

# **Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia**

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Presented as a Midday Symposium at the  
44<sup>th</sup> ASHP Midyear Clinical Meeting and Exhibition

Monday, December 7, 2009  
Las Vegas, Nevada

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# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## **A G E N D A**

- 11:30 a.m. – 11:50 a.m.      **Overview of Heparin-Induced Thrombocytopenia and Clinical Care Guidelines**  
Edith Nutescu, Pharm.D., FCCP
- 11:50 a.m. – 12:25 p.m.      **Review of Current and Emerging Therapies for Heparin-Induced Thrombocytopenia**  
Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)
- 12:25 p.m. – 12:55 p.m.      **Practical Management of Patients with Heparin-Induced Thrombocytopenia**  
Maureen Ann Smythe, Pharm.D.
- 12:55 p.m. – 1:15 p.m.      **Heparin-Induced Thrombocytopenia (HIT) Clinical Pearls**  
Faculty
- 1:15 p.m. – 1:30 p.m.      **Panel Discussion and Questions and Answers**  
Faculty

## **F A C U L T Y**

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Director, Antithrombosis Center

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The University of Illinois at Chicago

Chicago, Illinois

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Dr. Nutescu declares that she has no relationships pertinent to this activity.

### **Maureen Ann Smythe, Pharm.D.**

Dr. Smythe declares that she is on the GlaxoSmithKline speaker's bureau.

### **Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)**

Dr. Spinler declares that she is on the on the GlaxoSmithKline speaker's bureau and consults for Baxter.

### **Erika Thomas, M.B.A., B.S.Pharm.**

Ms. Thomas declares that she has no relationships pertinent to this activity.

# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## **ACTIVITY OVERVIEW**

Annually, millions of patients receive heparin for indications from routine catheter flushes to preventing the formation of thrombi during cardiac bypass surgery. Although heparin is an extremely effective anticoagulant, like any drug, it is not without adverse effects. Heparin-induced thrombocytopenia (HIT) is an immune-mediated response to heparin.

Faculty in this interactive symposium will provide attendees with an overview of HIT, including current treatment guidelines. Emphasis will be placed on the challenges associated with currently available treatments and highlight emerging therapeutic options, including both drugs currently undergoing clinical trials and novel use of currently available antithrombotics. The recently updated clinical guidelines for the treatment and prevention of HIT, published by the American College of Chest Physicians, will be highlighted. This symposium will also feature clinical pearls showcasing where pharmacists can have the greatest impact in the treatment of patients with HIT.

## **ACTIVITY OBJECTIVES**

At the conclusion of this knowledge-based educational activity, participants should be able to

- Define the criteria for diagnosis of heparin-induced thrombocytopenia (HIT).
- Summarize the current guidelines for the monitoring and treatment of HIT.
- Describe the most common challenges associated with currently available treatments for HIT.
- Name at least two emerging therapeutic options for the treatment of HIT.
- Identify three opportunities for pharmacist intervention to improve the care of patients with HIT.

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**Available soon at <http://ashpmedia.org/symposia/HIT>**

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# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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Date of Activity	Activity Code	Session Code (announced during the live activity)	CPE credit hours
Monday, December 7	09432		2

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# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## **Edith Nutescu, Pharm.D., FCCP, Chair**

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Edith A. Nutescu, Pharm.D., FCCP, is Clinical Professor in the Department of Pharmacy Practice and Center for Pharmacoeconomic Research at the University of Illinois at Chicago College of Pharmacy. She also serves as Director of the Antithrombosis Center at the University of Illinois at Chicago Medical Center. As a clinician and educator, Dr. Nutescu has contributed extensively to the care of patients and the education of students and health care providers on topics related to cardiovascular therapeutics.

Dr. Nutescu maintains an active clinical practice and research program. Her research and practice interests are in the areas of comparative effectiveness, health services and outcomes, with emphasis in cardiovascular diseases, stroke, thrombosis, and antithrombotic therapies. Dr. Nutescu has authored or co-authored over 100 scientific articles, book chapters, and abstracts published in the science and medical literature and has served as a reviewer for the literature in her field. She serves on the Editorial Boards for the *American Journal of Health-System Pharmacy (AJHP)* and *Annals of Pharmacotherapy*. She has lectured extensively both nationally and internationally on topics related to hyperlipidemia, thrombosis, stroke, and cardiovascular diseases. Dr. Nutescu serves as the Vice-President and on the Board of Directors of the Anticoagulation Forum, and has served on the National Consumers League Senior Outpatient Medication Safety Coalition - Oral Anticoagulant National Advisory Board. Dr. Nutescu was the only pharmacist member nominated to serve on the Steering Committee for the National Quality Forum and the Joint Commission on the Accreditation of Healthcare Organizations - National Consensus Standards for the Prevention and Care of Venous Thrombosis. She has been recognized as a Fellow of the American College of Clinical Pharmacy and is the 2009 recipient of the American College of Clinical Pharmacy's Clinical Practice Award.

Dr. Nutescu earned her Doctor of Pharmacy with high honors at the University of Illinois at Chicago College of Pharmacy. After graduation, Dr. Nutescu went on to complete an American Society of Health-System Pharmacists–accredited Pharmacy Practice Residency at Lutheran General Hospital–Advocate Health Care and a Primary Care Specialty Residency at the University of Illinois at Chicago Medical Center.

# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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**Edith Nutescu, Pharm.D., FCCP, Chair**

## **P R E S E N T A T I O N**

Overview of Heparin-Induced Thrombocytopenia and Clinical Care Guidelines

## **O V E R V I E W**

Heparin-induced thrombocytopenia (HIT) is an uncommon but extremely serious adverse effect associated with heparin use. The immune-mediated platelet activation and thrombin generation seen during HIT can lead to severe and unusual thrombotic complications. Morbidity and mortality associated with HIT is disturbingly high—up to 50% of patients who develop the disorder will suffer a thrombotic complication or die within 30 days in the absence of treatment. The diagnosis of HIT is based on laboratory findings that confirm heparin antibody formation and platelet activation. Platelet counts typically begin to fall 5 to 10 days following initiation of heparin and reach a nadir by days 7 to 14. The development of thrombocytopenia can be delayed (delayed-onset HIT) up to 30 days, and begin several days after heparin has been stopped in patients naive to heparin therapy. Conversely, so-called rapid-onset HIT can occur rapidly and abruptly (within 24 hours following heparin initiation) in patients with a recent exposure to heparin (i.e., previous 3 months).

Platelet counts commonly fall below 150,000 mm<sup>3</sup> but rarely nadir as low as 20,000 mm<sup>3</sup>. In some cases, overt thrombocytopenia may not occur, but a drop in platelet count greater than 50% from baseline is considered indicative of HIT. The frequency of immune-mediated HIT is most powerfully related to the duration and type of heparin used and to a lesser extent the dose and route of administration. The estimated overall incidence of HIT after 5 days of UFH use is 1% to 3% but the cumulative incidence may be as high as 6% after 14 days of continuous intravenous use. The incidence of HIT with low dose subcutaneous UFH in medical patients has been reported to be approximately 1%. Low-molecular-weight heparins are associated with a significantly lower risk of HIT (<1%). The incidence of HIT is higher with bovine UFH versus porcine UFH. In addition, the HIT risk varies with the exposed patient population: surgical patients > medical patients > pregnant patients. The relatively high frequency of thrombotic complications and poor outcomes associated with HIT emphasize the need for prompt recognition and diagnosis. The diagnosis of immune-mediated HIT is made based on clinical findings supplemented by laboratory tests confirming the presence of antibodies to heparin or platelet activation induced by heparin.

## **L E A R N I N G O B J E C T I V E S**

At the conclusion of this knowledge-based educational activity, participants should be able to

- Review the epidemiology and incidence of heparin-induced thrombocytopenia (HIT).
- Discuss approaches for laboratory and clinical diagnosis of HIT.
- Formulate an appropriate treatment plan for a patient who develops HIT consistent with clinical practice guidelines.

