VENOUS THROMBOEMBOLIC DISEASE

Acute pulmonary embolism 2:
treatment

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Patients with pulmonary embolism are at risk for death, recurrence of embolism or chronic morbidity. Appropriate treatment can reduce the incidence of all. The mortality attributable to pulmonary embolism can be up to 30% in untreated patients, more than 10 times the annual mortality for patients treated with anticoagulant drugs (2.5%). Balanced against the danger of non-treatment are the risks of treatment.

As the primary process leading to pulmonary embolism is deep venous thrombosis (DVT), antithrombotic regimens are the mainstay of treatment. These include drugs that inhibit blood coagulation (heparin, oral anticoagulants, direct thrombin inhibitors), and thrombolytic drugs. Anticoagulation, by preventing clot propagation, allows endogenous fibrinolytic activity to dissolve existing thromboemboli. Anticoagulant treatment is essentially prophylactic, since these agents only interrupt progression of the thrombotic process; unlike thrombolytic agents, they do not actively resolve it. Direct mechanical resolution of the pulmonary vascular obstruction caused by pulmonary embolism can be performed by surgical embolectomy or catheter techniques.

Unfractionated heparin (UFH), low molecular weight heparin (LMWH), direct thrombin inhibitors, and thrombolytic agents in appropriate doses, as well as surgical or catheter embolectomy, are used to treat acute pulmonary embolism. Oral anticoagulants, dextran, physical techniques that counteract venous stasis, inferior vena caval procedures, and lower doses of UFH or LMWH are used for prevention, but these prophylactic regimens are not appropriate for treatment of acute disease.

A general scheme for the treatment of pulmonary embolism is shown in fig 1. When there is a suspicion of pulmonary embolism and no strong contraindication to heparin it is wise to start treatment with a bolus of 5000-10000 U while the diagnostic work up is pursued. If subsequent tests rule out the diagnosis then heparin can be stopped. With established diagnosis, the treatment depends on the circulatory state of the patient. With severely impaired circulation—that is, in patients with hypotension or shock—the relief of pulmonary vascular obstruction must be as fast as possible, and in these patients thrombolytic treatment, perhaps combined with mechanical fragmentation of the clot, is indicated. If these measures fail or if thrombolysis is contraindicated, then emergency embolectomy should be undertaken. If thrombolysis is successful, it is followed by heparin and oral anticoagulants.

Patients with minor embolism, or even massive embolism but stable circulation, are treated with heparin followed by oral anticoagulants. If recurrent pulmonary embolism occurs during this treatment or if anticoagulation is contraindicated, then venous interruption should be considered.

General supportive measures in acute massive pulmonary embolism

Patients in pain should receive analgesia but opiates should be used with caution in the hypotensive patient. When hypoxaemia is refractory to oxygen supplementation by face mask, intubation and mechanical ventilation may be necessary, but this may cause the haemodynamic situation to deteriorate further by impeding venous return. When the cardiac output is reduced, the dilated right ventricle is hypoxic and already near maximal stimulation from the high concentration of endogenous catecholamines; it is unlikely to respond to inotropic agents, which may do no more than precipitate arrhythmias. When necessary because of a dangerous fall of systemic pressure, the judicious use of noradrenaline (norepinephrine) titrated against a moderate increase in blood pressure might be beneficial in improving right ventricular function and systemic haemodynamics. The right atrial pressure should be maintained at a high level (15 mm Hg) since this filling pressure is necessary for the failing right ventricle to maintain its output; if the right atrial pressure falls for any reason, administration of fluid is helpful. However, fluid loading might be detrimental in case of frank right ventricular distention and high filling pressure, since it may augment ventricular interaction both by increasing pericardial pressure and by shifting the ventricular septum leftwards, thus decreasing left ventricular preload and output. Vasodilators should be avoided at all times; an exception to this rule may in the future be selective pulmonary vasodilatation by inhalation of nitric oxide or prostacyclin.

In the absence of circulatory failure, routine monitoring is sufficient. In patients with shock, at least a central venous line should be inserted to permit repeated measurements of pressure and the administration of drugs. Monitoring with a pulmonary artery catheter is useful in estimating the response to treatment. When thrombolytic treatment is considered, the antecubital route should be preferred and insertion of arterial lines avoided.

Heparin

UFH is the standard treatment after thrombolysis and for all patients who do not have severe circulatory embarrassment. Heparin acts by catalysing the effect of antithrombin III (ATIII), so that this inhibitor efficiently combines with and inactivates a number of serine proteases, notably thrombin (factor IIa), factor

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Figure 1. A general scheme for the treatment of pulmonary embolism.

Xa (fXa), and factor IXa. Of these three enzymes, thrombin is the most sensitive to inhibition by heparin-ATIII. In addition, heparin catalyses the inactivation of thrombin by another plasma cofactor, heparin cofactor II, which acts independently of ATIII.^{1 2}

Heparin actually constitutes “secondary prevention” of recurrent pulmonary embolism rather than primary treatment. It substantially reduces morbidity and mortality from pulmonary embolism by preventing further fibrin deposition on the thrombus. This stops the formation and growth of thrombi and allows the patient’s native fibrinolytic mechanisms to destroy both the emboli that have occurred already and thrombi that are potential further emboli. However, heparin does not directly dissolve thrombus that already exists.

The efficacy of heparin treatment depends on achieving a critical therapeutic concentration of heparin within the first few hours of treatment. Prompt and adequate treatment with UFH, followed by oral anticoagulation for at least three months, results in an 80–90% risk reduction for both recurrent venous thromboembolism and death. UFH also rapidly reduces the mediator induced pulmonary vasoconstriction and bronchoconstriction from thrombin activation and platelet aggregation.

