

UCLA Department of Medicine

Guidelines for the Prevention and Treatment of Venous Thromboembolism (Deep Vein Thrombosis and Pulmonary Embolism) and Management of Heparin-Induced Thrombocytopenia

I. *Statement of Purpose.* Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a very common clinical problem. Despite numerous phase III studies of outstanding design and statistical power on the prevention and treatment of VTE reported over the last several years, and the recommendations of the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy published late in 2004,¹ clinical practices remain highly variable at UCLA and elsewhere. In order to optimize treatment practices by UCLA Department of Medicine housestaff and faculty, this evidence-based set of guidelines has been developed.

II. *Frequency of VTE.* The annual occurrence in the U.S. is about 2,000,000 DVT and 600,000 PE cases. About 800,000 develop post-phlebotic complications, and about 30,000 develop VTE-related chronic pulmonary hypertension annually. Approximately 60,000 die annually from VTE.² Paradoxical VTE is responsible for a small portion of thromboembolic cerebral infarction and other arterial thromboembolic disease.

III. *Therapeutic goals.* Prevent VTE, prevent extension of acute VTE, prevent sequelae of VTE, maximize anticoagulant efficacy, minimize risks of bleeding and heparin-induced thrombocytopenia (HIT)/thrombosis, and manage favorable-risk acute DVT patients as outpatients.³

IV. *Classes of anticoagulants available for prevention and treatment of VTE.*

- A. *Glycosaminoglycans (GAGs).* (1) Unfractionated heparin (UFH). (2) Low molecular weight heparins (LMWHs, including enoxaparin [Lovenox®], dalteparin [Fragmin®], and tinzaparin [Innohep®]). (3) Fondaparinux (pentasaccharide, [Arixtra®]). — GAGs act mostly by facilitating antithrombin III, which inhibits activated clotting factors, mainly thrombin (factor IIa) and factor Xa.

Pharmacology and selected drug characteristics.

	<i>UFH</i>	<i>LMWH</i>	<i>fondaparinux</i>
Source	porcine/bovine	UFH	synthetic
Mean # saccharides (range)	36 (10-100)	13 (3-30)	5
Mean mol. wt. (range)	12 kD (3-35)	4.5 kD (1-10)	1.7 kD
Plasma protein/cell binding	+++	+	–
Bioavailability	variable	90%	100%
Route	IV or SQ	SQ only	SQ only
Half-life (hr)	variable (SQ) ^a <1-3 (IV) ^a	6 (SQ)	17 (SQ)
PF4 binding	+++	+	–
Effect of liver dysfunction	–	–	–
Effect of renal dysfunction	++	++	++
Action	ATIII, IIa>Xa	ATIII, IIa<Xa	ATIII, Xa only
Binds clot-bound thrombin	No	No	No
Effect on PTT	+++	+	+/-
Monitoring	PTT ^b	anti-Xa ^c	anti-Xa ^d
Effect of protamine	+++	+/-	–
Pregnancy Category	C	B	B

^a Dependent upon binding to acute phase reactants.

^b Some practitioners use anti-Xa monitoring in addition to or instead of the PTT.

^c Not routinely indicated, but consider if full-dose therapy must be assured in (1) pregnant patients, who may require higher doses, (2) dialysis patients, who usually require lower doses, and (3) morbidly obese patients, who have variable responses.

^d A standardized anti-Xa assay for fondaparinux is not widely available.

UFH, LMWHs, and fondaparinux differ with respect to plasma protein binding. This difference is the most important attribute distinguishing the three types of GAGs.

Plasma protein binding. UFH: Extensive plasma protein binding is responsible for widely variable bioavailability, unpredictable dose requirements, and the need for PTT (and/or anti-Xa) monitoring during full-dose therapy. UFH binds to platelet factor 4, forming a complex that is immunogenic and which underlies HIT. *LMWHs and fondaparinux:* Plasma protein binding is far less significant, bioavailability is nearly complete, dosing is predictable and is therefore fixed or weight-based, and monitoring is not usually required. LMWHs cause HIT only about 10-30% as often as UFH. HIT is thus far unreported in association with fondaparinux therapy.⁴

Patients with lupus anticoagulants and a prolonged PTT. UFH dosing is difficult during intravenous therapy, because of the required monitoring using the PTT assay.

