bjh guideline

Guidelines on the diagnosis and management of heparin-induced thrombocytopenia: second edition

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Keywords: clinical haematology, heparin, heparin antibody, heparin-induced thrombocytopenia.

Summary of recommendations

- **Patients who are to receive any heparin should have a baseline platelet count (2C).**
- **Post-operative patients including obstetric cases receiving unfractionated heparin (UFH) should have platelet count monitoring performed every 2–3 d from days 4 to 14 or until heparin is stopped (2C).**
- **Post-cardiopulmonary bypass patients receiving low molecular weight heparin (LMWH) should have platelet count monitoring performed every 2–3 d from days 4 to 14 or until heparin is stopped (2C).**
- **Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring (2C).**
- **Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 d and are receiving any type of heparin should have a platelet count determined 24 h after starting heparin (2C).**
- **Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring (2C).**
- **If the platelet count falls by 30% or more and/or the patient develops new thrombosis or skin allergy or any of the other rarer manifestations of heparin-induced thrombocytopenia (HIT) between days 4 and 14 of heparin administration, HIT should be considered and a clinical assessment made (2C).**
- **HIT can be excluded by a low pre-test probability score without the need for laboratory investigation (2B).**
- **If the pre-test probability of HIT is not low, heparin should be stopped and an alternative anticoagulant started in full dosage whilst laboratory tests are performed (1C).**
- **Platelet aggregation assays using platelet-rich plasma (PRP) lack sensitivity and are not recommended (2C).**
- **Platelet activation assays using washed platelets [heparin-induced platelet activation assay (HIPA) and serotonin release assay (SRA)] have a higher sensitivity than platelet aggregation assays using PRP and are regarded as the reference standard, but are technically demanding and their use should be restricted to experienced laboratories (2C).**
- **Non-expert laboratories should use an antigen assay of high sensitivity. Only the IgG class needs to be measured. Useful information is gained by reporting the actual optical density, degree of inhibition by high dose heparin, and the cut-off point for a positive test rather than simply reporting the test as positive or negative (1B).**
- **In making a diagnosis of HIT, the clinician's estimate of the pre-test probability of HIT, together with the type of assay used and its quantitative result [enzyme-linked immunosorbent assay (ELISA) only] and information on reversal using higher doses of heparin should be used to determine the post-test probability of HIT (2B).**
- **HIT can be excluded in patients with an intermediate pre-test score who have a negative particle gel immunoassay (2B).**
- **HIT can be excluded in all patients by a negative antigen assay of high sensitivity (1A).**
- **Clinical decisions should be made following consideration of the risks and benefits of treatment with an alternative anticoagulant (1C).**
- **For patients with suspected (non-low pre-test probability) or confirmed HIT, heparin should be stopped and full dose anticoagulation with an alternative anticoagulant commenced (1B).**
- **LMWH should not be used in the treatment of HIT (1A).**
- **Warfarin should not be used until the platelet count has recovered to the normal range. When introduced, an alternative anticoagulant must be continued until the International Normalized Ratio (INR) is therapeutic. Argatroban affects the INR and this needs to be considered when using this drug. A minimum overlap of 5 d between non-heparin anticoagulants and vitamin K antagonist (VKA) therapy is recommended (1B).**

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- **Platelets should not be given for prophylaxis (1C) but may be used in the event of bleeding (2C).**
- **If the patient has received a VKA at the time of diagnosis it should be reversed by administering intravenous vitamin K (2C).**
- **Danaparoid in a therapeutic dose regimen is a suitable alternative anticoagulant for use in patients with HIT (1B).**
- **Danaparoid at prophylactic doses is not recommended for the treatment of HIT (1B).**
- **Monitoring the anticoagulant effect of danaparoid using an anti-Xa assay with specific danaparoid calibrators should be considered in patients >90 kg and in patients with renal impairment (glomerular filtration rate <30 ml/min) (2C).**
- **An argatroban infusion adjusted to an activated partial thromboplastin time (APTT) ratio of 1·5–3·0 (but not exceeding 100 s) is a suitable alternative anticoagulant for the treatment of patients with HIT (1C).**
- **Patients on argatroban undergoing transition to warfarin should have an INR $\geq$4 for 2 d prior to discontinuing argatroban (2C).**
- **Therapeutic dose fondaparinux is an acceptable alternative anticoagulant for managing HIT but it is not licensed for this indication. (2C).**
- **Patients should be therapeutically anticoagulated for 3 months after HIT with a thrombotic complication (1A) and for 4 weeks following HIT without a thrombotic complication (2C).**
- **Women with HIT in pregnancy should be treated with a non-cross reacting anticoagulant. Danaparoid should be used where available and fondaparinux also considered (2C).**
- **Patients with previous HIT who are antibody negative (usually so after >100 d) who require cardiac surgery should receive intra-operative UFH in preference to other anticoagulants, which are less validated for this purpose. Pre- and post-operative anticoagulation should be with an anticoagulant other than UFH or LMWH (1B).**
- **Patients with recent or active HIT should have the need for surgery reviewed and delayed until the patient is antibody-negative if possible. They should then proceed as above. If deemed appropriate, early surgery should be carried out with an alternative anticoagulant (1C).**
- **As an alternative anticoagulant in cases where urgent surgery is required we suggest bivalirudin (2B).**
- **In patients with previous or present HIT who require coronary intervention including angiography and percutaneous coronary intervention we recommend the use of bivalirudin (2B).**

Methods

The guideline was drafted by a writing group identified by the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology (BCSH). The 2006 guideline (Keeling *et al*, 2006) was reviewed along with additional information published since 2005. A search was performed of PubMed and Embase using the term 'heparin induced thrombocytopenia' combined with 'diagnosis', 'treatment' and 'clinical presentation'. The search covered articles published from January 2006 to April 2012. References in recent reviews were also examined. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemostasis and Thrombosis Task Force of the BCSH. The guideline was then reviewed by a sounding board of approximately 50 UK Haematologists, the BCSH, and the British Society for Haematology Committee and comments incorporated where appropriate. The 'GRADE' system was used to quote levels and grades of evidence, details of which can be found at: http://www.bcshguidelines.com/BCSH_PROCESS/EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION/43_GRADE.html.