## Overview of Heparin-Induced Thrombocytopenia and Clinical Care Guidelines

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The University of Illinois at Chicago  
Chicago, Illinois

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## Learning Objectives

- Review the epidemiology and incidence of heparin-induced thrombocytopenia (HIT)
- Discuss approaches for laboratory and clinical diagnosis of HIT.
- Formulate an appropriate treatment plan for a patient who develops HIT consistent with clinical practice guidelines.

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## Heparin-Induced Thrombocytopenia

- Serious immune-mediated prothrombotic disease induced by heparin
- Defined by a falling platelet count during or following heparin treatment, with or without thrombotic complications
- Paradoxical hypercoagulable state that can potentially lead to new thromboses, amputation, and death
- Patients receiving any type of heparin at any dose by any route of administration may be at risk of developing HIT, making it difficult to diagnose

Levy JH, et al. *Hematol Oncol Clin North Am.* 2007;21(1):65-88. Warkentin TE. *Hematology Am Soc Hematol Educ Program.* 2006;408-414. Jang IK, et al. *Circulation.* 2005;111(24):2671-2683.

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## Incidence

- More than 12 million patients are exposed to heparin each year in the United States
- Estimated that 600,000 new cases of HIT occur each year. Of these, as many as:
  - 300,000 patients develop thrombotic complications
  - 90,000 patients die
- HIT occurs in
  - 1%-5% of patients receiving unfractionated heparin (UFH)
  - 0.2%-0.8% of patients treated with LMWH

1. Levy JH, et al. *Hematol Oncol Clin North Am.* 2007;21(1):65-88. 2. Arepally GM, Ortel TL. *N Engl J Med.* 2006;355:909-917. 3. Levine RL. *Chest.* 2005;127:1489-1490. 4. Warkentin TE. *Chest.* 2005;127:355-455. 5. Martel N et al. *Blood.* 2005;106:2710-2715. 6. Rice L. *Arch Intern Med.* 2004;164:1961-1964.

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## Frequency of HIT

Patient Population	Frequency
<b>Cardiac surgery</b>	
Adults (UFH postoperatively)	1.0% to 2.4%
Pediatrics	1.3%
<b>Cardiac transplant</b>	11%
<b>Orthopedic surgery</b>	
UFH postoperatively	4.8%
LMWH postoperatively	0.6%
<b>Medical</b>	
Cardiovascular disease	0.3%
Critical care	0.4%
Those treated with subcutaneous,UFH	0.8%
Newly treated with hemodialysis	3.2%
<b>Obstetrics</b>	Rare
<b>Overall (hospital-wide surveillance studies)</b>	1.0% to 1.2%

Jang IK. *Circulation* 2005;111:2671-2683.

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## The Risk of HIT

- Bovine > porcine heparin
- Surgical patients > than medical
- Female > male
- Recent heparin exposure – rapid onset HIT
- Minimized by use of LMWH over heparin in surgical patients
- Contaminated heparin ?

Davoren A, Aster RH. *Am J Hematol.* 2006;81:36. Prandoni P, et al. *Blood.* 2005;106:3049. Warkentin TE, Greinacher A. *Chest.* 2008;133: 340s – 380s. *N Engl J Med* 1998; 359:12: 1291-1293.

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## Heparin Contamination

- Jan 2007 – April 13<sup>th</sup> 2008: 131 reports to FDA of deaths of patients receiving heparin
- 1<sup>st</sup> 75 days of 2008: 123 deaths with 78 having one or more allergic / hypotensive symptoms
- Heparin contaminant: oversulfated chondroitin sulfate (OSCS), can activate contact system to generate bradykinin

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## Contaminated Heparin and HIT

Patients with Positive Tests for HIT				
Country	OSCS-heparin Distributed	Period Before Contamination (n)	Period After Contamination (n)	% Increase in Positive Tests
Canada	No	45 / 373	51 / 409	13.3
Germany	Yes	32 / 459	64 / 405	100

Positive tests include IgG EIA and functional assay

*New Engl J Med* 2008; 359: 1291-1293.

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## Diagnosis of HIT

- Timing of thrombocytopenia
- Degree of thrombocytopenia
- Associated clinical syndromes
- Thrombosis
- Response to therapy
- Supportive laboratory studies

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## Differential Diagnosis of HIT

- Hemodilution post-surgery
- Sepsis
- DIC (multiple causes besides HIT)
- Cancer-associated DIC
- Antiphospholipid syndrome
- Thrombolytic therapy
- EDTA-induced pseudothrombocytopenia
- GP IIb/IIIa inhibitor-induced thrombocytopenia
- Drug-induced thrombocytopenia (other than heparin)
- Post-transfusion purpura
- Thrombotic thrombocytopenic purpura
- Non-immune heparin-associated thrombocytopenia

Berkman N, et al. *Am J Hematol*. 1991; 36: 195-201  
Hackett T, et al. *Seminars in Thrombosis & Hemostasis*. 1982; 8: 116-137  
Warkentin TE. *Brit J Haematol*. 2003; 121: 535-555

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## Diagnosis of HIT

- Seroconversion without TCY is not HIT
- Diagnosis of HIT is made when HIT antibody is present along with:
  - otherwise unexplained fall in platelet count of  $\geq 50\%$
  - skin lesions at heparin injection sites
  - acute systemic reactions
  - +/- thrombotic complications

TCY = thrombocytopenia

Warkentin TE Chest 2008.

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## HIT: Unusual Presentation

- Heparin-induced skin lesions at injection sites
- Acute anaphylactoid reactions
- Warfarin associated venous limb gangrene
- Classic warfarin-induced central skin necrosis
- Adrenal hemorrhagic infarct

Warkentin TE, et al. *Chest*. 2005;127:1857-1861.

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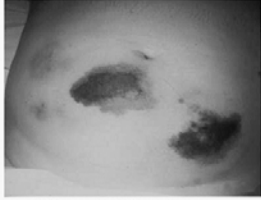
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## Thromboembolic Complications

Skin Necrosis



Venous Limb Gangrene



Warkentin TE. Br J Haematol 1996;92:494-497.  
Warkentin TE. Ann Intern Med 1997;127:804-812.

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A typical HIT case will occur at  
(on average)

- A. 1-2 days post-heparin exposure.
- B. 9 days post-heparin exposure.
- C. More than 10 days post-heparin exposure.
- D. No mean time has been determined.

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## Clinical Presentation

Typical Presentation:

- Thrombocytopenia typically develops 5-14 days following initiation of heparin. Platelet count reduction may be:
  - At least a 50% drop from pre-heparin level<sup>1</sup>
  - $\leq 150 \times 10^9/L$ 
    - Very low platelet counts are rare

Less Common Presentations:

- Rapid-onset
  - Occurs within minutes to hours of re-exposure to heparin or LMWH
- Delayed-onset
  - Occurs up to several weeks after heparin cessation and often after hospital discharge

1. Levy JH, et al. *Hematol Oncol Clin North Am.* 2007;21(1):65-88.  
2. Jang IK, et al. *Circulation.* 2005;111(24):2671-2683.  
3. Warkentin TE, et al. *CHEST.* 2008;133:340S-360S.