Rapidity of drug effect offset. UFH administered intravenously has the fastest *offset* of action compared to other GAGs.

FDA Approvals.

Heparin (unfractionated heparin, UFH). VTE treatment and prophylaxis. (Also approved for arterial thromboembolism, atrial fibrillation, disseminated intravascular coagulation, cardiopulmonary bypass, peritoneal dialysis, and vascular catheters.) ***On the UCLA Formulary.***

Enoxaparin (Lovenox®). *VTE prophylaxis:* (1) Total hip or knee replacement, 30 mg SQ q12h, beginning 12-24 hr after surgery, *or* 40 mg SQ q24h beginning 9-15 hr before surgery in total hip replacement. (2) High-risk abdominal surgery, 40 mg SQ q24h beginning 2 hr before surgery. (3) High-risk medical patients newly hospitalized for exacerbations of chronic heart or lung disease, infections, or inflammatory disorders, 40 mg SQ q24h. *Acute VTE (DVT or PE):* 1 mg/kg SQ q12h *or* 1.5 mg/kg q24h. Favorable-risk DVT patients may be treated as outpatients. (Also approved for acute coronary syndromes at 1 mg/kg SQ q12h with aspirin. To compare enoxaparin to other available LMWHs, 1 mg = 100 anti-Xa units.) ***On the UCLA Formulary.***

Tinzaparin (Innohep®). *Acute VTE (DVT or PE):* 175 anti-Xa units/kg SQ q24h. ***Not on the UCLA Formulary.***

Dalteparin (Fragmin®). *VTE prophylaxis:* (1) Total hip replacement, 5,000 anti-Xa units SQ QD. (2) High-risk abdominal surgery, 2,500 or 5,000 anti-Xa units SQ QD. (Also approved for acute coronary syndromes at 120 anti-Xa units /kg, up to 10,000 units, SQ q12h with aspirin.) ***Not on the UCLA Formulary.***

Fondaparinux (Arixtra®). *VTE prophylaxis:* (1) Total hip or knee replacement, and hip fracture, 2.5 mg SQ q24h beginning not before 6 hr after surgery. (2) High-risk surgical patients, 2.5 mg SQ q24h. *Acute VTE (DVT and PE):* 5 mg SQ q24h (weight <50 kg), 7.5 mg SQ q24h (weight 50-100 kg), 10 mg SQ q24h (weight >100 kg). ***On the UCLA Formulary.***

B. *Direct antithrombins.* (1) Argatroban (Argatroban®). (2) Lepirudin (Refludan®). — These anticoagulants inhibit thrombin directly, i.e., they do not require antithrombin III.

Pharmacology and selected drug characteristics.

	<i>argatroban</i>	<i>lepirudin</i>
Trade name	Argatroban	Refludan
Mol. wt.	527	6,979
Inhibits clot-bound thrombin?	yes	yes
Standard loading dose	none	0.4 mg/kg
Standard infusion dose	2 µg/kg/min	0.15 mg/kg/hr
How monitored	PTT ^a	PTT ^b
Target PTT range	1.5-3.0 x	1.5-2.5 x
Antidote	none	none
Half-life	45 min	75 min
Effect of renal dysfunction on half-life	-	++++
Effect of hepatic dysfunction on half-life	++	-
Antibodies that cause anaphylaxis ⁵	-	+ ^c
Antibodies that prolong drug half-life ⁶	-	+
Pregnancy Category	B	B

^a comparable effect on PT; when converting to warfarin, continue argatroban until INR >4 (assuming PTT in the therapeutic range for argatroban)

^b not an ideal test; ecarin clotting time more accurate but not generally available

^c risk about 1/6,000 after first drug exposure, 1/600 after repeat exposure; risk greatest after bolus dose; about half of the reported cases were fatal

FDA approvals

Lepirudin (Refludan®). HIT. **Soon to be deleted from the UCLA Formulary.**

Argatroban (Argatroban®). HIT. (Also has an indication for percutaneous coronary intervention in HIT patients. Dosing differs from standard anticoagulation and includes aspirin.⁷) **On the UCLA Formulary.**

