Review: Clinical Trial Outcomes

CLINICAL INVESTIGATION

Treatment of heparin-induced thrombocytopenia: what are the contributions of clinical trials?

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Heparin-induced thrombocytopenia (HIT) creates an extreme thrombotic diathesis that requires emergent alternative anticoagulation. The discovery of the disorder, its complications and treatment principles, emanated from observational retrospective clinical case series. These established the need to urgently begin an alternative (non-heparin) anticoagulant even with isolated HIT, and to shun early warfarin use. Danaparoid emerged as a favored alternative anticoagulant, based on a large registry database and expert opinion. The direct thrombin inhibitors lepirudin and argatroban were approved for HIT by the US FDA based on prospective clinical trials that used historical controls; active controls were impossible because there were no established alternative agents, whilst placebos were not ethically acceptable. Postmarketing observational case series improved recommended dosing and other nuances for optimal use of these drugs. The only two attempts at randomized controlled trials have consisted of danaparoid versus dextran, which begun 25 years ago, and recently, desirudin versus argatroban. Both studies experienced very poor accrual. Currently, argatroban is the only FDA-approved agent on the market; however, bivalirudin and fondaparinux enjoy increasing use despite the absence of validated clinical trial data. Dabigatran, rivaroxaban, apixaban and other new anticoagulants will have future roles in disease prevention and treatment. HIT illustrates how major advances in understanding and therapy of a disease can advance rapidly even without major controlled trials, and gives testimony to the willingness of physicians to use agents perceived beneficial without trials or formal approvals. In an age emphasizing importance of the randomized prospective trial, HIT gives credence to the ever-present value of clinical case series and of insightful observations made by the prepared mind.

Keywords: argatroban • clinical trials • danaparoid • desirudin • fondaparinux • heparin-induced thrombocytopenia • heparin-induced thrombocytopenia and thrombosis • lepirudin

Given its frequency and potential for dire consequences, heparin-induced thrombocytopenia (HIT) may be the most important drug reaction faced in hospitals today. IgG antibodies form against a PF4–heparin complex provoking platelet activation, release of procoagulant platelet microparticles and endothelial injury. This extreme hypercoagulable state requires emergent initiation of alternative anticoagulation. The authors review how understanding of this disorder and its treatment have evolved and, particularly, what the contributions of clinical trials have been.

The early years

Thrombocytopenia due to heparin was observed soon after its introduction into clinical medicine. A total of 21 patients suffered repetitive catastrophic blood clots

FUTURE SCIENCE part of fsg

related to heparin therapy reported in case series in 1958 and 1964 [1,2]. Observational case series from the University of Missouri (MO, USA) in the mid-1970s delineated the clinical features of the HIT syndrome: a fall in platelet count occurring 5–12 days after beginning heparin and frequently accompanied by thromboemboli [3,4]. The immunologic basis was being elucidated at the same time [5,6].

When a patient was recognized to have HIT but no thrombosis (isolated HIT), one would simply stop anticoagulants, unless there were other pressing reasons for anticoagulation to continue. It 'seemed' that most patients did well with this strategy, but when Warkentin retrospectively reviewed data collected over 14 years on the outcomes of 65 such isolated HIT patients, he found that 50% of them developed venous or arterial thrombotic complications within 1 month; with 5% of these presenting as sudden death [7]. Thus, published guidelines and the standard of care now mandate immediate initiation of alternative anticoagulants for those with isolated HIT, the first few days being the most dangerous for the emergence of thromboses [8].

The early strategy for those identified to have HIT with thrombosis (HITT) was first to interdict further heparin exposure, including catheter flushes that were found to often promulgate the syndrome [9,10]. Warfarin was initiated, generally, with 'loading doses' of 10–15 mg. It was appreciated that warfarin takes several days to become therapeutic, and in the absence of established or readily available alternative anticoagulant drugs, inferior vena cava filters were frequently inserted in those with pulmonary emboli or at high risk. Later it was learned (from case series observations) that these strategies likely aggravated the risk for severe thrombotic complications. When initiated, warfarin depletes the short-lived natural anticoagulant protein C well before it impacts the important procoagulants factors II and X; thus, if initiated early, warfarin can exacerbate the extreme thrombotic diathesis. Warfarin use early in the course of HIT has precipitated venous limb gangrene or central skin necrosis, as documented in case-control and observational case series in the last 15 years [11,12]. Warfarin is now considered to be contraindicated in the acute phase of HIT, and once started, warfarin should not be used 'unopposed' and should be dosed with caution. Furthermore, foreign body inferior vena cava filters have been found to often serve as a nidus for accelerated blood clotting in this prothrombotic maelstrom [13].

A need for alternative (non-heparin) anticoagulants for these patients was apparent. Observational clinical experience and laboratory studies with low molecular weight heparins quickly revealed that these would not help, cross-reacting with the pathogenic anti-bodies while more complications emerged. A registry was launched with the defibrinating snake venom, ancrod [14]. Bivalirudin (then called hirulog) was given to a small number of cases (before the drug was temporarily taken out of development when it did not meet end points in coronary disease trials) [15].

