Pulmonary Thromboembolism — Prophylaxis and Management Issues

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Venous thromboembolism (VTE) is a common and potentially lethal disease that recurs frequently and is associated with long-term impairment and suffering. Patients with pulmonary embolism (PE) are at risk of death, recurrence of embolism or chronic morbidity. The mortality of PE can be up to 30% in untreated patients. The short-term objectives for the treatment of VTE are to prevent extension of the thrombus, (fatal) PE and the early recurrence of the disease. Long-term aims are to prevent delayed recurrences and sequelae such as the post-thrombotic syndrome and pulmonary hypertension.

RISK STRATIFICATION

Pulmonary Embolism (PE) represents a spectrum of syndromes ranging from small peripheral emboli causing pleuritic pain to massive PE resulting in cardiogenic shock or cardiac arrest. Risk assessment of patients is important for selecting the appropriate management strategy. Risk stratification in PE includes (a) clinical evaluation and ECG, (b) cardiac biomarkers, (c) echocardiography, and (d) chest computed tomography (CT).

Clinical Examination

The history and physical examination provide the starting point for risk stratification. The International Cooperative Pulmonary Embolism Registry (ICOPER) identified age >70 years, cancer, congestive heart failure, chronic obstructive pulmonary disease, and systolic blood pressure less than 90 mmHg as significant predictors of increased mortality[1]. The Geneva Prognostic Index is a predictive model of clinical outcome in

Table 1: The Geneva Point Score to assess pulmonary embolism prognosis

Variable	Point score
Cancer	+2
Heart Failure	+1
Prior DVT	+1
Hypotension (systolic BP < 100 mmHg)	+2
Hypoxemia	+1
DVT on ultrasonogram	+1

PE (Table 1) [2]. This index was used to identify low-risk patients who were managed successfully on outpatient basis. The score had to be less than or equal to 2 to qualify patient for outpatient treatment.

Cardiac Biomarkers

Elevated cardiac biomarkers correlate with the presence of RV dysfunction, a powerful independent predictor of early mortality. Elevations of troponin (T and I) levels in PE patients are mild and of short duration compared to those in patients with acute coronary syndromes. A level > 0.1 ng/ml troponin T identifies patients at high risk for adverse clinical outcomes[3]. The stimulus for BNP synthesis and secretion is RV shear stress. Elevations of BNP and NT-proBNP are associated with the presence of right ventricular dysfunction in acute PE. The cut off level for the BNP triage assay to predict a benign clinical outcome in PE patients is lower (< 50 pg/ml) than the "congestive heart failure" cutoff level of 90 pg/ml. The negative predictive value for in-hospital death is high for the biomarker assays and thus helps in identifying low-risk PE patients. In hemo-

dynamically stable PE patients with increased troponin and/or BNP levels, further risk stratification with echocardiography should be done due to low specificity of the assays for PE-related right ventricular dysfunction.

Transthoracic Echocardiography

Echocardiography is an important tool for risk stratification in PE. Patients with RV dysfunction on echo have an increased risk of hypotension, cardiogenic shock, and early death. Echocardiography helps to classify patients into three groups:

1. Low-risk PE (No right ventricular dysfunction) with a hospital mortality of <4%

2. Submassive PE (right ventricular dysfunction and preserved blood pressure) with a hospital mortality of 5 to 10%

3. Massive PE (right ventricular dysfunction and cardiogenic shock) with a hospital mortality of approximately 30%.

One of the limitations of echocardiography is its limited availability at all times and at every medical center. Also obese patients or patients with chronic lung disease may have poor imaging quality of the right ventricle.

Computed Tomography (CT) of the chest is not widely used to stratify patients with PE due to its limited availability and high costs. Using measurements from a reconstructed CT 4-chamber view, RV enlargement, defined as a ratio of RV to LV dimension of greater than 0.9, was a significant independent predictor of 30-day mortality[4].

TREATMENT OF PULMONARY EMBOLISM

Patients with acute PE presenting with a normal blood pressure and no evidence of RV dysfunction generally have a stable course when treated with anticoagulation alone. Normotensive patients with PE and evidence of RV dysfunction are classified as having submassive PE and represent a population at elevated risk for adverse events and early mortality. Massive PE describes patients presenting in cardiogenic shock. Primary therapy for pulmonary embolism consists of clot dissolution with thrombolysis or removal of embolic clot by embolectomy. Primary therapy is generally considered for patients presenting with either massive or submassive PE. Anticoagulation with heparin and warfarin or placement of an inferior vena caval filter constitutes secondary prevention of recurrent PE.