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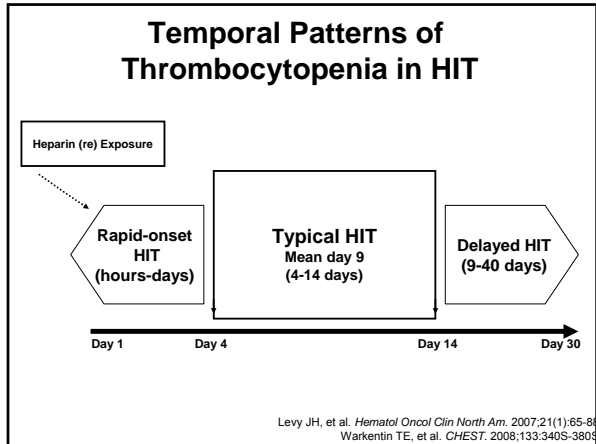
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- ### Insights into Clinical Presentation
- 20% of patients have platelet count nadir > 100 x 10<sup>9</sup>/L
  - In ICU Patients thrombosis is a better clinical indicator of HIT than thrombocytopenia; if not evident look
  - Thrombosis may precede thrombocytopenia
  - Thrombotic risk correlates with the magnitude of the platelet count decrease
  - Consider delayed onset HIT: thrombosis + thrombocytopenia 5-30 days after heparin stopped

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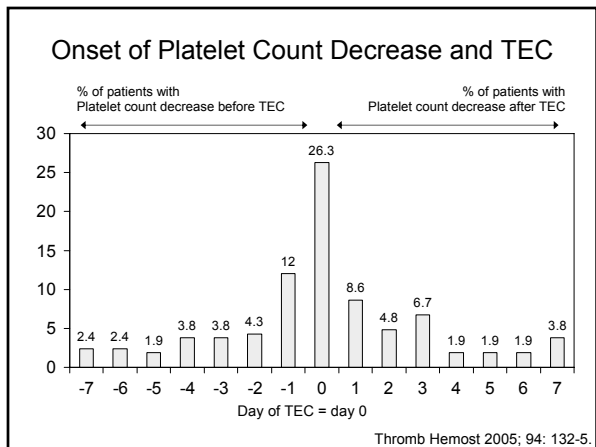
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## Pathophysiology

How does an anticoagulant cause life threatening clotting?

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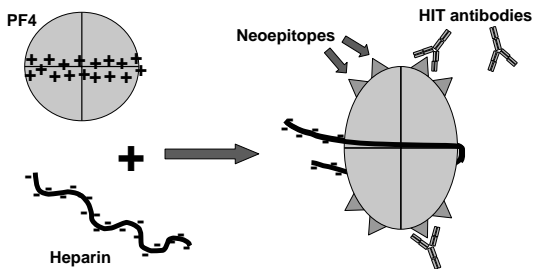
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## Depiction on Heparin-induced Epitopes on PF4



Adapted from Darvoren A, Aster RH. *Am J Hematol.* 2006;81:36-44.

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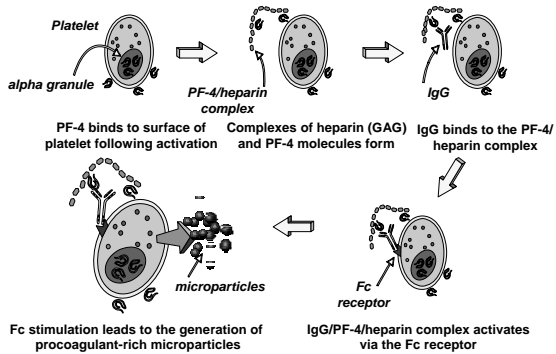
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## Pathophysiology of HIT



Hirsh et al. *Arch Intern Med.* 2004;164:361-369.; Levy JH, et al. *Hematol Oncol Clin North Am.* 2007;21(1):65-88.

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## Laboratory Assays to Confirm HIT Following Initiation of Therapy

Assay	Component measured	Advantages	Disadvantages
Serotonin-release assay (SRA) <sup>1,2</sup>	<sup>14</sup> C-serotonin released from platelets	Highly sensitive and specific	Costly, time-consuming, and technically demanding (involves radioisotopes)
Heparin-induced platelet aggregation assay (HIPA) <sup>3</sup>	Platelet aggregation	Highly specific, easy	Low sensitivity and technique-dependent
Enzyme-linked immunosorbent assay (ELISA) <sup>3</sup>	Presence of heparin-dependent antibodies	Highly sensitive, easy, rapid turnaround time	Low specificity (false positives)
PIFA <sup>®</sup> Heparin/PF4 Rapid Assay <sup>4</sup>	Presence of PF4 antibodies	Highly sensitive and specific, easy and rapid turnaround time	Fairly new with limited clinical history, positive and negative controls not provided

1. Fabris, et al. *Arch Pathol Lab Med.* 2000;124:1657-1666. 2. Messmore HL, et al. *Drug Safety.* 2003;26:625-641. 3. Leo A, et al. *Clin Diagn Lab Immunol.* 2003;10:731-740. 4. PIFA<sup>®</sup> Heparin/Platelet Factor 4 Rapid Assay [package insert]; 2005.

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Which of the following statements is true?

- A. Discontinuation of heparin eliminates risk for HIT.
- B. Platelet transfusions are contraindicated in HIT.
- C. Arterial and venous HIT occur at about the same rate.
- D. All of the above.

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## The Burden of HIT

- Risk of new thrombosis ~ 30%-75% in HIT patients ... despite d/c of heparin
- Platelet transfusions are contraindicated; 4/5 HIT patients died after platelet transfusion
- Venous 4x more frequent than arterial
  - DVT (50%)
  - PE (25%)
  - Cerebral vein; adrenal hemorrhagic infarction
- Arterial
  - Aortic (10%)
  - Myocardial infarction (3%-5%)
  - Miscellaneous arteries...renal, mesenteric, spinal (rare)
- Amputation: 10% risk
- Death: 20%-30%
- Financial impact
  - HIT cases had incremental cost ↑ of \$41,133/case

Napolitano LM et al. *Crit Care Med.* 2006;34:2898-2911.  
Gettings EM et al *Crit Care.* 2006;10:R161.

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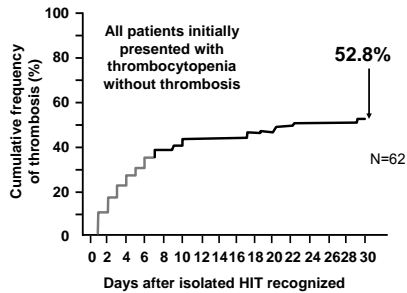
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### 14-Year Study of HIT: Results After Heparin Discontinuation



Warkentin TE, Kelton JG. *Am J Med.* 1996;101:502-507.

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### Objectives of Treatment for HIT

#### Why

- Minimize complications of HIT, including thrombosis, morbidity, and mortality

#### How

- Interrupt the immune response
  - Immediately discontinue heparin use  
*AND*
- Inhibit effects of thrombin
  - Stabilize hypercoagulable state
  - Treat active thrombosis
  - Prevent new thrombosis

Jang IK, et al. *Circulation.* 2005;111(24):2671-2683.; Warkentin TE, et al. *Chest* 2008; 133: 340S-380S.

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### Management of Suspected or Confirmed HIT The 6 "A's"

- **A**void and discontinue all heparin; including LMWH
- **A**dminister non-heparin anticoagulant
- **A**nit-PF4/heparin antibody test for confirmation
- **A**void platelet transfusions
- **A**wait platelet count recovery before initiation of warfarin
- **A**ssess for lower extremity thrombosis

*Crit Care Med* 2006;34: 2898-2911.

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## HIT Management

- Initiate alternative non-heparin anticoagulant for strongly suspected or confirmed HIT whether or not complicated by thrombosis

- Danaparoid 1B
- Lepirudin 1C
- Argatroban 1C
- Fondaparinux 2C
- Bivalirudin 2C

Chest 2008; 133: 340-380s.

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# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## SELECTED REFERENCES AND RESOURCES

1. Arepally GM, Ortel TL. Heparin-induced thrombocytopenia. *N Engl J Med*. 2006;355:809-817.
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3. Davoren A, Aster RH. Vancomycin-induced immune thrombocytopenia. *Am J Hematol*. 2006;81:36.
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8. Warkentin TE, Greinacher A. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence based clinical practice guidelines (8th edition). *Chest*. 2008;133:340S-380S.

# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## SELF-ASSESSMENT QUESTIONS

1. Patients receiving any type of heparin at any dose by any route of administration may be at risk of developing HIT
  - a. True
  - b. False
  
2. A typical HIT case will occur at (on average):
  - a. 2-3 days post heparin exposure
  - b. 9 days post heparin exposure
  - c. More than 10 days post heparin exposure
  - d. No mean time has been determined
  
3. Rapid-onset HIT occurs within minutes to hours of re-exposure to heparin or LMWH.
  - a. True
  - b. False
  
4. The ELISA assay is more sensitive and more specific than the serotonin release assay used to confirm the diagnosis of HIT.
  - a. True
  - b. False

## Answers

1. a
2. b
3. a
4. b

## Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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### **Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)**

Professor of Clinical Pharmacy  
Residency and Fellowship Program Coordinator  
University of the Sciences in Philadelphia  
Philadelphia, Pennsylvania

Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology) is Professor of Clinical Pharmacy in the Department of Pharmacy Practice and Pharmacy Administration at the Philadelphia College of Pharmacy, University of the Sciences in Philadelphia. She is also an adjunct faculty member in the Cardiovascular Division in the Department of Medicine at the University of Pennsylvania. Dr. Spinler serves as a preceptor to pharmacy students and performs clinical research at the Hospital of the University of Pennsylvania, coronary intensive care unit.

Dr. Spinler has authored more than 150 research articles, reviews, and books chapters and given more than 300 continuing education programs in the area of acute coronary syndrome, antiplatelets and anticoagulants. In 2004, she was awarded the American Society of Health-System Pharmacist Award for Sustained Contributions to the Literature of Pharmacy Practice. She currently serves on the editorial boards of several biomedical journals including *Annals of Pharmacotherapy*, *Pharmacotherapy*, *American Journal of Managed Care*, and *Drugs*. Dr. Spinler chaired the 2005-2010 Council of Experts, United States Pharmacopeia, Cardiovascular Expert Committee and served on USP's Medicare Model Guidelines Committee. She was a member of the Steering Committee for the CRUSADE Registry and is currently a member of the American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR<sup>®</sup>) Practice Innovation and Clinical Excellence (PINNACLE Registry<sup>™</sup>) Steering Committee, serves on the Executive Team of the ACC/Institute for Health Care Improvement (IH) Hospital to Home (H2H) National Quality Improvement, the Steering Committee of the Interdisciplinary Working Group of the American Heart Association (AHA) Quality of Care and Outcomes Research (QCOR) Interdisciplinary. In 2009 she was appointed to the National Quality Forum Consensus Standards for Patient Outcomes Cardiology Technical Advisory Panel.

Dr. Spinler received her Bachelor of Science and Doctor of Pharmacy degrees from the University of Minnesota in Minneapolis. She completed a pharmacy residency and research fellowship in cardiovascular critical care pharmacy at the University of Illinois at Chicago. Dr. Spinler is a Board Certified Pharmacotherapy Specialist with Added Qualifications in Cardiology. She is a Fellow of the American College of Clinical Pharmacy (ACCP) and was awarded Fellow of AHA Cardiovascular Clinical Council and inaugural QCOR Fellow in 2009.

# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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**Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ Cardiology)**

## **P R E S E N T A T I O N**

Review of Current and Emerging Therapies for Heparin-Induced Thrombocytopenia

## **O V E R V I E W**

The 2008 American College of Chest Physicians heparin-induced thrombocytopenia (HIT) guidelines recommend lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], or bivalirudin [Grade 2C] over the further use of unfractionated heparin or low-molecular-weight heparin for patients with strongly suspected (or confirmed) HIT, with or without thrombosis. Argatroban and lepirudin are direct thrombin inhibitors (DTIs) that carry FDA-approved labeled treatment indications for HIT with/without thrombosis. American College of Chest Physician 200 guideline-recommended dosing for argatroban and lepirudin, as well as target activated partial thromboplastin time (aPTT) for lepirudin are lower than those recommended in the product labeling.

Clinical considerations when using argatroban include the need for dosing adjustment downward for initial infusions for patients with hepatic dysfunction, heart failure, multiple organ system failure, severe anasarca, and for patients in the early post-cardiac surgery period secondary to reduced clearance. There is one published nomogram for dosing adjustments of argatroban based upon achieving a target aPTT. Lepirudin is renally eliminated and should not be administered to patients with acute renal failure or those receiving dialysis. Lepirudin administration is associated with the development of antihirudin antibodies. Readministration of lepirudin has been associated with anaphylaxis and the ACCP guidelines recommend selection of an alternative nonhirudin anticoagulant for those patients.

When transitioning between an injectable anticoagulant and warfarin, direct thrombin inhibitors (argatroban > bivalirudin > lepirudin) increase the INR and make the transition to stable oral anticoagulation difficult. Clinicians may incorrectly interpret the elevation and stop the DTI prematurely putting the patient at risk of thrombosis. They may incorrectly administer vitamin K thereby increasing the length of time to achieve the target INR with warfarin. Fondaparinux offers the advantage of subcutaneous administration, lower costs than DTI, and no effect on the INR but has a long half-life and no specific antidote making reversal difficult. Fondaparinux is contraindicated in patients with creatinine clearance of less than 30 mL/min. When administering fondaparinux in patients with acute HIT, weight-based “treatment” doses, identical to those given for treatment of acute venous thromboembolism are recommended rather than a “prophylaxis” dose. Bivalirudin offers the advantage of significant experience in the setting of percutaneous coronary intervention and cardiopulmonary bypass for cardiac surgery. It is also the lowest cost DTI. Data using with fondaparinux and bivalirudin are limited to case series and small observational studies.

Desirudin is a subcutaneously administered DTI previously approved in the U.S. for venous thromboembolism prophylaxis in patients undergoing hip replacement. It is currently being compared to argatroban in a clinical trial of patients with suspected HIT. There are advantages and disadvantages to each currently recommended treatment for HIT. Clinicians should use patient-specific information to select the best therapy.

# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## **LEARNING OBJECTIVES**

At the conclusion of this knowledge-based educational activity, participants should be able to

- List advantages and disadvantages of argatroban, lepirudin, fondaparinux and bivalirudin for treatment of heparin-induced thrombocytopenia (HIT).
- Given a patient case, select initial dosing of argatroban.

## Current and Emerging Therapies for HIT

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Professor of Clinical Pharmacy  
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## Learning Objectives

- List advantages and disadvantages of argatroban, lepirudin, fondaparinux and bivalirudin for treatment of HIT.
- Given a patient case, select initial dosing of argatroban.

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## Argatroban Clinical Considerations

- FDA approved for HIT/HITTS and PCI in setting of HIT/HITTS
  - More patients treated with bivalirudin for PCI than argatroban
- Hepatic clearance requiring dose adjustment for patients with hepatic disease
- 2008 ACCP Chest Guideline dosing lower than product labeled dose
- Reports of reduced clearance and increased effect in fluid-overloaded patients
- Lacks data in patients undergoing CPB during cardiac surgery
- Increases INR so makes transition to warfarin difficult
  - Greater INR effect than lepirudin

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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## Argatroban Dosing

- Product Label
  - 2 mcg/kg/min (or 0.5 mcg/kg/min if hepatic impairment)
  - No initial bolus
  - Adjusted to achieve aPTTs 1.5-3 times the baseline value
- 2008 ACCP Chest Guidelines
  - Initial infusion rate, 2 mcg/kg/min IV
  - No initial bolus
  - Reduced initial infusion rate (0.5–1.2 mcg/kg/min) is appropriate in certain patient populations
    - Heart failure
    - Multiple organ system failure
    - Severe anasarca
    - During the early post-cardiac surgery period
  - Target aPTT not specified

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.  
Encysive Pharmaceuticals Inc. and GlaxoSmithKline; 2008.