By the 1990s, the favored alternative anticoagulant was the glycosaminoglycan danaparoid, with a large registry experience accumulated to support its use [16]. Danaparoid had been approved in the USA and other countries as a prophylactic agent for orthopedic surgery, but was little used for that indication (given its cost compared with other strategies). Danaparoid can commonly cross-react *in vitro* with heparin-PF4 antibodies, but the strength of the reactions are generally low and of inconsequential clinical importance for most [17,18]. It has a relatively long half-life and problematic clearance with renal insufficiency. Published dosing algorithms vary greatly in different clinical situations, including the frequent recommendation for continuous intravenous (iv.) infusion despite the 24-h duration of action.

Clinical trials

Prospective clinical trials for HIT have been performed in the past 25 years. None has used prospective randomization against placebo: there was no established comparator for the registration trials of direct thrombin inhibitors, and it has generally been deemed unethical to use a placebo given the very high thrombotic risks attendant to HIT. When prospective clinical trials have been attempted, recruiting patients has been a major challenge for a number of reasons. Such reasons include patients being frequently critically ill with multiple comorbidities; the fact that the certainty of diagnosis may be problematic initially and that there are often litigation concerns, especially since the problem is iatrogenic and unexpected. These factors therefore create additional barriers to obtaining consent from patients or their surrogate decision-makers. In fact, both early and more recently attempted prospective randomized trials have battled slow accrual. Nevertheless, clinical trials have contributed to our understanding of HIT and its treatment, which will now be reviewed.

Danaparoid

Like heparin, danaparoid exerts anticoagulant effects through binding to antithrombin. Danaparoid was first used for HIT in the 1980s because of its low cross-reactivity with heparin-PF4 antibodies. A randomized prospective trial of danaparoid for treatment of HIT was conducted in Australia from January 1988 to June 1994 with results reported in 2001 [19]. A total of 42 patients with recent thrombosis and a clinical diagnosis of HIT were randomized to danaparoid iv. or dextran 70 iv., an agent that inhibits platelet function and has

been used for thromboprophylaxis following surgery. A positive HIT antibody was not required to enter this study, but samples obtained at presentation proved positive for heparin-dependent platelet antibody by platelet aggregometry or 14C-serotonin release in 19 out of 25 patients on danaparoid and 15 out of 17 on dextran 70. There was no blinding due to differences in administration of the two agents; danaparoid was given as an iv. bolus of 2400 units, followed by continuous iv. infusion of 400 units/h for 2 h, then 300 units/h for 2 h and finally 200 units/h for 5 days. Dextran 70 was given as an iv. infusion of 1000 ml on day 1, followed by 500 ml daily infusion for the next 4 days. Both arms received warfarin on day 1 with a goal 'International Normalized Ratio' of 2–4. The primary end point was the proportion of initial thromboembolic events clinically resolved by discharge. Positive treatment response was observed in 22 out of 25 patients on danaparoid versus 8 out of 17 patients on dextran (88 vs 47%; p = 0.01). Some weaknesses of this study include the small number of enrollees, subjective clinical end point, and the open study design. The slow accrual and possible referral biases into the study could have been related to perceived superiority of danaparoid therapy at the time the study began. Dextran and other antiplatelet function agents are no longer routinely used for HIT. This study merits attention as the first attempted randomized prospective clinical trial of a therapy for HIT. Impetus for danaparoid use for HIT was generated more from published registry data and expert opinions [16,20].

Lepirudin

Lepirudin is a recombinant form of the leech-derived direct thrombin inhibitor, hirudin. It was approved in Europe in 1997, and 1 year later became the first FDA approved drug for HITT. Approval was based on three prospective, historically controlled trials performed in Germany – HAT-1, HAT-2 and HAT-3 – which shared similar study designs and included only patients with laboratory-confirmed HIT [21–23].

In HAT-1, HIT patients were treated with four different regimens depending on clinical scenario: HITT with or without thrombolysis, isolated HIT, or HIT in the context of cardiopulmonary bypass surgery. A total of 71 evaluable patients were compared with a 120 historical controls who had received best-available care from 1989 to 1993. The combined end point of deaths, new thromboembolic complications and limb amputations was 25.4% in the lepirudin group and 52.1% in the historical control group at day 37 (p = 0.014), while bleeding rates were not significantly different [21]. HAT-2 confirmed the efficacy and safety of lepirudin in 112 patients with laboratory-confirmed cases of HITT with or without thrombolysis, and isolated HIT [22]. HAT-3 enrolled 205 patients with laboratory-confirmed active HIT or past history of HIT. A combined analysis of HAT-1, HAT-2 and HAT-3 revealed that lepirudin therapy significantly reduced new thromboembolic complications, while there were no statistical differences in death and limb amputation. There was a significantly higher incidence of major bleeding in the lepirudin group (Table 1) [23–26]. A serum creatinine value greater than 90 µmol/l was associated with higher risk of major bleeding (10.8 vs 33.3%; p = 0.001) [23]. When timing of thromboembolic complications was examined, the majority experiencing these complications were found to be in the pretreatment period while waiting for laboratory confirmation of HIT (5.1% per patient day during pretreatment period vs 0.4% per patient day during active treatment). Thus, this study contributes to our understanding of the natural history of HIT and reinforces the mandate to initiate alternative anticoagulation on reasonable clinical suspicion for HIT while waiting for serologic confirmation.

