Heparin-induced thrombocytopenia without thrombosis: an evidence-based review of current literature

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ABSTRACT

Background and aim: There has been a recent change in the management guidelines for patients with heparin-induced thrombocytopenia with the addition of a recommendation to commence parenteral anticoagulation in patients with isolated HIT without evidence of thrombosis. We assessed the evidence supporting this recommendation, to answer the following questions: in a patient with isolated HIT, should alternative anticoagulation be commenced, what alternative agent should be used, what is the recommended duration of anticoagulation, and when should warfarin be used?

Methods: We searched MEDLINE (using keywords "heparin-induced thrombocytopenia", "heparin induced thrombocytopaenia", "HIT" and "HITTS") and PubMed (using MeSH terms "thrombocytopenia" and "heparin") from 1966 to 2006 and selected articles for further assessment according to specified criteria.

Results: We assessed 12 non-randomised studies, five large case series and multiple small case series.

Conclusion: Although patients with isolated HIT are at considerable risk of new thrombosis, there is limited evidence to support or reject the use of non-heparin anticoagulation in this group. Non-randomised, historically controlled trials support the use of lepirudin and argatroban; evidence favouring danaparoid is limited to large case series and one retrospective observational study. Duration of parenteral anticoagulation and warfarin use are guided by consensus opinion alone.

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Heparin-induced thrombocytopenia is an uncommon complication of heparin use that occurs when antibodies are formed and directed against the heparin/platelet factor 4 (PF4) complex, resulting in a state of excess thrombosis.[1] Although up to 20.7% of patients receiving unfractionated heparin develop antibodies to the heparin/PF4 complex, only 1%–3% develop clinical heparin-induced thrombocytopenia (HIT).[2-4] This can present with isolated thrombocytopenia or with new thrombosis (HIT with thrombosis, HITT). Most cases of HIT follow therapy with unfractionated heparin, but cases can also occur after therapy with low molecular weight heparins.[5,6]

As patients presenting with isolated HIT have a significant risk of arterial and venous thromboses, and as this risk may not be reduced by heparin alone, it seems reasonable to treat them with anticoagulants, unless this increases morbidity or mortality.[2,7] A review of the literature reveals a recent change in advice on therapy.[6] The traditional approach was to consider alternative pharmacological anticoagulation for patients presenting with thromboses (HITT) and for those with isolated HIT who had a further indication for anticoagulation (eg, dialysis filters or cardiopulmonary bypass).[8,9] Current guidelines recommend initiation of alternative parenteral anticoagulation in patients diagnosed with isolated HIT.[6,9]

Recently, we managed a patient with HIT and no clinical evidence of thrombosis with a danaparoid infusion titrated to a therapeutic level of 0.5–0.8 anti-factor Xa U/mL. Within 72 hours of treatment, the patient developed a psoas haematoma, prompting us to appraise the evidence for the recommendation of parenteral anticoagulation in patients with isolated HIT. We undertook a literature search to determine, in patients with isolated HIT and no evidence of thrombosis:

- Should systemic anticoagulation be commenced?
- What anticoagulant should be used?
- How long should anticoagulation be continued?
- When should oral anticoagulation be commenced?

Methods

We searched MEDLINE and PubMed databases from 1966 to 2006. For MEDLINE, we used a keyword search with the terms "heparin-induced thrombocytopenia", "heparin induced thrombocytopaenia", "HIT" and "HITTS". We searched PubMed using the MeSH terms "thrombocytopenia" (restricted to major topic headings) and "heparin", combining them for a general and clinical query search. In addition, we examined reference lists in recent reviews for any further articles.

We selected abstracts and further examined articles published in English which evaluated one or more of the following:

- the effect of active treatment or cessation of heparin on thrombotic complications or mortality in adults with isolated HIT;

Table 1. National Health and Medical Research Council levels of evidence[10]

Level 1: Evidence from a systematic review or meta-analysis of all relevant randomised controlled trials.