UFH can be given by subcutaneous injection, by continuous infusion or as intermittent boluses four hourly. Haemorrhage is slightly more common with the bolus technique; however, 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 heparin administration or to the difference in the total dose of UFH given. With subcutaneous injection an adequate anticoagulant response is not achieved in the first 24 hours unless a starting dose of at least 17 500 U (or 250 U/kg) every 12 hours is used.¹

Before initiation of heparin treatment, a screening test for the activated partial thromboplastin time (aPTT), prothrombin time, and platelet count are usually sufficient. The main purpose of the screen is to obtain a pretreatment aPTT from the individual patient as a basis of therapeutic control. The presence of antiphospholipid antibodies can be suspected by a prolongation of the aPTT. It is also important to establish a baseline platelet count should heparin induced thrombocytopenia complicate subsequent treatment. Pretherapeutic screening is particularly desirable in patients with a high risk of bleeding, and those with liver or renal disorders.

Because UFH binds to several plasma, platelet, and endothelial proteins (some of them are acute phase reactants, the concentrations of which are raised in sick patients), its plasma concentrations and anticoagulant response are unpredictable, even with weight based dosing. Therefore, careful control of the level of anticoagulation and dose adjustments for the prevention of complications and for the improvement of therapeutic efficacy are mandatory.

The most commonly used clotting test is the aPTT, which is a global coagulation test (sensitive to the inhibitory effects of heparin on thrombin, fXa, and fIXa). Different reagents and coagulation timers make the aPTT quite variable relative to a given heparin concentration. The current recommendation is to give sufficient UFH to prolong the aPTT to a range that corresponds to a plasma heparin concentration of 0.2–0.4 U/ml by protamine titration. This relation can be established a priori by a simultaneous comparison of aPTT and plasma heparin concentrations in 20–30 patients receiving heparin. Once the therapeutic range for the aPTT is known, monitoring of plasma heparin concentrations is seldom necessary. If the laboratory changes its coagulation timer or uses a different thromboplastin for the aPTT,

Table 1 Weight based heparin dosing nomogram

Initial dose	Bolus 80 U/kg, then 18 U/kg/h
aPTT < 35 s (< 1.2 × control)	Bolus 80 U/kg, increase infusion by 4 U/kg/h
aPTT 35–45 s (1.2–1.5 × control)	Bolus 40 U/kg, increase infusion by 2 U/kg/h
aPTT 46–70 s (1.5–2.3 × control)	No change
aPTT 71–90 s (2.3–3 × control)	Decrease infusion rate by 2 U/kg/h
aPTT > 90 s (> 3 × control)	Hold infusion 1 hour, then decrease rate by 3 U/kg/h

aPTT is measured 6 hours after change of dosage, or at least once daily. Data from Raschke *et al.* *Ann Intern Med* 1993;119:874.

the correlation between aPTT and plasma heparin concentrations should be reestablished.

The aPTT test should be performed 4–6 hours after initiation of the treatment and repeated six hours after any change of dosage, and subsequently at least daily. The aPTT should be maintained at 1.5–2.5 times the patient pretreatment or the laboratory mean control value. Failure to achieve this range is associated with an increased risk of recurrent venous thromboembolism. In contrast, there is only a weak association between supratherapeutic aPTT response and the risk of bleeding. A weight based UFH dosing nomogram is useful in rapidly achieving therapeutic goals while avoiding prolonged periods of excessive anticoagulation (table 1). When the bolus method is used, control is difficult because of the wide swings that occur in the plasma heparin concentrations. The best that can be achieved to prevent gross over- or under-anticoagulation is ensuring that there is only a slight prolongation of clotting just before the next dose. If the aPTT is prolonged before UFH is started the possibility of antiphospholipid antibodies should be considered, and in these circumstances the concentration of heparin itself should be assayed. A heparin dose greater than 40 000 U/day should not be administered unless a heparin concentration < 0.2 U/ml is confirmed. True heparin resistance is mainly caused by ATIII deficiency.

The correct duration of heparin treatment for a major pulmonary embolism should be at least a week. Oral anticoagulants are started together with heparin treatment and these should be administered jointly for at least five days; heparin then may be discontinued when the prothrombin time yields an international normalised ratio (INR) above 2.0 on two consecutive days.

Recurrent pulmonary embolism may occur during the first few days of heparin treatment before the clot becomes adherent to the endothelium and does not constitute a therapeutic failure. Many patients who suffer recurrence while receiving heparin will be found to be inadequately anticoagulated as reflected by an aPTT below the therapeutic range. Increasing the dose of heparin should be the initial alteration in treatment in these patients.

Haemorrhagic complications occur in up to 15% of patients on full dose heparin, but are serious in less than 5%. They are most likely if the patient has a potential source of bleeding such as an active peptic ulcer or any of a wide variety of risk factors, the most important of which are a pre-existing bleeding tendency, uraemia, advanced age, recent surgery or

trauma, severe hypertension, previous gastrointestinal haemorrhage, and concomitant antiplatelet treatment. Blood transfusion will correct massive blood loss, but protamine in a slow infusion (10–20 minutes) is the specific antidote. One milligram of protamine neutralises about 100 U of UFH, but no more than 50 mg should be given with a single infusion unless a large overdose of heparin is known to have occurred. Heparin treatment is absolutely contraindicated if the patient has had a recent haemorrhagic stroke.

Occasionally, prolonged administration of high dose heparin (over two months at > 15 000 U daily, used mainly in pregnant patients) leads to osteoporosis. The patient receiving long term heparin should be monitored with tests of bone density, and heparin should be discontinued when bone loss is shown to be progressive. No preventive treatment has been proven effective for heparin induced osteopenia, although supplements of calcium and vitamin D are often given. Skin necrosis and hypersensitivity reactions to heparin are rare. Very rarely, continuous heparin infusion over a few days causes aldosterone depression by an unknown mechanism, which may cause clinically important hyperkalaemia in certain patients—for example, those with renal failure or diabetes.

