Preventing venous thromboembolism in surgical patients

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Venous thromboembolism (VTE) is a common cause of postoperative morbidity and mortality that can be prevented effectively with well-established, hospital-based prevention strategies. VTE prophylaxis should be considered for all hospitalized patients, although not all surgical patients will ultimately receive it based on their risk factor profile. This article discusses the extent of VTE and provides guidance for appropriate pharmacologic and nonpharmacologic strategies for prophylaxis in surgical patients.

PREVENTION EFFORTS NEED TO BE INCREASED

Many cases of VTE, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), could be prevented by increasing efforts at prophylaxis. In a recent study of 2,726 patients with DVT diagnosed from 183 hospitals in the United States, only 42% received prophylaxis within 30 days before their diagnosis.[1]

Prophylaxis appears to be practiced more consistently by surgeons than by other specialists.[2] The incidence of fatal PE is less in surgical patients (< 0.6%) compared with hospitalized medical patients (3.3%).[3] In a series in Sweden, patients admitted for general surgery had a lower incidence of fatal PE than patients admitted for orthopedic surgery, infectious diseases, general medicine, or cancer.[4] The trends may reflect that strategies for prophylaxis were introduced more than 30 years sooner for surgical patients than for medical patients.[5]

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Disclosure: Dr. Michota reported that he has received grants from the Sanofi-Aventis and Bacchus Vascular corporations and is a consultant to the Sanofi-Aventis, Bacchus Vascular, and GlaxoSmithKline corporations.

Recommendations abound, requirements coming

Guidelines from the Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy in 2004 recommend that every hospital develop a formal strategy to prevent the complications of thromboembolism.[6] In addition, the Agency for Healthcare Research and Quality (AHRQ) lists appropriate prophylaxis against VTE for patients at risk as one of its top 10 safety practices,[7] and a similar recommendation has been made by the National Quality Forum.[8] Although recommendations for VTE/DVT prophylaxis have been promulgated by various organizations since 1986, fewer than one in 10 acute care hospitals has such a program.

The Centers for Medicare and Medicaid Services is expected to eventually require an appropriate prophylaxis strategy for VTE as part of public reporting, with federal financing of hospitals dependent on such a strategy being in place.

Asymptomatic thromboemboli are appropriate targets

Traditionally, clinically relevant thromboembolism (ie, likely to cause an acute, and possibly fatal, pulmonary embolism) has been defined as thrombi in the proximal system that cause symptoms. In contrast, asymptomatic distal venous thrombi, which are typically only discovered by ultrasonography or venography in research studies, are generally deemed clinically unimportant. These silent thromboemboli are often used as surrogate markers for clinically relevant thromboemboli, and meta-analyses of orthopedic trials have found that prevention of venographic clots mirrors a reduction in clinical events.[9]

The consequences of VTE are large

Each year, DVT develops in an estimated 2 million people worldwide, of whom about 600,000 develop a PE and 100,000 die.[10] About one third of patients who survive VTE develop venous stasis syndrome within 10 years.[11–13]

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SURGICAL PATIENTS AT HIGH RISK

Risk assessment models and scoring systems have been developed for determining who is at risk for venous stasis, endothelial damage, or hypercoagulation (Table 1).[14,15] Most hospitalized patients, whether medical or surgical patients, have at least one risk factor for DVT, with obesity being the most common, and many have multiple risk factors.[16]

In the absence of prophylaxis, rates of postoperative DVT are high and vary with the type of procedure. This risk is greatest in patients undergoing knee surgery (65%), followed by hip surgery (50%), neurosurgery (29%), general surgery (20%), gynecologic surgery (19%), and prostate surgery (11%). Without prophylaxis, surgery for hip fracture has the highest rate of fatal PE (5%).[6]

Such estimates have enabled the categorization of risk for developing DVT or PE in the absence of prophylaxis (Table 2).[17] In practice, however, relying on complicated risk stratification is probably less advisable than considering nearly all hospitalized patients who are sick, old, or having surgery as being at risk for developing thromboembolism. In general, patients who are undergoing minor same-day procedures and are ambulatory have a low risk, and patients who require a hospital stay of more than 1 to 2 days have a greater risk.

