

Guidelines on the use and monitoring of heparin

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The guideline group was selected to be representative of UK-based medical experts. The drafting group met and communicated by e-mail. Draft guidelines were revised by consensus. Since the initial guideline published by the British Committee for Standards in Haematology (BCSH; Colvin & Barrowcliffe, 1993) evidence-based guidelines on the use and monitoring of heparin have been included in the American College of Chest Physicians Consensus Conferences on Antithrombotic Therapy (ACCP; Hirsh & Raschke, 2004) and the Scottish Intercollegiate Guidelines Network (SIGN; <http://www.sign.ac.uk/guidelines/fulltext/36/section12.html>). Reference to these guidelines is advised for a comprehensive review of the evidence. The recommendations in this BCSH guideline generally reflect those of the ACCP and SIGN and are updated where appropriate to encompass recent studies. The guideline was reviewed by a multidisciplinary sounding board, the BCSH and the British Society for Haematology (BSH) and comments incorporated where appropriate. Criteria used to quote levels and grades of evidence are as in Appendix 3 of the Procedure for Guidelines Commissioned by the BCSH (<http://www.bcs-guidelines.com>).

The target audience for this guideline is healthcare professionals involved in the management of patients receiving heparin.

Guideline update

This guideline will be reviewed in 2008. Interim addendums will be published as required on the BCSH website (<http://www.bcs-guidelines.com>).

Heparin remains the most widely used parenteral anti-thrombotic. The general adoption of low-molecular weight heparins (LMWHs) represents a significant therapeutic advance in terms of ease and convenience of administration. There may also be some advantages in terms of efficacy and fewer side-effects. A further development has been the introduction into clinical practice of the synthetic pentasac-

charide factor Xa inhibitor, fondaparinux. This compound may have additional advantages although its role in prophylaxis and treatment has yet to be fully defined.

The chemistry of heparins

Heparin is a naturally occurring glycosaminoglycan produced by the mast cells of most species. The pharmaceutical drug is extracted from porcine or bovine mucosa. All the products currently used in the United Kingdom are of porcine origin. Heparin consists of alternating chains of uronic acid and glucosamine, sulphated to varying degrees, and has a molecular weight (MW) range of 5000–35 000 Da. Samples of heparin over the last 50 years have shown a steady rise in MW with a concomitant rise in specific activity (Mulloy *et al*, 2000); current preparations have a mean MW of about 13 000–15 000 Da and specific activity of 180–220 IU/mg.

Although unfractionated heparin (UFH) is still employed, for many indications there has been a trend towards use of fractionated or LMWHs. These are manufactured from UFH by controlled depolymerisation using chemical (nitrous acid or alkaline hydrolysis) or enzymatic (heparinase) methods. Although the processes yield different end groups, there is no evidence that these differences in chemical structure affect biological function. The biological properties of any LMWH are primarily determined by its MW distribution. As shown in Table I, the products currently available for clinical use have an average MW between 3000 and 5000 Da. They are heterogeneous in MW, although the polydispersity is less than that of UFH and 60–80% of the total polysaccharides lie between MW 2000 and 8000 Da.

Anticoagulant activities of heparins

All anticoagulant properties of UFH and LMWH depend on the presence of a specific pentasaccharide sequence, which binds with high affinity to antithrombin and potentiates its activity (Lindahl *et al*, 1979). This sequence is present in about one-third of the chains in UFH but in lower proportions in LMWHs because some of these sequences are destroyed by the depolymerisation process. Acceleration of inhibition of factor Xa (anti-Xa activity) requires only the pentasaccharide sequence (approximate MW 1700 Da), but potentiation of thrombin inhibition [anti-IIa activity, also prolongation of

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Table I. Properties of LMWHs

Product	Mean MW (Da)	Anti-Xa/anti-IIa ratio
Tinzaparin	4800	1.6
Enoxaparin	3200	3.9
Dalteparin	5000	2.5
Certoparin	3100	2.4
Parnaparin	3700	2.3
Reviparin	3600	4.2
Bemiparin	2900	9.6
Nadroparin	3600	3.3

LMWH, low-molecular weight heparin; MW, molecular weight.

activated partial thromboplastin time (APTT)] requires a minimum total chain length of 18 saccharides (MW approximately 5400 Da; Lane *et al*, 1984). Therefore, in all LMWH preparations the anti-Xa activity exceeds the anti-IIa activity. The ratio of anti-Xa to anti-IIa activity varies between 1.6 to 4.2 for all except one product, which has the lowest MW and an anti-Xa to anti-IIa ratio of 9.6 (Table I).

There has been much debate about the relative importance of anti-Xa and anti-IIa activity in the anticoagulant effect of LMWHs *in vivo*. Biochemical studies have shown that the fractions with anti-IIa activity are largely responsible for the inhibition of thrombin generation in plasma (Béguin *et al*, 1988). However, fractions with only anti-Xa activity have antithrombotic activity in animals, including the synthetic pentasaccharide, which has now been shown to be an effective antithrombotic agent in clinical trials (Buller *et al*, 2003). Dosage of the various LMWHs correlates better with anti-Xa rather than anti-IIa activity (Barrowcliffe, 1995), and for practical purposes, anti-Xa activity is the only measurement that can be used for monitoring LMWHs. Overall, it seems likely that both types of action contribute to the antithrombotic effects of LMWHs, although the efficacy of fondaparinux as an antithrombotic indicates that anti-Xa activity alone is also effective.

Standardisation of heparins

Unfractionated heparins are assayed in either International Units (IU), defined by the World Health Organization (WHO) International Standard, or United States Pharmacopoeial (USP) Units, defined by the USP standard and assay method. There is a 7–10% difference between the two units. Most products available in Europe are assayed in IU, using the European Pharmacopoeia method, based on prolongation of the APTT of sheep plasma.

When initially developed, LMWHs were assayed against the UFH standard by a variety of different methods and the units for the different products could not be compared readily. An international standard for LMWHs was established in 1986 (Barrowcliffe *et al*, 1988).

Heparin pharmacology

Unfractionated heparin is available as sodium or calcium salt. After subcutaneous injection of equal amounts the overall anticoagulant activity is lower with calcium than with sodium salt, but this does not affect clinical efficacy. There may be a lower incidence of ecchymoses after subcutaneous injection of the calcium than of the sodium salt, but there is no clear evidence for any major differences in the incidence of other haemorrhagic effects. All LMWHs are in the sodium form except fraxiparine (Nadroparin), which is a calcium salt.

Both UFH and LMWHs are given parenterally, either by intravenous or subcutaneous injection. Metabolism is by a saturable mechanism, involving binding to endothelial cells and clearance by the reticuloendothelial system, and a non-saturable mechanism involving mainly renal clearance. Both mechanisms are important for UFH, but renal clearance predominates for LMWHs. This is clinically important as accumulation of LMWHs may occur, with increased bleeding risk, in renal failure. There is no evidence that UFH or LMWHs cross the placenta.