UFH causes transient mild thrombocytopenia in about 10% of patients and severe thrombocytopenia in less than 5%. The milder variety occurs within the first four days of heparin administration and is the result of the direct aggregation effect of UFH on platelets. The platelet count is generally $100\text{--}150 \times 10^9/\text{l}$. The patient is usually asymptomatic and thrombocytopenia resolves spontaneously in spite of continuation of heparin treatment. The severe heparin induced thrombocytopenia occurs five or more days after starting heparin treatment (or sooner with re-exposure to heparin). It is caused by heparin dependent IgG antibodies that activate platelets leading to arterial or venous thrombus formation. It differs from other types of drug induced thrombocytopenia as it gives rise to both arterial or venous thrombosis as well as haemorrhagic complications. The platelet count is below $100 \times 10^9/\text{l}$ or less than half of the pretreatment value. In established cases, heparin must be stopped, and danaparoid (a heparinoid said to be free of contaminating heparin) or recombinant hirudin (lepirudin) given for temporary anticoagulation. Administering oral anticoagulants in the acute phase of heparin induced thrombocytopenia may actually aggravate the thrombotic tendency, possibly by suppressing protein C synthesis. Adjunctive measures include manoeuvres to salvage ischaemic limbs (thrombectomy or thrombolysis), plasmapheresis, and antiplatelet drugs. Platelet transfusion may worsen the problem and should be avoided. The complications and morbidity related to the heparin induced thrombocytopenia can be prevented if thrombocytopenia is recognised and heparin stopped immediately. It is therefore essential to monitor

Heparin in pulmonary embolism

- The risk of recurrence of thromboembolism is high in patients receiving inadequate initial heparin treatment (aPTT ratio < 1.5)
- The use of a heparin dosing nomogram assures that all patients will achieve the therapeutic range for the aPTT
- Heparin administered by the subcutaneous route cannot be recommended as the initial treatment of pulmonary embolism
- Heparin should be given for at least seven days; oral anticoagulants should overlap with heparin for at least five days. For massive pulmonary embolism, a longer duration of heparin treatment may be considered
- Heparin can be discontinued if the INR > 2.0 for two consecutive days
- Measurement of plasma heparin concentration is useful in patients with baseline elevated aPTT caused by antiphospholipid antibodies and in those requiring large daily doses of heparin (> 40 000 U)

the platelet count in all patients receiving heparin.^{1 2}

Low molecular weight heparin

LMWH is progressively replacing standard UFH for treatment of venous thromboembolism. LMWH is obtained by depolymerisation of UFH, yielding molecules of smaller size. Like UFH, LMWH produces its major anticoagulant effect by activating ATIII. A minimum chain length of 18 saccharides is needed for ternary complex formation of heparin, ATIII, and thrombin. Fewer than half of the LMWH molecules of the different commercial preparations contain > 18 saccharide units needed to inhibit thrombin. In contrast, all LMWH chains catalyse the inhibition of fXa. Consequently, LMWHs have ratios of anti-fXa to anti-fIIa that vary between 4:1 and 2:1, depending on their molecular size distribution. Because virtually all molecules of UFH have > 18 saccharide units, UFH has a ratio of anti-fXa to anti-fIIa of 1:1.¹

Because of reduced binding to plasma proteins, macrophages, platelets, and endothelial cells, the bioavailability of LMWH after subcutaneous injection is better and the half life longer than that of UFH. Therefore, LMWH produces a more predictable anticoagulant response than UFH. The anticoagulant response of a given dose correlates with body weight, so that LMWH may be given in standard doses (anti-fXa U/kg) once or twice daily subcutaneously without laboratory monitoring. Monitoring is usually necessary only in the presence of renal failure or extreme obesity.

Because of its relatively more pronounced anti-fXa effect, LMWH in the therapeutic doses cannot be monitored using the aPTT, which is determined by the antithrombin activity, and anti-fXa assay must be used. For treatment of active venous thromboembolism, the anti-fXa activity should be targeted to the range of 0.4–1.0 U/ml.

The therapeutic index of LMWH (the potential for benefit versus the risk of bleeding) appears to be higher than that of standard UFH. The treatment is cost-effective (despite the higher costs of LMWH) and convenient since it allows early mobilisation and requires less nursing and laboratory supervision. LMWH interacts with platelets and platelet factor 4 less readily and the incidence of heparin induced thrombocytopenia is lower than with standard UFH. The incidence of osteopaenia during long term use also appears to be less than with UFH.

LMWH once or twice daily subcutaneously has been shown to be as effective and safe as standard full dose UFH in the treatment of proximal DVT and acute pulmonary embolism.^{3–6} Some unsolved issues remain to be addressed in specific trials before LMWHs can definitively replace UFH in the treatment of all forms of PE. The therapeutic role of LMWH in patients with massive pulmonary embolism who are haemodynamically unstable remains to be determined. Different preparations of LMWH vary with respect to their mean molecular weights, ratios of anti-fXa to anti-fIIa activity, and degree of binding to plasma proteins (table 2). Properties associated with one LMWH cannot be extrapolated to a different LMWH. For this reason, the findings of clinical trials apply only to the particular LMWH evaluated and should not be generalised to the LMWH at large.^{1 2}

Direct thrombin inhibitors

Clinical evaluation of highly specific, ATIII independent thrombin inhibitors, such as hirudin or hirudin fragments, is just beginning. Hirudin is a progenitor of a family of peptides that directly inhibit thrombin independent of an interaction with ATIII. These peptides, particularly the low molecular weight analogues, more effectively inhibit fibrin deposition in the interstices of a thrombus than does the larger heparin-ATIII complex. They are therefore more effective than heparin in inactivating thrombin bound to fibrin which is a potent stimulus for thrombus growth. Their dose-response curve exhibits linearity over a range greater than that of UFH, and the aPTT test is well suited to monitor their anticoagulant effect. Recombinant hirudin (lepirudin) is available for treatment of heparin induced thrombocytopenia. The half life of lepirudin is relatively short (about 1.3 hours), which is helpful in patients who develop bleeding or who require surgery or invasive procedures. There is no known antidote.