TABLE 1
Risk factors for venous stasis and endothelial damage[14,15]

Risk factors for venous stasis
Age > 40 yr
Immobilization
Varicose veins
Myocardial infarction
Congestive heart failure
Stroke
Paralysis
Spinal cord injury
Hyperviscosity syndromes
Polycythemia vera
Severe chronic obstructive pulmonary disease
Anesthesia
Repair or ligation of major venous injury
Risk factors for endothelial damage
Surgery (orthopedic, pelvic, neurologic, abdominal)
Prior deep vein thrombosis
Central venous access
Trauma

NONMEDICATION STRATEGIES FOR PROPHYLAXIS

Ambulation

Many regard ambulation as a preventive strategy, but it has never been tested as such. Studies in which aggressive ambulation has been encouraged have not included a nonambulating control group. Although ambulation is appropriate postoperative care, it should not be regarded as a sufficient strategy for DVT prophylaxis.

Compression stockings

The evidence to recommend the use of elastic or graded compression stockings as a prevention strategy is insufficient. Although stockings have been shown to prevent DVT compared with placebo,[18] the effect is only modest, and most studies have enrolled only low-risk patients. Another unresolved issue is whether thigh-high stockings are superior to calf-high stockings, as most studies combine both types.

Studies that show that compression stockings are helpful when combined with additional measures for prophylaxis are also not applicable to modern practice. They tend to be early studies that compared stockings with treatments such as aspirin or dextran that are no longer deemed sufficient today.

The best evidence for benefit with elastic stockings is as an adjunct to other methods of VTE prophylaxis following gynecologic surgery, especially for cancer.

Mechanical devices

Mechanical devices such as sequential compression devices improve venous flow. Compliance is a barrier to their use as indicated: to be effective, these devices need to be worn nearly 90% of the day.[19] In the surgical setting, mechanical devices should be placed on the patient before inducing anesthesia.

New small, portable devices offer continuous compression therapy, and if they prove successful may bring about a major advance in this strategy.

The 2004 ACCP guidelines recommend that mechanical devices be used primarily for prophylaxis of VTE in patients at high risk for bleeding.[6] This practice is especially applicable to specific surgical situations in which the use of prophylactic drugs has not been studied carefully, such as neurosurgery, complicated orthopedic spine surgery, and plastic surgery.

PHARMACOLOGIC PREVENTION STRATEGIES

Pharmacologic strategies entail the risk of bleeding, and although the drugs used for VTE prophylaxis

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TABLE 2
Levels of thromboembolic risk in surgical patients without prophylaxis

Risk level (examples)	Calf DVT, %	Proximal DVT, %	Clinical PE, %	Fatal PE, %
Low risk (minor surgery in patients < 40 yr with no additional risk factors)	2	0.4	0.2	0.002
Moderate risk (minor surgery in patients with additional risk factors; nonmajor surgery in patients aged 40–60 yr with no additional risk factors; major surgery in patients < 40 yr with no additional risk factors)	10–20	2–4	1–2	0.1–0.4
High risk (nonmajor surgery in patients > 60 yr or with additional risk factors; major surgery in patients > 40 yr or with additional risk factors)	20–40	4–8	2–4	0.4–1.0
Highest risk (major surgery in patients > 40 yr plus prior VTE, cancer, or molecular hypercoagulable state; hip or knee arthroplasty, hip fracture surgery; major trauma; spinal cord injury)	40–80	10–20	4–10	0.2–5

DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism
Adapted, with permission, from reference 17.

have been well assessed for safety, individual variation must be considered. Doses of drugs that are cleared by the kidneys (ie, low-molecular-weight heparins [LMWHs], fondaparinux, direct thrombin inhibitors, and other antithrombotic agents) should be determined only after taking into account the possibility of renal impairment, especially in elderly patients or those at high risk for bleeding.[6]

Aspirin: Controversies continue

The use of aspirin as prophylaxis against thromboembolism has become controversial. The 2004 ACCP guidelines recommend that aspirin not be used for VTE prophylaxis in any patient group.[6]

Two large studies show that aspirin reduces the risk of VTE. The Antiplatelet Trialists' Collaboration[20] conducted an overview of 53 trials that involved 8,400 patients undergoing general or orthopedic surgery who received an average of 2 weeks of antiplatelet therapy or control. Twenty-five percent of patients assigned to antiplatelet therapy developed DVT compared with 34% of controls (two-sided $P < .00001$), and 1.0% of patients allocated antiplatelet drugs developed PE vs 2.7% of controls (two-sided $P < .00001$).

