



DVT prophylaxis and anticoagulation in the surgical patient

Peter Kaboli, MD, MS^a,
Mark C. Henderson, MD, FACP^b,
Richard H. White, MD, FACP^{b,*}

^a*Division of General Medicine, University of Iowa Hospitals and Clinics,
200 Hawkins Drive, Iowa City, IA 52242, USA*

^b*Division of General Medicine, University of California—Davis, 4150 V Street/Suite 2400,
PSSB, Sacramento, CA 95817, USA*

To complete a comprehensive preoperative medical assessment prior to major surgery, the consultant must invariably address the issue of the prevention of postoperative thromboembolic complications. Venous thromboembolism (VTE), a term encompassing deep vein thrombosis and pulmonary embolism (PE), is one of the most common postoperative complications. In a study from Olmsted County, Minnesota, surgery was associated with an over twentyfold increase in the odds of being diagnosed with VTE [1]. In an analysis of over 2 million inpatient surgical procedures performed in California, 0.8% of cases were diagnosed with symptomatic VTE, 44% occurring during the hospitalization for surgery and the remainder within the first 3 months after surgery [2].

Overview of thromboembolism after surgery

Scope of the problem

Certain procedures, such as craniotomy for brain malignancy, are associated with a 3-month incidence of symptomatic VTE as high as 7.5% [3]. Because of the absence of reliable autopsy data, it is not clear how often fatal PE occurs after surgery. In a comprehensive study of patients undergoing total hip arthroplasty, Seagroatt estimated an excess of 0.7 deaths from PE for every 1000 operations during the first 90 days after surgery,

* Corresponding author.

E-mail address: rhwhite@ucdavis.edu (R.H. White).

compared with the ensuing 9-month period [4]. This compares with an estimated excess of 3.2 deaths/1000 from ischemic heart disease, 0.7 deaths/1000 from stroke, and an overall excess mortality of 6.5 deaths/1000 total hip operations. Thus, PE may account for 10% of all postoperative deaths following total hip arthroplasty. Fatal PE accounts for approximately 3–4% of all symptomatic VTE events [5]. For high-risk surgical procedures such as total hip arthroplasty, this translates to a rate of death caused by PE approximately 0.18–0.36% [6]. As discussed below, additional risk factors such as presence of a cancer, advanced age, and prolonged immobilization are likely to be associated with an increase in the incidence of fatal PE.

Interpreting the literature

The incidence of asymptomatic VTE is dramatically higher than that of symptomatic VTE, with asymptomatic VTE developing in 20–25% of patients after general surgery and 45–60% after orthopedic surgery involving the hip or knee [7]. Most clinical trials of thromboprophylaxis have evaluated a surrogate end point, venographic evidence of thrombosis, or asymptomatic VTE, primarily because the low incidence of symptomatic VTE events makes the sheer size and cost of conducting a sufficiently powered study prohibitive. Unfortunately, the precise relationship between the surrogate outcome of asymptomatic VTE and symptomatic VTE is not clear [8]. Most asymptomatic clots lyse spontaneously without treatment and they do not cause postphlebotic stasis or ulceration [9]. Fewer than one in eight venographically defined clots progresses to symptomatic VTE, although a somewhat higher proportion of proximal deep venous system clots become symptomatic compared with calf venous clots [7]. Relying on a one time “snapshot” of thrombosis using venography does not reflect the dynamic nature of clot formation and dissolution, a process that varies over time. For example, in one study of patients who had a negative venogram 7–10 days after total hip arthroplasty, 20% had a demonstrable clot 21 days later [10]. Unfortunately, the vast majority of thromboprophylaxis studies assess efficacy based on the incidence of asymptomatic VTE at one point in time [7]. The most valuable studies of thromboprophylaxis are those that demonstrate a significant reduction in hard end points such as incidence of symptomatic VTE or fatal PE.

Implementing an optimal thromboprophylaxis regimen requires simultaneous assessment of the risks of VTE and the risks of bleeding. After combining these estimates with evidence-based knowledge regarding the efficacy and safety of various thromboprophylaxis modalities, one can make an appropriate treatment recommendation. If any recommendations are going to be followed, however, the consulting internist must also establish a working relationship with the surgeon and reach an agreement about: (1) the relative risks of bleeding and thrombosis for each prophylaxis regimen, and (2) the optimal duration of prophylaxis.

Assessing the risk of VTE

The risk of symptomatic VTE is directly related to: (1) the type of surgery being performed, (2) presence of other risk factors for VTE, (3) duration and extent of postoperative immobilization, and (4) use or nonuse of specific thromboprophylactic measures. Risk factors that have been shown to affect the incidence of postoperative venous VTE are outlined in Table 1.

Age

Essentially, all epidemiologic studies have shown that advancing age is a risk factor for incident VTE events, including postoperative VTE [1,11]. The incidence of VTE developing after surgery among patients less than 40 years old is quite low but rises linearly with age [12].

Table 1
Risk factors associated with venous thromboembolism (VTE)

Risk factor	Effect	References
Age	Exponential increase in risk	[1,11,143]
Ethnicity	Asians have two- to three fold lower risk	[13]
Type of surgery	Major associated with up to six-fold higher risk ^a	[2]
Trauma	Increased risk with pelvic, femur, leg fractures	[144,145]
Previous VTE	Three- to fourfold higher risk	[2]
Varicosities or venous stasis changes	Increased risk	
Presence of a malignancy	Twofold higher risk	[18,2]
Obesity	Increase with BMI	[5,19]
Left or right sided heart failure, COPD	Higher risk	[21,146]
Thrombophilic disorder	Increased, but absolute risk low	[16,17,147]
Stroke, immobilization	Increased	[148–151]
Hematologic disorders: Polycythemia vera, essential thrombocytosis, paroxysmal nocturnal hemoglobinuria, others	Increased	
Medical disorders: nephrotic syndrome, inflammatory bowel disease, systemic lupus erythematosus, MI	Increased, unknown magnitude	[152,153]
Pregnancy or estrogen use	Some increase in risk	

^a Major: neurosurgery, abdominal, thoracic, vascular, or orthopedic surgery on lower extremity.

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; VTE, venous thromboembolism.

Race/ethnicity

Studies have shown that individuals with Asian/South Pacific Islander ethnicity have an approximately threefold lower risk of VTE, and this is also true for postoperative VTE [13]. Whether this simply reflects the lower prevalence of factor V Leiden and other thrombophilic disorders in this population is not known [14]. African Americans have a slightly higher relative risk of developing VTE compared with Caucasians, whereas Latinos appear to have a modestly lower risk of developing VTE [13].

Surgical procedure

The particular surgical procedure is perhaps the strongest risk factor for developing VTE. We recently conducted a study of patients undergoing elective and urgent surgery in California [2]. Neurosurgery involving entry into brain or meningeal tissue and orthopedic surgery involving the hip (total or hemi-arthroplasty) was associated with the highest incidence of symptomatic VTE on the order of 6% and 3%, respectively. This compares with an incidence of approximately 0.3% following laparoscopic cholecystectomy or appendectomy. Other procedures associated with a substantially increased risk of VTE include major vascular surgery involving the aorta, iliac or arteries of the leg, general surgery involving removal of a portion of the small or large bowel, radical cystectomy, gastric bypass for obesity, and kidney transplantation. Surgical procedures associated with a very low risk of VTE include radical neck dissection, inguinal hernia repair, laparoscopic cholecystectomy, transurethral resection of the prostate, and thyroid or parathyroid surgery.

