Prevention of venous thromboembolism in medical and surgical patients

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ABSTRACT

Prophylaxis against venous thromboembolism (VTE) should be considered in all hospitalized patients, as VTE is a significant cause of morbidity and mortality in the hospital. Although VTE risk is greatest and VTE prophylaxis is more established in surgical patients, most hospitalized medical patients have one or more risk factors for VTE and are candidates for prophylaxis. Selection of a prophylaxis strategy should be guided by the patient's risk factors for VTE and the risks associated with prophylaxis options. This review surveys evidence and recommendations for various VTE prophylaxis methods in medical and surgical patients.

The importance of venous thromboembolism (VTE) as a preventable cause of morbidity and mortality in hospitalized patients cannot be overstated. Although not all patients in the hospital need to receive prophylaxis against VTE, prophylaxis needs to be considered in all hospitalized patients. While recent years have seen significant strides in the use of VTE prophylaxis in many hospital settings, thanks in part to the work of hospitalists,[1] many patients—particularly medical patients—still do not receive adequate prophylaxis in community or tertiary care settings.

This review surveys pharmacologic and nonpharmacologic methods of prophylaxis against VTE (including pulmonary embolism [PE] and deep vein thrombosis [DVT]) in surgical and medical patients. It also discusses considerations for prophylaxis in special surgical situations and identifies general strategies for optimizing VTE prophylaxis.

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RELATIONSHIPS MATTER IN THE SURGICAL SETTING

One of the keys to successful VTE prophylaxis in surgical patients is a close working relationship among the surgeon, the anesthesiologist, nurses, and medical consultants. Because evidence and guidelines support many methods of prophylaxis in a variety of surgical settings, individual practice preferences need to be considered and respected. If a medical consultant recommends a form of prophylaxis that the surgeon is not comfortable with or the anesthesiologist is not aware of, complications or management conflicts can occur.

NONPHARMACOLOGIC PROPHYLAXIS IN SURGICAL PATIENTS

Aggressive postoperative ambulation and physical therapy should be an integral part of all postsurgical management as well as of a global approach to VTE prophylaxis. Although there are scant data from randomized trials showing that early ambulation and physical therapy reduce the risk of VTE, the nonambulatory postoperative period is a high-risk time for thrombosis development and venous stasis. Physical therapists, nurses, and nurses' aides should all work together to get patients out of bed and ambulating as soon as possible. Moreover, early postoperative ambulation helps to reduce length of stay in the hospital, and optimizing mobility prior to discharge is important to patients.[2] For surgical patients considered to be at low risk (ie, < 40 years of age with no VTE risk factors), early ambulation is adequate VTE prophylaxis.

Elastic stockings have been shown to be effective in reducing VTE risk by reducing venous stasis through provision of compression gradients on the legs.[3] Stockings should be applied before surgery, continued throughout the hospitalization, and continued into the

TABLE 1
Summary of options for prophylaxis of venous thromboembolism

	Nonpharmacologic methods			Pharmacologic methods				
	Early ambulation	Elastic stockings	SCD	Aspirin	LDUFH	Warfarin	LMWH	Pentasaccharide
General surgery								
Low risk	A	A	A					
Moderate risk	X	B	B		A*		A	
High risk	X	X	B		A**		A	
Very high risk	X	X	B§		A**+		A+	
Gynecologic surgery								
Low risk	A							
Moderate risk	X	X	B		A*		B	
High risk	X	X	A		A** or +		A or +	
Urologic surgery								
Low risk	A							
Moderate risk	X	B	B		A* or **		B	
High risk	X	X	B§		A**+		A+	
Orthopedic surgery								
Hip fracture#	X	X	B§	X	B** or +	B or +	B or +	A
Total hip arthroplasty#	X	X	B§	X		A or +	A or +	A
Total knee arthroplasty	X	X	B	X		A or +	A or +	A
Neurosurgery	X	X	A or +		B+		B+	
Trauma	X	B or +	B or +				A	
Medical patients								
Low risk	A							
High risk	X		B§		A* or **		A	

