



LOYOLA  
UNIVERSITY  
HEALTH SYSTEM  
Loyola University Chicago

## Heparin-Induced Thrombocytopenia

Jeanine M. Walenga, Ph.D.

Cardiovascular Institute  
Loyola University Chicago  
Maywood, Illinois USA

## Heparin is a meritorious anticoagulant, but there are concerns .....

- Widespread use of heparin
  - 1 trillion units/12 million patients per year
  - Many clinical uses of heparin
- Major adverse effects
  - Bleeding
  - **HIT**
    - Severe thrombosis
    - Amputation & death
    - Difficulty in diagnosis
    - Lack of awareness



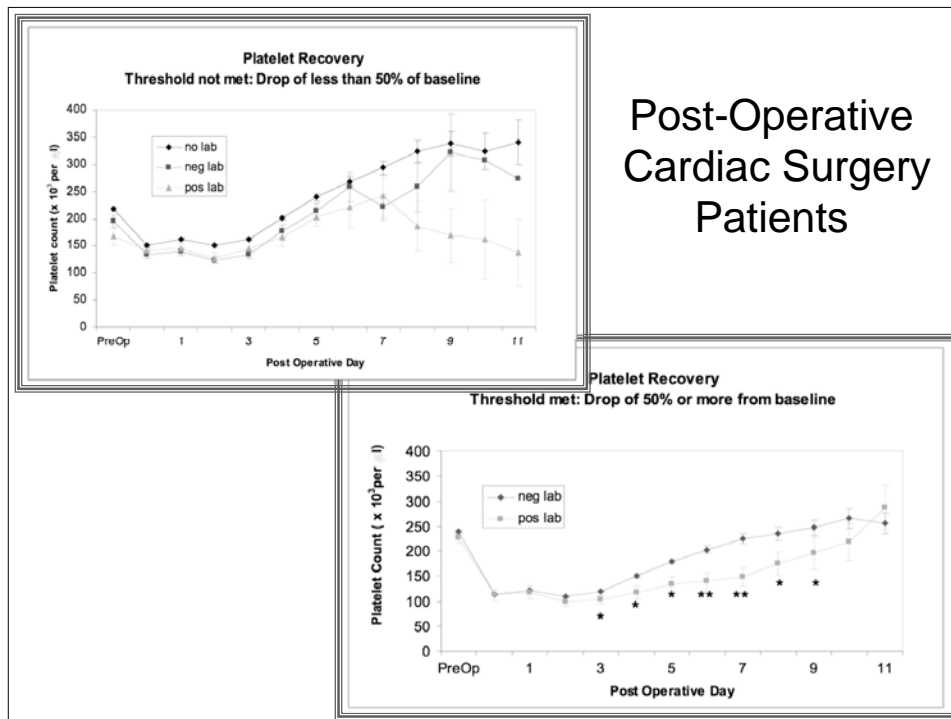
## Consequences of HIT

- 50% of patients exposed to UFH develop HIT antibodies.
- Of these, 1-5% develop symptomatic HIT.
- Of the patients with HIT 30-40% develop thrombosis.
- Of the patients with HIT/thrombosis, there is a 30% mortality and a 20% limb amputation rate.
- Patients with co-morbidities (sepsis, vascular pathology, renal impairment) have a higher risk of a poorer outcome.

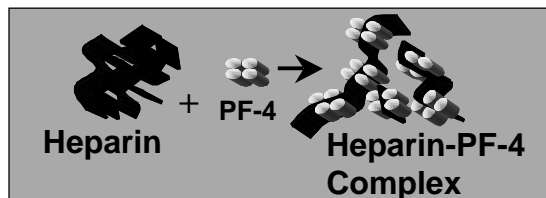
## Clinical Definition of HIT

- Onset of thrombocytopenia
  - Typically: 4-14 days after heparin exposure
  - Early onset HIT
  - Delayed HIT: thrombotic complications 9-40 days after discharge
  - Some patients do not have thrombocytopenia
- Platelet count:
  - 50% decrease or less than  $150,000 \times 10^9/L$
  - Should resolve when heparin is withdrawn
- Unexplained thrombosis (any arterial or venous site)
- No apparent reason other than heparin