Prior thromboembolism

Prior VTE, particularly within the past 6 months, is a major risk factor for developing postoperative VTE, with an over three-fold higher relative risk [2]. This increased risk may reflect a higher propensity for a clot to form because of endothelial damage of the veins, or the presence of one or more underlying genetic or acquired thrombophilic conditions.

Presence of a thrombophilic disorder

The interplay between thrombophilic disorders and postoperative VTE has been clarified in recent years. In a large study of asymptomatic carriers of either factor V Leiden or activated protein C resistance, the absolute risk of manifesting VTE by age 65 years was small, on the order of 5–10%, but the relative risk of developing VTE was increased compared with noncarriers (relative risk [RR]=3.3, CI 1.7–6.1), particularly after surgery (RR = 5.1, confidence interval [CI] 2.2–11.8) [15]. Other studies have confirmed these findings [16]. Based on these studies, it appears that the absolute risk of postoperative VTE among carriers is low (1 event per 100

surgical procedures) and that patients should not be screened for inherited thrombophilic disorders prior to surgery.

Presence of a lupus anticoagulant or anticardiolipin antibody in moderate or high titer among patients with no prior history of VTE is associated with a five to tenfold increase in the relative risk of developing VTE [17]. Patients with systemic lupus erythematosus plus either anticardiolipin antibodies or the lupus anticoagulant are probably at even higher risk for developing postoperative VTE.

Cancer

Presence of a malignancy is a potent risk factor that increases the risk of postoperative symptomatic VTE by at least twofold [2] and likely places such patients at increased risk for a longer period of time following the surgical procedure. Advanced clinical stage and pathology showing adenocarcinoma are strongly associated with VTE [18].

Obesity

Obesity, defined as a body mass index (BMI) over 30, appears to confer an increased risk of symptomatic VTE, at least in patients undergoing total hip arthroplasty [5,19]. This may reflect a combination of greater physical restriction of venous outflow, higher right-sided cardiac filling pressures, decreased propulsion of blood because of reduced physical activity, or the presence of an underlying inflammatory state associated with obesity [20]. Another factor may be inadequate thromboprophylaxis. For instance, although the dose of heparin or low molecular weight heparin (LMWH) for treatment of VTE is adjusted for weight, the recommended dose for prophylaxis is usually fixed, which could potentially result in under-dosing. In addition, mechanical prophylaxis using pneumatic compression may be ineffective in obese individuals [19].

Medical conditions

Congestive heart failure and chronic obstructive pulmonary disease (COPD) are associated with a higher incidence of VTE among hospitalized medical patients [21]. By extrapolation, it seems likely that these conditions also confer increased VTE risk in postoperative patients, with the mechanism being increased venous stasis.

Immobilization-stasis

Anything that leads to venous stasis likely increases the risk of VTE. Conversely, early mobilization of patients has been associated with a decreased relative risk of developing postoperative VTE [19,22]. Conditions such as marked obesity, stroke with hemiparesis, and prolonged bed rest in

the hospital probably increase the risk of VTE by leading to increased venous stasis.

Assessing the risk of bleeding

Risk factors for bleeding have not been specifically defined in a large cohort of surgical patients. Factors likely to contribute to the risk of post-operative bleeding include: the type of surgery, the underlying problem leading to surgery (eg. cancer), the surgical technique, and other known bleeding risk factors.

Widely appreciated bleeding risk factors during medical thromboprophylaxis include a known bleeding disorder, use of antiplatelet agents or non-steroidal anti-inflammatory drugs (NSAIDs), previous gastrointestinal bleeding, cancer, and hepatic or renal insufficiency [23]. The relationship between age and bleeding risk during anticoagulant therapy has been noted in some studies [24,25] but not in others [24,26].

Risk stratification

The American College of Chest Physicians (ACCP) criteria for VTE risk stratification are widely endorsed (Table 2). Patients are categorized on the basis of age, type of surgery, and presence or absence of additional thromboembolic risk factors. The obvious deficiencies of this schema are: (1) the

Table 2
Risk stratification for thromboembolism after surgery

Level of risk	Age (yrs)	Type of surgery	Additional risk factors	Incidence of proximal DVT (%)	Incidence of PE (%)
Low	<40	Minor	None	0.4	<0.5
Moderate				2–4	1–2
A	Any	Minor	Present		
B	<40	Major	None		
C	40–60	Nonmajor	None		
High				4–8	2–4
A	>60	Nonmajor	± Other		
B	>40	Major	None		
C	<40	Major	Present		
Highest risk				10–20	4–10
A		Hip or knee arthroplasty or hip fracture surgery Or major trauma or spinal cord injury			
B	>40	Major	Prior VTE Cancer Hypercoagulable state		

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

absence of a precise definition of what constitutes major and nonmajor or minor surgery, and (2) absence of appropriate weighting of other known VTE risk factors. Furthermore, there is nothing magical about the ages of 40 or 60 that suddenly affects the risk of VTE. Nevertheless, it provides some estimates of the risk of developing clinical VTE.

Efficacy and safety of available prophylaxis

Before making recommendations regarding perioperative VTE prophylaxis, one must have a working knowledge of the efficacy and safety of the various thromboprophylaxis modalities. This information must be combined with an appreciation of individual patient characteristics, the type of surgical procedure, and the preferences of the surgeon before an appropriate recommendation can be made.

The Sixth ACCP Consensus Conference on Antithrombotic Therapy provides the most comprehensive evidence-based guidelines for the prevention of VTE in surgical patients [7]. Table 3 was adapted from the most recent literature and the ACCP review and outlines the appropriate regimens for various surgical procedures, including simple risk stratification.

Thromboprophylaxis methods can be broadly divided into nonpharmacologic and pharmacologic regimens. Nonpharmacologic interventions include: early ambulation, elastic stockings, intermittent pneumatic compression (IPC) devices, and inferior vena caval filters. Pharmacologic methods include aspirin, unfractionated heparin, warfarin, LMWH, and synthetic pentasaccharides. We will also discuss newer agents including thrombin inhibitors and recombinant hirudin as future potential options for prophylaxis.

Nonpharmacologic prophylaxis

Early ambulation

Early ambulation should be a routine part of postoperative care for all patients, unless an absolute contraindication exists. The risks and benefits of early ambulation are well established, especially among lower-extremity orthopedic surgery patients [27,28]. In total hip arthroplasty patients who began progressive weight bearing immediately after surgery, the rate of ultrasound-proven VTE was significantly less than in patients who delayed weight-bearing rehabilitation [29]. Early ambulation has also been shown to be associated with a lower incidence of symptomatic thromboembolism after hip arthroplasty [19]. In addition, early ambulation with physical therapy after hip fracture has been associated with an earlier return to the community, shorter hospital length of stay, fewer complications, and a lower 6-month mortality [30]. Early postoperative ambulation is acceptable as VTE prophylaxis for patients undergoing low-risk surgical procedures such as general, gynecologic, and urologic surgery (Table 3). In practice, elastic stockings are often routinely used in these lowest-risk patients.