Level 2: Evidence from at least one well designed randomised controlled trial.

Level 3-i: Evidence from well designed pseudorandomised controlled trials.

Level 3-ii: Evidence from comparative studies with concurrent controls and allocation not randomised (cohort studies), case–control studies or interrupted time series with parallel control group.

Level 3-iii: Evidence from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group.

Level 4: Evidence from case reports or case series. ◆

- the use of active treatment as compared with control in HIT;
- the comparison of two active treatments in HIT;
- the duration of anticoagulation in HIT; and
- the use of warfarin in HIT.

We based our conclusions on the level of evidence of evaluated articles, graded according to National Health and Medical Research Council guidelines (Table 1).[10]

Results

Should systemic anticoagulation be commenced in patients with isolated HIT and no evidence of thrombosis?

Two studies[2,7] examined the benefit of heparin cessation in HIT(T), while seven compared a group which received an anticoagulant with a control group: an historical control group in six,[1,3,11-14] and a contemporaneous control group in the other[15] (summarised in Table 2).

Studies of heparin cessation

Warkentin et al[2] undertook a retrospective chart review of 127 patients over 14 years whose platelet counts fell below 150×10^9/L on Day 5 or later after commencing heparin and who had a positive result on a serotonin-release assay for heparin-dependent IgG. The patients were divided into those with thrombosis ($n = 65$) and those without thrombosis ($n = 62$).

In patients with isolated HIT, there was a cumulative risk of thrombosis of 53% in the 30 days after diagnosis, most thromboses occurring in the first week. There was a 4:1 ratio of venous to arterial thromboses. There was no difference in the subsequent incidence of thrombosis whether heparin was discontinued or warfarin was substituted for heparin. The authors concluded that heparin cessation was insufficient to protect against thrombotic complications of HIT.

Wallis et al[7] conducted a retrospective chart review of 113 patients with confirmed HIT (isolated HIT, $n = 70$; HITT, $n = 43$). Forty three patients developed new thromboses, 16 of whom had a pulmonary embolism. There was a 3:2 ratio of venous to arterial clots. Twenty-one of these 43 patients had thromboses occurring a mean of 4 days (SD, 8 days) after heparin cessation. Mortality was 28% and 27% in patients with isolated HIT and HITT, respectively.

Of the 113 patients, heparin was ceased early (< 48 hours) in 40 and late (5 ± 2 days [mean ± SD]) in 73. There were no

Table 2. Study design and results of trials of therapeutic anticoagulation in patients with heparin-induced thrombocytopenia (HIT) with or without thrombosis

Study	Study drug	Observation period	Control	Duration of therapy (days)*	New TEC (%)			Composite end-point (%)†		
					Treatment	Control	*P*	Treatment	Control	*P*
HAT-1[3]	Lepirudin	From HIT diagnosis to 14 days after study drug ceased	Historical	15 (2–58)	na	32.1%	na	na	52.1%	na
HAT-2[11]	Lepirudin	As HAT-1	Historical	8 (1–67)	na	32.1%	na	na	52.1%	na
HAT-3[13]	Lepirudin	As HAT-1	Historical	10 (1–47)	10.7%	32.1%	na	27.4%	52.1%	na
Lubenow[1]	Lepirudin	From commencement to 14 days after cessation of study drug	Historical, matched for isolated HIT	12.5–17.5	4.4%	14.9%	0.02	19.8%	29.8%	0.28
ARG-911[12]	Argatroban	37 days from commencement of study drug	Historical, matched for isolated HIT	5.3 ±0.3	8.1%	22.4%	<0.001	25.6%	38.8%	0.01
ARG-915[14]	Argatroban	As ARG-911	As ARG-911	5.1 ±4.2	5.8%	23.0%	<0.001	28%	38.8%	0.04
Wester[15]	Danaparoid	na	Contemporaneous, without HIT	na	50%	0	<0.001	na	na	na

TECs = thromboembolic complications. na = not available. * Duration of therapy is expressed as the median (range),[3,11,13] mean ± SD[12,14] or range.[1]
† Composite end-point = death, new thromboembolic complication or limb amputation within the observation period. ◆

differences in nadir of thrombocytopenia, incidence of early or late thromboses, or mortality between these two groups. The authors concluded that stopping heparin early in the evolution of HIT(T) did not alter outcome.