Recommendation grades and notes
A = acceptable for solo prophylaxis with highest level of evidence
B = acceptable as an alternative method of prophylaxis with less evidence than grade A
+ = combine with a nonpharmacologic method (ie, elastic stockings, SCD, or both)
X = beneficial but inadequate for solo prophylaxis
* LDUFH at 5,000 U twice daily
** LDUFH at 5,000 U three times daily
§ If pharmacologic prophylaxis is contraindicated
# These patients should be considered for extended prophylaxis (ie, 28–35 days postoperatively).
If no grade is provided, then that form of prophylaxis is not indicated either due to low risk of VTE or because its efficacy for that condition is not established.

Abbreviations/identifications
SCD = sequential compression device
LDUFH = low-dose unfractionated heparin
LMWH = low-molecular-weight heparins:
- enoxaparin 40 mg/day subcutaneously (or 30 mg twice daily for total knee arthroplasty)
- dalteparin 5,000 IU/day subcutaneously

Pentasaccharide = fondaparinux 2.5 mg once daily subcutaneously

Risk definitions for surgical patients
General surgery: Low risk = minor procedure, <40 years of age, and no risk factors for venous thromboembolism (VTE). Moderate risk = minor procedure but with VTE risk factors; *or* minor procedure between ages 40 and 60 with no additional risk factors; *or* major procedure but <40 years of age. High risk = minor procedure and over age 60 or other VTE risk factors; *or* major procedure and over age 40 or with additional risk factors. Very high risk = major procedure with multiple VTE risk factors.

Gynecologic surgery: Low risk = brief procedure for benign disease. Moderate risk = major procedure for benign disease without additional VTE risk factors. High risk = extensive procedure for malignancy.

Urologic surgery: Low risk = transurethral resection of the prostate or other low-risk urologic procedure. Moderate risk = major open urologic procedure. High risk = major procedure with additional VTE risk factors.

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posthospitalization period if ambulation remains limited. Although effective, elastic stockings are not without risk. If not fitted properly, they can produce a reverse pressure gradient and increase the risk of VTE, as has been shown in orthopedic patients.[4] For patients with very large legs or other reasons why stockings cannot be fitted properly, they should be avoided. Finally, elastic stockings likely have a synergistic effect when used with other methods of VTE prophylaxis, although data supporting this are lacking.

Pneumatic compression devices, also referred to as sequential compression devices (SCDs) or intermittent pneumatic compression devices, are available as foot pumps and in calf or thigh lengths. These devices reduce the risk of VTE by squeezing the venous system (ie, plantar plexus, calf and thigh veins) to combat venous stasis, and they may promote the clearance of prothrombotic factors from the vasculature.[5]

SCDs have been studied in many surgical settings and are considered by the American College of Chest Physicians in their guidelines on antithrombotic therapy[6] as a 1A recommendation (highest level of evi-

dence) for patients undergoing gynecologic surgery for malignancy or intracranial neurosurgery **(Table 1)**. SCDs are also the method of choice when pharmacologic prophylaxis is contraindicated because of bleeding risk or other factors. Emerging data also support the use of SCDs as adjunctive prophylaxis with pharmacologic methods, such as in neurosurgical procedures, in which SCDs can be started preoperatively and continued until unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) therapy can be initiated.[7] They have also been shown to be effective in total hip and knee replacement when used in conjunction with a LMWH, significantly reducing thrombosis rates relative to a LMWH alone.[8]

Comparisons between foot pumps and calf or thigh devices are limited, but one study in trauma patients showed a higher rate of DVT in patients randomized to foot pumps.[9] Although foot pumps offer slightly greater ease of use and comfort, they may not be as effective as calf or thigh devices.

A fundamental limitation of SCDs is that they cannot be worn while the patient is ambulatory and they must be worn at all times when the patient is in bed to be maximally effective. While use of up to 15 hours per day has been achieved in clinical trials, this is unlikely in clinical practice.[10] If SCDs are to be used, nurses must be able to keep the SCDs on patients when they are in bed while still encouraging ambulation as much as possible. As patients become more ambulatory, the clinical utility of SCDs declines.

