Prevention of Venous Thromboembolism*

American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)

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This article discusses the prevention of venous thromboembolism (VTE) and is part of the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Grade 1 recommendations are strong and indicate that the benefits do or do not outweigh risks, burden, and costs. Grade 2 suggestions imply that individual patient values may lead to different choices (for a full discussion of the grading, see the "Grades of Recommendation" chapter by Guyatt et al). Among the key recommendations in this chapter are the following: we recommend that every hospital develop a formal strategy that addresses the prevention of VTE (Grade 1A). We recommend against the use of aspirin alone as thromboprophylaxis for any patient group (Grade 1A), and we recommend that mechanical methods of thromboprophylaxis be used primarily for patients at high bleeding risk (Grade 1A) or possibly as an adjunct to anticoagulant thromboprophylaxis (Grade 2A).

For patients undergoing major general surgery, we recommend thromboprophylaxis with a low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (LDUH), or fondaparinux (each Grade 1A). We recommend routine thromboprophylaxis for all patients undergoing major gynecologic surgery or major, open urologic procedures (Grade 1A for both groups), with LMWH, LDUH, fondaparinux, or intermittent pneumatic compression (IPC).

For patients undergoing elective hip or knee arthroplasty, we recommend one of the following three anticoagulant agents: LMWH, fondaparinux, or a vitamin K antagonist (VKA); international normalized ratio (INR) target, 2.5; range, 2.0 to 3.0 (each Grade 1A). For patients undergoing hip fracture surgery (HFS), we recommend the routine use of fondaparinux (Grade 1A), LMWH (Grade 1B), a VKA (target INR, 2.5; range, 2.0 to 3.0) [Grade 1B], or LDUH (Grade 1B). We recommend that patients undergoing hip or knee arthroplasty or HFS receive thromboprophylaxis for a minimum of 10 days (Grade 1A); for hip arthroplasty and HFS, we recommend continuing thromboprophylaxis > 10 days and up to 35 days (Grade 1A). We recommend that all major trauma and all spinal cord injury (SCI) patients receive thromboprophylaxis (Grade 1A). In patients admitted to hospital with an acute medical illness, we recommend thromboprophylaxis with LMWH, LDUH, or fondaparinux (each Grade 1A). We recommend that, on admission to the ICU, all patients be assessed for their risk of VTE, and that most receive thromboprophylaxis (Grade 1A). ***(CHEST 2008; 133:381S–453S)***

Key words: aspirin; deep vein thrombosis; fondaparinux; graduated compression stockings; heparin; intermittent pneumatic compression; low-molecular-weight heparin; pulmonary embolism; thromboprophylaxis; venous foot pump; venous thromboembolism; warfarin

Abbreviations: CABG = coronary artery bypass graft; CI = confidence interval; CVC = central venous catheter; DUS = Doppler ultrasonography; DVT = deep vein thrombosis; FUT = fibrinogen uptake test; GCS = graduated compression stockings; HFS = hip fracture surgery; HIT = heparin-induced thrombocytopenia; INR = international normalized ratio; IPC = intermittent pneumatic compression; IVC = inferior vena cava; LDUH = low-dose unfractionated heparin; LMWH = low-molecular-weight heparin; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; OR = odds ratio; PE = pulmonary embolism; RAM = risk assessment model; RRR = relative risk reduction; SC = subcutaneous; SCI = spinal cord injury; THR = total hip replacement; TKR = total knee replacement; VFP = venous foot pump; VKA = vitamin K antagonist; VTE = venous thromboembolism

Summary of Recommendations

1.0 General Recommendations

Hospital Thromboprophylaxis Policy

1.2.1. For every general hospital, we recommend that a formal, active strategy that addresses the prevention of VTE be developed (Grade 1A)**.**
1.2.2. We recommend that the local thromboprophylaxis strategy be in the form of a written, institution-wide thromboprophylaxis policy (Grade 1C)**.**
1.2.3. We recommend the use of strategies shown to increase thromboprophylaxis adherence, including the use of computer decision support systems (Grade 1A)**, preprinted orders** (Grade 1B)**, and periodic audit and feedback** (Grade 1C)**. Passive methods such as distribution of educational materials or educational meetings are not recommended as sole strategies to increase adherence to thromboprophylaxis** (Grade 1B)**.**

Mechanical Methods of Thromboprophylaxis

1.4.3.1. We recommend that mechanical methods of thromboprophylaxis be used primarily in patients at high risk for bleeding (Grade 1A)**, or possibly as an adjunct to anticoagulant-based thromboprophylaxis** (Grade 2A)**.**
1.4.3.2. For patients receiving mechanical methods of thromboprophylaxis, we recommend that careful attention be directed toward ensuring the proper use of, and optimal adherence with, these methods (Grade 1A)**.**

Aspirin as Thromboprophylaxis

1.4.4. We recommend against the use of aspirin alone as thromboprophylaxis against VTE for any patient group (Grade 1A)**.**

Anticoagulant Dosing

1.4.5. For each of the antithrombotic agents, we recommend that clinicians follow the manufacturer-suggested dosing guidelines (Grade 1C)**.**

Renal Impairment and Anticoagulant Dosing

1.4.6. We recommend that renal function be considered when making decisions about the use and/or the dose of LMWH, fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients, patients with diabetes mellitus, and those at high risk for bleeding (Grade 1A)**. Depending on the circumstances, we recommend one of the following options in this situation: avoiding the use of an anticoagulant that bioaccumulates in the presence of renal impairment, using a lower dose of the agent, or monitoring the drug level or its anticoagulant effect** (Grade 1B)**.**

Antithrombotic Drugs and Neuraxial Anesthesia/ Analgesia or Peripheral Nerve Blocks

1.5.1. For all patients undergoing neuraxial anesthesia or analgesia, we recommend appropriate patient selection and caution when using anticoagulant thromboprophylaxis (Grade 1A)**.**
1.5.2. For patients receiving deep peripheral nerve blocks, we recommend that the same cautions considered for neuraxial techniques be applied when using anticoagulant thromboprophylaxis (Grade 1C)**.**

2.0 General, Vascular, Gynecologic, Urologic, Laparoscopic, Bariatric, Thoracic, and Coronary Artery Bypass Surgery

2.1 General Surgery

2.1.1. For low-risk general surgery patients who are undergoing minor procedures and have no additional thromboembolic risk factors, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A)**.**
2.1.2. For moderate-risk general surgery patients who are undergoing a major procedure for benign disease, we recommend thromboprophylaxis with LMWH, LDUH, or fondaparinux (each Grade 1A)**.**
2.1.3. For higher-risk general surgery patients

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who are undergoing a major procedure for cancer, we recommend thromboprophylaxis with LMWH, LDUH three times daily, or fondaparinux (each Grade 1A).

2.1.4. For general surgery patients with multiple risk factors for VTE who are thought to be at particularly high risk, we recommend that a pharmacologic method (*ie*, LMWH, LDUH three times daily, or fondaparinux) be combined with the optimal use of a mechanical method (*ie*, graduated compression stockings [GCS] and/or IPC) [Grade 1C].

2.1.5. For general surgery patients with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted GCS or IPC (Grade 1A). **When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C).

2.1.6. For patients undergoing major general surgical procedures, we recommend that thromboprophylaxis continue until discharge from hospital (Grade 1A). **For selected high-risk general surgery patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered** (Grade 2A).

2.2 Vascular Surgery

2.2.1. For patients undergoing vascular surgery who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use specific thromboprophylaxis other than early and frequent ambulation (Grade 2B).

2.2.2. For patients undergoing major vascular surgery procedures who have additional thromboembolic risk factors, we recommend thromboprophylaxis with LMWH, LDUH, or fondaparinux (Grade 1C).

2.3 Gynecologic Surgery

2.3.1. For low-risk gynecologic surgery patients who are undergoing minor procedures and have no additional risk factors, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A).

2.3.2. For gynecology patients undergoing entirely laparoscopic procedures, we recommend against routine thromboprophylaxis, other than early and frequent ambulation (Grade 1B).

2.3.3. For gynecology patients undergoing entirely laparoscopic procedures in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of LMWH, LDUH, IPC, or GCS (Grade 1C).

2.3.4. For all patients undergoing major gynecologic surgery, we recommend that thromboprophylaxis be used routinely (Grade 1A).

2.3.5. For patients undergoing major gynecologic surgery for benign disease without additional risk factors, we recommend LMWH (Grade 1A), **LDUH** (Grade 1A), **or IPC started just before surgery and used continuously while the patient is not ambulating** (Grade 1B).

2.3.6. For patients undergoing extensive surgery for malignancy and for patients with additional VTE risk factors, we recommend routine thromboprophylaxis with LMWH (Grade 1A), **or LDUH three times daily** (Grade 1A), **or IPC, started just before surgery and used continuously while the patient is not ambulating** (Grade 1A). **Alternative considerations include a combination of LMWH or LDUH plus mechanical thromboprophylaxis with GCS or IPC, or fondaparinux** (all Grade 1C).

2.3.7. For patients undergoing major gynecologic procedures, we recommend that thromboprophylaxis continue until discharge from hospital (Grade 1A). **For selected high-risk gynecology patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered** (Grade 2C).

2.4 Urologic Surgery

2.4.1. For patients undergoing transurethral or other low-risk urologic procedures, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A).

2.4.2. For all patients undergoing major, open urologic procedures, we recommend that thromboprophylaxis be used routinely (Grade 1A).

2.4.3. For patients undergoing major, open urologic procedures, we recommend routine thromboprophylaxis with LDUH twice daily or three times daily (Grade 1B), **GCS and/or IPC started just before surgery and used continuously while the patient is not ambulating** (Grade 1B), **LMWH** (Grade 1C), **fondaparinux** (Grade 1C), **or the combination of a pharmacologic method (*ie*, LMWH, LDUH, or fondaparinux) with the optimal use of a**

mechanical method (*ie*, GCS and/or IPC) [Grade 1C].

2.4.4. For urologic surgery patients who are actively bleeding, or who are at very high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

2.5 Laparoscopic Surgery

2.5.1. For patients undergoing entirely laparoscopic procedures who do not have additional thromboembolic risk factors, we recommend against the routine use of thromboprophylaxis, other than early and frequent ambulation (Grade 1B).

2.5.2. For patients undergoing laparoscopic procedures in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of LMWH, LDUH, fondaparinux, IPC, or GCS (all Grade 1C)**.**

2.6 Bariatric Surgery

2.6.1. For patients undergoing inpatient bariatric surgery, we recommend routine thromboprophylaxis with LMWH, LDUH three times daily, fondaparinux, or the combination of one of these pharmacologic methods with optimally used IPC (each Grade 1C).

2.6.2. For patients undergoing inpatient bariatric surgery, we suggest that higher doses of LMWH or LDUH than usual for nonobese patients be used (Grade 2C)**.**

2.7 Thoracic Surgery

2.7.1. For patients undergoing major thoracic surgery, we recommend routine thromboprophylaxis with LMWH, LDUH, or fondaparinux (each Grade 1C)**.**

2.7.2. For thoracic surgery patients with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted GCS and/or IPC (Grade 1C)**.**

2.8 Coronary Artery Bypass Surgery

2.8.1. For patients undergoing coronary artery bypass graft (CABG) surgery, we recommend the use of thromboprophylaxis with LMWH, LDUH, or optimally used bilateral GCS or IPC (Grade 1C)**.**

2.8.2. For patients undergoing CABG, we suggest the use of LMWH over LDUH (Grade 2B)**.**

2.8.3. For patients undergoing CABG with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted bilateral GCS or IPC (Grade 1C)**.**

3.0 Orthopedic Surgery

3.1 Elective Hip Replacement

3.1.1. For patients undergoing elective total hip replacement (THR), we recommend the routine use of one of the following anticoagulant options: (1) LMWH (at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day); (2) fondaparinux (2.5 mg started 6 to 24 h after surgery); or (3) adjusted-dose VKA started preoperatively or the evening of the surgical day (international normalized ratio [INR] target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A).

3.1.2. For patients undergoing THR, we recommend against the use of any of the following: aspirin, dextran, LDUH, GCS, or venous foot pump (VFP) as the sole method of thromboprophylaxis (all Grade 1A).

3.1.3. For patients undergoing THR who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with the VFP or IPC (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

3.2 Elective Knee Replacement

3.2.1. For patients undergoing TKR, we recommend routine thromboprophylaxis using LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose VKA (INR target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A)**.**

3.2.2. For patients undergoing TKR, the optimal use of IPC is an alternative option to anticoagulant thromboprophylaxis (Grade 1B).

3.2.3. For patients undergoing TKR, we recommend against the use of any of the following as the only method of thromboprophylaxis: aspirin (Grade 1A)**, LDUH** (Grade 1A)**, or VFP** (Grade 1B).

3.2.4. For patients undergoing TKR who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with IPC

(Grade 1A) **or VFP** (Grade 1B)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

3.3 Knee Arthroscopy

3.3.1. For patients undergoing knee arthroscopy who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use thromboprophylaxis other than early mobilization (Grade 2B)**.**
3.3.2. For patients undergoing arthroscopic knee surgery who have additional thromboembolic risk factors or following a complicated procedure, we recommend thromboprophylaxis with LMWH (Grade 1B)**.**

3.4 Hip Fracture Surgery

3.4.1. For patients undergoing HFS, we recommend routine thromboprophylaxis using fondaparinux (Grade 1A)**, LMWH** (Grade 1B)**, adjusted-dose VKA (INR target, 2.5; INR range, 2.0 to 3.0)** [Grade 1B]**, or LDUH** (Grade 1B)**.**
3.4.2. For patients undergoing HFS, we recommend against the use of aspirin alone (Grade 1A)**.**
3.4.3. For patients undergoing HFS in whom surgery is likely to be delayed, we recommend that thromboprophylaxis with LMWH or LDUH be initiated during the time between hospital admission and surgery (Grade 1C)**.**
3.4.4. For patients undergoing HFS who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

3.5 Other Thromboprophylaxis Issues in Major Orthopedic Surgery

3.5.1 Commencement of Thromboprophylaxis

3.5.1.1. For patients receiving LMWH as thromboprophylaxis in major orthopedic surgery, we recommend starting either preoperatively or postoperatively (Grade 1A)**.**
3.5.1.2. For patients receiving fondaparinux as thromboprophylaxis in major orthopedic surgery, we recommend starting either 6 to 8 h after surgery or the next day (Grade 1A)**.**

Screening for Deep Vein Thrombosis Before Hospital Discharge

3.5.2. For asymptomatic patients following major orthopedic surgery, we recommend against the routine use of DUS screening before hospital discharge (Grade 1A)**.**

Duration of Thromboprophylaxis

3.5.3.1. For patients undergoing THR, TKR, or HFS, we recommend thromboprophylaxis with one of the recommended options for at least 10 days (Grade 1A)**.**
3.5.3.2. For patients undergoing THR, we recommend that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 1A)**. The recommended options for extended thromboprophylaxis in THR include LMWH** (Grade 1A)**, a VKA** (Grade 1B)**, or fondaparinux** (Grade 1C)**.**
3.5.3.3. For patients undergoing TKR, we suggest that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 2B)**. The recommended options for extended thromboprophylaxis in TKR include LMWH** (Grade 1C)**, a VKA** (Grade 1C)**, or fondaparinux** (Grade 1C)**.**
3.5.3.4. For patients undergoing HFS, we recommend that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 1A)**. The recommended options for extended thromboprophylaxis in HFS include fondaparinux** (Grade 1A)**, LMWH** (Grade 1C)**, or a VKA** (Grade 1C)**.**

3.6 Elective Spine Surgery

3.6.1. For patients undergoing spine surgery who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use specific thromboprophylaxis other than early and frequent ambulation (Grade 2C)**.**
3.6.2. For patients undergoing spine surgery who have additional thromboembolic risk factors such as advanced age, malignancy, presence of a neurologic deficit, previous VTE, or an anterior surgical approach, we recommend that one of the following thromboprophylaxis options be used: postoperative LDUH (Grade 1B)**, postoperative LMWH** (Grade 1B)**, or optimal use of perioperative IPC** (Grade 1B)**. An alternative consideration is GCS** (Grade 2B)**.**
3.6.3. For patients undergoing spine surgery who have multiple risk factors for VTE, we suggest that a pharmacologic method (*ie*,

LDUH or LMWH) be combined with the optimal use of a mechanical method (*ie*, GCS and/or IPC) (Grade 2C).

3.7 Isolated Lower-Extremity Injuries Distal to the Knee

3.7.1. For patients with isolated lower-extremity injuries distal to the knee, we suggest that clinicians not routinely use thromboprophylaxis (Grade 2A).

4.0 Neurosurgery

4.0.1. For patients undergoing major neurosurgery, we recommend that thromboprophylaxis be used routinely (Grade 1A), **with optimal use of IPC** (Grade 1A). **Acceptable alternatives to IPC are post operative LMWH** (Grade 2A) **or LDUH** (Grade 2B).
4.0.2. For patients undergoing major neurosurgery who have a particularly high thrombosis risk, we suggest that a mechanical method (*ie*, GCS and/or IPC) be combined with a pharmacologic method (*ie*, postoperative LMWH or LDUH) (Grade 2B).

5.0 Trauma, Spinal Cord Injury, Burns

5.1 Trauma

5.1.1. For all major trauma patients, we recommend routine thromboprophylaxis if possible (Grade 1A).
5.1.2. For major trauma patients, in the absence of a major contraindication, we recommend that clinicians use LMWH thromboprophylaxis starting as soon as it is considered safe to do so (Grade 1A). **An acceptable alternative is the combination of LMWH and the optimal use of a mechanical method of thromboprophylaxis** (Grade 1B).
5.1.3. For major trauma patients, if LMWH thromboprophylaxis is contraindicated due to active bleeding or high risk for clinically important bleeding, we recommend that mechanical thromboprophylaxis with IPC or possibly with GCS alone be used (Grade 1B). **When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C).
5.1.4. In trauma patients, we recommend against routine DUS screening for asymptomatic deep vein thrombosis (DVT) (Grade 1B). **We do recommend DUS screening in patients who are at high risk for VTE (*eg*, in the presence of a spinal cord injury [SCI], lower-extremity or pelvic fracture, or major head injury), and who have received suboptimal thromboprophylaxis or no thromboprophylaxis** (Grade 1C).
5.1.5. For trauma patients, we recommend against the use of an inferior vena cava (IVC) filter as thromboprophylaxis (Grade 1C).
5.1.6. For major trauma patients, we recommend the continuation of thromboprophylaxis until hospital discharge (Grade 1C). **For trauma patients with impaired mobility who undergo inpatient rehabilitation, we suggest continuing thromboprophylaxis with LMWH or a VKA (target INR, 2.5; range, 2.0 to 3.0)** (Grade 2C).

5.2 Acute Spinal Cord Injury

5.2.1. For all patients with acute SCI, we recommend that routine thromboprophylaxis be provided (Grade 1A).
5.2.2. For patients with acute SCI, we recommend thromboprophylaxis with LMWH, commenced once primary hemostasis is evident (Grade 1B). **Alternatives include the combined use of IPC and either LDUH** (Grade 1B) **or LWMH** (Grade 1C).
5.2.3. For patients with acute SCI, we recommend the optimal use of IPC and/or GCS if anticoagulant thromboprophylaxis is contraindicated because of high bleeding risk early after injury (Grade 1A). **When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C).
5.2.4. For patients with an incomplete SCI associated with evidence of a spinal hematoma on CT or MRI, we recommend the use of mechanical thromboprophylaxis instead of anticoagulant thromboprophylaxis at least for the first few days after injury (Grade 1C).
5.2.5. Following acute SCI, we recommend against the use of LDUH alone (Grade 1A).
5.2.6. For patients with SCI, we recommend against the use of an IVC filter as thromboprophylaxis (Grade 1C).
5.2.7. For patients undergoing rehabilitation following acute SCI, we recommend the continuation of LMWH thromboprophylaxis or conversion to an oral VKA (INR target, 2.5; range, 2.0 to 3.0) (Grade 1C).

5.3 Burns

5.3.1. For burn patients who have additional risk factors for VTE, including one or more of the following: advanced age, morbid obesity, extensive or lower-extremity burns, concomitant lower-extremity trauma, use of a femoral venous catheter, and/or prolonged immobility, we recommend routine thromboprophylaxis if possible (Grade 1A).
5.3.2. For burn patients who have additional risk factors for VTE, if there are no contraindications, we recommend the use of either LMWH or LDUH starting as soon as it is considered safe to do so (Grade 1C).
5.3.3. For burn patients who have a high bleeding risk, we recommend mechanical thromboprophylaxis with GCS and/or IPC until the bleeding risk decreases (Grade 1A).

6.0 Medical Conditions

6.0.1. For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with LMWH (Grade 1A), **LDUH** (Grade 1A), **or fondaparinux** (Grade 1A).
6.0.2. For medical patients with risk factors for VTE, and for whom there is a contraindication to anticoagulant thromboprophylaxis, we recommend the optimal use of mechanical thromboprophylaxis with GCS or IPC (Grade 1A).

7.0 Cancer Patients

7.0.1. For cancer patients undergoing surgical procedures, we recommend routine thromboprophylaxis that is appropriate for the type of surgery (Grade 1A). **Refer to the recommendations in the relevant surgical subsections.**
7.0.2. For cancer patients who are bedridden with an acute medical illness, we recommend routine thromboprophylaxis as for other high-risk medical patients (Grade 1A).
Refer to the recommendations in Section 6.0.
7.0.3. For cancer patients with indwelling central venous catheters, we recommend that clinicians not use either prophylactic doses of LMWH (Grade 1B). **or minidose warfarin** (Grade 1B) **to try to prevent catheter-related thrombosis.**
7.0.4. For cancer patients receiving chemotherapy or hormonal therapy, we recommend against the routine use of thromboprophylaxis for the primary prevention of VTE (Grade 1C).
7.0.5. For cancer patients, we recommend against the routine use of primary thromboprophylaxis to try to improve survival (Grade 1B).

8.0 Critical Care

8.1. For patients admitted to a critical care unit, we recommend routine assessment for VTE risk and routine thromboprophylaxis in most (Grade 1A).
8.2. For critical care patients who are at moderate risk for VTE (*eg*, medically ill or postoperative general surgery patients), we recommend using LMWH or LDUH thromboprophylaxis (Grade 1A).
8.3. For critical care patients who are at higher risk (*eg*, following major trauma or orthopedic surgery), we recommend LMWH thromboprophylaxis (Grade 1A).
8.4. For critical care patients who are at high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 1A). **When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C).

9.0 Long-Distance Travel

9.1. For travelers who are taking flights > 8 h, we recommend the following general measures: avoidance of constrictive clothing around the lower extremities or waist, maintenance of adequate hydration, and frequent calf muscle contraction (Grade 1C).
9.2. For long-distance travelers with additional risk factors for VTE, we recommend the general measures listed above. If active thromboprophylaxis is considered because of a perceived high risk of VTE, we suggest the use of properly fitted, below-knee GCS, providing 15 to 30 mm Hg of pressure at the ankle (Grade 2C), **or a single prophylactic dose of LMWH injected prior to departure** (Grade 2C).
9.3. For long-distance travelers, we recommend against the use of aspirin for VTE prevention (Grade 1B).

This article systematically summarizes the literature related to the prevention of venous thromboembolism (VTE) and provides evidence-based recommendations. It refers frequently to the seventh American College of Chest Physicians guidelines,[1] which contain additional discussion and references.

1.1 Methods

This chapter adhered closely to the model for developing American College of Chest Physicians guidelines that is described by Schunemann et al in this supplement ("Methodology" chapter). *A priori* criteria for inclusion of studies were applied (Table 1). The number needed to treat (NNT) was used to estimate the number of patients who would need to receive a specific thromboprophylaxis regimen to prevent one additional deep vein thrombosis (DVT), compared with patients receiving no thromboprophylaxis or another thromboprophylaxis regimen. The number needed to harm (NNH) was defined as the number of patients who would need to receive the thromboprophylaxis regimen to result in one additional adverse event, such as major bleeding.

Table 1—*Criteria for Inclusion of Studies (Section 1.1)**

Variables	Description
Patients	Identifiable as belonging to the group of interest
Outcome assessment	
Nonorthopedic studies	Symptomatic, objectively confirmed thromboembolic events, or Contrast venography, fibrinogen leg scanning, or DUS
Orthopedic studies	Symptomatic, objectively confirmed thromboembolic events, or Contrast venography (bilateral or ipsilateral) or DUS (although the results of trials using these two outcomes were not pooled)
Sample size	At least 10 patients per group
Numerator	Objectively demonstrated DVT
Denominator	Patients with adequate outcome assessments for VTE
Baseline risks of thrombosis	
Design	Either prospective cohort studies or the control groups within randomized clinical trials
Interventions	No thromboprophylaxis used
Thromboprophylaxis efficacy	
Design	Randomized clinical trials only
Interventions	Clinically relevant, commercially available options; for drugs, currently approved or utilized agents and doses

*English-language publications.

Although the recommendations are evidence based, we also provide expert, consensus-based suggestions that clinicians might find useful when the evidence is weak.

1.2 Rationale for Thromboprophylaxis

The rationale for use of thromboprophylaxis is based on solid principles and scientific evidence (Table 2).[1,2] Almost all hospitalized patients have at least one risk factor for VTE, and approximately 40% have three or more risk factors (Table 3).[2–11] Without thromboprophylaxis, the incidence of objectively confirmed, hospital-acquired DVT is approximately 10 to 40% among medical or general surgical patients and 40 to 60% following major orthopedic surgery (Table 4).[1,2] Among >7 million patients discharged from 944 American acute care hospitals, postoperative VTE was the second-most-common medical complication, the second-most-common cause of excess length of stay, and the third-most-common cause of excess mortality and excess charges.[12] The mortality, acute and long-term morbidities, and resource utilization related to unprevented VTE strongly support effective preventive strategies at least for moderate-risk and high-risk patients.[1,13,14] Finally, a vast number of randomized clinical trials over the past 30 years provide irrefutable evidence that primary thromboprophylaxis reduces DVT and pulmonary embolism (PE), and there are studies that have also shown that fatal PE is prevented by thromboprophylaxis.[1] PE is the most common preventable cause of hospital death and the number-one strategy to improve patient safety in hospitals.[15] Routine use of thromboprophylaxis reduces adverse patient outcomes while at the same time decreasing overall costs.[16–18] With respect to complications of thromboprophylaxis, abundant data from metaanalyses and blinded, randomized clinical trials have demonstrated little or no increase in the rates of clinically important bleeding with prophylactic doses of low-dose unfractionated heparin (LDUH), low-molecular-weight heparin (LMWH), or a vitamin K antagonist (VKA).[19–26] In summary, there is strong evidence that appropriately used thromboprophylaxis has a desirable benefit-to-risk ratio and is cost-effective.[1,16–18,27]

VTE is an important health-care problem, resulting in significant mortality, morbidity, and resource expenditure. Despite the continuing need for additional data, we believe that there is sufficient evidence to recommend routine thromboprophylaxis for most hospitalized patient groups. The implementation of evidence-based and thoughtful thromboprophylaxis strategies provides benefit to patients, and should also help protect their caregivers and

Table 2—*Rationale for Thromboprophylaxis in Hospitalized Patients (Section 1.2)*

High prevalence of VTE
Almost all hospitalized patients have one or more risk factors for VTE
DVT is common in many hospitalized patient groups
Hospital-acquired DVT and PE are usually clinically silent
It is difficult to predict which at-risk patients will develop symptomatic thromboembolic complications
Screening at-risk patients using physical examination or noninvasive testing is neither cost-effective nor effective
Adverse consequences of unprevented VTE
Symptomatic DVT and PE
Fatal PE
Costs of investigating symptomatic patients
Risks and costs of treating unprevented VTE
Increased future risk of recurrent VTE
Chronic postthrombotic syndrome
Efficacy and effectiveness of thromboprophylaxis
Thromboprophylaxis is highly efficacious at preventing DVT and proximal DVT
Thromboprophylaxis is highly effective at preventing symptomatic VTE and fatal PE
The prevention of DVT also prevents PE
Cost-effectiveness of thromboprophylaxis has repeatedly been demonstrated

hospitals from legal liability. Unfortunately, despite the hundreds of randomized trials demonstrating the benefit of thromboprophylaxis and >20 practice guidelines recommending the use of thromboprophylaxis since 1986, low adherence with evidence-based thromboprophylaxis compromises the optimal benefits of this key patient safety practice.[28–38] Successful strategies to improve the adherence with appropriate thromboprophylaxis have been summarized.[39,40] Passive strategies such as distribution of guidelines or single educational events are not successful, while multicomponent approaches,[41] audit and feedback,[42] and the use of automatic reminders such as preprinted orders and computer reminders have been demonstrated to be highly effective.[39,40,43,44]

Table 3—*Risk Factors for VTE (Section 1.2)*

Surgery
Trauma (major trauma or lower-extremity injury)
Immobility, lower-extremity paresis
Cancer (active or occult)
Cancer therapy (hormonal, chemotherapy, angiogenesis inhibitors, radiotherapy)
Venous compression (tumor, hematoma, arterial abnormality)
Previous VTE
Increasing age
Pregnancy and the postpartum period
Estrogen-containing oral contraceptives or hormone replacement therapy
Selective estrogen receptor modulators
Erythropoiesis-stimulating agents
Acute medical illness
Inflammatory bowel disease
Nephrotic syndrome
Myeloproliferative disorders
Paroxysmal nocturnal hemoglobinuria
Obesity
Central venous catheterization
Inherited or acquired thrombophilia

Table 4—*Approximate Risks of DVT in Hospitalized Patients (Section 1.2)**

Patient Group	DVT Prevalence, %
Medical patients	10–20
General surgery	15–40
Major gynecologic surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–40
Stroke	20–50
Hip or knee arthroplasty, HFS	40–60
Major trauma	40–80
SCI	60–80
Critical care patients	10–80

*Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.