Studies of lepirudin

In the HAT-1 study,[3] Greinacher et al prospectively evaluated the role of lepirudin, a direct thrombin inhibitor, in 82 patients (HITT, $n = 56$; isolated HIT, $n = 18$) who had a definite need for antithrombotic therapy or prophylaxis. Four treatment regimens were used according to diagnostic group (HITT, $n = 55$; HITT receiving thrombolysis, $n = 5$; isolated HIT, $n = 18$; known HIT and cardiopulmonary bypass, $n = 8$), but therapy was titrated to an activated partial thromboplastin time (APTT) of 1.5–2.5 times normal in all groups. These groups were combined and compared with an historical control group. Patients treated with lepirudin showed a significant reduction in the cumulative end-point of death, new thromboembolic complications (TECs) and limb amputations at Day 35 (25% versus 52%, $P = 0.01$). New TECs occurred in 18% of the treatment group and 32% of the control group ($P = 0.27$). There was a non-significant trend towards increased bleeding events in the treatment group. Study end-points were not analysed separately in patients with isolated HIT.

In the HAT-2 study,[11] Greinacher et al prospectively evaluated lepirudin therapy in 112 patients (HITT, $n = 69$; isolated HIT, $n = 43$) and compared them with the same historical control group from HAT-1. Treatment regimens varied as in the HAT-1 study.[3] Although there was a trend towards a reduced cumulative incidence of death, new TECs and limb amputations at Day 35 with lepirudin therapy, this difference was not statistically significant. New TECs occurred in 17% of the treatment group and 32% of the control group at 5 weeks ($P = 0.26$). There was a significant increase in bleeding events ($P < 0.001$) but not in events requiring transfusion ($P = 0.23$), in the group receiving lepirudin. Outcome analysis was not performed for patients with isolated HIT.

In the HAT-3 study,[13] 205 patients received lepirudin for HIT(T), and their outcomes were compared with the HAT-1 historical control group. In contrast to the previous HAT studies,[3,11] HAT-3 analysed outcomes separately for patients with HIT and HITT. Of the 84 patients with isolated HIT, nine (11%) and 23 (27%) developed a new TEC and a positive combined end-point, respectively. Although these values differed significantly from those of the control group, this was expected as the control group was matched for patients with HIT *and* HITT. When the data from patients with isolated HIT were pooled from the HAT-1–3 studies, 13.1% and 27.5% had a new TEC and one of three composite end-points, respectively.

Lubenow et al[1] pooled the data from patients with isolated HIT in HAT-1–3[3,11,13] and compared them with matched historical controls. They demonstrated an impressive reduction in incidence of new thromboses in the group treated with lepirudin compared with the control group (four of 91 patients [4%] versus seven of 47 [15%]; $P = 0.02$). There was a trend towards reduced mortality and increased frequency of bleeding events in the treatment group, but neither difference reached significance. Interpretation of these results is limited by the same factors that limited interpretation of HAT-1–3: non-randomisation, non-blinded therapy, non-standardisation of other therapies and the use of historical controls.