C. *Vitamin K antagonists*. Warfarin (Coumadin®, generics) depletes procoagulant factors II (prothrombin), VII, IX, and X, and the anticoagulants proteins C and S. Half-lives of factor VII and protein C are short (about 5-6 hours); the prothrombin time is very sensitive to factor VII depletion, and therefore a rapidly rising INR during the first 1 to 2 days of treatment signifies depletion primarily of factor VII and protein C. This may denote paradoxical hypercoagulability due to protein C depletion and risk of warfarin-induced skin necrosis, particularly in congenitally protein C-depleted patients. Drug interactions are numerous. Anticoagulant effect is very sensitive to changes in hepatobiliary and gastrointestinal function and dietary changes in vitamin K intake. Vitamin K and fresh frozen plasma reverse anticoagulation. Warfarin is teratogenic: 30% of fetuses exposed during weeks 5 to 10 gestation develop bone and cartilage defects. Warfarin

exaggerates hemorrhagic disease of the newborn in the third trimester. Warfarin is Pregnancy Category X (all trimesters).

FDA approvals. VTE treatment and prophylaxis. (Also approved for prosthetic heart valves, acute myocardial infarction, and atrial fibrillation.) ***On the UCLA Formulary.***

V. *Heparin-induced thrombocytopenia/thrombosis*

Frequency of HIT. UFH: about 1-5%. LMWHs: about 0.3-0.8%. Fondaparinux: rarely if at all. Thrombosis occurs in about 30% of HIT cases. The highest HIT incidence is seen in orthopedic, cardiac, and vascular surgery patients during full-dose UFH therapy.⁸ The rate in medical patients during LMWH therapy is 0.8%.⁹

Clinical forms. Drug-dependent HIT (common): Occurs during UFH or LMWH administration. Platelet consumption begins on day 4 to 14 of *de novo* therapy, sooner if antibody is already present from prior/recent drug exposure. Platelet count drops to <100,000/ μ L or <50% of baseline and recovers within 48 to 72 hr after drug discontinuation. *Drug-independent HIT (rare, also known as “delayed-onset” HIT):*¹⁰ UFH or LMWH are no longer being given. About 5 to 19 days after drug exposure, thrombocytopenia occurs, often presenting as new thrombosis. A high index of clinical suspicion is required. In both clinical forms, the heparin-platelet factor 4 EIA (commonly known as the “heparin-associated platelet antibody” test, or “HAPA”) is almost always positive, very seldom negative. A positive result is specific for antibodies but not HIT; a negative result has strong negative predictive value.

Clinical thrombosis. Venous (DVT, PE, cerebral veins and dural sinuses, other), arterial (extremity, coronary, cerebral, splanchnic, other), skin necrosis at GAG injection sites (indistinguishable from warfarin-induced skin necrosis). Without alternative anticoagulation, new thrombotic events are common for the first two weeks after discontinuation of UFH or LMWH.

Overdiagnosis of HIT. HIT is overdiagnosed because physicians have a high index of suspicion stemming from the serious consequences of thrombosis, thrombocytopenia is common in hospitalized patients, many UFH- or LMWH-exposed patients develop antibodies picked up in the HAPA test even though most are non-pathogenic, and because insufficient attention has been paid to other causes of thrombocytopenia and whether the time course is consistent. An erroneously applied diagnosis of HIT is a particularly serious matter in patients anticipating cardiac surgery with cardiopulmonary bypass for whom UFH remains the strongly preferred anticoagulant.

VI. Results of clinical studies and meta-analyses

A. Risk factors for VTE

Acute cardiac and/or respiratory decompensation, acute infectious or inflammatory illnesses requiring hospitalization, leg immobilization or paresis, obesity, estrogen (including tamoxifen, estramustine) or thalidomide administration, hypercoagulable states, myeloproliferative disorders, major trauma, major orthopedic surgery on the lower extremities, major general, neurosurgical, gynecologic, or urologic surgery (especially age >60 yr, active malignancy, or prior VTE), pregnancy, postpartum period.¹¹