Table 2: Thrombolytic regimens for pulmonary embolism

Lytic agent	Dose regimen
Streptokinase	250,000 to 500,000 U IV as a loading dose over 15 min., followed by 100,000 U/h for 24 h Or 1.5 million U over 60 min
Urokinase	4400 U/kg as a loading dose over 10 min, followed by 4400 U/kg/h for 12-24 h Or 1 million U in 10 min, followed by 2 million U over 2h
Alteplase (t-PA)	100 mg infusion over 2 h
Reteplase	Two IV bolus injections of 10 U, 30 min apart

Thrombolytic Therapy

By relieving pulmonary artery obstruction, thrombolysis can quickly reduce the load on the right ventricle and reverse right heart failure. It prevents the continued release of serotonin and other neurohumoral factors that might otherwise lead to chronic pulmonary hypertension. Thrombolysis may reduce the chance of recurrent embolism by dissolving the residual thrombus in the deep veins. The thrombolytic agents currently in use are presented in Table 2. None of the thrombolytic agents have been shown to be superior to others. All thrombolytics appear to be equally effective and safe when equivalent doses are delivered. It is much more important to ensure that patients receive one of these drugs quickly. In contrast to myocardial infarction, thrombolysis in acute PE appears to be effective for up to 10-14 days after the onset of symptoms. Thrombolytics are equally effective given through a peripheral vein or via a catheter positioned in the pulmonary artery. There is no need to obtain clotting tests during therapy as such tests are of no value in predicting complications or adjusting dosage. The only contemporary FDA-approved thrombolytic regimen is a continuous infusion of 100 mg alteplase over 2 hours. Alteplase is produced by recombinant DNA technology; like urokinase it is non-antigenic and directly converts plasminogen to plasmin, but is relatively more fibrin specific.

Evidence for reduction in morality with the use of thrombolytic agents is sparse. With the exception of one small study, which was terminated when all four patients given thrombolysis survived while all four given heparin died, none of the trials comparing thrombolytic agents with UFH in PE detected any significant difference in mortality[5]. The extent of clinical benefit of fibrinolysis in patients with massive PE is unclear. In a recent analysis of the ICOPER data, fibrinolytics did not reduce the rate of mortality or recurrent PE at 90 days[6]. In submassive PE, Management Strategies and Prognosis

of Pulmonary Embolism-3 Trial (MAPPET-3), the largest clinical trial of thrombolytic therapy versus heparin alone, demonstrated a reduction in the need for escalation of therapy among patients receiving alteplase[7]. Compared to therapy with heparin alone, thrombolysis significantly reduced adverse clinical outcomes, including the need for cardiopulmonary resuscitation, mechanical ventilation, administration of pressors, secondary "rescue" thrombolysis, or surgical embolectomy without an increase in major bleeding.

Every patient being considered for fibrinolysis requires meticulous screening for contraindications because the bleeding risk may be as high as 3.0% for intracranial hemorrhage. Contraindications to thrombolysis such as intracranial disease, active peptic ulcer, uncontrolled hypertension, recent surgery, or trauma, preclude its use in some patients who can safely receive heparin alone.

Surgical Embolectomy

Pulmonary embolectomy with cardiopulmonary bypass is an effective method for managing patients with massive PE who have contraindications for thrombolysis[8]. This strategy is useful for patients with right heart thrombi, patent foramen ovale or atrial septal defect where surgical excision of thrombus or closure of the septal defect is warranted to prevent systemic (paradoxical) embolism. The main predictor of operative death is cardiac arrest with the need for resuscitation before the operation. Mortality is in the range of 0-33% in patients who did not require external cardiac massage and increases to 29-100% in those resuscitated.