Recommendations: Hospital Thromboprophylaxis Policy

1.2.1. For every general hospital, we recommend that a formal, active strategy that addresses the prevention of VTE be developed (Grade 1A)**.**

1.2.2. We recommend that the local thromboprophylaxis strategy be in the form of a written, institution-wide thromboprophylaxis policy (Grade 1C)**.**

1.2.3. We recommend the use of strategies shown to increase thromboprophylaxis adherence, including the use of computer decision support systems (Grade 1A)**, preprinted orders** (Grade 1B)**, and periodic audit and feedback** (Grade 1C)**. Passive methods such as distribution of educational materials or educational meetings are not recommended as sole strategies to increase adherence to thromboprophylaxis** (Grade 1B)**.**

1.3 Thromboembolism Risk Stratification

There are two general approaches to making thromboprophylaxis decisions. One approach considers the risk of VTE in each patient, based on their individual predisposing factors and the risk associated with their current illness or procedure. Thromboprophylaxis is then individually prescribed based on the composite risk estimate. Formal risk assess-

ment models (RAMs) for DVT have been proposed to assist with this process.[45–50] The approach of individual thromboprophylaxis prescribing based on formal RAMs is not used routinely by most clinicians because it has not been adequately validated and is cumbersome. Furthermore, there is little formal understanding of how the various risk factors interact in a quantitative manner to determine the position of each patient along a continuous spectrum of thromboembolic risk. Finally, individual RAMs may not be worth the effort because there are only a limited number of thromboprophylaxis options, and one of the principles of effective thromboprophylaxis is to reduce complexity in decision making. One simplification of the risk assessment process for surgical patients involves assigning them to one of four VTE risk levels based on the type of operation (minor, major), age (< 40 years, 40 to 60 years, and > 60 years), and the presence of additional risk factors (such as cancer or previous VTE).[1] Although this classification scheme has been used in some centers, its limitations include risk quantitation that is based on studies that are > 25 years old, uncertainty about the influence of each factor on overall risk, lack of definitions for minor and major surgery, and arbitrary cutoffs for age and duration of surgery.

Another approach to making thromboprophylaxis decisions involves implementation of group-specific thromboprophylaxis routinely for all patients who belong to each of the major target groups, for example patients undergoing major general surgery or major orthopedic surgery. At the present time, we support this approach for several reasons. First, although an increasing number of patient-specific thrombosis risk factors contribute to the substantial variability in VTE rates, the principal factor is the patient's primary reason for hospitalization, whether this is a surgical procedure or an acute medical illness. Furthermore, at this time, we are not able to confidently identify the small population of patients in the various groups who do not require thromboprophylaxis.[51] Second, an individualized approach to thromboprophylaxis has not been subjected to rigorous clinical evaluation, while group risk assignment and thromboprophylaxis are the basis for most randomized trials of thromboprophylaxis and for evidence-based, clinical practice guidelines. Third, individualizing thromboprophylaxis is complex and may be associated with suboptimal compliance unless ongoing, institution-wide efforts for implementation are in place. A further simplification of our previous classification system allows clinicians to readily identify the general risk group for their patients and makes general thromboprophylaxis recommendations (Table 5). Details related to each specific patient group are provided below in Sections 2.0 to 9.0.

1.4 Important Issues Related to Studies of Thromboprophylaxis

The appropriate interpretation of published information about thromboprophylaxis requires consideration of a number of important issues.

Table 5—*Levels of Thromboembolism Risk and Recommended Thromboprophylaxis in Hospital Patients (Section 1.3)**

Levels of Risk	Approximate DVT Risk Without Thromboprophylaxis, %†	Suggested Thromboprophylaxis Options‡
Low risk		
Minor surgery in mobile patients	< 10	No specific thromboprophylaxis
Medical patients who are fully mobile		Early and "aggressive" ambulation
Moderate risk		
Most general, open gynecologic or urologic surgery patients	10–40	LMWH (at recommended doses), LDUH bid or tid, fondaparinux
Medical patients, bed rest or sick		
Moderate VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§
High risk		
Hip or knee arthroplasty, HFS	40–80	LMWH (at recommended doses), fondaparinux, oral vitamin K antagonist (INR 2–3)
Major trauma, SCI		
High VTE risk plus high bleeding risk		Mechanical thromboprophylaxis§

*The descriptive terms are purposely left undefined to allow individual clinician interpretation.

†Rates based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.

‡See relevant section in this chapter for specific recommendations.

§Mechanical thromboprophylaxis includes IPC or VFP and/or GCS; consider switch to anticoagulant thromboprophylaxis when high bleeding risk decreases.

1.4.1 Limitations of DVT Screening Methods

A detailed discussion of the various methods used to screen for DVT in clinical trials can be found in the previous edition of these guidelines.[1] In summary, each of the screening tests for DVT has strengths and limitations. Contrast venography is sensitive for detecting DVT and can be adjudicated centrally in a blinded manner; however, venography is invasive, 20 to 40% of venograms are considered nondiagnostic, and the clinical relevance of small thrombi is uncertain. Venous Doppler ultrasonography (DUS) is widely available, noninvasive, and repeatable; however, the accuracy of DUS is reduced for the calf veins, it is operator dependent, and central adjudication of DUS in clinical trials is difficult.[52,53]

1.4.2 Appropriate End Points in Clinical Trials of Thromboprophylaxis

This topic is also discussed in the previous edition of these guidelines.[1] The optimal outcome measures for both efficacy and safety in thromboprophylaxis trials remain controversial.[2,54–60] Because of the strong concordance between asymptomatic DVT and clinically important VTE, we believe that DVT detected by a sensitive screening test such as contrast venography is an appropriate outcome in the early assessment of new thromboprophylaxis interventions.[61] We encourage investigators to subsequently conduct large clinical trials that use clinically important thromboembolic outcomes such as symptomatic, objectively confirmed VTE (or the combination of symptomatic VTE and asymptomatic proximal DVT), as well as clinically important safety outcomes.

1.4.3 Mechanical Methods of Thromboprophylaxis

Early and frequent ambulation of hospitalized patients at risk for VTE is an important principle of patient care. However, many patients cannot be fully ambulatory early after hospital admission or after surgery. Furthermore, the majority of hospital-associated, symptomatic thromboembolic events occur after patients have started to ambulate, and mobilization alone does not provide adequate thromboprophylaxis for hospital patients. Specific mechanical methods of thromboprophylaxis, which include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices, and the venous foot pump (VFP), increase venous outflow and/or reduce stasis within the leg veins. As a group, mechanical thromboprophylaxis modalities have important advantages and limitations (Table 6). The primary attraction of mechanical thromboprophylaxis is the lack of bleeding potential. These modalities, therefore, have advantages for patients with high bleeding risks. While all three of the mechanical methods of thromboprophylaxis have been shown to reduce the risk of DVT in a number of patient groups,[1,2,62–70] they have been studied much less intensively than anticoagulant-based approaches and they are generally less efficacious than anticoagulant thromboprophylaxis.[1,63,71–76]

No mechanical thromboprophylaxis option has been studied in a large enough sample to determine if there is a reduction in the risk of death or PE. Special caution should be exercised when interpreting the reported risk reductions ascribed to mechanical methods of thromboprophylaxis for a number of reasons. First, most trials were not blinded, increasing the chance of diagnostic suspicion bias. Second, in the earlier studies that used fibrinogen leg scanning to screen for DVT, mechanical thromboprophylaxis may have lowered the 10 to 30% false-positive rate seen with the fibrinogen uptake test (FUT) [caused by venous pooling], while the rate remained unchanged in the nonmechanical treatment/control group.[77,78] Third, a great variety of mechanical devices are available without any accepted physiologic standards and with minimal comparative data. IPC devices differ with respect to their length (calf only vs calf-plus-thigh), single-chamber vs sequential compression, asymmetric compression vs circumferential compression, and the particular pump param-

Table 6—*Advantages and Limitations of Mechanical Thromboprophylaxis Modalities (Section 1.4.3)*

Advantages
Do not increase the risk of bleeding
Can be used in patients at high bleeding risk
Efficacy has been demonstrated in a number of patient groups
May enhance the effectiveness of anticoagulant thromboprophylaxis
May reduce leg swelling
Limitations
Not as intensively studied as pharmacologic thromboprophylaxis (fewer studies and smaller)
No established standards for size, pressure, or physiologic features
Many specific mechanical devices have never been assessed in any clinical trial
Almost all mechanical thromboprophylaxis trials were unblinded and therefore have a potential for bias
In high-risk groups are less effective than anticoagulant thromboprophylaxis
Greater effect in reducing calf DVT than proximal DVT
Effect on PE and death unknown
May reduce or delay the use of more effective anticoagulant thromboprophylaxis
Compliance by patients and staff often poor
Trials may overestimate the protection compared with routine use
Cost: associated with purchase, storage, dispensing, and cleaning of the devices, as well as ensuring optimal compliance

eters (compression/relaxation cycle, cycle duration, pressure generation characteristics). GCS are also heterogeneous with respect to stocking length, ankle pressure, gradients in pressure, and fit. The effects of the specific design features of each of the mechanical devices on the prevention of DVT are unknown.[66,79,80] In fact, mechanical thromboprophylaxis methods do not even have to demonstrate that they provide any protection against VTE in order to be approved and marketed. Although many of these devices have never been assessed in any clinical trial, there is an unsubstantiated assumption that they are all effective and equivalent. Because of relatively poor compliance with optimal fitting and use of all mechanical options, they are unlikely to be as effective in routine clinical practice as in research studies where major efforts are made to optimize proper use.[81–84] Finally, the use of all of the mechanical methods of thromboprophylaxis are associated with substantial costs related to their purchase, storage, and maintenance, as well as to their proper fitting and the intensive strategies required to ensure optimal compliance.

In the recommendations that follow, use of mechanical thromboprophylaxis is the preferred option for patients at high risk for bleeding.[1,85,86] If the high bleeding risk is temporary, consideration should be given to starting pharmacologic thromboprophylaxis once this risk has decreased. Mechanical thromboprophylaxis may also be considered in combination with anticoagulant thromboprophylaxis to improve efficacy in patient groups for which this additive effect has been demonstrated.[67,68,70,87–91] In all situations where mechanical thromboprophylaxis is used, clinical staff must carefully select the correct size of the devices, must properly apply them,[82,92] and must ensure optimal compliance (*ie*, they should be removed for only a short time each day when the patient is actually walking or for bathing). Furthermore, care should be taken to ensure that the devices do not actually impede ambulation.

Recommendations: Mechanical Methods of Thromboprophylaxis

1.4.3.1. We recommend that mechanical methods of thromboprophylaxis be used primarily in patients at high risk of bleeding (Grade 1A)**, or possibly as an adjunct to anticoagulant-based thromboprophylaxis** (Grade 2A)**.**

1.4.3.2. For patients receiving mechanical methods of thromboprophylaxis, we recommend that careful attention be directed toward ensuring the proper use of, and optimal adherence with, these methods (Grade 1A)**.**

1.4.4 Aspirin as Thromboprophylaxis

Aspirin and other antiplatelet drugs are effective at reducing major thrombotic vascular events in patients who are at risk for or who have established atherosclerotic disease.[93] Evidence suggests that antiplatelet agents also provide some protection against VTE in hospitalized patients.[94–98] However, we do not recommend the use of aspirin alone as prophylaxis against VTE primarily because more effective methods of thromboprophylaxis are readily available.[1,2] Furthermore, much of the evidence citing a benefit for the use of antiplatelet drugs as VTE thromboprophylaxis is based on methodologically limited studies. For example, the Antiplatelet Trialists' Collaboration metaanalysis[94] pooled data from generally small studies that were conducted > 30 years ago and that were of variable quality. Only one third of the studies included a group that received aspirin alone; and, of these, generally accepted methods of screening for DVT were performed in only 38%.[94,99] A number of trials have reported no significant benefit from aspirin VTE prophylaxis,[96,100–102] or found that aspirin was inferior to other thromboprophylaxis modalities.[102–104] For example, the relative risk reductions (RRRs) for DVT and proximal DVT among patients who have received thromboprophylaxis with a VFP plus aspirin over that with aspirin alone following total knee arthroplasty were 32% and $> 95\%$, respectively ($p < 0.001$ for both comparisons).[102] Among hip fracture surgery patients who were randomized to receive either aspirin or danaparoid, a low-molecular-weight heparinoid, VTE was detected in 44% and 28% of the patients, respectively ($p = 0.028$).[104] Finally, aspirin use is associated with a small but significant increased risk of major bleeding, especially if combined with other antithrombotic agents.[94,96]

Recommendation: Aspirin

1.4.4. We recommend against the use of aspirin alone as thromboprophylaxis against VTE for any patient group (Grade 1A)**.**

1.4.5 Application of Evidence to Individual Patients

In this review, thromboprophylaxis is recommended for groups of patients for whom the benefits of this intervention appear to outweigh the risks. Decisions about prescribing thromboprophylaxis for the individual patient are best made by combining knowledge of the literature (including the recommendations provided herein) with clinical judgment, the latter based on specific knowledge about each patient's risk factors for VTE, the potential for

adverse consequences with thromboprophylaxis, and the availability of various options within one's center. Since most thromboprophylaxis studies excluded patients who were at particularly high risk for either VTE or adverse outcomes, their results may not apply to those with previous VTE or with an increased risk of bleeding. In these circumstances, clinical judgment may appropriately warrant use of a thromboprophylaxis option that differs from the recommended approach.

Recommendation: Anticoagulant Dosing

1.4.5. For each of the antithrombotic agents, we recommend that clinicians follow manufacturer-suggested dosing guidelines (Grade 1C)**.**

1.4.6 Renal Impairment and Anticoagulant Dosing

Renal clearance is the primary mode of elimination for several anticoagulants, including LMWH and fondaparinux. With reduced renal function, these drugs may accumulate and increase the risk of bleeding.[105–107] There appears to be considerable variability in the relationship between renal impairment and drug accumulation for the various LMWHs, which may be related to the chain length distribution of the different LMWH preparations.[108–110] Among 120 critical care patients, all of whom had creatinine clearances < 30 mL/min, there was no evidence of bioaccumulation of dalteparin at 5,000 U qd used as thromboprophylaxis based on serial anti-factor Xa levels.[111]

Recommendation: Renal Impairment and Anticoagulant Dosing

1.4.6. We recommend that renal function be considered when making decisions about the use and/or the dose of LMWH, fondaparinux, and other antithrombotic drugs that are cleared by the kidneys, particularly in elderly patients, patients with diabetes mellitus, and those at high risk for bleeding (Grade 1A)**. Depending on the circumstances, we recommend one of the following options in this situation: avoiding the use of an anticoagulant that bioaccumulates in the presence of renal impairment, using a lower dose of the agent, or monitoring the drug level or its anticoagulant effect** (Grade 1B)**.**

1.5 Antithrombotic Drugs and Neuraxial Anesthesia/Analgesia or Peripheral Nerve Blocks

Systematic reviews[68,112–117] of neuraxial blockade (spinal or epidural anesthesia and continuous epidural analgesia) have demonstrated a significant reduction in cardiac and pulmonary morbidity, and in bleeding when compared with general anesthesia or with narcotic-based systemic analgesia. Furthermore, pain control and patient satisfaction are both improved with these techniques.[118–122] However, the risk of a rare but potentially devastating complication after neuraxial blockade, spinal or epidural hematoma, may be increased with the concomitant use of antithrombotic drugs.[1,123,124] Bleeding into the enclosed space of the spinal canal can produce spinal cord ischemia and paraplegia. Risk factors that have been associated with the development of spinal hematomas after neuraxial blockade include the following: underlying hemostatic disorder, anatomic vertebral column abnormalities, traumatic needle or catheter insertion, repeated insertion attempts, insertion in the presence of high levels of anticoagulation, use of continuous epidural catheters, and older age.[1,125] Removal of an epidural catheter, especially in the presence of an anticoagulant effect, has also been associated with hematoma formation.[125] Unfortunately, the prevalence of spinal hematoma without or with neurologic defects, and the predictive value of the various risk factors remain unknown.[124] The seriousness of this complication mandates cautious use of all antithrombotic medication in patients with neuraxial blockade. A detailed discussion of this topic is also available through the American Society of Regional Anesthesia and Pain Medicine at www. asra. com.[123] We believe that neuraxial anesthesia plus or minus postoperative epidural analgesia can be used concomitantly with prophylactic doses of LDUH or LMWH with appropriate caution.[1,123,126–128]

The following suggestions may improve the safety of neuraxial blockade in patients who have or will receive anticoagulant thromboprophylaxis: (1) neuraxial anesthesia/analgesia should be avoided in patients with a known systemic bleeding disorder. (2) Neuraxial anesthesia should also be avoided in patients with significant impairment of hemostasis by antithrombotic drugs at the time of the anticipated epidural or spinal procedure. Most patients with an important underlying bleeding disorder, and those receiving agents that affect hemostasis or platelet function can be detected by history. Nonsteroidal antiinflammatory agents and aspirin do not appear to increase the risk of spinal hematoma when no additional antithrombotic agents are used concomitantly. Clopidogrel should probably be stopped approximately 7 days before a neuraxial block if temporary discontinuation of this drug is safe. If the risk of stopping clopidogrel is high (*eg*, recent coronary artery stent), an alternate modality of anesthesia should be considered. In patients receiving a preoperative anticoagulant, insertion of the spinal needle

or epidural catheter should be delayed until the anticoagulant effect of the medication is minimal. This is usually at least 8 to 12 h after a subcutaneous (SC) dose of heparin or a twice-daily prophylactic dose of LMWH, or at least 18 h after a once-daily prophylactic dose of LMWH. (3) Anticoagulant thromboprophylaxis should be delayed if a hemorrhagic aspirate ("bloody tap") is encountered during the initial spinal needle placement. (4) Removal of an epidural catheter should be done when the anticoagulant effect of the thromboprophylaxis is at a minimum (usually just before the next scheduled subcutaneous injection). (5) Anticoagulant thromboprophylaxis should be delayed for at least 2 h after spinal needle or epidural catheter removal. (6) If thromboprophylaxis with a VKA such as warfarin is used, we recommend that continuous epidural analgesia either be avoided altogether or used for < 48 h because of the unpredictable anticoagulant effect of the VKA. Furthermore, if thromboprophylaxis with a VKA is used at the same time as epidural analgesia, the catheter should be removed while the INR is < 1.5.[129] (7) Although postoperative fondaparinux appears to be safe in patients who have received a spinal anesthetic, it is not known if postoperative continuous epidural analgesia is safe in the presence of this anticoagulant. The long half-life of fondaparinux and its renal mode of excretion raise concerns about the potential for accumulation of the drug, especially in the elderly. Until further data are available, we recommend that fondaparinux not be administered along with continuous epidural analgesia. Using epidural analgesia for 24 to 48 h and then starting fondaparinux after the epidural has been removed is another option. (8) With concurrent use of epidural analgesia and anticoagulant thromboprophylaxis, all patients should be monitored carefully and regularly for the symptoms and signs of spinal cord compression. These symptoms include progression of lower-extremity numbness or weakness, bowel or bladder dysfunction, and new onset of back pain. (9) If spinal hematoma is suspected, diagnostic imaging and definitive surgical therapy must be performed rapidly to reduce the risk of permanent paresis. (10) We encourage every hospital that uses neuraxial anesthesia/analgesia to develop written protocols that cover the most common scenarios in which these techniques will be used along with antithrombotic agents.[127]

Peripheral nerve blocks are increasingly being used alone or as adjuncts to other modalities because of their superior pain control, decreased postoperative blood loss, earlier mobilization, and fewer side effects compared with parenteral narcotics.[130–132] The bleeding risk associated with plexus and peripheral nerve block techniques (without or with anticoagulants) is unknown. However, compression neuropathy due to perineural hematoma after peripheral nerve blocks appears to be very uncommon.[133] The risk of clinically important bleeding associated with superficial nerve blocks appears to be so low that no precautions other than those appropriate to the surgical procedure are required. However, bleeding complications have been described with the use of continuous deep nerve blocks. Bleeding may be related to the experience of the anesthesiologist and may be reduced by use of ultrasound-guided catheter placement. Until further data become available, we recommend that the above suggestions for neuraxial blocks also be considered for deep peripheral nerve blocks.[123]

Recommendations: Neuraxial Anesthesia/Analgesia or Peripheral Nerve Blocks

1.5.1. For all patients undergoing neuraxial anesthesia or analgesia, we recommend appropriate patient selection and caution when using anticoagulant thromboprophylaxis (Grade 1A)**.**
1.5.2. For patients receiving deep peripheral nerve blocks, we recommend that the same cautions considered for neuraxial techniques be applied when using anticoagulant thromboprophylaxis (Grade 1C)**.**

2.0 General, Vascular, Gynecologic, Urologic, Laparoscopic, Bariatric, Thoracic, and Coronary Artery Bypass Surgery

2.1 General Surgery

Studies[20,134,135] performed > 20 years ago found that the rates of asymptomatic DVT in patients undergoing general surgical procedures without thromboprophylaxis varied between 15% and 30%, while the rates of fatal PE ranged between 0.2% and 0.9%. The risk of VTE in contemporary general surgical patients is uncertain because studies without thromboprophylaxis are no longer performed. Factors that may tend to reduce the risk of VTE in current patients include improvements in general perioperative care, more rapid mobilization, and greater use of regional anesthesia and thromboprophylaxis. However, more extensive operative procedures in older and sicker patients, the use of preoperative chemotherapy, and shorter lengths of stay in the hospital (leading to shorter durations of thromboprophylaxis) may well heighten the risk of VTE in contemporary patients undergoing inpatient general surgery.

The type of surgery is the primary determinant of

the risk of DVT.[11,14,135–138] Most individuals undergoing outpatient surgery have low rates of DVT.[139] For example, only one symptomatic VTE occurred in the first month following 2,281 day-case hernia repairs (0.04%).[140] Additional factors that affect the risk of VTE in general surgery patients include the following: (1) traditional risk factors such as cancer, previous VTE, obesity, and delayed mobilization[11,91,138]; (2) increasing age, an independent risk factor for VTE[11,91,138]; (3) type of anesthesia; in the absence of pharmacologic thromboprophylaxis, the risk of DVT is lower following spinal/epidural anesthesia than after general anesthesia[141]; this protective effect is less apparent when pharmacologic thromboprophylaxis is used[142]; (4) duration of surgery[11,91]; and (5) postoperative infection.[11]

Based on the results of numerous randomized clinical trials and metaanalyses,[1,2,27,97,143] the routine use of thromboprophylaxis is recommended following major general surgical procedures. Both LDUH and LMWH reduce the risk of asymptomatic DVT and symptomatic VTE by at least 60% in general surgery compared with no thromboprophylaxis.[1,19,20] Most thromboprophylaxis trials of SC LDUH administered 5,000 U 1 to 2 h before surgery, followed by 5,000 U bid or tid for approximately 1 week. A metaanalysis of 46 randomized clinical trials in general surgery[19] compared thromboprophylaxis using LDUH with no thromboprophylaxis or with placebo. The rate of DVT was significantly reduced (from 22 to 9%; odds ratio [OR], 0.3; NNT, 7), as were the rates of symptomatic PE (from 2.0 to 1.3%; OR, 0.5; NNT, 143), fatal PE (from 0.8 to 0.3%; OR, 0.4; NNT, 182), and all-cause mortality (from 4.2 to 3.2%; OR, 0.8; NNT, 97). Thromboprophylaxis with LDUH was associated with a small increase in the rate of bleeding events (from 3.8 to 5.9%; OR, 1.6; NNH, 47), most of which were not major. These findings were supported by a subsequent analysis[20] in which the rate of wound hematomas was increased with use of LDUH (from 4.1% in control subjects to 6.3% in those who received LDUH; OR, 1.6; NNH, 45), although the rate of major bleeding was not increased (0.3% in both control and LDUH groups). While these reviews concluded that the administration of heparin, 5,000 U tid, was more efficacious than 5,000 U bid, without increasing the rate of bleeding, this was based on indirect comparisons. There are no reported studies that directly compared these two LDUH regimens.

LMWHs have also been extensively evaluated in general surgery.[1,144] A metaanalysis[134] found that LMWH thromboprophylaxis reduced the risk of asymptomatic DVT and symptomatic VTE by $>70\%$ compared with no thromboprophylaxis. When LDUH and LMWH were directly compared, no single study showed a significant difference in the rates of symptomatic VTE. The therapeutic equivalence of LDUH and LMWH in terms of both efficacy and safety in the general surgical population is confirmed by at least 10 metaanalyses and systematic reviews.[21,23,25,90,134,144–148] In high-risk general surgery patients, higher doses of LMWH provide greater protection than lower doses of the same LMWH.[144,149–152] However, when thromboprophylaxis with nadroparin at 2,850 IU was compared with enoxaparin at 4,000 IU in 1,288 patients who underwent colorectal surgery for cancer,[153] there were no significant differences in the rates of asymptomatic VTE or proximal DVT at day 12, while the rates of symptomatic VTE (0.2% vs 1.4%) and major bleeding (7.3% vs 11.5%) were significantly lower in the nadroparin group. The interpretation and clinical importance of these findings are unclear.