Patients receiving lepirudin can develop anti-hirudin antibodies. HAT reported that 121 patients (30%) had anti-hirudin antibodies at the end of the first treatment cycle, and up to 70% in re-exposed patients after the second cycle. In this study, only 17 patients (4.2%) experienced an allergic reaction and there were no anaphylactic reactions [23]. Other postmarketing studies have seen anaphylactic reactions, some fatal [27], so the American College of Chest Physicians guidelines recommend not to retreat patients with lepirudin [8]. In addition, the anti-hirudin antibodies formed during a treatment course can delay the drug's clearance, necessitating downward adjustments to dosing and/or increased bleeding tendencies. In 2012, business concerns (sales/profits) led the manufacturer to cease lepirudin production [101].

Argatroban

Argatroban is a synthetic arginine-derived direct thrombin inhibitor. The efficacy and safety of argatroban for HIT were examined in two parallel prospective multi-center historically controlled trials conducted in the mid-1990s and reported in 2001. In Argatroban-911, Lewis *et al.* recruited 160 patients with isolated HIT, and 144 patients with HITT, to receive activated partial thomboplastin time-adjusted iv. argatroban, initially 2 µg/kg/min, with a goal activated partial thomboplastin time of 1.5 to three-times baseline. This was a 'real world' study in which suspicion for HIT qualified for enrollment; serologic tests proved positive in 57% of those tested. Clinical outcomes for the first 37 days were compared with a historical control group. The primary efficacy end point was a composite of all-cause death, all-cause amputation or new thrombosis, and this was

Table 1. Pivotal trials of US FDA-approved direct thrombin inhibitors.

	Patient number	Death from all causes	Death from thrombosis	Amputation	New TEC	Composite end point	Major bleeding
Combined Arg911 and Arg915 HIT (n = 460)							
Argatroban	321	63 (19.6%)	1 (0.3%)	11 (3.4%)	24 (7.5%)	94 (29.3%)	15 (4.7%)
Control	147	32 (21.8%)	7 (4.8%)	3 (2.0%)	22 (15.0%)	57 (38.8%)	12 (8.2%)
HR	–	–	0.072 (0.009–0.60)	0.54 (0.15–2.03)	0.29 (0.17–0.50)	0.33 (0.20–0.54)	–
p value	–	–	0.015	0.36	<0.001	<0.001	–
Combined Arg911 and Arg915 HITT (n = 422)							
Argatroban	376	79 (21.0%)	7 (1.9%)	50 (13.3%)	58 (15.4%)	158 (42.0%)	30 (8.0%)
Control	46	13 (28.3%)	7 (15.2%)	4 (8.7%)	16 (34.8%)	26 (56.5%)	1 (2.2%)
HR	–	–	0.13 (0.045–0.40)	1.22 (0.44–3.39)	0.32 (0.18–0.55)	0.39 (0.25–0.62)	–
p value	–	–	<0.001	0.7	<0.001	<0.001	–
All HAT							
Lepirudin	403	47 (11.7%)	–	26 (6.5%)	56 (13.9%)	109 (27.0%)	71 (17.6%)
Control	120	21 (17.5%)	–	8 (6.7%)	37 (30.8%)	53 (44.2%)	7 (5.8%)
p value	–	0.095	–	0.933	<0.0001	0.0001	0.0015

Due to the fact that entry criteria, patient populations treated and so on were different, argatroban and lepirudin results are not meant to be directly compared; rather, outcomes against historical 'best treatments' are illustrated.

HIT: Heparin-induced thrombocytopenia; HITT: Heparin-induced thrombocytopenia with thrombosis; HR: Hazard ratio; TEC: Thromboembolic complications.

Data taken from [24–26]

significantly reduced in the argatroban arm in patients with HIT (25.6 vs 38.8%; p = 0.014). A trend favored argatroban in patients with HITT, but this did not reach statistical significance (43.8 vs 56.5%; p = 0.13). Significantly reduced by argatroban therapy were the incidence of new thrombosis (HIT: 8.1 vs 22.4%; p < 0.001; HITT: 19.4 vs 34.8%; p = 0.044) and death caused by thrombosis (HIT: 0 vs 4.8%; p = 0.005; HITT: 0.7 vs 15.2%; p < 0.001). Major and minor bleeding rates were not significantly different between argatroban and historical controls (Table 1) [25].