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## Lepirudin

- Derived from the saliva of the medicinal leech *Hirudo medicinalis*
  - Shares 63 of 65 amino acids
- Renally eliminated
  - Dosing adjustment required if CrCl  $\leq$  60 mL/min
  - Avoid in acute renal failure and dialysis
- Increases INR making warfarin transition difficult
  - Less than argatroban and bivalirudin
- Anaphylaxis/anaphylactoid reactions estimated to occur in 0.015%
  - Increased risk with readministration (0.16%)
  - If readministering, consider ICU/ICU Step-down setting
  - Administer non-hirudin anticoagulant
- 2008 ACCP Chest Guideline dosing and aPTT target lower than product labeled dose

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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## Lepirudin Dosing

- Product label
  - Bolus dose: 0.4 mg/kg IVP (over 15-20 seconds) (maximum initial bolus dose: 44 mg)
  - Continuous infusion at 0.15 mg/kg/hour (maximum initial infusion dose: 16.5 mg/hour)
  - aPTT target is 1.5-2.5 x the median of the aPTT normal range
- 2008 ACCP Chest Guidelines
  - Administer bolus only in life-threatening situations
  - Bolus 0.2–0.4 mg/kg IV
  - Maximum initial infusion rate 0.10 mg/kg/h IV
  - aPTT target is 1.5–2.0 x patient's baseline or mean of laboratory normal range

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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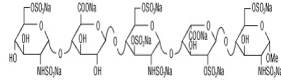
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## Emerging Treatments

- Fondaparinux



- Bivalirudin



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## Fondaparinux

- Advantages

- Does not cause HIT
  - While heparin anti- PF4 antibodies have been observed during administration of fondaparinux
    - They do not bind well to PF4 *in vitro* in the presence of fondaparinux, even though they recognize well the epitopes on PF4 in the presence of UFH or LMWH.
    - Platelet count recovery in patients observed during administration of fondaparinux in patients with HIT
    - One case of fonda-associated thrombocytopenia could have been delayed HIT from heparin administration
- Avoids elevated INR seen with DTIs
- Facilitates transition to warfarin
  - More “consistent” anticoagulant treatment during warfarin transition

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S. Warkentin TE. *Thromb Haemost* 2008;99:2-3. Warkentin TE, et al. *NEJM* 2007;356:2653-5. Rota E, et al. *Thromb Haemost* 2008;99:779-81. Alsaleh KA et al. *Am J Hematol* 2008;83:876-8. Warkentin TE, et al. *J Thrombos Haemost* 2008;6:1243-6.

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## Fondaparinux

- Advantages

- Acquisition cost less expensive than DTIs
- Easier transition to warfarin
  - No effect on INR
- Can be administered in the outpatient setting
- Listed as a 2C recommendation in the 2008 ACCP guidelines
  - For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant (danaparoid [Grade 1B], lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], bivalirudin [Grade 2C]) over the further use of UFH or LMWH therapy or initiation/continuation of a VKA (Grade 1B).

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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## Fondaparinux

- Disadvantages
  - Does not inhibit circulating thrombin
    - Indirect-acting Factor Xa inhibitor prevents production of thrombin
  - No antidote *and* long half-life
    - DTIs have shorter half lives
    - May be reversed with recombinant factor VIIa
  - Contraindicated if CrCl < 30 mL/min
  - Published data supporting its use are weak
    - Most are case reports, uncontrolled case series
    - < 100 patients total
    - Limited information on fondaparinux dosing in some reports

Kuo KHM, et al. *Hematology*. 2005;10:271-5.  
Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.  
Warkentin TE. *Thromb Haemost*. 2008;99:2-3.  
Blackmer AB, et al. *Ann Pharmacother* 2009;43:1636-46.

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## "Best" Data: Lobo et al.

- Eligible patients
  - Otherwise unexplained > 50% fall in platelet count with recent (within 2 weeks) exposure to heparin
  - + heparin PF4 Ab test or + SRA
- Excluded patients with CrCl < 30 mL/min
- Excluded patients at high bleeding risk

Lobo B, et al. *Thromb Haemost*. 2008;99:208-14.

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## "Best" Data – Lobo et al.

- Historical control group identified from list of patients with + heparin PF4 Ab test from 4/03 to 10/05 and chart review performed.
  - N=10 (8 with arterial and/or venous thrombosis)
  - DTI treatment with either lepirudin or argatroban according to a standard hospital protocol required
- Fondaparinux
  - N=7
  - Subjects without thrombosis (N=1)
    - 2.5 mg subcut once daily
  - Subjects with arterial and/or venous thrombosis (N=6)
    - 5 mg subcut once daily in patients weighing < 50 kg
    - 7.5 mg subcut once daily in patients weighing 50-100 kg
    - 10 mg subcut once daily in patients weighing > 100 kg

Lobo B, et al. *Thromb Haemost*. 2008;99:208-14.

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### Study Outcomes – Lobo et al.

- Platelet count recovery
  - 7/7 fonda patients versus 8/10 historical controls
- Patient Deaths
  - 2 in historical control group versus 0 in fonda group
- New thromboembolic events
  - No new thromboembolic events in fonda group
  - No new thromboembolic events in historical control group while being treated with DTI

Lobo B, et al. *Thromb Haemost.* 2008;99:208-14.

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### Study Outcomes – Lobo et al.

- Limb amputation
  - 1 in the fonda group after unsuccessful thrombectomy
  - 1 in historical control group associated with venous limb gangrene
- Venous limb gangrene
  - 0 in the fonda group
  - 4/10 in the DTI group all associated with warfarin initiation prior to or on same day as DTI
- Bleeding complications
  - ( $\geq 2$  g/dL Hg drop)
    - 3/7 in fonda group; occurred off treatment
    - 5/10 in historical control group occurring during DTI treatment
  - Transfusion
    - 4/7 in fonda group
    - 4/10 in historical control group

Lobo B, et al. *Thromb Haemost.* 2008;99:208-14.

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### “Best” Data – Grouzi et al.

- Retrospective study
- Chart review Jan 2003 and Jan 2008
- Eligible Patients
  - 50% platelet count fall
  - + PF4 ELISA and + particle gel immunoassay
- 24 patients with HIT treated with fondaparinux
  - 5 mg < 50 kg, 7.5 mg 50-100 kg, 10 mg > 100 kg
- 20 patient in control group treated with lepirudin
  - 0.15 mg/kg/hr (no bolus) adjusted to aPTT 2-3 x control
- No patients with renal dysfunction included
- IVIG given to about 20% of patients
- Oral anticoagulation initiated in all patients when platelet count >  $150 \times 10^9/L$ 
  - Fonda discontinued when INR > 2 for 2 consecutive days
  - Overlap procedure with lepirudin not described

Grouzi E, et al. *Clin Appl Thromb Hemost.* 2009;Oct 13.

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## Study Outcomes – Grouzi et al.

- Platelet count recovery
  - All study patients
- Patient deaths
  - 1/24 fonda versus 2/20 lepirudin patients
- New thromboembolic events
  - 14/24 fonda patients versus 19/20 lepirudin patients

Grouzi E, et al. *Clin Appl Thromb Hemost.* 2009;Oct 13.

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## Study Outcomes – Grouzi et al.

- Limb amputation
  - 1/24 fonda patients versus 2/20 lepirudin patients
- Venous limb gangrene
  - 1/24 fonda patients versus 2/20 lepirudin patients
  - All occurred before treatment began
- Bleeding complications
  - None

Grouzi E, et al. *Clin Appl Thromb Hemost.* 2009;Oct 13.

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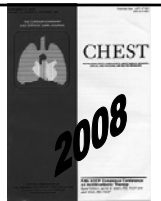
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## Is Fondaparinux Really Recommended in the 2008 ACCP Guidelines?