Table 3
Venous thromboembolism prophylaxis options in surgical patients

	Nonpharmacologic methods			Pharmacologic methods			
	Early ambulation	Elastic stockings	IPC	Aspirin	LDUH	Warfarin	LMWH
General surgery							
Low risk	A	A	A				
Moderate risk	X	A	A		A		A
High risk	X	X	A		A		A
Very high risk	X	X	X		A+		A+
GYN surgery							
Low risk	A						
Moderate risk	X	X	A		A		B
High risk	X	X	A		A or +		A
Urologic surgery							
Low risk	A						
Moderate risk	X	A	A		A		A
High risk	X	X	X		A+		A+
Orthopedic surgery							
Hip fracture	X	X	X	X	B	A	A ^a
THA	X	X	X	X	X	A	A ^a
TKA	X	X	B	X		A	A ^a
Neurosurgery	X	X	A or +		B or +		B or +
Trauma	X	B or +	B or +				A

^a Pentasaccharide approved.

Abbreviations: A, acceptable for solo prophylaxis, with highest level of evidence; +, combine with a nonpharmacologic method (ie, ES, IPC, or both); B, acceptable as an alternative method of prophylaxis with less evidence compared to A; X, beneficial, but inadequate prophylaxis alone; ES, elastic stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparins; THA, total hip arthroplasty; TKA, total knee arthroplasty.

Risk definitions

General surgery

- Low risk:
 - Minor procedure, <40 years of age, and no additional risk factors for VTE
- Moderate risk:
 - Minor procedure, but having additional VTE risk factors
 - Minor procedure between the ages 40 and 60 with no additional risk factors
 - Major surgery, but < 40 years of age
- High risk:
 - Minor procedure and over age 60 or additional VTE risk factors
 - Major surgery over age 40 or with additional VTE risk factors
- Very high risk: Major surgery with multiple VTE risk factors

GYN surgery:

- Low risk: brief procedure for benign disease
- Moderate risk: major surgery for benign disease, without additional VTE risk factors
- High risk: extensive surgery 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

Elastic stockings

Elastic stockings were first shown to reduce VTE events in 1952 [31]. Their benefit is attributed to improved venous flow and reduced vessel wall damage caused by the passive venous dilation that occurs during surgery [32]. The relative risk reduction with stockings is estimated to be at least 60% in general, neurologic, and gynecologic surgery [33–35]. Although there is no direct evidence of benefit in the lowest-risk surgery patients, there is some indirect evidence of harm. This concern comes from the observation that improperly fitted stockings may cause a “garter” effect that increases venous pressure below the knees and results in delayed venous emptying and an increased risk of VTE [36]. In a recent study of stocking use in orthopedic hip and knee surgery patients, 54% were found to have a “reversed gradient,” and these patients experienced a significantly higher incidence of VTE compared with patients who had correctly fitted stockings (25.6% versus 6.1%) [37]. This potential adverse effect underscores the need for proper fitting. Stockings should be applied preoperatively and continued throughout the hospital and rehabilitation period. There have been no controlled trials of prolonged out-of-hospital prophylaxis using stockings. It is reasonable, however, to recommend prolonged prophylaxis with stockings in patients who are relatively immobile after hospital discharge.

Although stockings reduce the risk of VTE in patients undergoing higher-risk general surgery [38], orthopedic surgery [39,40], neurologic surgery [35], and trauma surgery, there is very strong evidence that other modalities are more effective. Therefore, stockings are not recommended as solo prophylaxis but are recommended as an adjunct for all moderate or higher-risk patients unless the patient’s anatomy precludes proper fitting.

Intermittent pneumatic compression devices

There are two principal types of intermittent pneumatic compression (IPC) devices used to prevent VTE. The first provides sequential pneumatic compression of the leg, either to the level of the calf or thigh. The second is a “foot-pump” device that compresses the venous plantar plexus of the foot. Although the two devices have not been directly compared, they are considered to be equivalent. Individual institutions, physicians, or nurses may have a preference based on ease of use or patient comfort. The mechanism of action causing the reduced incidence of VTE is unclear. The principal mechanism is likely a direct effect of pumping venous blood, thereby reducing stasis. It is also possible that there is promotion of clearance of prothrombotic clotting factors [41] and an increase in local plasminogen activators leading to enhanced fibrinolysis [42]. More recent studies have not found enhanced fibrinolysis [43]. In a case-control study, White et al showed that use of IPCs was associated with a striking reduction in the incidence of symptomatic VTE after total hip arthroplasty, but only among patients with a body mass index of less than 25 [19].

These findings suggest that IPCs may not be effective in obese individuals, perhaps because of failure to transmit sufficient pressure to the deep veins.

IPC devices have an excellent safety profile, with no known complications except for patient discomfort and potential for skin breakdown. The primary drawback of IPC devices is that they are only effective if used continuously while patients are nonambulatory. Although the precise number of hours such devices need to be worn in order to be effective is not known, presumably the longer the better. In one randomized trial, IPC devices (worn for a median of 15 hours a day) were as effective as LMWH for VTE prevention after total hip replacement surgery [44]. As IPC devices have the potential to reduce ambulation, nurses and other members of the health care team must also be vigilant about encouraging patients to ambulate.

The efficacy of IPC devices has been evaluated after many different types of surgical procedures. They may be used as the primary prophylaxis modality in many surgical settings, but the use of IPC is not recommended as the only thromboprophylactic modality in: (1) highest-risk general surgery patients [45], (2) high-risk urologic surgery patients [46], and (3) orthopedic surgery patients undergoing hip or knee surgery [7] (Table 3). IPC devices are the method of choice for VTE prophylaxis when patients are at increased risk for bleeding with anticoagulants. They are used extensively in conjunction with pharmacologic methods because of a presumed “additive” prophylactic effect suggested in some studies.

There are few studies that directly compare IPC devices with warfarin or LMWH [44,47,48]. A recent trial showed no difference between IPC devices and LMWH for VTE prevention in women undergoing surgery for presumed gynecologic malignancy. Interestingly, there was no difference in the incidence of bleeding between the groups [49]. Based on this study and others [50], there is good evidence to support the use of IPC devices as solo thromboprophylaxis in patients undergoing moderate to high-risk gynecologic surgery.

One potential unintended benefit of IPC devices is reduced bleeding at the surgical site, which has been suggested by several small studies [44,51,52]. In a meta-analysis, IPC devices were found to have a 0.0% incidence of clinically important bleeding, which was no different from the control rate and significantly better than in the warfarin group (1.3%, $P=0.6$) or LMWH group (1.8%, $P=0.02$) [53]. A possible physiologic explanation for this finding relates to the aforementioned effects on the fibrinolytic and clotting cascades. Thus, there is good evidence that IPC devices do not increase the risk of clinically apparent bleeding and may actually decrease bleeding risk.

In summary, nonpharmacologic VTE prophylaxis methods are widely used and very safe. Early ambulation should be a part of routine care for all postsurgical patients. If properly fitted, elastic stockings (ESs) have essentially no adverse effects and may be appropriate for almost all surgical patients until full ambulation is achieved. IPC devices may be used as the primary method in selected patients, and they likely have an additive effect when used in conjunction with pharmacologic methods. IPC is the method

of choice when anticoagulation is contraindicated, but efficacy may be reduced in patients who are obese or who have very large legs.

Inferior vena caval filters

The currently accepted indications for inferior vena caval (IVC) filters include: (1) an absolute contraindication to anticoagulation, (2) life-threatening hemorrhage on anticoagulation, and (3) failure of adequate anticoagulation. When used appropriately, IVC filters are safe and effective in reducing the incidence of PE to 0.3–3.8% in patients with a contraindication to anti-coagulation [54]. The risks of IVC filter placement include migration of the filter, recurrent deep vein thrombosis (DVT), IVC thrombosis, and postphlebotic syndrome.