The Argatroban-915 study included 198 patients with isolated HIT and 299 patients with HITT, compared with historical controls. The primary efficacy end point was again a composite of all-cause death, amputation, or new thrombosis. The composite end point was significantly reduced by argatroban in patients with HIT (28.0 vs 38.8%; p = 0.04) and strongly trended toward improvement with HITT (41.5 vs 56.5%; p = 0.07). Bleeding rates were similar between groups [26]. The Arg911 and Arg915 studies formed the bases for FDA approval of argatroban for HIT therapy in 2001.

Weaknesses of these studies include the use of historical controls and the open study design. In fact, the first analyses showed inferior outcomes for the argatroban treated patients when there was no correction for the severity of illness – this finding delayed FDA approval until a more similar historical control group could be collected. On the other hand, these studies recruited the largest number of HIT patients to date and provide valuable information on outcomes and treatment strategies for HIT.

A subgroup study from Argatroban-911 and Argatroban-915 selected patients with a history of HIT who had indications for anticoagulation. A total of 36 patients with past serologically confirmed HIT were now treated with argatroban. The median time between the diagnosis of HIT and initiation of argatroban was 7.5 months (0.4–114.6). No patients had new thrombosis, amputation or major bleeding, but six experienced minor bleeding [28]. Subsequent retrospective case series have clarified the safety and efficacy of argatroban, how best to transition to warfarin and have refined optimal dosing guidelines [29]. Argatroban is also approved in the USA for use with percutaneous coronary intervention. Generic versions of the drug are now marketed.

■ Desirudin

Desirudin is a potent bivalent direct thrombin inhibitor, approved in the USA for orthopedic prophylaxis (but little used for this indication). Its half-life makes it appropriate for either iv. or subcutaneous use. Desirudin was compared with argatroban in a randomized, prospective, open-label trial by the PREVENT-HIT investigators. The study was designed to enroll 120 patients [30]; however, it was terminated with

eight patients in each arm due to slow accrual. One patient in the argatroban group experienced worsening thrombosis. Three major bleeding complications occurred in the argatroban group and one patient in each group experienced minor bleeding [31]. This marks only the second randomized, prospective study of HIT therapies, and the first comparing direct thrombin inhibitors. It highlights the difficulties of conducting clinical trials in the setting of an acute and unexpected illness for which approved therapies are available.

Bivalirudin

Bivalirudin is a reversible direct thrombin inhibitor, a synthetically modified hirudin that binds to circulating and clot-bound thrombin. Favorable pharmacokinetic properties make this attractive for acutely ill intensive-care unit (ICU) patients, including its short half-life (25 min), 80% metabolism by circulating proteases, only 20% renal and negligible hepatic clearance. In addition, cardiac physicians are familiar with this agent due to its wide use with percutaneous coronary interventions.

With HIT, bivalirudin has been examined systematically in the settings of cardiac surgery or percutaneous coronary intervention (PCI). A prospective, open-label study evaluated efficacy and safety of bivalirudin in patients with HIT or HITT who were to undergo PCI [32]. A total of 52 patients were treated with either high- or low-dose bivalirudin beginning 4 h prior to PCI. There were high procedural and clinical success rates; 98 and 96%, respectively. One patient from the high-dose group had major bleeding and one patient from the low-dose group died from cardiac arrest.

Choose-On and Choose-Off were prospective, open-label, multicenter trials that examined the efficacy and safety of bivalirudin in cardiac surgery on and off cardiopulmonary bypass pump. Bivalirudin is particularly attractive in the setting of cardiac surgery because of its short half-live and the fact that a point-of-care test, the activated clotting time, may be adequate to assure therapeutic levels and minimize peri-operative bleeding complications. The Choose-On trial treated 49 patients with confirmed or suspected HIT and/or positive anti-PF4/heparin antibodies judged significant; 43 had acute HIT or HITT at the time of surgery. Procedural success at day 7 or discharge (whichever occurred first) was achieved in 46 patients (94%), and at 30 days and 12 weeks were 86 and 82%, respectively. There were 4 deaths (8.2%) at 12 weeks. Major bleeding or reexploration was reported in two patients (4.1%) [33].

The Choose-Off trial looked at off-pump surgical techniques to minimize the use of anticoagulation. A total of 51 patients with anti-PF4/heparin anti-bodies and/or HIT/HITT underwent off-pump coronary artery bypass with bivalirudin anticoagulation. Procedural success was achieved in 47 patients (92%) at day 7 or discharge. Day 30 and 12 weeks procedural success was 88% [34].

These trials have provided evidence of the efficacy and safety of bivalirudin for HIT patients under-going PCI or cardiac surgery. This experience has been extrapolated to provide confidence that bivalirudin can be used more broadly for HIT in place of FDA-approved direct thrombin inhibitors, especially in view of its favorable pharmacokinetic profile and the fact that physicians in the cardiovascular arena are already familiar with its use. Retrospective case series have reported favorable efficacy and safety [35,36], providing rationale for the use in HIT despite the lack of formal FDA approval for this indication.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide that re-capitulates the antithrombin-binding moiety of heparins, resulting in very selective factor Xa inhibition without activity against thrombin. The evidence for fondaparinux use in HIT, besides theoretic and laboratory studies showing no cross-reactivity with HIT antibodies, comes from case series and retrospective cohort studies. A review of six studies of HIT patients treated with fondaparinux comprised 65 patients – 96% with positive serology and 65% with HIT-related thrombosis – found no patient with new or progressive thrombosis; 3% had major bleeding [37]. Rare reports have described heparin-PF4 antibodies or the HIT syndrome emerging in patients on fondaparinux prophylaxis, but the drug does not react with these antibodies [38].