Some studies[22,154,155] have reported significantly fewer wound hematomas and other bleeding complications with LMWH than with LDUH, while other trials[156–158] have shown the opposite effect. Two metaanalyses[134,146] that reported similar efficacy for LDUH and LMWH found differences in bleeding rates that were dependent on the dose of LMWH used. Lower doses of LMWH (*ie*, $\leq$ 3,400 U/d) were associated with less bleeding than LDUH (3.8% vs 5.4%, respectively; OR, 0.7), while higher doses of LMWH resulted in more bleeding events (7.9% vs 5.3%; OR, 1.5).[146]

Several large studies in general surgery have evaluated the risk of death among patients treated prophylactically with LDUH or LMWH. Two clinical trials[159,160] were specifically designed to test the effectiveness of LDUH in preventing fatal PE, compared with no thromboprophylaxis. Both studies[159,160] demonstrated a significant benefit (overall RRR for fatal PE with LDUH, 91%; NNT, 106). A placebo-controlled, multicenter study[161] found that the LMWH fraxiparine significantly reduced all-cause mortality (from 0.8 to 0.4%) among 4,498 general surgery patients (NNT, 250). Two additional randomized trials[26,162] with a combined sample of 35,000 surgical patients found no difference in the rates of total mortality, fatal PE, or bleeding between LDUH (5,000 U tid) and the LMWH certoparin (3,000 U qd).

The selective Factor Xa inhibitor fondaparinux has been evaluated in a randomized, blinded clinical trial[163] among almost 3,000 patients undergoing major abdominal surgery. Thromboprophylaxis with fondaparinux at 2.5 mg SC qd started postoperatively was compared with dalteparin at 5,000 U SC qd started before surgery. There were no significant differences between the two groups in the rates of VTE (4.6% vs 6.1%, respectively), major bleeding

(3.4% vs 2.4%), or death (1.0% vs 1.4%). Another blinded randomized controlled trial[91] compared postoperative fondaparinux to placebo in 1,309 patients who had major abdominal surgery, all of whom also received IPC. The rates of VTE and proximal DVT were significantly lower with fondaparinux plus IPC than IPC alone (1.7% vs 5.3%, p = 0.004; and 0.2% vs 1.7%, p = 0.04, respectively). However, major bleeding was increased with fondaparinux (1.6% vs 0.2%, p = 0.006). When the rates of proximal DVT were combined with the rates of major bleeding, there were no significant differences between the groups.

Although mechanical methods of thromboprophylaxis (*ie*, GCS and IPC) are attractive options in patients who have a high risk of bleeding, they have not been studied as extensively as has pharmacologic thromboprophylaxis.[20] A systematic review[70] reported a significant 52% reduction in the rate of DVT with the use of GCS (13%) compared with no thromboprophylaxis (27%), which is equivalent to a pooled OR of 0.3 (NNT, 7). The use of GCS appears to enhance the protective effect of LDUH against DVT by a further 75% compared with LDUH alone (DVT rates of 15% and 4% in the LDUH and combined groups, respectively), for a pooled OR of 0.2 (NNT, 9).[70] No effect of GCS on the risk of proximal DVT or symptomatic PE has been shown,[68] and the effectiveness of GCS in patients with malignancies is unknown. Thromboprophylaxis with IPC might reduce the incidence of DVT in general surgical patients to an extent similar to LDUH.[164] However, the studies of IPC are small, and there is insufficient evidence to determine if IPC alone has any effect on the rates of PE, symptomatic VTE, or mortality.[68]

Although the risk of postoperative DVT is highest within the first week or two after general surgery, VTE complications including fatal PE may occur later.[6,165–168] Three clinical trials[167,169,170] have addressed the use of extended thromboprophylaxis with LMWH beyond the period of hospitalization following general surgery. A double-blind, multicenter trial[169] in 322 patients undergoing abdominal or pelvic cancer surgery compared the administration of enoxaparin at 40 mg/d for an average of 9 days or 28 days. Routine venography performed between days 25 and 31 showed a significant reduction in DVT rates with the prolonged thromboprophylaxis (from 12 to 5%; OR, 0.36; p = 0.02). However, proximal DVT was identified in only three patients in the short-duration group and in one patient in the extended thromboprophylaxis group. Over the entire 3-month follow-up period, there were only two symptomatic thromboembolic events among the short-duration patients and one symptomatic VTE in the extended thromboprophylaxis group. A second randomized controlled trial[170] in 427 patients who had major abdominal surgery found DVT on routine venography in 16% of patients who received dalteparin for 1 week and in 7% of those who received the same dose of LMWH for 4 weeks (p = 0.012). The extended thromboprophylaxis in this trial was not blinded. When the three randomized trials of extended thromboprophylaxis in general surgery are combined, the RRRs for DVT and proximal DVT associated with 1 month of LMWH thromboprophylaxis are 53% (from 12.6 to 5.9%; p = 0.002) and 76% (from 4.9 to 1.2%; p < 0.00001), respectively. Symptomatic VTE rates over the 3 months after surgery were 1.4% and 0.3%, respectively (p = 0.24). A rigorous economic analysis[2] did not find that postdischarge LMWH was cost-effective.

In conclusion, among patients undergoing major general surgical procedures, routine thromboprophylaxis is strongly recommended.[1,2,27,97,143] The options that have clearly been shown to reduce DVT and PE are LDUH and LMWH. The clinical advantages of LMWH over LDUH include its once-daily administration and the lower risk of heparin-induced thrombocytopenia (HIT).[171,172] Fondaparinux appears to be as effective and safe as LMWH. Mechanical prophylactic methods (*ie*, GCS and/or IPC) also reduce DVT rates and should be considered for patients who are at particularly high risk of bleeding. Thromboprophylaxis with LMWH for 2 to 3 weeks after discharge reduces the incidence of asymptomatic DVT in cancer surgery patients compared with LMWH thromboprophylaxis that is discontinued at hospital discharge.

Recommendations: General Surgery

2.1.1. For low-risk general surgery patients who are undergoing minor procedures and have no additional thromboembolic risk factors, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A)**.**

2.1.2. For moderate-risk general surgery patients who are undergoing a major procedure for benign disease, we recommend thromboprophylaxis with LMWH, LDUH, or fondaparinux (each Grade 1A)**.**

2.1.3. For higher-risk general surgery patients who are undergoing a major procedure for cancer, we recommend thromboprophylaxis with LMWH, LDUH three times daily, or fondaparinux (each Grade 1A)**.**

2.1.4. For general surgery patients with multiple risk factors for VTE who are thought to be at particularly high risk, we recommend that a

pharmacologic method (*ie*, LMWH, LDUH three times daily, or fondaparinux) be combined with the optimal use of a mechanical method (*ie*, GCS and/or IPC) (Grade 1C)**.**

2.1.5. For general surgery patients with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted GCS or IPC (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

2.1.6. For patients undergoing major general surgical procedures, we recommend that thromboprophylaxis continue until discharge from hospital (Grade 1A)**. For selected high-risk general surgery patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered** (Grade 2A)**.**

2.2 Vascular Surgery

In order to prevent occlusion after vascular reconstruction, most patients undergoing vascular surgery routinely receive antithrombotic agents, including heparins or dextran, which are administered during vascular clamping, and platelet inhibitors, such as aspirin or clopidogrel[173] (see the "Peripheral Artery Occlusive Disease" chapter by Sobel and Verhaeghe in this supplement). The use of postoperative anticoagulants or antiplatelet drugs is also common in these patients[173,174] (see the "Peripheral Artery Occlusive Disease" chapter by Sobel and Verhaeghe in this supplement). Asymptomatic DVT has been reported in 15 to 25% of patients after vascular surgery if specific thromboprophylaxis is not used.[1,175] Among 142 patients who underwent a variety of vascular surgical procedures, all of whom received thromboprophylaxis with IPC and LDUH, the rates of DVT and proximal DVT, which were detected by routine screening with DUS performed between postoperative days 7 and 10, were 10% and 6%, respectively.[176] The incidence of symptomatic VTE within 3 months of major vascular surgery was 1.7 to 2.8% in a population-based study of 1.6 million surgical patients.[14] Symptomatic VTE was reported in only 0.9% of patients within 30 days after lower-extremity bypass surgery or abdominal aortic aneurysm repair.[11]

Aortic aneurysm repair or aortofemoral bypass surgery appear to confer a higher risk of DVT than femorodistal bypass.[176–178] Additional thromboembolic risk factors in vascular surgery include advanced age, limb ischemia, long duration of surgery, and intraoperative local trauma, including possible venous injury.[3] There is some evidence[179,180] that atherosclerosis may also be an independent risk factor for VTE.

There have been four randomized clinical trials[177,181–183] of prophylaxis against VTE after arterial surgery. All patients received IV heparin during the procedure. The first trial[181] compared LDUH twice daily to placebo in 49 patients undergoing elective aortic bifurcation surgery. DVT was detected in 24% of placebo recipients and 4% of LDUH recipients using FUT as the screening test for DVT (confirmed by venography if positive). However, clinical bleeding was significantly greater in those who received LDUH, leading to the premature termination of the study. A second study[182] with only 43 patients found no benefit of LDUH over no thromboprophylaxis. In the third trial,[183] 100 patients undergoing aortic surgery were randomized to LDUH plus GCS or no thromboprophylaxis. Proximal DVT was detected in 2% of patients in both groups using DUS. The final study[177] compared LDUH, 7,500 U bid, with enoxaparin, 40 mg/d, each administered for ≤ 2 days, among 233 patients undergoing aortic or infrainguinal reconstructions. DUS between day 7 and day 10 showed DVT in 4% and 8% of patients, respectively (not statistically significant). Major bleeding occurred in 2% of patients in both groups.

For the following reasons, we do not recommend the routine use of thromboprophylaxis in vascular surgery patients: (1) the risk of VTE appears to be relatively low with contemporary vascular surgery; (2) most vascular surgery patients receive intraoperative anticoagulant and postoperative antiplatelet therapy; and (3) results of the limited number of thromboprophylaxis trials in these patients do not provide evidence that the benefits of VTE thromboprophylaxis outweigh the adverse effects. Surgeons are encouraged to make VTE thromboprophylaxis decisions based on individual patient risk factors or on local hospital policy. If thromboprophylaxis is considered to be appropriate for a patient undergoing vascular surgery, we recommend the use of LMWH, LDUH, or fondaparinux largely on the basis of the effectiveness of these agents in general surgery.

Recommendations: Vascular Surgery

2.2.1. For patients undergoing vascular surgery procedures who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use specific thromboprophylaxis other than early and frequent ambulation (Grade 2B)**. 2.2.2. For patients undergoing ma-**

jor vascular surgery who have additional thromboembolic risk factors, we recommend thromboprophylaxis with LMWH, LDUH, or fondaparinux (Grade 1C)**.**

2.3 Gynecologic Surgery

The rates of DVT, PE, and fatal PE in major gynecologic surgery are comparable to those after general surgical procedures, and the thromboprophylaxis recommendations are similar.[1] The factors that appear to increase the risk of VTE following gynecologic surgery include an abdominal (vs a vaginal) surgical approach, malignancy, older age, previous VTE, perioperative blood transfusion, and prior pelvic radiation therapy.[1,184] Gynecologic oncology patients have a particularly high thrombosis risk.[138,185–189]

Unfortunately, there have been few randomized clinical trials[190–194] of thromboprophylaxis in gynecologic surgery in the past decade. A metaanalysis[194] of anticoagulant thromboprophylaxis showed a significant decrease in the DVT rate with LDUH (OR, 0.3 vs placebo); among the five studies that compared LDUH with LMWH, there were no significant differences for VTE or bleeding complications.

Among 266 consecutive women undergoing laparoscopic gynecologic procedures for nonmalignant disease without thromboprophylaxis, no asymptomatic DVTs were detected by routine proximal DUS at 1 week and 2 weeks after surgery, and no symptomatic thromboembolic events occurred on clinical follow-up to 90 days.[195] Although the risk of VTE after laparoscopic gynecologic surgery appears to be low,[195–197] we recommend that a decision to provide thromboprophylaxis (or not) take into consideration a patient's comorbid and procedure-related risk factors (see also Section 2.5).

Patients who are otherwise well and who undergo brief procedures, typically defined as < 30 min, do not require any specific thromboprophylaxis but should be encouraged to mobilize early after surgery. LDUH twice daily and IPC both appear to be effective in patients undergoing gynecologic surgery for benign disease in the absence of additional risk factors.[1] IPC thromboprophylaxis should be started just before surgery, used continuously while the patient is not ambulating, and stopped at discharge. Formal strategies to optimize compliance with IPC by patients and nursing staff are essential.

Patients undergoing surgery for gynecologic cancers appear to derive less protection from twice-daily dosing of LDUH than those with benign disease, while LDUH administered three times daily or LMWH at daily doses of at least 4,000 U appear to be more effective in these patients.[152,193,198,199] Four randomized clinical trials[152,192,200,201] compared LDUH administered three times daily with LMWH in gynecologic cancer surgery patients, and suggested similar effectiveness and safety with either approach. A randomized trial[193] in 211 patients undergoing gynecologic surgery for cancer compared LMWH and IPC; there were no symptomatic thromboembolic events within the month after surgery in either group, and only three asymptomatic proximal DVTs were detected by routine DUS performed 3 to 5 days after surgery. Combining mechanical thromboprophylaxis with LDUH or LMWH may enhance efficacy, although to our knowledge this has not been studied in gynecology patients.

Another unresolved issue is the duration of antithrombotic thromboprophylaxis following gynecologic surgery. In a randomized, blinded study[169] comparing 1 week with 1 month of LMWH in patients undergoing curative surgery for abdominal or pelvic malignancy (8% of the patients had a gynecologic oncology procedure), extended thromboprophylaxis conferred an RRR of 60% for venographically screened DVT. While this trial,[169] also discussed in Section 2.1, suggests a potential advantage of postdischarge thromboprophylaxis in certain high-risk surgical oncology patients, the specific risk factors that warrant consideration of extended thromboprophylaxis remain to be defined.

Recommendations: Gynecologic Surgery

2.3.1. For low-risk gynecologic surgery patients who are undergoing minor procedures and have no additional risk factors, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A)**.**

2.3.2. For gynecology patients undergoing entirely laparoscopic procedures, we recommend against routine thromboprophylaxis, other than early and frequent ambulation (Grade 1B)**.**

2.3.3. For gynecology patients undergoing entirely laparoscopic procedures in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of LMWH, LDUH, IPC, or GCS (Grade 1C)**.**

2.3.4. For all patients undergoing major gynecologic surgery, we recommend that thromboprophylaxis be used routinely (Grade 1A)**.**

2.3.5. For patients undergoing major gynecologic surgery for benign disease without additional risk factors, we recommend LMWH (Grade 1A)**, LDUH** (Grade 1A)**, or IPC started just before surgery and used continuously while the patient is not ambulating** (Grade 1B)**.**

2.3.6. For patients undergoing extensive surgery for malignancy and for patients with additional VTE risk factors, we recommend routine thromboprophylaxis with LMWH (Grade 1A)**, or LDUH three times daily** (Grade 1A)**, or IPC, started just before surgery and used continuously while the patient is not ambulating** (Grade 1A)**. Alternative considerations include a combination of LMWH or LDUH plus mechanical thromboprophylaxis with GCS or IPC, or fondaparinux** (all Grade 1C)**.**
2.3.7. For patients undergoing major gynecologic procedures, we recommend that thromboprophylaxis continue until discharge from the hospital (Grade 1A)**. For selected high-risk gynecology patients, including some of those who have undergone major cancer surgery or have previously had VTE, we suggest that continuing thromboprophylaxis after hospital discharge with LMWH for up to 28 days be considered** (Grade 2C)**.**

2.4 Urologic Surgery

VTE is one of the most important nonsurgical complications following major urologic procedures with rates of symptomatic VTE between 1% and 5%.[1,138,202,203] Risk factors for VTE in these patients include advanced age, malignancy, open (vs transurethral) procedures, pelvic surgery with or without lymph node dissection, and use of the lithotomy position intraoperatively. Most of the information about VTE and its prevention has been derived from patients undergoing open prostatectomy. Other urologic procedures, including major renal surgery and transplantation, radical cystectomy, and urethral reconstruction, are also associated with a sufficiently high risk for thrombosis to warrant consideration of thromboprophylaxis.

We identified only one randomized clinical trial[204] of thromboprophylaxis in urologic surgery published within the past 2 decades that met the minimal methodologic criteria (Table 1). Thus, the optimal approach to thromboprophylaxis is not known specifically in these patients. Furthermore, consideration of bleeding risk is particularly important in urologic surgery, especially following prostatectomy.[205] Despite a sparse literature on thromboprophylaxis in urologic surgery, the risks of VTE and the protection offered by various thromboprophylaxis methods appear to be similar to those seen in major general or gynecologic surgery.[1,19,97]

For patients undergoing transurethral procedures, the risks of VTE are low,[14,19,206] and perioperative use of anticoagulant thromboprophylaxis may increase the risk of bleeding. Therefore, early postoperative mobilization is the only intervention warranted in these and other low-risk urologic surgery patients. For laparoscopic urologic procedures, the risk of VTE appears to be low, anticoagulant thromboprophylaxis may increase the bleeding risk, and there are no randomized trials evaluating thromboprophylaxis in these patients; therefore, we cannot make specific recommendations for this group.[207–211] Routine thromboprophylaxis is recommended for more extensive, open procedures including radical prostatectomy, cystectomy, or nephrectomy. Until further data are available, thromboprophylaxis options to consider for these patients include the following: LDUH, LMWH, fondaparinux, GCS, and IPC.[1,205] For urology patients at particularly high thromboembolic risk, commencing GCS with or without IPC just prior to surgery and then adding LMWH or LDUH postoperatively is recommended even though this approach has not been formally evaluated in this patient population. For patients at high risk for bleeding, a similar approach is suggested: starting GCS with or without IPC just before the procedure and then adding LMWH or LDUH when the bleeding risk decreases. With the current brief lengths of hospitalization for major urologic procedures, the risk of post-hospital discharge, symptomatic VTE is likely increased.[14,169,212] However, continuation of thromboprophylaxis after hospital discharge has not been evaluated in these patients.

Recommendations: Urologic Surgery

2.4.1. For patients undergoing transurethral or other low-risk urologic procedures, we recommend against the use of specific thromboprophylaxis other than early and frequent ambulation (Grade 1A)**.**
2.4.2. For all patients undergoing major, open urologic procedures, we recommend that thromboprophylaxis be used routinely (Grade 1A)**.**
2.4.3. For patients undergoing major, open urologic procedures, we recommend routine thromboprophylaxis with LDUH twice or three times daily (Grade 1B)**, GCS and/or IPC started just before surgery and used continuously while the patient is not ambulating** (Grade 1B)**, LMWH** (Grade 1C)**, fondaparinux** (Grade 1C)**, or the combination of a pharmacologic method (*ie*, LMWH, LDUH, or fondaparinux) with the optimal use of a mechanical method (*ie*, GCS and/or IPC)** (Grade 1C)**.**
2.4.4. For urologic surgery patients who are actively bleeding, or who are at very high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 1A)**. When the high bleeding risk**

decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis (Grade 1C)**.**

2.5 Laparoscopic Surgery

There is considerable uncertainty related to the thromboembolic risk after laparoscopic procedures, and the use of thromboprophylaxis is controversial.[1,213–216] Surgical trauma is generally less with laparoscopic than with open abdominal surgery, but activation of the coagulation system is similar to or only slightly less with laparoscopic procedures.[1,217–220] Laparoscopic operations may be associated with longer surgical times than comparable open procedures. Both pneumoperitoneum and the reverse Trendelenburg position reduce venous return from the legs, creating venous stasis. Patients undergoing laparoscopic procedures may have shorter hospital stays, but they may not mobilize more rapidly at home than those who have had open procedures.

The rates of VTE following laparoscopic procedures appear to be low.[1,14,195,211,221–225] Among 25 patients undergoing laparoscopic cholecystectomy without any thromboprophylaxis, screening contrast venography between postoperative days 6 and 10 failed to detect any DVT.[226] Among 50 laparoscopic cholecystectomy patients who received in-hospital thromboprophylaxis with dextran and/or LMWH, contrast venography detected one calf DVT.[224] No DVT or PE were reported in the first month following laparoscopic cholecystectomy among 587 cases, of whom only 3% received thromboprophylaxis.[227] Eight cases of DVT (0.3%) and no cases of PE were seen in another series[228] of 2,384 consecutive patients who underwent GI laparoscopic procedures followed by a short course of LMWH thromboprophylaxis. A review[229] of 50,427 gynecologic laparoscopies reported symptomatic VTE in only 2 per 10,000 patients. In a literature review[230] that included 153,832 laparoscopic cholecystectomies using various types of thromboprophylaxis, the average rates of clinical DVT, PE, and fatal PE were 0.03%, 0.06%, and 0.02%, respectively. Finally, in a population-based study[14] of 105,850 laparoscopic cholecystectomies performed in California, the risk of symptomatic VTE within 3 months of the procedure was 0.2%, compared with 0.5% after open cholecystectomy. These low rates are virtually identical to those reported by the National Surgical Quality Improvement Program for laparoscopic and open cholecystectomy patients.[11]

Table 7 shows the rates of objectively proven DVT after laparoscopic procedures that were reported in prospective studies[195,222,224,226,231–238] that used various forms of thromboprophylaxis and routine screening for DVT. Although the studies were generally small, with a single exception, the rates of asymptomatic DVT were

Table 7—*DVT After Laparoscopic Procedures: Clinical Descriptions and Results (Section 2.5)**

Study/Year	Thromboprophylaxis	Diagnostic Test for DVT	Day Screened	Patients, No.	Patients With DVT, No. (%)
Caprini et al[231]/1995	GCS plus IPC (plus LDUH in 26%)	DUS	7	100	1 (1)
Patel et al[232]/1996	GCS plus LDUH (plus ECS in 80%)	DUS	1, 7, 30	20	11 (55)
Baca et al[233]/1997	GCS	DUS	5–7	359	01
	GCS plus LMWH			359	(0.3)
Bounameaux et al[226]/1997	Placebo	Venography	6–10	25	0
	LMWH			15	0
Healey et al[234]/1998	ECS	DUS	1–3, 7	20	0
Lord et al[235]/1998	GCS plus IPC plus LMWH	DUS	1, 14–28	59	1 (2)
Wazz et al[236]/2000	None	DUS	1	61	0
Mall et al[237]/2001	IPC plus LMWH	DUS	5	32	0
Schaepkens van Riempst et al[238]/2002	None	DUS	10	133	1 (2)
	LMWH			105	1 (1)
Tincani et al[222]/2005	GCS plus LMWH × 4 d	DUS	30	105	1 (1)
	GCS plus LMWH × 11 d			104	0
Lindberg et al[224]/2006	Dextran and/or LMWH × 1–4 d	Venography	7–11	50	1 (2)
Ageno et al[195]/2007	None	DUS	7, 14	266	0

*Prospective studies of patients who had routine screening for DVT following laparoscopic procedures. ECS = electrical calf stimulation. The laparoscopic procedures performed in the studies were as follows: laparoscopic cholecystectomy,[224,226,231,232,235,238] gynecologic laparoscopy,[195,234] colon resection,[237] and various procedures.[222,233,236]

very low. Among the 10 prospective studies that used routine postoperative DUS screening, the pooled rate of asymptomatic DVT was 1.2% (18 of 1,457 patients). Excluding the single 20-patient outlier study, the DVT rate was only 0.5% among the 1,437 patients. Only 1 of the 424 patients who received no thromboprophylaxis was found to have asymptomatic DVT.

There are only three randomized clinical trials[222,226,233] of thromboprophylaxis in laparoscopic surgery patients. Contrast venography was the DVT screening test in one trial[226] that randomized 82 laparoscopic cholecystectomy patients to receive thromboprophylaxis with either dalteparin, 2,500 U qd, or placebo for 6 to 10 days. Among the 40 patients who had adequate venograms, none were found to have DVT. In the second trial,[233] 718 patients undergoing laparoscopic surgery were randomized to receive thromboprophylaxis with GCS alone or GCS plus the LMWH reviparin at a dose of 1,750 U SC qd. Patients with three or more risk factors for VTE were excluded, and 88% underwent laparoscopic cholecystectomy. Using DUS at 5 to 7 days after surgery, only one calf DVT and one nonfatal PE were observed, with equal bleeding rates in both groups. In the third study,[222] 209 patients who underwent various laparoscopic procedures received in-hospital thromboprophylaxis with LMWH plus GCS. At discharge, the patients were randomized to either continue dalteparin for 1 more week or to receive no further thromboprophylaxis. DUS performed 4 weeks after discharge detected asymptomatic DVT in none of the 104 patients who received postdischarge dalteparin and in 1 of the 105 patients discharged without thromboprophylaxis. While IPC may prevent the reduced femoral vein flow associated with pneumoperitoneum,[239,240] no trial has shown that IPC prevents DVT in these patients.

Despite the paucity of evidence, the European Association for Endoscopic Surgery has recommended that intraoperative IPC be used for all prolonged laparoscopic procedures.[241] In 2006, the Society of American Gastrointestinal Endoscopic Surgeons recommended the use of similar thromboprophylaxis options for laparoscopic procedures as for the equivalent open surgical procedures.[216] However, we believe that the available evidence does not support a recommendation for the routine use of thromboprophylaxis in these patients.[214,227,242] Furthermore, with anticoagulant thromboprophylaxis, the risk of major bleeding may exceed the rate of thrombotic complications.[208] Patients who are at particularly high thromboembolic risk can be considered for thromboprophylaxis with any of the modalities currently recommended for surgical patients.

Recommendations: Laparoscopic Surgery

2.5.1. For patients undergoing entirely laparoscopic procedures who do not have additional thromboembolic risk factors, we recommend against the routine use of thromboprophylaxis, other than early and frequent ambulation (Grade 1B)**.**

2.5.2. For patients undergoing laparoscopic procedures, in whom additional VTE risk factors are present, we recommend the use of thromboprophylaxis with one or more of LMWH, LDUH, fondaparinux, IPC, or GCS (all Grade 1C)**.**

2.6 Bariatric Surgery

Over the past 15 years, there has been an exponential increase in the rate of bariatric procedures: > 100,000 operations for morbid obesity are performed in the United States annually.[243] The most frequently performed bariatric surgical procedure is the Roux-en-Y gastric bypass; other procedures include gastric banding, vertical-banded gastroplasty, and biliopancreatic diversion.[244] These operations may be performed either as open or laparoscopic procedures; postoperative hospital length of stay is generally shorter for laparoscopic procedures.[14,245] An increasing proportion of the laparoscopic gastric bypasses are now being performed entirely as outpatient procedures.[246]

The reported incidence of VTE after bariatric surgery varies widely due to differences in study samples, use of thromboprophylaxis, and outcome measures used.[247] The National Bariatric Surgery Registry[248] reported that the 30-day cumulative incidence rates of PE and DVT among 14,641 patients undergoing weight-reduction surgery over the 11-year period from 1986 to 1996 were 0.2% and 0.1%, respectively. Among the 69,072 patients who underwent bariatric surgery in the United States in 2002, the incidence of VTE was found to be 3.4/1,000 discharges.[249] Surprisingly, this rate was less than the incidence of VTE after all surgical discharges (9.6/1,000 discharges). In another study,[246] PE was found within 30 days of surgery in only 1 of 2,000 consecutive outpatient gastric bypass procedures for obesity. Two single-center studies[250,251] reported PE rates of 1.1% and 1.0%, respectively, among 2,011 patients and 779 patients undergoing bariatric surgery. Among 4,075 patients undergoing gastric bypass surgery from 1992 to 1996, the 3-month cumulative incidence of symptomatic VTE was 1.0% (95% confidence interval [CI], 0.8 to 1.3%).[14] Fatal PE occurred within 1 month of obesity surgery in 11 of 5,554 patients (0.2%) over a 24-year period.[252] As with most other surgical procedures, the ma-

jority of thromboembolic events following bariatric surgery occur after hospital discharge.[14,253] Risk factors for VTE after bariatric surgery include older age,[249,254] prior VTE.[245,254] and the presence of an anastomotic leak.[254] In one literature review,[221] the incidence of PE was nonsignificantly higher after open (0.8%) than after laparoscopic (0.4%) gastric bypass. In a limited survey[255] of members of the American Society of Bariatric Surgery, 86% of the surgeons considered bariatric surgery patients to be at high risk for VTE, and 95% reported that they routinely provided thromboprophylaxis, which included LDH (50%), IPC (33%), LMWH (13%), or a combination of two methods of thromboprophylaxis (38%).