Thrombolytic treatment

Thrombolytic treatment, by actively dissolving the clot, has several potential advantages over anticoagulation in the treatment of patients with pulmonary embolism. By relieving pulmonary artery obstruction, thrombolysis can quickly reduce the load on the right ventricle and reverse right heart failure; consequently, it has the potential to prevent death in the haemodynamically unstable patient who would otherwise not survive the many hours or days required for spontaneous fibrinolysis. Thrombolytic treatment is reserved mainly for patients in whom there is evidence of a severely compromised circulation—for example, hypotension, oliguria or severe hypoxaemia. In patients with pulmonary embolism who also have major proximal DVT, thrombolytic treatment reduces the late morbidity from the thrombosis that often can be considerable. A further potential but unproven advantage of thrombolytic treatment over heparin in such patients is that it may reduce the chance of recurrent embolism by dissolving thrombus before it embolises, and so may reduce the chances of chronic thromboembolic pulmonary hypertension developing at a later date. Although some authorities widen the indication of thrombolysis to patients with pulmonary embolism who have echocardiographic evidence of right ventricular dysfunction, additional information is needed to determine whether right ventricular dysfunction, by itself, is an indication for thrombolysis.

Thrombolytic agents dissolve thrombi by activating plasminogen to plasmin. Plasmin, when in proximity to a thrombus or a haemostatic plug, degrades fibrin to soluble peptides. Circulating plasmin also degrades soluble fibrinogen and, to some extent, factors II, V, and VIII. Moreover, raised concentrations of fibrin and fibrinogen degradation products contribute to the coagulopathy by both inhibiting the conversion of fibrinogen to fibrin and interfering with fibrin polymerisation.

The thrombolytic agents currently in use are streptokinase, urokinase, recombinant tissue

plasminogen activator (rt-PA, alteplase), anisoylated plasminogen streptokinase activator complex (APSAC, anistreplase), and reteplase. Streptokinase is a purified bacterial protein; it binds to plasminogen non-covalently to form an activator complex, which converts other plasminogen molecules to plasmin. Streptokinase is antigenic and cannot be readministered for at least six months, as circulating antibodies may both inactivate the drug and produce allergic reactions. Urokinase is isolated from human urine or cultured embryonic renal cells; unlike streptokinase, urokinase is not antigenic and produces a lytic state by directly converting plasminogen to plasmin. rt-PA is produced by recombinant DNA technology; like urokinase, it is non-antigenic and directly converts plasminogen to plasmin, but it is more fibrin specific (that is, it produces less systemic plasminogen activation) than either streptokinase or urokinase. Fibrin specificity is relative, however, and systemic fibrinogenolysis may occur after the administration of rt-PA. Other thrombolytic agents are either not approved or only seldom used for the treatment of pulmonary embolism in most countries. Some new agents (so called second generation thrombolytics), notably mutants of t-PA (tenecteplase, lanoteplase), staphylokinase, and saruplase (prourokinase) are in clinical testing.

With the exception of one small study that is difficult to interpret, none of the trials comparing thrombolytic agents with UFH in pulmonary embolism has been large enough to detect any significant difference in the most important end point—mortality. Consequently, the degree of angiographic or scintigraphic resolution and changes in haemodynamics were used as surrogate measures. Accelerated early resolution of pulmonary embolism as compared with UFH has been proven in all these agents.⁷ However, this benefit is short lived and there is no difference after several days. Definite evidence that thrombolytic treatment as opposed to heparin reduces mortality in pulmonary embolism is lacking and it is unlikely to be forthcoming because of the logistic problems involved in mounting such a study. The low mortality at three months (< 10%) of patients treated with UFH and oral anticoagulants has

Table 2 Low molecular weight heparins (LMWH)

LMWH	Brand name	Mean molecular weight (daltons)	Ratio of anti-Xa to anti-IIa	Dosage in prophylaxis of VTE (subcutaneously)	Dosage in treatment of VTE (subcutaneously)
Ardeparin	Normiflo	6000	1.9	50 U/kg q12h	130 U/kg q12h
Certoparin	Mono-Embolex	5200		3000 U qd	8000 U q12h
Dalteparin	Fragmin	6000	2.7	2500–5000 U qd	120 U/kg q12h or 200 U/kg qd
Enoxaparin	Lovenox, Clexane	4200	3.8	2000–4000 U qd	100 U/kg q12h
Nadroparin	Fraxiparin	4500	3.6	3100 U qd or 40–60 U/kg qd	< 55 kg: 4000 U q12h 55–80 kg: 6000 U q12h > 80 kg: 8000 U q12h
Reviparin	Clivarin	4000	3.5	1750 U qd	< 60 kg: 4200 U q12h > 60 kg: 6300 U q12h
Tinzaparin	Innohep, Logiparin	6500	1.9	3500 U qd or 50 U/kg qd	175 U/kg qd

VTE, venous thromboembolism; U, international anti-fXa units; qd, every day; q12h, every 12 hours

always precluded the identification of a mortality effect of thrombolytic treatment when a relatively small number of patients were studied. A further factor contributing to the lack of significant reduction of mortality despite impressive early acceleration of thrombus resolution is that patients who survive long enough to be entered into a clinical trial probably make up a group with an improved prognosis, since the most severely affected patients will have died before receiving treatment. Therefore, the numbers of patients required to demonstrate a difference in mortality far exceeds the numbers treated in the centres.

There is only some indirect evidence of better prognosis with thrombolysis. The rate of treatment failure (that is, progression to another form of treatment such as heparin to thrombolysis or thrombolysis to embolectomy) in patients with very severe pulmonary embolism is lower in those treated with thrombolytics than in those who receive UFH. Further indirect evidence comes from a non-randomised study (multicentre registry) of 719 patients without shock, in which 169 patients initially received thrombolytics and 550 were treated with heparin alone. In the group undergoing thrombolysis, mortality at 30 days was significantly lower (4.7% *v* 11.1%) and recurrent pulmonary embolism significantly less frequent (7.7% *v* 18.7%) than in the heparin treated group.⁸ Therefore, a more rapid resolution of pulmonary embolism seems desirable, because prolonged haemodynamic disturbance can only cause harm, and if further emboli develop their haemodynamic effect will be lessened if previous emboli have been partially removed.