In the Pulmonary Embolism Prevention (PEP) trial,[21] more than 17,000 patients who were undergoing surgery for hip fracture or elective hip or knee arthroplasty were randomized to at least 160 mg of aspirin for 35 days or no aspirin. Both groups continued to have access to prophylaxis strategies as recommended by their treating physicians. In the overall study population, the relative risk of PE or DVT was reduced by 34% ($P = .0003$) among aspirin recipients.

Among patients with hip fracture in the PEP trial, a subgroup that also received LMWH did not derive significant additional benefit from aspirin, although the hazard ratio for PE and symptomatic DVT was less than 1.0 among aspirin users. No significant benefit to aspirin was observed during the first postoperative week, a period during which the risk of thromboembolism may be greatest.

Patients in the PEP trial who underwent elective hip or knee arthroplasty did not benefit significantly from aspirin, but their absolute risk of thromboembolism was lower compared with the much larger group of patients with hip fracture. In addition, one third of the patients undergoing elective hip or knee arthroplasty received prophylaxis with LMWH, which may have masked a possible favorable effect of aspirin.

Often overlooked in the PEP data is the significant risk of bleeding with aspirin. The risks of gastrointestinal bleeding and wound bleeding in the PEP trial were higher in aspirin recipients. This risk of bleeding outweighed the benefit of a reduction in the risk of DVT events: for every symptomatic DVT

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TABLE 3
FDA-approved thromboembolic prophylaxis indications of available anticoagulants

Indication	Low-molecular-weight heparins			Fondaparinux	UFH
	Enoxaparin	Dalteparin	Tinzaparin		
Prevention of DVT in hip replacement	Yes	Yes	No	Yes	No
Extended DVT prophylaxis in hip replacement	Yes	Yes	No	No	No
Prevention of DVT in knee replacement	Yes	No	No	Yes	No
Prevention of DVT in abdominal surgery	Yes	Yes	No	Yes	No

DVT = deep vein thrombosis; UFH = unfractionated heparin

averted, an increase of one wound hemorrhage and 10 gastrointestinal hemorrhages was observed in patients assigned to aspirin.

Although aspirin may have a role for thromboembolic prophylaxis in patients with hip fracture, or as extended prophylaxis (beyond the first week following surgery), it offers no clear benefit for prophylaxis among patients undergoing hip or knee arthroplasty.

Unfractionated heparin and low-molecular-weight heparins

Both low-dose unfractionated heparin (UFH) and, more recently, LMWHs have been standard therapies for VTE prophylaxis in a wide range of surgical settings. As opposed to UFH, which must be given two or three times daily, LMWHs can be given once or twice daily because of their longer plasma half-lives. The anticoagulant response to LMWH is also more predictable than the response to UFH. For prophylactic use, neither UFH nor LMWH requires monitoring.

In a 1994 meta-analysis of 56 trials that compared various therapies (aspirin, dextran, warfarin, UFH, LMWH, and compression stockings) to prevent VTE following total hip replacement, all therapies except aspirin were found to reduce the risks of DVT and proximal venous thrombosis compared with controls, but only LMWH and stockings reduced the risk of PE.[22]

Vitamin K antagonists

In a 2004 meta-analysis, Mismetti et al[23] found that LMWH strategies were superior to vitamin K antagonists (eg, warfarin) for prophylaxis against VTE in patients undergoing major orthopedic surgery. LMWHs performed better than vitamin K antagonists in preventing total and proximal DVT. No significant difference was found between the two strategies in the prevention of clinical PE or death, or in rates of wound hematomas or major bleeding.

Although vitamin K antagonists such as warfarin are convenient to use because they are available in oral form, they are less effective than the newer anticoagulants and require titration to achieve and maintain a therapeutic level, defined as an international normalized ratio (INR) of 2.0 to 3.0. Furthermore, achieving a full therapeutic window takes a minimum of 72 hours, which means patients will not receive the benefit of prophylaxis for the first 3 or 4 days after surgery.

New medications

Fondaparinux is the first drug in a new class of synthetic inhibitors of factor Xa.[24,25] In four large phase 3 trials, fondaparinux was found to be equal or superior to LMWHs in preventing VTE in patients undergoing orthopedic surgery.[26–29]

In the setting of hip arthroplasty, an analysis of the aforementioned phase 3 studies of fondaparinux for thromboembolic prophylaxis demonstrated outcomes comparable to those achieved with LMWH, using efficacy endpoints established by the 2004 ACCP guidelines.[30] Using these same endpoints, fondaparinux was found to be superior as prophylaxis in hip fracture surgery and knee arthroplasty.