- 2C recommendation
  - “Weak recommendation, low or very low quality recommendation”
- “... there is uncertainty whether the usual prophylactic or therapeutic doses of fondaparinux would be effective in a patient with severe HIT-associated hypercoagulability.” – 2008 ACCP Guidelines
- “In summary, fondaparinux has the likely advantage (vs. DTI) of improving bridging to warfarin, but (unlike DTIs) its efficacy as a primary non-heparin anticoagulant for severe HIT-associated hypercoagulability is not established.” – Ted Warkentin

Warkentin TE, et al. *Chest.* 2008;133 (Suppl):340S-380S. Warkentin TE. *Thromb Haemost* 2008;99:2-3. Guyatt GH et al *Chest.* 2008;133 (Suppl):123S-131S.



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## Considerations when using Fondaparinux for HIT

- 2008 ACCP Guideline Recommendations
  - If HIT is unlikely (4 Ts score 0-3), can continue therapeutic dose heparin for patients with “treatment” indication, or give 2.5 mg fondaparinux for patients with “prophylaxis” indication
- Use DTI during initial thrombocytopenic phase then transition to DTI-fondaparinux to avoid DTI-warfarin bridge
  - “In this way, one circumvents the “off-label” use of fondaparinux as the primary treatment of HIT,...” – Ted Warkentin

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.  
Warkentin TE. *Thromb Haemost* 2008;99:2-3.

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## Considerations when using Fondaparinux for HIT

### Compensation for HIT: Heparin Lawsuits

Due to the severity of heparin induced thrombocytopenia, patients who develop this condition will likely be entitled to a settlement by pursuing a heparin lawsuit. If you or a loved one has been injured after taking heparin, you may be eligible to recover compensation for the hefty medical bills, long-term treatment costs, physical pain and emotional suffering associated with heparin-caused injuries such as HIT.

Heparin lawyers provide confidential, complimentary consultations for individuals and families harmed by heparin and other defective drugs. An experienced heparin attorney will thoroughly evaluate your situation and will discuss your legal options in detail.

### If You Have Been Injured by Heparin

Have you or a loved one been injured after taking Heparin? If so, contact us to speak with an experienced Heparin attorney who specializes in drug recall litigation & lawsuits. Let us help you win the compensation you need and deserve.

[click to contact](#)

Popular Drug Recall: Avandia | Yaz Birth Control | Zantac | Ranitidine | Home | Drug Index | News Archive | Resources  
Home | Benchmark Site | Legal Disclaimer | Site Map  
© 2009 Defective Drugs - adrugrecall.com

Google Search: Heparin-induced thrombocytopenia litigation revealed 2,640 hits  
Available from: <http://www.adrugrecall.com/heparin-induced-thrombocytopenia.html>; Accessed Nov 10, 2009.

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## Bivalirudin

- Advantages
  - Inhibits both circulating and clot-bound thrombin
  - Less expensive than argatroban and lepirudin
  - Has FDA approval for PCI in patients with HIT/HITTS
    - Grade 1B recommendation
  - Short-acting
    - Half-life 25 min (shorter than argatroban and lepirudin)
    - Coagulation normalizes within 60 min after discontinuation)

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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## Bivalirudin

- Advantages (continued)
  - Listed as a 2C recommendation in the 2008 ACCP guidelines
    - For patients with strongly suspected (or confirmed) HIT, whether or not complicated by thrombosis, we recommend use of an alternative, nonheparin anticoagulant (danaparoid [Grade 1B], lepirudin [Grade 1C], argatroban [Grade 1C], fondaparinux [Grade 2C], bivalirudin [Grade 2C]) over the further use of UFH or LMWH therapy or initiation/continuation of a VKA (Grade 1B).
  - Case series and small studies for on- and off-pump cardiac surgery in patients with acute or subacute HIT
    - Grade 1B recommendation
    - Koster et al (largest)

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.  
Koster A, et al. *Perfusion* 2009;24:7-11.

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## Bivalirudin

- Disadvantages
  - No reversal agent
  - INR effect makes transition to warfarin difficult
  - Cross-reactivity to antilepirudin antibodies
  - Renally cleared and increased half-life in patients with moderate to severe renal dysfunction (3.5 hours)
    - Removed by hemodialysis
  - Limited data outside of PCI and CABG surgery
  - Not FDA approved for HIT/HITTS in absence of PCI

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.  
Eichler P, et al. *Blood*. 2004;103:613-16.

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## Bivalirudin Dosing

- Initial infusion rate 0.15–0.20 mg/kg/h IV
- No initial bolus
- Target aPTT 1.5–2.5 patient's baseline or mean of laboratory normal range (no initial bolus)

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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### “Best” Data – Kiser et al

- Retrospective study
- Jan 1, 2004 – Mar 31, 2007
- HIT (N=29) or recent history of HIT (N=8)
  - Only 1/5 tested +SRA
  - Only 46% had some + HIT test (17/37)
  - Only 62% had platelet count drop > 50%
- Included patients with renal failure
  - 35% required RRT during admission
- 95% treated in ICU
- Target aPTT was 1.5-2.5 x ULN

Kiser TH, et al. *Pharmacother* 2008;28:1115-24.

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### Study Outcomes – Kiser et al.

- Thrombosis
  - 10/37 occurred prior to bival
  - 1/37 new DVT
- 8 patient deaths (22%)
  - No patient death secondary to known thrombotic event
- No limb amputations
- Clinically significant bleeding
  - 2/37 patients both requiring discontinuation of bival and transfusion (aPTT within target at time of bleed)
- INR during bival infusion 1.5

Kiser TH, et al. *Pharmacother* 2008;28:1115-24.

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### Study Outcomes – Kiser et al.

- Bivalirudin median dosing requirements to maintain therapeutic range
  - CrCl > 60 mL/min
    - 0.15 mg/kg/hr
  - CrCl 30-60 mL/min
    - 0.1 mg/kg/hr
    - 33% reduction
  - CrCl < 30 mL/min or receiving RRT
    - 0.03 mg/kg/hr
    - 69% reduction

Kiser TH, et al. *Pharmacother* 2008;28:1115-24.

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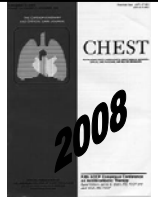
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## Is Bivalirudin Really Recommended in the 2008 ACCP Guidelines?



- 2C recommendation
  - “Weak recommendation, low or very low quality recommendation”
- “For bivalirudin (outside the setting of PCI) and fondaparinux, dosing, efficacy, and safety for the management of HIT are not established.”

Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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## Ongoing Clinical Trial: Desirudin

- Desirudin is a recombinant hirudin structurally similar to lepirudin
  - Differ by 1/65 amino acids
  - Desirudin is valine-valine and lepirudin is leucine-threonine at N-terminus
  - Desirudin MW = 6.96 KDa while lepirudin MW = 6.98 KDa
  - Antihirudin antibodies also reported following administration
- Subcut desirudin FDA approved for VTE prophylaxis 15 mg BID in THR in US in April 2003 based upon 3 prospective trials
- Available in Europe
- Ongoing clinical trial in patients with suspected HIT comparing
  - Desirudin 15mg subcut in patients without thrombosis and 30mg subcut with thrombosis
  - Argatroban (labeled product dosing)

ClinicalTrials.gov NCT00787332

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## Summary

- Limited data supporting acute treatment with either fondaparinux or bivalirudin in acute HIT
- Recommendations in 2008 Chest Guidelines 2C for fondaparinux and bivalirudin
- Ongoing clinical trial with DTI desirudin
- There are advantages and disadvantages to each currently recommended treatment for HIT.
- Clinicians should use patient-specific information to select the best therapy.

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In a patient admitted to ICU for pneumonia who develops a 60% platelet count drop from baseline, HIT (+ SRA) with new DVT on day 10 of subcut heparin, estimated CrCl 45 mL/min without hepatic disease or congestion, which of the following agents would you recommend as initial therapy (in addition to discontinuing heparin)?

- A. Argatroban
- B. Lepirudin
- C. Fondaparinux
- D. Bivalirudin
- E. Warfarin

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In a patient admitted for colon resection with a PMH significant for HIT with thrombosis secondary to UFH 6 months ago, which one of the following would you recommend as VTE prophylaxis?