## Post-Operative Cardiac Surgery Patients



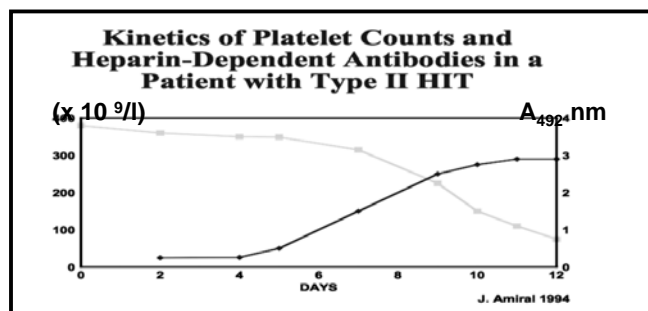
## Mechanism of HIT



- Heparin binds to PF4 and produces a conformational change in PF4
- Antibodies recognize PF4/heparin complexes
- IgG binds PF4/heparin complexes via the Fab region
- IgG binds platelets via the Fc region (FcγIIa platelet receptor)
- Platelets activate (release PF4) and aggregate creating a positive feedback cycle

## HIT Antibodies

- Most often IgG antibodies with high affinity to the PF4-heparin complex are found in HIT patients with:
  - Platelet activation
  - Thrombocytopenia
  - Thrombosis
  - SRA positive response

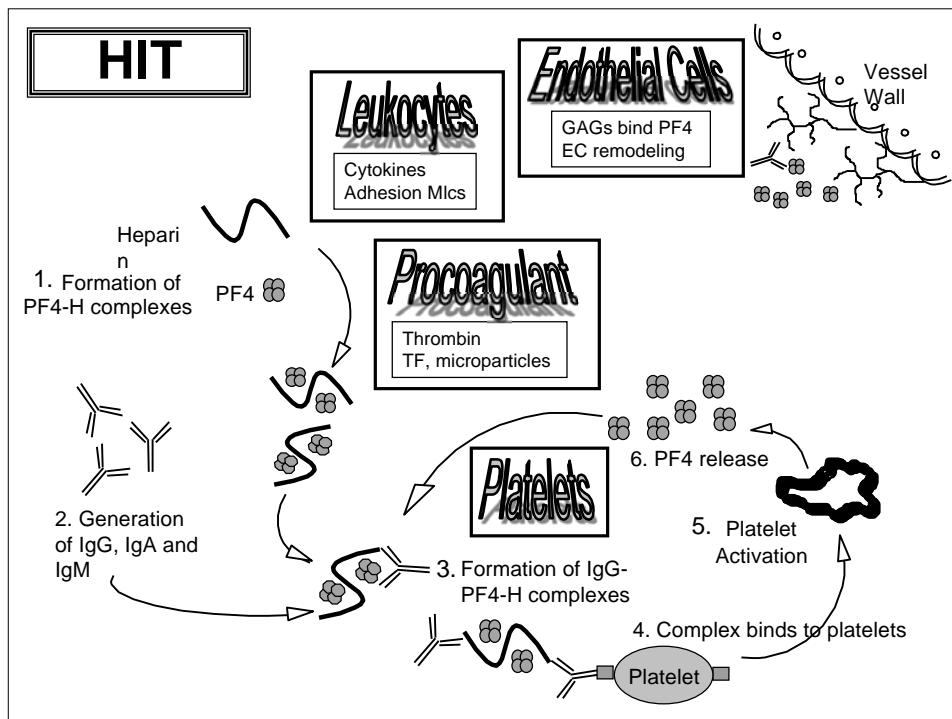


## HIT Antibodies

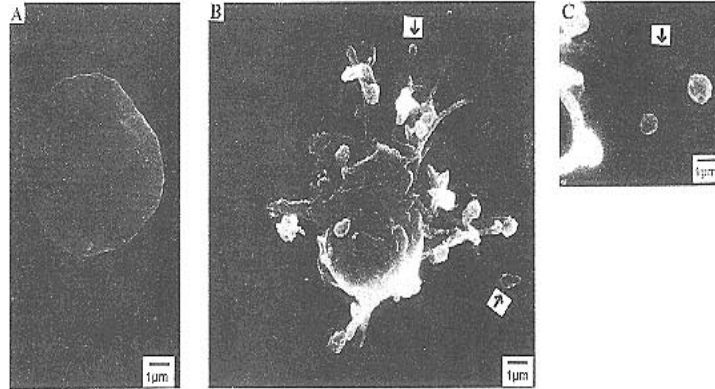
- IgG, IgA, and IgM antibodies are found in patients with HIT
- IgM is the initial response which seroconverts to IgG
- Some HIT patients do not seroconvert to IgG
- HIT antibodies are reactive to other heparin binding proteins (NAP-2, IL-8)
- HIT antibodies are heterogeneous in affinity and specificity
- Not all antibodies generate thrombocytopenia / thrombosis