The optimal regimen, dosage, timing, and duration of thromboprophylaxis in bariatric surgery patients are unknown. Only one small randomized clinical trial[256] of VTE thromboprophylaxis after bariatric surgery has been published. Sixty consecutive patients undergoing Roux-en-Y gastric bypass were randomized to either 5,700 IU or 9,500 IU of nadroparin starting preoperatively and continued once daily until hospital discharge.[256] DUS was obtained on the day of discharge and at 3 months and 6 months later. There were no thrombotic events in either group; major bleeding occurred in two of the higher-dose patients. In a nonrandomized study,[257] among 481 consecutive patients undergoing primary or revision bariatric surgery from 1997 to 2000, routine thromboprophylaxis consisted of early ambulation, GCS, and IPC. In addition, the first 92 patients (group 1) received enoxaparin at 30 mg SC q12h, while the subsequent 389 patients (group 2) received enoxaparin at 40 mg q12h. Symptomatic postoperative DVT was diagnosed in 5.4% of group 1 patients and 0.6% of the patients in group 2. Only one patient in each group required treatment for hemorrhage. Other data[258] demonstrate a strong negative correlation between body weight and anti-Xa activity after injection of a prophylactic dose of LMWH. Because of the paucity of studies of thromboprophylaxis in bariatric surgery and the unpredictable pharmacokinetics of subcutaneous heparin, some investigators[259,260] have administered low-dose, continuous IV heparin as thromboprophylaxis in these patients with very low rates of clinical VTE and bleeding. We are not aware of any randomized trials that have evaluated this approach.

Based on these limited data, and extrapolating from other surgical groups, we recommend that the thromboprophylaxis recommendations for higher risk general surgical patients (Section 2.1) be used to guide decision making in bariatric surgery patients. We suggest that higher than standard doses of LMWH or LDUH be used.[261]

Recommendations: Bariatric Surgery

2.6.1. For patients undergoing inpatient bariatric surgery, we recommend routine thromboprophylaxis with LMWH, LDUH three times daily, fondaparinux, or the combination of one of these pharmacologic methods with optimally used IPC (each Grade 1C)**.**

2.6.2. For patients undergoing inpatient bariatric surgery, we suggest that higher doses of LMWH or LDUH than usual for nonobese patients be used (Grade 2C)**.**

2.7 Thoracic Surgery

The risk of VTE in patients undergoing thoracic surgery may be underestimated because few prospective studies have recorded this complication. Most thoracic surgery patients have cancer, many are elderly, and a substantial proportion have delayed mobilization after surgery. PE occurs in up to 5% of cases after major thoracic procedures, especially after lung resection.[262,263] Fatal PE has been observed in up to 1.3% of thoracic surgery patients.[262,264] The incidence of DVT after lobectomy or pneumonectomy ranged from 18 to 51% when FUT was used as the screening test,[265,266] and from 4 to 14% using DUS to screen for DVT.[262,267] Symptomatic DVT was found in 1.6% of almost 13,000 patients who underwent lung resection.[14] However, symptomatic VTE was reported in only 0.7% of lung resection patients in the National Surgical Quality Improvement Program.[11] Despite the routine use of thromboprophylaxis with LDUH and IPC, symptomatic VTE was reported in 7.4% of 336 patients in the first month following pneumonectomy for malignancy.[268] Symptomatic VTE was also reported in 7.9% of 328 patients who had extrapleural pneumonectomies for mesothelioma, and PE was the most common cause of death within the first 30 days after surgery.[269] Therefore, thoracic surgery appears to be associated with VTE risks similar to those seen after major general surgery.

We identified only two RCTs of thromboprophylaxis in thoracic surgery patients published over the past 3 decades that met our inclusion criteria (Table 1). The first study[270] compared the efficacy of two doses of heparin, 5,000 U and 7,500 U SC bid, in 100 patients who underwent major thoracic surgery for cancer. The rates of DVT, as detected by the FUT, were 33% and 22%, respectively (p = not significant [NS]). Proximal DVT was found in only 2% of the combined groups, and no patient had excessive

bleeding. The second study[271] was a nonblinded randomized controlled trial comparing a fixed low dose of nadroparin to nadroparin administered in two higher doses according to body weight in 150 lung cancer resection patients. Only one calf DVT was detected in the entire study population based on routine DUS at 8 days, while there was a nonsignificant trend toward more bleeding in the group that received one of the two higher LMWH doses.

There are few data about risks of VTE and its prevention in thoracic surgery patients. However, based on the limited available evidence in thoracic surgery and extrapolating from general surgical patients, we suggest that physicians consider the use of thromboprophylaxis using the recommendations for general surgery found in Section 2.1.

Recommendations: Thoracic Surgery

2.7.1. For patients undergoing major thoracic surgery, we recommend routine thromboprophylaxis with LMWH, LDUH, or fondaparinux (each Grade 1C)**.**

2.7.2. For thoracic surgery patients with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted GCS and/or IPC (Grade 1C)**.**

2.8 Coronary Artery Bypass Surgery

The incidence of VTE associated with contemporary cardiac surgery is uncertain, and the need for thromboprophylaxis remains controversial.[272] VTE after cardiac surgery is often not considered to be a serious clinical problem because most cardiac surgeries are performed with systemic heparin anticoagulation, cardiac surgery patients generally receive aspirin, a thienopyridine (such as clopidogrel) or oral anticoagulation after surgery, and early ambulation is encouraged. Most of the limited data regarding VTE incidence after cardiac surgery come from retrospective studies in which the patient inclusion criteria, use and type of VTE prophylaxis (if any), duration and completeness of patient follow-up, and accuracy of VTE diagnosis are uncertain. Furthermore, these studies generally did not consider the possibility that HIT could account for some of the thromboembolic events after cardiac surgery. Only CABG surgery will be considered in this section because other cardiac procedures, such as heart valve replacement, generally require postoperative therapeutic anticoagulation, and VTE rates have not been prospectively assessed in these patients.[14,273]

There are no studies in cardiac surgery in which contrast venography was performed routinely to assess the prevalence of asymptomatic DVT. The reported incidence of asymptomatic DVT after CABG surgery using routine DUS ranges from 16 to 48%.[274–276] In a prospective study[274] of only 29 nonconsecutive CABG patients who underwent venous ultrasonography of the legs before hospital discharge, 48% of the patients had asymptomatic DVT. All but one was isolated calf vein thrombosis. Among 330 CABG patients who received mechanical thromboprophylaxis, predischarge DUS detected asymptomatic DVT in 20% and proximal DVT in 3%.[275] In a prospective cohort study[276] of 270 patients who had undergone CABG surgery, DUS screening on admission to three rehabilitation units identified asymptomatic DVT in 43 patients (16%) despite the use of thromboprophylaxis in 89% of patients in the surgical centers (GCS in 74%, LMWH in 55%, LDUH in 8%). Repeat DUS 7 days later identified four additional asymptomatic DVTs. Proximal DVT was detected in 3% of the patients either on hospital admission or during their rehabilitation stay. In each of these studies, the thrombi were equally distributed between the leg from which the saphenous vein was harvested and the opposite leg.

The incidence of symptomatic VTE is considerably lower, ranging from 0.5 to 3.9% for VTE, 0.3 to 0.5% for DVT, 0.2 to 3.9% for PE, and 0.06 to 0.7% for fatal PE.[14,89,273,275,277–280] In a retrospective cohort study,[277] 0.7% of 10,638 patients undergoing open-heart surgery (75% CABG) between 1975 and 1988 received a diagnosis of symptomatic VTE within 10 days after surgery (DVT in 0.3%, PE in 0.4%). In another retrospective study,[278] 0.6% of 5,694 patients undergoing open-heart surgery had PE develop within 60 days after surgery. Preoperative predictors of PE included bed rest, prolonged hospitalization before surgery, and cardiac catheterization within 15 days of surgery. Postoperative predictors of PE included congestive heart failure and prolonged bed rest. Among 819 patients, PE was diagnosed in 3.9% during the hospital stay after CABG[273]; in this study, HIT was diagnosed in 18% of the patients with PE and in only 0.3% of those without PE. In a more recent retrospective cohort study[279] in which thromboprophylaxis was not used, 1% of 500 patients undergoing off-pump CABG surgery and 0.5% of 1,476 patients undergoing on-pump CABG surgery had symptomatic VTE develop. Among the combined group of 1,976 CABG patients, there were two fatal PEs (0.1%). Using administrative data from the California Patient Discharge Data Set, 1.1% of 66,180 patients undergoing CABG surgery between 1992 and 1996 had symptomatic VTE during the initial hospital admission or within 3 months of surgery.[14] Two thirds of the thromboembolic events occurred after discharge.

Finally, using administrative data from the New York State Cardiac Surgery Reporting System, 0.8% of 16,325 patients undergoing isolated CABG surgery in 1999 were readmitted for VTE within 30 days after hospital discharge.[280]

We identified only two randomized controlled trials of thromboprophylaxis in CABG patients published over the past 2 decades that met our inclusion criteria.[89,275] In the first study,[275] 344 patients undergoing CABG were randomized to either IPC plus GCS or GCS alone. Predischarge ultrasonography detected DVT in 19% of patients assigned to IPC plus GCS and in 22% of those assigned to GCS alone (p = NS). Therefore, the addition of IPC did not appear to provide significant additional protection compared with GCS alone. The second study[89] compared twice-daily LDUH with the combination of LDUH and IPC in the prevention of PE among 2,551 patients who underwent cardiac surgery over a 10-year period. The diagnosis of PE was made in 4% of the patients who received LDUH and in 1.5% of those who had combined methods of thromboprophylaxis ($p < 0.001$). However, diagnostic suspicion bias cannot be excluded in this unblinded study. In both of these trials, the proportion of patients who were able to comply with early bilateral mechanical thromboprophylaxis was not reported.

Because of the limited evidence, we are uncertain if routine thromboprophylaxis should be administered to all CABG patients, for whom the overall risk of clinically important VTE appears to be low. However, since some of these patients have multiple risk factors for VTE and some have a prolonged duration of hospital stay with limited mobility, we do recommend thromboprophylaxis with LMWH, LDUH, or optimally used bilateral IPC or GCS primarily to avoid missing the opportunity to provide early thromboprophylaxis in the patients who will have a more complicated postoperative course than usual. A high proportion of CABG patients are not able to tolerate early bilateral mechanical thromboprophylaxis if they have had saphenous vein harvesting.[276] Because cardiac surgery patients represent a high-risk group for HIT[281] and, since the risk of HIT is much lower with LMWH than with unfractionated heparin, we suggest that LMWH be considered in preference to LDUH in cardiac surgery patients[172,282,283] (see "Treatment and Prevention of HIT" in this supplement by Warkentin et al). If either LDUH or LMWH thromboprophylaxis are used after cardiac surgery, we recommend platelet count monitoring (see "Treatment and Prevention of HIT" in this supplement by Warkentin et al).

Recommendations: CABG Surgery

2.8.1. For patients undergoing CABG surgery, we recommend the use of thromboprophylaxis with LMWH, LDUH, or optimally used bilateral GCS or IPC (Grade 1C)**.**

2.8.2. For patients undergoing CABG surgery, we suggest the use of LMWH over LDUH (Grade 2B)**.**

2.8.3. For patients undergoing CABG surgery with a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with properly fitted bilateral GCS or IPC (Grade 1C)**.**

3.0 Orthopedic Surgery

Patients undergoing major orthopedic surgery, which includes THR, TKR, and HFS, represent a group that has a particularly high risk for VTE, and routine thromboprophylaxis has been standard of care for > 20 years.[1,284–287] Randomized clinical trials[1,288] have demonstrated that the rates of venographic DVT and proximal DVT 7 to 14 days following major orthopedic surgery in patients who received no thromboprophylaxis are approximately 40 to 60% and 10 to 30%, respectively (Table 8). With the routine use of thromboprophylaxis in these patients, fatal PE is now uncommon,[115,286,289–295] although symptomatic VTE continues to be reported in 1.3 to 10% of patients within 3 months after surgery.[11,14,115,291,295–301] Most symptomatic VTE occurs after hospital discharge, and the risk continues to be higher than expected for at least 2 months after surgery.[297,302–305] Furthermore, VTE is the most common cause for readmission to the hospital following THR.[289]

The natural history of VTE after major orthopedic surgery has become better defined over the past 30 years. Asymptomatic DVT is common and, in the absence of thromboprophylaxis, affects at least half of all patients. Most of these thrombi are clinically silent and resolve spontaneously without any long-term sequelae.[306,307] However, for some patients, persistent venous injury, stasis due to continued reduced mobility,[308] impairment of the endogenous anticoagulant or fibrinolytic systems,[309,310] prolonged impairment of venous function,[311] or a combination of these factors allow an existing silent postoperative thrombus to propagate (or a new thrombus to develop). This thrombus may then produce symptoms as a result of venous occlusion or embolization to the lungs. Symptomatic VTE most commonly presents after orthopedic patients are discharged from hospital.[303] Among some patients with post-hospital dis-

Table 8—*VTE Prevalence After Major Orthopedic Surgery (Section 3.0)

Procedures	DVT, %		PE, %	
	Total	Proximal	Total	Fatal
Hip arthroplasty	42–57	18–36	0.9–28	0.1–2.0
Knee arthroplasty	41–85	5–22	1.5–10	0.1–1.7
HFS	46–60	23–30	3–11	0.3–7.5

*DVT rates are based on the use of mandatory venography in prospective clinical trials published between 1980 and 2002 in which patients received either no thromboprophylaxis or placebo. PE rates were derived from prospective studies that may have used thromboprophylaxis. From Geerts et al.[1]

charge DVT, the thrombus is present early after surgery and, as thromboprophylaxis is discontinued, the silent DVT extends.[312] For others who do not have DVT at hospital discharge, a new thrombosis may develop during recovery in a rehabilitation center or at home.[115,295] In one study,[313] approximately 20% of THR patients who had a negative venogram at discharge had a new DVT develop over the subsequent 3 weeks based on repeat venography. Unfortunately, there is currently no way to identify the orthopedic patients in whom symptomatic VTE will develop.[314] Therefore, thromboprophylaxis is recommended for all patients undergoing major orthopedic surgery of the lower extremity.

The possible relation between anticoagulant thromboprophylaxis and the development of subsequent wound infections is controversial. In a cohort study[315] of 2,437 hip and knee arthroplasty patients, the method of thromboprophylaxis (LMWH, aspirin, mechanical compression, or warfarin) was not associated with wound infection. Anticoagulant thromboprophylaxis was also not a predictor of wound infection among 2,305 hip and knee arthroplasty patients in another study.[316]

The following sections summarize data derived from numerous randomized clinical trials of thromboprophylaxis following THR, TKR, and HFS. Areas of orthopedic surgery for which there are much less data, including knee arthroscopy, elective spine surgery, and isolated lower extremity injuries, are also reviewed. We discuss important aspects of thromboprophylaxis such as the timing of initiation of thromboprophylaxis and its optimal duration, as well as the role of noninvasive screening for DVT. In our summary of the evidence, we placed a strong value on bleeding complications associated with thromboprophylaxis and we considered the impact of large, carefully conducted cohort studies.

3.1 Elective Hip Replacement

THR is a common surgical procedure that is being performed with increasing frequency among the aging population.[317,318] Patients undergoing elective THR are at high risk for both asymptomatic DVT (incidence, 40 to 60%) and symptomatic VTE (incidence, 2 to 5%).[1,115,287,288,319,320] If thromboprophylaxis is not used, fatal PE occurs in approximately one patient per 300 elective hip arthroplasties, but this complication is very rare with use of contemporary thromboprophylaxis.[286,293,321–324] The routine use of thromboprophylaxis has been recommended for THR patients since the first consensus conference on the prevention of VTE, published in 1986.[284]

Several nonpharmacologic thromboprophylaxis methods have been studied in THR patients, including GCS, IPC, and venous foot compression.[1] While each of these mechanical thromboprophylaxis methods reduce the risk of DVT, their efficacy has generally been found to be lower than current anticoagulant-based thromboprophylaxis strategies, especially for preventing proximal DVT.[1,72,78,325,326] There is no evidence that GCS are effective in THR. The use of IPC has been shown to significantly reduce DVT rates with a smaller effect on preventing proximal DVT.[72] Three small studies[327–329] have suggested that pneumatic foot pumps reduce the risk of total DVT. However, because the published experience with foot pumps in THR patients is so limited, we cannot recommend this modality for primary thromboprophylaxis with the same level of confidence that we recommend pharmacologic thromboprophylaxis. Other limitations of mechanical methods of thromboprophylaxis are discussed in Section 1.4.3.

Although multimodal thromboprophylaxis strategies are commonly used in major orthopedic surgery, we are not aware of any randomized clinical trials comparing these approaches with single modalities. Studies that have combined epidural anesthesia, IPC plus aspirin,[330,331] or IPC plus warfarin[332] or aspirin plus GCS or IPC,[333] or LMWH plus mechanical thromboprophylaxis[67] cannot be compared with other approaches because they had no comparison groups and/or did not use contrast venography to assess efficacy outcomes. The combination of LMWH and IPC was shown to be more effective than the combination of LMWH and GCS in the prevention of DVT in 131 arthroplasty patients, with ultrasound-detected DVT rates of 0% and 29%, respectively.[67] Although a number of multimodal strategies are very likely to be effective,[334] they are more complex and more costly than single modality options.[335]

Many different anticoagulant-based thromboprophylaxis regimens have been studied in THR patients. Although metaanalyses have shown that thromboprophylaxis with LDUH[19] or aspirin[94] is

superior to no thromboprophylaxis, both agents are less effective than other thromboprophylaxis regimens in this high-risk group.[1] Aspirin should not be used as the only prophylactic agent after THR. In one trial,[96] among 4,088 hip and knee arthroplasty patients who were randomized to receive aspirin or placebo, with other thromboprophylaxis measures administered according to individual physician practice, the rates of symptomatic VTE were not significantly reduced with aspirin (1.1% vs 1.3%, respectively).

The use of adjusted-dose oral VKAs such as warfarin is a common form of thromboprophylaxis used in North America following THR.[336] VKAs have been shown to reduce the incidence of DVT, proximal DVT, and PE in THR patients, while being associated with a significant increase in wound hematoma rates.[1,63,287,326] The primary advantages of VKAs are their oral route of administration, delayed onset of action that allows surgical hemostasis, and the ability to be continued after hospital discharge (as long as the infrastructure is in place to do this effectively and safely). In Europe, VKAs have largely been abandoned as thromboprophylaxis out of concerns about their delayed onset of action, variable responses among patients, lower efficacy compared to LMWH, need for frequent monitoring, and the complexity of both in-hospital and post-hospital discharge supervision.[326,337] If VKAs are used, we believe that they should be administered in doses that are sufficient to prolong the INR to a target of 2.5 (range, 2.0 to 3.0). Although lower target ranges are often used for orthopedic thromboprophylaxis, we recommend an INR of 2.0 to 3.0, the range that has been used in most of the published efficacy trials. Furthermore, a lower INR may not provide optimal protection against VTE or even reduce the risk of bleeding. The initial dose of VKA should be administered either the evening before surgery or the evening after surgery. With this approach, the target INR range is usually not reached until at least the third postoperative day.[301,338–341] In a large cohort study,[301] the use of a VKA dosing nomogram simplified the management of warfarin in hip and knee arthroplasty patients. However, another study[341] of the same warfarin dosing nomogram demonstrated that only 19% of arthroplasty patients reached the target INR range by the fourth postoperative day, the average day of discharge.

LMWH has been the most intensively studied thromboprophylaxis option in THR patients, and provides highly effective and safe VTE thromboprophylaxis.[1] LMWH is more efficacious than LDUH following THR.[21,25,63,342–344] Three of the clinical trials[338,345,346] comparing LMWH to adjusted-dose warfarin thromboprophylaxis found no difference in either total or proximal DVT or in major bleeding. Another study[347] compared LMWH thromboprophylaxis, started at half the usual daily dose, either < 2 h before surgery or at least 4 h after surgery, with warfarin started postoperatively. The use of LMWH was associated with a significant reduction in the risk of both total and proximal DVT compared with warfarin, and with a lower incidence of symptomatic, objectively confirmed DVT (2.2% vs 4.4%, respectively). The rate of major bleeding was significantly greater in the patients who started LMWH before surgery than in those who received warfarin; the rates of blood transfusions were 43%, 38%, and 28%, respectively, in the groups who started LMWH before surgery, who started LMWH postoperatively or who were administered warfarin.

When the results from the five large clinical trials[338,339,345–347] that directly compared adjusted-dose warfarin thromboprophylaxis with LMWH among THR patients are pooled, the respective rates of all DVT were 20.7% (256 of 1,238 patients) and 13.7% (238 of 1,741 patients; $p = 0.0002$). The proximal DVT rates were 4.8% and 3.4%, respectively ($p = 0.08$). The pooled rates of major bleeding, using somewhat different definitions in the five studies,[338,339,345–347] were 3.3% in the VKA recipients and 5.3% in the LMWH recipients ($p = 0.002$). The rates of major bleeding in the placebo groups of other randomized trials in THR patients were similar (4%).[348,349] In a large, nonblinded clinical trial,[298] $> 3{,}000$ THR patients randomly received in-hospital thromboprophylaxis with either enoxaparin at 30 mg SC bid, started postoperatively, or warfarin dose-adjusted for an INR of 2.0 to 3.0. The in-hospital rates of symptomatic, objectively documented VTE were 0.3% and 1.1%, respectively ($p = 0.008$). Because of a trend to a higher rate of DVT after discharge in the LMWH group, the overall rates of VTE by 3 months after surgery were not significantly different. Major bleeding occurred in 1.2% of LMWH recipients and 0.5% of warfarin recipients ($p = 0.06$). A metaanalysis[326] of randomized trials of thromboprophylaxis in orthopedic surgery patients confirmed that LMWH was significantly more effective than VKA in preventing venographically detected DVT and proximal DVT, with no difference in the frequency of PE, and with comparable or slightly greater bleeding with LMWH.[350]

The synthetic pentasaccharide fondaparinux selectively inhibits coagulation Factor Xa and has been shown to be highly efficacious in the prevention of DVT among THR patients in two large clinical trials.[351–353] In the European study,[351] 2,309 patients were randomized to fondaparinux at 2.5 mg SC qd starting 4 to 8 h after surgery, or enoxaparin at 40 mg SC qd starting 12 h before surgery. The overall rates

of asymptomatic DVT were 4% and 9%, respectively ($p < 0.0001$). The rate of proximal DVT was also lower among recipients of fondaparinux (1%) compared to recipients of enoxaparin (2%; $p = 0.002$). In the North American study,[352] the same fondaparinux regimen was compared to enoxaparin at 30 mg bid starting 12 to 24 h after elective THR in 2,275 patients. Neither the overall rates of VTE (6% vs 8%, respectively; $p = 0.1$) nor the rates of proximal DVT (2% vs 1%, respectively; $p = 0.5$) differed significantly between the groups. The first postoperative dose of fondaparinux was administered approximately 6 h after surgery, while enoxaparin was started approximately 18 h after surgery. Both trials showed nonsignificant trends toward increased bleeding with fondaparinux (combined major bleeding rates of 1.6% with enoxaparin and 2.6% with fondaparinux); these findings are consistent with other comparisons of LMWH and fondaparinux.[292,354,355] Another study[356] compared the safety and efficacy of initiating fondaparinux at 6 to 8 h after hip or knee arthroplasty or starting the morning after surgery in 2,000 patients. Neither symptomatic VTE nor bleeding events were significantly different between the two regimens, suggesting that a brief delay in initiating fondaparinux is an option available to orthopedic surgeons for patients undergoing total joint arthroplasty.

Because of its long half-life (approximately 18 h) and renal clearance, patients with renal dysfunction may have an accumulation of fondaparinux and thus may be at greater risk of bleeding. The safety of fondaparinux among patients receiving postoperative analgesia with an indwelling epidural catheter also has not been established.[123]

A number of new anticoagulants, including oral Factor Xa inhibitors and oral direct thrombin inhibitors, are undergoing evaluation in the prevention of thrombosis in major orthopedic surgery. Although large randomized clinical trials[357–360] have shown that the oral direct thrombin inhibitor, ximelagatran, is efficacious as thromboprophylaxis after THR and TKR, this agent is no longer being developed.

From the data currently available, we conclude that the LMWHs, and likely fondaparinux by indirect comparison, are more effective than VKAs in preventing asymptomatic and symptomatic in-hospital VTE. There is a slight increase in surgical site bleeding and wound hematoma with these more effective forms of thromboprophylaxis. The greater efficacy and bleeding risks are likely attributable to the more rapid onset of anticoagulant activity with LMWH and fondaparinux compared to VKAs.

In summary, decisions about thromboprophylaxis around the time of THR, using LMWH, fondaparinux, or a VKA, should be made at a hospital level and, on occasion, at the level of the individual patient. These decisions may be based on comparative drug pricing, the ability to safely monitor oral VKA use, and the planned duration of thromboprophylaxis.

Recommendations: Elective Hip Replacement

3.1.1. For patients undergoing elective THR, we recommend the routine use of one of the following anticoagulant options: (1) LMWH (at a usual high-risk dose, started 12 h before surgery or 12 to 24 h after surgery, or 4 to 6 h after surgery at half the usual high-risk dose and then increasing to the usual high-risk dose the following day); (2) fondaparinux (2.5 mg started 6 to 24 h after surgery); or (3) adjusted-dose VKA started preoperatively or the evening of the surgical day (INR target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A)**.**

3.1.2. For patients undergoing THR, we recommend against the use of any of the following: aspirin, dextran, LDUH, GCS, or VFP as the sole method of thromboprophylaxis (all Grade 1A)**.**

3.1.3. For patients undergoing THR who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with the VFP or IPC (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

3.2 Elective Knee Replacement

The risk of DVT without thromboprophylaxis is even higher after TKR than after THR.[288,295] However, proximal DVT occurs less commonly after TKR and the period of increased risk for symptomatic VTE after discharge is shorter.[1,288,295,303]

The results of five small studies[67,100,361–363] have suggested that IPC devices provide efficacious thromboprophylaxis in TKR patients. These devices should be applied intraoperatively or immediately after surgery and should be used continuously at least until the patient is fully ambulatory. The optimal method of leg compression has not been established. However, a randomized trial[66] compared a sequential and circumferential compression device to a rapid-inflation device that compressed the posterior calf in 423 TKR patients who also received aspirin and GCS. DVT, assessed by DUS, was detected in 15% of the patients who had used the sequential compression device and in 7% of those who used the posterior compression device ($p =$

0.007). Poor compliance, patient intolerance, and the inability to be continued after hospital discharge limit the utility of IPC. Because the combined patient enrollments in the LMWH and warfarin thromboprophylaxis trials are > 25 times greater than in the combined IPC trials, more confident estimates of the protection against VTE are available for LMWH and warfarin thromboprophylaxis than for IPC. IPC may be useful as an in-hospital adjunct to anticoagulant-based thromboprophylaxis. The use of IPC alone has not been compared to combined thromboprophylaxis with IPC and either LMWH or adjusted-dose VKA in a randomized clinical trial.

The use of a VFP was shown to be efficacious in two small clinical trials[102,364] among TKR patients, but was considerably less efficacious than LMWH in two other trials.[73,365] Another study[366] found that VFP and LMWH were equally ineffective, although the 54% rate of DVT in the LMWH group was higher than expected. While the rates of proximal DVT in this study were low, there were two PE-related deaths in the VFP group. Limited data suggest that GCS provide little or no protection in TKR patients.[367,368] Because of their relatively low efficacy in TKR patients, LDUH[369,370] and aspirin[95,96,100,102,362,371] are not recommended as sole thromboprophylaxis modalities.