B. Orthopedic surgery VTE prophylaxis

LMWHs are superior to warfarin, with no excess bleeding complications.¹² LMWH (enoxaparin 30 mg SQ q12h beginning after surgery) is superior to UFH 15,000 units/day in divided doses in total hip replacement.¹³ UFH carries a high risk of HIT and HIT thrombosis in orthopedic surgery.¹⁴ Extending LMWH (enoxaparin) in total hip replacement from 4 to 15 days an additional 3 to 6 weeks reduces imaged and symptomatic VTE.¹⁵ Fondaparinux is superior to LMWH (enoxaparin) in total hip and knee replacement and hip fracture surgery by reduced imaged DVT from 13.7% to 6.8% in the first 11 days, with no excess bleeding complications in patients with glomerular filtration rates >30 cc/min and not treated until 6 hr after surgery.¹⁶ Extending fondaparinux in hip fracture patients from 5 to 9 days an additional 21 days dramatically reduces imaged VTE and also symptomatic VTE from 2.7% to 0.3%.¹⁷

C. Non-orthopedic surgery VTE prophylaxis

UFH 15,000 units/day in divided doses beginning 2 hr before surgery is superior to placebo.¹⁸ LMWH is equivalent to or superior to UFH.¹⁹ Fondaparinux is equivalent to LMWH (dalteparin) starting after surgery in patients at high risk for VTE.²⁰

D. Hospitalized medical patient VTE prophylaxis

UFH (10,000-15,000 units/day divided) is superior to placebo.²¹ LMWHs and UFH are equivalent in preventing DVT, PE, and death; LMWHs cause less bleeding.²² Enoxaparin 40 mg QD is superior to 20 mg QD (which is no better than placebo).²³ Fondaparinux is superior to placebo in patients at high risk for VTE (5.6% vs. 10.5%), with a slight excess of minor bleeding (2.6% vs. 1.0%) and no excess major bleeding.²⁴

E. *Miscellaneous considerations in selecting VTE prophylaxis*

LMWHs and fondaparinux make possible QD dosing (rather than BID or TID required with UFH).

When factoring in drug costs, administration costs, and cost of HIT thrombosis (and potential litigation costs), fondaparinux is highly cost-effective in orthopedic surgery patients. Drug cost differences between UFH (inexpensive), and LMWH and fondaparinux (more expensive) are notable; however, LMWH and fondaparinux may also be cost-effective in non-orthopedic settings.

The Seventh ACCP Consensus Conference discouraged aspirin as VTE prophylaxis in any setting and considered discretionary the use of pneumatic compression or graduated compression stockings as adjuncts to anticoagulation while declining to recommend stockings alone.²⁵

F. *Initial anticoagulant treatment of acute VTE (DVT and PE)*

LMWH is superior to UFH in reducing recurrent thrombosis, serious bleeding complications, and death (reductions up to 20% to 50% in several meta-analyses). The Sixth ACCP Consensus Conference on Antithrombotic Therapy, 2001, recommended that whenever possible clinicians use LMWH rather than UFH.²⁶ This recommendation was perpetuated in the Seventh ACCP Consensus Conference of 2004.²⁷ Clinically stable, low-risk acute DVT patients may be managed as outpatients.²⁸ Fondaparinux is at least as effective and safe as UFH in the initial treatment of PE; it is at least as effective and safe as LMWH (enoxaparin) in the initial treatment of acute DVT. Rates of fatal PE, recurrent VTE, major bleeding, and all clinically relevant bleeding were similar between treatment groups.²⁹

G. *Other management decisions in acute VTE (DVT and PE)*

The only strong indications for IVC filter placement are (1) an absolute indication to anticoagulate for acute proximal DVT or PE with a co-existing absolute contraindication to anticoagulation, (2) convincing failure of anticoagulation with recurrent PE (a rare occurrence), and (3) patients with massive PE and hemodynamic compromise not suitable for thrombolytic therapy. Astute clinical judgment is required for IVC filter placement in less compelling circumstances. Whenever possible, a temporary (retractable) filter should be used.

Thrombolytic therapy and other regional interventions may be useful in acute proximal DVT with severe clinical signs. Thrombolytic therapy (systemic or regional) may be useful in acute PE with hemodynamic compromise or acute pulmonary hypertension.