Catheter Transvenous Embolectomy

Catheter embolectomy is an alternative technique in patients with massive embolus who can still maintain their blood pressure with vasopressor support[9]. It may be combined with local or systemic thrombolysis if the bleeding risk is not very high. Interventional catheterization techniques include mechanical fragmentation of thrombus with a standard pulmonary artery catheter, clot pulverization with a rotating basket catheter, percutaneous rheolytic thrombectomy, and pigtail rotational catheter embolectomy[10]. Catheter-based embolectomy is most useful when applied to fresh thrombus within the first 5 days of symptoms of PE.

Anticoagulation

Whether or not patients undergo primary therapy, anticoagulation is a critical component of the manage-ment of PE. When PE is diagnosed or strongly suspected, anticoagulation therapy should be initiated immediately unless contraindications exist. The diagnosis should be confirmed if anticoagulation is to be continued.

Standard Unfractionated Heparin

Unfractionated heparin (UFH) is the mainstay of treatment after thrombolysis and for all patients who do not have circulatory embarrassment, and remains the reference therapy for initial anticoagulation. Heparin does not directly dissolve thrombus, but it allows the fibrinolytic system to act unopposed and lyse clot that has already formed. The efficacy of heparin is limited because clot-bound thrombin is protected from heparin-antithrombin III inhibition. Also, heparin resistance can occur because UFH binds to plasma proteins. The dose response to intravenous UFH is highly variable.

Initiating Heparin Therapy

Before heparin therapy is begun, risk factors for bleeding should be considered, such as a prior history of bleeding with anticoagulation, thrombocytopenia, vitamin K deficiency, increasing age, and concomitant drug therapy. UFH can be given by subcutaneous injection, by continuous infusion or as intermittent boluses 4-hourly. Hemorrhage is slightly more common with the bolus technique but, because patients receiving UFH in boluses usually receive greater doses of the drug, it is uncertain whether the difference noted in the rates of bleeding is related to the method of administration or to the difference in the total dose of UFH given[11].

Heparin can be administered by several protocols, but a weight-based approach has been shown to enhance the chances of attaining the therapeutic range quickly. Heparin can be administered as an intravenous bolus of 5000 U followed by a maintenance dose of at least 30,000 U every 24 hours by continuous infusion[12]. Another approach recommended by the American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy is the 'Raschke Nomogram' (Table 3)[13,14]. The regimen consists of a bolus of 80 U/kg followed by 18 U/kg/h, with subsequent weight-based adjusting of the dose. When intravenous UFH is instituted, the aPTT should be aggressively followed at 6-h intervals until it is consistently in the therapeutic range of 1.5 to 2.0 times control values. This range corresponds to a heparin level of 0.2 to 0.4 U/ml as measured by protamine sulfate titration. If the aPTT is prolonged before UFH is started, the possibility of antiphospholipid antibodies should be considered

Table 3: "Raschke Nomogram" for heparin therapy in VTE

Variable	Action
Initial heparin bolus	80 U/kg bolus, then 18 U/kg/h
aPTT <35 seconds (<1.2 x control)	80 U/kg bolus, then increase by 4 u/kg/h
aPTT 35 to 45 seconds (1.2 to 1.5 x control)	40 U/kg bolus, then increase by 2 U/kg/h
aPTT 46 to 70 seconds (1.5 to 2.3 x control)	No change
aPTT 71 to 90 seconds (2.3 to 3.0 x control)	Decrease infusion rate by 2 U/kg/h
aPTT > 90 seconds (>3 x control)	Hold infusion 1 h, then decrease infusion rate by 3 U/kg/h

and, in such patients, the concentration of heparin itself should be assayed. A heparin dose greater than 45000 U/day should not be administered unless a heparin level < 0.2 U/ml is confirmed. True heparin resistance is mainly due to antithrombin deficiency. Neither hepatic nor renal disease seems to interfere notably with the clearance of the drug at therapeutic concentrations. Unfractionated heparin, which can be rapidly reversed, is preferred in patients undergoing fibrinolysis or embolectomy. In contrast to fibrinolysis in myocardial infarction, heparin is withheld during the administration of t-PA for PE and is not restarted until the activated partial thromboplastin time has fallen to less than twice the upper limit of normal.

Treatment with 4-5 days of heparin is as effective as a longer course of 9-10 days[15]. In addition to reducing the length of hospital stay, the shorter heparin course leads to reduction in the risk of heparin-induced thrombocytopenia (HIT) that usually requires at least 5 days of heparin exposure to manifest. The usual duration of therapy for a major PE is about 1 week. Vitamin K antagonists are started together with heparin therapy and should be administered jointly with heparin for at least 5 days; heparin may then be discontinued when the prothrombin time shows an INR above 2.0 on two consecutive days.