The objective of this guideline is to provide healthcare professionals with clear guidance on the clinical features of heparin-induced thrombocytopenia (HIT), the indications for monitoring of patients on heparins for HIT, the investigation of suspected HIT and the treatment of HIT.

Pathology

The pathophysiology of HIT has been described in several reviews (Warkentin, 2003; Kelton, 2005; Greinacher *et al*, 2010). HIT is caused by the development of IgG antibodies directed against a complex of platelet factor 4 (PF4) and heparin. The antibodies primarily recognize a heparin-induced conformational change in the PF4 tetramers (Horsewood *et al*, 1996) which is affected by the chain length and degree of sulphation of the heparin. This partially explains the differences in incidence of HIT observed with different preparations. Theoretically, the optimal concentration of heparin to produce conditions that favour the development of HIT are thought to be associated with prophylactic rather than therapeutic doses of heparin. The IgG/PF4/heparin complexes bind to and activate platelets through their Fc receptors and may also generate thrombin by other actions (Qian *et al*, 2010) resulting in a prothrombotic condition that is associated with venous and arterial thrombosis.

Incidence, clinical presentation and platelet monitoring

The frequency of HIT in different settings has been comprehensively reviewed (Lee & Warkentin, 2004; Linkins *et al*, 2012). It is important to distinguish between the frequency of antibody detection, antibody formation with thrombocytopenia (HIT), and HIT with thrombosis. The incidence of HIT is greater with bovine than with porcine heparin

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and for thromboprophylaxis is greater with unfractionated heparin (UFH) than with low molecular weight heparin (LMWH) (Martel *et al*, 2005). All heparins used in the United Kingdom are of porcine origin. The frequency of HIT is greater in surgical than medical patients. In trauma cases the severity of injury and the need for major surgery strongly affects the risk of developing HIT (Lubenow *et al*, 2010). In orthopaedic patients given subcutaneous prophylactic heparin, the incidence is approximately 5% with UFH and 0·5% with LMWH (Warkentin *et al*, 2000; Lee & Warkentin, 2004). We previously recommended platelet count monitoring in orthopaedic patients receiving LMWH thromboprophylaxis. This has become a significant issue with the move to extended thromboprophylaxis in hip and knee surgery. The American College of Chest Physicians (ACCP) recently made a 2C recommendation that platelet count monitoring be restricted to those where the risk is >1% (Linkins *et al*, 2012), whereas previously monitoring was recommended where the risk was >0·1% (Warkentin & Greinacher, 2004a; Keeling *et al*, 2006; Warkentin *et al*, 2008a); we agree with this approach.

In medical patients given therapeutic porcine UFH the risk of HIT is approximately 0·7% (Lee & Warkentin, 2004) and in medical patients given subcutaneous UFH a rate of 0·8% was reported (Girolami *et al*, 2003). A study in medical patients given LMWH for prophylaxis or treatment reported an incidence of 0·8% (Prandoni *et al*, 2005). This was surprising given that, in a meta-analysis, LMWH had been found to carry a 10-fold lower risk than UFH (Martel *et al*, 2005), and while this analysis contained mostly orthopaedic studies, other studies in medical patients had shown a similar pattern (Lindhoff-Last *et al*, 2002; Pohl *et al*, 2005). The results reported by Prandoni *et al* (2005) was the principal reason our previous guideline (Keeling *et al*, 2006) recommended monitoring the platelet count in medical patients receiving LMWH in contrast to the 2004 ACCP guideline (Warkentin & Greinacher, 2004a). The 2008 ACCP guideline (Warkentin *et al*, 2008a) reconsidered this paper but at that time concluded that it overestimated the incidence of HIT and still did not recommend routine platelet count monitoring in medical patients receiving LMWH (Warkentin *et al*, 2008a). The 2012 ACCP guidelines (Linkins *et al*, 2012) do not recommend routine platelet count monitoring in medical patients receiving LMWH as the risk is under the new 1% threshold. This is a particularly important issue given the move towards higher rates of thromboprophylaxis for medical patients. Further, a recent study has suggested that higher rates of venous thromboembolism (VTE) prophylaxis do not increase the rate of HIT and that surveillance in patients on VTE prophylaxis may have a very low yield (Jenkins *et al*, 2011). A recent analysis of 25 653 medical in-patients found rates of $\leq$0·2% in patients on prophylactic LMWH, treatment dose LMWH, and prophylactic UFH, but 0·7% on treatment dose UFH (Kato *et al*, 2011).

The risk of HIT is very low in obstetric patients given LMWH. A systematic review identified 2777 pregnancies in which LMWH was given (Greer & Nelson-Piercy, 2005). In the 2603 given LMWH as prophylaxis there were two cases of thrombocytopenia not thought to be related to heparin, and in the 174 given LMWH as treatment there was one case of thrombocytopenia also not thought to be related to heparin treatment.

