among patients with spinal trauma (2.2% despite near-universal prophylaxis), acute spinal cord injury (5%-6%), or traumatic brain injury (3%-5% among those who received pharmacologic prophylaxis within 24 to 48 h; up to 15% when initiation of pharmacologic prophylaxis was delayed beyond 48 h).[180-185] A systematic review identified patients with spinal fractures (OR, 2.3; 95% CI, 1.4-3.6) or spinal cord injury (OR, 3.0; 95% CI, 1.8-5.4) as having a higher risk of VTE than other patients with trauma.[186] Older age has also been implicated as a risk factor for VTE in a number of studies.[177,178,187]

Other independent risk factors for VTE, inconsistent across studies, included blood transfusion, surgery, femoral or tibial fracture, and spinal cord injury[177]; head injury, major operation, lower-extremity fracture, venous injury, and (especially) > 3 days of mechanical ventilation[178]; and male sex, black race, complete paraplegia (vs tetraplegia), and multiple comorbidities.[181] Based on results of these studies, we believe that the baseline risk of VTE in most patients with major trauma is at least 3% to 5% and that the risk is even higher (8%-10%) among patients with traumatic brain or spinal cord injury and among those who require spinal surgery.

8.2 Baseline Risk, Risk Factors, and Risk Stratification for Major Bleeding Complications

Few studies have examined bleeding complications associated with thromboprophylaxis in trauma. In a prospective study of 525 patients with traumatic brain injury who were judged to be eligible to receive LMWH prophylaxis within 48 h of admission, progressive hemorrhagic changes were seen on head CT scan in 18 patients (3.4%), including in six (1.1%) in whom there was a change in management or outcome.[188] In a retrospective study of nosocomial complications in 525 adult patients with trauma, the reported risk of bleeding requiring red cell transfusion of > 4 units was 4.7%.[179]

Another source of data to estimate the baseline risk of major bleeding complications comes from patients who were assigned to receive nonpharmacologic management in randomized trials of thromboprophylaxis. Unfortunately, only three trials in patients with trauma reported major bleeding complications in four groups that did not receive pharmacologic prophylaxis.[189-191] In these groups, the pooled (random-effects) risk of major bleeding was 0.7% (95% CI, 0.2%-1.7%). This is likely to represent a lower boundary for the baseline risk of bleeding because patients judged to be at increased risk for bleeding were excluded from most trials of thromboprophylaxis. Relative contraindications to pharmacologic prophylaxis in trauma include severe head injuries, nonoperatively managed liver or spleen injuries, renal failure, spinal column fracture with epidural hematoma, severe thrombocytopenia, and coagulopathy.[192]

8.3 Explanation of Evidence Profiles

For patients with major trauma who are at average risk for VTE and average risk for major bleeding, low-quality evidence suggests that pharmacologic prophylaxis with LDUH or LMWH can be expected to prevent approximately four times as many nonfatal VTE events as nonfatal bleeding complications caused (Tables S23, S24). Low-quality evidence suggests that mechanical prophylaxis with ES or IPC can be expected to prevent a similar number of nonfatal VTE events (Tables S25, S26) at a cost of an uncertain number of skin complications.

For patients with major trauma who are at especially high risk for VTE and average risk for bleeding complications (eg, acute spinal cord injury, spinal surgery for trauma), low-quality evidence suggests that pharmacologic prophylaxis with LDUH or LMWH can be expected to prevent almost 10 times as many nonfatal VTE events as nonfatal bleeding complications

caused (Tables S23,S24). Moderate-quality evidence suggests that both LDUH and LMWH can also be expected to prevent four deaths from PE per 1,000 patients treated. The addition of mechanical prophylaxis can be expected to prevent 15 additional nonfatal VTE events per 1,000 patients treated (Table S27) at a cost of an uncertain number of skin complications.

For patients with major trauma at high risk for major bleeding (including those with traumatic brain injury), low-quality evidence suggests that the numbers of nonfatal VTE events prevented by pharmacologic methods are only slightly larger than the numbers of nonfatal major bleeding complications caused (Tables S23, S24). In these patients, mechanical prophylaxis with ES or IPC prevents sizable numbers of nonfatal VTE events at the expense of skin complications but without increasing the risk of bleeding (Tables S25,S26).

Few studies address the optimal duration of prophylaxis for patients with acute spinal cord injury. However, in a retrospective study of > 16,000 patients discharged from California hospitals between 1991 and 2001, > 90% of all thromboembolic events reported within 1 year after injury occurred in the first 91 days.[178] Pending further evidence, we agree with others[193] that 3 months is a reasonable time for VTE prophylaxis in most patients with acute spinal cord injury. Shorter durations may be appropriate for patients who regain purposeful movement of the lower extremities before 3 months, but further study is needed. For information about the use of IVC filters and DVT surveillance with VCU in trauma patients, please see sections 2.12, 2.13 and 3.5, and Table 22.

8.4 Recommendations for Patients With Trauma

Recommendations for patients with isolated lower-extremity injuries are provided by Falck-Ytter et al[35] in this supplement.