Low-Molecular-Weight Heparin (Table 4)

Low-molecular-weight heparin (LMWH) is formed by chemical or enzymatic depolymerization of UFH. Owing to reduced non-specific binding to cationic proteins and cell surfaces, the bioavailability of LMWH after subcutaneous injection is better, dose response is more predictable and the half-life longer than that of UFH. This allows its administration as fixed-dose, once-daily or twice-daily subcutaneous injections, without the need for laboratory monitoring. Unlike UFH, LMWH can inhibit platelet-bound factor Xa and is more resistant to neutralization by platelet factor 4.

LMWH is progressively replacing standard UFH for therapy of venous thromboembolism (VTE). Body-weight adjusted LMWH has been shown to be as effective and safe as standard full-dose UFH in the treatment of proximal DVT and acute hemodynamically stable PE[16]. Meta-analysis show that LMWH therapy results in slightly less recurrent VTE, less major bleeding and slightly lower all-cause mortality over 3 months[17]. The therapeutic index of LMWH is higher than standard UFH. The treatment is cost effective (despite the higher costs of LMWH) and convenient as it allows early mobilization and requires less laboratory supervision. Whereas UFH is largely hepatically cleared, LMWHs are renally cleared. Patients with chronic kidney disease, massive obesity, pregnancy, or unanticipated bleeding or thromboembolism despite correct weight-based dosing of LMWH may benefit from laboratory monitoring of plasma anti-Xa levels. A therapeutic level of anti-Xa for full anticoagulation is in the range of 0.5 to 1.0 units/ml. The peak level is reached 3 to 6 hours after subcutaneous injection.

Complications of Heparin

The most important adverse effect of heparins (UFH and LMWH) is hemorrhage. Hemorrhagic complications occur in up to 15% of patients on full dose UFH, but are serious in less than 5%. Bleeding is more likely if the patient has a potential source, such as active peptic ulcer or any of the risk factors, such as uremia, advanced age, obesity, recent surgery or trauma, severe hypertension, or previous gastrointestinal hemorrhage. Heparin therapy is absolutely contraindicated if the patient has

Table 4: Low-molecular-weight heparins

Name	Treatment dose
Enoxaparin (FDA approved for DVT treatment)	1.0 mg/kg twice daily, or 1.5 mg/kg once daily
Dalteparin (FDA approved, but not for DVT treatment)	100 U/kg twice daily, or 200 U/kg once daily
Nadroparin	4100 U twice daily for <50 kg 6150 U twice daily for 50-70 kg 9200 U twice daily for >70 kg
Reviparin	3500 U twice daily for 35-45 kg 4200 U twice daily for 46-60 kg 6300 U twice daily for >60 kg
Tinzaparin (FDA approved for DVT treatment)	175 U/kg once daily

had a recent hemorrhagic stroke. The management of bleeding on heparin treatment will depend on its location and severity, the risk of recurrent VTE and the aPTT. For most cases, cessation of heparin will suffice, and the aPTT usually returns to normal within 6 hours. In the event of life-threatening or intracranial hemorrhage, protamine sulfate can be administered, which being a strongly basic protein, reverses the anticoagulant activity by forming a stable complex with the acidic heparin. Protamine only partially inhibits the anticoagulant activity of LMWH. One milligram of protamine neutralizes about 100 U of UFH, but no more than 50 mg should be given with a single infusion over 10-30 minutes. Protamine sulfate may cause allergic reactions, particularly in diabetic patients who have had prior exposure to protamine after using neutral protamine Hagedorn (NPH) insulin. A benign transient decrease in platelets may be seen in up to 15% of patients within the first few days of heparin administration. This non-immune- mediated type of thrombocytopenia does not require discontinuation of heparin.