The principal way in which UFH and LMWHs differ is in their pharmacokinetics.

Pharmacokinetics of heparins

Low-molecular weight heparins have longer half-lives than UFH, after both intravenous and subcutaneous injection (Boneu *et al*, 1990). The intravenous half-life is about 2 h, measured as anti-Xa activity, although somewhat shorter (about 80 min) when measured by anti-IIa assay. The half-life of UFH is dose-dependent but, at usual intravenous doses, it is 45–60 min by both assay methods. The subcutaneous half-life of LMWHs is about 4 h, measured as anti-Xa activity although there are some differences in pharmacokinetic profiles between LMWHs. Unlike subcutaneous UFH, which has a bioavailability of <50%, all LMWHs have a bioavailability after subcutaneous injection of 90–100%. These differences in pharmacokinetics and bioavailability are responsible for the successful clinical use of once daily subcutaneous injections of LMWH.

Several proteins interact strongly with heparin to antagonise its anticoagulant activity, the most important being platelet factor 4 (PF4) and protamine. Binding affinity to these proteins is reduced with decreasing MW, so that LMWH preparations require higher concentrations of PF4 or protamine to neutralise their activity than does UFH. Below 18 saccharides, heparin chains become increasingly resistant to neutralisation by either of these agents, so that all LMWHs have a portion of their anti-Xa activity that is non-neutralisable (Holmer & Söderström, 1983; Lane *et al*, 1984). Animal studies suggest that this does not affect the ability of protamine to neutralise the haemorrhagic action of LMWHs (Diness & Ostergaard, 1986), although the lack of a fully efficient method of reversal of LMWHs has been raised as a concern in relation to clinical practice (see below).

Low-molecular weight heparins bind less strongly than UFH to endothelial cells, and this is partly responsible for the difference in pharmacokinetics, because endothelial binding and processing is an important mechanism of clearance for UFH. LMWHs also interact with platelets less readily than UFH, whether measured as potentiation of spontaneous aggregation or inhibition of agonist-induced aggregation (Salzman *et al*, 1980). Finally, LMWHs release lower concentrations of the enzymes lipoprotein lipase and hepatic lipase from the vascular endothelium than UFH. The clinical significance of this is unclear.

Do the LMWH preparations have clinically important differences?

Debate continues about whether LMWH should be regarded as a generic drug or whether each product should be treated as a separate entity (Prandoni & Nenci, 2003). As indicated in Table I, there are clearly recognisable differences in the *in vitro* properties of the various products. For regulatory purposes each manufacturer has to produce specific data on the pharmacology, toxicology and clinical effectiveness of a LMWH. However, there are a number of reasons for considering LMWHs as a family of closely related drugs. They share the same mechanism of action, and although produced by different chemical methods they have similar physicochemical properties. The differences in MW and anticoagulant activity seen *in vitro* are likely to be of diminished significance *in vivo* for two reasons. First, the molecules with high affinity to antithrombin tend to have a higher MW distribution than the low-affinity molecules. Secondly, after subcutaneous injection there is a filtering effect, whereby the highest MW molecules, which have the highest anti-IIa activity, are absorbed least. Thus, the MW and anticoagulant activities of the active species circulating after injection of the various products are likely to be much more similar than would appear from consideration of their *in vitro* properties.

From a clinical point of view, the evidence published so far indicates that any differences in effectiveness and safety among the products, if they exist, must be extremely small, although there have been very few direct comparisons. However, this conclusion may only hold for the group of relatively similar LMWHs. Products, such as Bemiparin, which has a lower MW distribution and much lower anti-IIa activity than the others (Table I), and fondaparinux, the synthetic pentasaccharide with only anti-Xa activity and no anti-IIa activity and a longer half-life of 17 h, could conceivably demonstrate clinical differences; further studies are needed if such differences relative to the LMWHs with higher mean MW are to be substantiated.

Which heparin and when?

In the United Kingdom LMWHs have replaced UFH as the preferred option in many clinical situations. For example, LMWH therapy is now considered the treatment of choice for

the prevention and treatment of venous thromboembolism (VTE) and treatment of acute coronary syndromes in most patients. A further recent development has been the introduction of fondaparinux for the prevention of VTE in patients with hip fracture and those having total knee or hip replacements (Heit, 2002). When deciding on which heparin preparation and what dose to use, clinicians must consider for each patient episode.

- 1 The patient haemostatic potential and hence the intrinsic patient risk of thrombosis or bleeding (patient risk).
- 2 The risk of thrombosis and bleeding associated with the procedure or condition of the patient (disorder risk).
- 3 The relative efficacy of different heparin preparations and doses and the relative bleeding risk associated with these (heparin risk).

The recommendations in this BCSH guideline generally reflect those of the ACCP and SIGN and are updated where appropriate to encompass recent studies. The clinician should refer to the latest edition of the British National Formulary for guidance on product information for licensed indications and dosing regimens of each heparin preparation in each situation. In some instances the antithrombotic superiority of LMWHs over UFH has not been proven but the lower risk of heparin-induced thrombocytopenia with thrombosis (HITT) generally favours their use over UFH (Warkentin *et al*, 1995). In view of the uncertainty of whether LMWHs are interchangeable, generic recommendations have been made in this guideline.

Prevention of venous thromboembolism

Patients should be assessed for risk of VTE and given prophylaxis according to the degree of risk (Thromboembolic Risk Factors (THRIFT) Consensus Group, 1992). Both heparin and non-pharmacological methods should be considered as combined modalities are most effective (Geerts *et al*, 2004).

General and gynaecological surgery

Subcutaneous UFH at a dose of 5000 units 8–12 hourly reduces the risk of symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE) and death because of PE in patients having major general and gynaecological surgery (Collins *et al*, 1988; Clagett & Reisch, 1998). LMWHs are at least as effective and whilst bleeding rates are similar (Koch *et al*, 1997, 2001) there is a lower risk of heparin-induced thrombocytopenia and LMWHs can be administered by once daily subcutaneous injection (Warkentin *et al*, 1995).

Recommendation

Patients undergoing major non-orthopaedic surgery should be considered for LMWH or UFH at recommended prophylactic dose (grade A).

Major elective orthopaedic surgery

The value of thromboprophylaxis in orthopaedic surgery is clear (Collins *et al*, 1988). Collins *et al*'s (1988) meta-analysis showed that UFH resulted in a statistically significant two-thirds reduction in all three outcomes of efficacy in the orthopaedic surgery subgroup: subclinical and clinical DVT, clinical PE and fatal PE. This meta-analysis also showed a 21% reduction in total mortality for all surgical patients primarily because of reduction in fatal PE. LMWHs have been compared with UFH in numerous studies and several meta-analyses have shown at least equivalence in safety and efficacy and in some a small but significant advantage in efficacy (Nurmohamed *et al*, 1992; Koch *et al*, 1997).