Bauer et al[29] randomized more than 1,000 patients undergoing knee arthroplasty to fondaparinux (2.5 mg/day) or LMWH (enoxaparin 30 mg twice daily) and found significantly more bleeding events in patients randomized to fondaparinux.

Table 3 profiles the prophylaxis indications approved by the US Food and Drug Administration for the various available heparin products and fondaparinux.

Appropriate timing and dosing is critical

There is often a gap in the rates of safety and efficacy when drugs are used in clinical trials as opposed to clinical practice. One cannot expect to achieve the same results unless the same protocols are followed,

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TABLE 4
Guidelines for thromboembolic prophylaxis in surgical patients[6]

Risk category	Prophylaxis strategy
Very low (for minor, same-day surgery)	Aggressive ambulation
Moderate (for gynecologic surgery in patients aged < 60 yr and laparoscopic procedures)	Elastic stockings, intermittent pneumatic compression boots, low-dose UFH (twice daily), or LMWH
High (for general surgery, colorectal surgery, gynecologic surgery in patients aged > 60 yr, urologic surgery)	Low-dose UFH (every 8 hours) or LMWH, with or without intermittent pneumatic compression boots
Very high (for orthopedic surgery, trauma, spinal cord injury, cancer surgery)	LMWH or warfarin or fondaparinux

UFH = unfractionated heparin; LMWH = low-molecular-weight heparin

both for dosing and for timing of administration.

For example, in clinical trials fondaparinux was given 6 to 8 hours after major joint replacement, but in practice in the United States it is usually initiated only on postoperative day 1. Similarly, LMWHs are usually initiated in general surgery patients (in the absence of neuraxial anesthesia) on postoperative day 1 even though their package inserts recommend initiation 2 hours before surgery.

OUTPATIENT EXTENDED PROPHYLAXIS

The evidence is now clear to support extended prophylaxis for patients following hip replacement, and programs should be established to ensure that extended prophylaxis in this setting becomes standard care.

Bergqvist et al[31] randomized 262 patients following total hip replacement to receive either LMWH for 30 days following surgery or LMWH inpatient prophylaxis followed by placebo. The incidences of both VTE and DVT were significantly reduced in patients who received extended prophylaxis compared with those who received hospital prophylaxis only.

Planes et al[32] studied 179 consecutive patients who had undergone total hip replacement, randomizing them to the LMWH enoxaparin (40 mg once daily) or placebo at hospital discharge 13 to 15 days after surgery. At day 21 after discharge, the rate of DVT was significantly lower in the enoxaparin group than in the placebo group (7.1% vs 19.3%; $P = .018$). The reduction in the risk of proximal DVT with extended prophylaxis was not statistically significant, although the study population may not have been large enough to detect a significant difference.

In a meta-analysis of nine studies that included nearly 4,000 patients, Eikelboom et al[33] found that extended prophylaxis after total hip or knee replacement significantly reduced the risk of symptomatic VTE. The incidence of minor bleeding events but not major bleeding events was increased with extended prophylaxis.

Hull et al[34] conducted a review of six double-blind randomized trials in which extended out-of-hospital LMWH prophylaxis was compared with placebo in patients who had undergone elective hip arthroplasty. The frequencies of DVT, proximal venous thrombosis, and symptomatic VTE were all reduced significantly with extended out-of-hospital prophylaxis.

Comp et al[35] randomized 873 patients following elective total hip or knee replacement to receive 4 weeks of enoxaparin (40 mg/day) or placebo and found that extended therapy reduced the risk of VTE in patients following hip replacement but produced no significant benefit for patients following knee replacement.

GUIDELINES FOR PROPHYLAXIS

Table 4 presents prophylaxis recommendations for surgical patients from the 2004 ACCP guidelines.[6] The higher the risk, the more reliance is placed upon pharmacologic methods for prophylaxis.

Because patients undergoing orthopedic surgery constitute a high-risk subgroup of surgical patients, guidelines for prophylaxis have been developed specifically for them (Table 5).[6] The guidelines recommend LMWH therapy of various durations depending on the type of orthopedic surgery.