Fondaparinux use is increasing for HIT; its long half-life, subcutaneous administration and renal clearance make it attractive for 'less-sick' patients with isolated HIT or uncomplicated venous thrombosis who are not in the ICU. Fondaparinux has also been used after iv. direct thrombin inhibitors to simplify transition to warfarin.

New agents

New oral anticoagulants in development or recently approved include the direct thrombin inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixiban. These drugs have shown broad applicability to prophylaxis and treatment of thromboembolic disorders. They clearly do not cross-react with heparin-PF4 antibodies [39], and have numerous advantages over warfarin in the setting of HIT, including prompt anticoagulant action and no effect on natural anticoagulants (so they would not predispose to early

exacerbation of the prothrombotic diathesis). While there is no experience with these agents in HIT yet, they are likely to find a place in acute and subacute management. Furthermore, increasing use of these agents over heparins for more routine thromboembolic prophylaxis and therapy is likely to reduce the incidence of clinical HIT. A single-arm prospective Phase III trial of rivaroxaban for suspected HIT is being planned [102].

In preclinical studies, desulfated heparin is promising as an agent that can prevent or treat complications of HIT. It has been shown to interfere with heparin-PF4 antibody interactions with platelets [39].

Conclusion

Thrombocytopenia was first linked to heparin use by case reports, and more than 50 years ago case series implicated heparin in thrombotic events. The existence and clinical features of the HIT syndrome were gleaned from retrospective observational case series. From such case series, some with historical or case cohort controls, principles of treatment were learned, such as the need to begin an alternative anti-coagulant even with isolated HIT [40] and to avoid early unopposed warfarin. Danaparoid emerged as a favored alternative anticoagulant, based largely on registry studies and expert opinion. A prospective multicenter randomized trial comparing danaparoid to dextran could enroll only forty patients over several years. Recently there was a second attempt to perform an open-label prospective randomized trial comparing therapeutic agents, this time desirudin versus argatroban; however, it could enroll only 16 patients. These attempts to perform prospective randomized trials for HIT treatment mainly highlight the difficulties inherent in such endeavors.

There have been prospective studies in HIT looking at such things as incidence in various clinical situations, at test-ordering triggers, but our review concentrates on treatment studies. There has never been a blinded prospective trial. Perhaps it is ironic that a fully blinded randomized trial, which compared enoxaparin to unfractionated heparin in orthopedic prophylaxis, initially underestimated the incidence of HIT even with prospective monitoring in place; the incidence of 3% in the unfractionated heparin group emerged from reanalysis after serologic testing of stored frozen samples [41].

It was prospective nonrandomized trials that that led the FDA to approve the direct thrombin inhibitors argatroban and lepirudin for HIT therapy. The vagaries of such studies are well-illustrated by the fact that the initial argatroban trials presented to the FDA actually demonstrated some superior outcomes in the historical 'best-available-care' control group; when this was attributed to 'less-sick' control patients, the FDA required recruitment of a more comparable historic control group. Argatroban remains a mainstay of HIT therapy; however, proper use has been informed by postmarketing case series that have demonstrated improved safety and efficacy of lower initial dosing (still not reflected on the approved product label) and have provided guidance for warfarin transition. Lepirudin also had recommendations for initial dosing revised downward and warnings given about re-administration appreciated from postmarketing case series. Lepirudin is now withdrawn from the market in the face of declining use (related to a perception of increased bleeding and other risks). Therefore, bivalirudin and fondaparinux are being more frequently used for HIT, despite the absence of validating prospective trials. This has occurred on the basis of theoretic advantages (pharmacokinetic and laboratory studies), case series reports, expert opinions and clinicians' comfort with these agents gained from use for other disorders. The current American College of Chest Physician guideline recommends the use of lepirudin, argatroban or danaparoid over other non-heparin anticoagulants (grade 2C) in either HITT or isolated HIT. In patients with renal insufficiency, argatroban is preferred over other non-heparin anticoagulants because the main route of its metabolism is hydroxylation and aromatization in the liver and it is excreted in the feces by biliary secretion (grade 2C). When an acute or subacute HIT patient is undergoing urgent cardiac surgery, bivalirudin is a preferred non-heparin anticoagulant (grade 2C). When undergoing PCI, bivalirudin (grade 2B) or argatraban (grade 2C) are preferred agents [8].