Adjusted-dose oral VKAs such as warfarin have been assessed in 12 randomized clinical trials[95,338,345,346,363,372–378] following TKR with routine venography. As with most of the thromboprophylaxis interventions in patients undergoing TKR, the residual rate of asymptomatic DVT detected by routine contrast venography was quite high (25 to 50%) with use of a VKA. However, the rate of symptomatic VTE with VKA thromboprophylaxis is low.[295] In one clinical trial[379] that included 257 TKR patients who received approximately 10 days of warfarin thromboprophylaxis (target INR range, 1.8 to 2.5), only 0.8% had symptomatic VTE by 3 months. In a similar study[290] of 815 patients who received VKA for an average of 12 days after TKR, only 1.3% had symptomatic VTE by 3 months and none had fatal PE. While adjusted-dose VKA is an effective method of thromboprophylaxis after TKR, it is less efficacious than LMWH or fondaparinux, and proper post-hospital discharge management of VKA thromboprophylaxis is more complex.[64,338,345,346,374,375]

Extensive data have shown that LMWH thromboprophylaxis is safe and effective after TKR.[73,297,338,345,346,354,365,367,369,370,373–375,380–383] Considering the six randomized clinical trials[338,345,346,373–375] that directly compared the use of VKA with LMWH after TKR, the pooled DVT rates were 48% and 33%, respectively. The respective rates of proximal DVT were 10.4% and 7.1%. The risk of major bleeding was slightly higher with LMWH thromboprophylaxis compared with VKA in these comparative trials (4.5% vs 2.7%, p = 0.02). Two metaanalyses[384,385] have confirmed the superior efficacy of LMWH over both LDUH and warfarin but did not show a significant difference in bleeding. While LMWH prevents more venographic total DVTs and proximal DVTs than warfarin, starting LMWH within 12 h after surgery may be associated with a small increase in wound hematomas. We are not aware of any clinical trials that compared LMWH and warfarin thromboprophylaxis among TKR patients using symptomatic, objectively confirmed VTE as the primary measure of effectiveness.

Fondaparinux at 2.5 mg SC qd starting approximately 6 h after surgery has been compared to enoxaparin at 30 mg SC bid starting 12 to 24 h after surgery in a blinded clinical trial of 1,049 patients undergoing elective major knee surgery.[354] The rates of VTE (12.5% vs 27.8%, respectively; p < 0.001) and proximal DVT (2.4% vs 5.4%, respectively; p = 0.06) were more than halved using fondaparinux. However, major bleeding was significantly more common in the fondaparinux group (2.1% vs 0.2%, respectively; p = 0.006). In a metaanalysis[292] of the four phase III clinical trials comparing fondaparinux and enoxaparin thromboprophylaxis in patients undergoing orthopedic surgery, major bleeding was significantly more common with fondaparinux when the first dose of fondaparinux was administered < 6 h following surgery (but not if started later). The oral direct thrombin inhibitor ximelagatran has been shown to be an efficacious thromboprophylaxis agent after TKR,[376–378] but this agent is no longer being developed.

Combining different methods of thromboprophylaxis may be considered as a strategy to reduce the high VTE rate after TKR. Various combinations of the following interventions have been assessed in TKR: mechanical thromboprophylaxis with IPC or VFP with or without GCS, hypotensive epidural anesthesia, intraoperative IV heparin, LMWH, warfarin, or aspirin.[66,102,294,366,386–392] Although multimodality thromboprophylaxis methods have been reported to be associated with low rates of symptomatic VTE, there have been few rigorous randomized trials with routine objective assessment for DVT. In one study,[392] all 275 TKR patients received spinal epidural anesthesia followed by postoperative epidural analgesia plus a calf IPC device. In addition, the patients were randomized to receive aspirin or enoxaparin for 4 weeks after surgery. A DUS obtained before discharge and again 4 to 6 weeks later detected DVT in 18% of the aspirin recipients and

14% of the enoxaparin recipients; unfortunately, the study was not powered to detect a difference between these methods.

In summary, among patients undergoing TKR we recommend that thromboprophylaxis include LMWH, fondaparinux, or a VKA. Optimal use of IPC is an alternative consideration especially for patients with a high bleeding risk or in combination with other thromboprophylactic options.

Recommendations: Elective Knee Replacement

3.2.1. For patients undergoing TKR, we recommend routine thromboprophylaxis using LMWH (at the usual high-risk dose), fondaparinux, or adjusted-dose VKA (INR target, 2.5; INR range, 2.0 to 3.0) (all Grade 1A)**.**
3.2.2. For patients undergoing TKR, the optimal use of IPC is an alternative option to anticoagulant thromboprophylaxis (Grade 1B)**.**
3.2.3. For patients undergoing TKR, we recommend against the use of any of the following as the only method of thromboprophylaxis: aspirin (Grade 1A)**, LDUH** (Grade 1A)**, or VFP** (Grade 1B)**.**
3.2.4. For patients undergoing TKR who have a high risk of bleeding, we recommend the optimal use of mechanical thromboprophylaxis with IPC (Grade 1A) **or VFP** (Grade 1B)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

3.3 Knee Arthroscopy

Knee arthroscopy and arthroscopy-assisted knee surgery (*eg*, meniscectomy, synovectomy, and reconstruction of the cruciate ligaments) are common orthopedic procedures that are generally performed in relatively young patients, and the vast majority are done as outpatients. Epidemiologic data suggest that the risk of VTE following knee arthroscopy is very low and is much less common than after arthroplasty.[1,242,393,394] Among 1,355 patients who underwent diagnostic knee arthroscopy without the use of any thromboprophylaxis, symptomatic, objectively confirmed DVT was found in only 0.6% of patients, and only 1 patient had proximal DVT.[299] When the prospective studies of knee arthroscopy performed without thromboprophylaxis are pooled, the rates of asymptomatic DVT and asymptomatic proximal DVT are 9% and 3%, respectively, using venography as the screening test (four studies, 461 patients)[1,395] and 5% and 0.7%, respectively, using DUS as the screening test (seven studies, 1,002 patients).[1,396] Symptomatic VTE was reported in $< 1\%$ of these patients.[1] In a prospective study,[396] none of the 16 patients with calf or muscle vein thrombi had either extension of the DVT on DUS performed 1 week later or symptomatic VTE at 8 weeks despite the absence of anticoagulant therapy. It appears that therapeutic arthroscopy is associated with a higher VTE risk than diagnostic arthroscopy, and tourniquet time, perhaps reflecting the complexity of the surgery, also appears to be a risk factor.[397,398] The degree of postoperative immobilization may not be a strong risk factor for DVT in these patients.[396] We are not aware of VTE risk data in patients undergoing major arthroscopic surgery such as repair of tibial plateau fractures.

We are aware of only three randomized clinical trials[399–401] of thromboprophylaxis in knee arthroscopy patients (Table 9). In the first trial,[399] patients received either no thromboprophylaxis or the LMWH reviparin for 7 to 10 days. Among the 239 patients with adequate DUS, DVT was found in 4% of control subjects and in 1% of patients who received LMWH ($p = 0.2$). This study had a number of methodologic limitations that render the findings uncertain. In the second trial,[400] 130 patients undergoing diagnostic or therapeutic arthroscopy received either no thromboprophylaxis or dalteparin for up to 30 days. DUS was obtained at 12 days and 30 days after surgery. The DVT rates in the

Table 9—*Thromboprophylaxis Trials in Patients Undergoing Knee Arthroscopy: Clinical Descriptions and Results (Section 3.3)**

Study/Year	Method of Diagnosis	Intervention		DVT†	
		Control	Experimental	Control	Experimental
Wirth et al[399]/2001	DUS day 7–10	No thromboprophylaxis	Reviparin, 1,750 AXa U/d × 7–10 d	5/117 (4)	1/116 (1); p = NS
Michot et al[400]/2002	DUS days 12 and 31	No thromboprophylaxis	Dalteparin, 2,500 U or 5,000 U/d ≤ 30 d	10/63 (16)	1/61 (2); p = 0.01
Camporese et al[401]/2007	DUS at 8 ± 1 days	Ipsilateral GCS (30–40 mm Hg at the ankle) × 7 d	Nadroparin 3,800 AXa U/d × 7 d	16/660 (2)	6/657 (1); p = NS

*Randomized clinical trials in which routine screening with objective diagnostic tests for DVT were performed in arthroscopy patients.
†Values given as No. of patients with DVT/total No. of patients (%).

control and LMWH groups were 16% and 2%, respectively ($p = 0.01$), with no cases of proximal DVT in either group. No major bleeding complications were reported in any of the 182 patients who received LMWH in these two thromboprophylaxis trials.[399,400] The third trial[401] randomized 1,976 knee arthroscopy patients to receive either ipsilateral, thigh-length GCS, or nadroparin for 7 days at which time a screening DUS was obtained. VTE was detected in 2.7% of the GCS group and in 1.2% of the patients who received nadroparin ($p = 0.08$), while the rates of symptomatic VTE were 1.2% and 0.6%, respectively ($p = 0.4$). There were no significant differences in bleeding events between the groups (3.3% vs 4.4%, respectively). A systematic review[402] concluded that the clinical benefit of LMWH compared with no thromboprophylaxis in knee arthroscopy patients was uncertain since the NNT to prevent one asymptomatic, distal DVT with LMWH was 20 while the NNH (most were nonmajor bleeding) was similar at 17.

In summary, although uncertainty remains about the risks of VTE in patients undergoing knee arthroscopy, compared to most major orthopedic surgery procedures, the risk appears to be low. The results of three trials[399–401] have suggested that LMWHs reduce the rate of asymptomatic DVT, but there were more bleeding events in the patients who received LMWH. Before recommendations for routine thromboprophylaxis can be made in knee arthroscopy patients, stronger evidence is required.[403,404] In the meantime, thromboprophylaxis decisions should be made at the institutional or individual patient level. At a minimum, patients should be encouraged to ambulate early and frequently after the procedure if this is appropriate, and they should be made aware of the symptoms of VTE so that they will present for investigation if there is a reasonable suspicion of this complication.

Recommendations: Knee Arthroscopy

3.3.1. For patients undergoing knee arthroscopy who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use thromboprophylaxis other than early mobilization (Grade 2B)**.**

3.3.2. For patients undergoing arthroscopic knee surgery who have additional thromboembolic risk factors or following a complicated procedure, we recommend thromboprophylaxis with LMWH (Grade 1B)**.**

3.4 Hip Fracture Surgery

It has been known for decades that HFS patients are at very high risk for VTE.[1,26] The rates of total and proximal DVT derived from eight prospective studies in which contrast venography was routinely obtained after HFS,[1] were approximately 50% and 27%, respectively, without the use of thromboprophylaxis. Symptomatic, objectively confirmed VTE has been reported in 1.3 to 8.2% of patients within 3 months among HFS patients who received routine anticoagulant thromboprophylaxis.[405–407] Fatal PE rates were found to vary from 0.4 to 7.5% within 3 months after HFS, a range that is higher than that seen after hip or knee arthroplasty.[286,305,405,406,408,409] In addition to the initial injury and its surgical repair, factors that may further increase the risk of VTE after HFS include advanced age and delayed surgery.[410–413]

Compared with elective hip and knee arthroplasty, fewer studies[1,65] of thromboprophylaxis have been conducted in patients undergoing HFS. However, as demonstrated by Sevitt and Gallagher[414] almost 50 years ago, symptomatic VTE and fatal PE after HFS can be prevented with thromboprophylaxis. A prospective, regional audit[409] observed no fatal PE among 261 HFS patients who received thromboprophylaxis vs 4% among the 305 patients who receivedno thromboprophylaxis.

While mechanical methods of thromboprophylaxis (*ie*, GCS, IPC, or VFP) might be effective in HFS, we are not aware of any randomized trials of mechanical thromboprophylaxis that meet our study inclusion criteria; furthermore, poor compliance with these devices remains a major problem.[65] In one randomized clinical trial[415] of 231 HFS patients, the rates of DVT, using serial DUS screening, were 12% in patients who received no thromboprophylaxis and 4% in patients who were treated prophylactically with IPC ($p = 0.03$). Combined mechanical and anticoagulant thromboprophylaxis are likely to be effective in HFS patients,[416] although we are not aware of any randomized trials that address this approach.

Aspirin and other antiplatelet drugs provide much less protection against VTE compared with other thromboprophylaxis methods. In the Pulmonary Embolism Prevention Trial,[96] 13,356 HFS patients were randomly allocated to thromboprophylaxis with either 160 mg of enteric-coated aspirin or placebo for 35 days after surgery. Additional thromboprophylaxis with LDUH, LMWH, or GCS was used in 30%, 26%, and 18% of patients, respectively. The primary effectiveness outcome in the trial, vascular death, was not significantly reduced by aspirin (rates of 3.8% and 3.5% in the placebo and aspirin groups, respectively). However, the secondary outcome, symptomatic VTE, was significantly lower in the patients who received aspirin (2.5% vs 1.6%, $p = 0.003$). All-cause mortality was not reduced

(6.9% vs 6.7%), and there were significant increases in wound-related and GI bleeding among the aspirin-treated patients. Compared with placebo, for every 1,000 HFS patients treated prophylactically with aspirin, 9 fewer patients had symptomatic VTE (including 4 fewer fatal PEs), but there were 7 more cardiac deaths, strokes, or myocardial infarctions, 10 more GI bleeds, and 6 more wound hematomas. In the subgroup of 3,424 patients who also received thromboprophylaxis with a LMWH, no statistically significant benefit in symptomatic VTE was detected with the use of aspirin compared to placebo.

LDUH has been assessed in only one small randomized clinical trial[417] that used routine venography after HFS. In this study,[417] heparin at 5,000 U tid was more efficacious than dalteparin at 5,000 U qd (DVT was detected in 6 of 30 LDUH recipients and in 14 of 32 LMWH recipients; $p = 0.04$). With one exception,[355] the five trials[355,417–420] of LMWH in HFS patients had small sample sizes. The single placebo-controlled clinical trial[419] reported DVT in 21% of 72 placebo-treated patients and in 12% of 74 patients who received enoxaparin ($p = 0.15$). Two studies found no significant difference in bleeding rates when LMWH thromboprophylaxis was compared with placebo[419] or with LDUH,[417] although the sample sizes were small. A prospective, multicenter cohort study[406] found symptomatic VTE within 3 months of HFS in only 1.3% of 6,860 patients who received LMWH thromboprophylaxis.

A Cochrane systematic review[65] of VTE thromboprophylaxis after HFS included 31 trials and 2,958 patients. Both LDUH and LMWH were found to be protective against DVT without increasing bleeding rates; the superiority of one agent over the other could not be determined due to insufficient power. Limited evidence suggests that thromboprophylaxis with an oral VKA is effective and safe in HFS patients.[326] One randomized clinical trial[101] compared postoperative thromboprophylaxis with warfarin (target INR, 2.0 to 2.7) to aspirin (650 mg bid) and to no thromboprophylaxis. The rates of DVT were 20%, 41%, and 46%, respectively ($p = 0.005$), and the rates of proximal DVT were 9%, 11% and 30%, respectively ($p = 0.001$). Bleeding rates were similar across the three groups. The pooled results from the three studies of adjusted-dose VKA thromboprophylaxis demonstrate a 61% RRR for DVT, and a 66% RRR for proximal DVT, compared with no thromboprophylaxis.[101,421,422] The largest trial[101] found no difference in bleeding in the patients who received VKA compared with those who received placebo.

The synthetic, selective Factor Xa inhibitor fondaparinux, at a dose of 2.5 mg SC qd, has been assessed in the largest of the thromboprophylaxis trials[355,423] in patients undergoing HFS. Eriksson and coworkers[355] randomized 1,711 HFS patients to receive either enoxaparin at 40 mg SC qd starting 12 to 24 h postoperatively, or fondaparinux at 2.5 mg SC qd starting 4 to 8 h after surgery. The rates of VTE by postoperative day 11 were 19.1% and 8.3%, respectively ($p < 0.001$). Proximal DVT was also significantly reduced with fondaparinux (rates of 4.3% vs 0.9%, respectively; $p < 0.001$). The improved efficacy with fondaparinux was not accompanied by more bleeding.

A delay between the hip fracture and surgery appears to heighten the risk of VTE.[411–413,424,425] For example, among 21 patients who had HFS delayed by at least 48 h, DVT was detected by preoperative venography in 62%, and proximal DVT was found in 14%.[413] Therefore, if surgery is likely to be delayed, thromboprophylaxis should generally be administered during the preoperative period, although we are not aware of any thromboprophylaxis trials that specifically address this issue. When there is uncertainty about the timing of "on call" surgery, preoperative use of a short-acting anticoagulant such as LMWH or LDUH appears to be the most feasible option.

It is recommended that routine thromboprophylaxis be provided to all patients undergoing HFS, including those with major comorbidity or cognitive impairment, given the morbidity associated with symptomatic VTE and the resource utilization associated with investigation and treatment when VTE arises. The recommended thromboprophylaxis options for HFS patients are fondaparinux, LMWH, a VKA, or LDUH. Because the risk of VTE begins soon after the fracture, thromboprophylaxis should commence preoperatively if surgery is likely to be delayed, and should be restarted once postoperative hemostasis has been demonstrated.

Recommendations: Hip Fracture Surgery

3.4.1. For patients undergoing HFS, we recommend routine thromboprophylaxis using fondaparinux (Grade 1A)**, LMWH** (Grade 1B)**, adjusted-dose VKA (INR target, 2.5; INR range, 2.0 to 3.0)** [Grade 1B]**, or LDUH** (Grade 1B)**.**

3.4.2. For patients undergoing HFS, we recommend against the use of aspirin alone (Grade 1A)**.**

3.4.3. For patients undergoing HFS in whom surgery is likely to be delayed, we recommend that thromboprophylaxis with LMWH or LDUH be initiated during the time between hospital admission and surgery (Grade 1C)**.**

3.4.4. For patients undergoing HFS who have a high risk of bleeding, we recommend the optimal

use of mechanical thromboprophylaxis (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

3.5 Other Thromboprophylaxis Issues in Major Orthopedic Surgery

3.5.1 Timing of Thromboprophylaxis Initiation

Two important issues should be highlighted about the timing of thromboprophylaxis in major orthopedic surgery. The first relates to preoperative vs postoperative initiation of thromboprophylaxis, and the second concerns how early after surgery anticoagulant thromboprophylaxis should be started.[426]

Because DVT may begin during the operation itself, it has been common practice to start thromboprophylaxis before surgery. In Europe, LMWH thromboprophylaxis has generally been started 10 to 12 h before surgery, usually the night before. In North America, thromboprophylaxis with LMWH usually commences 12 to 24 h after surgery to minimize the risk of intraoperative and early postoperative bleeding and to simplify both same-day hospital admission for elective surgery and decisions related to the method of anesthesia. This controversy was addressed by the North American Fragmin Trial,[347,427] in which THR patients were randomly allocated to receive the following: (1) preoperative dalteparin, 2,500 U SC, started about 1 h before surgery, followed by a second dose of 2,500 U approximately 7 h after surgery, and then 5,000 U qd; (2) postoperative dalteparin at 2,500 U SC started about 7 h after surgery, and then 5,000 U qd; or (3) postoperative adjusted-dose warfarin. Based on the results of venography obtained before hospital discharge, the rates of total and proximal DVT in the preoperative LMWH group (10.7% and 0.8%, respectively) and postoperative LMWH group (13.1% and 0.8%, respectively) were not significantly different. DVT and proximal DVT rates among the warfarin recipients (24.0% and 3.0%, respectively) were significantly higher than those for either LMWH regimen. The rate of major bleeding was significantly higher with preoperative LMWH thromboprophylaxis than with warfarin, and there was also a nonsignificant trend toward more bleeding with preoperative LMWH when compared with postoperative LMWH. There was no statistically significant increased risk of bleeding when postoperative administration of LMWH was compared to warfarin, although transfusion requirements were increased with LMWH. A subsequent systematic review[428] also concluded that starting LMWH thromboprophylaxis postoperatively provided comparable protection to the preoperative initiation of LMWH.

The administration of thromboprophylaxis in close proximity to surgery has been shown to enhance its efficacy as well as its potential to cause bleeding.[426,428] In a systematic review[429] that compared thromboprophylaxis with LWMH to that with a VKA, a large risk reduction in venographic DVT was observed when LMWH was initiated at half the usual high-risk dose in close proximity to THR (*ie*, either < 2 h before surgery or 6 to 8 h after surgery). In the studies in which LMWH thromboprophylaxis was started either 12 to 24 h before surgery or 18 to 24 h after surgery, this efficacy advantage over a VKA was not observed. Only starting LMWH just before THR was associated with an increased risk of major bleeding.

Studies using fondaparinux, hirudin, or melagatran/ximelagatran also support the concept that dosing in close proximity to orthopedic surgery enhances prophylactic efficacy of the drug.[106,292,430,431] For fondaparinux, the incidence of major bleeding was significantly higher in patients who received a first dose within 6 h of skin closure (3.2%), compared to waiting > 6 h (2.1%).[106]

Therefore, although the efficacy/bleeding ratio may differ among anticoagulant drugs, there is greater efficacy, but also greater bleeding, associated with earlier postoperative initiation of anticoagulation thromboprophylaxis.[426,431] For most patients undergoing major, elective orthopedic surgery, we recommend that the first dose of anticoagulant thromboprophylaxis be administered either before or after surgery, although there appears to be little or no advantage to the former. Postoperative initiation of anticoagulant thromboprophylaxis has a number of advantages including the following: this approach does not interfere with decisions about the use of regional anesthetic techniques, facilitates same day admission and cannot contribute to intraoperative bleeding. For patients who are at high risk for bleeding, the initial dose of LMWH or fondaparinux should be delayed for 12 to 24 h after surgery, and until primary hemostasis has been demonstrated based on examination of the surgical site.

Recommendations: Commencement of Thromboprophylaxis

3.5.1.1. For patients receiving LMWH as thromboprophylaxis in major orthopedic surgery, we recommend starting either preoperatively or postoperatively (Grade 1A)**.**

3.5.1.2. For patients receiving fondaparinux as thromboprophylaxis in major orthopedic sur-

gery, we recommend starting either 6 to 8 h after surgery or the next day (Grade 1A)**.**

3.5.2 Screening for DVT Before Hospital Discharge

Historically, some clinicians have advocated for high-risk orthopedic surgery groups the routine screening for and subsequent treatment of asymptomatic DVT before the thrombus could extend to produce symptomatic DVT or PE.[432] We do not advocate this approach because it has not been shown to be effective in preventing clinically important VTE. Routine screening for asymptomatic DVT using DUS was not shown to be beneficial in five large studies[297,379,433–436] of THR and TKR patients. Only 3 of 1,936 arthroplasty patients (0.15%) who received in-hospital LMWH thromboprophylaxis were found to have asymptomatic DVT on prehospital discharge DUS.[297] Another study[434] found asymptomatic proximal DVT in only 0.9% of 441 hip or knee arthroplasty patients, using DUS before hospital discharge. The strongest evidence against routine screening comes from a trial[379] in which hip and knee arthroplasty patients were randomized to receive prehospital discharge DUS or sham ultrasound. Active DUS screening detected DVT in 2.5% of patients, who then received therapeutic anticoagulation. However, this strategy was not associated with a reduction in symptomatic VTE. These findings were confirmed in another trial,[433] in which 346 hip and knee arthroplasty patients received LMWH thromboprophylaxis for 10 days and were then randomized to continue LMWH for another 3 weeks, or to have prehospital discharge DUS screening, with anticoagulant therapy if the findings were positive. DUS screening identified almost twice as many proximal thrombi but did not reduce the rate of symptomatic VTE over the subsequent 3-month follow-up. Finally, another study[435,436] showed that proximal DVT rates were similar irrespective of whether screening DUS was performed 3 days or 2 weeks after surgery among 2,364 patients who underwent hip or knee arthroplasty. Each of the 6 symptomatic pulmonary emboli detected in this study occurred in patients in whom the screening DUS result was negative for DVT. Therefore, prehospital discharge screening using contrast venography or DUS has not been shown to predict which patients do or do not require posthospital discharge thromboprophylaxis.[115,295,435–438] Furthermore, this strategy would be very costly, logistically impractical for many hospitals, uses a technique that has considerable interobserver variability and the potential to falsely diagnose DVT, and often identifies patients with asymptomatic thrombi in whom treatment may not be necessary. The failure of routine prehospital discharge screening for asymptomatic DVT to do more good than harm lends support for the practice of extended postdischarge thromboprophylaxis as the best means to prevent clinically important thromboembolic complications in major orthopedic surgery.

Recommendation: Screening for DVT Before Hospital Discharge

3.5.2. For asymptomatic patients following major orthopedic surgery, we recommend against the routine use of DUS screening before hospital discharge (Grade 1A)**.**

3.5.3 Duration of Thromboprophylaxis

The duration of thromboprophylaxis after surgery has been discussed previously.[1,439] Although thromboprophylaxis is routinely administered to patients who have undergone major orthopedic surgery, it is frequently stopped at the time of hospital discharge.[440] However, a substantial proportion of these patients leave the hospital with clinically silent DVT, including proximal DVT. For example, when in-hospital thromboprophylaxis with LMWH was administered for 1 to 2 weeks, 15 to 20% of THR patients had venographic evidence of DVT at hospital discharge.[115,441,442] There is evidence that activation of coagulation persists for at least 4 weeks after THR,[443,444] and the increased risk of symptomatic VTE continues for up to 3 months after THR.[299,302,303,305,320,443,445–448] In one epidemiologic study[303] of almost 24,000 THR patients, in which the mean length of stay was 7 days, 76% of the thromboembolic events were diagnosed after hospital discharge. Among the 26,000 TKR patients also studied, the rate of posthospital discharge VTE (2.1%) was only slightly lower than after THR (2.7%), although this diagnosis was made earlier following discharge from hospital in TKR patients (mean time, 7 days for TKR and 17 days after THR). These observations suggest that the optimal duration of thromboprophylaxis might be shorter for TKR than for those undergoing THR. In an analysis[449] of patients undergoing THR, the risk factors for rehospitalization for symptomatic VTE were a body mass index ≥ 25 kg/m^2, a history of previous VTE, and age > 85 years. Ambulation before the second postoperative day and the use of warfarin after hospital discharge were protective factors against VTE.

Four large prospective cohort studies[291,297,298,309] and one randomized clinical trial[379] examined the in-hospital use of LMWH or warfarin thromboprophylaxis for an average of 7 to 15 days after THR or TKR. Symptomatic VTE occurred in only 1 to 3% of

patients between hospital discharge, when thromboprophylaxis was discontinued, and 3 months later. Despite the low absolute risk of symptomatic events seen in these studies, 45 to 80% of all symptomatic VTEs related to THR or TKR occurred after hospital discharge.[14,297,298,300,303,321]

Six randomized, placebo-controlled, clinical trials[313,427,441,448,450,451] have evaluated extended LMWH thromboprophylaxis for up to 35 days among THR patients who completed in-hospital thromboprophylaxis with either LMWH (*ie*, enoxaparin or dalteparin) or warfarin. Each study observed lower rates of venographic DVT with extended thromboprophylaxis. A systematic review[452] of these six trials demonstrated significant decreases in the rates of both total and proximal DVT with extended LMWH use, as well as reduced symptomatic VTE. The combined rates of out-of-hospital symptomatic VTE were 4.2% with in-hospital thromboprophylaxis and 1.4% with extended thromboprophylaxis (relative risk, 0.36; $p < 0.001$; NNT, 36). Another clinical trial[300] randomized 1,195 THR or TKR patients to receive in-hospital LMWH or LMWH thromboprophylaxis that was continued for 5 weeks after hospital discharge. Venography was not performed. In this study, extended thromboprophylaxis did not prevent symptomatic VTE compared with patients in whom LMWH was stopped at hospital discharge.