## HIT Antibodies – cont'd

- Implications of an IgG only focus:
  - Timing of blood sample for lab diagnostic workup
    - If not IgG yet SRA is negative
    - Better to treat HIT early than to wait and have the pathology progress
  - IgM can cause thrombosis
    - Patient may not have thrombocytopenia
    - SRA negative
    - New IgG only Elisa would be negative
  - Elisa negative
    - If HIT antibody is not PF4 based



## Prothrombotic Platelet Microparticles



Hughes, *et al.*, *Blood* 96:188, 2000

## Platelet Counts for HIT Diagnosis

- It is essential to monitor platelet counts in heparin treated patients:
  - LMWH
    - Every 2 days for first 14 days
  - UFH
    - Daily for first 14 days
  - Patients at high risk of developing HIT
    - Daily
  - Medical and obstetric patient treated with LMWH and no prior exposure to UFH
    - No monitoring

## Laboratory Tests for HIT

- Platelet activation (function) tests
  - Heparin-Induced Platelet Aggregation (HIPA)
    - Detects IgG, IgM and IgA platelet antibodies
  - Serotonin Release Assay (SRA)
    - Only IgG with high affinity to H-PF4 cause positive SRA
- Antigen assays
  - ELISA tests for IgG, IgA, IgM to the PF4-heparin complex
  - Some tests detect IgG only

## Clinical Use of the ELISA Test for HIT

- It is more relevant to use the ELISA for patients with clinical symptoms of HIT.
  - Positive ELISA helps confirm clinical suspicion.
  - A negative ELISA should only rule out HIT *if the clinical probabilities are very weak.*
  - Measurable antibody without strong clinical indication should not be considered HIT.
- Screening all patients over-estimates the occurrence of HIT.
- Presence of antibody may not be predictive of thrombocytopenia or thromboembolic risk.

## Laboratory Tests for HIT

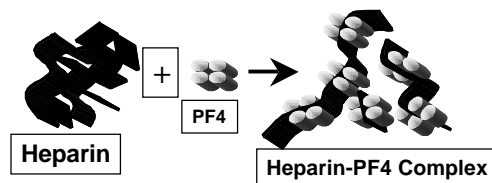
- **HIT is a clinical diagnosis** which should be confirmed by a lab test to guide future therapy
- Lab test results should *not* be used to guide *initial* therapeutic decisions (do *not* wait for lab results to treat)
- There is no optimal test for HIT
  - There is no gold standard test today
  - Not all patients will be positive by today's tests
  - Each HIT test provides unique information
- **Combined test results** from HIPA, SRA and ELISA improves chance of a true positive test
- **Multiple testing** over several days improves chance of a positive test
- **Knowledgeable use and interpretation** of the ELISA and functional test results are important

## How Should HIT be Managed?

- Patients
  - HIT antibody test positive only: no thrombocytopenia or thrombosis
  - HIT: thrombocytopenia without thrombosis
  - HITTS: thrombocytopenia with thrombosis
- Thrombosis Risk
  - Prevention of thrombosis
  - Treatment of thrombosis/ischemic stroke
  - Interventional procedures
    - PCI
    - CV surgery

## Antithrombotic Agents for Management of HIT Patients

Select a drug that has a chemical structure different from heparin to avoid interaction with the HIT antibody



## Treatment of Suspected HIT

- Discontinue all heparin immediately
  - Heparin flushes, heparin-coated catheters, guidewires, devices containing heparin, dialysate
- Diagnosis/treatment decisions should be based on clinical suspicion
  - Do *not* rely on laboratory test confirmation to initiate alternative anticoagulation treatment

## Treatment of HIT

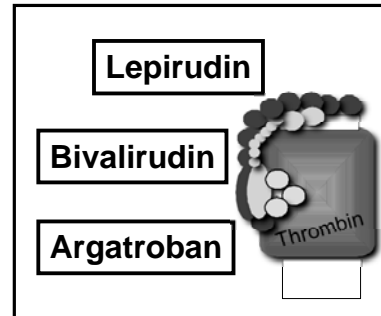
- For patients with strongly suspected/confirmed HIT, with or without thrombosis
  - Use an alternative, non-heparin anticoagulant
    - Danaparoid (1B)
    - Lepirudin (1C+)
    - Argatroban (1C)
    - Bivalirudin (2C)