One might wonder why HIT does not seem to lend itself to prospective randomized, controlled trials. It is clearly common enough. Some of the factors may be its acuity, its unpredictable emergence, frequent initial diagnostic ambiguity (and sometimes diagnostic delay) and the litigious risks that have existed. Impeding therapeutic trials is the availability of effective agents, even if these have not been proven in rigorous randomized trials. There are no patient societies lobbying for trials (as there are for some forms of cancer), and pharmaceutical firms have generally not seen it financially advantageous to pursue such trials (when an effective agent can achieve most goals with 'off-label' use). Even with the new emerging therapies (oral direct thrombin and Xa inhibitors), prospects for direct comparisons with currently used agents in clinical trials appears problematic.

On the other hand, discoveries and advances in the field of HIT dramatically illustrate the continuing importance of keen observations made by prepared minds. In this day where 'evidence-based medicine' emphasizes the randomized controlled trial, this

disorder reminds us that there will always be a place in medicine and science for carefully performed and analyzed case series. Were we to rely mainly on randomized studies, the current plight of patients afflicted with HIT would be much the worse.

Future perspective

HIT has always been shrouded by paradoxes [42], yet a new one has emerged: at a time when the incidence of the disease is declining, awareness is at an all-time high. This dichotomy is creating problems with over-diagnosis and over-treatment. All indicators point to the fact that HIT is declining and will continue to decline, driven partly by an increasing use of low molecular weight heparin at the expense of unfractionated heparins. Low molecular weight heparins (with generic formulations now available in the USA) cause HIT a tenth as often as unfractionated heparin. There is also good reason to project increasing use of non-heparin anticoagulants such as dabigatran, rivaroxaban and apixiban, particularly for venous thromboembolism prophylaxis, and this is another reason to anticipate a continuing decline in HIT. It is likely that these new oral anticoagulants will also take on an increasing role in the therapy for those with unconfirmed mild or moderate suspicion for HIT or for those with HIT that is isolated or associated with venous thromboemboli that are not severe.

The over-diagnosis of HIT has, in part, been driven by the wide availability of ELISA laboratory tests for heparin–PF4 antibodies, but also by the 'laziness' of physicians who yearn for a test to tell them who has HIT and who does not, rather than to learn about the disease characteristics, when they should suspect the diagnosis and when it should not be a reasonable consideration [42,43]. ELISA tests are wonderful for their ease of performance, reproducibility and sensitivity, but 'false positives' are a major problem, more so when the test is ordered on patients who, based on clinical criteria, do not have a reasonable pretest probability of the disease. Optical density values (surrogate for antibody titers) above 0.4 are generally cited as 'positive'; however, studies show that more than 95% of those with optical density values between 0.4 and 1.0 do not have the platelet-activating antibodies that cause HIT [44].

Lepirudin is no longer available (and had been less and less used), so argatroban (now generic) and bivalirudin ('off-label') will continue to be given to ill patients in ICUs with HIT or strongly suspected HIT. Those with isolated HIT, HIT with milder manifestations or suspected HIT, are likely to be treated with fondaparinux or the newer oral anticoagulants. The use of the latter is likely to be accelerated by future retrospective case series (using what is considered best care available) or possibly prospective case series, but there will not be prospective randomized trials – these drugs are targeted to the common conditions of atrial fibrillation and venous thromboembolic disease, so it would not make sense to invest resources in studies for the 'niche' disease of HIT. Again, retrospective case series drove current treatment paradigms for HIT, and this is likely to be the case with emerging future therapies.

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Executive summary

Hypercoagulability of heparin-induced thrombocytopenia

- Heparin-induced thrombocytopenia (HIT) is an extremely hypercoagulable state that requires an immediate initiation of alternative anticoagulation.
- Without alternative anticoagulation, patients with isolated HIT may develop thromboembolic complications at 1 month in up to 50% and sudden death in 5% of these patients.
- The majority of thromboembolic complication of HIT was found during the pretreatment period whilst waiting for laboratory confirmation of HIT; therefore, a prompt initiation of non-heparin anticoagulants is required before laboratory confirmation.

Current guideline

- Lepirudin, argatroban and danaparoid are recommended non-heparin anticoagulants according to the 9th American College of Chest Physicians guideline.

Challenges in performing randomized clinical trials in HIT

- Randomized head-to-head trial of direct thrombin inhibitor is difficult to perform due to acuity of disease, frequently ambiguous initial diagnosis and patient comorbidities leading to very slow accrual.

References

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable

1 Weismann RE, Tobin RW. Arterial embolism occurring during systemic heparin therapy. *Arch. Surg.* 76(2), 219–227 (1958).

2 Roberts B, Rosato FE, Rosato EF. Heparin – a cause of arterial emboli? *Surgery* 55(55), 803–808 (1964).

3 Rhodes GR, Dixon RH, Silver D. Heparin induced thrombocytopenia with thrombotic and hemorrhagic manifestations. *Surg. Gynecol. Obstet.* 136(3), 409–416 (1973).

4 Rhodes GR, Dixon RH, Silver D. Heparin induced thrombocytopenia: eight cases with thrombotic-hemorrhagic complications. *Ann. Surg.* 186(6), 752–758 (1977).