Several trials compared different thrombolytics or different dosages of a given thrombolytic. No clear cut advantage of a given drug or a given dosage has been found. rt-PA produces a faster improvement at 2–4 hours than urokinase, but at 12–24 hours there is no significant difference. All thrombolytics appear to be equally effective and safe when equivalent doses are delivered. It probably matters little which agent is used; it is much more important to ensure that patients receive it quickly.⁷

With experiments showing that rt-PA produces continuing thrombolysis after it is cleared from the circulation, and that thrombolysis is both increased and accelerated, and bleeding reduced when the drug is administered over a short period, interest was awakened in using very high doses over a short interval. The rationale supporting such treatment as opposed to prolonged infusion is that the initially high concentration of the drug overwhelms plasminogen activator inhibitor-1 and renders negligible any attenuating effects of this inhibitor on the drug activity. The higher peak plasma concentration results in a higher concentration of the activator on the surface and inside the thrombi. Further, the bolus is cleared rapidly from the circulation, thus preventing large amounts of degradation products from the lysed emboli interacting with continuously infused plasminogen activator which converts circulating (rather than fibrin

bound) plasminogen to plasmin, and in turn, induces the systemic lytic state. However, all studies to date failed to show any significant difference in the early resolution of pulmonary embolism or in bleeding complications. No trial has assessed use of a large bolus dose of streptokinase which, as in the treatment of myocardial infarction, would probably be just as effective and considerably cheaper.⁷

Before initiation of thrombolytic treatment, prothrombin time, aPTT, fibrinogen, and platelets should be measured to make sure that there is no pre-existing coagulation disorder which would complicate thrombolysis. Contraindications include intracranial or intraspinal disease, active internal bleeding, recent major surgery or trauma (within 10 days), and uncontrolled severe hypertension. A blood sample should also be obtained for haemoglobin and for blood typing in case transfusion is required. When streptokinase or APSAC is used, 100 mg hydrocortisone reduces the incidence of side effects. Both agents are not recommended for repeated use or after a recent streptococcal infection.

In contrast to myocardial infarction, thrombolysis in acute massive pulmonary embolism appears effective for up to 10–14 days after the onset of symptoms. Thrombolytics are equally effective when given through a peripheral vein or via a catheter in the pulmonary artery. Generally accepted fixed dosage regimens are given in table 3. There is no need to obtain clotting tests during treatment as such tests are of no value in predicting complications or adjusting dosage. After the conclusion of the thrombolytic treatment, measurements of aPTT and fibrinogen are mandatory in order to determine when heparin (without a bolus) should be instituted. If the post-thrombolysis aPTT exceeds twice the upper limit of normal or the fibrinogen concentration is below 1 g/l, these tests should be repeated every four hours until they reach these concentrations, at which point heparin can be started (or resumed) safely. After the patient has been adequately heparinised, oral anticoagulation is initiated; even if the prothrombin time quickly reaches the target range, it should overlap with heparin for at least five days.

The main complication of thrombolytic treatment is bleeding. All thrombolytics are administered in regimens that are designed to activate fibrinolysis systematically throughout the body. None of these agents will distinguish a pathologic thrombus from a beneficial haemostatic plug. Although rt-PA and APSAC are somewhat more fibrin specific than streptokinase and urokinase, all agents have the

Table 3 Thrombolytic regimens for massive pulmonary embolism

Streptokinase	250000 to 500000 U as a loading dose over 15 mins, followed by 100 000 U/h for 24 hours
Urokinase	4400 U/kg as a loading dose over 10 min, followed by 4400 U/kg/h for 12 hours
rt-PA	10 mg as a bolus, followed by 90 mg in a continuous infusion over 2 hours
APSAC	30 mg in 5 mins
Reteplase	Two bolus injections of 10 U, 30 mins apart

Before treatment, stop heparin

potential to lyse a fresh platelet–fibrin plug anywhere and cause bleeding at this site. The two major factors which increase bleeding risk are prolonged administration of thrombolytics and the use of procedures which involve vessel puncture.

The reported incidence of haemorrhage has varied greatly. If major haemorrhage is arbitrarily defined as fatal bleeding, intracranial haemorrhage, or bleeding that requires either surgery or transfusion, the average overall incidence of major haemorrhage with pulmonary embolism thrombolysis is about 10%, and is similar among the thrombolytic agents used.

The incidence of cerebral bleeding is about 0.5–1.5 % irrespective of the agent or ancillary treatment used. The elderly, patients with uncontrolled hypertension, and those with recent stroke or craniotomy appear to be at especially high risk for cerebral bleeding. Acute profuse gastrointestinal bleeding is usually the consequence of giving thrombolytics to a patient with unsuspected active peptic ulcer. Late bleeding (2–3 days) may be caused by stress ulceration, particularly in very ill patients; thrombolysis is probably irrelevant but subsequent anticoagulation makes things worse. More common than profuse gastrointestinal bleeding is “coffee ground” vomiting, which is often the result of a combination of thrombolysis and superficial gastric mucosal congestion and erosions, and tends to follow a benign clinical course. Iatrogenic bleeding ranges from trivial to life threatening. Rupture of the heart, liver or spleen during attempted resuscitation may lead to fatal bleeding. Arterial or venous puncture should be avoided if possible. Retroperitoneal bleeding can occur during the femoral vein catheterisation for pulmonary angiography if an artery is inadvertently punctured above the inguinal ligament. Microscopic haematuria is common; macroscopic haematuria is rare and may indicate an unsuspected urinary tract neoplasm.