SPECIAL ISSUES IN PROPHYLAXIS

Heparin-induced thrombocytopenia (HIT). Patients exposed to any heparin product may develop HIT antibodies if a second exposure occurs within 100 days. Although LMWH is less likely to stimulate antibody production than UFH, cross-reaction does occur. The section of the 2004 ACCP guidelines on HIT recommends establishing a baseline platelet count and monitoring levels during therapy.[36]

Neuraxial anesthesia, when used with anticoagulation, increases the risk of epidural hematoma.

Epidural hematoma had been a particular concern with fondaparinux, but a study by Eriksson et al[27]

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TABLE 5
Options for prophylaxis in orthopedic patients[6]

Hip replacement (prophylaxis for 30 days)
- Enoxaparin 30 mg every 12 hours
- Dalteparin 5,000 IU every 12 hours
- Warfarin (St. Francis method: target INR 2.0–3.0)
- Fondaparinux 2.5 mg daily

Knee replacement (prophylaxis for 7–14 days)
- Enoxaparin 30 mg every 12 hours
- Warfarin (St. Francis method: target INR 2.0–3.0)
- Fondaparinux 2.5 mg daily

Hip fracture
- Enoxaparin 40 mg daily
- Fondaparinux 2.5 mg daily

INR = international normalized ratio

TABLE 6
Recommendations on anticoagulant administration in patients undergoing neuraxial anesthesia[39]

Preoperative

Needle can be placed:
- 12 hours after a prophylactic dose of LMWH
- 24 hours after a treatment dose of LMWH

Other anticoagulants and platelet inhibitors contraindicated

Postoperative

Once-daily LMWH dosing
- First dose can be given 6–8 hours postoperatively
- Second dose given at least 24 hours after first dose
- Epidural catheter can be removed 12 hours after LMWH dose

Twice-daily LMWH dosing
- First dose should be given at least 24 hours postoperatively and 2 hours after removal of epidural catheter

LMWH = low-molecular-weight heparin

indicated that this risk is no greater than with LMWH. In this study, fondaparinux (2.5 mg/day) was compared with enoxaparin (40 mg/day) in more than 17,000 patients undergoing surgery for hip fracture, almost 70% of whom received neuraxial anesthesia; overall, no significant difference in clinically relevant bleeding was found between the fondaparinux and enoxaparin groups.

Some studies have specifically addressed risk factors for spinal hematoma following neuraxial anesthesia.[37,38] One of the biggest factors is poor communication between the anesthesia team, surgeons, medical consultants, and nurses. Ensuring that orders for timing medications are carried out properly can reduce the risk of spinal hematoma.

Guidelines issued in 2003 by the American Society of Regional Anesthesia specifically addressed timing of anticoagulant administration for neuraxial anesthesia (Table 6).[39] Some of the specific recommendations are avoiding needle placement for 24 hours after a full dose of LMWH and for 12 hours following the final prophylactic dose, waiting at least 2 hours to give LMWH after epidural catheter removal, and avoiding anticoagulants in patients who have had traumatic needle or catheter insertion.

Patients with a preexisting coagulopathy, such as from liver disease or another cause, are at a much greater risk of bleeding from anticoagulant prophylaxis. In some studies, patients with alcoholic cirrhosis were found to have a lower risk of developing DVT than patients with normal liver function.

When considering a drug-based strategy for a patient with a coagulopathy, first consider whether the patient would be a candidate for pharmacologic therapy or a filter should a clinical DVT develop. If a drug would be chosen to treat a clinical DVT, then a medication is appropriate for prophylaxis. If instead a filter would be the treatment of choice for a clinical DVT, then a mechanical device is probably best for prophylaxis.

Patients with mild to moderate thrombocytopenia are generally good candidates for pharmacologic prophylaxis, as they are at very high risk of DVT. If the cause of thrombocytopenia is unknown or if the platelet count drops suddenly, I recommend a mechanical device for prophylaxis.

SUMMARY

Hospital strategies to prevent VTE are important to reduce acute morbidity and mortality as well as the long-term consequences caused by venous stasis syndrome. Patients at low risk (eg, those who are ambulatory or undergoing a same-day procedure) or who are at high risk for bleeding (including those with severe renal impairment) are candidates for nonpharmacologic strategies for thromboembolic prophylaxis. Mechanical devices are effective if used appropriately, but compliance is a challenge. Patients who require a hospital stay of more than a day or two should receive a medication-based strategy, preferably using LMWH or fondaparinux. Patients undergoing hip replacement should receive extended prophylaxis with LMWH.

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