Studies of argatroban

The ARG-911 study[12] was a non-randomised, open-label trial evaluating the use of argatroban, a direct thrombin inhibitor, in patients with HIT(T). Three hundred and four patients (HIT, $n = 160$; HITT, $n = 144$) were treated with a continuous argatroban infusion titrated to an APTT 1.5–3.0 times baseline, and compared with an historical control group. In patients with isolated HIT, the addition of argatroban reduced the rate of new thrombotic events (22.4% versus 8.1%; $P < 0.001$) and the rate of death caused by thrombosis (4.8% versus 0; $P = 0.005$) when compared with controls. There were no significant differences in bleeding complications between treatment and control groups. Criticisms of this trial include the use of an historical control group, and patient inclusion based on clinical rather than immunological diagnosis of HIT(T).[7] Moreover, there was a numerical difference in baseline platelet counts between the isolated HIT treatment and control groups.

In the ARG-915 study,[14] 418 patients (isolated HIT, $n = 189$; HITT, $n = 229$) were treated with argatroban infusion and compared with the ARG-911 control group. When compared with the control group, patients with isolated HIT had a lower incidence of the composite end-point of death, amputation and new TEC (28.0% versus 38.8%; $P = 0.04$), new thrombosis (5.8% versus 23.0%; $P < 0.001$) and death due to thrombosis (0.5% versus 4.3%; $P = 0.04$). There were no differences in incidences of bleeding complications between treatment and control groups. Again, there was a significant difference between baseline platelet counts in treatment and control groups with isolated HIT ($P < 0.001$).

Studies of danaparoid

Wester et al[15] conducted a prospective case–control study in 20 intensive care patients with laboratory-proven isolated HIT. Patients were treated with prophylactic ($n = 5$) and therapeutic ($n = 15$) danaparoid, and compared with a contemporaneous control group receiving unfractionated

Table 3. Alternative anticoagulants used in the treatment of heparin-induced thrombocytopenia with or without thrombosis

Anticoagulant	Reference number
Hirudins	
Lepirudin	1, 3, 11, 13
Bivalirudin	24–26
Danaparoid	15–20
Argatroban	12, 14, 27
Fondaparinux	28, 29
Activated protein C	30
Prostacyclin	31
Warfarin	32–36

heparin but without HIT. Despite danaparoid therapy, 50% of patients in the treatment group developed a new thrombosis, compared with no patients in the control group ($P < 0.001$). Moreover, 85% of those receiving danaparoid had a bleeding complication, compared with 35% of the control group ($P = 0.001$). At the study conclusion, patients with HIT were more likely to have a subsequent thrombosis than patients without HIT, and critically ill patients treated with danaparoid were more likely to have a haemorrhage than those not treated with danaparoid.

Lubenow et al[16] undertook a retrospective cohort study in patients with HIT(T), comparing a group who received non-standardised danaparoid therapy with a control group who received ancrod (a defibrogenating snake venom), with or without concomitant warfarin therapy. Although there was a significant reduction in the incidence of new TECs and the composite end-point with the use of danaparoid, only 10% of patients had isolated HIT, and this group was not analysed independently.

Magnani and Gallus[17] recently reported on danaparoid use in 1418 patients with HIT(T) over a 22-year period. Although 60% of patients had isolated HIT, results were not individually reported for this group. Despite this, the authors concluded that danaparoid should be used in the highest recommended prophylactic doses for patients with isolated HIT. They also confirmed its favourable safety profile in treating HIT(T) when compared with current data on lepirudin and argatroban.

Two case series[18,19] reported on 40 adult patients with isolated HIT. Tardy-Poncet et al[18] administered subcutaneous danaparoid 600–750 U twice daily to 16 patients with laboratory-confirmed HIT and no thrombosis. No new thrombotic events occurred in this group during treatment, but one case of deep venous thrombosis was identified at 1-month follow-up. In Scheck et al,[19] 24 patients with isolated HIT received subcutaneous danaparoid 10 U/kg for a mean duration of 16 days. No new haemorrhagic or thrombotic events occurred during follow-up.