H. *Intermediate to long-term anticoagulant management of acute VTE*

Allowing for different interpretations of available studies, the standard course of treatment after acute VTE is warfarin (INR 2.0 to 3.0) for 3 to 12 months.³⁰ Factors that may prolong the duration of prophylaxis include a history of recurrent VTE, residual leg venous obstruction demonstrated clinically or by ultrasound, hypercoagulable states, active malignancy, male gender,³¹ necessity for systemic estrogen (including tamoxifen or estramustine), thalidomide, frequent long-distance airline travel, persistent immobility (paresis, casting), and patient preference. Factors that may shorten the duration of prophylaxis include patient preference or physician concern over compliance or safety. For long-term management, an INR target range of 1.5 to 2.0 is superior to placebo,³² but an INR target range of 1.5 to 1.9 is not as effective as a range of 2.0 to 3.0 and does not reduce the incidence of major bleeding complications significantly, nor the need for careful monitoring.³³

VII. *Treatment recommendations*

- A. *VTE prophylaxis, general comments.* We recommend that the benefits and risks of VTE prophylaxis be assessed in every hospitalized medical and surgical patient. Caution with anticoagulation is advised if advanced renal insufficiency or other condition predisposing to bleeding is present. Among UFH, LMWH, and fondaparinux, UFH is the least expensive (when drug cost only is considered) but requires multiple daily injections and produces more HIT. Aspirin is ineffective. Use of compression leg stockings is discretionary; stockings do not substitute for anticoagulants.
- B. *VTE prophylaxis in orthopedic surgery patients (total hip and knee replacement, hip fracture repair).* We recommend fondaparinux 2.5 mg SQ QD beginning at least 6 hr post-operatively. Enoxaparin 40 mg SQ QD beginning pre-operatively or 30 mg SQ BID beginning 12 to 24 hr post-operatively is less preferred. Warfarin alone is acceptable according to the Seventh ACCP Consensus Conference, but we discourage it because onset of anticoagulation is delayed and unpredictable, and short-term hypercoagulability may occur. We recommend against UFH as it is less effective and carries substantial HIT risk. Pre-operative prophylaxis with enoxaparin 30 mg SQ q12h, with its shorter half-life than fondaparinux, may be considered for hip fracture patients awaiting surgery. We recommend a one-month course of treatment after surgery; if fondaparinux cost is prohibitive, after initiating fondaparinux the patient may be transitioned to warfarin.
- C. *VTE prophylaxis in non-orthopedic surgery patients.* We recommend either fondaparinux 2.5 mg SQ QD or enoxaparin 40 mg SQ QD. UFH 5,000 units SQ BID or TID may also be used but requires multiple daily injections, carries a greater risk of HIT, and while drug cost is less than LMWH or

fondaparinux may not provide cost benefit when the expenses of multiple daily injections and HIT thrombosis are factored in.

- D. *VTE prophylaxis in medical patients acutely hospitalized for cardio-respiratory decompensation, infectious or inflammatory illnesses, or others at high VTE risk.* We recommend either enoxaparin 40 mg SQ QD (FDA-approved) or fondaparinux 2.5 mg SQ QD. While only a placebo-controlled trial has been completed with fondaparinux,³⁴ and the drug is not FDA approved in this setting, fondaparinux is likely comparable in efficacy and safety to enoxaparin and likely causes less HIT. UFH 5,000 units SQ BID or TID may also be used but requires multiple daily injections, carries a greater risk of HIT, and while drug cost is less than LMWH or fondaparinux may not provide overall cost benefit when the expenses of multiple daily injections and HIT thrombosis are factored in.
- E. *Acute VTE treatment, general comments.* We recommend that patients with acute DVT be treated as outpatients when clinical status permits. Patients with significant co-morbid conditions, who may not be reliable for initial outpatient therapy, who are considered at elevated bleeding risk, or whose clinical signs are sufficiently severe that thrombolytic or regional intervention is being considered should be hospitalized. Patients with symptoms referable to acute PE should be hospitalized. Patients in whom minimal PE is discovered incidentally may be considered for outpatient care. IVC filter placement should be considered when (1) there is an absolute indication to anticoagulate for acute proximal DVT or PE with a co-existing absolute contraindication to anticoagulation; (2) there is convincing failure of anticoagulation with recurrent PE (a rare occurrence); or (3) the patient has massive PE and hemodynamic compromise and thrombolytic therapy is contraindicated.
- F. *Acute VTE treatment, unstable patients.* Because UFH given intravenously has the most rapid offset of action when discontinued, we recommend that patients with severe clinical signs of acute DVT (massive leg swelling, phlegmasia cerulea dolens) or PE (hemodynamic instability, pulmonary hypertension) be treated with standard full-dose UFH while decisions about thrombolytic therapy, regional interventions, and/or IVC filter placement are pending.
- G. *Acute VTE treatment, stable patients.* We recommend either fondaparinux 7.5 mg SQ q24h (5 mg if body weight is <50 kg; 10 mg if body weight is >100 kg), or enoxaparin 1 mg/kg SQ q12h or 1.5 mg/kg SQ q24h for patients with adequate renal function. UFH is also an option. We recommend UFH for patients with advanced renal insufficiency so that anticoagulation intensity (with PTTs) can be monitored accurately and quickly. Warfarin may be started simultaneously with the GAG anticoagulant. We recommend a starting warfarin dose of 5 to 7.5 mg daily for most patients, with protime