Following total hip replacement the incidence of fatal PE is at least 0.37% as shown in the Norwegian Hip Arthroplasty Registry of 67 548 patients (Lie *et al*, 2002). This figure applied to patients who were receiving standard thromboprophylaxis with a LMWH. Unprotected patients would be expected to have a mortality rate of around three times that frequency. Prospective registries confirm that the incidence of fatal PE may have declined over recent years. However, this decline is not to the degree found in British studies, which have been retrospective and subject to incomplete follow up and data collection and are therefore contentious and not accepted internationally (Murray *et al*, 1996; Gillespie *et al*, 2000).

Aspirin has also been assessed in the context of lower limb orthopaedic surgery. The PEP study reported that 160 mg of aspirin started preoperatively and continued for 35 d after hip fracture reduced the incidence of the secondary outcome of VTE by approximately one-third (Pulmonary Embolism Prevention (PEP) Trial, 2000). However, aspirin had no effect on the primary outcome of this study, major vascular events and vascular mortality. Aspirin also had no effect on VTE in hip or knee replacement surgery. The analysis and interpretation of the trial data have been criticised and strong recommendations have been made against aspirin use (Cohen & Quinlan, 2000; Geerts *et al*, 2004). Despite this, many orthopaedic surgeons now use suboptimal therapy with aspirin rather than a LMWH or UFH. There has been no direct comparison of aspirin with either UFH or a LMWH.

Scottish Intercollegiate Guidelines Network concluded in 2002 that patients having total hip or knee replacement (or other elective major orthopaedic surgery) could be considered for UFH, LMWH or aspirin. The aspirin recommendation has recently been strongly discouraged (Geerts *et al*, 2004). Although this was presented as a grade A recommendation, the advice was that 'treatment could be considered'. Furthermore, no preference was indicated between UFH, LMWH and aspirin (<http://www.sign.ac.uk/guidelines/fulltext/36/section12.html>). In contrast, the 7th Consensus Conference of the American College of Chest Physicians on Antithrombotic Agents concluded that subcutaneous LMWH

is the preferred prophylactic option for both elective hip and knee replacement (Hirsh & Raschke, 2004). For hip replacement, adjusted dose UFH was considered an acceptable but more complex alternative and aspirin was considered to be less effective and was not recommended. UFH and aspirin were not recommended for knee replacement.

The optimal duration of prophylaxis after hip or knee replacement remains uncertain. Nowadays hospitalisation is usually for <5 d but DVT risk may persist for up to 2 months after hip replacement. Extended prophylaxis (usually 5 weeks) reduces the incidence of asymptomatic total and proximal DVT and symptomatic VTE by at least 50% (Cohen *et al*, 2001). The ACCP recommended LMWH prophylaxis for at least 7–10 d after surgery with extended prophylaxis for high-risk patients.

In randomised-clinical trials, postoperative administration of fondaparinux has been shown to reduce the risk of asymptomatic VTE in patients undergoing major elective orthopaedic surgery compared with preoperative LMWH (Turpie *et al*, 2002). The rate of 'clinically relevant bleeding' (defined as leading to death or re-operation, or into a critical organ) was said to be not increased. However, there was a significant excess of 'major bleeding' in the fondaparinux group and an indication that excessive bleeding occurred in patients receiving fondaparinux <6 h after surgery. Subgroup analyses later allowed clinical and regulatory approval for commencing fondaparinux at least 6 h postoperatively. Fondaparinux may therefore be superior to LMWH for the prevention of VTE in this group of patients when given as recommended, but some uncertainties have still to be resolved (Heit, 2002). Fondaparinux does not appear to cross-react with anti-PF4/heparin antibodies.

Recommendation

Patients undergoing major elective orthopaedic surgery should be considered for LMWH (or fondaparinux) at recommended prophylactic dose for at least 7–10 d (grade A).

Hip fracture

Venous thromboembolism rates and risk of fatal PE are higher in hip fracture patients than those having elective total hip or knee replacements. Heparins (UFH and LMWH) reduce the risk of asymptomatic VTE but there are insufficient data to establish the effect on symptomatic VTE or mortality (Handoll *et al*, 2002). Aspirin appeared to reduce the risk of VTE in the PEP study; however, there was no effect on mortality. Fondaparinux was shown to be more effective than a LMWH in a single randomised study (Eriksson *et al*, 2001). A more recent study has shown the benefit of prolonged therapy with fondaparinux resulting in a highly significant reduction in both asymptomatic and clinical outcomes (Eriksson & Lassen, 2003).

Scottish Intercollegiate Guidelines Network has recommended that all patients with hip fracture should receive aspirin unless contraindicated (<http://www.sign.ac.uk/guidelines/fulltext/36/section12.html>). The 7th Consensus Conference of the American College of Chest Physicians on Antithrombotic Agents recommended LMWH for patients having hip fracture surgery. Aspirin was not recommended as it was considered less effective.

Recommendation

Thromboprophylaxis with LMWH (or fondaparinux) at recommended prophylactic dose should be considered for hip fracture patients (grade A).

Major trauma

At present there is no evidence that heparins reduce the risk of symptomatic VTE or fatal PE in trauma patients. A meta-analysis of UFH did not indicate benefit (Upchurch *et al*, 1995). A LMWH reduced the risk of asymptomatic VTE in trauma patients compared with UFH (Geerts *et al*, 1996).

Recommendation

Thromboprophylaxis with LMWH at recommended prophylactic dose should be considered for major trauma when not contraindicated by bleeding risk (grade B).

Lower limb plaster casts

Low-molecular weight heparins have been shown to reduce the incidence of asymptomatic DVT in outpatients with lower limb plaster casts (Koch *et al*, 1995; Jorgensen *et al*, 2002; Lassen *et al*, 2002). An effect on fatal PE has not been established.

Recommendation

Patients considered to be at high risk of VTE associated with lower limb plaster cast immobilisation may be considered for thromboprophylaxis with LMWH at recommended prophylactic dose (grade B)

Neurosurgery

Because of the particularly serious consequences of surgery-associated bleeding in neurosurgical patients the antithrombotic role of heparin has been less well defined. Whilst UFH and LMWHs do reduce the risk of VTE there is a significant risk of major bleeding (Iorio & Agnelli, 2000) and for this reason mechanical methods of thromboprophylaxis may be preferable. When assessing the most suitable method of thromboprophylaxis consideration should be given to the

relative risks from bleeding in relation to whether cranial surgery is intracranial or extracranial and whether spinal surgery is intradural or extradural.

Other types of surgery

The principles of risk assessment apply to other types of invasive procedure and the clinician is referred to the Scottish Intercollegiate Guideline 62: prophylaxis of VTE (<http://www.sign.ac.uk/guidelines/fulltext/62/index.html>) for further recommendations in specific subgroups of patients, including those having spinal and epidural anaesthesia.