Although other studies have evaluated danaparoid in HIT(T), patients in these studies have had HIT with thrombosis.[20-22]

Summary

- There is a high risk of new arterial and venous thromboses occurring after diagnosis of isolated HIT.
- Cessation of unfractionated heparin does not reduce this risk significantly (Level 4), and there is no difference between early and late heparin cessation with respect to incidence of thrombosis (Level 4).
- There is no Level 1 or 2 evidence in support of anticoagulation for isolated HIT.
- Seven studies address the use of anticoagulation in HIT(T), and four support its use in isolated HIT.[1,12-14] These trials support the use of lepirudin and argatroban in therapeutic infusions titrated to an APTT 1.5–2.5/3.0 times baseline (Level 3-iii). The weaknesses of these trials have been discussed.
- Evidence supporting the use of danaparoid in isolated HIT is limited to case series and expert opinion (Level 4).

What anticoagulant should be used?

One retrospective cohort study compared lepirudin and danaparoid in the treatment of HIT(T),[23] while four non-randomised trials[1,3,11,13] examined the role of lepirudin, and two studies evaluated the role of argatroban[12,14] in patients with HIT(T). All six studies used historical controls.

Apart from these studies, numerous case reports and case series have reported other pharmacological agents used primarily to treat HIT(T) or to facilitate interventions such as continuous dialysis, cardiopulmonary bypass or percutaneous coronary interventions in patients with known HIT(T).[8] Agents that have been used in the treatment of HIT(T) are summarised in Table 3.

There are potential disadvantages associated with some currently available therapies for HIT(T). Low molecular weight heparins and danaparoid have structural overlap with unfractionated heparin and can induce HIT antibodies, although this does not imply treatment failure.[37-40] Warfarin causes an initial transient prothrombotic state by inhibition of protein C production, potentially exacerbating thrombosis and causing venous limb gangrene.[9,32,33] Lepirudin therapy can lead to generation of anti-lepirudin antibodies, which may in turn complicate its anticoagulant properties and therapeutic monitoring.[41,42] The hirudins and danaparoid are cleared renally, and their pharmacokinetics are less predictable in patients with renal impairment.[17,43] In contrast, argatroban, a direct thrombin inhibitor, does not have

cross-reactivity with HIT antibody, does not lead to generation of antibodies against itself and can be easily and inexpensively monitored with the APTT.[12,42,44]

Farner et al[23] conducted a cohort study on patients with HIT(T), comparing prophylactic and therapeutic doses of danaparoid and lepirudin in isolated HIT and HITT. They compared patients from the HAT-1 and HAT-2 trials with contemporaneous patients diagnosed with HIT(T) who received non-standardised danaparoid therapy. They concluded that patients with isolated HIT treated with danaparoid had a higher risk than those treated with lepirudin of the cumulative end-point of new TEC, limb amputation or death ($P = 0.02$), principally because of an increased incidence of new TECs (20% [95% CI, 8.4%–36.9%] versus 6.3% [95% CI, 1.3%–17.2%]; $P = 0.09$). This could be explained by two factors. Firstly, lepirudin was more likely to be given in therapeutic doses than danaparoid. Secondly, because lepirudin dosing is adjusted according to aPTT, prophylactic dosing effectively becomes therapeutic over time.[45] Not surprisingly, the incidence of new TECs in patients receiving prophylactic and therapeutic regimens of lepirudin was similar (8.6% versus 7.9%). In contrast, the incidence of new TECs in patients receiving therapeutic danaparoid was about one half that with prophylactic dosing (18.6% versus 9.4%), and was numerically similar to the incidence in patients receiving lepirudin. A safety analysis confirmed that more major bleeding events occurred in the group receiving lepirudin (10.4% versus 2.5%; $P = 0.009$). The authors affirm the benefit of both agents in the treatment of patients with HITT but conclude that a prophylactic dose of danaparoid (750 U twice daily) may be insufficient to treat those with isolated HIT.