If HIT develops the platelet count typically begins to fall 5–10 d after starting heparin, although in patients who have received heparin in the previous 3 months it can have a rapid onset due to pre-existing antibodies. Occasionally, the onset can occur after more than 10 d of heparin exposure but it is rare after 15 d. In patients undergoing cardiopulmonary bypass a significant fall in platelet count is very common in the 72 h post-surgery (Nader *et al*, 1999). In these patients platelet recovery followed by a secondary fall in counts between post-operative days 5–14 is much more suspicious of HIT than a low count that persists beyond 4 d (Selleng *et al*, 2010). A very rare prothrombotic disorder characterized by thrombocytopenia that is similar to HIT, but occurs without heparin exposure has been described (Warkentin *et al*, 2008b). In HIT the platelet count normally falls by >50%; the median nadir is 55×10^9/l (Warkentin & Kelton, 2001; Warkentin, 2003). Severe thrombocytopenia (platelet count $<15 \times 10^9$/l) is unusual. Ten to 20 percent of patients who develop HIT whilst receiving subcutaneous injections develop skin lesions at the heparin injection site (Warkentin, 1996). Half of the patients who develop HIT will have associated thrombosis. Furthermore, in those presenting without thrombosis (isolated HIT) the risk of subsequent thrombosis is up to 50% if heparin is not stopped and an alternative anticoagulant given in therapeutic doses (Warkentin & Kelton, 1996).

If HIT is suspected in a patient receiving heparin on the basis of a fall in the platelet count, the probability of HIT should initially be judged on clinical grounds. Four features are particularly helpful in estimating the likelihood of HIT (Warkentin, 2003): the degree of thrombocytopenia, the timing of the onset, the presence of new or progressive thrombosis, and whether an alternative cause of thrombocytopenia is likely. A '4Ts' scoring system (Table I) was devised to assess the pre-test probability (Warkentin, 2003; Warkentin & Heddle, 2003). It has subsequently been shown that if the score is low, HIT can be excluded without the need for laboratory investigation (Lo *et al*, 2006; Pouplard *et al*, 2007; Bryant *et al*, 2008; Sachs *et al*, 2011). If the pre-test probability is not low, heparin should be stopped and an alternative anticoagulant given whilst laboratory tests are performed. An alternative, more detailed, HIT Expert Probability (HEP) score has been developed (Cuker *et al*, 2010). This scoring system demonstrates greater inter-observer agreement and better concordance between laboratory testing and expert diagnosis, potentially enabling more patients to have the diagnosis appropriately excluded clinically (52% vs. 38% in

Table I. 4Ts score.

	Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)		
	2	1	0
Thrombocytopenia	>50% fall and platelet nadir $\geq 20 \times 10^9$/l	30–50% fall or platelet nadir 10–19 $\times 10^9$/l	Fall <30% or platelet nadir <10 $\times 10^9$/l
Timing* of platelet count fall or other sequelae	Clear onset between days 5 and 10; or ≤ 1 d (if heparin exposure within past 30 d)	Consistent with immunization but not clear (e.g. missing platelet counts) or onset of thrombocytopenia after day 10; or fall ≤ 1 d (if heparin exposure 30–100 d ago)	Platelet count fall ≤ 4 d (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; post- heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other cause for thrombocytopenia not evident	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present

Pretest probability score: 6–8 = High; 4–5 = Intermediate; 0–3 = Low.
*First day of immunizing heparin exposure considered day 0; the day the platelet count begins to fall is considered the day of onset of thrombocytopenia (it generally takes 1–3 d more until an arbitrary threshold that defines thrombocytopenia is passed).
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this preliminary study). Further evaluation of this tool is awaited.

A possible further use of clinical scores is that they may allow the use of more rapid but less sensitive tests to rule out the diagnosis in patients with intermediate pre-test probability, for example no patient who had an intermediate pre-test probability 4Ts score and a negative particle gel immunoassay had HIT in two studies (Pouplard *et al*, 2007; Bryant *et al*, 2008) ($n = 79$ and $n = 105$ respectively); a positive result mandates an alternative anticoagulant whilst more specific tests are performed.

Recommendations

- **Patients who are to receive any heparin should have a baseline platelet count (2C).**
- **Post-operative patients, including obstetric cases, receiving UFH should have platelet count monitoring performed every 2–3 d from days 4 to 14 or until heparin is stopped (2C).**
- **Post-cardiopulmonary bypass patients receiving LMWH should have platelet count monitoring performed every 2–3 d from days 4 to 14 or until heparin is stopped (2C).**
- **Post-operative patients (other than cardiopulmonary bypass patients) receiving LMWH do not need routine platelet monitoring (2C).**
- **Post-operative patients and cardiopulmonary bypass patients who have been exposed to heparin in the previous 100 d and are receiving any type of heparin should have a platelet count determined 24 h after starting heparin (2C).**
- **Medical patients and obstetric patients receiving heparin do not need routine platelet monitoring (2C).**
- **If the platelet count falls by 30% or more and/or the patient develops new thrombosis or skin allergy or any of the other rarer manifestations of HIT (see Table II) between days 4 and 14 of heparin administration HIT should be considered and a clinical assessment made (2C).**
- **HIT can be excluded by a low pre-test probability score without the need for laboratory investigation (2B).**
- **If the pre-test probability of HIT is not low, heparin should be stopped and an alternative anticoagulant started in full dosage whilst laboratory tests are performed (1C).**

Table II. Manifestations of HIT.

Deep vein thrombosis*
Pulmonary embolism*
Arterial thrombosis* stroke, acute coronary syndrome, peripheral arterial thrombosis
Skin lesions
Adrenal haemorrhage
Venous limb gangrene
Total global amnesia
Acute systemic reaction – chills, rigors
Acute onset with collapse and death
Warfarin-induced skin necrosis

*More common manifestations.

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Laboratory tests

Tests for HIT antibodies can be classified as platelet activation assays or immunological assays using PF4 or heparin as the antigen.