Medical patients

Most cases of VTE occur in non-surgical patients. However, there are fewer randomised interventional studies with heparin and individual patient risk assessment is less structured and validated than in surgical patients. Meta-analysis has shown that heparin significantly reduces the risk of symptomatic VTE but there is no proven antithrombotic advantage of LMWHs over UFH (Mismetti *et al*, 2000). However, a lower bleeding risk and a lower risk of HIT favours the use of LMWH (Mismetti *et al*, 2000). Validated risk-assessment tools are required to determine which categories of medical patients should be routinely offered LMWH thromboprophylaxis. For example, in the Medenox study, patients more than 40 years old with an anticipated hospital stay of at least 6 d and either congestive heart failure or acute respiratory failure, or a medical condition with an additional risk factor for VTE (as specified in the inclusion criteria), were randomised to enoxaparin or placebo. Treatment with 40 mg enoxaparin was associated with a 63% reduction of venographically documented DVT or PE. Enoxaparin 20 mg was ineffective. More recently, the Prevention of Recurrent Venous Thromboembolism (PREVENT) study, a randomised, prospective, double-blinded study analysed the efficacy and safety of 5000 IU dalteparin compared with placebo as thromboprophylaxis in a total of around 3700 moderate risk hospitalised medical patients for a total of 14 d. Patients were then assessed for the presence of asymptomatic proximal DVT and a significant 45% ($P = 0.0015$) reduction in VTE was observed in the treatment group (Leizorovicz *et al*, 2004). In addition to this, the ARTEMIS study has evaluated the use of the factor Xa inhibitor, fondaparinux, in thromboprophylaxis of medical patients. A significant 47% ($P = 0.029$) reduction in VTE and in fatal PE was seen (Cohen *et al*, 2003).

Recommendation

Medical patients determined to be at high risk of VTE should be considered for thromboprophylaxis with LMWH at recommended prophylactic dose (grade A).

Heparin and cancer

Retrospective meta-analysis of heparin trials suggests that patients with cancer treated with LMWHs for VTE have a survival advantage. This observation has now also been made in some small prospective studies in which patients without VTE were randomised to a LMWH or placebo, in addition to chemoradiotherapy (Altinbas *et al*, 2004; Kakkar *et al*, 2004). The mechanism remains unclear and long-term benefit has not yet been proven. Future studies are required to confirm a beneficial effect and address issues, such as patient selection, dose and duration of therapy. At this stage we do not recommend that patients should receive heparin as an antineoplastic agent outside clinical trials. However, many hospitalised patients with cancer will fall into a high-risk group for VTE and should be considered for thromboprophylaxis with LMWH. The randomised comparison of LMWH *versus* oral anticoagulant therapy for the prevention of recurrent VTE in patients with cancer (CLOT) study (Lee *et al*, 2003) indicated that secondary thromboprophylaxis with a LMWH was more effective than with oral anticoagulant in a cohort of patients with VTE and cancer.

Recommendation

Heparins are not recommended for use as antineoplastic agents outside clinical trials.

Heparin and sickle syndromes

Antithrombotic therapy has not yet been shown to alter the incidence or severity of sickle cell crisis. The incidence of VTE during sickle cell crisis is unclear. The BCSH General Haematology Task force has given an ungraded recommendation that prophylactic anticoagulation should be considered for all patients confined to bed for more than 16 h/d, particularly if there are additional risk factors for VTE, such as a history of previous thromboembolism or insertion of a femoral line. A LMWH at prophylactic dose would seem reasonable. Sickle cell disease is considered an additional risk factor for pregnancy-associated VTE and should be taken into consideration in assessing the need for thromboprophylaxis in pregnancy (<http://www.rcog.org.uk/index.asp?PageID=533>).

Recommendation

Patients in sickle cell crisis should be considered for LMWH at recommended prophylactic dose until recovery from crisis (grade C).

Pregnancy and the puerperium

Heparins, including LMWHs do not cross the placenta and are the anticoagulant of choice for prevention and treatment of

pregnancy-associated VTE. Randomised trials of prophylaxis and treatment have not been performed specifically in pregnant women. Guidelines for thromboprophylaxis have been published by the BCSH (Walker *et al*, 2001) and for treatment by the Royal College of Obstetricians and Gynaecologists (RCOG; <http://www.rcog.org.uk/index.asp?PageID=533>). The principal considerations are:

- 1 due to the altered pharmacokinetics a twice daily dosing regimen for LMWHs is recommended;
- 2 frequent anti-Xa monitoring is not recommended but, if possible, anti-Xa activity should be measured to confirm appropriate dosing, at least until more information is available on the therapeutic use of LMWH in pregnancy (but see below regarding the limitations of monitoring);
- 3 the platelet count should be monitored in the early stages of administration to avoid delayed diagnosis of heparin-induced thrombocytopenia. However, this complication is exceedingly uncommon when LMWH is used prophylactically in asymptomatic pregnant women and in this situation monitoring is not required;
- 4 the duration of therapeutic anticoagulation in the non-pregnant subject with VTE is usually 6 months. As pregnancy is associated with prothrombotic changes in the coagulation system and venous flow, and as the increased coagulation activation persists for some weeks after delivery, a similar duration of anticoagulation is prudent in pregnancy VTE. Thus, therapeutic anticoagulation should usually be continued for at least 6 months. If the VTE occurs early in the pregnancy, provided that there are no additional risk factors, reduction of the dose of LMWH or UFH to prophylactic levels could be considered after 6 months of treatment; and
- 5 the woman should be advised that once she is established in labour or thinks that she is in labour, she should not inject any further heparin. She should be reassessed on admission to hospital and further doses should be prescribed by medical staff.

Decisions regarding the use of spinal anaesthesia in relation to heparin administration should be guided by the perceived benefits in the individual case balanced against the potentially catastrophic effects of local bleeding and should be made by an experienced anaesthetist.

Heparin-associated skin reactions appear to be more common in pregnant women. This may relate to the unusual duration of heparin exposure. Cross-reactivity between heparin preparations, including LMWHs is common and several different heparins may have to be tried.

Ovarian hyperstimulation syndrome during assisted reproduction may be complicated by arterial or VTE. There are insufficient data to reach conclusions on the efficacy of heparin thromboprophylaxis in this situation.

In vitro data suggest fondaparinux is also unlikely to cross the placental barrier (Lagrange *et al*, 2002), but there is very little experience of its use in pregnancy to date.