- A. Intermittent pneumatic compression
- B. Enoxaparin
- C. Fondaparinux
- D. Subcut lepirudin

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# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## SELECTED REFERENCES AND RESOURCES

1. Lobo B, Finch C., et al. Fondaparinux for the treatment of patients with heparin-induced thrombocytopenia. *Thromb Haemost.* 2008;99:208-14.
2. Ansara AJ, Arif S, Warhurst RD, et al. Weight-based argatroban dosing nomogram for treatment of heparin-induced thrombocytopenia *Ann Pharmacother.* 2008;43:9-18.
3. Warkentin TE, et al. Heparin-induced thrombocytopenia associated with fondaparinux. *NEJM* 2007;356:2653-5.
4. Rota E, Bazzan M, Fantino G., et al. Fondaparinux-related thrombocytopenia in a previous low-molecular-weight heparin-induced heparin-induced thrombocytopenia. *Thromb Haemost* 2008;99:779-81.
5. Warkentin TE, Greinacher A. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence based clinical practice guidelines (8th edition). *Chest.*2008;133:340S-380S.

# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## SELF-ASSESSMENT QUESTIONS

1. Which of the following has the greatest effect on the INR during transition to warfarin therapy?
  - a. Argatroban.
  - b. Lepirudin.
  - c. Bivalirudin.
  - d. Fondaparinux.
2. Which of the following is recommended by the 2008 American College of Chest Physicians guidelines as an initial argatroban dose for a patient with heart failure?
  - a. 1 mcg/kg/min.
  - b. 2 mcg/kg/min.
  - c. Bolus plus 1 mcg/kg/min.
  - d. Bolus plus 2 mcg/kg/min.
3. Which of the following agents would be the best choice for anticoagulation during percutaneous coronary intervention in a patient with a history of HIT?
  - a. Argatroban.
  - b. Lepirudin.
  - c. Bivalirudin.
  - d. Fondaparinux.
4. Which of the following would you recommend as an anticoagulant during cardiopulmonary bypass for cardiac surgery in a patient with a history of HIT?
  - a. Argatroban.
  - b. Lepirudin.
  - c. Bivalirudin.
  - d. Fondaparinux.

## Answers

1. a
2. a
3. c
4. c

## Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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### **Maureen Ann Smythe, Pharm.D.**

Clinical Professor of Pharmacy Practice  
Wayne State University  
Detroit, Michigan  
Coordinator of Student and Resident Education  
Beaumont Hospital,  
Royal Oak, Michigan

Maureen A. Smythe, Pharm.D., FCCP, is a Professor of Pharmacy Practice at the Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University in Detroit, Michigan. She holds a cross appointment as Coordinator of Student and Resident Education with the Department of Pharmaceutical Services at William Beaumont Hospital in Royal Oak, Michigan. Dr. Smythe has established a practice based research program in the area of inpatient anticoagulation.

Previously, Dr. Smythe has held positions of Doctor of Pharmacy Clerkship Coordinator, Associate Professor of Pharmacy Practice (Clinical), and Assistant Professor of Pharmacy Practice (Clinical) at Wayne State University College of Pharmacy & Allied Health Professions located in Detroit, Michigan and Staff Pharmacist at William Beaumont Hospital in Royal Oak, Michigan. She has presented numerous papers nationally and internationally in the area of anticoagulation. She has authored over 100 abstracts and papers. She serves as a reviewer for *Annals Pharmacotherapy*, *Pharmacotherapy*, *American Journal Health-System Pharmacy (AJHP)*, and *Critical Care Medicine* and is on the Editorial Board for the *Annals of Pharmacotherapy*. Dr. Smythe had received numerous awards for precepting and teaching.

Dr. Smythe received her Bachelor of Science in Pharmacy and her Doctor of Pharmacy degrees from Wayne State University in Detroit, Michigan. She completed a fellowship in critical care at Henry Ford Hospital in Detroit, Michigan. Dr. Smythe has been a Board Certified Pharmacotherapy Specialist (BCPS) since 1992 and a Fellow of the American College of Clinical Pharmacy since 2000.

# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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**Maureen Ann Smythe, Pharm.D.**

## **P R E S E N T A T I O N**

Practical Management of Patients with Heparin-Induced Thrombocytopenia

## **O V E R V I E W**

Initiation of direct thrombin inhibitor (DTI) therapy requires a careful consideration of factors which may impact dose. Several factors can result in a need to lower the initial dose depending upon the DTI selected. For lepirudin the dose needs to be reduced in the presence of renal dysfunction, dialysis and critical illness. For argatroban the dose needs to be reduced in the presence of hepatic dysfunction, critical illness, anasarca and post cardiothoracic surgery. The transition of a patient with heparin induced thrombocytopenia (HIT) and thrombosis to warfarin must be carefully managed. Warfarin should not be started until after adequate platelet count recovery and it must be overlapped with DTI therapy for a minimum of five days. For patients with isolated HIT (i.e. no thrombosis) the benefit of a short course of warfarin after DTI therapy is uncertain. Patients with a history of HIT should avoid a repeat prolonged exposure to heparin. If cardiac surgery is required heparin can be given intraoperatively if the testing for the HIT antibody yields negative results. An HIT management protocol can help to standardize the management of this clinically significant but infrequent adverse drug reaction.

## **L E A R N I N G O B J E C T I V E S**

At the conclusion of this knowledge-based educational activity, participants should be able to

- Review dosing of direct-thrombin inhibitor (DTI) therapy in special patient populations.
- Discuss the transition of the DTI therapy to warfarin therapy.
- Summarize the data available on the length of anticoagulant therapy in patients with isolated heparin-induced thrombocytopenia (HIT).
- Outline the considerations in rechallenging a HIT patient with heparin.
- Describe the potential benefit of HIT management protocols.

## Practical Management of Patients with Heparin Induced Thrombocytopenia

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Beaumont Hospital,  
Royal Oak, Michigan

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### Learning Objectives

- Review dosing of direct-thrombin inhibitor (DTI) therapy in special patient populations.
- Discuss the transition of the DTI therapy to warfarin therapy.
- Summarize the data available on the length of anticoagulant therapy in patients with isolated heparin-induced thrombocytopenia (HIT).
- Outline the considerations in rechallenging a HIT patient with heparin.
- Describe the potential benefit of HIT management protocols.

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### DTI aPTT Therapeutic Range

DTI	Prescribing Info	ACCP Guideline	Clinical Trials
Argatroban	• 1.5 – 3 x baseline value • (not > 100 seconds)	NA	1.5 – 3 x baseline
Lepirudin	• 1.5 – 2.5 x median normal	• 1.5 – 2 x patient's baseline or mean lab normal	• 1.5 – 2.5 x baseline or median normal*
Bivalirudin	NA	1.5 – 2.5 x patient's baseline or mean lab normal	NA

DTI = direct thrombin inhibitor, \* 1.5 – 3x for Actin FS and Neothrombin Warkentin TE. Chest 2008; 133: 340-380, Verme Gibboney C. Ann Pharmacother 2003; 37: 970-975, Greinacher A. Circ 1999; 99:73-80, Greinacher A. Circ 1999; 100: 587-593, Lubenow N. J Thromb Haemost 2005; 3: 2428-2436.

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### Argatroban Dosing & Outcomes in ICU

Ref	Initial dose (mcg/kg/min)	N	Major Bleeding	Thrombosis (after Arg)	% HIT
1	0.2	19	0%	0%	26.3
2	0.5	17	17.6%	0%	NA
3	0.8	38	11%	16% (31% HIT +)	34
4	0.9	34	29%	3%	46
5	1.14	65	13.8%	16.9%	42

2 studies have shown dose requirements ↓ as # of organ failures ↑

<sup>1</sup>Beiderlinden M. *Ann Pharmacother* 2007; 41:749-54, <sup>2</sup>Ansara AJ. *Ann Pharmacother* 2009; 43:9-18, <sup>3</sup>Smythe MA. *Pharmacother* 2009; 29: 1073-1081, <sup>4</sup>Keegan SP. *Ann Pharmacother* 2009; 43:19-27, <sup>5</sup>J Int Care Med 2008; 23: 313-320.