In the perioperative period, the scenario that most commonly arises is when a patient needs urgent surgery after a recent (<4 weeks) diagnosis of acute VTE. In such a patient, the risk of acute recurrent thromboembolism is significantly higher in the first month of treatment than after 4 or more weeks of treatment [55,56]. If anticoagulation therapy must be discontinued, placement of an IVC filter would be appropriate to prevent fatal PE. Placement of a temporary retrievable filter such as the Gunther Tulip™ (Cook Inc., Bloomington, IN) or Tempofilter (B. Braun Celsa, Chasseneuil Cedex, France) would be preferred, so it can be removed once the contraindication for anticoagulation has passed [57,58].

To date, there has been only one controlled trial of IVC filter use in patients with acute DVT. Use of a filter was associated with a nonsignificant reduction in the incidence of fatal pulmonary embolism, but there was a significant increase in the incidence of subsequent recurrent deep vein thrombosis [59]. Use of a prophylactic filter is not recommended simply because a patient is undergoing a procedure associated with a high incidence of venous thromboembolism.

Pharmacologic prophylaxis

There are a variety of effective pharmacologic agents available for preventing VTE after surgery. We will briefly review the most widely used agents: low-dose unfractionated heparin (LDUH), aspirin, warfarin, low molecular weight heparins (LMWH), and synthetic pentasaccharides.

Low dose unfractionated heparin

Efficacy

LDUH is a very effective prophylactic agent that clearly reduces the incidence of fatal postoperative PE [46]. Many studies performed in the late 1970s and 1980s documented the efficacy of subcutaneously administered

heparin [60,61] in doses of either 5000 international units (IU) every 12 hours or 5000 IU every 8 hours, with the first dose being given 2 hours preoperatively. Initiating prophylaxis postoperatively also appears to be effective, although randomized trials of this approach are sorely needed [62]. Studies comparing LDUH with low-dose LMWH (40 mg enoxaparin or equivalent) in general surgery patients show equivalent efficacy with a moderate increase in the risk of bleeding associated with use of LDUH [63]. Use of LDUH is associated with a modestly higher incidence of bleeding compared with IPC devices [50]. Elastic stockings or IPC may provide additional protective effect when added to LDUH in higher-risk patients.

Safety

The risks of LDUH include excess bleeding and heparin-induced thrombocytopenia (HIT). In a meta-analysis of thromboprophylaxis after total hip arthroplasty, the incidence of bleeding associated with LDUH (usually 7500 IU every 12 hours subcutaneously) was 2.6% (versus 0.3% in placebo patients) and 1.8% in patients treated with LMWH [53]. In a meta-analysis of general surgery trials, LDUH had a higher rate of minor bleeding (RR = 1.3; $P < .05$), but a similar rate of major bleeding when compared with LMWH [64]. Another meta-analysis found increased bleeding complications with LDUH versus low-dose LMWH after general surgery [63]. Thus, the major argument for using LMWH in place of LDUH among general surgery patients is a lower risk of bleeding [65].

Indications

LDUH, in addition to LMWH, is one of the recommended medical prophylactic agents for most general surgical procedures [7], as well as high-risk urologic or gynecologic surgery patients [50,66] with or without the addition of nonpharmacologic methods. Recommended dosages for LDUH are 5000 IU subcutaneously every 12 hours for moderate-risk patients and 5000 IU every 8 hours (or 7500 IU every 12 hours) for high-risk patients. LDUH (7500 IU every 12 hours subcutaneously) is less effective compared with LMWH (30 mg of enoxaparin q 12 hours subcutaneously or equivalent) in very high-risk orthopedic or neurosurgical [63,65] and is therefore not the prophylactic agent of choice for very high-risk procedures.

In summary, LDUH is a very effective drug for the prevention of VTE, and it is the drug of choice for many indications (Table 3). It is associated, however, with a modest increase in the incidence of bleeding and HIT compared with LMWH, and it must be given 2–3 times a day.

Aspirin

The use of aspirin as a thromboprophylactic agent is controversial. The Sixth ACCP Consensus Conference statement does not recommend aspirin

as sole prophylaxis for any surgical procedure (Table 3) [7]. There is some evidence from the recently conducted Pulmonary Embolism Prevention (PEP) trial that aspirin may have a beneficial effect in the subgroup of patients with hip fracture. Over 13,000 subjects with hip fracture in hospitals all over the world were randomized to 160 mg of aspirin per day for 5 weeks or placebo and allowed to receive routine thromboprophylaxis prescribed by their physician [67]. There was a significant reduction in the incidence of PE diagnosed during hospitalization in the aspirin group (0.7%) compared with placebo (1.2%, $P < 0.001$) and an impressive 58% reduction in the incidence of fatal PE ($P = 0.02$, 18 in aspirin group, 43 in placebo). Aspirin prevented approximately 4 fatal pulmonary emboli for every 1000 patients treated and resulted in 6 excess episodes of bleeding requiring transfusion.

The results of the PEP study suggest that aspirin may have a role for VTE prophylaxis among hip fracture patients. A potential role for aspirin may be postdischarge prophylaxis in hip fracture patients if no other medical prophylactic agent is used. More studies are needed to evaluate the role of aspirin after other surgical procedures. The findings do provide an additional rationale for using aspirin in postoperative patients who may benefit from primary or secondary prevention of cardiovascular events. Until further studies are done, however, aspirin alone is not recommended as a principal thromboprophylactic agent in surgical patients.

Warfarin

The use of warfarin for VTE prophylaxis has been limited primarily to very high-risk patients with lower-extremity orthopedic and neurologic surgery. Warfarin has not been commonly used in general, gynecologic, and urologic surgery patients because of the proven efficacy of other available agents, including IPC devices, LDUH, and LMWH (Table 3). Warfarin requires more intensive monitoring, and the potential risk for bleeding has been a concern. It is very useful among patients who require extended thromboprophylaxis, which is necessary in certain very high-risk patients. One of the major advantages of warfarin is that the onset of its anticoagulant effect is delayed for several days after starting treatment. This leads to a lower incidence of bleeding complication, which surgeons appreciate, but a higher incidence of asymptomatic thrombosis, particularly in calf veins. A large clinical study of patients undergoing total hip arthroplasty has shown that the incidence of symptomatic VTE within a 3-month period of surgery is comparable after 7–10 days of treatment with warfarin or enoxaparin [5].

Warfarin is recommended as one of the principal prophylactic agents among patients undergoing hip fracture repair, total hip arthroplasty (THA), and total knee arthroplasty (TKA) (Table 3). Numerous clinical trials [5,47,48] and meta-analyses [53,68,69] support the use of warfarin in patients undergoing such procedures. Warfarin can be initiated preoperatively using a “two-stage” approach of starting with a very low dose of

warfarin 10–14 days preoperatively targeting an international normalized ratio (INR) of less than 1.5, and then increasing the dose postoperatively to a target INR of 2.5. Alternatively, warfarin can be started the night before surgery or immediately after surgery. Such a regimen is perhaps associated with a lower risk of bleeding complications [70]. Many elderly patients require very low doses of warfarin, particularly if they are acutely ill or recovering from surgery because serum albumin levels are low and result in higher levels of free warfarin. In general, an initial dose of 5.0 mg is recommended, with a lower dose of 2.5 mg for patients over 75 years old [71].