Treatment of VTE

Limb deep vein thrombosis and pulmonary embolus

Heparin has been shown to reduce the risk of fatal recurrence in patients with symptomatic PE (Barritt & Jordan, 1960) and to result in a low risk of recurrent non-fatal VTE (Carson *et al*, 1992; Douketis *et al*, 1998). LMWHs are at least as effective as UFH for treatment of submassive PE and DVT (Gould *et al*, 1999). LMWHs are preferable in view of the lower risk of HIT. Patients with massive PE should be considered for treatment with thrombolytic therapy (British Thoracic Society Standards of Care Committee, 2003), which should be followed by heparin treatment.

Recommendation. LMWH at recommended therapeutic dose should be used in patients with VTE who are candidates for anticoagulant treatment (grade A).

Patients with DVT can be treated as effectively at home with a LMWH as in hospital (Koopman *et al*, 1996; Levine *et al*, 1996) and home treatment of patients with PE has also been safely achieved.

There are limited data on the use of LMWHs for massive DVT or PE and whilst there is no evidence that LMWHs are likely to be less effective, some clinicians consider UFH the treatment of choice because of its rapid effect and because of clinical experience. When treatment with UFH is started an initial intravenous bolus of 5000 U (or 75 U/kg body weight) is followed by a continuous intravenous infusion (18 U/kg/h). The APTT is generally used to guide dosage (see below).

Twelve hourly subcutaneous UFH is as effective as continuous infusion in patients with DVT (Hommes *et al*, 1992). Monitoring and dose adjustment should be the same as for intravenous therapy. There are no data on subcutaneous administration to patients with PE.

Recommendation. If UFH is used for treatment of VTE a bolus dose of 5000 U (75 U/kg) should be followed by an intravenous infusion of 18 U/kg/h with adjustment of the dose according to at least once daily APTT measurement, with repeat measurement at around 4 h after any dose adjustment. Alternatively an equivalent daily dose can be given by two subcutaneous injections (grade A).

Cerebral venous sinus thrombosis

Unfractionated heparin has been shown to be beneficial. Without heparin treatment mortality is 25–30%. With heparin, mortality is close to 0% (Bousser *et al*, 1985; Einhaupl *et al*, 1991). When given at therapeutic dose (25 000–65 000 U to double the APTT ratio) improvement may be observed within the first few days. Intracerebral haemorrhage is not a contraindication to treatment (Einhaupl *et al*, 1991). There are no data on the use of LMWHs.

Recommendation. Patients with cerebral venous thrombosis should be treated with heparin. If UFH is used it should be at a standard therapeutic dose sufficient to prolong the APTT ratio to twice that of normal (grade B). If a LMWH is used it should be given at a conventional therapeutic dose (grade C).

Intra-abdominal venous thrombosis

Mesenteric vein thrombosis is less common than mesenteric artery thrombosis. Other intra-abdominal pathology is often present. Some cases complicate abdominal surgery. Diagnosis is often made at laparotomy when infarcted bowel is identified and removed. Postoperative heparin therapy is usually commenced.

Portal vein thrombosis often presents as splenomegaly with ascites without evidence of progressive liver disease. Hepatic vein thrombosis is more commonly secondary to myeloproliferative disorders and paroxysmal nocturnal haemoglobinuria than are portal or mesenteric vein thrombosis. Heparin has been used in management. Renal vein thrombosis is also often treated with anticoagulant therapy.

There is no strong evidence base for treatment of intra-abdominal venous thrombosis with anticoagulant therapy. Heparin use is based on the observed benefit in patients with venous thrombosis at other sites and anecdotal case reports of favourable outcome in intra-abdominal thrombosis. Mesenteric, hepatic and portal vein thrombosis are typically managed with anticoagulant therapy. Heparin may be given if acute thrombosis is diagnosed but patients with a chronic presentation may be managed with oral anticoagulation alone. When heparin is given either a LMWH or UFH can be used. Traditionally UFH was given at low dose following surgery, 5000–7500 U 8 hourly (Abdu *et al*, 1987), but more recently full therapeutic doses have also been used. Thrombolytic therapy has been used with apparently favourable outcome in some patients.

Splenic vein thrombosis is rarely diagnosed acutely and when discovered it is often not treated with anticoagulant therapy.

Recommendation. Patients with intra-abdominal venous thrombosis should be considered for treatment with heparin. If UFH is used it may be at low dose or at a therapeutic dose sufficient to prolong the APTT ratio to twice that of normal (grade C). If a LMWH is used it should be given at either conventional prophylactic or therapeutic doses (grade C).

Superficial vein thrombosis

Most cases of superficial vein thrombosis are self-limiting. However, some patients have concurrent DVT or extension into the deep venous system may occur. This is most likely with proximal involvement of the long saphenous vein. A

recent systematic review of the very few studies available concluded that therapeutic or prophylactic doses of LMWH reduce progression and recurrence of superficial thrombophlebitis but there are insufficient data to demonstrate any reduction in the development of DVT (Wichers *et al*, 2005). If warfarin is introduced without heparin, it may be prudent to prescribe a reduced loading dose (for example, 5 mg/d rather than 10 mg/d) as a transient hypercoagulable state may develop with warfarin loading, because of reduction in the plasma concentrations of protein C and protein S. If heparin is given then a higher loading dose of warfarin can be given. Either a LMWH or UFH can be used (grade C)

Recommendation. If heparin treatment is given it can be either LMWH or UFH at either prophylactic or therapeutic dose (grade C).

Arterial thromboembolism

The management of arterial thrombosis may involve both pharmacological and surgical interventions. Thrombolytic and antiplatelet drugs have a primary role but heparin is also often used. Clinicians, units and hospitals should produce local guidelines, policies and procedures to reflect local resources and arrangements. Haematologists will not typically be primarily responsible for defining patient care pathways in these patient groups but will often be asked to advise on the role of monitoring, the risk of bleeding and the management of complications arising from heparin therapy.

Myocardial infarction

Aspirin and thrombolytic therapy are first-line treatments for patients with acute myocardial infarction (MI) without contraindications. In a meta-analysis heparin was not shown to reduce the risk of recurrent ischaemic events in patients with coronary thrombosis treated with thrombolytic therapy (Collins *et al*, 1996). However, the ACCP 6th Consensus Conference on Antithrombotic Therapy recommended that all patients be offered anticoagulant therapy unless a specific contraindication exists (Hirsh & Raschke, 2004). The SIGN guideline on antithrombotic therapy (number 36) largely mirrors this advice (<http://www.sign.ac.uk/guidelines/fulltext/36/section12.html>). Guidance regarding scheduling and dose of heparin depends on the specific thrombolytic drug that is used. Intravenous UFH is recommended for the first 48 h with continued therapeutic anticoagulation (UFH, LMWH or warfarin) recommended in patients at high risk of systemic emboli or VTE, for example, those with:

- 1 anterior Q wave infarction;
- 2 severe left ventricular dysfunction;
- 3 congestive cardiac failure;
- 4 history of systemic or pulmonary embolism;

- 5 echocardiographic evidence of mural thrombus; and
- 6 atrial fibrillation.