Four systematic reviews,[304,453–455] which included both THR and TKR patients, found that posthospital discharge thromboprophylaxis was both effective at reducing VTE and safe. Major bleeding did not occur in any of the out-of-hospital LMWH recipients, suggesting that the risk/benefit ratio favored the use of extended thromboprophylaxis. Patients who underwent THR tended to derive greater protection from symptomatic VTE using extended thromboprophylaxis (pooled OR, 0.33; 95% CI, 0.19 to 0.56; NNT, 62) than patients who underwent TKR (pooled OR, 0.74; 95% CI, 0.26 to 2.15; NNT, 250).[453] In another metaanalysis[456] restricted to blinded THR trials, the rates of symptomatic VTE among patients who received in-hospital LMWH thromboprophylaxis and those who were administered postdischarge LMWH were 2.7% and 1.1%, respectively (absolute risk reduction, 1.6%; 95% CI, − 0.2 to 3.3; NNT, 64). The absolute risk reduction for symptomatic PE was 0.4% (95% CI, − 0.3 to 1.4; NNT, 278), and for fatal PE it was 0.1% (95% CI, − 0.1 to 0.3; NNT, 1,093). Thus, while extended thromboprophylaxis reduces the relative risk of symptomatic VTE by approximately 60%, the absolute risk reduction is small, especially for PE.

The benefit of posthospital discharge thromboprophylaxis with VKA has also been confirmed.[457] More than 350 patients undergoing THR were randomized to receive warfarin thromboprophylaxis (target INR, 2 to 3) until hospital discharge (mean duration, 9 days) or continued for another 4 weeks after hospital discharge. DUS was performed 1, 2, and 4 weeks after discharge. The study was terminated prematurely because of the demonstrated superiority of extended thromboprophylaxis. VTE occurred in 5.1% of the patients who stopped warfarin at hospital discharge and in 0.5% of those who continued warfarin, a relative risk of 9.4 (95% CI, 1.2 to 73.5). The NNT to prevent one VTE using extended warfarin thromboprophylaxis was 22. Only one patient had major bleeding. In another trial[337] of 1,279 patients undergoing THR, the LMWH reviparin (4,200 U SC qd) was compared with a VKA (target INR, 2 to 3), both administered for 6 weeks. Objectively confirmed, symptomatic VTE occurred in 2.3% of patients receiving LMWH, and in 3.3% of those who were administered the VKA ($p = 0.3$). However, the rates of major bleeding were 1.3% and 5.5%, respectively ($p = 0.001$). Thus, these studies and another study[115] indicate that VKAs provide effective extended thromboprophylaxis after THR, although major bleeding is more frequent with the use of these anticoagulants than with LMWH and considerable effort is required to maintain arthroplasty patients in the target INR range as outpatients.

Among patients who had undergone TKR, extending LMWH thromboprophylaxis to postoperative day 28 did not significantly reduce the combined rate of asymptomatic DVT and symptomatic VTE (17.5%) compared with 7 to 10 days of thromboprophylaxis (20.8%).[451] The extended use of a VKA is also associated with very low rates of readmission for symptomatic VTE in TKR patients.[295]

The optimal duration of thromboprophylaxis has also been assessed in patients undergoing HFS. In a blinded clinical trial,[423] 656 HFS patients were administered fondaparinux at 2.5 mg SC qd for approximately 7 days, followed by randomization to placebo or continuation of fondaparinux for an additional 3 weeks. Venography, performed 3 weeks after randomization, documented DVT in 35.0% of placebo recipients and in 1.4% of the extended thromboprophylaxis patients (RRR, 96%; $p < 0.001$). The rates of symptomatic VTE were 2.7% and 0.3%, respectively (RRR, 89%; $p = 0.02$). Bleeding rates were not significantly different.

One blinded, randomized trial[458] compared 2 weeks vs 6 weeks of thromboprophylaxis with the LMWH certoparin in 360 patients who underwent hip or knee arthroplasty or hip fracture repair. Prolonged thromboprophylaxis reduced both asymptomatic DVT, assessed by weekly DUS (from 14.2%

to 5.0%, respectively; p = 0.02), and symptomatic VTE (from 5.4% to 1.2%; p = 0.04). No patient had major or clinically important nonmajor bleeding.

Several studies[455,459–462] in developed countries have examined the cost implications of longer vs shorter duration of VTE thromboprophylaxis after THR. Based on somewhat different assumptions and methods, most investigators have concluded that prolonged thromboprophylaxis was either cost saving[459,461] or more costly but a good value in consideration of net benefits.[460,462] The most important factor driving these results was the cost savings provided by thromboprophylaxis (due to reduced medical costs for VTE) relative to the cost of thromboprophylaxis. Efforts to identify the number of days of thromboprophylaxis that are either cost saving or cost-effective are based on significant conjecture about patterns of care (*eg*, use of diagnostic tests) and the relationship between risk and time following surgery.[460] From a local perspective, the value of longer periods of thromboprophylaxis is dependent on several factors in addition to estimated efficacy in reducing VTE, specifically, the cost of thromboprophylaxis, the proportion of patients requiring home care, the cost of treating DVT and, to a lesser extent, the cost of treating PE.[455,461,462] The cost of thromboprophylaxis includes both drug acquisition and administration; the value of prolonged thromboprophylaxis may substantially diminish when drug acquisition cost is high,[462] or when the cost of administration increases (as when nursing care is needed to provide injections at home).[455,460] In summary, postdischarge thromboprophylaxis after THR is likely to be a good value from a societal perspective. Local resource considerations that must be addressed to assure maximal value are drug acquisition costs and the cost of drug administration following discharge.

Based on all of the data about the duration of thromboprophylaxis in major orthopedic surgery, we recommend that these patients receive thromboprophylaxis with LMWH, fondaparinux or a VKA for at least 10 days. Given that current hospital stays are generally < 5 days, this recommendation implies that post-hospital discharge thromboprophylaxis should be provided to most patients.[115,449,452,463] For patients undergoing THR or HFS, more prolonged thromboprophylaxis beyond 10 days and up to 35 days is recommended especially for patients who are considered to be at high risk for VTE. Although further studies are needed to define who is at high risk, factors that have been shown to predispose to VTE following major orthopedic surgery include a history of previous VTE, current obesity, delayed mobilization, advanced age, and cancer.[308,449,457,464] The extended use of a VKA (INR target, 2.5; range, 2.0 to 3.0) is an accepted alternative to LMWH, although the incidence of major bleeding may be higher with oral anticoagulants.[337] Fondaparinux is recommended for extended thromboprophylaxis following HFS. The use of either LMWH or an oral VKA is also likely to be effective in HFS patients, although prolonged use of these agents has not been properly studied in this patient group.

Recommendations: Duration of Thromboprophylaxis

3.5.3.1. For patients undergoing THR, TKR, or HFS, we recommend thromboprophylaxis with one of the recommended options for at least 10 days (Grade 1A)**.**

3.5.3.2. For patients undergoing THR, we recommend that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 1A)**. The recommended options for extended thromboprophylaxis in THR include LMWH** (Grade 1A)**, a VKA** (Grade 1B)**, or fondaparinux** (Grade 1C)**.**

3.5.3.3. For patients undergoing TKR, we suggest that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 2B)**. The recommended options for extended thromboprophylaxis in TKR include LMWH** (Grade 1C)**, a VKA** (Grade 1C)**, or fondaparinux** (Grade 1C)**.**

3.5.3.4. For patients undergoing HFS, we recommend that thromboprophylaxis be extended beyond 10 days and up to 35 days after surgery (Grade 1A)**. The recommended options for extended thromboprophylaxis in HFS include fondaparinux** (Grade 1A)**, LMWH** (Grade 1C)**, or a VKA** (Grade 1C)**.**

3.6 Elective Spine Surgery

Unfortunately, there are few prospective data related to the risks of VTE and its prevention in patients undergoing elective spine surgery.[465,466] Although the incidence of VTE in these patients appears to be considerably lower than that following major lower-extremity surgery, some patients seem to be at high enough risk to consider thromboprophylaxis.[1] Possible risk factors for VTE following spine surgery include increased age, previous VTE, an anterior surgical approach, malignancy, a prolonged procedure, and reduced preoperative or postoperative mobility.

Several small randomized trials[467–469] of thromboprophylaxis in elective spine surgery suggest that both anticoagulant methods, with LDUH or LMWH, and mechanical methods, with GCS plus or minus IPC, may reduce the DVT rate in these

patients. Given the paucity of data, we cannot make firm recommendations about thromboprophylaxis in spine surgery patients. However, some patients may not require any specific thromboprophylaxis.

The risk of VTE appears to be low when any of the following methods of thromboprophylaxis is used: postoperative LDUH or LMWH, or intraoperative and then postoperative GCS and/or IPC. For spine surgery patients with additional VTE risk factors, such as a neurologic deficit or prolonged immobility, advanced age, malignancy, previous VTE, or an anterior surgical approach, thromboprophylaxis with one of these options is recommended.

Recommendations: Elective Spine Surgery

3.6.1. For patients undergoing spine surgery who do not have additional thromboembolic risk factors, we suggest that clinicians not routinely use specific thromboprophylaxis other than early and frequent ambulation (Grade 2C)**.**
3.6.2. For patients undergoing spine surgery who have additional thromboembolic risk factors such as advanced age, malignancy, presence of a neurologic deficit, previous VTE, or an anterior surgical approach, we recommend that one of the following thromboprophylaxis options be used: postoperative LDUH (Grade 1B)**, postoperative LMWH** (Grade 1B)**, or optimal use of perioperative IPC** (Grade 1B)**. An alternative consideration is GCS** (Grade 2B)**.**
3.6.3. For patients undergoing spine surgery who have multiple risk factors for VTE, we suggest that a pharmacologic method (*ie*, LDUH or LMWH) be combined with the optimal use of a mechanical method (*ie*, GCS and/or IPC) (Grade 2C)**.**

3.7 Isolated Lower-Extremity Injuries Distal to the Knee

Lower-extremity fractures distal to the knee are very common in persons of all ages. An increasing proportion of below-knee fractures are being surgically repaired, sometimes without hospital admission; the remainder are immobilized using plaster casts or braces. In addition to fractures, this topic includes ligament and cartilage injuries of the knee and ankle, and rupture of the Achilles tendon. Patients with major trauma, and those with pelvic or femoral fractures, are considered in Section 5.1.

The rates of asymptomatic DVT in four small prospective studies in which patients with isolated lower-extremity fractures, who had not received thromboprophylaxis, were routinely screened using contrast venography varied between 10% and 45%.[1] When DUS was used to screen patients who sustained lower-extremity injuries (including fractures or soft-tissue injuries), the rates of DVT were 17%[470] and 4%[471] without thromboprophylaxis. The corresponding rates of DVT in the subgroups with fractures were 29% and 6%. However, in a prospective cohort[472] of 1,174 patients with isolated fractures distal to the knee, symptomatic VTE was detected in only 0.6% of patients (two nonfatal PEs, two proximal DVT, and three calf DVT) over the 3-month follow-up period. Although there are no definitive studies, the risk factors for VTE following isolated lower-extremity injury appear to include advanced age, the presence of fractures rather than soft-tissue injuries alone, operative repair, and obesity. The risk of DVT increases with proximity of the fracture to the knee, such that tibial plateau fractures pose the highest risk, followed by those of the tibial shaft and then the ankle.[473] The risk of DVT after Achilles tendon rupture appears to be at least as high as that following lower-extremity fracture.[474–476] Among 91 patients with surgically repaired Achilles tendon rupture, DUS detected DVT and proximal DVT in 36% and 7% of patients, respectively.[476]

The five randomized clinical trials of thromboprophylaxis in patients with isolated lower extremity injuries are summarized in Table 10. Each of the studies compared LMWH with no thromboprophylaxis; three studies used a placebo control. In the two clinical trials[470,471] in which patients were screened for DVT using DUS at the time of cast removal, LMWH was found to significantly reduce the rates of DVT without causing any bleeding events. However, there were major methodologic problems with both studies. A multicenter trial[477] randomized 265 patients who underwent surgical repair of isolated fractures distal to the knee to thromboprophylaxis with either LMWH or placebo once daily for 14 ± 2 days. Proximal DUS was performed at that time. Asymptomatic DVT or symptomatic VTE was detected in three patients who received placebo and two patients who received LMWH ($p = 0.68$). Two multicenter trials[474,475] used screening venography to detect DVT in patients with lower-extremity injuries who were administered either LMWH or no prophylaxis. The pooled DVT rate for all 576 patients in these two trials was 18% among control subjects and 10% with LMWH thromboprophylaxis (OR, 2.1; $p = 0.005$); however, among the 443 patients with fractures combined in these two trials,[474,475] LMWH did not significantly reduce the risk of DVT (16.5% vs 10.6%; $p = 0.1$). One trial[476] randomized patients with Achilles tendon ruptures to LMWH or placebo and obtained DUS 3 weeks and 6 weeks after surgical repair. DVT

Table 10—*Prevention of VTE in Patients With Isolated Lower-Extremity Injuries: Clinical Descriptions and Results (Section 3.7)**

Study/Year	Patients	Diagnostic Test for DVT	Interventions		DVT†	
			Control	Experimental	Control	Experimental
Kujath et al[470]/1993	Outpatients with leg injuries managed with plaster casts	DUS when cast removed	No thromboprophylaxis	Nadroparin, approximately 3,000 U/d	21/127 (17)	6/126 (5)
Kock et al[471]/1995	Outpatients with leg injuries managed with plaster casts	DUS when cast removed	No thromboprophylaxis	Certoparin, 3,000 U/d	7/163 (4)	0/176
Selby et al[477]/2007	Below-knee fractures repaired surgically	Proximal DUS 14 d	Placebo	Dalteparin, 5,000 U/d	3/131 (2)	2/134 (1)
Lassen et al[474]/2002	Below-knee fractures	Venography ≥ 5 wk	Placebo	Reviparin, 1,750 U/d	29/159 (18)	14/134 (10)
	Achilles tendon repair				6/28 (21)	3/48 (6)
Jorgensen et al[475]/2002	Below-knee fractures	Venography ≥ 5 wk	No thromboprophylaxis	Tinzaparin, 3,500 U/d	10/77 (13)	8/73 (11)
	Tendon ruptures				6/21 (29)	2/20 (10)
Lapidus et al[476]/2007	Achilles tendon repair	DUS at 3 wk and 6 wk	Placebo	Dalteparin, 5,000 U/d	16/44 (36)	16/47 (34)

*Randomized clinical trials with routine screening using an objective diagnostic test for DVT.
†Values given as No. of patients with DVT/total No. of patients with adequate imaging (%).

was detected in 36% of patients who received placebo and in 34% of those administered LMWH ($p = 0.8$). In a prospective cohort study[478] of 201 patients with surgery of the foot and ankle, DVT was detected by routine DUS at the first postoperative visit in 3.5%; none of these 7 patients were treated or showed progression on follow-up DUS.

Among patients with below-knee injuries, thromboprophylaxis with LMWH appears to reduce the frequency of asymptomatic calf DVT, particularly in those with Achilles tendon ruptures. The use of thromboprophylaxis, usually with LMWH, is considered to be standard of care for such patients in some European countries.[479] However, we do not believe that routine thromboprophylaxis can be recommended in patients with isolated lower-extremity injuries distal to the knee because it is uncertain whether thromboprophylaxis similarly reduces the risk of clinically important VTE or is cost-effective. Pending further data, clinicians may choose to provide no thromboprophylaxis, in-hospital thromboprophylaxis only, or thromboprophylaxis that is continued until the patient has regained mobility. The limited evidence also does not allow us to help clinicians decide which patients, if any, might benefit from thromboprophylaxis, or the dose or duration of thromboprophylaxis.

Recommendation: Isolated Lower-Extremity Injuries Distal to the Knee

3.7.1. For patients with isolated lower-extremity injuries distal to the knee, we suggest that clinicians not routinely use thromboprophylaxis (Grade 2A)**.**

4.0 Neurosurgery

Patients undergoing major neurosurgery are considered to be at moderately increased risk for postoperative VTE, and warrant the routine use of thromboprophylaxis.[1] In several randomized clinical trials, which included a spectrum of neurosurgery patients, the rate of DVT detected by FUT among the control subjects was 22%, and proximal DVT was detected in 5%.[480] Intracranial (vs spinal) surgery, malignancy, prolonged procedures, leg weakness, and advanced age have all been shown to increase the rate of VTE in these patients.[1,481] Patients with malignant brain tumors are at particularly high risk for VTE, both perioperatively and during subsequent follow-up.[481–484] In one study[485] of 264 patients with gliomas, 31% had symptomatic, venographically confirmed DVT within 5 weeks of surgery.

The evidence-based, recommended thromboprophylaxis options in these patients are the following:

(1) perioperative use of IPC, (2) perioperative use of LDUH, or (3) postoperative use of LMWH.[1,74] Mechanical thromboprophylaxis is commonly used in neurosurgery out of concern for potential intracranial or spinal bleeding. IPC appears to be highly effective at preventing DVT in neurosurgical patients, producing an average RRR of 68% compared with no thromboprophylaxis (lowering the absolute DVT rate from 22% in control subjects to 7% in those receiving IPC).[1] Turpie et al[85] found comparable DVT rates in patients who received GCS alone and in those who received GCS plus IPC (both options were more effective than no thromboprophylaxis). However, more recent studies[86,486–488] have raised concerns about the efficacy of thromboprophylaxis with GCS alone.

One small randomized clinical trial[489] found an 82% RRR with perioperative LDUH compared to no thromboprophylaxis in 100 craniotomy patients. The two largest trials[486,488] performed in neurosurgical patients compared thromboprophylaxis with GCS alone with a combination of GCS plus LMWH, started postoperatively. Using routine venography as the efficacy end point, both studies[486,488] found a significant reduction in the risk of DVT when combined thromboprophylaxis was administered rather than GCS alone.

Perioperative use of GCS combined with IPC was applied routinely to 150 patients undergoing craniotomy for a brain tumor who were randomized to receive either LDUH at 5,000 U SC bid, or enoxaparin at 40 mg SC qd.[490] Prehospital discharge DUS detected DVT in 7% and 12%, respectively, of the LDUH and LMWH patients. Proximal DVT was found in 3% of patients in both groups. A pilot study[491] randomized 100 patients undergoing craniotomy to thromboprophylaxis with IPC plus LDUH at 5,000 U SC bid, or IPC plus dalteparin at 2,500 U SC qd. LDUH and LMWH were started just prior to surgery, and patients underwent a routine DUS 1 week after surgery. Among the 49 IPC-plus-LDUH recipients, there were no DVTs and one surgically managed intracranial hemorrhage compared to two asymptomatic DVTs, and two conservatively managed intracranial bleeds among the 51 patients who received combined IPC and LMWH.

The risk of intracranial bleeding has not been shown to be increased in prospective studies[489,492–494] of neurosurgical patients who received perioperative LDUH thromboprophylaxis. However, caution should be exercised when considering the use of preoperative or early postoperative LMWH in craniotomy patients.[74,486–488,492,493,495] In one small, nonblinded clinical trial,[495] intracranial bleeding was found in 5 of 38 patients who had been randomized to commence LMWH preoperatively, and in none of the 19 patients who received IPC. The pooled rates of intracranial hemorrhage in randomized trials[486,488] of neurosurgery patients were 2.1% for postoperative LMWH and 1.1% for mechanical or no thromboprophylaxis. Most of these bleeds occurred within the first 2 days after surgery. In a metaanalysis,[74] bleeding at any site was twice as common in patients who received postoperative LMWH thromboprophylaxis as in those who received mechanical thromboprophylaxis (6.1% vs 3.0%, respectively; $p = 0.02$).

In summary, IPC is recommended as thromboprophylaxis in patients undergoing elective major neurosurgery. Other acceptable options include the use of perioperative LDUH or postoperative LMWH. The combination of thromboprophylaxis with LMWH and GCS is more efficacious than that with GCS alone. The combination of LDUH and mechanical thromboprophylaxis also appears to be highly effective.[490] In some centers, mechanical thromboprophylaxis is started at the time of surgery; and then, if a CT scan obtained the following day does not show bleeding, anticoagulant thromboprophylaxis is either added or substituted.

Recommendations: Neurosurgery

4.0.1. For patients undergoing major neurosurgery, we recommend that thromboprophylaxis be used routinely (Grade 1A)**, with optimal use of IPC** (Grade 1A)**. Acceptable alternatives to IPC are postoperative LMWH** (Grade 2A) **or LDUH** (Grade 2B)**.**

4.0.2. For patients undergoing major neurosurgery who have a particularly high thrombosis risk, we suggest that a mechanical method (*ie*, GCS and/or IPC) be combined with a pharmacologic method (*ie*, postoperative LMWH or LDUH) (Grade 2B)**.**

5.0 Trauma, Spinal Cord Injury, Burns

5.1 Trauma

Among hospitalized patients, those recovering from major trauma have among the highest risks for VTE.[1,496–498] Without thromboprophylaxis, patients with multisystem or major trauma have a DVT risk that exceeds 50%, and PE is the third-leading cause of death in those who survive beyond the first day. Factors that are independent predictors of VTE in trauma patients include the following: spinal cord injury (SCI), lower-extremity or pelvic fracture, need for a surgical procedure, insertion of a femoral venous line or repair of a major vein, increasing age, prolonged immobility, and delay in commencement of thromboprophylaxis.[1,496–501]

Despite the high thrombosis risks in trauma, there

have been relatively few randomized trials[415,502–509] of thromboprophylaxis in this patient group (Table 11). Recommendations for thromboprophylaxis are based on data from these trials, as well as from studies[1,497] conducted in other high-risk, nontrauma patient groups.

Mechanical thromboprophylaxis methods are widely used in trauma because they do not increase the risk of bleeding. The use of GCS has never been evaluated in trauma patients. One randomized trial[506] demonstrated that thromboprophylaxis with IPC was significantly more efficacious than foot pumps in trauma patients without lower-extremity fracture, and three additional studies[86,504,510] found that IPC was effective in patients with head injuries. However, a metaanalysis[511] was unable to demonstrate any significant DVT reduction with IPC vs no thromboprophylaxis (OR, 0.77; 95% CI, 0.27 to 2.24). In addition to suboptimal protection, other important limitations of IPC include its inability to be used in approximately one third of trauma patients (due to lower-extremity injuries), and consistent evidence of poor compliance with proper use of these devices by both patients and nursing staff.[81,83,512] Although IPC and GCS cannot be recommended as routine thromboprophylaxis in trauma, they are recommended in patients with a contraindication to anticoagulant thromboprophylaxis, such as those with active bleeding or with a high risk for bleeding (until anticoagulants can be administered later).[86]

LDUH should not be used alone as thromboprophylaxis in trauma patients.[1,497] A metaanalysis[511] has demonstrated that LDUH was not more effective than no thromboprophylaxis (OR, 0.97; 95% CI, 0.35 to 2.64). A blinded, randomized clinical trial[502] compared LDUH with the LMWH enoxaparin, both initiated within 36 h of injury, among 344 major trauma patients without frank intracranial bleeding or ongoing bleeding at other sites. The LMWH was significantly more efficacious than LDUH for both DVT (RRR, 30%) and proximal DVT (RRR, 58%) [$p = 0.01$ for each of these comparisons]. The superiority of LMWH was seen in both higher-risk patients with lower-extremity fractures and in patients without leg fractures. The overall rate of major bleeding was $< 2\%$, and there were no significant differences in the rates of bleeding, blood transfusion, or changes in hematocrit. Another study[507] randomized 486 major trauma patients to thromboprophylaxis with LMWH or IPC; weekly DUS screening was performed. Proximal DVT or PE was

Table 11—*Thromboprophylaxis Trials in Trauma Patients: Clinical Descriptions and Results (Section 5.1)**

Study/Year	Patient Group (Mean Age, yr/Mean ISS/LEF)	Diagnostic Test for DVT	Intervention		DVT†	
			Control	Experimental	Control	Experimental
Fisher et al[415]/ 1995	Pelvic fracture (NR/ NR/100%)	DUS every 5 d	No thromboprophylaxis	IPC	4/38 (11)	2/35 (6)
Geerts et al[502]/ 1996	ISS ≥ 9, no intracranial bleeding (38/23/54%)	Venography day 10–14	LDUH bid	Enoxaparin, 30 mg bid	60/136 (44)	40/129 (31)
Haentjens et al[503]/ 1996	Orthopedic trauma (61/ NR/96%)	DUS or IPG day 10	Nadroparin 3,075 U/d	Nadroparin weight adjusted	0/106	3/109 (3)
Knudson et al[504]/1996	Moderate trauma (39/ 15/17%)	DUS every 5–7 d	IPC or VFP	Enoxaparin, 30 mg bid	2/82 (2)	1/120 (1)
Cohn et al[505]/ 1999	Moderate trauma (41/ 11/NR)	DUS weekly	LDUH bid	Enoxaparin, 30 mg bid	2/32 (6)	0/34
Elliott et al[506]/ 1999	Major trauma excluding LEF (32/31/0%)	DUS day 8	IPC	VFP	4/62 (6)	13/62 (21)
Ginzburg et al[507]/2003	ISS ≥ 9, no contraindication to anticoagulant (41/17/ 35%)	DUS weekly	IPC	Enoxaparin 30 mg bid	7/224 (3)	2/218 (1)
Fuchs et al[508]/ 2005	Orthopedic trauma (50/ NR/100%)	DUS weekly	LDUH tid	LDUH tid plus ankle CPM	29/116 (25)	4/111 (4)
Stannard et al[509]/2006	Orthopedic trauma (40/ 14/100%)	DUS plus MRV before discharge	Enoxaparin 30 mg bid started < 48 h after injury	VFP started on admission plus enoxaparin 30 mg bid started day 5	13/97 (13)	9/103 (9)

*Includes randomized clinical trials in which routine screening with an objective diagnostic test for DVT was used. CPM = continuous passive motion; ISS = injury severity score; LEF = lower-extremity fractures; MRV = magnetic resonance venography; NR = not reported.
†Values given as No. of patients with DVT/total No. of patients (%).

detected in 3% of the IPC group and in 1% of the patients who received LMWH. Major bleeding was also seen in < 2% of patients in both groups, confirming the safety of LMWH in trauma patients who do not have an overt contraindication. As trauma care physicians become more familiar with use of prophylactic LMWH, concerns about bleeding also appear to be decreasing.

Although combining mechanical with pharmacologic thromboprophylaxis, either simultaneously or sequentially, may provide additive protection against VTE as well as increased safety, this approach not been studied rigorously in trauma patients. Such an approach would also increase costs and could result in suboptimal compliance with both methods. A randomized trial[508] in 227 orthopedic trauma patients found that LDUH combined with a device that flexed the ankle joint every 2 s was significantly more efficacious than LDUH alone. The proximal DVT rates in the LDUH group and the combined thromboprophylaxis group were 22% and 3%, respectively ($p < 0.001$), based on weekly DUS.

Another study[509] randomized 200 orthopedic trauma patients to thromboprophylaxis with LMWH started within 48 h after injury or to pulsatile foot pumps started soon after admission combined with LMWH started 5 days later. There was no significant difference in DVT rates using predischarge DUS and magnetic resonance venography or in bleeding between the two thromboprophylaxis strategies. This study provides some support for both approaches: initiation of LMWH within the first 2 days after injury, as well as the early initiation of mechanical thromboprophylaxis with the delayed addition of LMWH in trauma patients with an early high bleeding risk.

