

Heparin-Induced Thrombocytopenia – Retrospective Analysis of Data on Incidence and Outcomes Study (HIT-RADIO Study)

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PROTOCOL SYNOPSIS

Heparin-induced thrombocytopenia (HIT) is a major complication of the administration of heparin and can result in life-threatening thrombosis with or without thrombocytopenia (HIT-T) or can produce thrombocytopenia without clinically symptomatic thrombosis (“isolated” HIT). Isolated heparin-induced thrombocytopenia is defined as a fall in platelet count associated with a positive heparin PF-4 antibody test, in the absence of clinically overt thrombosis. While the treatment of HIT-T (HIT with thrombosis) with anticoagulation is well established, the risks and treatment of isolated HIT are unclear. To determine the incidence and outcome of isolated HIT, a trial (the HIT Observational Thromboembolism Trial) was designed and patients screened and enrolled from 1/21/2008 through 9/25/2008. After screening 503 subjects with a positive heparin PF-4 antibody test, only 10 patients with isolated HIT were enrolled into the study and the study was stopped. The low frequency of patients with isolated HIT found in this prospective, multi-center trial was surprising since prior estimates of the frequency suggested rates 4-10 fold higher.

Although the HIT Observational Thromboembolism Trial did not proceed as planned, it did identify a large cohort of patients with a positive heparin PF-4 antibody test over a defined period of time in a large number of clinical centers. These subjects provide a large database which can now be used to assess the incidence, characteristics, and outcome of a positive heparin PF-4 antibody test.

The purpose of this study is to analyze specific data from all subjects with a positive heparin PF-4 antibody test occurring between 1/21/2008 and 9/25/2008 in those centers that participated in the HIT Observational Thromboembolism Trial. It is anticipated that this data analysis will provide a current overview of the implications of a positive heparin PF-4 antibody test in clinical practice. It should determine the percentage of positive heparin PF-4 antibody tests that are associated with thrombocytopenia and thrombosis (HIT-T) or “isolated” HIT at diagnosis and the subsequent major clinical outcomes of death, limb amputation/gangrene, and new thrombosis. No “snapshot” of such HIT patients has been conducted in the past decade and the results will be important in assessing the impact of HIT in current medical care as well as documenting current treatment strategies.

Primary objective:

To determine the rate of the triple endpoint of death, limb amputation/gangrene, and new thrombosis after the time the positive heparin PF-4 antibody test was drawn.

Study Design:

This is a retrospective chart review study conducted at all those centers (all part of the NIH Transfusion Medicine and Hemostasis Network) that participated in the HIT Observational Thromboembolism Trial. All subjects with a positive heparin PF-4 antibody test occurring between 1/21/2008 and 9/25/2008 will be identified and relevant data collected to define the pooled incidence of HIT, isolated HIT, thromboembolism, death, limb amputation/gangrene as well as the platelet count, treatment modality, discharge outcome, and discharge medications. From the HIT Observational Thromboembolism Trial, it is estimated that about 500 patients will be eligible for this retrospective analysis.