Bleeding from vascular sites can usually be controlled with manual pressure or compression dressings. Management of severe bleeding from an inaccessible site dictates the reversal of thrombolysis. The basic principles are to stop the administration of the thrombolytic and any concomitant anticoagulation, to inhibit plasmin activity, and to replenish fibrinogen and coagulation factors. There is seldom time for elaborate laboratory tests but a prolonged cutaneous bleeding time is a useful bedside marker of continuing plasmin generation. Plasmin activity is inhibited with intravenous aprotinin, with or without additional tranexamic acid orally. Fibrinogen is replaced with fresh frozen plasma or fibrinogen concentrate, but since both of these contain plasminogen it is prudent to give a plasmin inhibitor first, or at least concurrently. Intracranial bleeding is an emergency, and a neurosurgical consultation must be obtained at the first sign of altered mental status or focal neurologic findings.

The second complication of thrombolytic treatment is an allergic reaction to either streptokinase or APSAC, which are bacterial proteins that regularly induce an antigenic

Thrombolysis in pulmonary embolism

- Thrombolysis is indicated in massive pulmonary embolism with right ventricular overload and hypotension
- Thrombolysis is effective up to 10 days after pulmonary embolism
- Laboratory monitoring and dosage adjustments during treatment are not necessary

response in man. Anaphylaxis is very rare (< 0.5%) but flushing, rashes, and fever are relatively common (5–7%). It is unclear whether these are true allergic reactions; they usually respond to hydrocortisone and an anti-histamine.

Pulmonary embolectomy

Embolectomy continues to be undertaken in emergency situations when more conservative measures have failed. The only indication for embolectomy is to prevent death. Unfortunately, it is difficult to identify accurately those who will die without embolectomy. Certainly patients in extremis requiring prolonged resuscitation are indicated for embolectomy; there are only very few reports suggesting that such patients may survive with thrombolytic treatment. Patients who deteriorate haemodynamically after the start of thrombolytic treatment, and whose blood pressure remains below 90 mm Hg in spite of vasopressors, would also seem candidates for surgical intervention. Further, there are still patients in whom thrombolytic treatment is contraindicated or too slow in producing benefit. In all these patients, every attempt should be made to confirm the diagnosis of massive pulmonary embolism before surgery, even if it requires partial cardiopulmonary bypass while definitive diagnostic procedures are being performed. Mortality of patients referred for embolectomy with an incorrect diagnosis approaches 100%.

Statistics regarding mortality following embolectomy are difficult to compare. Data are largely derived from retrospective reviews of historical series, often predating the advent of thrombolysis. In some series, considerable numbers of patients have been operated on more than 24 hours after embolism, questioning the need for the procedure. The results depend greatly on the indications used and the haemodynamic impairment of the patients. Mortality will be high in those patients most in need of embolectomy, and low in patients who would survive without it. Until 1985, the overall mortality was 51% for those done without, and 40% for those done with cardiopulmonary bypass. These results have been improved in recent years, mainly due to routine administration of vasopressors before the induction of anaesthesia and to the use of partial (femoro-femoral) bypass in moribund patients as a means of maintaining the circulation while the

patient and the equipment are prepared to get on to full bypass.⁷ There has been no randomised trial of embolectomy versus thrombolytic treatment and it is unlikely that one of value will ever be performed because of the relative scarcity of these patients.

The main predictor of operative death is cardiac arrest with the need of resuscitation before the operation. Provided the patients reach the operating room without requiring external cardiac massage the mortality is in the range of 0–33%, but it is between 43–84% in those resuscitated. Postoperative complications include acute respiratory distress syndrome (ARDS), mediastinitis, acute renal failure and, of particular concern, severe neurologic sequelae. Late morbidity of patients successfully operated upon is principally neurological in nature; late mortality is low.⁷

Catheter transvenous embolectomy

An alternative technique in patients with massive pulmonary embolism who still can sustain a blood pressure with vasopressor support is catheter embolectomy employing a large steerable catheter with a suction cup on its end, inserted via cutdown in the femoral or jugular vein. Syringe suction captures the embolus in the cup and holds it there while the catheter and the embolus are withdrawn. However, this procedure is rarely undertaken. The results of the only two studies published show that embolus extraction is achieved in about two thirds of the patients, and the mortality in these studies was about 30%.⁷

An alternative manoeuvre of attempting to fragment the embolus is certainly much easier. If angiography shows massive emboli in the main pulmonary arteries it may be possible to break these up, using a pigtail catheter and a guide wire or an angiographic basket. The rationale is that the cross sectional area of the pulmonary vascular bed increases progressively from proximal to distal. Thus the fragmented clot obstructs a smaller percentage of the whole cross sectional area of the pulmonary vascular bed when displaced distally. The pulmonary vascular resistance will thus decrease and the pulmonary blood flow increase. A further advantage of this mechanical disruption of emboli would be enhanced clot exposure to lytic treatment by creation of multiple channels within the emboli.

A number of rotational devices for percutaneous mechanical thrombolysis has been experimentally evaluated; they work by high speed clot fragmentation and aspiration. Embolectomy can also be accomplished with the use of a catheter that delivers high velocity jets of saline that draw the clot toward the catheter tip and subsequently pulverise it. None of these devices has been extensively used in patients to date.

Oral anticoagulants

Oral anticoagulants act in the liver by inhibiting the synthesis of four vitamin K dependent coagulant proteins (factors II, VII, IX, and X), and at least two vitamin K dependent anticoagulant factors, proteins C and S. They do not act immediately because time is required for coagulation factors already present in the plasma to be cleared. It is therefore essential to overlap oral anticoagulants with heparin for at least five days, even if the prothrombin time reaches the target range sooner (the level of protein C declines quickly after initiation of oral anticoagulants, creating a thrombogenic potential).

The prothrombin time, used to adjust the dose of oral anticoagulation, should be reported according to the INR, not the prothrombin time ratio or the prothrombin time expressed in seconds. The INR is essentially a “corrected” prothrombin time that adjusts for the many different assays used. Effective treatment of venous thromboembolism is reflected by an INR of 2.0–3.0. Every effort should be made to maintain the patient in this range. This is facilitated by always aiming for an INR level that is in the mid-level of the INR range (that is, 2.5). Patients with the antiphospholipid syndrome may require a higher INR (2.5–3.5). In some settings, home monitoring of INR is convenient and cost-effective, and may ultimately improve anticoagulation control.