Data from current trials of anticoagulation in HIT(T) are shown in Table 2. Only three studies had a control group matched for patients with isolated HIT,[1,12,14] while only four performed outcome analyses on these patients.[1,12-14] Differences in duration of therapy and observation period make direct comparison difficult, but patients with HIT treated with argatroban or lepirudin have been shown to have a lower incidence of new TECs and the composite end-point of death, new TECS or limb amputation when compared with historical control groups.

There were some differences in the safety profiles of the two agents. Despite titration of lepirudin to an APTT 1.5–2.5 times baseline and argatroban to an APTT 1.5–3.0 times baseline, there was a consistently higher incidence of major bleeding episodes in patients treated with lepirudin compared with argatroban (13.4%–19% versus 5.7%–6.9%, respectively). Definitions of "major bleeding" were similar across the studies.

Summary

- Although there are theoretical advantages to certain anticoagulant therapies, there is little direct comparative evidence.
- Lepirudin and argatroban reduce the risk of subsequent thrombosis in patients with acute isolated HIT (Level 3-iii). The low risk of HIT antibody cross-reactivity and the predictable pharmacokinetic profile in renal failure may favour treatment with argatroban.[12,42,44]
- Bleeding complications may be more frequent in patients treated with lepirudin than with either argatroban or danaparoid (Level 3-iii).
- Lepirudin is superior to danaparoid for preventing thrombotic complications in patients with isolated HIT, but this benefit may be reduced or negated if danaparoid is administered in therapeutic doses (Level 3-ii).
- Drug availability also influences choice of agent: lepirudin and argatroban are available in the United States, and lepirudin and danaparoid in Australia.
- Current data support the availability of argatroban in Australasia for the treatment of patients with HIT(T).

How long should anticoagulation be continued?

No studies examined the effect of duration of anticoagulation on primary or secondary outcomes in patients with HIT(T). Several observational studies examined the transition from parenteral to oral anticoagulation.[32-35,46,47] Current guidelines advise alternate parenteral anticoagulation until platelet counts exceed 100×10^9/L, cautious initiation of warfarin to avoid an overshoot of the international normalised ratio (INR), and co-administration of warfarin and parenteral therapy for 4–5 days before warfarin monotherapy.[9,33,47]

It is difficult to extrapolate the effect of treatment duration on clinical end-points from available studies (Table 2) because of the following factors.

Different durations of therapy: In general, studies of lepirudin in HIT(T) involved longer durations of therapy than those with argatroban (lepirudin 11.1–13.5 days versus argatroban 5.1–5.3 days).[1,3,11,13,14,45] Moreover, therapy duration varied in patients with isolated HIT. In HAT-1, HIT patients received lepirudin for a median of 15 days (range, 2–58 days), in HAT-2 for 8 days (range, 1–67 days) and in HAT-3 for 10 days (range, 1–47 days).[3,11,13] These differences may have influenced the incidence of end-points in the studies.

Different observation periods: In the studies of argatroban,[12,14] patients were followed up for 37 days after commencement of the study drug. In the HAT studies,[3,11,13] patients were observed until 14 days after discontinuing

lepirudin, implying a variable period of observation which depended on duration of therapy.

Incomplete information about the transition to oral anticoagulation: Coumarin use was standardised in three studies,[3,11,13] and three studies reported its use in 41%–63% of patients.[1,13,14] One study neither standardised nor reported use of coumarin,[12] and none reported duration of coumarin therapy. A subsequent review confirmed that 83% of patients in the HAT-1 and HAT-2 studies and 62.5% of patients in the ARG-911 and ARG-915 studies received warfarin,[45] but independent outcome data were not available for these groups.

Incomplete information about changes in platelet counts: No study legislated that duration of parenteral anticoagulation was to be influenced by platelet count. Indeed in the ARG-911 study, 19% of the patients with isolated HIT had parenteral anticoagulation discontinued before restoration of platelet count.[12] In one study,[3] 88% of subjects had a platelet count $>100\times 109$/L by Day 10 despite a treatment duration of 14.0 ± 9.9 (mean ± SD) days. Two studies had no information on platelet counts.[1,13] A subsequent review of patients in ARG-911 and ARG-915[47] showed a median platelet count of 94 (range, 30–324) $\times 10^9$/L at the time warfarin was commenced.