determinations at least every other day at first. Patients already known to require lower dosage, who have impaired liver function or nutritional status, or who are taking drugs known to promote anticoagulant effect, should be started on lower dosage. Starting doses higher than 7.5 mg daily should be reserved for patients known to require higher dosage or who are on drugs known to impair warfarin effect. The GAG anticoagulant should be continued for at least several days, and it may be discontinued when the INR is ≥ 2.0 .

- H. *Acute VTE, long-term management.* We recommend 3 to 12 months' warfarin with an INR target range of 2.0 to 3.0 after a first episode of acute VTE. See section VI.H. concerning factors that may influence duration of therapy. Warfarin interacts with numerous drugs, and we strongly advise that when any new drug is added or a current drug is deleted, or dose changed, the prescribing individual check on-line information concerning drug-warfarin interaction and advise the patient accordingly. Patients should be advised to check over-the-counter drugs for warnings concerning warfarin or bleeding disorders. Patients must also be instructed in the necessity of careful laboratory monitoring, reporting clinical bleeding, reporting significant changes in diet, avoiding excessive alcohol use, and planning pregnancy. Reliable patients requiring indefinite warfarinization may be considered for home protime monitoring. Patients with acute VTE in the context of metastatic malignancy in the absence of other risk factors, particularly those with consumption coagulopathy, often fail warfarin therapy and are better treated with a GAG anticoagulant while malignancy is active.
- I. *HIT treatment, general comments.* The frequency of HIT can be reduced by selecting the safest anticoagulant when a choice exists. Fondaparinux appears to be the safest, followed by LMWH, followed by UFH. HIT remains primarily a clinical diagnosis: one must consider other causes of thrombocytopenia, the time course of thrombocytopenia, whether there has been new thrombosis, the non-specificity of a positive HAPA test, and high negative predictive value of a negative test. We recommend against routine HAPA testing during GAG anticoagulant therapy in the absence of a 50% fall in the platelet count, new thrombosis, or skin necrosis at GAG injection sites; we recommend against HAPA testing when other explanations for thrombocytopenia and the clinical context render HIT an unlikely diagnosis.
- J. *HIT treatment.* UFH and LMWH must not be given.³⁵ Because new thrombotic events are common during the first 2 weeks after discontinuation of UFH or LWMH without alternate anticoagulation,³⁶ we recommend anticoagulation for at least 2 weeks. Argatroban and lepirudin are FDA-approved for this purpose; patients may be transitioned to warfarin once the platelet count has stabilized.³⁷ We recommend argatroban rather than lepirudin because the PTT is a more reliable indicator of anticoagulant intensity, the drug is easier to use in hepatic insufficiency than lepirudin is in

renal insufficiency, argatroban has not been associated with antibody formation, and limiting familiarity to one drug rather than two is advantageous. If lepirudin is selected, we recommend not using a loading dose in order to reduce the risk of anaphylaxis, and we discourage a repeat course of treatment because of the higher anaphylaxis risk. Fondaparinux has anecdotally been used safely and effectively off-label, but its use in HIT is not established; we therefore decline to offer a recommendation.