PROTOCOL SCHEME

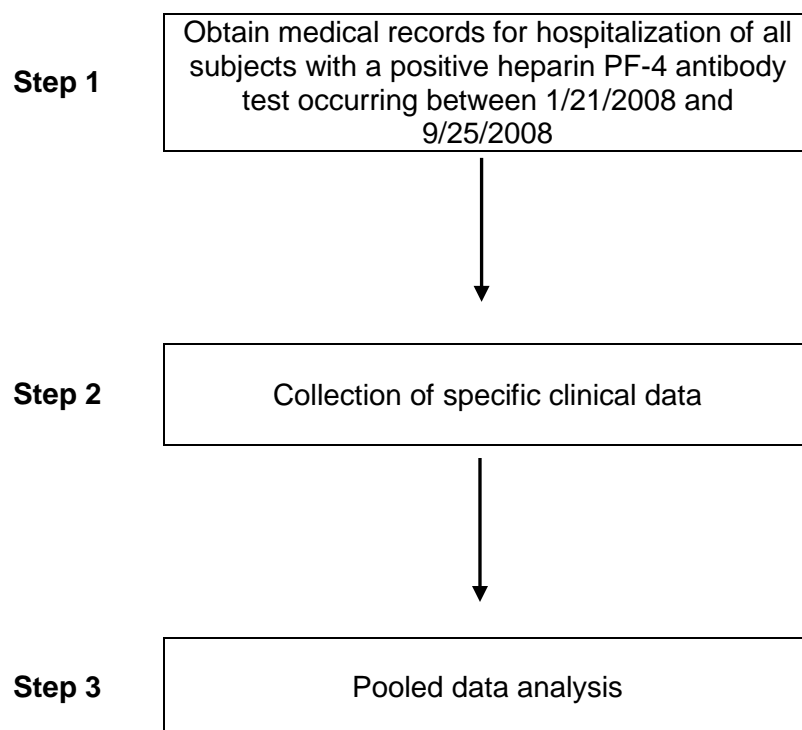


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1. BACKGROUND AND SIGNIFICANCE

Heparin-induced thrombocytopenia (HIT) is a common and often severe complication of heparin therapy¹. Depending upon the patient population and the type and route of heparin used, the incidence of HIT ranges from 0.3-5% of patients exposed. HIT is an immunologic drug reaction that is mediated by IgG antibodies against the heparin-platelet factor 4 (PF4) complex. These IgG-heparin-PF4 complexes activate platelets leading to platelet aggregation, thrombocytopenia, the generation of platelet microparticles and thrombin, and thrombosis. This antibody-mediated reaction typically occurs on days 5-10 after initiation of therapy but it can occur as quickly as a few hours after exposure in patients who previously received heparin.

Although thrombocytopenia is a cardinal feature of HIT, the platelet count is rarely low enough to present major bleeding problems and is the least worrisome complication of this disorder. The major problem with HIT is potentially life-threatening arterial and venous thrombi. Such patients with thrombosis are felt to have HIT-T indicating the presence of thrombosis along with a positive heparin-PF4 antibody test² with or without thrombocytopenia. In contradistinction are patients with HIT who have no clinical evidence for thrombosis but who do have thrombocytopenia and a positive heparin-PF4 antibody test (hereafter referred to as “isolated” HIT). Per the recent ACCP (“CHEST”) Guidelines³ the current standard of care for patients who develop isolated HIT is the institution of a direct thrombin inhibitor until the platelet count is greater than 100,000 (usually for 3-4 days), the overlap of the direct thrombin inhibitor with coumadin for at least 5 days, and an unspecified total duration of anticoagulation (although 28 days from the onset of this complication is often recommended). As stated in the Guidelines, “The optimal management strategy for isolated HIT remains uncertain.” The treatment of isolated HIT often results in a major increase in the hospital length of stay as well as increased financial obligations.

However, these guidelines are based upon a sparse amount of data, no randomized placebo-controlled studies, and few prospective studies. The basis for the recommendation of 28 days of anticoagulation for patients with isolated HIT is several retrospective studies that show an up to 50% VTE rate in untreated patients with isolated HIT in the 28 days after diagnosis⁴. Another justification for anticoagulation in isolated HIT patients is the suggestion that anywhere from 15-50% of isolated HIT patients have asymptomatic clot at the time of the diagnosis of isolated HIT⁵.

To address some of these issues we designed a clinical trial, the HIT Observational Thromboembolism Trial, to determine prospectively the incidence of isolated HIT and whether such patients had an increased rate of symptomatic and asymptomatic (identified by non-invasive methods) clots. To conduct this trial a large number of consecutive subjects were identified who had a positive heparin PF-4 antibody test and were subsequently screened for isolated HIT. Unfortunately only a small number of eligible subjects with isolated HIT were identified and the study was unsuccessful. But a large cohort of consecutive patients with a positive heparin PF-4 antibody test was identified prospectively in a large number of sites. This cohort of subjects now provides an important resource to provide a current view of HIT (“isolated HIT” and HIT-T), outcome and treatment.