8.4.1. For major trauma patients, we suggest use of LDUH (Grade 2C)**, LMWH** (Grade 2C)**, or mechanical prophylaxis, preferably with IPC** (Grade 2C)**, over no prophylaxis.**

8.4.2. For major trauma patients at high risk for VTE (including those with acute spinal cord injury, traumatic brain injury, and spinal surgery for trauma), we suggest adding mechanical prophylaxis to pharmacologic prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury.**

8.4.3. For major trauma patients in whom LMWH and LDUH are contraindicated, we suggest mechanical prophylaxis, preferably with IPC, over no prophylaxis (Grade 2C) **when not contraindicated by lower-extremity injury. We suggest adding pharmacologic prophylaxis with either LMWH or LDUH when the risk of bleeding diminishes or the contraindication to heparin resolves** (Grade 2C)**.**

8.4.4. For major trauma patients, we suggest that an IVC filter should not be used for primary VTE prevention (Grade 2C)**.**

8.4.5. For major trauma patients, we suggest that periodic surveillance with VCU should not be performed (Grade 2C)**.**

9.0 Suggestions for Good Clinical Practice

The following general considerations for good clinical practice apply to thromboprophylaxis in all surgical groups:

- It may be advisable for every institution to have a formal, written policy for preventing VTE in surgical patients.
- Adherence with IPC often is less than optimal and, therefore, should be monitored actively. Portable, battery-powered devices capable of recording and reporting proper wear time may facilitate monitoring. Efforts should be made to achieve at least 18 h of use daily.
- Proper fit and adherence with ES is necessary to ensure efficacy. The correct pressure at the ankle level for primary prophylaxis is 18 to 23 mm Hg, which is lower than for therapeutic stockings used to treat postthrombotic syndrome (30-40 mm Hg). Based on indirect evidence from patients with stroke,[29] we favor thigh-high elastic stockings over calf-high stockings.
- Relative contraindications to IPC and ES include dermatitis, skin breakdown, or ulceration; peripheral vascular disease; lower-extremity bypass procedure; and lower-extremity trauma with plaster cast. Unilateral compression in an unaffected limb should not be used as the sole means of prophylaxis.
- In the overwhelming majority of trials that demonstrated efficacy, LDUH and LMWH were given 2 h preoperatively, although LMWH appears to be effective and is possibly associated with a lower risk of bleeding when the first dose is given 12 h preoperatively.[194,195]
- When using pharmacologic prophylaxis, we suggest following the manufacturer's recommendations for dosing. It may be prudent to consult with a pharmacist regarding dosing in

bariatric surgery patients and other patients who are obese who may require higher doses of LDUH or LMWH.

10.0 Recommendations for Research

Most of the recommendations in this guideline are based on low-quality evidence. Many older randomized controlled trials were limited by small samples, incomplete blinding, unclear concealment of treatment allocation, and measurement of surrogate outcomes. Future randomized trials should enroll representative samples (ideally in community settings) and be adequately powered to show differences in patient-important outcomes, including objectively confirmed, symptomatic VTE events and clearly defined bleeding complications. Reporting of bleeding outcomes in trials involving surgical patients should be standardized to include fatal bleeding, bleeding requiring reoperation, critical organ bleeding, and other consequential bleeding as recommended by the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[196-198]

One high-priority target for randomized controlled trials is a comparison of pharmacologic prophylaxis (preferably with LMWH) with mechanical prophylaxis (preferably with IPC) in nonorthopedic surgical patients at moderate risk for VTE. Other priorities include a trial of IPC plus pharmacologic prophylaxis vs pharmacologic prophylaxis alone in patients at high risk for VTE and a trial of retrievable IVC filter placement vs no IVC filter placement in high-VTE-risk patients who are not candidates for pharmacologic prophylaxis.

The VTE risk assessment models cited in this article have important limitations. Rigorously developed and extensively validated models of VTE risk in well-defined surgical populations are urgently needed. There is a similar need for validated models that stratify the risk of bleeding complications in specific groups of surgical patients.

Relatively few studies have examined methods for implementing thromboprophylaxis guidelines in hospital settings. Although passive dissemination alone appears to be inadequate, the relative effectiveness of electronic reminders, clinical champions, audit and feedback, and decision support requires further study.[199]

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Dr Garcia: contributed as deputy editor.
Dr Wren: contributed as frontline clinician.
Dr Karanicolas: contributed as panelist.
Dr Arcelus: contributed as panelist.
Dr Heit: contributed as panelist.
Dr Samama: contributed as panelist.
Financial/nonfinancial disclosures: The authors of this guideline provided detailed conflict of interest information related to each individual recommendation made in this article. A grid of these disclosures is available online at http://chestjournal.chestpubs.org/content/141/2_suppl/e227S/suppl/DC1. In summary, the authors have reported to *CHEST* the following conflicts of interest: Dr Arcelus participated as an invited speaker in three lectures in Australia in March 2010 sponsored by Sanofi-Aventis LLC. Dr Samama reports serving as co-investigator for two observational studies of VTE prophylaxis in surgical patients with cancer, sponsored by Sanofi-Aventis. Dr Samama has also received consulting honoraria from companies that manufacture hemostatic agents (LFB, Octapharma, CSL, and Behring) and from companies that manufacture anticoagulants (Boehringer Ingelheim, Bayer, and Daichii Sankyo), though most of the funds have gone to his institution. Dr Samama's travel expenses to two recent conferences were paid by Bayer. Drs Gould, Garcia, Heit, Karanicolas, and Wren have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.
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