Platelet activation assays

Standard light transmission platelet aggregometry (LTA) using platelet-rich plasma (PRP) has been used to detect aggregation of normal platelets in the presence of patient plasma and heparin (Chong *et al*, 1993; Warkentin & Greinacher, 2004b). HIT antibodies produce activation of platelets at 0·1–0·5 iu/ml heparin that is no longer seen at 100 iu/ml heparin. At best, the sensitivity of this method is 85% (Warkentin & Greinacher, 2004b). Donor selection is important, as platelet responsiveness to HIT antibodies varies among normal donors, with approximately one in seven donors being responsive.

Greater sensitivity can be achieved using washed platelet assays. The Heparin Induced Platelet Activation Assay (HIPA) (Greinacher *et al*, 1991; Eichler *et al*, 1999) and the Serotonin Release Assay (SRA) (Sheridan *et al*, 1986; Warkentin *et al*, 1992) are generally accepted as the reference standard assays for HIT. However, they are only available at a few centres because the use of washed platelet assays is difficult (Eichler *et al*, 1999) and the SRA requires working with radiation.

The multiple electrode platelet aggregometer Multiplate® (Verum Diagnostics, Munich, Germany) has recently generated a renewed interest in impedance aggregation-based HIT assays. This uses whole blood, avoiding any platelet preparatory step, but still requires a HIT reactive donor. It has recently undergone a multi-centre validation which has shown it to be superior to LTA and as good as the SRA with a reported sensitivity of 90% (Morel-Kopp *et al*, 2012).

Antigen assays

There are five commercial enzyme-linked immunosorbent assays (ELISAs) available to detect either IgG only or IgG/A/M antibodies. They vary in the way PF4 is presented in the assay, e.g., surface-bound PF4-heparin (Asserachrom HPIA; Diagnostica Stago, Asnières, France) or polyvinylsulphate-PF4 surface bound (GTI-PF4; Quest, Knowle, UK). One ELISA variation is to use heparin bound to a solid phase (Zymutest; Hyphen, Quadratech, Surrey, UK), which allows heparin complexes and other chemokines that exhibit heparin affinity to bind to the so-called functionally active heparin. The following commercial companies all produce IgG-only ELISAs available in the UK, Stago Diagnostica, GTI, AESKU, Pathway diagnostics, Hyphen. All assays take approximately 1–2 h to perform and have quality control material provided. If positive, the ELISA can be repeated using high dose heparin (100 iu/ml). Inhibition of a positive result by more than 50% reduction in the optical density (OD) is characteristic of clinically significant HIT antibodies (Whitlatch *et al*, 2010). Very high OD levels may sometimes not correct using the confirmatory step in the presence of very strong HIT antibodies (Bakchoul *et al*, 2011). These immunological tests have a very high sensitivity but the specificity is low. A strongly positive test indicates a much greater likelihood of HIT than a weakly positive test (Warkentin, 2005; Warkentin *et al*, 2005a). Furthermore, higher ELISA OD measurements have been significantly correlated with thrombosis (Zwicker *et al*, 2004). Patients with isolated HIT and an OD $\geq$1·0 demonstrated an increased risk of thrombosis (five out of 14) compared with those with optical densities between 0·4 and 0·99 (three out of 34), odds ratio 5·7 [95% confidence interval (CI) 1·7–19·0]. Warkentin *et al* (2005a) investigated whether the additional detection of IgM and IgA antibody classes improves or worsens assay-operating characteristics. They found that additional detection of IgA and IgM antibodies by the GTI enzyme immunoassay (EIA) worsened test specificity by detecting numerous non-pathogenic antibodies.

A new nanoparticle qualitative immunochromatography assay that is IgG-specific has recently become available (Stago, Asnières, France); the test takes 10 min to perform (Sachs *et al*, 2011). There is little validation data of this method available at the present time. There are other rapid screening tests available some of which are automated (Chemiluminescent HIT screen IgG/A/M and IgG specific and IgG/A/M immunoturbidometric assay, Hemosil; Instrumentation Laboratory, Cheshire, UK). Others include the gel particle agglutination method (Diamed, Midlothian, UK), using polymer particles coated with heparin/PF4 that act as the solid phase, or the PIFA Heparin/PF4 mini reactor (Akers Biosciences, Quadratech, Surrey, UK). All of these assays provide rapid results but although the sensitivity of some may match standard ELISAs they all also have poor specificity.

Diagnostic interpretation

In clinically suspected HIT, washed-platelet activation assays (HIPA and SRA) and antigen assays have similar high sensitivity and a negative test renders HIT unlikely. Sensitivity is significantly less using standard platelet aggregometry with PRP (Greinacher *et al*, 1994). Diagnostic specificity is greater with the washed-platelet activation assays (HIPA and SRA) compared with antigen assays, as the latter are more likely to detect clinically insignificant antibodies (Warkentin *et al*, 2000). The clinician's estimate of the pre-test probability of HIT should be taken into account together with the type of assay used and its quantitative result to determine the post-test probability of HIT (Warkentin *et al*, 2003). We suggest laboratories report the actual OD, inhibition by heparin, and the cut-off for a positive test rather than simply reporting the test as positive or negative. The sensitivities, specificities and so likelihood ratios for tests depend on the cut-off

points chosen. It has been estimated that a positive SRA (90% release) and a strongly positive EIA (OD > 1·5) have likelihood ratios of 20 and 10, respectively, for HIT post-cardiac surgery (Warkentin & Greinacher, 2004b).

We recognize that, in routine clinical practice, most clinicians do not have access to platelet activation assays (HIPA and SRA). Ideally, the diagnosis of HIT should be confirmed by a washed-platelet assay but in reality, the vast majority of clinicians will manage the patient using pre-test probability assessment of HIT together with the results of an antigen assay (Nellen *et al*, 2012).