2. OBJECTIVES

2.1. Primary Objective

To determine the time to occurrence of a composite triple endpoint consisting of death, limb amputation/gangrene, and new thrombosis from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge or day 45, whichever occurred first.

2.2. Secondary Objectives

1. To determine the time to occurrence of radiographically confirmed thromboembolism from the time the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.
2. To determine the time to death from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge or day 45, whichever occurred first.
3. To determine the time to occurrence of limb amputation or limb gangrene from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.
4. To determine the proportion of subjects with HIT-T and isolated HIT in those with a heparin PF-4 antibody test.
5. To determine the type of heparin exposure prior to the positive heparin PF-4 antibody test.
6. To determine the relationship of the heparin PF-4 antibody titer to the clinical diagnosis, degree of thrombocytopenia, and the primary endpoint.
7. To assess the type of treatment (direct thrombin inhibitor, fondaparinux, warfarin, no treatment) provided to subjects in hospital and at the time of discharge.
8. To determine the time to platelet recovery from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first, among subjects with a decreased platelet count
9. To determine the time to occurrence of major bleeding from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.
10. To assess the impact of treatments received on the time to occurrence of major bleeding from the time that the positive heparin PF-4 antibody test was drawn until hospital discharge, death, or day 45, whichever occurred first.

3. STUDY POPULATION

3.1. Inclusion Criteria

1. All subjects with a positive heparin PF-4 antibody test occurring between 1/21/2008 and 9/25/2008 (the dates during which the HIT Observational Thromboembolism Trial was open).
2. Medical record available for the admission during which the positive heparin PF-4 antibody test was obtained.

3.2 Exclusion Criteria

1. None.

4. TRIAL ENROLLMENT

4.1 Number Of Patients To Be Enrolled

Approximately 500 patients. (This estimate is based on the fact that 503 patients with a positive heparin PF-4 antibody test were screened for the HIT Observational Thromboembolism Trial between 1/21/2008 and 9/25/2008.)

4.2 Stratification And Randomization

This will not be necessary for this retrospective chart review.

5. INTERVENTIONS

None. This is a retrospective chart review only of patients found to have a positive heparin PF-4 antibody test between 1/21/2008 and 9/25/2008.

6. MEASUREMENTS

6.1. Measurement Procedures. Study personnel will review the medical record for the hospital visit (during time period of 1/21/2008-9/25/2008) during which the positive heparin PF-4 antibody test was reported. The data below will be abstracted onto case report forms. Prior medical records and medical records from other institutions will not be sought, unless already part of the medical record for the hospital visit during which the positive heparin PF-4 antibody test was reported. The chart review will involve the single hospital admission during which the positive heparin PF-4 antibody test was obtained and will include no more than the 28 days prior and no more than 45 days after the date the positive heparin PF-4 antibody test was sent.

The reference time (T=0) for all measurements will be the date the positive HIT assay was sent (not the date it returned positive)

6.2. Measurements to be Obtained

- Admission date
- Discharge date
- Age
- Gender
- Weight
- Height
- Was patient enrolled into the HIT Observational Thromboembolism Study
- History of thrombosis prior to this admission (yes/no; venous –DVT, PE, central venous access device, CNS venous sinus, intra-abdominal venous thrombosis, other; arterial – MI, CVA, arterial thrombosis of limb, other)
- History of HIT prior to this admission
- Other obvious causes of thrombocytopenia