All patients should be considered for prophylactic LMWH or UFH until fully mobile, to prevent VTE.

Recommendation. Low-molecular weight heparin thromboprophylaxis should be considered for all patients with acute MI (grade A). Patients at high risk of systemic or PE should be considered for initial treatment with intravenous UFH at therapeutic dose (grade A). Patients treated with thrombolytic therapy may be considered for initial treatment with intravenous UFH at therapeutic dose for the first 48 h.

Acute coronary syndromes

The term acute coronary syndrome is generally used to describe non-ST elevation MI (NSTEMI), non-Q wave MI and unstable angina. Acute ST elevation MI or Q wave MI are distinguished as thrombolytic therapy may be indicated.

In patients with unstable angina therapeutic doses of UFH reduce the risk of MI or death, additional to the beneficial effect of aspirin (Oler *et al*, 1996). LMWHs and UFH result in a similar reduction in death, recurrent angina and bleeding but LMWH therapy is associated with a lower risk of MI, need for revascularisation procedures and thrombocytopenia (Magee *et al*, 2003). Antiplatelet drugs including aspirin and glycoprotein IIb/IIIa inhibitors are also used to treat patients with acute coronary syndromes and local policies should also consider these treatment options.

Recommendation. Low-molecular weight heparin (dose regimens from trials and in the British National Formulary) or intravenous UFH at therapeutic dose should be considered in patients with acute coronary syndromes in addition to the administration of aspirin (grade A).

Coronary angioplasty

It is common practice to give intravenous heparin before and during coronary angioplasty and to continue this for up to 24 h after the procedure using the activated clotting time to determine heparin dose.

Heparin therapy is not routinely indicated postoperatively in patients undergoing coronary artery bypass grafting.

Stroke

Aspirin produces a small but definite net benefit in stroke patients (Chinese Acute Stroke Trial (CAST) Collaborative Group, 1997). There are a small number of studies of heparin use in acute ischaemic stroke that demonstrate benefit, including a recent comparison of UFH with a LMWH (Hillbom *et al*, 2002). However, overviews have shown that neither UFH (International Stroke Trial (IST) Collaborative Group, 1998) nor a

LMWH (Bath *et al*, 2001) have a net benefit in patients with acute stroke. This is because any benefit is offset by the effects of bleeding, especially intracranial haemorrhage.

Recommendation. Stroke patients should be assessed for VTE risk and considered for thromboprophylaxis. If heparin is used then standard prophylactic doses of either UFH or LMWH should not be exceeded.

Peripheral vascular reconstructive surgery

Intraoperative and early postoperative heparin is used in patients having peripheral vascular reconstructive procedures. There is no consensus on practice. If heparin is given it is generally considered that at least conventional therapeutic dose heparin should be used. In a multicentre randomised trial of heparin or not in patients having elective aortic aneurysm repair there was no difference in blood loss, transfusion or arterial thrombosis but there was a reduction in MI in the heparin group (Thompson *et al*, 1996).

Recommendation. If heparin is given to prevent thromboembolic complications it should be given at therapeutic dose (grade C).

Acute critical limb ischaemia

There is no evidence to date of a definite beneficial effect of heparin in patients with acute thromboembolic arterial occlusion. However, heparin is frequently administered at therapeutic dose.

Recommendation. When heparin is given it should be at therapeutic dose.

Special situations

Central venous catheters

Catheter-related thrombosis is common, particularly in patients with femoral vein access (Merrer *et al*, 2001). Low-dose oral anticoagulation reduces the risk of thrombosis but the role of and need for heparin at the time of catheter insertion is unclear. It is common practice to give a prophylactic dose of UFH or a LMWH at the end of the insertion procedure and a small dose of heparin may also be used to flush the catheter. Established thrombosis is treated with standard doses of heparin and oral anticoagulation with or without removal of the catheter (grade C).

Arterial catheters

Prevention and management of thrombosis associated with arterial catheters is similar to that with central venous catheters (grade C).

Haemodialysis

Heparin is used extensively during haemodialysis and haemofiltration to prevent extracorporeal coagulation. For haemodialysis the standard procedure is to administer a bolus dose of UFH followed by a continuous infusion at 250–1000 U/h until the procedure is completed. Treatment is not usually monitored. For haemofiltration heparin is typically monitored by the APTT in much the same way as during treatment of VTE, with a bolus dose followed by an infusion aiming to keep the APTT ratio at two to three times normal. Haemofiltration can also be performed without heparin use, for example, with prostacyclin or in some patients without anticoagulant therapy. There is no randomised trial from which to recommend a preferred heparin regimen and consequently no evidence-based guidelines have been published.

A meta-analysis of randomised trials of use of LMWHs in haemodialysis concluded that there is apparent equivalence with UFH in relation to efficacy and safety, but that more randomised trials are required (Lim *et al*, 2004).

Disseminated intravascular coagulation

Given the heterogeneity of the causes of disseminated intravascular coagulation (DIC) and its severity, it is often difficult to decide on the optimum management of individual patients. Heparin is not used generally but situations in which it may be considered are:

- 1 retained dead fetus syndrome;
- 2 giant haemangioma;
- 3 solid tumour; and
- 4 acute promyelocytic leukaemia.

Heparin is not typically administered to patients with sepsis, placental abruption or liver disease.

In principle UFH is preferable to LMWHs as there is a high risk of bleeding, and rapid reversal, usually by simply stopping a heparin infusion, is often required. The optimal dose of UFH has not been determined but a lower dose than that used to treat localised thrombosis is often used. For example, an infusion of 500 U/h, which equates to 5–10 U/kg/h (a typical standard dose is 15–20 U/kg/h) may be appropriate. In some patients the heparin dose may be titrated to the clinical response, for example, a rise in fibrinogen may be used to determine heparin dose in patients with chronic DIC with hypofibrinogenaemia as in giant haemangioma or aortic aneurysm.

For many years UFH was used in patients presenting with acute promyelocytic leukaemia. The beneficial effect of all *trans*-retinoic acid (ATRA) on the associated coagulopathy has obviated the need for heparin in most patients. The benefit of heparin in ATRA-resistant patients is unknown.

Contraindications to heparin

Relative contraindications are untreated haemophilia and other haemorrhagic disorders, thrombocytopenia with platelets $<80 \times 10^9/l$, a history of heparin-induced thrombocytopenia, peptic ulcer, recent cerebral haemorrhage, severe hypertension, severe liver disease, oesophageal varices, major trauma and recent neurosurgery or eye surgery. Treatment doses of heparin should not be given in conjunction with spinal or epidural anaesthesia. Some patients develop hypersensitivity to heparin. The LMWH formulation Innohep (tinzaparin) contains sulphites, which may cause hypersensitivity.