Although the risk is lower with LMWH, use of both UFH and LMWH is associated with the development of immune form of heparin-induced thrombocytopenia (HIT). HIT results from heparin-dependent immunoglobulin G antibodies directed against heparin-platelet factor 4 complex, which results in the activation of platelets and monocytes and may lead to devastating arterial and venous thromboembolism. In HIT, patients develop absolute or relative (greater than 50 percent drop in platelet count) thrombocytopenia. Although it typically occurs within 4 to 14 days of heparin exposure, HIT may occur earlier if the patient has been previously exposed to heparin. Delayed-onset HIT should be considered in patients recently exposed to heparin who present with thromboembolism and experience thrombocytopenia on re-exposure. When HIT is suspected, any source or route of heparin (UFH and LMWH) must be discontinued and clinicians should administer a direct thrombin inhibitor such as argatroban or lepirudin. Vitamin K antagonists may actually aggravate the thrombotic tendency, possibly by suppressing protein C synthesis. Other side effects of heparin include dose-dependent osteoporosis, skin necrosis, alopecia, hypersensitivity reactions, and hypoaldosteronism.

Synthetic Pentasaccharide

Fondaparinux is a synthetic pentasaccharide that selectively catalyzes the inactivation of factor Xa by antithrombin without inhibiting thrombin and is approved by FDA for the initial treatment of venous thromboembolism including PE. In hemodynamically stable patients with acute symptomatic PE, fondaparinux is as safe and effective as intravenous UFH[18]. It is rapidly absorbed following subcutaneous administration and exhibits 100% bioavailability. It exhibits no non-specific binding to plasma or cellular proteins. These properties lead to a predictable dose-response effect. In contrast to heparin compounds, fondaparinux does not cause HIT. Fondaparinux is administered subcutaneously on a once-daily basis in fixed doses of 5 mg for body weight < 50 kg, 7.5 mg for body weight of 50 to 100 kg, and 10 mg for body weight > 100 kg. Unlike UFH, fondaparinux does not require dose adjustment with laboratory coagulation tests. It is contraindicated in patients with severe renal disease.

Direct Thrombin Inhibitors

Direct thrombin inhibitors inactivate both free (fluid-phase) thrombin and fibrin-bound thrombin. Drugs investigated so far include lepirudin (a recombinant hirudin), bivalirudin (semi-synthetic), argatroban (synthetic arginine analogue), desirudin, melagatran and ximelagatran (oral prodrug). Direct thrombin inhibitors have been evaluated in trials of VTE prophylaxis in hip and knee arthroplasty, and were found to be safe and effective. Results from larger phase 3 trials with the oral ximelagatran failed to show any clear superiority to warfarin or enoxaparin in VTE prophylaxis after hip and knee surgery. At present there are no large controlled clinical trials evaluating direct thrombin inhibitors in the treatment of acute PE.

Oral Anticoagulants (Vitamin K antagonists)

Oral vitamin K antagonists such as warfarin have remained the mainstay of outpatient anticoagulation for venous thromboembolism (VTE). The full anticoagulant effect of warfarin may take upto several days even if the INR is in the intended therapeutic range. Elevation of prothrombin time may initially reflect depletion of coagulation factor VII, which has a half-life of about 6 hours, whereas factor II has a half-life of about 5 days. Oral anticoagulation is initiated simultaneously with heparin, LMWH, or fondaparinux and overlapped for at least 5 days to avoid a paradoxical prothrombotic state due to rapid depletion of proteins C and S and until full therapeutic efficacy has been achieved.

Because of multiple drug and dietary interactions with vitamin K antagonists, therapy must be frequently monitored and dose of drug adjusted. The target international normalized ratio (INR) is between 2.0 and 3.0 for the majority of patients with PE. The INR should

be measured daily until it reaches the therapeutic range, then two to three times a week for 2 weeks and, later, in the presence of stable values, once every 2-4 weeks. The initial dose of warfarin should ordinarily be approximately 5 mg. and it should be lowered for debilitated and elderly patients. 'Loading doses' of warfarin should not be employed in initiating oral anticoagulation. Quinolone antibiotics and amiodarone may cause an increase in the INR, whereas vitamin K—containing green vegetables lower the INR. Risk factors for warfarin-related bleeding include hepatic disease, renal dysfunction, alcoholism, drug interactions, trauma, cancer and history of gastrointestinal bleeding.