Routine screening of high-risk trauma patients for asymptomatic DVT using DUS is not feasible, nor is it an effective strategy to prevent clinically important VTE.[513,514] At least 25% of trauma patients have inadequate ultrasound studies of the deep venous system because of local injuries or poor patient cooperation,[46,515] and both false-positive and false-negative results can be expected. In a thromboprophylaxis trial,[516] 215 SCI patients underwent both contrast venography and DUS approximately 14 days after injury; 53% of the abnormal DUS scan results were proven to be false positive, while DUS missed 71% of the DVTs detected by venogram. The costs of routine screening even among high-risk trauma patients are also prohibitive.[514,515,517–519] Finally, there is evidence that screening provides no incremental gain in patient protection over the early use of appropriate thromboprophylaxis.[513,514,517,519,520] Although routine screening for DVT cannot be justified in most trauma patients, selective screening might be beneficial in a limited proportion of high-risk patients in whom early thromboprophylaxis has not been possible,[520] or prior to a major surgical procedure when optimal thromboprophylaxis was not provided preoperatively.

Prophylactic inferior vena cava (IVC) filter insertion has been recommended by some clinicians for use in trauma patients believed to be at very high risk for VTE.[521–524] No randomized trials have studied the prophylactic use of IVC filters in any patient population, and we are not aware of evidence that their use is of any benefit when added to the most effective thromboprophylaxis modality appropriate for the clinical status.[525] A metaanalysis[499,526] of prospective studies found no difference in the rates of PE among patients with and without prophylactic IVC filters. Furthermore, IVC filter use is associated with both short-term and long-term complications, and may result in inappropriate delays in the use of effective thromboprophylaxis as well as increased risk of DVT at the vascular access site and in the IVC.[526–530] There is no direct evidence that prophylactic IVC filter insertion would prevent any deaths or otherwise benefit trauma patients.[519] Both PE and fatal PE still occur despite the presence of an IVC filter.[521,522,525,526] With current insertion techniques performed by experienced clinicians, including bedside filter insertion,[531] use of retrievable filters,[530,532–536] and ultrasound guidance,[537–539] the short-term complication rates associated with IVC filter use are low.[497,540,541] However, the lack of any direct evidence of efficacy, the inability to predict which patients might benefit, and the high costs pose the greatest challenges to their use. Contrary to recent trends, the availability of retrievable IVC filters should not expand the indications for filter insertion.[536,542] In a multicenter study[530] of retrievable IVC filter use (n = 446; 76% for prophylactic indications), the average time for filter placement was 6 days after injury, well beyond the high risk period for bleeding in most patients.[543] Furthermore, the majority of retrievable IVC filters are never removed,[530,536,544,545] a second central venous procedure is required to remove them (with attendant risks, radiation exposure, and costs), and there is very little long-term follow-up information with these devices. Until these issues are resolved, we and others do not recommend the use of an IVC filter as thromboprophylaxis, even in patients who are at high risk for VTE.[501,518,519,526,546,547] IVC filter insertion is indicated for patients with proven proximal DVT, and either an absolute contraindication to full-dose anticoagulation or planned major surgery in the near future. In either case, even with an IVC filter, therapeutic anticoagulation should be commenced as soon as the contraindication resolves.

The routine use of thromboprophylaxis in major trauma patients has become standard of care.[1,497] Accordingly, every trauma unit should develop a management guideline for the prevention of VTE, and every trauma patient should be assessed for his or her VTE risk and should be prescribed optimal thromboprophylaxis consistent with thromboembolic and bleeding risks.

The use of LMWH, started once primary hemostasis has been achieved, is the most efficacious and simplest option for the majority of moderate-risk and high-risk trauma patients.[1,497,543] Current contraindications to the early initiation of LMWH thromboprophylaxis include the presence of intracranial bleeding, ongoing and uncontrolled bleeding elsewhere, and incomplete SCI associated with suspected or proven spinal hematoma. The presence of a head injury without frank hemorrhage, lacerations, or contusions of internal organs (such as the lungs, liver, spleen, or kidneys), the presence of a retroperitoneal hematoma associated with pelvic fracture, or complete SCIs are not themselves contraindications to LMWH thromboprophylaxis, provided that there is no evidence of ongoing bleeding.[543,548–550] Most trauma patients can be started on thromboprophylaxis with LMWH within 36 h of injury. Among 743 major trauma patients (including 174 with brain injury) who started receiving dalteparin at 5,000 U qd an average of 3 days after injury, there were no cases of new or increased intracranial hemorrhage.[543] Thromboprophylaxis should not be delayed while awaiting most surgical procedures, nor should it be withheld before most surgical procedures.[543]

For patients with contraindications to LMWH thromboprophylaxis, mechanical modalities, like GCS and/or IPC devices, should be considered despite evidence that they provide only limited protection. These devices should be applied to both legs as soon as possible after hospital admission, and they should be used continuously except when the patient is actually walking.[81,83]

Although the optimal duration of thromboprophylaxis is not known for these patients, it should generally continue until discharge from the hospital. If the hospital stay, including the period of rehabilitation, extends beyond 2 weeks, and if there is an ongoing risk of VTE, thromboprophylaxis should continue either with LMWH or a VKA. Therapeutic VKA (target INR, 2.5; range, 2.0 to 3.0) is a suggested method of rehabilitation-phase thromboprophylaxis once the risk of major bleeding is low, and if no surgical procedures are planned for the near future. While we are not aware of any clinical trials that have specifically addressed the extended use of a VKA in trauma patients, there is evidence for its use in other high-risk groups (see Section 3.5.3). Although many trauma patients are not fully mobile at hospital discharge, and the potential for delayed symptomatic VTE exists, there are no data to quantify this risk. Until evidence becomes available, we cannot recommend the routine use of postdischarge VTE thromboprophylaxis. We are aware that some trauma centers continue thromboprophylaxis with LMWH or a VKA after hospital discharge in selected patients with impaired mobility.[551]

Recommendations: Trauma

5.1.1. For all major trauma patients, we recommend routine thromboprophylaxis if possible (Grade 1A)**.**
5.1.2. For major trauma patients in the absence of a major contraindication, we recommend that clinicians use LMWH thromboprophylaxis starting as soon as it is considered safe to do so (Grade 1A)**. An acceptable alternative is the combination of LMWH and the optimal use of a mechanical method of thromboprophylaxis** (Grade 1B)**.**
5.1.3. For major trauma patients, if LMWH thromboprophylaxis is contraindicated due to active bleeding or high risk for clinically important bleeding, we recommend that mechanical thromboprophylaxis with IPC, or possibly with GCS alone, be used (Grade 1B)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**
5.1.4. In trauma patients, we recommend against routine DUS screening for asymptomatic DVT (Grade 1B)**. We do recommend DUS screening in patients who are at high risk for VTE (*eg*, in the presence of a SCI, lower-extremity or pelvic fracture, or major head injury), and who have received suboptimal thromboprophylaxis or no thromboprophylaxis** (Grade 1C)**.**
5.1.5. For trauma patients, we recommend against the use of an IVC filter as thromboprophylaxis (Grade 1C)**.**
5.1.6. For major trauma patients, we recommend the continuation of thromboprophylaxis until hospital discharge (Grade 1C)**. For trauma patients with impaired mobility who undergo inpatient rehabilitation, we suggest continuing thromboprophylaxis with LMWH or a VKA (target INR, 2.5; range, 2.0 to 3.0)** (Grade 2C)**.**

5.2 Acute Spinal Cord Injury

Without thromboprophylaxis, patients with acute SCI have the highest incidence of DVT among all hospitalized groups.[1,497,552] Asymptomatic DVT occurs in 60 to 100% of SCI patients who are subjected to routine screening,[1,516] and PE remains the third-

leading cause of death.[553,554] Among SCI patients, the factors that are associated with greater rates of DVT include the following: increasing age, paraplegia vs tetraplegia, the injury degree (complete vs incomplete), concomitant lower-extremity fractures, cancer, and delayed initiation of thromboprophylaxis.[1,555,556] VTE after SCI results in considerable long-term disability because these patients have low rates of venous recanalization following DVT, and are subject to more bleeding complications associated with prolonged anticoagulation.

A number of small randomized clinical trials[502,516,557–561] suggest that the use of LDUH[502,558–560] or IPC[557] are ineffective methods of thromboprophylaxis when used alone in SCI patients, while LMWH[502,560–562] appears to be substantially more efficacious. In the largest trial,[516] 476 patients with acute SCI were randomized to receive either the combination of LDUH at 5,000 U SC q8h plus IPC or enoxaparin at 30 mg SC q12h. DVT was demonstrated by venography in 63% of the LDUH-IPC group and 66% of the enoxaparin patients, while the rates of major VTE (either proximal DVT or PE) were 16% and 12%, respectively; no patient died of PE. Therefore, despite the use of thromboprophylaxis, DVT rates remain very high in this patient group. Major bleeding was seen in 5% of LDUH-IPC patients and in 3% of those who received enoxaparin.

Uncontrolled studies[1] suggest that the use of an oral VKA started shortly after hospital admission reduces the occurrence of symptomatic VTE in SCI patients compared with no anticoagulant thromboprophylaxis. The insertion of a prophylactic IVC filter has been advocated by some authors[563,564] but not by others.[1,547] If suboptimal thromboprophylaxis is used, IVC filters might reduce the occurrence of PE (although this has not been proven). However, these devices are unlikely to be necessary if appropriate thromboprophylaxis is used. IVC filter use is associated with major complications that may be at least as common as massive PE, and they add a substantial financial burden to the care of these patients.[547] It has been estimated that, if IVC filters are effective, they would need to be placed in 50 SCI patients receiving thromboprophylaxis to prevent one nonfatal PE at a cost of $250,000.[547]

Although the period of greatest risk for VTE following SCI is the acute care phase, symptomatic DVT or PE, and fatal PE also occur during the rehabilitation phase.[559,565–567] Chen and colleagues[568] observed that 10% of 1,649 SCI patients undergoing rehabilitation had symptomatic DVT develop, and 3% had PE. A prospective study[566] followed up 119 patients who had a normal DUS 2 weeks after acute SCI for another 6 weeks, at which time the DUS was repeated. During this time, all patients received LDUH q8h or enoxaparin at 40 mg SC qd in a nonrandomized manner. The rates of new VTE were 22% (one fatal PE) and 8% in the LDUH and LMWH groups, respectively.

The very high risk of VTE following SCI, combined with the results of currently available prevention studies,[1,516,552] support the use of early thromboprophylaxis in all SCI patients. LDUH, IPC, or GCS do not provide adequate protection when used alone and are not recommended as single thromboprophylaxis modalities. LMWH or the combination of LMWH (or LDUH) plus IPC are the recommended early options.[1] Before commencing anticoagulant thromboprophylaxis, there should be clinical evidence that primary hemostasis has been achieved. If there are major concerns about bleeding at the injury site or elsewhere, mechanical thromboprophylaxis should be initiated as soon as possible after hospital admission, and anticoagulant thromboprophylaxis should be started once the bleeding risk has decreased.

Prospective studies have not addressed the value of routine DUS screening of SCI patients, although this is a reasonable consideration in those for whom thromboprophylaxis has been delayed for several days.[552,569,570] After the acute injury phase, continuing thromboprophylaxis with LMWH or conversion to a full-dose oral VKA (target INR, 2.5; range, 2.0 to 3.0) for the duration of the rehabilitation phase is likely to protect patients from delayed thromboembolic events.[1,552,566] It is recommended that thromboprophylaxis be continued for a minimum of 3 months, or until completion of the inpatient phase of rehabilitation.

For patients with incomplete SCI, the initiation of LMWH should be delayed for at least 1 to 3 days in the presence of a spinal hematoma on CT scan or MRI. The use of long-term, full-dose anticoagulation with a VKA should probably also be delayed for at least 1 week following injury in such patients because of the unpredictable response to dosing with these agents.

Recommendations: Acute Spinal Cord Injury

5.2.1. For all patients with acute SCI, we recommend that routine thromboprophylaxis be provided (Grade 1A)**.**

5.2.2. For patients with acute SCI, we recommend thromboprophylaxis with LMWH, commenced once primary hemostasis is evident (Grade 1B)**. Alternatives include the combined use of IPC and either LDUH** (Grade 1B) **or LWMH** (Grade 1C)**.**

5.2.3. For patients with acute SCI, we recom-

mend the optimal use of IPC and/or GCS if anticoagulant thromboprophylaxis is contraindicated because of high bleeding risk early after injury (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

5.2.4. For patients with an incomplete SCI associated with evidence of a spinal hematoma on CT or MRI, we recommend the use of mechanical thromboprophylaxis instead of anticoagulant thromboprophylaxis at least for the first few days after injury (Grade 1C)**.**

5.2.5. Following acute SCI, we recommend against the use of LDUH alone (Grade 1A)**.**

5.2.6. For patients with SCI, we recommend against the use of an IVC filter as thromboprophylaxis (Grade 1C)**.**

5.2.7. For patients undergoing rehabilitation following acute SCI, we recommend the continuation of LMWH thromboprophylaxis or conversion to an oral VKA (INR target, 2.5; range, 2.0 to 3.0) (Grade 1C)**.**

5.3 Burns

Although there have been no published thromboprophylaxis trials in this area, the frequency of VTE appears to be high enough to warrant thromboprophylaxis in burn patients who have one or more additional VTE risk factors.[1,571,572] Extrapolating from other patient groups, we recommend the use of mechanical thromboprophylaxis if the bleeding risk is high and if this option is possible. If the bleeding risk is no longer high, we recommend either LMWH or LDUH.

Recommendations: Burns

5.3.1. For burn patients who have additional risk factors for VTE, including one or more of the following: advanced age, morbid obesity, extensive or lower-extremity burns, concomitant lower-extremity trauma, use of a femoral venous catheter, and/or prolonged immobility, we recommend routine thromboprophylaxis if possible (Grade 1A)**.**

5.3.2. For burn patients who have additional risk factors for VTE, if there are no contraindications, we recommend the use of either LMWH or LDUH, starting as soon as it is considered safe to do so (Grade 1C)**.**

5.3.3. For burn patients who have a high bleeding risk, we recommend mechanical thromboprophylaxis with GCS and/or IPC until the bleeding risk decreases (Grade 1A)**.**

6.0 Medical Conditions

Although VTE is most often considered to be associated with recent surgery or trauma, 50 to 70% of symptomatic thromboembolic events and 70 to 80% of fatal PEs occur in nonsurgical patients.[1,573] From the perspective of the general population, hospitalization for an acute medical illness is independently associated with about an eightfold-increased risk for VTE[574] and accounts for almost one fourth of all VTE events.[6] The risks of VTE and its prevention in stroke patients are discussed in detail in Chapter 15.

On average, general medical inpatients not receiving thromboprophylaxis are at low-to-moderate risk for the development of VTE, with typical rates of asymptomatic DVT of approximately 15% using venography[575–577] and 5 to 7% using DUS as the screening test.[578,579] As in other low-to-moderate risk patient groups, symptomatic VTE is uncommon in hospitalized medical patients. For example, in one retrospective review[580] of 6,332 medical patients, there were just 39 cases (0.6%) of hospital-acquired symptomatic VTE. In a prospective cohort study,[581] only a single case of symptomatic VTE was detected over the 41-day observation period among 297 acutely ill hospitalized medical patients who were administered an LMWH. One study[578] observed a 6% rate of asymptomatic DVT among 234 patients who were screened with DUS on admission to a general internal medicine unit. Because 90% of the thrombi were limited to the calf, the clinical importance of this finding is uncertain. In this study, DVT was diagnosed in 18% of patients $>$ 80 years of age, but in no one $<$ 55 years old. Over the course of their hospital stay, an additional 2% of patients had new DVTs, all of whom were $>$ 70 years of age.

Apart from advanced age, additional risk factors for VTE in medical patients include previous VTE, cancer, stroke with lower-extremity weakness, heart failure, COPD exacerbation, sepsis, and bed rest.[48,575,582–585] Many medical patients have multiple risk factors.

To our knowledge, no randomized clinical trials have evaluated any mechanical methods of thromboprophylaxis in general medical patients, although one small study[586] found that the use of GCS reduced DVT after acute stroke. Seven thromboprophylaxis trials[575,576,579,587–590] in medical patients have compared LDUH, LMWH, or fondaparinux with no thromboprophylaxis or placebo (Table 12). Compared with no thromboprophylaxis, the use of LDUH or LMWH, reduced the relative risk of FUT-detected DVT by approximately 70% without increased risk of bleeding.[587–590] There is no compelling evidence that LDUH should be administered

Table 12—*Thromboprophylaxis Trials of LDUH, LMWH, or Fondaparinux vs No Thromboprophylaxis in General Medical Patients: Clinical Descriptions and Results (Section 6.0)**

Study/Year	Patients (Mean Age, yr/ Cancer Rate, %)	Method of DVT Screening	Intervention		DVT†	
			Control	Experimental	Control	Experimental
Gallus et al[587]/1973	CHF (NR/NR)	FUT × 11 d	No thromboprophylaxis	LDUH tid	7/15 (46.7)	1/11 (9.1)
Belch et al[588]/1981	CHF, pneumonia (66/NR)	FUT up to 14 d	No thromboprophylaxis	LDUH tid	13/50 (26.0)	2/50 (4.0)
Cade[589]/1982	Medical patients plus second risk factor (NR/ NR)	FUT × 4–10 d	Placebo	LDUH bid	7/67 (10.4)	1/64 (1.6)
Dahan et al[590]/1986	Age > 65 yr (80/13)	FUT × 10 d	Placebo	Enoxaparin, 60 mg/d	12/131 (9.2)	4/132 (3.0)
Samama et al[575]/1999	Age > 40 yr plus second risk factor (73/14)	Venography or DUS day 6–14	Placebo	Enoxaparin, 20 mg/d Enoxaparin, 40 mg/d	43/288 (14.9)	43/287 (15.0) 16/291 (5.5)
Leizorovicz et al[579]/2004	Age ≥ 40 yr plus acutely ill medical patients (69/5)	DUS day 21	Placebo	Dalteparin, 5,000 U/d	73/1473 (5.0)‡	42/1518 (2.8)‡
Cohen et al[576]/2006	Acutely ill medical patients plus age > 60 yr (75/15)	Venography day 6–15	Placebo	Fondaparinux, 2.5 mg/d	34/323 (10.5)	18/321 (5.6)

*Includes randomized clinical trials in which routine screening with an objective diagnostic test for DVT was used. CHF = congestive heart failure; see Table 11 for expansion of abbreviation.

†Values given as No. of patients with DVT/total No. of patients (%).

‡Clinically important VTE (composite of objectively verified symptomatic DVT or PE, sudden death, and asymptomatic proximal DVT).

three times daily in preference to twice daily in medical patients, although these two regimens have never been directly compared. In a metaanalysis[591] that included almost 8,000 patients, three-times-daily LDUH was associated with significantly more major bleeding events, while there was a nonsignificant trend toward more thromboembolic events with twice-daily LDUH. Subsequent large randomized clinical trials have demonstrated the efficacy of enoxaparin at 40 mg qd,[575] dalteparin at 5,000 U qd,[579] and fondaparinux at 2.5 mg qd[576] compared with placebo in medical patients.

A metaanalysis[592] of nine randomized trials that included almost 20,000 medical patients found that anticoagulant thromboprophylaxis reduced fatal PE by 64%, symptomatic PE by 58%, and symptomatic DVT by 53% with no significant increase in major bleeding compared with no thromboprophylaxis. However, the absolute benefits of thromboprophylaxis were small, with an NNT to prevent one symptomatic PE of 345, and with no effect on all-cause mortality.

In medical patients, LDUH and LMWH have been directly compared in four randomized clinical trials[593–596] with routine screening for DVT (Table 13); none of these studies showed a significant difference in DVT rates or bleeding. A systematic review[597] also found similar rates of major bleeding with LDUH and LMWH thromboprophylaxis. Thus, it can be concluded that thromboprophylaxis with LMWH, LDUH, or fondaparinux lowers the risk of asymptomatic DVT by at least 50% in a broad spectrum of medical patients compared with no thromboprophylaxis. Among 1,762 patients with acute ischemic strokes, LMWH (enoxaparin at 40 mg qd) was shown to provide greater protection against DVT and proximal DVT than twice-daily LDUH with no greater bleeding.[60,598] The effect of thromboprophylaxis on symptomatic VTE and on mortality in this patient group remains unclear because the available studies[575,590,599–601] have not been adequately powered to demonstrate a reduction in these outcomes. Similarly, the optimal duration of thromboprophylaxis in medical patients remains unclear.[602] In a study[603] of extended, post-hospital discharge thromboprophylaxis, > 4,000 acutely ill medical patients with at least two additional thromboembolic risk factors were randomized to receive either 6 to 14 days or approximately 1 month of LMWH. DUS was then obtained. Both the rates of total VTE (4.9% vs 2.8%) and symptomatic VTE (1.1% vs 0.3%) were significantly reduced in the group who received extended thromboprophylaxis. However, bleeding and major bleeding were both significantly increased in the extended thromboprophylaxis group, while all-cause mortality was not significantly different.

Medical patients account for a high proportion of patients in hospital. Therefore, the appropriate use

Table 13—*Thromboprophylaxis Trials of LDUH vs LMWH in General Medical Patients: Clinical Descriptions and Results (Section 6.0)**

Study/ Year	Patients (Mean Age, yr/Cancer Rate, %)	Method of DVT Screening	Intervention		DVT†	
			LDUH	LMWH	LDUH	LMWH
Bergmann et al[593]/ 1996	Bedridden, age ≥ 65 yr (83/7)	FUT × 10 d	5,000 U bid	Enoxaparin, 20 mg/d	10/216 (4.6)	10/207 (4.8)
Harenberg et al[594]/ 1996	Bedridden, age 50–80 yr plus second risk factor (70/8)	Proximal DUS days 8–11	5,000 U tid	Nadroparin, 3,400 AXa U/d	4/780 (0.5)	6/810 (0.7)
Lechler et al[595]/ 1996	Immobile ≥ 7 d plus second risk factor (74/14)	DUS day 7	5,000 U tid	Enoxaparin, 40 mg/d	6/377 (1.6)	1/393 (0.3)
Kleber et al[596]/ 2003	Severe respiratory disease or congestive heart failure (70/6)	Venography if d-dimer or fibrin monomer positive days 8–12	5,000 U tid	Enoxaparin, 40 mg/d	22/212 (10.4)	20/239 (8.4)

*Includes randomized clinical trials in which LDUH and LMWH were compared and routine screening with an objective diagnostic test for DVT was used. AXa = anti-Factor Xa.
†Values given as No. of patients with DVT/total No. of patients (%).

of thromboprophylaxis in medical patients offers an important opportunity to substantially reduce the overall burden of disease due to VTE.[1,573,604] However, the use of thromboprophylaxis in medical patients is generally poor, and most at-risk patients are left unprotected.[32,33,37,585,605,606]

Recommendations: Medical Conditions

6.0.1. For acutely ill medical patients admitted to hospital with congestive heart failure or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, acute neurologic disease, or inflammatory bowel disease, we recommend thromboprophylaxis with LMWH (Grade 1A)**, LDUH** (Grade 1A)**, or fondaparinux** (Grade 1A)**.**
6.0.2. For medical patients with risk factors for VTE, and for whom there is a contraindication to anticoagulant thromboprophylaxis, we recommend the optimal use of mechanical thromboprophylaxis with GCS or IPC (Grade 1A)**.**

7.0 Cancer Patients

Patients with cancer have at least a sixfold-increased risk of VTE compared to those without cancer,[574,607] and active cancer accounts for almost 20% of all new VTE events occurring in the community.[6] Furthermore, VTE is one of the most common and costly complications seen in cancer patients.[607–610] Once VTE develops in a cancer patient, the VTE recurrence rate is high both after and during traditional anticoagulation.[609–612] The development of VTE in cancer patients is also associated with a significant reduction in survival.[613–615] The risk of VTE varies by cancer type and extent, and is especially high among patients with malignant brain tumors; adenocarcinomas of the lung, ovary, pancreas, colon, stomach, prostate, and kidney; and hematologic malignancies.[138,484,607,610,615–622]

Cancer patients undergoing surgery have at least twice the risk of postoperative DVT and more than three times the risk of fatal PE encountered by noncancer patients who are undergoing similar procedures.[14,26,138,166,623–626] Cancer is also an independent predictor of thromboprophylaxis failure (*ie*, the development of postoperative DVT despite the use of thromboprophylaxis).[137,138,166,623,627] In a multicenter, prospective study[138] of 2,373 patients who underwent cancer surgery, VTE was the most common cause of 30-day mortality even though thromboprophylaxis was used in 82% of patients. There is strong evidence that LDUH effectively reduces the risk of DVT and fatal PE following cancer surgery.[20,159] LMWH is at least as efficacious as LDUH in these patients.[26,134,152,158] In cancer surgery, the dose of prophylactic anticoagulants is important. For example, among gynecologic oncology patients, LDUH administered three times daily appears to be more efficacious than twice-daily dosing.[198,199,628] Among general surgery patients with malignancy, thromboprophylaxis with dalteparin at 5,000 U SC qd was shown to be more efficacious than 2,500 U.[150] In the cancer patient subgroup of the PEntasaccharide GenerAl SUrgery Study (or PEGASUS),[163] fondaparinux was associated with a statistically significant reduction in VTE compared with dalteparin. This finding would need to be confirmed in a trial specifically in cancer patients before it can be con-

cluded that fondaparinux is superior to LMWH in these patients. Two clinical trials[169,170] in cancer surgery patients have shown that the continuation of LMWH thromboprophylaxis for 3 weeks after hospital discharge reduced the risk of late venographic DVT by 60%.

Nonsurgical cancer therapies also increase the risk of VTE.[619,620,629] Compared to patients without cancer, those receiving chemotherapy have at least a sixfold-increased risk of VTE.[574,629,630] Hormonal manipulation also affects the thrombosis risk.[610,631–633] The rate of VTE increases by twofold to fivefold among women whose breast cancer has been treated with the selective estrogen receptor modulator tamoxifen.[619,634] This risk was even greater in postmenopausal women and when tamoxifen was combined with chemotherapy.[635] The use of one of the aromatase inhibitors anastrozole, letrozole, or exemestane is associated with approximately half the risk of VTE compared with tamoxifen.[636–639] Angiogenesis inhibitors have been shown to increase thromboembolic complications in cancer patients.[640] Thalidomide and lenalidomide are also associated with VTE especially when they are combined with chemotherapy and/or high-dose dexamethasone.[641–644] Nonrandomized studies[643–645] suggest that prophylactic doses of LMWH or aspirin may be effective in reducing the incidence of thalidomide-associated VTE. A metaanalysis[646] of 35 trials in 6,769 cancer patients concluded that treatment with erythropoietin or darbepoietin increased the risk of thromboembolic events by 67% compared with patients not receiving this therapy. Survival has also been shown to be decreased in some studies[647,648] of cancer patients receiving one of the erythropoiesis-stimulating agents.

The presence of a central venous catheter (CVC) in cancer patients predisposes to upper-extremity DVT.[649–652] This may result in arm swelling and discomfort, PE, a predisposition to catheter-related sepsis, and the need to replace the catheter.[651,653] Peripherally inserted CVCs appear to be associated with a greater risk of thrombosis than subclavian vein or internal jugular vein access.[654,655] If the CVC tip is placed in the upper superior vena cava or more peripherally, the DVT risk is higher than when the catheter tip is located at or just above the right atrium.[656] Eight randomized trials[657–664] have evaluated anticoagulant thromboprophylaxis in the prevention of CVC-associated DVT (Table 14). One study[657] found that fixed-dose warfarin, 1 mg/d, dramatically reduced the rate of venographic DVT at 90 days compared to no thromboprophylaxis. However, two subsequent clinical trials[659,662] failed to show any benefit from a 1-mg daily dose of warfarin compared to no thromboprophylaxis. Furthermore, even low-dose warfarin involves a substantial risk of bleeding associated with elevated INR values.[665] Higher doses of warfarin may reduce the risk of CVC-associated thrombosis but are associated with unacceptable risks of major bleeding.[666]

One study[661] randomized 111 patients to receive either a continuous infusion of heparin at 100 U/kg/d (approximately one fourth the usual therapeutic dose) through the CVC or to saline solution for the duration of hospital stay (approximately 24 days). There were significantly fewer thrombi detected by DUS at the time of catheter removal, as well as a reduction in catheter-related bloodstream infections in the patients who received the heparin infusions.[667] The partial thromboplastin time was not prolonged in any heparin infusion patient, and heparin-induced thrombocytopenia was not encountered.