Because of its principally renal route of elimination, LMWH must be used with caution in subjects with renal failure. When creatinine clearance is known to be <30 ml/min or such a degree of renal impairment is suspected, UFH may be preferred. Where therapeutic anticoagulation is required, use of UFH with monitoring of the APTT is an option. Alternatively, if LMWH is administered as prophylaxis or treatment there is a risk of accumulation and reduced dosage should be used with careful clinical observation for increased bleeding. Monitoring using anti-Xa assay can also be considered in order to detect unacceptably high anticoagulant levels, but the limitations of this approach to monitoring should be appreciated (see below).

Because HIT is a life-threatening complication of heparin use, the platelet count must be monitored. A high index of suspicion for the diagnosis of HIT is essential if the diagnosis is not to be delayed, with potentially lethal consequences. Performance of daily platelet counts from day 4 of first exposure or day 1 of repeat exposure is ideal, but may be difficult to implement in some situations, for example, when thromboprophylaxis with a LMWH is used in pregnancy. Fortunately the complication appears to be very uncommon where a LMWH is introduced in healthy subjects, without active thrombosis or tissue trauma. Development of the condition is unlikely after 14 d of exposure to heparin. The diagnosis and management HIT is the subject of a BCSH evidence-based guideline in preparation.

There is some evidence that UFH and LMWHs may cause a rise in serum potassium concentration through inhibition of aldosterone. However, development of symptomatic hyperkalaemia appears to be unlikely in the absence of an additional cause of hyperkalaemia (Gheno *et al*, 2003).

Heparins and osteoporosis

Long-term heparin use can cause osteoporosis but the absolute risk of symptomatic osteoporosis is unknown (Dahlman, 1993; Monreal *et al*, 1994). Symptomatic vertebral fractures have been reported in approximately 2–3% of patients receiving treatment doses of UFH for more than 1 month. In a matched cohort study of heparin therapy during pregnancy, women receiving heparin had lower bone density compared with

untreated controls (Douketis *et al*, 1996). In another study of 184 women receiving long-term heparin therapy in pregnancy, 2.2% developed vertebral fracture (Dahlman, 1993). A further small, randomised trial reported spinal fractures in six of 40 patients (15%) receiving 20 000 units/d UFH for 3–6 months (Monreal *et al*, 1994). The reason for these discrepant findings is unclear. In the non-randomised study, only women who reported severe back pain were investigated for fracture, whereas in the randomised trial all women were screened for spinal fracture. In addition, women in the randomised trial were significantly older.

The mechanism by which heparin exerts its effects on bone appears to be a decrease in the number of bone-forming cells (osteoblasts), and a decrease in the amount of unmineralised collagen (osteoid) lining the bone surface. In contrast to its effect on osteoblasts, heparin increases the activity of cells that resorb bone (osteoclasts) (Muir *et al*, 1996). Biochemical analysis for markers of bone turnover confirmed these observations. Thus, heparin causes bone loss by decreasing rates of bone formation while increasing rates of bone resorption. In an animal model it was shown that the effects of heparin on bone are reversible (Shaughnessy *et al*, 1995), an important observation that is relevant to the potential of heparin therapy to increase the risk of postmenopausal osteoporosis. However, the results suggested that heparin-induced osteoporosis is only slowly reversible, because heparin binds to bone matrix proteins.

Several lines of evidence now suggest that LMWHs are associated with a lower risk of osteoporosis than UFH. In a study by Monreal *et al* (1994), the LMWH dalteparin was compared to UFH in 80 patients with venous thrombosis treated for 3–6 months. Six of the 40 patients who received UFH developed spinal fractures compared with only one of 40 receiving dalteparin. Loss of bone density has been reported during prolonged exposure to LMWHs (Wawrzynska *et al*, 2003) and occasional reports of severe osteoporosis in young women may indicate individual susceptibility (Sivakumaran *et al*, 1996). However, animal models of heparin-induced osteoporosis also suggest a low risk of osteoporosis with LMWHs compared with UFH (Muir *et al*, 1997).

The conclusion from these data are that LMWH is preferred for long-term use and clinicians and patients should be aware of the risks of osteoporosis and consider this knowledge when determining the risk–benefit ratio of heparin therapy.

Heparins and bleeding

Unfractionated heparin has a short half-life after intravenous administration. Furthermore, its anticoagulant effect is reliably and rapidly reversed using protamine sulphate. The dose of protamine is determined by the heparin exposure: 1 mg of protamine neutralises 80–100 U of UFH when administered within 15 min of the heparin dose. Less is required if protamine is given after a longer period because of the short half-life of intravenous UFH.

Protamine reverses the anticoagulant effect of LMWHs incompletely (Makris *et al*, 2000; Crowther *et al*, 2002), although there is anecdotal evidence of clinical benefit in the bleeding patient (van Veen *et al*, 2005). Protamine has no significant neutralising effect on fondaparinux.

As expected from the mode of action of heparins, plasma infusion is ineffective for reversal of the anticoagulant effect and should not be used for this purpose. Recombinant factor VIIa has been used in the management of life-threatening bleeding because of a LMWH (Ng *et al*, 2003), although experience of use of rVIIa for this purpose is very limited. Recombinant VIIa has been shown to reverse the anticoagulant effect of fondaparinux in healthy volunteers (Bijsterveld *et al*, 2002) but, again, experience in the situation of clinical bleeding is lacking.

Monitoring of heparin dosage

Monitoring of the intensity of the anticoagulant effect of heparins has been considered desirable, especially in the treatment of acute VTE, in an attempt to secure maximal antithrombotic effect without excessive risk of bleeding through overanticoagulation. Accurate laboratory monitoring has proven to be difficult to achieve for both UFH and LMWHs.

Monitoring of therapeutic doses of UFH

Although the thrombin time has been employed in the monitoring of dosage, the great sensitivity to heparin of the standard thrombin time test renders monitoring and dosage adjustment using this test difficult. An alternative method, which employs a high concentration of thrombin, has been advocated, but has not been widely adopted (Ray *et al*, 1996). The APTT has been used most widely for monitoring of therapeutic doses of UFH in VTE. A target ratio *versus* mid-point of normal range of 1.5–2.5 is employed. This is based on the apparent efficacy and safety of a plasma heparin concentration by protamine titration of 0.2–0.4 U/ml, which corresponds to an APTT ratio of 1.5–2.5 in some assays. The evidence that rapid achievement of this 'therapeutic range' is clinically important has been questioned (Hull *et al*, 1992; Anand *et al*, 1996). Furthermore, standardisation between laboratories in the control of heparin therapy using the APTT has not been achieved because of the considerable reagent and instrument variability employed in the APTT, which results in inconsistency in sensitivity to heparin. APTT reagents from different manufacturers, and even different batches, show considerable and clinically important variation when heparin concentration by protamine assay is compared with APTT ratio (Brill-Edwards *et al*, 1993). In addition, the anticoagulant employed, the sample storage time, the conditions used for plasma separation as well as the clot detection method employed in the test each introduce additional variations (Contant *et al*, 1983; Van den Besselaar *et al*, 1987; D'Angelo

et al, 1990). Therefore, local calibration of the APTT assay for each new batch of reagents should be employed in the construction of the therapeutic range for UFH therapy if consistency is to be achieved, as well as standardisation of preanalytical variables. Because the protamine sulphate titration method is not widely used an anti-Xa assay may be used for calibration. A range of 0.35–0.7 anti-Xa units/ml corresponds to 0.2–0.4 heparin units/ml by protamine titration (Hirsh, 1991). In relation to sample storage time, the substantial loss of heparin activity over time in citrated blood can be avoided by use of citrate-theophylline-adenosine-dipyridamole (CTAD) as an alternative anticoagulant, or centrifugation within 1–2 h of collection if citrate is employed.