Recommendations

- **Platelet aggregation assays using PRP lack sensitivity and are not recommended (2C).**
- **Platelet activation assays using washed platelets (HIPA and SRA) have a higher sensitivity than platelet aggregation assays using PRP and are regarded as the reference standard, but are technically demanding and their use should be restricted to experienced laboratories (2C).**
- **Non-expert laboratories should use an antigen assay of high sensitivity. Only the IgG class needs to be measured. Useful information is gained by reporting the actual OD, degree of inhibition by high dose heparin, and the cut-off point for a positive test, rather than simply reporting the test as positive or negative (1B).**
- **In making a diagnosis of HIT, the clinician's estimate of the pre-test probability of HIT, together with the type of assay used and its quantitative result (ELISA only) and information on reversal using higher doses of heparin should be used to determine the post-test probability of HIT (2B).**
- **HIT can be excluded in patients with an intermediate pre-test score who have a negative particle gel immunoassay (2B).**
- **HIT can be excluded in all patients by a negative antigen assay of high sensitivity (1A).**

Treatment

General principles

In the United Kingdom, the alternative anticoagulants licensed for use in HIT are danaparoid and argatroban. Fondaparinux and bivalirudin have UK licences but not for this specific indication. Off-licence use of fondaparinux is becoming widespread and will be considered. The use of bivalirudin will be considered for the specific cases of percutaneous coronary intervention (PCI) and cardio-pulmonary bypass (CPB). The main principle of treatment is that patients with a high suspicion of, or proven, HIT discontinue UFH or LMWH and commence treatment with an alternative non-cross reacting anticoagulant. The initial anticoagulant treatment of HIT should be the same whether or not it is already complicated by thrombosis at the time of diagnosis. LMWH is not an appropriate alternative if HIT develops during treatment with UFH because there is cross-reactivity *in vivo* in approximately 50% of cases. Argatroban and bivalirudin are both non-cross reacting. Danaparoid demonstrates cross reactivity *in vitro* (Pouplard *et al*, 1997) which is only rarely evidenced *in vivo* (Keng & Chong, 2001) while fondaparinux is highly immunogenic but is not well recognized by anti-fondaparinux-PF4 antibodies generated during exposure, suggesting that it should be associated with a low risk of developing HIT (Warkentin *et al*, 2005b). Warfarin, especially when used in isolation, can increase the risk of microvascular thrombosis in HIT and its introduction should be delayed until there has been substantial resolution of the thrombocytopenia. It should then be introduced with overlap of the alternative anticoagulant (Warkentin *et al*, 1997; Smythe *et al*, 2002). Where argatroban is being used care is required in the interpretation of the International Normalized Ratio (INR).

Bleeding is uncommon in HIT. Uneventful and efficacious platelet transfusion has been documented in a series of four patients with suspected HIT based on good clinical and laboratory evidence (Hopkins & Goldfinger, 2008). There is some residual concern that platelet transfusions could theoretically contribute to thrombotic risk (Greinacher & Warkentin, 2004). Based on this, it is reasonable to consider platelet transfusion for patients with HIT and bleeding but prophylactic platelet transfusion is generally not advised.

Whichever alternative anticoagulant is used, it is important to administer it in appropriate therapeutic doses as discussed below, as there is evidence for treatment failure in cases where doses deemed appropriate for prophylaxis in other circumstances have been used in active HIT. This pertains to all cases whether or not they are complicated by thrombosis at the time of diagnosis. The evidence for this is the high failure rate of a prophylactic dose of danaparoid (750 u b.d. or t.i.d.) in comparison to dose adjusted lepirudin, or higher ('therapeutic') doses of danaparoid (2500 u bolus followed by continuous infusion) in the Heparin Associated Thrombocytopenia (HAT) studies (Farner *et al*, 2001). Major bleeding commonly complicates the treatment of HIT with an alternative anticoagulant (Greinacher *et al*, 2000). Clinical decision-making should address the likely risks and benefits of the available treatment strategies.

Probably because of depletion of the natural anticoagulants proteins C and S, vitamin K antagonists (VKAs) can worsen the prothrombotic state in HIT. In view of this, it is suggested that VKAs should be discontinued and reversed at the diagnosis of HIT and that warfarin is only restarted after the platelet count has risen into the normal range and then using low dose rather than high dose initiation regimens (Linkins *et al*, 2012).

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Recommendations

- **Clinical decisions should be made following consideration of the risks and benefits of treatment with an alternative anticoagulant (1C).**
- **For patients with suspected (non-low pre-test probability) or confirmed HIT, heparin should be stopped and full dose anticoagulation with an alternative anticoagulant commenced (1B).**
- **LMWH should not be used in the treatment of HIT (1A).**
- **Warfarin should not be used until the platelet count has recovered to the normal range. When introduced, an alternative anticoagulant must be continued until the INR is therapeutic. Argatroban affects the INR and this needs to be considered when using this drug. A minimum overlap of 5 d between non-heparin anticoagulants and VKA therapy is recommended (1B).**
- **Platelets should not be given for prophylaxis (1C) but may be used in the event of bleeding (2C).**
- **If the patient has received a VKA at the time of diagnosis it should be reversed by administering intravenous vitamin K (2C).**

Alternative anticoagulants

Danaparoid. Danaparoid is a heparinoid composed of heparan sulphate, dermatan sulphate and chondroitin sulphate. It indirectly inhibits Xa and, to a lesser degree, thrombin. It has a predictable dose response and a long half-life of approximately 24 h. Danaparoid does not prolong the prothrombin time (PT) and has a minimal effect on the activated partial thromboplastin time (APTT), which cannot be used to monitor it. If monitoring is required, a specific anti-Xa assay calibrated for danaparoid should be used. The chromogenic anti-Xa assay is not affected by factors that may affect the APTT, such as lupus anticoagulant or warfarin. Monitoring may be of value only in patients with severe renal impairment and body weight >90 kg (Farner *et al*, 2001). Danaparoid is approved in the European Union for use in two distinct dosing regimens. Published data report use of a low dose ('prophylactic') regimen of 750 anti-Xa units b.d. or t.i.d. subcutaneously and a higher dose ('therapeutic') regimen, which consists of a bolus injection followed by a reducing dose continuous infusion (bolus determined by weight 1250–3750 units i.v. followed by 400 u/h for 4 h then 300 u/h for 4 h then 200 or 150 u/h as a maintenance dose).