Summary

- Current evidence guiding duration of anticoagulation in isolated HIT is limited to consensus opinion. In particular, parenteral anticoagulation should be continued until platelet count exceeds 100×10^9/L.

When should oral anticoagulation be commenced?

There are insufficient data from the Level 3 studies[1,3,11-14] to guide the use of warfarin in HIT. From 41% to 83% of patients received warfarin, initiation was not standardised, and duration of warfarin therapy was not stated. No study specified the proportion of patients with isolated HIT receiving warfarin. Of note, there were no reports of complications of warfarin therapy.

Several case reports and series have highlighted the risks of commencing warfarin in patients with HIT(T).

Warkentin et al[32] reported two case–control studies in which the occurrence of venous limb ischaemia in patients with HIT(T) was associated with warfarin monotherapy, a higher INR, higher in-vivo thrombin–antithrombin complex levels and lower protein C activity. In addition, resolution of this ischaemia was seen in one patient with reversal of warfarin with vitamin K and plasma. The authors hypothesised that the initial decrease in levels of endogenous anticoagulant protein C seen with warfarin initiation predisposes to thrombus generation, and that this effect may be exaggerated in patients with HIT(T).

Srinivasan et al[33] reported six patients with HITT who developed venous skin gangrene in the setting of warfarin therapy. Four had warfarin monotherapy, but two developed thrombosis during overlap between lepirudin and warfarin. Peak INR levels in these two patients were 4.5 and 5.8, respectively. Smythe et al[34] reported two cases of venous limb gangrene in patients with HIT. In both cases, warfarin was commenced before platelet recovery, and direct thrombin inhibitor therapy was temporarily discontinued, precipitating the skin gangrene. Bartholomew et al[47] have since reviewed the data from ARG-911 and ARG-915 and showed that, with argatroban–warfarin co-therapy, risk of thrombosis exceeded that of bleeding when INR was >4.0. Hursting et al[35] have since shown an acceptable risk of thrombosis in patients with HIT(T) during transition from argatroban to warfarin with a 4-day overlap of co-therapy and median INR of 3.2.

Summary

- In patients with HITT, warfarin therapy should commence after platelet count has been restored and should overlap with parenteral anticoagulation for at least 5 days, while attempts should be made to prevent overshoot of the INR (Level 4).
- Evidence supporting warfarin therapy in isolated HIT is lacking and is extrapolated from HITT data. If warfarin therapy is chosen, the same precautions with co-therapy and INR overshoot should be followed (Level 4).

Conclusion

Patients with isolated HIT are at risk of developing new arterial and venous thromboses. Although it would seem intuitive to anticoagulate these patients, there is no strong evidence supporting this intervention. In addition, there are significant risks associated with therapeutic anticoagulation which differ between agents (eg, danaparoid may have cross reactivity with the HIT antibody), particularly in critically ill patients with renal impairment. These risks are often justified in patients with known thromboses, but the risk–benefit ratio in patients with isolated HIT is less defined. Level 3-iii studies support the use of argatroban or lepirudin infusion titrated to an INR of 1.5–2.5/3.0 times baseline in isolated HIT. Danaparoid probably has similar efficacy to lepirudin in preventing new thromboses when therapeutic dosing schedules are used. The safety profiles of argatroban and danaparoid may be superior to that of lepirudin. There are no original studies guiding duration of anticoagulation or utilisation of oral anticoagulants in isolated HIT, although consensus guidelines have been published.[6]

After 10 years of original research, controversy still exists regarding the management of patients with isolated HIT,

much of which would be addressed by a multicentre, blinded, randomised trial.

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