7th ACCP Guidelines  
*Chest* 2004;126:311S

## Additional Treatment Options for HIT

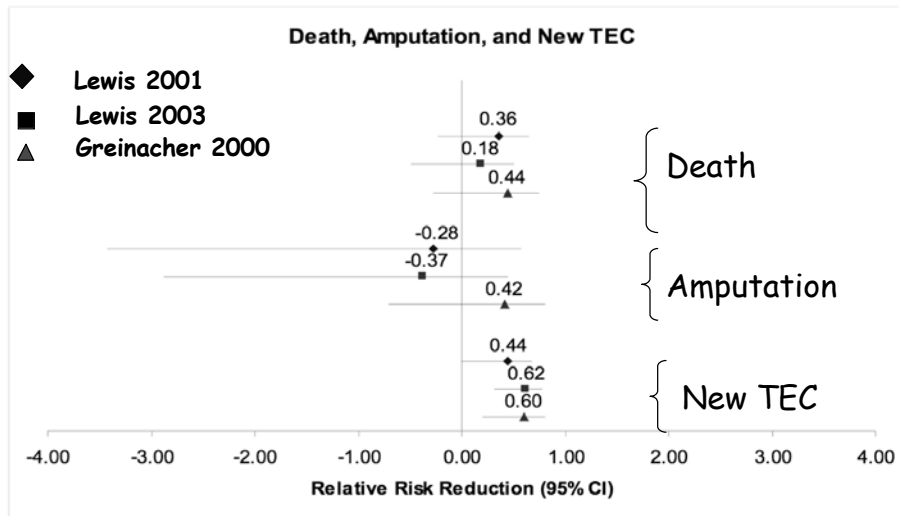
- Factor Xa inhibitors
  - Fondaparinux (not established for HIT)
  - Oral Xals (not established for HIT)
- VKA antagonists
  - Only initiate after platelet count recovery with overlapping DTI
  - Use for long-term anticoagulation

## Direct Thrombin Inhibitors for HIT



- Each DTI has individual pharmacologic characteristics.
- No head-to-head clinical trials have been done to compare the DTIs.
- Consider differences between drugs when making a clinical treatment decision.

## HITTS Patients Treated with Argatroban or Lepirudin



Hirsh, Heddle, Kelton. *Arch Int Med* 2004;164:361

## Differences Between DTIs

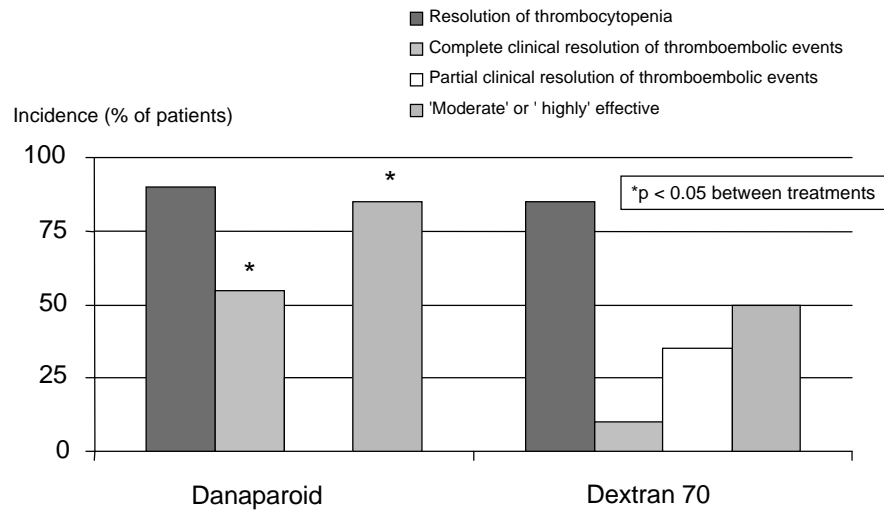
- Argatroban
  - Anticoagulant response rapidly reversed (40-50 min)
  - Clearance through liver
  - Adjust dose in hepatic impaired patients
  - Effects INR
- Lepirudin (hirudin)
  - Anticoagulant response more slowly reversed (1.3-3 hours; safety issue since no antidote available)
  - Renal excretion
  - Adjust dose in renal impaired patients
  - Antibodies are generated in 45% of treated patients
    - (severe anaphylactic reactions; 5 deaths)