5 Natelson EA, Lynch EC, Alfrey CP Jr, Gross JB. Heparin-induced thrombocytopenia. An unexpected response to treatment of consumptive coagulopathy. *Ann. Int. Med.* 71, 1121–1125 (1969).

6 Babcock RB, Dumper CW, Scharfman WB. Heparin-induced immune thrombocytopenia. *N. Engl. J. Med.* 295(5), 237–241 (1976).

7 Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am. J. Med.* 101(5), 502–507 (1996).

8 Linkins L-A, Dans AL, Moores LK *et al.* Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 141(Suppl. 2), e495S–530S (2012).

■■ **The most recent American College of Chest Physicians guideline on treatment of heparin-induced thrombocytopenia (HIT). Grade of evidence is provided based upon extensive literature review.**

9 Rice L, Jackson D. Can heparin cause clotting? *Heart Lung* 10(2), 331–335 (1980).

10 Rice L, Huffman DM, Levine ML, Udden MM, Waddell CC, Luper WE. Heparin-induced thrombocytopenia/thrombosis syndrome: clinical manifestations and insights. *Blood* 68(Suppl. 1), 339a (1986).

11 Warkentin TE, Elavathil LJ, Hayward CP *et al.* The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. *Ann. Int. Med.* 127(9), 804–812 (1997).

12 Srinivasan AF, Rice L, Bartholomew JR *et al.* Warfarin-induced skin necrosis and venous limb gangrene in the setting of heparin-induced thrombocytopenia. *Arch. Intern. Med.* 164(1), 66–70 (2004).

13 Jung M, McCarthy J, Baker K, Rice L. Safety of IVC filters with heparin-induced thrombocytopenia: a retrospecive study. *Blood* 118(Suppl.), 2225 (2011).

14 Demers C, Ginsberg JS, Brill-Edwards P *et al.* Rapid anticoagulation using ancrod for heparin-induced thrombocytopenia. *Blood* 78, 2194–2197 (1991).

15 Nand S. Hirudin therapy for heparin-associated thrombocytopenia and deep vein thrombosis. *Am. J. Hematol.* 43, 310–311 (1993).

16 Magnani HN. Orgaran (danaparoid sodium) use in the syndrome of heparin-induced thrombocytopenia. *Platelets* 8, 74–81 (1997).

17 Koster A, Meyer O, Hausmann H *et al. In vitro* cross-reactivity of danaparoid sodium in patients with heparin-induced thrombocytopenia type II undergoing cardiovascular surgery. *J. Clin. Anesthes.* 12(4), 324–327 (2000).

18 Kodityal S, Manhas AH, Udden M, Rice L. Danaparoid for heparin-induced thrombocytopenia: an analysis of treatment failures. *Eur. J. Haematol.* 71(2), 109–113 (2003).

19 Chong BH, Gallus A, Cade JF *et al.* Prospective randomised open-label comparison of danaparoid with dextran 70 in the treatment of heparin-induced thrombocytopaenia with thrombosis: a clinical outcome study. *Thromb. Haemost.* 86(5), 1170–1175 (2001).

■ **This is the first attempted randomized prospective clinical trial of treatment for HIT.**

20 Magnani HN, Gallus A. Heparin-induced thrombocytopenia (HIT). A report of 1,478 clinical outcomes of patients treated with danaparoid (Orgaran) from 1982 to mid-2004. *Thromb. Haemost*. 95(6), 967–981 (2006).

21 Greinacher A, Volpel H, Janssens U *et al.* Recombinant hirudin (lepirudin) provides safe and effective anticoagulation in patients with heparin-induced thrombocytopenia: a prospective study. *Circulation* 99(1), 73–80 (1999).

22 Greinacher A, Janssens U, Berg G *et al.* Lepirudin (recombinant hirudin) for parenteral anticoagulation in patients with heparin-induced thrombocytopenia. *Circulation* 100(6), 587–593 (1999).

23 Lubenow N, Eichler P, Lietz T, Greinacher A. Lepirudin in patients with heparin-induced thrombocytopenia – results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. *J. Thromb. Haemost.* 3(11), 2428–2436 (2005).

■ **Three prospective, historically controlled trials of lepirudin in HIT – HAT-1, HAT-2 and HAT-3 – were analyzed in combination.**

24 Lewis BE, Wallis DE, Hursting MJ *et al.* Effects of argatroban therapy, demographic variables, and platelet count on thrombotic risks in heparin-induced thrombocytopenia. *Chest* 129, 1407–1416 (2006).

25 Lewis BE, Wallis DE, Berkowitz SD *et al.* Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. *Circulation* 103(14), 1838–1843 (2001).

■ **The first prospective, multicenter, historically controlled trial of argatroban in HIT.**

26 Lewis BE, Wallis DE, Leya F, Hursting MJ, Kelton JG. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia. *Arch. Int. Med.* 163(15), 1849–1856 (2003).

27 Greinacher A, Lubenow N, Eichler P. Anaphylactic and anaphylactoid reactions associated with lepirudin in patients with heparin-induced thrombocytopenia. *Circulation* 108(17), 2062–2065 (2003).