PHARMACOLOGIC PROPHYLAXIS IN SURGICAL PATIENTS

Aspirin. The routine use of aspirin alone as VTE prophylaxis is not recommended.[6] However, aspirin (160 mg daily) was shown to reduce the risk of PE following hip fracture surgery when added to routine prophylaxis, resulting in a 58% relative reduction in fatal PE compared with placebo (from 1.2% to 0.7%).[11] Use of aspirin in the postoperative setting, especially in patients with cardiovascular risks who may benefit from it, should be considered.

Low-dose UFH has been a standard and well-accepted mode of VTE prophylaxis in a wide range of surgical procedures for decades.[12] In moderate-risk surgical patients, 5,000 U twice daily is effective, but in higher-risk patients, the dosage should be 5,000 U three times daily.

LMWHs are replacing UFH for prophylaxis in most surgical settings, owing to their improved efficacy, especially in orthopedic patients,[13] and their modestly lower rates of bleeding complications,[13–15] reduced incidence of heparin-induced thrombocytopenia,[15,16] and convenient once-daily dosing.

Two important considerations influence LMWH dosing for VTE prophylaxis: timing (preoperative vs postoperative) and frequency (once vs twice daily). For general surgical patients, initiating a LMWH 2 hours before surgery is recommended. For orthopedic surgical patients, the timing of dosing has been debated because thrombus formation begins intraoperatively, but preoperative dosing is associated with increased bleeding complications. A recent pooled analysis found no reduction in VTE rates with preoperative dosing for elective hip surgery and suggested that it may be associated with an increase in postoperative bleeding.[17] For this reason, and because of issues related to neuraxial anesthesia, postoperative dosing is often preferred.

SCDs, elastic stockings, or both are often used intraoperatively until postoperative LMWH dosing can begin, usually 12 to 24 hours after surgery, provided that adequate hemostasis has been established. For other high-risk bleeding conditions (eg, neurosurgery, multiple trauma), postoperative initiation is indicated once the bleeding risk is minimized, with concomitant use of SCDs and/or elastic stockings.

Once-daily dosing of LMWHs has replaced twice-daily dosing for most indications, with the exception of total knee replacement. In general, once-daily dosing is more convenient, has equal efficacy, and costs one third less.

Vitamin K antagonists such as warfarin are often used in orthopedic surgery; they were the most common form of prophylaxis for total hip and knee arthroplasty in a recent survey of orthopedic surgeons.[18] Warfarin is typically initiated immediately after surgery to achieve an international normalized ratio (INR) of 2.0 to 3.0, often in conjunction with SCDs and/or elastic stockings. Though it can be started at a low dose 10 to 14 days before surgery and then increased postoperatively to achieve an INR of 2.0 to 3.0, this is less frequently done, and reportedly only in higher-risk patients.[18] Because warfarin takes up to 5 days to achieve its maximal antithrombotic effect, it may leave patients relatively unprotected compared with immediately acting anticoagulants such as LMWH or nonpharmacologic methods. This risk was demonstrated in a recent case-control study of patients undergoing lower extremity total joint arthroplasty in which prophylactic warfarin monotherapy initiated postoperatively had an odds ratio of 11.3 for proximal VTE compared with postoperative enoxaparin.[19]

Besides orthopedic surgery, there are no other well-studied indications for warfarin for VTE prophylaxis in surgical patients.

Fondaparinux is a pentasaccharide approved for VTE prophylaxis in total hip or knee arthroplasty and hip fracture surgery. It was shown to be more efficacious than the LMWH enoxaparin in a meta-analysis of orthopedic trials, though the risk of major bleeding was increased.[20] Fondaparinux has 100% bioavailability when given subcutaneously, a rapid onset of effect, a long half-life allowing for once-daily dosing, and no association with HIT. In spite of these potential benefits, it has not been widely adopted, in part because of concerns over increased bleeding rates,[21] lack of an antidote, acquisition cost, risks associated with neuraxial anesthesia, and delayed clearance in patients with renal impairment.