Monitoring of treatment with LMWHs

The APTT is generally insensitive to LMWHs and cannot be used for dosage monitoring. The anti-Xa assay is more informative but there are significant limitations. As described above, the process of manufacture of LMWHs reduces the anti-IIa activity, in relation to anti-Xa activity but this relationship varies between LMWH preparations (Eriksson *et al*, 1995; Fareed *et al*, 1998). It is likely that the significant residual anti-IIa activity contributes to the anticoagulant effect. Indeed the antithrombin activity appears to be the more important action in kinetic studies (Hemker *et al*, 1986; Béguin *et al*, 1989a,b, 1992 ; Béguin & Hemker, 1990). Therefore, the degree of anticoagulation induced by different LMWHs may not be comparable at the same plasma anti-Xa concentration. Furthermore, the precise mechanism of the antithrombotic action of LMWHs is not fully understood and indeed may not depend upon anti-Xa and anti-IIa activities alone. For example, heparin administration releases tissue factor pathway inhibitor (TFPI) from vascular sites and this could explain some of the antithrombotic effect of subcutaneously administered LMWHs (Hoppensteadt *et al*, 1995). LMWHs vary in their interactions with PF4 and heparin cofactor II present in plasma, and these interactions may also influence the anticoagulant effect. Finally, LMWHs have been standardised ultimately against the 4th International Heparin Standard but there is evidence that this has resulted in an overestimation of the anti-Xa and underestimation of the anti-IIa activity (Hemker & Béguin, 1993; Peyrou *et al*, 1997).

The limitations of monitoring of LMWHs by anti-Xa assay are compounded by the observation that comparability between commercially available assays is poor (Kitchen *et al*, 1999; Kovacs *et al*, 1999). In order to improve accuracy, assays should be LMWH method- and equipment-specific.

Against this background it is unsurprising that anti-Xa assay appears to have poor predictive value for bleeding or thrombosis in subjects receiving a LMWH. For example, in the study by Leizorovicz *et al* (1993), in which 1290 subjects were randomised to a LMWH or UFH as thromboprophylaxis for general surgery, anti-Xa levels did not correlate significantly with haemorrhage, and only weakly with

thrombosis. Also, in a study of treatment of venous thrombosis using a LMWH, dosage adjustment between 0.5 and 1 anti-Xa IU/ml appeared to improve neither efficacy nor safety, although some relationship between degree of coagulation inhibition and antithrombotic efficacy was suggested by a relationship between improvement in Marder score and both anti-Xa and anti-IIa levels (Alhenc-Gelas *et al*, 1994). In relation to bleeding associated with LMWH therapy for VTE, as would be expected, the dose administered is a predictor of bleeding. More major bleeds occur in subjects given the highest doses and this is independent of the anti-Xa level (Niewenhuis *et al*, 1991). In this study, clinical assessment (WHO performance status) was the most important risk factor predicting major bleeding. In summary, monitoring of LMWH administration using anti-Xa assay requires careful assay validation, provides an incomplete picture of the anticoagulant effect and is poorly predictive of antithrombotic efficacy and risk of haemorrhage. At best it provides some indication of the pharmacokinetics of the LMWH administered in an individual subject.

In view of the lack of an ideal method for monitoring of LMWHs it is fortunate that randomised trials have demonstrated the efficacy and safety of LMWH when administered in fixed dosage and without laboratory monitoring for the treatment of VTE (Lensing *et al*, 1995). It is concluded that monitoring is not required as a routine for thromboprophylaxis and treatment with a LMWH. However, clinical trials have excluded subjects at increased risk of bleeding, the very obese and those with severe renal failure and the results may not be generalised for such individuals. Also it has been established that the pharmacokinetics of LMWHs differ in infants younger than 3 months (Massicotte *et al*, 1996) and may also change in pregnancy (Hunt *et al*, 1997; Crowther *et al*, 2000; Bombeli *et al*, 2001). Provided the limitations are recognised, monitoring by anti-Xa assay may provide some guidance on dosage in these situations.

If monitoring of LMWH is undertaken, it is recommended that an anti-Xa chromogenic assay is used. The standard should be a sample of the administered LMWH. Alternatively the WHO Standard for LMWH may be used. Samples taken at 4–6 h after subcutaneous administration are suitable for assessment of peak anti-Xa level. If accumulation of LMWH is suspected, for example in renal failure, additional measurements, including a trough level on a sample taken 24 h after the last dose may be informative.

The Control of Anticoagulation Subcommittee of the Scientific and Standardisation Committee of the International Society for Thrombosis and Haemostasis has made the following recommendations on monitoring of heparin (Greaves, 2002).

- 1 Monitoring of prophylactic doses of UFH is not required.
- 2 Monitoring of prophylactic doses of LMWH is not required routinely. Anti-Xa assay can be employed to detect drug accumulation and risk of overdose in severe renal failure.

- 3 Monitoring of therapeutic doses of LMWH is not required routinely.
- 4 Monitoring of therapeutic doses of UFH can be achieved using the APTT. However, local calibration of the test should be employed to determine the recommended target APTT ratio.
- 5 Use of anti-Xa assays may provide some clue to the pharmacokinetics of LMWH when used to treat thrombosis in those in whom standard or weight-adjusted dosing is likely to be unreliable, especially subjects with severe renal failure, the obese, the pregnant, neonates and infants. Anti-Xa assay may also be of some value in the investigation of unexpected bleeding in a subject receiving a LMWH.
- 6 Where anti-Xa assay is employed to monitor LMWH therapy, local laboratory assay validation for the heparin in use is important and the limited predictive value of the results in terms of antithrombotic efficiency and bleeding risk of LMWH should be appreciated.

Recommendations 1–3 are based on results of randomised-clinical trials of heparin/LMWH prophylaxis or treatment and are grade A. Recommendations 4–6 are based on observational and scientific data.

Audit

Clinicians, units and hospitals should develop written policies for the prevention and treatment of thrombosis that reflect national evidence-based guidelines and these should be incorporated into patient care plans and clinical audit activity.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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