Low molecular weight heparin and pentasaccharides

Available drugs

In the United States, there are currently three available LMWH preparations: dalteparin (Fragmin®, Kabi Vitram), enoxaparin (Lovenox®, Pharmion Boulder, CO), and tinzaparin (Innohep®, Aventis, Bridgewater, NJ) (Table 4). The U.S. Food and Drug Administration (FDA) recently approved a very low molecular weight product, the pentasaccharide fondaparinux (Arixtra®, Organon Sanofi-Synthelabo UC, Westorange, NJ), for prevention of VTE. As with LMWH, its mechanism of action is inhibition of factor Xa mediated by antithrombin [72]. Although there have been very few clinical trials that have directly compared LMWH preparations, they appear to be comparable for prevention and treatment of VTE. The dose of each agent is different, and FDA approval for VTE thromboprophylaxis is different for each product (Table 4). None of these products are FDA-approved for the prevention of VTE associated with pregnancy, spinal cord injury, trauma, or neurosurgery.

The newest agent, fondaparinux, has been compared with enoxaparin after hip arthroplasty [72], knee arthroplasty [73], and hip fracture surgery [74]. In these studies, fondaparinux was associated with a significantly lower

Table 4
Current FDA approved indications for use of LMWH/pentasaccharide

Indication	LMWH/pentasaccharide preparation			
	Enoxaparin	Dalteparin	Tinzaparin	Fondaparinux
Abdominal surgery	Yes	Yes	No	No
Total hip arthroplasty	Yes	Yes	No	Yes
Extended prophylaxis (THA) (3 weeks)	Yes	No	No	No
Total knee arthroplasty	Yes	No	No	Yes
Hip fracture surgery	No	No	No	Yes
DVT treatment—in hospital	Yes	No	Yes	No
DVT treatment—out-patient	Yes	No	No	No
Prophylaxis—high-risk medical patient (hospitalized)	Yes	No	No	No

incidence of venographically documented thrombi, but with no difference in the incidence of symptomatic VTE events. For example, following knee arthroplasty, the incidence of venographically defined thrombosis was 12.5% eleven days after surgery in the fondaparinux group and 27.8% in the enoxaparin group [73]. The incidence of symptomatic VTE was 0.5% in each group. Differences in the dose and timing of the administration of fondaparinux and the comparison drug, enoxaparin, make it difficult to know if the apparent efficacy is caused by the drug, the dose, or earlier administration of the drug. In this study of knee arthroplasty patients, there was an increase in the incidence of major bleeding in the fondaparinux group ($P < 0.009$) [72]. If the postmarketing experience of surgeons suggests that the incidence of bleeding is acceptably low, use of this agent may become widespread.

Indications

Among general and urologic surgery patients, some surgeons prefer LMWH as there is evidence indicating a modestly lower incidence of bleeding compared with LDUH [53,61,63,65,75]. Although LDUH is recommended for most patients undergoing general surgery, LMWH is approved for general surgical patients. It can be used in patients in all VTE prophylaxis categories, with the exception of low-risk patients who do not warrant pharmacologic prophylaxis [61,65].

In gynecologic surgery, use of LMWH is considered a second-line agent, as there is considerable evidence supporting the use of IPC devices or LDUH in moderate and high-risk patients, as noted above. In neurosurgery, IPC is the prophylaxis modality of choice because of the minimal risk of bleeding. LMWH is effective in preventing VTE, however, and safe when compared with placebo in terms of bleeding complications [76]. In trauma surgery, LMWH has become the agent of choice if the risk of bleeding is judged to be low [77]. But if bleeding risk is significant, elastic stockings and/or IPC devices are preferred in this high-risk group.

A large number of clinical trials have evaluated the efficacy of enoxaparin after major orthopedic surgery. It has been shown to be more effective than LDUH with equivalent safety after THA [53,77–79] and TKA [80]. LMWH appears to be comparable to warfarin when administered for comparable periods of time [5], although some studies have shown lower rates of venographically proven VTE with LMWH, particularly after total knee arthroplasty [81]. Dosing recommendations for LMWH and fondaparinux are shown in Table 5. Tinzaparin has been directly compared with enoxaparin after THA, and it appears that these two agents are comparable [82].

Safety

Bleeding is the primary complication associated with pharmacologic prophylaxis. As noted above, LMWH has similar efficacy as LDUH, with a lower

Table 5
Acceptable dosing of low molecular weight heparins and pentasaccharide

Drug	Prophylaxis: orthopedic surgery	Extended prophylaxis after hip arthroplasty	Prophylaxis: general surgery
Enoxaparin	30 mg q 12 hr (60 mg/day) Given every 12 hr starting 12–24 hours after surgery or 40 mg q 24 hr starting evening before surgery	4000 IU (40 mg) Once daily	4000 IU (40 mg) Once daily starting 1–2 hr before surgery
Dalteparin	5000 IU daily Or 2500 IU within 2 hr presurgery and 2500 IU at least 6 hr after surgery		2500 IU Once daily starting 1–2 hr before surgery
Tinzaparin	75 IU/kg Daily started 1–2 hr preoperatively or 4500 IU once daily started preoperatively		
Fondaparinux	2.5 mg Begin 6 hr post surgery		

Abbreviation: IU, international unit.

reported incidence of clinically important bleeding [53,61,63,65,75,78]. When compared with IPC devices, however, the incidence of bleeding complications is equivalent or higher in LMWH-treated patients. In a 1996 survey of U.K. orthopedists, 48% of those who had used LMWH discontinued use because of perceived excessive bleeding, and of those who continued using LMWH, 88% witnessed excessive bruising, and 53% reported wound bleeding and hematomas [81]. Because of the perceived risk of bleeding associated with the use of LMWH after orthopedic surgery, agreement must be reached with the surgeon prior to recommending these agents.

Epidural catheters

An important complication of LMWH is the potential for epidural/spinal hematoma when administered prior to removal of an epidural catheter placed for anesthesia and/or analgesia. This was initially reported in 1997 after several reports of hematoma development following concurrent use of enoxaparin prophylaxis and regional epidural or spinal anesthesia or spinal puncture [83]. Subsequent guidelines for use of LMWH and regional anesthesia have been developed and include [7,84]: (1) regional anesthesia should be avoided in patients with an abnormal bleeding history or those receiving drugs that affect hemostasis; (2) spinal needle insertion should be delayed for 10–12 hours after the initial LMWH prophylaxis dose, and regional anesthesia should be avoided in patients with a hemorrhagic aspirate during spinal needle placement; (3) single-dose anesthetic is preferable to continuous epidural anesthesia; (4) in patients receiving continuous epidural anesthesia, the epidural catheter should be left indwelling overnight

and removed the next day; (5) subsequent LMWH doses should be delayed for at least 2 hours after spinal needle placement or catheter removal; and (6) if LMWH prophylaxis is started postoperatively, the initial dose should be delayed at least 2 hours after catheter removal.

Other agents

Adjusted dose unfractionated heparin (ADH) has been utilized and studied [85]. Its use in practice and clinical trials, however, has all but disappeared since the emergence of LMWH. Although there is evidence to support its use in some surgical procedures for VTE prophylaxis, it is more cumbersome than other effective methods and, therefore, was not included in Table 4 and our review.