Two small studies of 40 patients (Tardy-Poncet *et al*, 1999; Schenk *et al*, 2003) reported favourable outcomes using 600–800 anti-Xa units b.d. or 10 u/kg b.d. However, larger studies showed that low dose danaparoid regimens are associated with a higher rate of new thrombotic events than therapeutic doses of lepirudin or danaparoid (Farner *et al*, 2001). Patients with HIT complicated by thrombosis were given a full dose regimen while those with HIT without thrombosis were given lower doses. Efficacy data on 294 patients (danaparoid 126) showed that at 42 d there were no differences between treatments for the composite end point of death, amputation or new thrombosis. There was a non-significant increase in new thrombotic events in patients given danaparoid at low doses compared to full dose danaparoid or dose-adjusted lepirudin. Patients treated with low dose danaparoid were significantly more likely to reach the combined end-point than those treated with lepirudin ($P = 0{\cdot}02$). These data suggest that low dose danaparoid is insufficient treatment in patients with active HIT. On the other hand, full dose danaparoid appears equivalent to dose-adjusted lepirudin at preventing new thrombosis.

In a randomized study of 42 patients, danaparoid was significantly superior to dextran (Chong *et al*, 2001).

Argatroban. Argatroban is a direct thrombin inhibitor that is administered intravenously. The key feature that makes it attractive in the management of HIT is its hepatic metabolism in a condition that is often complicated by established or developing renal impairment. The data describing its role in HIT are two non-randomized open-label studies (Lewis *et al*, 2001, 2003) where it was compared with historical controls, most often treated by discontinuation of heparin along with oral anticoagulation using a coumarin. The quality of these studies was further compromised by the fact that around a third of the patients included in the analysis were found to be HIT antibody negative on retrospective testing (Walenga *et al*, 1999) and by the fact that some of the patients included had a remote rather than an immediate history of HIT. The combined data from these studies describe the outcomes for 882 patients with HIT, of whom 697 were treated with argatroban (1·7–2·0 μg/kg/min for 5–7 d) to achieve an APTT ratio of 1·5–3·0, compared with 185 historical controls (Lewis *et al*, 2006). Argatroban treatment resulted in a significant reduction in the primary end point of a composite of death due to thrombosis, amputation secondary to HIT-associated thrombosis, or new thrombosis within 37 d of baseline for both patients with HIT without thrombosis at diagnosis [Hazard Ratio (HR), 0·33; 95% CI 0·2–0·54, $P < 0{\cdot}001$] and with thrombosis at diagnosis (HR, 0·39; 95% CI 0·25–0·62, $P < 0{\cdot}001$). More argatroban-treated patients remained thrombosis-free during the 37-d follow-up, again for patients both with and without thrombosis at the time of diagnosis and fewer died from thrombosis ($P \leq 0{\cdot}001$). Major bleeding, defined by a fall in Hb of ≥ 20 g/l, or that led to transfusion of ≥ 2 units of blood or that was into the central nervous system, retroperitoneum or a prosthetic joint was similar in both groups with no significant excess in the argatroban recipients. There has been discussion about the efficacy of argatroban in preventing amputation in HIT patients. Comparing amputation rates in patients treated with argatroban and lepirudin with controls suggests that, while lepirudin reduces amputation

rates, argatroban has little benefit compared with controls; relative risk (RR) 0·7 for lepirudin and 1·26 for argatroban (Warkentin *et al*, 2008a). It has been suggested that the effect of argatroban on the INR may result in premature discontinuation of argatroban (Bartholomew & Hursting, 2005). Alternatively, it has been suggested that, in the argatroban studies, severe ischaemic changes or gangrene were already established prior to the introduction of therapy so that these should not really be considered treatment failures (Lewis *et al*, 2006).

Dosing and transition to warfarin. Argatroban requires no dose adjustment in renal failure but it is contraindicated in severe hepatic failure and expert opinion suggests dose adjustment in critically ill patients in the intensive care setting (Alatri *et al*, 2012). Monitoring of argatroban therapy is most easily performed using an APTT test. The target range quoted in the summary of product characteristics (SmPC) is that used in the two multicentre studies (Lewis *et al*, 2001, 2003) an APTT ratio of 1·5–3·0 but not exceeding 100 s. A consensus meeting suggested each laboratory should generate its own dose response calibration curve though failed to recommend what argatroban concentration should be targeted (Alatri *et al*, 2012) but a Scientific Sub-Committee of the International Society for Thrombosis and Haemostasis communication found that the APTT ratios were similar when comparing seven different reagents (Gray & Harenberg, 2005).

For otherwise uncomplicated patients, standard initial dosing is with 2 μg/kg per min as a continuous infusion with dose adjustment based on the APTT. Clinical experience has resulted in advice for dose reduction in critically ill patients and the SmPC suggests an initial dose of 0·5 μg/kg per min. Dosing schedules based on clinical scoring systems for evaluation of critically ill patients, such as Acute Physiology and Chronic Health Evaluation (APACHE) II, Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiologic Score (SAPS) II, have been proposed (Alatri *et al*, 2012) and a simplified dosing schedule for this group of patients is given in Table III.