The oral direct thrombin inhibitor ximelagatran has been approved in some European nations for VTE prophylaxis in patients undergoing orthopedic surgery, but it has not been approved in the United States because of safety concerns.[22] Oral direct thrombin inhibitors hold considerable promise for VTE prophylaxis and other indications but are not likely to be available in the United States in the near future.

SPECIAL CONSIDERATIONS IN SURGICAL SETTINGS

Bariatric surgery for weight reduction is increasing in popularity. Because this surgery is extensive and obesity is an independent risk factor for VTE, patients undergoing gastric bypass surgery are at high risk for VTE and require aggressive prophylaxis. In an observational study of 481 patients undergoing bariatric surgery, enoxaparin was associated with fewer postoperative DVT complications when dosed at 40 mg twice daily than at 30 mg twice daily.[23] All patients also received elastic stockings and SCDs. This study supports the use of a higher prophylactic dose of enoxaparin in bariatric surgery, but further studies are needed.

Neuraxial anesthesia, when used concomitantly with anticoagulation, increases the risk of epidural hematomas and subsequent spinal cord injury. Good communication among the anesthesia team, surgeons, medical consultants, and nurses is critical. Guidelines for the use of neuraxial anesthesia when anticoagulation is indicated have been developed by the American Society of Regional Anesthesia and Pain Medicine.[24] Specific recommendations include avoiding needle placement for 24 hours after a full dose of LMWH and for 12 hours after the last prophylactic dose of LMWH, waiting at least 2 hours to give LMWH after removal of an epidural catheter, and avoiding anticoagulants in patients who have had traumatic needle or catheter insertion.

Inferior vena cava (IVC) filters are not recommended for primary prophylaxis in any surgical setting.[6] An evaluation of 2,868 consecutive trauma patients, 10% of whom were considered to be at high risk for VTE, found the use of prophylactic IVC filters to be unjustified.[25] However, a temporary IVC filter should be considered for PE prevention in the presence of DVT in patients who cannot receive anticoagulant therapy or in those who have received less than 6 weeks of anticoagulant therapy. Temporary filters can be retrieved within 2 to 3 weeks, allowing patients to be safely started on anticoagulation without requiring lifelong anticoagulation for an IVC filter. Alternatively, the filter can be left in permanently. Temporary IVC filters have been studied as primary prophylaxis in high-risk trauma patients,[26] but not in randomized trials comparing them with the current standard of care (SCDs combined with a LMWH once bleeding risk is minimized).

Routine screening duplex ultrasonography of the lower extremities is also not recommended as part of routine prophylaxis in surgical patients.[6] It has been studied most extensively in orthopedic surgery, but it is not cost-effective, does not reduce symptomatic VTE, and is limited by considerable interobserver variability.

The duration of VTE prophylaxis in surgical patients is controversial. All surgical patients except those at low thromboembolic risk should receive, at minimum, VTE prophylaxis while hospitalized and nonambulatory. High-risk patients and those undergoing orthopedic surgery should receive prophylaxis for a minimum of 7 to 10 days. The highest-risk patients, such as those undergoing hip arthroplasty or hip fracture surgery, deserve consideration for longer postdischarge prophylaxis. One month of VTE prophylaxis with a LMWH, warfarin, or fondaparinux (all of which can be given on an outpatient basis) reduces VTE risk relative to in-hospital prophylaxis.[6] Moreover, a recent study of patients undergoing surgery for abdominal or pelvic cancer showed that 4 weeks of LMWH therapy reduced the rate of venographically documented VTE compared with 1 week of LMWH therapy.[27]

VTE IN MEDICAL PATIENTS: WHAT IS THE RISK?