Direct thrombin inhibitors are a new class of anticoagulant drugs in various stages of development and testing. Desirudin, the recombinant form of hirudin, was tested for VTE prophylaxis after THA and was found to have a similar safety profile as enoxaparin, and was more effective in preventing VTE [86]. Lepirudin (Refludan®, Berlex, Montville, NJ), another form of recombinant hirudin, has been approved for the treatment of HIT. Argatroban®, (Glaxo Smith Klein Research triangle Park, NC) is another thrombin inhibitor that has been approved for the treat of HIT. The newest of the class, ximelagatran, an oral thrombin inhibitor, was recently tested in a phase 2 dose-finding trial compared with enoxaparin. When given after TKA surgery, ximelagatran (Exanta Astrogeneca Wilmington, DE) had a similar safety and efficacy profile as enoxaparin [87].

These and other agents will continue to be developed in an effort to discover the optimal VTE prophylaxis in surgical patients in terms of safety and efficacy.

Timing of prophylaxis

In most patients, it is appropriate to initiate VTE prophylaxis as soon as the risk of developing thrombosis begins. For trauma patients, this means as soon as they are hospitalized. For elective surgery patients, it is as soon as they are taken to the operating room. For recently immobilized patients, it may be prior to admission to the hospital.

Stockings and IPC devices should be initiated preoperatively as soon as the risk of immobility increases, then continued during the procedure and throughout the hospital stay. If aspirin is part of the VTE prophylaxis regimen, it should be started preoperatively [67]. Warfarin can be started at a low-dose 10–14 days preoperatively, or at a therapeutic dose on the night prior to surgery. For LMWH, the optimal timing to maximize efficacy and minimize bleeding is not yet clear (Table 5). Options include initiating LMWH 12 hours preoperatively, immediately prior to surgery, as soon as hemostasis is achieved after surgery, or 12–24 hours postoperatively. The clinical practice in North America tends to be to dose LMWH

postoperatively, whereas in European countries it is begun preoperatively. There is data to support both regimens; however, a 1999 meta-analysis by Hull et al found that LMWH initiated preoperatively was associated with lower rates of venographically proven VTE and lower rates of major bleeding [88]. The timing of pharmacologic prophylaxis should always be clarified with the anesthesia team, particularly if spinal or epidural anesthesia (or analgesia) is planned. The use of preprinted orders, computer reminders, or practice guidelines may be an effective method for prompting appropriate VTE prophylaxis [89].

Duration of prophylaxis

The optimal duration of thromboprophylaxis is not known. In the 1970s and 1980s when hospitalizations were longer, patients were given thromboprophylaxis for their 7–10 day stay in the hospital. As the duration of hospitalization decreased in the 1990s, the duration of thromboprophylaxis also decreased. Early studies looking for asymptomatic VTE after hospital discharge noted a high incidence of asymptomatic thrombosis [90], and this prompted many more studies, both in orthopedic surgery and after some general surgical procedures [91–93].

General surgery

A 1998 Danish trial evaluated extended thromboprophylaxis with tinzaparin in 118 patients who had undergone major abdominal and noncardiac thoracic surgery. At 4 weeks, there was no difference in the rate of venographic DVT in the control group (10%) and the placebo (5.2%) groups [94]; however, the study had low power. In a larger study, Bergqvist et al found that extended duration prophylaxis (27–31 days) with enoxaparin, 40 mg/day, led to a significant ($P=0.02$) reduction (4.8%) in the asymptomatic VTE after abdominal or pelvic surgery for cancer compared with control patients (12%) who were treated for only 6–10 days [95]. The cost of extended thromboprophylaxis using enoxaparin (40 mg/day, ~\$16.00) or dalteparin (5000 IU/day, ~\$12.00) in the United States is significant [23]. A cost-effectiveness analysis from 1996 concluded that prolonged DVT prophylaxis in general surgery patients could prevent out-of-hospital DVT, but at a marginal cost that was deemed inappropriate for routine use [96].

Orthopedic surgery

There is evidence that extended prophylaxis is important for patients undergoing lower-extremity orthopedic surgery, particularly total hip arthroplasty. A recent meta-analysis of eight hip arthroplasty studies and two knee arthroplasty studies found that extended prophylaxis using LDUH or LMWH significantly reduced the frequency of symptomatic and asymptomatic VTE [97]. Extended prophylaxis for 30–42 days was associated with a

significantly lower incidence of symptomatic VTE (1.3%) than placebo (3.3%), or one fewer symptomatic VTE for every 50 patients treated. A case control study also found that extended prophylaxis with warfarin was associated with absence of VTE [19]. Extended prophylaxis is associated with a modest increase in the risk of minor bleeding compared with placebo (3.7% versus 2.5%), or one more minor bleed for each 83 patients treated [97]. Extended prophylaxis does not appear to benefit patients who undergo total knee arthroplasty [92]. Knee arthroplasty patients develop symptomatic VTE early after surgery, with few additional cases diagnosed 3 or more weeks after the day of surgery, whereas symptomatic VTE is frequently diagnosed in hip arthroplasty patients up to 2 months after the day of surgery [98].

Recommendations

The only procedure for which there is strong evidence in favor of extended prophylaxis is total hip arthroplasty, and, although the most optimal duration of prophylaxis after this procedure is not known, 4–6 weeks appears reasonable. Existing evidence to support extended prophylaxis after hip fracture and total knee arthroplasty is weak, and more studies are needed to determine the optimal duration of thromboprophylaxis. Nevertheless, because the length of hospitalization after surgery is becoming so short, some extenuation in the duration of prophylaxis is certainly logical. Because of cost and safety concerns, it would be reasonable and appropriate to risk-stratify patients and recommend extended prophylaxis for the higher-risk patients. Unfortunately, there is not a validated risk stratification tool available at this time. The risk factors that are probably most important are: obesity (BMI > 30) and sedentary lifestyle, being bed- or wheelchair-bound, and a history of prior VTE [19]. Patients who have active cancer may also be excellent candidates for extended prophylaxis, but the optimal duration of prophylaxis is unknown. Continued use of well-fitted elastic stockings after patients are discharged from the hospital is reasonable, although there is no evidence to support this recommendation. Finally, it is reasonable to consider aspirin prophylaxis, particularly in patients who have risk factors that would warrant prophylaxis for cardiovascular disease.

If extended prophylaxis is recommended, the two logical choices are LMWH (enoxaparin 40 mg or dalteparin 5000 IU) or warfarin (target INR = 2.5). Three different cost-effectiveness studies suggest the difference in cost between warfarin and LMWH is small, but these conclusions are highly dependent on the cost of the drug and cost of monitoring [99–101]. Given the high price of LMWH in the United States, warfarin is currently cheaper and more cost-effective than LMWH [102].

Role of screening for asymptomatic VTE

This is a controversial topic. As noted earlier, most VTE events (including PE) are asymptomatic. Thus, screening using venous ultrasound imaging

is most likely to detect asymptomatic thrombi that are unlikely to become symptomatic. In addition, venous ultrasound is less accurate when used in asymptomatic individuals than in symptomatic individuals. In one randomized study of patients undergoing total hip or knee arthroplasty who received warfarin prophylaxis, screening with ultrasound did not reduce the incidence of symptomatic VTE but lead to treatment of 2.5 times more patients, one of whom developed a major bleeding complication [103]. Other studies have concluded that screening ultrasound testing is not cost-effective and not warranted [104–106].