Argatroban causes prolongation of the PT and this needs to be considered in the transition of patients to warfarin therapy. Warfarin and argatroban should be overlapped for at least 5 d and an INR of ≥ 4 should be observed for two consecutive days before argatroban is discontinued. An upper range target for the INR in this situation is not given but at very high INR levels the patient may be over-anticoagulated. We suggest that, at an INR > 5, the argatroban infusion should be discontinued for 4 h and the INR repeated.

Fondaparinux. Including two recent reports (Goldfarb & Blostein, 2011; Warkentin *et al*, 2011) there are six case series totalling 71 patients demonstrating that fondaparinux is not only an effective anticoagulant in the setting of HIT, but it appears to have a low risk of overall complications (Greinacher, 2011), Combining all 71 patients reported in these cohorts, no new thrombotic events occurred after initiating treatment with fondaparinux (95% CI, 0–5·1%), which looks promising that fondaparinux can provide effective anticoagulation in patients with HIT (Greinacher, 2011). The dosing of these patients was variable – some patients were given prophylactic doses of fondaparinux (2·5 mg OD) whilst others were given daily therapeutic doses dependent on their weight (<50 kg: 5 mg, 50–100 kg: 7·5 mg and >100 kg; 10 mg). Based on the inferior outcomes associated with the use of prophylactic doses of danaparoid, we would suggest that therapeutic doses should be given with consideration of age and renal function.

HIT in pregnancy. HIT is uncommon in pregnancy and, in particular, the rates of HIT in patients receiving LWWH are so low that routine monitoring of this population is not indicated (Greer & Nelson-Piercy, 2005). There are few data on the diagnostic process in pregnancy and so a general clinical approach using a scoring system, such as 4Ts, combined with laboratory testing as indicated above seems reasonable. In strongly suspected HIT and in proven HIT, heparin exposure should be discontinued and an alternative anticoagulant started. There are data on the use of danaparoid, argatroban and fondaparinux in HIT in pregnancy. The largest number of reports is on the use of danaparoid (Lindhoff-Last *et al*, 2005). In 51 pregnancies given danaparoid for heparin intolerance or HIT ($n = 32$), 37 healthy infants were delivered in mothers given danaparoid up to term, and danaparoid was

Table III. Licensed or suggested dosing schedules for treatment of HIT with danaparoid and argatroban.

	IV Bolus	IV Infusion	Monitoring
Danaparoid	<55 kg–1250 u 55–90 kg–2500 u >90 kg–3750 u	400 u/h for 2 h, 300 u/h for 2 h, then 200 u/h	If required, anti-Xa 0·5–0·8 u/ml
Argatroban Standard dose in routine patients without liver failure	None	Start at 2 μg/kg per min	APTT ratio 1·5–3·0 APTT repeated within 2 h of any dose adjustment and at least once daily
Critically ill, post-cardiac surgery, or in patients with liver failure	None	0·5 μg/kg/min	APTT ratio 1·5–3·0 APTT repeated within 4 h of any dose adjustment and at least once daily

APTT, activated partial thromboplastin time.

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discontinued in a further 14 pregnancies prior to delivery for a variety of reasons not neccesarily related to danaparoid treatment. There were four maternal bleeding events during pregnancy; two of these, which were fatal, were due to documented placental problems. There were three fetal deaths which were not attributable to danaparoid. There are a small number of case reports documenting the use of argatroban in pregnacy (Young *et al*, 2008; Ekbatani *et al*, 2010; Tanimura *et al*, 2012). In two of these cases, argatroban was used in combination with fondaparinux with successful pregnacy outcomes (Ekbatani *et al*, 2010; Tanimura *et al*, 2012), and in another, argatroban was used continuously for 6 weeks, again with a good pregnancy outcome (Young *et al*, 2008).

The option for subcutaneous injection favours the use of danaparoid and fondaparinux, especially in situations where prolonged anticoagulation is required; there are encouraging data using the latter in pregnancy (Knol *et al*, 2010).

Duration of anticoagulation. For patients with HIT and thrombosis we would regard HIT as a transient reversible risk factor and recommend anticoagulation with warfarin for 3 months (Keeling *et al*, 2011; Kearon *et al*, 2012). For isolated HIT not complicated by thrombosis we recommend therapeutic anticoagulation for 4 weeks to cover the main period of thrombosis risk, as suggested from observational studies (Warkentin & Kelton, 1996; Arepally & Ortel, 2006).

Recommendations

- **Danaparoid in a therapeutic dose regimen is a suitable alternative anticoagulant for use in patients with HIT (1B).**
- **Danaparoid at prophylactic doses is not recommended for the treatment of HIT (1B).**
- **Monitoring the anticoagulant effect of danaparoid using an anti-Xa assay with specific danaparoid calibrators should be considered in patients >90 kg and in patients with renal impairment (glomerular filtration rate <30 ml/min) (2C).**
- **An argatroban infusion adjusted to an APTT ratio of 1·5–3·0 (but not exceeding 100 s) is a suitable alternative anticoagulant for the treatment of patients with HIT (1C).**
- **Patients on argatroban undergoing transition to warfarin should have an INR $\geq$4 for 2 d prior to discontinuing argatroban (2C).**
- **Therapeutic dose fondaparinux is an acceptable alternative anticoagulant for managing HIT but it is not licensed for this indication (2C).**
- **Patients should be therapeutically anticoagulated for 3 months after HIT with a thrombotic complication (1A) and for 4 weeks following HIT without a thrombotic complication (2C).**
- **Women with HIT in pregnancy should be treated with a non-cross reacting anticoagulant. Danaparoid should be used where available and fondaparinux also considered (2C).**

Anticoagulation in patients with a history of HIT

Although recurrence is rare, where a patient with previous HIT requires a period of anticoagulation or anticoagulant prophylaxis an alternative to UFH or LMWH should be prescribed.