28 Matthai WH, Hursting MJ, Lewis BE, Kelton JG. Argatroban anticoagulation in patients with a history of heparin-induced thrombocytopenia. *Thromb. Res.* 116(2), 121–126 (2005).

29 Kodityal S, Nguyen PH, Kodityal A, Sherer J, Hursting MJ, Rice L. Argatroban for suspected heparin-induced thrombocytopenia: contemporary experience at a large teaching hospital. *J. Intens. Care Med.* 21, 86–92 (2006).

30 Frame J, Rice L, Bartholomew JR, Whelton A. Rationale and design of the PREVENT-HIT study: a randomized, open-label, pilot study to compare desirudin and argatroban in patients with suspected heparin-induced thrombocytopenia with or without thrombosis. *Clin. Ther.* 32, 626–636 (2010).

31 Boyce SW, Bandyk DF, Bartholomew JR, Frame JN, Rice L. A randomized, open-label pilot study comparing desirudin and argatroban in patients with suspected heparin-induced thrombocytopenia with or without thrombosis: PREVENT-HIT study. *Am. J. Ther.* 18(1), 14–22 (2011).

■ **The second attempted randomized, prospective study of desirudin and argatroban. The study was terminated prematurely due to slow accrual.**

32 Mahaffey KW, Lewis BE, Wildermann NM *et al.* The anticoagulant therapy with bivalirudin to assist in the performance of percutaneous coronary intervention in patients with heparin-induced thrombocytopenia (ATBAT) study: main results. *J. Invasive Cardiol.* 15(11), 611–616 (2003).

33 Koster A, Dyke CM, Aldea G *et al.* Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: results of the CHOOSE-ON trial. *Ann. Thorac. Surg.* 83(2), 572–577 (2007).

34 Dyke CM, Aldea G, Koster A *et al.* Off-pump coronary artery bypass with bivalirudin for patients with heparin-induced thrombocytopenia or antiplatelet factor four/heparin antibodies. *Ann. Thorac. Surg.* 84(3), 836–839 (2007).

35 Berilgen JE, Nguyen PH, Baker KR, Rice L. Bivalirudin treatment of heparin-induced thrombocytopenia. *Blood* 102(Suppl.), 537a, (2003).

36 Kiser TH, Burch JC, Klem PM, Hassell KL. Safety, efficacy, and dosing requirements of bivalirudin in patients with heparin-induced thrombocytopenia. *Pharmacotherapy* 28, 1115–1124 (2008).

37 Warkentin TE, Eikelboom JW. Fondaparinux and other emerging anticoagulants to treat heparin-induced thrombocytopenia. In: *Heparin-Induced Thrombocytopenia (5th Edition).* Warkentin TE, Greinacher A (Eds). CRC Press, FL, USA, 489–519 (2013).

38 Chong BH, Chong JJH. Heparin-induced thrombocytopenia associated with fondaparinux. *N. Engl. J. Med.* 8(1), 63–65 (2010).

39 Krauel K, Hackbarth C, Fürll B, Greinacher A. Heparin-induced thrombocytopenia: in vitro studies on the interaction of dabigatran, rivaroxaban, and low-sulfated heparin, with platelet factor 4 and anti-PF4/heparin antibodies. *Blood* 119(5), 1248–1255 (2012).

40 Elalamy I, Tardy-Poncet B, Mulot A *et al.* Risk factors for unfavorable clinical outcome in patients with documented heparin-induced thrombocytopenia. *Thromb. Res.* 124, 554–559 (2009).

41 Warkentin TE, Levine MN, Hirsh J *et al.* Heparin-induced thrombocytopenia in patients treated with low molecular-weight heparin or unfractionated heparin. *N. Engl. J. Med.* 332, 1330–1335 (1995).

42 Rice L. A clinician's perspective on heparin-induced thrombocytopenia: paradoxes, myths and continuing challenges. In: *Heparin-Induced Thrombocytopenia (5th Edition).* Warkentin TE, Greinacher A (Eds). Informa, Colchester, UK, 608–617 (2012).

43 Wanat M, Fitousis K, Hall J, Rice L. Heparin PF4 antibody testing and treatment of heparin-induced thrombocytopenia in the intensive care unit. *Clin. Appl. Thromb. Hemost.* doi: 10.1177/1076029612438709 (2012) (Epub ahead of print).

44 Warkentin TE, Sheppard JI, Moore JC, Sigouin CS, Kelton JG. Quantitative interpretation of optical density measurements using PF4-dependent enzyme-immunoassays. *J. Thromb. Haemost.* 6(8), 1304–1312 (2008).

■ Websites

101 American Society of Health-systempharmacists. www.ashp.org/DrugShortages/NotAvailable/bulletin.aspx?id=924 (Accessed 23 January 2013)

102 ClinicalTrials Database: NCT01598168. www.clinicaltrials.gov/ct2/show/NCT01598168 (Accessed 8 November 2012)