LMWH has also been assessed for the prevention of catheter-associated thrombosis. In one study,[658] cancer patients with CVCs were randomly allocated to receive either dalteparin at 2,500 U SC qd or no thromboprophylaxis for 90 days, followed by upper-extremity venography. The study was prematurely stopped after 8 of 13 control patients were found to have DVT, compared to only one patient assigned to receive LMWH ($p = 0.002$). These findings were challenged by the results of two larger, double-blind clinical trials.[663,664] In the first trial,[663] 385 cancer patients received enoxaparin at 40 mg qd or placebo starting before CVC insertion and continued for 6 weeks when a venogram was obtained. The rates of catheter-related thromboses were 18.1% and 14.2%, respectively, in the placebo and LMWH groups ($p = 0.35$). There was no significant reduction in symptomatic DVT, which occurred in 3% of the placebo patients and in 1% of those who received LMWH. In the second trial,[664] 439 cancer patients who were receiving chemotherapy through a CVC were randomized to receive dalteparin at 5,000 U SC qd or placebo for up to 16 weeks. Clinically relevant VTE occurred in 3.7% and 3.4%, respectively, of the dalteparin and placebo recipients. A small randomized trial,[660] compared 90 days of thromboprophylaxis with either nadroparin at 2,850 IU/d or with warfarin at 1 mg/d in cancer patients with a CVC. Among the 45 evaluable patients, venographic DVT was detected in 29% of those who received nadroparin and 17% of those who received warfarin ($p = 0.48$).

The incidence of venous thrombosis requiring catheter removal was only 3.4% (1.14 per 1,000 catheter-days) among 351 patients with a peripherally inserted central catheter who were not receiving thromboprophylaxis.[668] Furthermore, when 444 consecutive cancer patients who received a CVC were followed up prospectively while their catheter remained in place and for an additional 4 weeks, the

Table 14—*Thromboprophylaxis Trials To Prevent CVC-Associated Thrombosis in Cancer Patients: Clinical Descriptions and Results (Section 7.0)**

Study/Year	Method of Diagnosis	Intervention		DVT†		Comments
		Control	Experimental	Control	Experimental	
Bern et al[657]/1990	Venography at 90 d	No thromboprophylaxis	Warfarin, 1 mg/d	15/40 (37.5)	4/42 (9.5)	Unblinded interventions p < 0.001 Symptomatic DVT rate lower with warfarin (32.5% vs 9.5%) 34% of randomized patients did not complete the trial
Heaton et al[659]/2002	Symptomatic VTE	No thromboprophylaxis	Warfarin, 1 mg/d	5/43 (11.6)	8/45 (17.8)	Hematologic malignancies Unblinded interventions p = NS No difference in clot-free catheter survival
Couban et al[662]/2005	Symptomatic VTE during CVC life span (approximately 73 d)	Placebo	Warfarin, 1 mg/d	5/125 (4.0)	6/130 (4.6)	Solid tumors (65%) Leukemia (35%) p = NS No difference in CVC life span
Abdelkefi et al[661]/2004	DUS at CVC removal (mean, 24 d)	Saline	Heparin, 100 U/kg/d as a continuous infusion	8/63 (12.7)	1/65 (1.5)	Hematologic oncology inpatients p = 0.03
Monreal et al[658]/1996	Venography at 90 d	No thromboprophylaxis	Dalteparin, 2,500 U qd	8/13 (61.5)	1/16 (6.3)	Unblinded interventions p = 0.002
Verso et al[663]/2005	Venography at 6 wk	Placebo	Enoxaparin, 40 mg/d	28/155 (18.1)	22/155 (14.2)	11 centers p = NS
Karthaus et al[664]/2006	Symptomatic VTE or asymptomatic DVT at 16 wk	Placebo	Dalteparin, 5,000 U qd	5/145 (3.4)	11/204 (3.7)	48 centers p = NS
Mismetti et al[660]/2003	Venography at 90 d	Warfarin, 1 mg/d	Nadroparin, 2,850 IU qd	3/24 (12.5)	3/21 (14.3)	Pilot study Unblinded interventions p = NS

*Randomized clinical trials in cancer patients with CVCs in which routine screening with an objective diagnostic test for upper-extremity DVT was used or in which a clinical suspicion of DVT was confirmed by an objective diagnostic test.
†Values given as No. of patients with DVT/total No. of patients.

rate of symptomatic DVT was only 4% (0.3 per 1,000 catheter-days).[669] These studies[648,662,664,668,669] suggest that the 2 to 4% risk of symptomatic VTE related to CVCs may be too low to warrant routine thromboprophylaxis. Although this area remains controversial, neither minidose warfarin nor prophylactic doses of LMWH can be recommended as thromboprophylaxis for cancer patients with indwelling CVCs.[1,650,652]

A number of studies have assessed the role of anticoagulants in the prevention of VTE and/or death in cancer patients who did not have another indication for anticoagulant therapy.[670] In the only clinical trial[671] of thromboprophylaxis specifically during chemotherapy, 311 women with metastatic breast cancer received either low-dose warfarin (INR range, 1.3 to 1.9) or placebo. Warfarin reduced the incidence of VTE compared to placebo (from 4.4% to 0.7%; p = 0.03), with no increased risk of major bleeding. However, in the Fragmin Advanced Malignancy Outcome Study,[672] in which 374 patients with advanced cancer received dalteparin at 5,000 U SC qd or placebo for up to 1 year, the rates of symptomatic VTE did not differ significantly (2.4% vs 3.3%). For the primary outcome, survival at 1 year, there was also no significant improvement with long-term use of LMWH. A *post hoc* analysis of this trial[672] suggested that patients with a better prognosis (defined as those who survived > 17 months) who received dalteparin had improved survival. Another trial[673] found that cancer patients who were randomized to the LMWH nadroparin for 6 weeks had an improved median survival compared to those assigned to placebo, and that the improvement was greater in those who had a life expectancy > 6 months. In a third study,[674] 84 patients with small cell lung cancer were randomized to receive either chemotherapy alone or chemotherapy plus dalteparin at 5,000 U/d for up to 18 weeks. Both progression-free survival and overall survival were significantly prolonged in the group

who received dalteparin. Another study[675] did not find a survival advantage in patients with advanced cancer receiving dalteparin at 5,000 U/d. A systematic review of these studies[670] concluded that overall survival was improved by the addition of LMWH to usual cancer therapy, even in patients with advanced disease. Among these studies, there were no significant differences in VTE or in bleeding with the use of LMWH. Additional studies are required to resolve this controversy and to clarify which anticoagulant regimens (if any) are most likely to be beneficial in which cancer patients.

In summary, the use of appropriate thromboprophylaxis in hospitalized cancer patients with additional VTE risk factors provides an important opportunity to reduce the substantial burden of this complication. The prevention of VTE is important, not only because cancer patients have a particularly high risk for VTE, but also because VTE is often more difficult to diagnose in oncology patients, and the treatment of VTE may be less effective, and associated with more bleeding complications.[611,676,677] Cancer patients undergoing surgery should receive aggressive thromboprophylaxis, as recommended in the various surgical sections in this article. Cancer patients with an acute medical illness who are bedridden should also receive thromboprophylaxis using the recommendations for medical patients. We believe that thromboprophylaxis is also indicated in selected palliative care patients in order to prevent further reduction in their quality of life.[678] However, we do not believe that cancer patients who are fully ambulatory should routinely be given thromboprophylaxis. The results of additional trials are required before any recommendations can be made about the use of anticoagulants in cancer patients who do not have a traditional indication for thromboprophylaxis, or as a method to improve survival.

Recommendations: Cancer Patients

7.0.1. For cancer patients undergoing surgical procedures, we recommend routine thromboprophylaxis that is appropriate for the type of surgery (Grade 1A)**. Refer to the recommendations in the relevant surgical subsections.**

7.0.2. For cancer patients who are bedridden with an acute medical illness, we recommend routine thromboprophylaxis as for other high-risk medical patients (Grade 1A)**. Refer to the recommendations in Section 6.0.**

7.0.3. For cancer patients with indwelling CVCs, we recommend that clinicians not use either prophylactic doses of LMWH (Grade 1B) **or minidose warfarin** (Grade 1B) **to try to prevent catheter-related thrombosis.**

7.0.4. For cancer patients receiving chemotherapy or hormonal therapy, we recommend against the routine use of thromboprophylaxis for the primary prevention of VTE (Grade 1C)**.**

7.0.5. For cancer patients, we recommend against the routine use of primary thromboprophylaxis to try to improve survival (Grade 1B)**.**

8.0 Critical Care

While the risks of VTE in critically ill patients vary considerably depending primarily on their reason for intensive care, most ICU patients have multiple risk factors for VTE.[1,679,680] Some of these risk factors predate admission to the ICU, and include recent surgery, trauma, sepsis, malignancy, stroke, advanced age, heart or respiratory failure, previous VTE, and pregnancy. Other thrombotic risk factors may be acquired during the ICU stay, and include immobilization, pharmacologic paralysis, central venous lines, surgical procedures, sepsis, mechanical ventilation, vasopressor use, and renal dialysis.[1,680] However, neither d-dimer levels nor tests of molecular hypercoagulability (activated protein C resistance ratio, prothrombin 20210A gene mutation, levels of protein C, protein S, or antithrombin, anticardiolipin antibody, and lupus anticoagulant) had any predictive value for DVT in critically ill patients.[681] At the same time, critical care patients also frequently have risk factors for bleeding, including recent surgery, trauma or GI bleeding, thrombocytopenia, and renal insufficiency.

The reported incidence of DVT in ICU patients, using routine venography or Doppler ultrasound, ranges from $< 10\%$ to almost 100%, reflecting the wide spectrum of critically ill patients.[1,680] When DUS was performed at ICU entry in 1,164 patients included in six case series, the rate of unsuspected DVT was 6.3%.[1,682] Five studies prospectively screened patients who were not receiving thromboprophylaxis during their ICU stay. The rates of DVT using FUT, DUS or venography range from 13 to 31%.[1] The risks of VTE in surgical, trauma/SCI, and acutely ill medical patients are well established and are relevant to the critical care population, which is principally composed of these subgroups.[1]

We identified only two published, randomized clinical trials of thromboprophylaxis in ICU patients that routinely used objective screening for DVT (Table 15).[589,683] In the first trial,[589] LDUH was associated with an RRR of 55% over placebo in 119 general ICU patients ($p < 0.05$). The second study[683] compared a LMWH, nadroparin, to placebo in 223 patients who were receiving mechanical ventilation for exacerbations of COPD. After a mean of

Table 15—*Thromboprophylaxis Trials in Critical Care Patients: Clinical Descriptions and Results (Section 8.0)**

Study/Year	Method of Diagnosis	Intervention		DVT†	
		Control	Experimental	Control	Experimental
Cade[589]/1982	FUT for 4–10 d	Placebo	Heparin, 5,000 U SC bid	NR/NR (29)	NR/NR (13)
Fraisse et al[683]/ 2000	Venography before d 21	Placebo	Nadroparin, approximately 65 U/kg SC qd	24/85 (28)	13/84 (15)

*Randomized clinical trials in which routine screening with an objective diagnostic test for DVT was used in critical care unit patients. See Table 11 for expansion of abbreviations.

†Values given as No. of patients with DVT/total No. of patients (%).

12 days, DVT was detected by routine venography in 28% of control subjects and 15% of LMWH recipients (RRR, 45%; p = 0.045). Major bleeding rates were 3% and 6%, respectively (p = 0.3). A large, international trial[684] is currently underway to compare the effectiveness and safety of LDUH and LMWH in critical care patients.

When LMWH is administered as thromboprophylaxis to ICU patients, the concomitant use of vasoconstrictor drugs and possibly the presence of generalized edema are associated with significantly reduced anti-Xa levels presumably related to decreased subcutaneous perfusion and drug absorption.[685–688] However, the influence of these observations on the effectiveness of thromboprophylaxis remains uncertain. Prophylactic doses of the LMWH dalteparin do not appear to accumulate in ICU patients with renal dysfunction.[111,689]

It is essential for all ICUs to develop a formal approach to thromboprophylaxis.[1] On admission to the ICU, all patients should be assessed for risk of VTE, and most should receive thromboprophylaxis. The selection of thromboprophylaxis for these heterogeneous patients involves a consideration of the VTE and bleeding risks, both of which may vary from day to day in the same ICU patient. When the bleeding risk is high, mechanical thromboprophylaxis should be started using GCS alone, or GCS combined with IPC until the risk of bleeding decreases.[690] For ICU patients who are not at high risk for bleeding, anticoagulant thromboprophylaxis is recommended. For patients who are at moderate risk for VTE, such as those with medical or general surgical conditions, thromboprophylaxis with LMWH or LDUH is recommended. For patients who are at higher VTE risk, such as following major trauma or orthopedic surgery, LMWH provides greater protection than LDUH and is recommended. To prevent interruption of protection, specific thromboprophylaxis recommendations should be included in the patients' orders when they are transferred from the ICU.

Recommendations: Critical Care

8.1. For patients admitted to a critical care unit, we recommend routine assessment for VTE risk and routine thromboprophylaxis in most (Grade 1A)**.**

8.2. For critical care patients who are at moderate risk for VTE (*eg*, medically ill or postoperative general surgery patients), we recommend using LMWH or LDUH thromboprophylaxis (Grade 1A)**.**

8.3. For critical care patients who are at higher risk (*eg*, following major trauma or orthopedic surgery), we recommend LMWH thromboprophylaxis (Grade 1A)**.**

8.4. For critical care patients who are at high risk for bleeding, we recommend the optimal use of mechanical thromboprophylaxis with GCS and/or IPC at least until the bleeding risk decreases (Grade 1A)**. When the high bleeding risk decreases, we recommend that pharmacologic thromboprophylaxis be substituted for or added to the mechanical thromboprophylaxis** (Grade 1C)**.**

9.0 Long-Distance Travel

Prolonged air travel appears to be a risk factor for VTE, although this risk is mild.[1,582,691–698] Depending on differences in study design and populations, the magnitude of the reported risk of VTE associated with prolonged travel varies widely, ranging from no increased risk to a fourfold-increased risk.[582,691–693,699–702] The incidence of travel-related VTE is influenced by the type and duration of travel, and by individual risk factors.[703–705] Although comparative data are limited, thrombosis risk also appears to be increased for travel by car, bus, or train.[699,702,706] An association between air travel and VTE is strongest for flights > 8 to 10 h in duration,[693,697,701,703–705] although a case-control study[702] also found a twofold-increased thrombosis risk for people who had traveled > 4 h in the 8 weeks preceding the thromboembolic event. Immobility during the flight also appears to be an independent predictor of VTE, but the risk is not influenced by whether the passenger travels in economy class or business/first class.[707,708]

Most individuals with travel-associated VTE have one or more known risk factors for thrombosis, including previous VTE, recent surgery or trauma, active malignancy, pregnancy, estrogen use, advanced age,

Table 16—*Randomized Trials of Thromboprophylaxis in Air Travelers: Clinical Description and Results (Section 9.0)**

Study/Year	Interventions	Risk Group† Flight Duration, h	Patients Analyzed, No./Total (%)	Time to Screening, h	DVT, No./Total (%)	SVT, No./Total (%)	Edema Score, Mean (SD)‡	Comments
Compression stockings								
Scurr et al[711]/ 2001	No thromboprophylaxis Socks: Mediven below-knee stockings (ankle pressure, 8–22 mm Hg), starting before flight	Low 18–36	No thromboprophylaxis: 100/116 (86) Socks: 100/115 (87)	< 48	No thromboprophylaxis: 12/100 (12) Socks: 0/100 (0) RR: 0.04 (95% CI, 0.00–0.67)	No thromboprophylaxis: 0/100 (0) Socks: 4/100 (4) RR: 9.00 (95% CI, 0.49–165.0)	NR	No proximal DVT
Belcaro et al[714]/ 2001	No thromboprophylaxis Socks: below-knee stockings (maximum ankle pressure, 25 mm Hg)	High 10–15	Combined: 833/885 (94)	On arrival	No thromboprophylaxis: 19/422 (5) Socks: 1/411 (0) RR: 0.05 (95% CI, 0.01–0.40)	No thromboprophylaxis: 8/422 (2) Socks: 0/411 (0) RR: 0.06 (95% CI, 0.00–1.04)	NR	Proximal DVT NR
Belcaro et al[715]/ 2002	No thromboprophylaxis Socks: Scholl below-knee flight socks (ankle pressure, 4–17 mm Hg), starting 2–3 h before flight	Low to medium 7–12	No thromboprophylaxis: 314/331 (95) Socks: 315/326 (97)	On arrival	No thromboprophylaxis: 7/314 (2) Socks: 0/315 (0) RR: 0.07 (95% CI, 0.00–1.16)	No thromboprophylaxis: 5/314 (2) Socks: 0/315 (0) RR: 0.09 (95% CI, 0.01–1.63)	Short flight (7–8 h): No thromboprophylaxis (n = 179): 6.7 (3.1) Socks (n = 179): 2.2 (1.1); $p < 0.005$ Long flight (11–12 h): No thromboprophylaxis (n = 135): 8.1 (2.9) Socks: (n = 136): 2.6 (1.6); $p < 0.05$	Subjects on 7- to 8-h flights randomized separately from those on 11- to 12-h flights 5 of 7 DVTs in No Thromboprophylaxis group were proximal
Cesarone et al[717]/ 2003	No thromboprophylaxis Socks: Sigvaris Traveno below-knee stockings (ankle pressure, 12–18 mm Hg), starting 2–3 h before flight	Low to medium 7–12	No thromboprophylaxis: 169/190 (89) Socks: 172/186 (92)	On arrival	No thromboprophylaxis: 0/169 (0) Socks: 0/172 (0) RR: 0.98 (95% CI, 0.02–49.24)	No thromboprophylaxis: 0/169 (0) Socks: 0/172 (0) RR: 0.98 (95% CI, 0.02–49.24)	Short flight (7–8h): No thromboprophylaxis (n = 98): 6.4 (1.3) Socks: (n = 97): 2.4 (1.0); $p < 0.05$ Long flight (11–12 h): No thromboprophylaxis (n = 71): 8.9 (2.0) Socks: (n = 75): 2.56 (1.3); $p < 0.05$	Subjects in 7- to 8-h flights randomized separately from those in 11- to 12-h flights

(*Continued*)

Table 16—*Continued*

Study/Year	Interventions	Risk Group† Flight Duration, h	Patients Analyzed, No./Total (%)	Time to Screening, h	DVT, No./Total (%)	SVT, No./Total (%)	Edema Score, Mean (SD)‡	Comments
Cesarone et al[718]/ 2003	No thromboprophylaxis; Socks: Kendall below-knee travel socks (ankle pressure, 20–30 mm Hg), starting 2–3 h before flight	Low to medium 7–12	No thromboprophylaxis: 138/144 (96) Socks: 138/140 (99)	On arrival	No thromboprophylaxis: 2/138 (1) Socks: 0/138 (0) RR: 0.20 (95% CI, 0.01–4.13)	No thromboprophylaxis: 2/138 (1) Socks: 0/138 (0) RR: 0.2 (95% CI, 0.01- 4.13)	Short flight (7–8 h) No thromboprophylaxis: (n = 72): 6.9 (2) Socks: (n = 72): 2.3 (1); $p < 0.05$ Long flight (11–12 h) No thromboprophylaxis (n = 66): 7.9 (2) Socks: (n = 64): 3.3 (1.2); $p = 0.05$	Subjects in 7- to 8-h flights randomized separately from those in 11- to 12-h flights 2 of 2 DVTs in No-Thromboprophylaxis group were proximal
Belcaro et al[719]/ 2003	No thromboprophylaxis plus video Socks: Scholl below-knee flight socks (ankle pressure, 14–17 mm Hg), starting 3–4 h before flight plus video	High 11–13	No thromboprophylaxis: 102/114 (89) Socks: 103/110 (94)	On arrival	No thromboprophylaxis: 6/102 (6) Socks: 1/103 (1) RR: 0.17 (95% CI, 0.02–1.35)	No thromboprophylaxis: 0/102 (0) Socks: 0/103 (0) RR: 0.99 (95% CI, 0.02–49.44)	NR	5 of 6 DVTs in No-Thromboprophylaxis group were proximal
LMWH vs no thromboprophylaxis								
Cesarone et al[716]/ 2002	No thromboprophylaxis Enoxaparin, 1 mg/kg, 2–4 h before flight	High > 10	No thromboprophylaxis: 83/100 (83) Enoxaparin: 82/100 (82)	On arrival	No thromboprophylaxis: 4/83 (5) Enoxaparin: 0/82 (0) RR: 0.11 (95% CI, 0.00–2.06)	No thromboprophylaxis: 2/83 (2) Enoxaparin: 1/82 (1) RR: 0.51 (95% CI, 0.05–5.47)	NR	Weight-based LMWH dosing reduces feasibility
Aspirin vs no thromboprophylaxis								
Cesarone et al[716] 2002	No thromboprophylaxis Aspirin, 400 mg for 3 d, starting 12 h before flight	High > 10	No thromboprophylaxis: 83/100 (83) Aspirin: 84/100 (84)	On arrival	No thromboprophylaxis: 4/83 (5) Aspirin: 3/84 (4) RR: 0.74 (95% CI, 0.17–3.21)	No thromboprophylaxis: 2/83 (2) Aspirin: 3/84 (4) RR: 1.48 (95% CI, 0.25–8.64)	NR	

*SVT = superficial vein thrombosis; RR = relative risk; see Table 11 for expansion of abbreviations.

†Using the authors' definition of risk: generally, low risk = no thrombosis risk factors; high risk = one or more risk factors, including previous DVT, coagulation disorder, limited mobility, current or recent cancer, large varicose veins, or severe obesity.

‡Average level of edema score reported at end of flight. Edema score ranges from 0 (minimum) to 10 (maximum) edema.

limited mobility, severe obesity, or a thrombophilic disorder.[693,698,700–702,706,708–712] Among healthy volunteers, the activation of coagulation observed after an 8-h flight was greater in carriers of Factor V Leiden and in women taking oral contraceptives.[713] These findings support the observed increased VTE risk in travelers associated with thrombophilia and the use of oral contraceptives in case-control studies.[700,702] Particularly tall or short passengers may also have an increased thromboembolic risk.[702]

While the relative risk of VTE within the first 2 weeks after prolonged travel appears to be increased, the absolute risk is very low. Fifteen prospective studies[701,707,711,714–721] have enrolled subjects embarking on airline flights >4 h in duration to determine the incidence of DVT without thromboprophylaxis using screening venous ultrasound. The reported rates of asymptomatic DVT and asymptomatic proximal DVT among all 3,659 unprotected participants in the prospective studies were 2.0% and 0.6%, respectively. The pooled DVT rate was 1.1% among the 2,474 "low-risk" travelers,[701,707,711,714,715,717,718] and 3.9% among the 1,185 "high-risk" travelers.[714,716,719–721] Among prospective studies in which patients were screened for DVT using ultrasound, virtually all of the abnormalities were asymptomatic and confined to the calf veins. There are problems with the use of ultrasound to screen for DVT in low-risk patients. The accuracy and specificity of ultrasound in the detection of asymptomatic, predominantly calf DVT is less than for symptomatic thrombi or for asymptomatic proximal DVT. Furthermore, there is a potential for biased overcall because the interpretation of the test result is partially subjective. Finally, the relationship between asymptomatic calf vein thrombosis and clinically important thrombotic events is uncertain in this patient population.[695]

The symptomatic VTE rate within 30 days of a long-haul flight has been estimated to be approximately one in 2 million arriving passengers with a case fatality rate of only 2%.[722] In another study,[723] the risk of fatal PE associated with air travel >8 h was 1.3 per million people <60 years old.

We identified nine randomized clinical trials and a Cochrane review[711,714–721,724] of active thromboprophylaxis in long-distance air travelers (Tables 16, 17). All but one of these trials was conducted by a single group of investigators. Each of the studies used some form of ultrasound examination to screen for asymptomatic DVT. Unfortunately, all of these trials have major methodologic limitations that severely compromise their interpretation (Table 18, available in the online version of this article).

The use of various brands of below-knee GCS (providing 12 to 30 mm Hg compression at the ankle) was reported to lower the rate of asymptomatic DVT from 3.7% (46 of 1,245 control subjects) to 0.2% (2 of 1,239 stocking users) in six randomized trials.[711,714,715,717–719] Stockings were also reported to reduce postflight leg edema in each of the three trials in which this outcome was assessed.[715,717,718] In all of the stocking studies, the intervention was not blinded, while in five of the six trials an unvalidated DVT screening test was used by assessors who were not blinded to the intervention. One small study[716] found that a high dose of enoxaparin, 1 mg/kg, administered 2 to 4 h before travel appeared to eliminate DVT, while aspirin started 12 h before the flight and continued for 2 more days did not appear to be protective. There were no symptomatic DVT or PE in any of these trials, although there was no follow-up after the subjects left the airport in eight of the nine studies. External validation based on studies that are methodologically rigorous and are large enough to capture symptomatic outcomes is required before we can come to any firm conclusion about the benefits of any thromboprophylactic interventions in this patient group.

Table 17—*Summary of Thromboprophylaxis Interventions for Long-Distance Air Travel (Section 9.0)*

No. of Studies	No. of Patients With DVT/Total Patients (%)		Effect on DVT,* Risk Reduction (95% CI)	Quality
	Control	Interventions		
Compression stockings				
Six studies	46/1,245 (3.7)	2/1,239 (0.2)	0.09† (0.03-0.26)	Low
LMWH				
One study	4/83 (4.8)	0/82 (0)	0.11 (0.00-2.06)	Low
Aspirin				
One study	4/83 (4.8)	3/84 (3.6)	0.74 (0.17-3.21)	Low

*All metaanalysis results are based on random-effects models (more conservative), using Cochrane Collaboration Review Manager software (RevMan).

†Based on metaanalysis of five studies. One study[717] reported no cases of DVT in either the treatment (0/172) or control group (0/169) and was not included in the metaanalysis.

In summary, clinically important VTE is very uncommon in passengers returning from long flights, and almost all travelers with VTE have additional, overt risk factors for thrombosis. Although there are conflicting views about the use of thromboprophylaxis in travelers,[693–695,697,725–728] we believe that there is insufficient evidence to support the routine use of active thromboprophylaxis measures in any group of travelers. It is reasonable to advise passengers to reduce venous stasis and to avoid dehydration, although these measures have also not been assessed in clinical trials. Until further, methodologically appropriate studies are available, a decision about thromboprophylaxis for passengers who are believed to be at particularly high risk for VTE must be made on an individual basis, considering that the adverse effects of all active interventions may outweigh the benefit.

Recommendations: Long-Distance Travel

9.1. For travelers who are taking flights > 8 h, we recommend the following general measures: avoidance of constrictive clothing around the lower extremities or waist, maintenance of adequate hydration, and frequent calf muscle contraction (Grade 1C)**.**

9.2. For long-distance travelers with additional risk factors for VTE, we recommend the general measures listed above. If active thromboprophylaxis is considered because of a perceived high risk of VTE, we suggest the use of properly fitted, below-knee GCS, providing 15 to 30 mm Hg of pressure at the ankle (Grade 2C)**, or a single prophylactic dose of LMWH, injected prior to departure** (Grade 2C)**.**

9.3. For long-distance travelers, we recommend against the use of aspirin for VTE prevention (Grade 1B)**.**

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