Fondaparinux and danaparoid may be used, as may new anticoagulants such as dabigatran, rivaroxaban and apixaban, depending on the clinical circumstances, e.g., dabigatran, rivaroxaban and apixaban may be used as per licensed indications, such as orthopaedic surgery.

Haemodialysis. Danaparoid and argatroban have both been used (Fischer, 2004). Suitable regimens for the use of both drugs in renal replacement therapy are given in Table IV.

Cardiac surgery. In cardiac surgery, the depth of experience with UFH, the established near-patient monitoring, and the rapid reversal indicate that its use should be considered. There is therefore a rationale and some data that support the safe use of UFH in patients with previous HIT. Firstly, in patients who develop typical HIT, there is no relationship between the day of onset and previous heparin exposure. Further, in patients with rapid onset HIT, there is an association with recent heparin exposure (previous 100 d) but not with more remote heparin exposure. Finally, HIT antibodies are transient with a median time to disappearance of 50–80 d. These data suggest that the antibodies that mediate

Table IV. Regimens for danaparoid and argatroban for patients requiring renal replacement therapy (data from Alatri *et al*, 2012; Fischer, 2004).

	Renal replacement therapy	Dose	Monitoring
Danaparoid	Intermittent	3750 (2500)* u before 1st and 2nd dialyses; 3000 u before 3rd dialysis; Then according to pre-dialysis anti-Xa level <0·3 3000 (2000)* u 0·3–0·35 2500 (1500) u 0·35–0·4 2000 (1500) u >0·4 0 u	As per protocol opposite
Argatroban	Continuous	Bolus 100 μg/kg† Infusion 0·5 μg/kg/min‡	APTT 1·5–3·0
	Intermittent	Bolus 250 μg/kg Infusion 2·0 μg/kg/min	ACT 170–230 s

APTT, activated partial thromboplastin time; ACT, activated clotting time.

*For danaparoid use doses in parentheses for patients <55 kg.

†No bolus is required for patients already being treated with argatroban.

‡Dose should be adjusted according to SOFA-II, APACHE-II or SAPS-II or to a critically ill hepatic nomogram.

HIT are transient, that there is no anamnestic immune response in HIT and that acute onset HIT represents recurrence due to renewed heparin exposure.

There are reports of successful heparin re-exposure to permit cardiac and vascular surgery in patients with previous HIT (Potzsch *et al*, 2000; Warkentin & Kelton, 2001; Nuttall *et al*, 2003). In patients with recent or current HIT who require cardiac surgery the risk associated with further heparin exposure is probably much greater and therefore it should be avoided if possible. Several strategies, some including the use of UFH offset by the use of an anti-platelet agent, such as tirofiban or epoprostenol, have been reported (Koster *et al*, 2000a,b, 2001; Mertzlufft *et al*, 2000; Aouifi *et al*, 2001). The number of patients included in these reports is small and the experience confined to very few centres. The 2012 ACCP guideline (Linkins *et al*, 2012) favours the use of bivalirudin for cases of HIT where early cardiac surgery is required, primarily based on the results of two prospective cohort studies assessing bivalirudin in off-pump and on-pump cardiac surgery (Dyke *et al*, 2007; Koster *et al*, 2007). Amongst 100 (51 off-pump and 49 on-pump) patients successful clinical outcomes defined by absence of death, Q-wave myocardial infarction, repeat revascularization surgery, and stroke were observed in 88% and 86% respectively of patients at day 30. The largest series of lepirudin use in this context reported thrombosis-free survival in 54 of 57 (95%) patients (Koster *et al*, 2000b). Excessive blood loss and slow drug elimination was seen in the four patients with pre-existing renal failure but there were no haemorrhagic deaths. In 53 patients managed using a fixed dose danaparoid regimen severe post-operative bleeding occurred in 21% of patients. In addition clots were seen in the operative field in a third of patients (Magnani *et al*, 1997).

There are published protocols for the use of lepirudin, bivalirudin and danaparoid in cardiac surgery (Warkentin & Greinacher, 2003; Poetzsch & Madlener, 2004; Warkentin & Koster, 2005). Appropriate bivalirudin concentrations for anticoagulation in this setting have been established and these can be monitored by a validated activated clotting time (ACT) measurement. If the postoperative period is complicated by renal failure, problems with the prolonged half-life of the drugs and the absence of an antidote may emerge.

Recommendations

- **Patients with previous HIT who are antibody negative (usually so after >100 d) who require cardiac surgery should receive intra-operative UFH in preference to other anticoagulants, which are less validated for this purpose. Pre- and post-operative anticoagulation should be with an anticoagulant other than UFH or LMWH (1B).**
- **Patients with recent or active HIT should have the need for surgery reviewed and delayed until the patient is antibody-negative if possible. They should then proceed as above. If deemed appropriate, early surgery should be carried out with an alternative anticoagulant (1C).**
- **As an alternative anticoagulant in cases where urgent surgery is required we suggest bivalirudin (2B).**

Percutaneous coronary intervention. There is extensive experience of the use of bivalirudin for percutaneous coronary intervention (PCI) in the UK and it is licensed for use in patients requiring PCI who do not have HIT (Mahaffey *et al*, 2003).

Recommendation

- **In patients with previous or present HIT who require coronary intervention including angiography and percutaneous coronary intervention we recommend the use of bivalirudin (2B).**

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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