## Monitoring Thrombin Inhibitors

For HIT/HITTS:

- DTIs are administered as an IV bolus plus an infusion
- DTIs have a narrow therapeutic window
  - Bleeding risk
- Monitoring is recommended with both treatment and interventional use

## Danaparoid vs Dextran 70

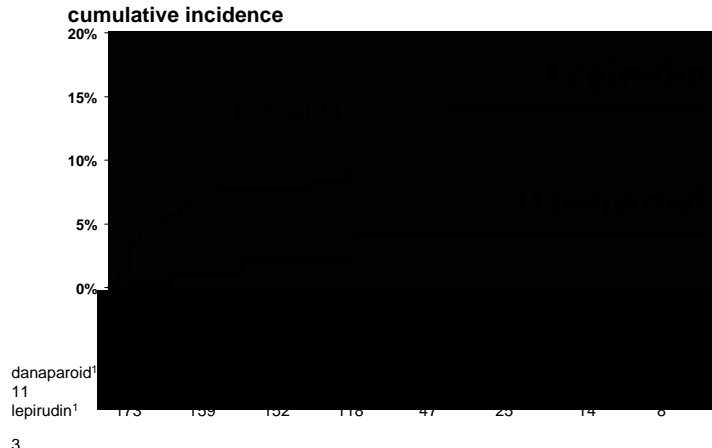


Chong et al Thromb Hemo (2001)

## Danaparoid in HIT

1. A non-heparin antithrombotic
2. Multiple sites of action, including anti-inflammatory effects
3. Clinical studies in HIT suggest a 94% success rate (over 100,000 treatments and clinical studies)
4. Low bleeding risk
5. Routine monitoring not required (only for low/high weight, renal failure)
6. Monitor platelet counts with treatment (potential HIT antibody cross-reactivity)
7. Sustained effects
8. Can be given both iv & sc (100% bioavailability)

## Risk of Major Bleeding



Time-to-event analysis of bleeding occurring in patients with HIT until hospital discharge or until day 60 (whichever occurred first).

Defined as bleeding requiring transfusions of two or more red blood cell concentrates or intracerebral bleeding (1 patient).

Farner B et al. *Thromb Haemost* 2001;85:950-957

## Treatment of Patients with HIT

- Patients with acute or previous HIT who require cardiac catheterization or PCI
  - Argatroban (1C) \*
  - Bivalirudin (1C)
  - Lepirudin (1C)
  - Danaparoid (2C)

\* FDA approved

7th ACCP Guidelines  
*Chest* 2004;126:311S

## Other HIT Patient Populations

- Interventional procedures (cardiology)
- Cardiac surgery
- Hemodialysis
- Pediatric
- Pediatric requiring cardiology procedures
- Neonate
- Pregnant
- Renal and carotid stent implants
- Stroke

## Bridging to an OAC for Long-Term Treatment

- Warfarin derivatives (oral anticoagulant)
  - not to be used as sole anticoagulant during the acute phase of HIT
    - loading period leaves patient unprotected
    - inhibition of PrC produces a pro-thrombotic state
    - risk of skin necrosis
  - Special dosing regimens for DTIs

## Summary

1. HIT is an immune response: antibodies to PF4/heparin complex (& other targets) cause platelet activation, endothelial cell activation, leading to an extreme hypercoagulable state and an inflammatory response.
2. HIT IgG causes the typical severe thrombocytopenia-thrombosis-SRA+ but HIT also presents in other non-typical ways.
3. Lab tests for HIT vary in their correlation to clinical HIT. Each test provides unique information. There is no optimal HIT diagnostic test.
4. A thrombin inhibitor is the treatment of choice for HIT in the US. Each DTI is different in its pharmacology. Monitor with aPTT.
5. Thrombin inhibitors can be used for PCI in patients with HIT. Monitor with ACT.
6. Special patient populations with HIT (CV surgery, pediatrics, pregnant, stroke, etc) do not have defined treatment regimens at this time.
7. Warfarin is used for long-term treatment of HIT thrombosis but must follow a specific dosing regimen.
8. A high clinical awareness, prevention, early diagnosis and treatment are important for the clinical management of HIT.