Hospitalized medical patients are at increased risk for VTE because of immobility, stasis, and the potential release of procoagulant mediators during acute illness,[28] though the risk is lower than in patients hospitalized for surgery.[29] However, because medical admissions are more common than surgical admissions, it is estimated that hospitalization for medical illness accounts for a greater number of fatal pulmonary emboli than does hospitalization for surgery, and that hospital admissions for medical illness and for surgery account for similar proportions of all VTE events (22% and 24%, respectively).[30]

Most studies of VTE prophylaxis in medical

patients have excluded patients with no risk factors for VTE and thus give a reasonable estimate of the VTE rate for the target population in clinical practice. These trials have found the incidence of asymptomatic VTE (based on screening tests) in the absence of prophylaxis to be approximately 15%.[31,32]

Asymptomatic vs symptomatic VTE

The asymptomatic event rate, however, appreciably overestimates the incidence of potentially clinically significant events. Researchers from a university hospital in the Netherlands assessed the rate of symptomatic VTE among all medical patients admitted to the hospital from 1992 through 1996, reporting a hospital-acquired VTE rate of 0.6% (39/6,332).[33] Of the 39 patients with a symptomatic VTE event, 24 (61%) had a malignancy. Most patients did not receive prophylaxis; those who did received a regimen—enoxaparin 20 mg once daily—later shown to be ineffective.[31]

In a randomized study of 11,693 patients aged 55 years or older admitted to six hospitals in Sweden, Gardlund and the Heparin Prophylaxis Study Group[34] reported a 2.0% incidence of symptomatic VTE in patients randomized to no prophylaxis. A large cross-sectional study of patients admitted to the medical wards of a university hospital in France found the incidence of hospital-acquired VTE to be 1.4%.[35] A higher VTE incidence was noted among patients receiving prophylaxis with UFH than those not receiving prophylaxis (3.5% vs 0.8%), indicating that UFH was given primarily to patients deemed by the treating physician to be at increased risk for VTE.

Based on these studies, the rate of *symptomatic* VTE *without* prophylaxis is estimated at 0.5% to 1.0% for low-risk general medical inpatients and at 2.0% to 3.0% for patients with VTE risk factors. This suggests that:

- There is a subgroup of general medical inpatients without risk factors who are at very low risk of a clinical event and for whom VTE prophylaxis is unwarranted.
- Patients with VTE risk factors have a small but clinically important risk of symptomatic events and are expected to gain a substantial benefit from prophylaxis.

The VTE risk factors listed in major guidelines have been derived largely from data in surgical settings, although a limited number of studies examining general medical inpatients have reported factors associated with an increased incidence of VTE in medical patients **(Table 2)**.[33,35–37]

TABLE 2
Risk factors for hospital-acquired VTE

Active cancer[33]	Immobility[35]/paralysis
Acute ischemic stroke	Inflammatory bowel disease
Acute MI	Nephrotic syndrome
Age > 60 years[35]	Obesity
Central venous catheter	Prior ischemic stroke with paresis
Congestive heart failure[36]	Prior VTE[35,37]
Estrogen therapy	Thrombophilia
	Varicose veins

MI = myocardial infarction; VTE = venous thromboembolism

PROPHYLAXIS IN MEDICAL PATIENTS

Nonpharmacologic prophylaxis

We are unaware of any published randomized trials examining mechanical methods of prophylaxis, including elastic stockings and SCDs, for hospitalized general medical patients. These methods have been shown, however, to reduce the incidence of VTE in patients with acute stroke[38] and acute myocardial infarction.[39]

Pharmacologic prophylaxis

UFH and LMWH. Several studies have investigated the use of subcutaneous UFH and LMWH for general medical inpatients.

A large randomized study of patients aged 40 years or older admitted to medical wards of an Israeli hospital showed UFH (5,000 U twice daily) to significantly reduce mortality compared with no prophylaxis (8% vs 11%), although the study design was potentially limited by a lack of investigator blinding to patients' treatment assignment.[40] In contrast, Gardlund and the Heparin Prophylaxis Study Group[34] found that UFH did not reduce mortality or rates of autopsy-proven fatal PE compared with no prophylaxis among patients admitted to infectious disease wards. Additionally, a study of 2,472 general medical inpatients randomized to LMWH or to placebo found no difference in mortality.[15]

The large and rigorous study by Gardlund and the Heparin Prophylaxis Study Group[34] is the only trial we have identified that randomized patients to either prophylaxis or no prophylaxis, did not screen for asymptomatic events, and examined symptomatic VTE as an end point. It found that UFH (5,000 U twice daily) reduced the incidence of symptomatic VTE to 1.2% from 2.0% with no prophylaxis, a statistically significant difference.