- Reason for this hospitalization
- Indications for UFH or LMWH this admission (prophylaxis, flush, procedure –cv surgery, cardiac clot, other), thrombosis treatment (venous – dvt, pe, superficial thrombophlebitis; arterial – MI, CVA, arterial thrombosis of limb)
- History of use of central venous or arterial access devices during this admission
- Surgical procedure (orthopedic, cardiovascular, other general surgical) or medical procedure (chemotherapy, invasive cardiac intervention)
- Heparin exposure in the 90 days prior to admission, if available and documented in current medical record (yes/no/unknown)
- Heparin PF-4 antibody test type and degree of positivity (OD of patient sample vs OD cutoff for the assay)
- Date positive heparin PF-4 antibody test sent
- Date heparin PF-4 antibody test reported back positive
- Heparin exposure this admission: type, dose, duration, date stopped
- Platelet counts: daily platelet counts (if more than one platelet count per day, only the first platelet count of the day will be recorded)
- List of specific anticoagulant drugs used after heparin PF-4 antibody test sent: UFH, LMWH, warfarin, fondaparinux, argatroban, lepirudin, bivalirudin, abciximab (Reopro), eptifibatide (Integrilin), and tirofiban (Aggrastat), or no anticoagulant drugs used
- Platelet transfusion after heparin PF-4 antibody test sent (yes/no)
- Discharge home on warfarin, LMWH, fondaparinux, nothing, other anticoagulant
- Death (date)
- Limb amputation (date) performed (hand or part of hand; foot or part of foot)
- Thrombosis (date and location) prior to heparin PF-4 antibody test being sent
- Thrombosis (date and location) after heparin PF-4 antibody test sent
- Were screening ultrasound studies of the limbs (upper extremities; lower extremities) performed within 72 hours after the positive heparin PF-4 antibody test was sent?
- Bleeding events after positive heparin PF-4 antibody test sent
- Length of hospital admission
- Did the subject have cancer?
- If cancer present, solid or hematologic?
- If cancer present, was it under treatment?
- Any hospital admission within the 60 days prior to the admission date? If so, date of most recent hospitalization.

7. ADVERSE EVENT REPORTING

Not relevant to this chart review

8. DEFINITIONS

A **new thrombotic event** is any arterial or venous thrombosis not documented to be present on Day 0.

An **arterial thrombosis** is restricted to myocardial infarction, CVA, limb/digit thrombosis, abdominal vasculature clot, retinal artery clot, aortic clot.

A **venous thrombosis** is restricted to DVT, PE, intra-abdominal clot, calf vein thrombosis, retinal vein thrombosis, central venous catheter thrombosis, CNS venous thrombosis, intracardiac clot.

Isolated HIT is defined as a platelet count less than 50% of the **baseline platelet count** (see below) in the absence of any new thrombotic event while on heparin.

HIT-T is defined as new thrombotic event while receiving heparin and within the 5 days prior to Day 0.

The **baseline platelet count** is the highest platelet count in the patient record for the current hospitalization prior to the date the positive HIT assay was sent.

The **nadir platelet count** is the lowest platelet count within +/-5 days of the date the positive HIT assay was sent

A **major bleeding event** is defined as any 24 hour period in which 2 or more units of RBC are transfused OR radiographically confirmed intracranial hemorrhage.

Thrombocytopenia is defined as a nadir platelet count less than or equal to 50% of baseline platelet count.

A **positive HIT assay** is the first positive HIT ELISA assay in the medical record. Subsequent positive assays will not be considered or reported.

For subjects who had thrombocytopenia at the time the positive HIT assay was sent or within 5 days on either side of that date, **platelet recovery** is defined as occurring on the first date after the nadir platelet count that the platelet count was at least 100,000/ μ l.

9. STATISTICAL CONSIDERATIONS

9.1 Analysis of Baseline Characteristics

Subjects will be categorized into four groups, based on their platelet count on the date the positive HIT assay was sent, and on whether they had any arterial or venous thrombosis first documented at the time the positive HIT assay was sent or in the previous 5 calendar days.