The duration of oral anticoagulation must be tailored to the individual patient. One should balance the risk of bleeding against the risk of recurrence when treatment is discontinued. The later risk includes not only the likelihood of recurrence but also its potential clinical effect; patients with cardiopulmonary disease might tolerate recurrent pulmonary embolism poorly. For most patients, provided there is no persisting risk factor, six months’ treatment is indicated. In patients whose risk factors can be interrupted—for example, transient immobilisation or oestrogen use—treatment may be shorter, but additional clinical trials to test this are needed. Certain groups may require longer or indefinite treatment, including patients with active tumours, thrombophilic disorders, those with proven recurrence of venous thromboembolism, and patients who have chronic thromboembolic pulmonary hypertension. The single best predictor of an increased risk for venous thromboembolism is a prior episode. Patients who have had one episode are at high risk to have another, whether or not they have a defined thrombophilic state.⁹

The risk of haemorrhage is always present and with long term treatment the cumulative risk of serious bleeding is not inconsiderable (6–22 per 1000 patient months). The major determinants of oral anticoagulant induced bleeding are the intensity of the anticoagulant effect, the length of treatment, the patient’s underlying clinical disorder (past gastrointestinal bleeding, hypertension, cerebrovascular disease, renal insufficiency), advanced

Oral anticoagulants after pulmonary embolism

- Treatment with oral anticoagulants can be started together with UFH or LMWH
- Patients with reversible or time limited risk factors should be treated for 3–6 months with a INR target range of 2.0–3.0
- Patients with a first episode of idiopathic venous thromboembolism should be treated for at least six months
- Patients with recurrent venous thromboembolism, active cancer, antiphospholipid syndrome, inhibitor deficiency states, or homozygous factor V Leiden should probably be treated indefinitely
- When oral anticoagulation is either contraindicated (pregnancy) or inconvenient, an adjusted dose of LMWH or UFH to prolong the aPTT to a time corresponding to a therapeutic plasma heparin concentration can be used

age, and the concomitant use of drugs that interfere with haemostasis, above all aspirin. The risk of bleeding increases dramatically with an INR > 4.0. Increased variation in anticoagulant effect, as indicated by variation in the INR, is associated with an increased frequency of haemorrhage independent of the mean INR. If the patient has serious bleeding, the INR should be reduced to 1.0 as soon as possible. Reduction or reversal of the anticoagulant effect can be achieved by stopping treatment (effective after about two days), by administering 1–5 mg of vitamin K₁ orally or in slow infusion (effective within 24 hours), or immediately by replacement of vitamin K dependent coagulation factors with fresh frozen plasma or clotting factor concentrates.

Other side effects are rare (for example, skin necrosis) but the wide range of interactions with other drugs should never be forgotten. Although some drugs are more likely to interact with oral anticoagulants than others, clinicians should increase the frequency of INR monitoring when initiating, discontinuing, or altering the dose of any drug in patients receiving oral anticoagulants. The most frequent problems occur with broad spectrum antibiotics, most of which can lead to sudden over-anticoagulation by killing the natural gut flora which are an important source of vitamin K. Subjects receiving oral anticoagulants are sensitive to fluctuating concentrations of dietary vitamin K, which is obtained predominantly from plant material. Oral anticoagulants must not be used in the first trimester of pregnancy and if possible should be avoided throughout pregnancy.⁹

At discharge from hospital, the patient should be aware of side effects of anticoagulants and interactions with other drugs, and should have written information about the

treatment, as well as an appointment for anticoagulant supervision.

Venous interruption

Venous interruption procedures are designed to prevent emboli from reaching the lungs. They have no effect on the thrombotic process and do not prevent DVT. In the past the main methods were ligation, plication or the application of clips to the outside of the inferior vena cava. These procedures carried an appreciable mortality and morbidity, of which lower limb swelling after ligation was the worst. Nowadays the method of choice is the percutaneous placement of a filter in the inferior vena cava under fluoroscopic guidance.

There is no evidence that the filters have any advantages over anticoagulation for prophylaxis following an acute pulmonary embolism because the incidence of recurrence with anticoagulation alone is so low. Their place is in the rare case in which intensive and prolonged anticoagulation alone fails or adequate anticoagulation cannot be achieved because of strong contraindications (for example, serious multiple injuries, or during and after surgery). Although caval filtration is probably effective in these indications, there is a remarkable lack of controlled studies to support the use of this procedure.^{10 11}

Devices placed in the inferior vena cava may perforate the vessel wall or migrate within and outside the venous system. Thrombosis occurs frequently at the venous access site. Pulmonary emboli, either passing through or around the therapeutic obstruction or originating proximally, have been reported with all these measures. Other late sequelae include caval thrombosis, filter fractures, and leg oedema. Because of the lack of controlled data regarding eventual outcome and the true incidence of complications, if a permanent filter is used long term clinical follow up is appropriate.

Treatment of pulmonary embolism in pregnancy

The management of venous thromboembolism during pregnancy remains controversial because of the lack of prospective trials. Heparin does not cross the placenta, and therefore does not have the potential to cause fetal bleeding or teratogenicity, although bleeding at the utero-placental junction is possible. Oral anticoagulants cross the placenta and may cause fetal developmental abnormalities, fetal bleeding, spontaneous abortions, and stillbirth. Therefore, oral anticoagulants must not be administered in the first trimester of pregnancy (and preferably throughout the entire pregnancy), and all women of childbearing potential taking oral anticoagulants must avoid becoming pregnant.