Perioperative management of patients on long-term oral anticoagulation

Indications for long-term oral anticoagulation therapy (OAT) include prevention of systemic embolization in patients with prosthetic heart valves or atrial fibrillation (AF), as well as primary or secondary prevention of VTE. Other potential indications for chronic OAT include mitral stenosis, left ventricular aneurysm, severe left ventricular systolic dysfunction, coronary artery disease, previous inferior vena cava (IVC) filter placement, and presence of synthetic peripheral arterial bypass grafts. There is a paucity of clinical data available on the perioperative management of patients on long-term OAT, and experts' recommendations vary widely [55,107–109]. Perioperative management of patients on chronic OAT must be individualized, balancing the risks of thromboembolism if OAT is interrupted versus the risk of bleeding if such therapy is continued. Options for perioperative anticoagulation include the following regimens: (1) continue OAT and perform surgery with the patient fully anticoagulated; (2) discontinue OAT preoperatively, give prophylactic subcutaneous heparin perioperatively during hospitalization, and reinstitute OAT as soon as possible postoperatively; and (3) discontinue OAT preoperatively and administer "bridging therapy" with full-dose intravenous heparin or LMWH during the time that the INR is subtherapeutic. The risk of thromboembolism in patients who temporarily discontinue OAT depends on the particular indication and other patient-specific factors, which are discussed below.

Bleeding risk

Risk of bleeding depends on the operative procedure and characteristics of the individual patient. Patient-related factors include: a prior history of bleeding problems, concurrent use of antiplatelet agents (aspirin, NSAIDs, etc.), age >65, and acquired conditions associated with increased bleeding, such as chronic renal or liver disease and cancer. Bleeding risk is highly dependent on the type of surgery, the vascularity of the tissues, and the ability of the surgeon to control bleeding either by compression or other physical means (packing, cautery, topical coagulants) [110]. Guidelines for perioperative management of anticoagulation can be developed according to the patient's risk of bleeding.

Management of patients at low risk for bleeding complications

Procedures that appear to be associated with a low risk of bleeding despite OAT include cataract extraction [111,112], laparoscopic cholecystectomy [113], dermatologic procedures [114], and possibly transurethral resection of the prostate [115]. In general, patients who undergo these low-bleeding risk procedures may either continue OAT or have the intensity of OAT reduced to “low” therapeutic levels (ie, an INR of approximately 2.0) [108]. Delayed bleeding after colonoscopic polypectomy is not unusual and may be associated with OAT [116,117], so that many endoscopists recommend discontinuation of OAT if polypectomy is to be performed.

Dental procedures

Although many dentists recommend temporary interruption of OAT prior to tooth extractions and other dental procedures, a recent review found that serious bleeding is distinctly unusual when OAT is continued during tooth extraction, or during gingival and alveolar surgery [118]. Tranexamic acid mouthwash, a local fibrinolytic agent, has been shown to decrease bleeding in patients who undergo oral surgery while continuing to take OAT [119]. Most experts recommend that outpatient dental procedures be performed without discontinuing OAT or by slightly lowering the INR (to approximately 2.5) [110,118]. A recent prospective cohort study of 104 patients with a tilting disk or a bileaflet mechanical heart valve demonstrated that temporarily interrupting therapeutic OAT prior to tooth extraction and immediately restarting the normal daily dose of warfarin on the evening after surgery was both safe and effective [120]. There were 2 minor bleeding complications (treated with local measures) and no thromboembolic complications reported after 3 months, even though 40% of the patients had atrial fibrillation, a marker of high thromboembolic risk. The authors discontinued warfarin 2 days prior to the procedure if the INR was therapeutic (2.0–4.5) at the time, resulting in a mean procedural INR of 1.87.

Management of patients with high risk for bleeding complications

Surgical considerations

Neurosurgery in particular and almost all other major surgical procedures are considered high risk for bleeding [121], necessitating the transient discontinuation of OAT. Options include temporary discontinuation of OAT without “bridging” anticoagulation, or the use of perioperative bridging therapy. Whether or not bridging therapy should be used depends on underlying patient-specific risk factors for thromboembolism if OAT is stopped.

Patient considerations

Aside from the dental literature [118,120], there is very little clinical trial data available to inform the clinician about the risk of thromboembolism

during transient cessation of OAT for surgery or other procedures. Risk estimates must be extrapolated from epidemiologic studies of patients at risk for thromboembolism (prosthetic heart valves, atrial fibrillation [AF]) but who are not receiving OAT for a variety of reasons including gastrointestinal bleeding [122,123]. Such data suggest that patients at high risk for thromboembolism while not taking OAT include those with: mechanical prosthetic heart valves [124], AF, prior stroke or multiple stroke risk factors [125,126], and recent (<1 month) acute venous thromboembolism [55,56]. Using this epidemiologic data, estimates of the daily thromboembolic risk [55,108] among patients in whom OAT is discontinued range from 0.2–1% with VTE < 3 months and 0.04% with VTE > 3 months [56,127], 0.02% with mechanical prosthetic valves [124], and 0.003–0.05% with atrial fibrillation [125]. It should be kept in mind that these estimates may not apply to patients who temporarily interrupt anticoagulation to undergo surgery. There is also a possibility of a rebound hypercoagulable state following the cessation of OAT [128,129]. Some authors also feel that patients with inherited or acquired hypercoagulable states and recent or life-threatening thrombosis are also at high risk if OAT is interrupted [108].

Venous thromboembolism and atrial fibrillation

As mentioned above, there have been no clinical trials that have addressed the perioperative anticoagulation management of patients with either AF or VTE. Such patients may be managed as outlined in Table 6, with patients deemed at highest thromboembolic risk being treated with bridging therapy using either intravenous heparin or subcutaneous LMWH. The stroke risk in patients with AF increases with age (particularly if age is greater than 75 years), prior transient ischemic attack (TIA)/stroke or systemic embolus, hypertension, diabetes, reduced left ventricular function, prosthetic valves, and rheumatic mitral valve disease [125]. In patients with nonvalvular AF, those with previous TIA or stroke have the highest risk of recurrence (13%/year) [125,126] and should probably be given bridging therapy. VTE recurs commonly in the first 3 months after an acute event [56,130], and recurrence rates may be as high as 40% at 1-month without anticoagulation therapy [155]. Therefore, many experts recommend bridging therapy in patients who have had VTE in the preceding 3 months. In the first month after the diagnosis of acute VTE, full-dose anticoagulation with LMWH or intravenous heparin is recommended as bridging therapy. If a procedure is to be performed more than 1 month after acute VTE, some experts recommend that these patients be bridged with lower, prophylactic doses of LMWH (enoxaparin 40 mg or dalteparin 5000 IU). Patients with history of VTE occurring greater than 3 months earlier may be managed by simply interrupting OAT, without bridging therapy. Remember, prophylactic LDUH or LMWH is indicated in the perioperative period for many surgical procedures and should be administered to most hospitalized

Table 6
Suggested anticoagulation regimens for patients on chronic OAT undergoing noncardiac surgery

Clinical situation	Anticoagulation regimen
Procedures associated with low bleeding risk (dental, cataract, skin)	Continue OAT at usual dose or reduce dose to achieve INR in the low therapeutic range (target INR = 2.0)
Aortic valve prosthesis with no additional TE risk factors ^a , AF and low stroke risk	Discontinue OAT 4–5 days prior to surgery [154], operate when INR \leq 1.5; resume normal daily dosage on day of surgery if possible. Administer prophylactic dose SC heparin perioperatively if clinically indicated.
Mitral or multiple valve prostheses; aortic valve prosthesis with TE risk factors ^a ; recent VTE (<3 months); AF and high stroke risk	Discontinue OAT 3–5 days prior to surgery; start IV heparin (target APTT 2.0–3.0 \times control) when INR falls below 2.0; stop heparin 6 h prior to surgery; restart subcutaneous heparin prophylaxis and oral anticoagulation as soon as possible; stop heparin when INR becomes therapeutic on 2 consecutive days ^b .