Several trials have examined the efficacy of UFH and LMWHs for the reduction of asymptomatic events in medical patients. A small randomized trial found that UFH reduced the incidence of DVT from 26% to 4% compared with no prophylaxis.[32] Two larger randomized trials[31,41] found prophylaxis with LMWH to

reduce VTE rates by two thirds compared with placebo (from 15% to 5%[31] and from 9% to 3%[41]). The large randomized PREVENT study[42] found that prophylaxis with the LMWH dalteparin reduced the VTE rate to 2.8%, vs 5.0% with placebo. These lower VTE rates in the PREVENT study relative to other trials may have been due to this study's use of ultrasonography (rather than venography) as a screening test.

Several trials examining asymptomatic VTE have directly compared prophylactic UFH and LMWH; most used three-times-daily dosing for UFH. None of these studies in general medical patients found a significant difference in VTE incidence between the two prophylactic therapies. One study examining patients after acute stroke did find a lower incidence of VTE with LMWH (20%) than with UFH (35%).[43] In contrast, another trial found twice-daily UFH and enoxaparin (20 mg once daily) to have similar efficacy in VTE prevention among elderly hospitalized medical patients.[15] Despite the higher drug-acquisition cost of LMWHs, they are considered more cost-effective than UFH for prophylaxis in medical patients because of their lower complication rates.[44]

Newer and investigational anticoagulants. Newer anticoagulants that may enhance the prevention and treatment of VTE in medical patients are under investigation. We are unaware of published trials examining the efficacy or safety of the investigational oral direct thrombin inhibitor ximelagatran for prevention of VTE in medical inpatients. However, fondaparinux, which has been approved in the United States for VTE prophylaxis in orthopedic surgery patients (as well as for VTE treatment), has been evaluated in the ARTEMIS study[45] of hospitalized medical patients aged 60 years or older who were expected to be at bed rest for at least 4 days. In a preliminary report,[45] fondaparinux was associated with a 51% relative risk reduction for asymptomatic VTE compared with placebo (incidence of 5.6% vs 10.5%).

The bottom line on prophylaxis in medical patients

Although mortality reduction from VTE prophylaxis has not been definitively established in medical patients, prevention of symptomatic and asymptomatic DVT is an important goal of prophylaxis in view of the substantial morbidity associated with DVT, including leg pain and swelling due to the acute thrombosis, risk of PE, and development of the postthrombotic syndrome (PTS). PTS is a common sequela of DVT, occurring in up to 30% of patients.[46] PTS results from incomplete venous recanalization and destruction of valve cusps in the deep veins of the leg, leading to chronic leg edema, pain, induration, and, when severe, venous ulceration.

Most hospitalized medical patients have one or more risk factors for VTE **(Table 2)** and are at moderate (2.0% to 3.0%) risk of a symptomatic event. Since prophylaxis is often overlooked,[47] it should be considered at the time of admission for all hospitalized patients, and administered to those with risk factors for VTE who are nonambulatory. Prophylaxis may be unnecessary for medical patients without any risk factors, as the incidence of symptomatic VTE in this population is low (< 1.0%). Both UFH and LMWH are efficacious in preventing VTE in hospitalized medical patients, although there is no established reduction in mortality. Neither therapy has been proven superior to the other in this population. Data from other settings suggest that mechanical methods of prophylaxis are likely to be effective for patients who cannot tolerate anticoagulants because of bleeding risk.

FUTURE DIRECTIONS

Although VTE prophylaxis in surgical and medical patients is improving, VTE remains a significant patient safety concern and is at the center of efforts by the federal Agency for Healthcare Research and Quality to improve the care of hospitalized patients.[48] Systems-based approaches, including use of automated computer prompts and admission protocols, are more likely to lead to routine prophylaxis than is the sporadic implementation often seen in current practice. Ensuring adequate VTE prophylaxis involves a concerted effort of all interested parties, including physicians, nurses, patients, hospitals, and health systems.[1]

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