Pregnant women with pulmonary embolism are best treated initially with continuous intravenous UFH or weight adjusted dose of

subcutaneous LMWH, and then taught to self administer LMWH once daily for the remainder of pregnancy until the onset of labour and further on in the puerperium. If possible, measurement of anti-fXa concentrations approximately four hours after injection and adjustment to a concentration of approximately 0.5–1.2 U/ml should be performed. A high index of suspicion for the development of osteopenia and a two weekly assessment of the platelet count is important. Heparin should be discontinued 24 hours before elective induction of labour. If spontaneous labour occurs in women receiving adjusted dose heparin, careful monitoring of the aPTT is required and, if it is prolonged near delivery, protamine may be required to reduce the risk of bleeding.^{10 11}

Another acceptable approach is to give oral anticoagulants between the 13th and 36th week of gestation, and switch to heparin during the last two weeks of pregnancy. If the mother is admitted in premature labour while still on oral anticoagulants she should be given fresh frozen plasma. Treatment with oral anticoagulants can be resumed immediately after delivery, and continued for at least six weeks postpartum. Their effect on the baby persists for 7–14 days after they are stopped and therefore the baby should be given vitamin K at the time of delivery. Breast feeding is not contraindicated.

Current evidence suggests that thrombolysis is appropriate treatment for massive pulmonary embolism during pregnancy, but not within six hours of delivery or in the early postpartum period because of the high risk of bleeding complications.

The future

A widespread use of LMWHs for the treatment of acute pulmonary embolism is certain. Cost savings should prove substantial and will be directly proportional to the number of hospital days avoided. It is likely that heparinoids and specific thrombin inhibitors will replace UFH or LMWH for some indications, provided that their costs are not prohibitive. Decreased bleeding and less thromboembolic recurrence may also result as we gain experience with these new agents. It is also possible that

synthetic thrombin inhibitors will be developed for oral use; this would open up the possibility for long term use. Optimal duration of anticoagulant treatment in different subgroups of patients with venous thromboembolism have yet to be determined. The risk:benefit ratio of the treatment of small subsegmental pulmonary embolism without residual DVT in the absence of persisting risk factors should be tested. Inhalation of nitric oxide or prostacyclin might prove to be a useful adjunct in the treatment of acute massive pulmonary embolism.

1. Hirsh J, Warkentin TE, Raschke R, *et al*. Heparin and low-molecular-weight heparin. Mechanisms of action, pharmacokinetics, dosing considerations, monitoring, efficacy, and safety. *Chest* 1998;**114**:489S–510S.
• *Recommendations of the ACCP consensus conference on antithrombotic treatment.*
2. Hyers TM, Agnelli G, Hull RD, *et al*. Antithrombotic therapy for venous thromboembolic disease. *Chest* 1998;**114**:561S–78S.
• *Further recommendations of the ACCP consensus conference on antithrombotic treatment.*
3. Théry C, Simonneau G, Meyer G, *et al*. Randomized trial of subcutaneous low-molecular-weight heparin CY 216 (fraxiparine) compared with intravenous unfractionated heparin in the curative treatment of submassive pulmonary embolism. A dose-ranging study. *Circulation* 1992;**85**:1380–9.
• *The first study showing that LMWH (nadroparin) is as effective and safe as UFH in the treatment of submassive pulmonary embolism.*
4. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997;**337**:657–62.
• *In this randomised trial on 1021 patients, fixed dose subcutaneous reviparin given twice daily was as effective and safe as dose adjusted intravenous UFH for the initial management of venous thromboembolism, regardless of whether the patient had pulmonary embolism or a history of venous thromboembolism.*
5. Simonneau G, Sors H, Charbonnier B, *et al*. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. *N Engl J Med* 1997;**337**:663–9.
• *In a randomised study involving 612 patients with acute pulmonary embolism, initial subcutaneous treatment with tinzaparin in a dose of 175 U/kg once daily was as effective and safe as dose adjusted intravenous UFH.*
6. Hull RD, Raskob GE, Brant RF, *et al*. Low-molecular-weight heparin vs heparin in the treatment of patients with pulmonary embolism. *Arch Intern Med* 2000;**160**:229–36.
• *In this double blind randomized trial on 200 patients, tinzaparin given in a dose of 175 U/kg once daily subcutaneously was probably more effective than dose adjusted intravenous UFH for preventing recurrent venous thromboembolism in patients with pulmonary embolism associated with proximal DVT.*
7. Riedel M. Therapy of pulmonary thromboembolism. Part I: acute massive pulmonary embolism. *Cor Vasa* 1996;**38**:93–102.
• *An analysis and review of all reports on pulmonary embolectomy and of all randomised trials of thrombolysis in pulmonary embolism.*
8. Konstantinides S, Geibel A, Olschewski M, *et al*. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism. Results of a multicentre registry. *Circulation* 1997;**96**:882–8.
• *This study demonstrates a survival advantage and reduced risk of recurrence with thrombolytic treatment in patients with pulmonary embolism but without shock. Because of its non-randomised design and selection bias, however, this study has several important limitations.*
9. Hirsh J, Dalen JE, Anderson DR, *et al*. Oral anticoagulants. Mechanism of action, clinical effectiveness, and optimal therapeutic range. *Chest* 1998;**114**:445S–69S.
• *Recommendations of the ACCP consensus conference on antithrombotic treatment.*
10. British Thoracic Society, Standards of Care Committee. Suspected acute pulmonary embolism: a practical approach. *Thorax* 1997;**52**(suppl 4):S1–24.
• *Comprehensive guidelines with practical algorithms on diagnosis and management.*
11. Task Force on Pulmonary Embolism, European Society of Cardiology. Guidelines on diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2000;**21**:1301–6.
• *A comprehensive and authoritative "consensus" review with extensive literature references.*

Abbreviations

APSAC: anisoylated plasminogen streptokinase activator complex (anistreplase)
 ATIII: antithrombin III
 aPTT: activated partial thromboplastin time
 DVT: deep venous thrombosis
 fIIa: activated factor II (thrombin)
 fXa: activated factor X
 INR: international normalised ratio
 LMWH: low molecular weight heparin
 rt-PA: alteplase
 UFH: unfractionated heparin