The optimal duration of anticoagulation depends on the risk of recurrent VTE. For most patients with PE, provided there is no persisting risk factor, 6-12 months of treatment with oral anticoagulation is indicated. Patients who have a 10% estimated annual risk of recurrence and, consequently, a greater than 0.5% annual risk of fatal PE (e.g. those with an idiopathic event and those with ongoing risk factors), in association with a low risk of bleeding, should be considered for indefinite anticoagulation. The PREVENT trial showed that indefinite-duration anticoagulation can be administered safely and effectively with a low-intensity target INR of 1.5 to 2.0 after completion of 6-month full-intensity anticoagulation[19]. However, in the ELATE study, indefinite-duration, full-intensity warfarin was more effective and as safe as indefinite-duration, low-intensity warfarin therapy[20]. Current recommendations advise 6 months of full-intensity anticoagulation followed by indefinite-duration, low-intensity anticoagulation for patients with idiopathic VTE, i.e. in the absence of surgery/trauma within 90 days, metastatic cancer, gastrointestinal bleeding, hemorrhagic stroke, or antiphospholipid antibodies[21].

Ximelagatran, an oral fixed-dose direct thrombin inhibitor, has been favorably evaluated in the THRIVE-3 study, for long-term anticoagulation in patients with idiopathic VTE[22]. However, in another study in patients with chronic atrial fibrillation, it caused asymptomatic increases in liver function tests and so further studies are required before it can be recommended for long-term anticoagulation.

Inferior Vena Cava Filters

The indications for placement of inferior vena cava (IVC) filters are: (a) For patients in whom anticoagulation is contraindicated, (b) For patients who experience recurrent PE despite adequate anticoagulation and (c) For patients undergoing open surgical embolectomy.

IVC filters are associated with an increased incidence of DVT. Retrievable filters should be used for patients with transient contraindications to anticoagulation. Recent analysis from ICOPER demonstrated a significant reduction in 90-day mortality associated with IVC filters.

SUPPORTIVE MEASURES IN ACUTE PE

Patients in pain should receive analgesia, but opiates should be used with caution in the hypotensive patient. Intubation and mechanical ventilation may be needed in patients with hypoxia refractory to oxygen supplementation, but this may further deteriorate the hemodynamic situation by impeding venous return. Judicious use of noradrenalin or dopamine may be required to increase the arterial pressure. The right atrial pressure should be maintained high (15 mmHg), as this filling pressure is necessary for the failing right ventricle to maintain its output. However, fluid loading may be detrimental if there is frank right ventricular distension and a high filling pressure. Vasodilators should be avoided at all times; an exception to this rule in the future may be selective pulmonary vasodilatation by inhaled nitric oxide or prostacyclin.

PROPHYLAXIS OF VENOUS THROMBOEMBOLISM

The implementation of prophylaxis for the prevention of VTE continues to be inconsistent. Prophylactic regimens use mechanical and pharmacological modalities (Table 5)[23]. The specific prophylaxis modality that is chosen is not as important as far as it is understood that all hospitalized patients receive some preventive measure appropriate to their level of risk.

Mechanical Measures consist of graduated compression stockings and intermittent pneumatic compression devices that increase venous blood flow and enhance endogenous fibrinolysis.

Pharmacological Agents include subcutaneously administered unfractionated heparin, LMWH, warfarin, and fondaparinux.

Several studies have validated the use of extended VTE prophylaxis for 4 to 6 weeks in patients undergoing oncological or orthopedic surgery. Certain high-risk populations such as neurosurgical patients may benefit from a combination of mechanical and pharmacological prophylaxis. The safety and efficacy of various VTE prophylactic regimens in medically ill patients has been evaluated. Venous thromboses can be prevented with low, fixed, prophylactic doses of LMWH, such as enoxaparin 40 mg once daily or dalteparin 5000 units once daily. The ARTEMIS study found that fondaparinux