- K. *Anticoagulation during pregnancy.* For patients requiring prophylaxis, UFH, LMWH, and fondaparinux are acceptable. Because of the long period of anticoagulation involved, UFH carries higher bone demineralization risk, and LMWH and fondaparinux carry substantially higher cost; experience with fondaparinux is not extensive although it appears to be as safe as UFH and LMWH. For patients already on chronic warfarin therapy, waiting for the diagnosis of pregnancy must assume that pregnancy will be discovered before about week 5; warfarin up to about week 5 appears to be non-teratogenic. Switching to a GAG anticoagulant in anticipation of pregnancy adds more injections, cost, and risk of osteopenia. We thus recommend the former option along with patient education. The pregnant patient with HIT poses special problems because danaparoid is no longer available in the U.S. (and it still carried a 4-10% HIT crossover risk), and the efficacy and safety of fondaparinux are unproved. Nevertheless, fondaparinux is the only currently available practical alternative; we advise frequent platelet counts and clinical monitoring for thrombosis during the first 2 weeks of treatment.

VIII. *Summary of treatment recommendations (see section VII for expanded discussion and recommendations).*

VTE prophylaxis

General comments. Caution is advised if advanced renal insufficiency or other condition predisposing to bleeding is present. Aspirin is ineffective. Stockings do not substitute for anticoagulants.

Orthopedic surgery patients (total hip and knee replacement, hip fracture repair). Fondaparinux 2.5 mg SQ QD. Wait at least 6 hr post-operatively before starting. Treat for one month. If the cost is prohibitive, or in patients with renal insufficiency, initiate fondaparinux and transition to warfarin.

Non-orthopedic surgery patients. Fondaparinux 2.5 mg SQ QD or enoxaparin 40 mg SQ QD. The HIT risk of fondaparinux is likely lower than enoxaparin. UFH 5,000 units SQ BID or TID may also be considered but requires multiple daily injections and likely carries the greatest risk of HIT.

Acutely hospitalized medical patients with cardiac, pulmonary, infectious, inflammatory illnesses, and others considered at risk. Enoxaparin 40 mg SQ QD (FDA-approved) or fondaparinux 2.5 mg SQ QD (not FDA-approved). The HIT risk of fondaparinux is likely lower than enoxaparin. UFH 5,000 units SQ BID or TID may also be considered but requires multiple daily injections and likely carries the greatest risk of HIT.

Acute VTE treatment

General comments. Treat favorable-risk acute DVT patients as outpatients. Hospitalize acute PE patients. Consider IVC filter placement when (1) there is an absolute indication to anticoagulate with a co-existing absolute contraindication to anticoagulate; (2) convincing failure of anticoagulation with recurrent PE (rare); and (3) patients with massive PE and hemodynamic compromise not suitable for thrombolytic therapy.

Unstable patients (massive leg swelling, phlegmasia cerulea dolens, hemodynamic instability, pulmonary hypertension). Full-dose UFH while decisions about thrombolytic therapy, regional interventions, and/or IVC filter placement are pending.

Stable patients. Fondaparinux 7.5 mg SQ q24h (5 mg if body weight is <50 kg; 10 mg if body weight is >100 kg) or enoxaparin 1 mg/kg SQ q12h or 1.5 mg/kg SQ q24h for patients with adequate renal function. The HIT risk of fondaparinux is likely lower than enoxaparin. UFH for patients with advanced renal insufficiency so that rapid-turnaround PTTs can be monitored. Begin warfarin at the anticipated maintenance dose simultaneously.

Long-term management. Warfarin for 3 to 12 months' (INR 2.0 to 3.0). See section VI.H. concerning influencing factors. Metastatic cancer patients may be more appropriate for a GAG anticoagulant long-term.

Anticoagulation during pregnancy. UFH, LMWH, and fondaparinux are acceptable. Because of long duration of therapy, UFH carries higher bone demineralization risk, and LMWH and fondaparinux carry substantially higher cost. Warfarin is highly teratogenic between weeks 5 and 10, and it causes fetal bleeding in the last trimester. For the pregnant HIT patient, fondaparinux is a reasonable alternative although unproved.

HIT treatment

UFH and LMWH are contraindicated. Anticoagulate with argatroban. Anticoagulate for at least 2 weeks; may transition to warfarin.

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