- Group 1: Those with both thrombosis and thrombocytopenia
- Group 2: Those with thrombosis but not thrombocytopenia
- Group 3: Those with thrombocytopenia but not thrombosis
- Group 4: Those with neither thrombocytopenia nor thrombosis

The four groups will be compared with respect to baseline characteristics, based on data recorded through the time the positive HIT assay was sent. The baseline characteristics to be compared will include demographic information, medical history information, the optical density (OD) of the positive HIT ELISA test, the type of heparin exposure, and the indication for heparin. For binary outcomes, Fisher's Exact test will be used. For continuous variables with approximately normal distributions, analysis of variance will be used, and for continuous variables with non-normal distributions, a non-parametric Kruskal-Wallis test will be used.

The relationship between OD and Day 0 platelet count will be plotted using a scatterplot, with separate symbols for Groups 1 – 4. A linear regression model will be used to determine the relationship of Day 0 platelet count to OD overall, and analysis of covariance will be used to determine the relationship of Day 0 platelet count to OD, adjusting for Group. If necessary, suitable transformations will be used before fitting these models.

For those subjects with HIT-T, i.e. subjects in Groups 1 and 2, the types of thromboses diagnosed before the positive assay was sent will be tabulated.

9.2 Analysis Plan for the Primary Endpoint

9.2.1 Primary analysis of the primary endpoint

A Kaplan-Meier curve (and 95% confidence bands) will be used to describe the time to occurrence of the composite triple endpoint consisting of death, limb amputation/gangrene, and new thrombosis, with all four groups combined. The time-to-event will be calculated as the time from the positive heparin PF-4 antibody test was drawn until death, limb amputation/gangrene, or new thrombosis, whichever occurred first. Subjects will be censored at hospital discharge or 45 days after the positive heparin PF-4 antibody test was drawn, whichever occurred first. Estimated quartiles and 95% confidence intervals for time to the primary endpoint will be calculated.

9.2.2 Secondary analysis of the primary endpoint

Kaplan-Meier curves will be used to describe the rate of death, limb amputation/gangrene, and new thrombosis in each of Groups 1 – 4, in a manner similar to that described in section 9.1.1. A Cox proportional hazards model will be used to compare whether the risk of the triple endpoint differs between the four groups.

Additional Kaplan-Meier curves and Cox models will be used to determine whether the time to the primary outcome is associated with other baseline characteristics such as subject age, Day 0 platelet count, and medical history.

9.3 Analysis Plan for the Secondary Endpoints

For secondary endpoints 1, 3, and 9, analyses will be similar to those described in Section 9.2. The time-to-event will be calculated as the time from the positive heparin PF-4 antibody test was drawn until the first time the event of interest occurred. Subjects will be censored at death, hospital discharge, or 45 days after the positive test was drawn (whichever occurs first), if the event of interest has not occurred by that time.

For secondary endpoint 2, analyses will be similar to those described in Section 9.2, except that death is the event of interest rather than a censoring event.

For secondary endpoint 4, the percent of subjects with HIT-T (i.e. the percent of subjects in either Group 1 or 2) and the percent of subjects with isolated HIT (i.e. the percent of subjects in Group 3) will be reported. Exact 95% binomial confidence intervals will also be provided.

For secondary endpoint 5, descriptive statistics will be presented overall, and Groups 1-4 will be compared (see Section 9.1).

For secondary endpoint 6, the relationship between clinical diagnosis and heparin PF-4 antibody titer levels will be assessed using analysis of variance if the titer levels are approximately normally distributed within each diagnosis, and using a non-parametric Kruskal-Wallis test otherwise. The relationship between the degree of thrombocytopenia and the heparin PF-4 antibody titer level will be assessed using a scatter plot and linear regression. If necessary, transformations of one or both variables will be used. The relationship between the heparin PF-4 antibody titer level and time to occurrence of the primary endpoint will be assessed using a Cox model. Additional Cox models will be fit adjusting for covariates, such as the subject's group.

For secondary endpoint 7, descriptive statistics will be presented overall, and Groups 1-4 will be compared using Fisher's Exact tests.