Table 5: Regimens for venous thromboembolism prophylaxis

Indication	Prophylaxis
Medical patients	UFH 5000 units SC TID or Enoxaparin 40 mg SC QD or Dalteparin 5000 units SC QD or Fondaparinux 2.5 mg SC QD or Graduated Compression Stockings (GCS) / Intermittent Pneumatic Compression (IPC) for patients with C/I to anticoagulation. Combined pharmacological and mechanical prophylaxis for very high risk patients Consider surveillance lower extremity ultrasonography for ICU patients
General surgery	UFH 5000 units SC TID or Enoxaparin 40 mg SC QD or Dalteparin 2500 or 5000 units SC QD
Orthopedic surgery	Warfarin (target INR 2.0 to 3.0) or Enoxaparin 30 mg SC BID or Enoxaparin 40 mg SC QD or Dalteparin 2500 or 5000 units SC QD of Fondaparinux 2.5 mg SC QD
Neurosurgery	UFH 5000 units SC BID or Enoxaparin 40 mg SC QD and GCS/ IPC Consider surveillance lower extremity ultrasonography
Oncologic surgery	Enoxaparin 40 mg SC QD
Thoracic surgery	UFH 5000 units SC TID and GCS/ IPC

reduced the risk of VTE among medical patients by 47%[24].

APPROACH TO THERAPY FOR ACUTE PULMONARY EMBOLISM

When there is a suspicion of PE and no strong contraindication to heparin, it is better to start therapy with a bolus of 5000-10000 U of UFH while the diagnostic workup is pursued. Heparin can be stopped if subsequent tests rule out the diagnosis. High-risk patients (massive and submassive PE) should be treated with thrombolysis or embolectomy as primary therapy along with anticoagulation to prevent recurrent VTE. Anticoagulation alone is sufficient in low-risk patients. A general scheme for the therapy of PE is given in Fig. 1.

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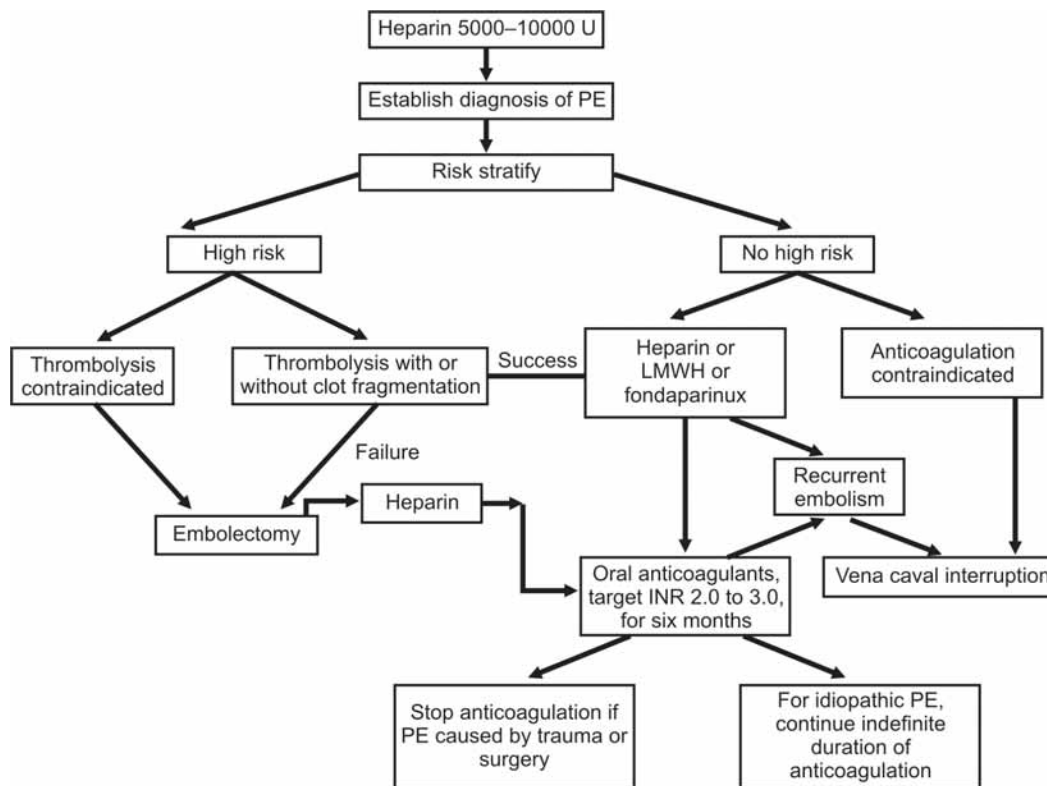3. Giannitsis E, Muller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients

Fig. 1: Approach to therapy for acute pulmonary embolism

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