^a TE risk factors include: atrial fibrillation, previous embolism, caged-ball valves, Bjork-Shiley single tilting disk valves, severe left ventricular dysfunction, and a hypercoagulable state (eg, surgery for cancer).

^b Low-molecular-weight heparin is currently being investigated as an alternative agent, but is not approved for use with mechanical prosthetic valves. Treatment doses not clear, but experts suggest: enoxaparin 1 mg/kg q 12 h, dalteparin 100 IU/kg q 12 h, or tinzaparin 175 IU/kg q day.

Abbreviations: AF, atrial fibrillation; APTT, activated partial thromboplastin time; INR, International Normalized Ratio; OAT, oral anticoagulation therapy; SC, subcutaneous; TE, thromboembolic; VTE, venous thromboembolism.

patients not receiving bridging therapy. Discontinuation of OAT for major surgery is not an indication for IVC filter placement and should be avoided in this setting because several studies have documented an increased long-term risk of lower extremity DVT [56,59]. Patients being treated with OAT for mitral stenosis, coronary artery disease, left ventricular dilatation, previous IVC filter placement, and synthetic arterial bypass grafts can probably be managed with temporary interruption of therapy [110].

Mechanical prosthetic heart valves

Several clinical studies of the management of patients with mechanical prosthetic valves have been published and may help to risk stratify these patients. In such patients, OAT is usually given to prevent arterial embolism (stroke, myocardial infarction) and prosthetic valve thrombosis, which are both potentially lethal complications. A retrospective study of 159 patients with mostly caged-ball (Starr-Edwards) prostheses undergoing 180 noncardiac procedures at the Mayo Clinic in Rochester, Minnesota, reported a low incidence of thromboembolism with discontinuation of OAT for an average of 3 days preoperatively and 3 days postoperatively [131]. Katholi

performed the only prospective study, a small nonrandomized cohort of 39 patients with older generation caged-ball aortic valves and caged-disk mitral valves undergoing noncardiac procedures. No thromboemboli occurred in 18 aortic valve patients undergoing 19 procedures who had OAT discontinued 3–5 days preoperatively and resumed 2 days postoperatively. Similarly, no thromboemboli were observed in 21 mitral valve patients undergoing 26 procedures who had rapid reversal of OAT using vitamin K [132]. A recent retrospective study of 235 patients with newer generation, bileaflet mechanical valves undergoing major noncardiac operations demonstrated a very high thromboembolic complication rate for tilting disk mitral valves despite bridging therapy being administered to most patients. Thromboembolic event rates were lowest for bileaflet aortic valves (0.7%). In a multivariate analysis, thromboembolic events were associated with surgery for malignancy and tilting disk mitral valves [133].

These studies and others suggest that the following factors are associated with a high risk for thromboembolic complications: all mitral prostheses, single tilting disk or Bjork-Shiley valves, double-position prosthetic valves, atrial fibrillation, severe left ventricular dysfunction, previous embolic event [134], and a hypercoagulable state (eg, cancer) [107,109,124]. It appears that OAT can be temporarily interrupted without bridging therapy in patients with isolated mechanical aortic valve prostheses who have none of the above risk factors. Patients with mitral prostheses or other embolic risk factors should receive bridging therapy (Table 6). Most authors also recommend that patients on chronic OAT receive prophylactic subcutaneous LDUH or LMWH any time their INR falls to below 2.0 [109,110]. Aspirin is often prescribed to patients with mechanical valves as an adjunct to OAT for prevention of systemic embolization [135,136]; it should be discontinued approximately 1 week prior to major surgery and resumed as soon as deemed safe by the surgeon [107].

Bridging therapy with low molecular weight heparins

LWMH is currently being investigated as a less costly alternative for bridging therapy because of the potential to avoid hospitalization prior to major surgery [137]. LMWH is not FDA-approved for use in patients with mechanical heart valves, although there is preliminary data suggesting that enoxaparin [138] and dalteparin [139] may be safe alternatives for bridging therapy during minor surgical procedures. Other preliminary studies have reported excess bleeding events in patients undergoing noncardiac surgery [140]. A recent small trial of 24 patients undergoing 26 procedures using subcutaneous dalteparin (200 anti-Xa IU/kg/day subcutaneously for an average of 5 days) for patients with high thromboembolic risk resulted in only 2 minor bleeding complications and 1 transient ischemic attack but avoided 2 days of hospitalization preoperatively [141]. Other LMWH regimens that have been used for bridging therapy include: dalteparin (100 anti-Xa IU/kg

SC q 12 h), enoxaparin (1 mg/kg SC q12 h or 1.5 mg/kg once daily), and tinzaparin (175 anti-Xa IU/kg SC once daily). Some experts recommend the following bridging regimen: start LMWH on the day the INR is anticipated to fall below 2.0, give the last preoperative dose on the morning prior to surgery; reinstitute OAT on the evening after surgery; restart LMWH at least 24–48 hours after the procedure (or when risk of postoperative bleeding becomes sufficiently low); and continue LMWH until the INR is therapeutic on 2 consecutive days [110]. The safety, efficacy, and optimal dosing regimens for LMWH as bridging therapy remain speculative and should be substantiated by further clinical studies.

Recommending and implementing a postoperative thromboprophylaxis regimen

In order to implement a thromboprophylaxis regimen successfully, consulting internists must balance the bleeding risk of using prophylactic agents such as heparin, LMWH, and warfarin against the risk of thromboembolism associated with the operative procedure. VTE risks and the effect of prophylaxis can be estimated from the literature, although clinical data on bleeding risks are much more limited. Bleeding complications such as wound hematomas tend to be very troublesome for surgeons, particularly when such bleeding may be harmful or even catastrophic [eg, central nervous system (CNS) surgery]. On the other hand, VTE is a major cause of morbidity and mortality, including over 150,000 deaths from PE each year in the United States [142], making this disorder the most common preventable cause of hospital death. Because internists care for large numbers of patients with VTE (but very few bleeding complications) and surgeons deal with bleeding complications (but very few VTE complications), it can be very difficult to reach consensus on the relative harms of a VTE versus a wound hematoma.

Regardless, internists should recommend effective thromboembolic regimens but recognize the potential harms caused by such recommendations. We strongly recommend direct consultation with the primary surgeon to determine the risk/benefit ratio of each thromboprophylaxis regimen. It is inappropriate to recommend intensive thromboprophylaxis when it is clear that the surgeon opposes this strategy and will obviously not follow your recommendation. Consensus must be reached before the time of surgery, and decisions based on a review of the available evidence.

Multi-disciplinary approaches include development of local guidelines that are endorsed by all interested parties (administration, internists, surgeons, anesthesia team, pharmacists, and nurses) under the umbrella of a clinical pathway for postoperative VTE prevention. Other important considerations include the availability and cost of the various options, whether or not the patient's insurance covers the prophylactic agent, and of course, whether or not the risk/benefit ratio is acceptable to the patient.

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