For secondary endpoint 8, a Kaplan-Meier plot will be used to describe the time to platelet recovery. The time-to-event will be calculated beginning on the date of the lowest platelet count during the period from the date five days prior to the date the positive assay was sent through the calendar date five days subsequent to that test being drawn, and will end on the date when platelet recovery has occurred. Subjects will be censored at death, hospital discharge, or 45 days after the positive test was drawn (whichever occurs first) if platelet recovery had not yet occurred.

The impact of treatments received on time to first major bleeding event after the positive heparin PF-4 antibody test was drawn will be analyzed using a Cox model with time-varying covariates for treatments. Censoring will occur at hospital discharge, death, or day 45, whichever occurred first. The four classes of treatments to be considered are (1) anti-platelets (which includes any use of anti-inflammatory agents, antiglycoprotein IIb/IIIa inhibitors, and ADP receptor blockers), (2) lytics, (3) anti-coagulants, and (4) transfusion of blood products (which includes fresh frozen plasma, cryoprecipitate, red blood cells, and platelets).

9.4 Power Calculations

The intent of this large retrospective study is to obtain as large a sample of recent patients with positive heparin PF4 antibody tests as possible, so that estimates for each of the specified outcomes are as precise as is feasible. The study is meant to be descriptive and hypothesis-generating, rather than powered to detect a particular difference between groups of patients.

Some comparisons are expected to have fairly good statistical power, whereas others will not have much statistical power. However, this study would be the largest multi-site retrospective study of this patient population in many years.

Based on a review of the literature, approximately 25% of the subjects are expected to have both thrombosis and thrombocytopenia, 10% of the subjects are expected to have thrombosis but not thrombocytopenia, 50% of the subjects are expected to have thrombocytopenia but not thrombosis, and 15% of the subjects are expected to have neither thrombocytopenia nor thrombosis. One hundred percent of subjects with thrombosis, regardless of thrombocytopenia, are expected to be treated, 50% of subjects with thrombocytopenia but not thrombosis are expected to be treated, and subjects with neither thrombocytopenia nor thrombosis are expected to remain untreated. With treatment, 30% of subjects are expected to experience the triple endpoint (death, limb amputation/gangrene, or new thrombosis) within 30 days. Fifty-five percent of untreated subjects with thrombocytopenia are expected to experience the triple endpoint within 30 days. The rate of the triple endpoint in subjects with neither thrombocytopenia nor thrombosis is unknown, but is estimated to be between 5% and 20%.

Approximately half the subjects are expected to be discharged from the hospital by Day 10 without first having experienced the primary outcome, and subjects are censored at hospital discharge or day 45, whichever occurs first.

Power was determined through simulations with 25,000 replications assuming fixed distributions of subjects into groups and treatment as specified above. Using the above assumptions, 500 subjects would result in approximately 250 subjects with thrombocytopenia but not thrombosis. Within this group, there would be approximately 80% power to detect a difference between treated and untreated subjects in time to occurrence of the primary endpoint. In addition, depending on the event rate in the group with neither thrombocytopenia nor thrombosis, the 500 subjects would provide between 61% and 99% power to reject the null hypothesis that the time to occurrence of the primary endpoint is the same in all four groups.

If only 400 subjects were studied, there would be 70% power to detect a difference between treated and untreated subjects in the 200 subjects with thrombocytopenia but not thrombosis. In addition, there would be between 50% and 95% power to reject the null hypothesis that the time to occurrence of the primary endpoint is the same in all four groups.

10. STUDY MANAGEMENT

10.1 Ethical approval and subject consent. This study will be subject to approval by the respective Human Research Board governing the respective sites and the Data Coordinating Center (New England Research Institutes, Inc). Given the retrospective nature of this observational study, individual consent cannot be attained and sites will request that IRB waive consent. Subject confidentiality will be assured as described in 10.2.

10.2 Subject confidentiality. This study will comply with the regulations found in 45 CFR part 160 and 164 (protected health information). Data collection will include only anonymous data without subject initials, hospital identification numbers, date of birth,

social security or other unique identifiers; and will be limited to data available in hospital records.

11. REFERENCES

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