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### Initial Bivalirudin Dose Requirements

Not FDA labeled for non PCI HIT

- Clcr > 60ml/min: 0.15 – 0.2 mg/kg/hr
- Clcr 30 – 60 ml/min: 0.08 – 0.1 mg/kg/hr
- Clcr < 30 ml/min: 0.03 – 0.05 mg/kg/hour
- CRRT: 0.03 – 0.05 mg/kg/hr

Warkentin TE. *Chest* 2008; 133:340s-380S, Kiser TH. *Pharmacother* 2008; 28:1115-1124, Dang CH. *Pharmacother* 2006; 26: 461-468

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### Warfarin Initiation in HIT

- No warfarin until substantial platelet count recovery, usually at least  $150 \times 10^9/L$
- Initiate with low maintenance doses (maximum 5 mg)
- Continue DTI therapy until:
  - Stable plateau in platelet count
  - INR is in target range
  - Minimum 5 days of overlap with DTI and warfarin
- Can use chromogenic X assay for transition

*Chest* 2008; 133: 340s – 380s, *Chest* 2008; 133:141-159

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### DTI Induced INR Elevation

- A drug lab interaction
- Argatroban clinically significant ↑ INR  
INR prolongation: argatroban > lepirudin > bivalrudin<sup>1</sup>
- Differing effect related to different molar concentrations in plasma<sup>2</sup>

<sup>1</sup>Chest 2008; 133:340-380, <sup>2</sup>Thromb Haemost 2005; 94: 958-964.

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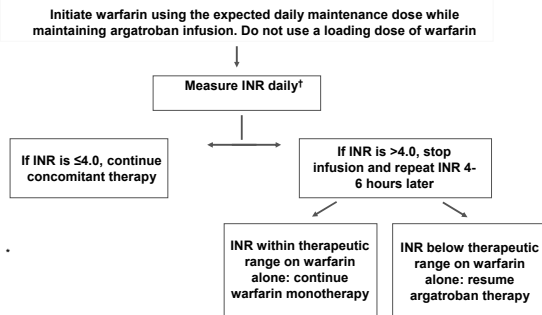
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### Conversion of Argatroban to Oral Anticoagulant Therapy



† If arg dose > 2mcg/kg/min reduce to 2 mcg/kg/min for 4-6 hrs before checking INR  
Adapted from HIT, 4<sup>th</sup> Edition 2008, Chapter 15, Argatroban Therapy in HIT, pg 395.

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### Chromogenic Factor X Conversion From Argatroban to Warfarin

- Chromogenic factor X measures amount factor X
- Levels of 11 – 42% are inversely correlated with INRs of 2 to 3.5 for warfarin patients
- Levels below 11% : → INR > 3.5
- Levels above 42%: → INR < 2
- Benefit: no interruptions in argatroban therapy

Pharmacother 2005; 25: 157-164.

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**How are patients with isolated HIT managed at your institution?**

- A. Heparin cessation alone
- B. DTI until platelet count recovery then no anticoagulation
- C. DTI until platelet count recovery, then warfarin  $\leq$  30 days
- D. DTI until platelet count recovery then warfarin  $>$  30 days
- E. Fondaparinux  $\pm$  DTI initially
- F. None of the above

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**Frequency of Thrombosis in Isolated HIT**

- Patients with isolated HIT identified over 14 year period and records reviewed for 30 days
- 62 patients identified
- Cumulative rate of thrombosis at 30 days was 52.8%
- Management:
  - heparin cessation 58%
  - change to warfarin ~ 34%

Warkentin TE. *Am J Med* 1996;101:502-507.

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**New thrombosis in Isolated HIT Patients Managed with DTI Therapy**

Clinical Trial	DTI	Incidence New Thrombosis
HAT 1,2,3 Meta-Analysis <sup>1</sup>	Lepirudin	4.4%
Post-marketing observational study <sup>2</sup>	Lepirudin	2.1%
ARG 911 <sup>3</sup>	Argatroban	8.1%
ARG 915 <sup>4</sup>	Argatroban	5.8%

argatroban trial data includes patients transitioned to warfarin  
<sup>1</sup>Lubenow N. *Blood* 2004; 104: 3072-3077., <sup>2</sup>Lubenow N. *Blood* 2002; 10(suppl 1):502a.,  
<sup>3</sup>Lewis BE. *Circ* 2001; 103: 1838-1843, Lewis BE. *Arch Int Med* 2003; 164: 1849-1856.

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### Duration of Anticoagulant Therapy Isolated HIT

Article	Recommendation
New Engl J Med 2006	<ul style="list-style-type: none"> <li>• alternative anticoagulant until stable platelet count plateau or return to baseline</li> <li>• consider warfarin for up to 4 weeks; risk of thrombosis is high for 2- 4 weeks</li> </ul>
Hem Oncol Clin North Am 2007	<ul style="list-style-type: none"> <li>• alternative anticoagulant until platelet count recovery</li> </ul>
Chest 2008	<ul style="list-style-type: none"> <li>• alternative anticoagulant until stable platelet count plateau</li> <li>• benefit of additional course of warfarin is uncertain</li> <li>• perform ultrasonography</li> </ul>
Thromb Haemost 2009	<ul style="list-style-type: none"> <li>• cease alternative anticoagulant when platelet count returns to baseline</li> </ul>

Arepally GM. *New Engl J Med* 2006; 355: 809-817, Warkentin TE, *Hem Onc Clin North Am* 2007; 21: 589-607  
 Warkentin TE. *Chest* 2008; 133: 340s-380s, Chong BG. *Thromb Haemost* 2009; 101: 279-283.

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### Rechallenge HIT Patients with Heparin?

HIT does NOT appear to demonstrate typical immune anamnesis

1. In pts with history of HIT, HIT does not occur earlier in those with recent heparin exposure
2. Rapid onset HIT occurs with heparin exposure within last 100 days
3. Median time to antibody negativity is 50 – 85 days
4. HIT patients re-exposed to heparin:
  - Antibodies typically do not develop
  - When antibodies develop, same time frame required, same strength of response seen

Warkentin TE. *Chest* 2008; 133: 340-380.

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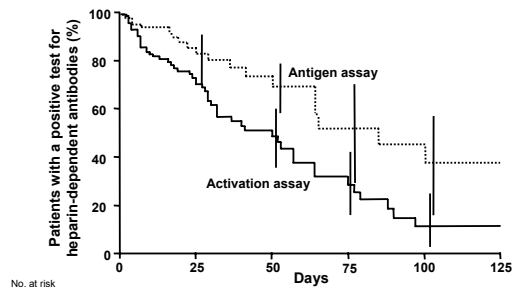
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### Proportion of Patients with Heparin-Dependent Antibodies After HIT



Copyright © 1996 Massachusetts Medical Society. All rights reserved. Warkentin TE, Kelton JG. *N Engl J Med*. 2001;344:1286-1292.

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## Heparin Rechallenge

- In situations with well defined alternative anticoagulant choices, avoid heparin
- Rechallenge may be needed for cardiac or vascular surgery
- Document antibody negativity, in emergent cases ensure at least 2-3 months have passed since episode of HIT
- Avoid prolonged course of heparin therapy

Warkentin TE. Chest 2008; 133: 340s-380s, Shantsila E. Chest 2009; 135:1651-1654.

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## Cardiac Surgery with History of HIT ACCP Recommendations

- Antibody negative → UFH Level 1 B
- Antibody negative by PF4 dependent EIA, antibody positive by washed platelet activation assay → UFH Level 2 C

Avoid post-operative heparin exposure

PF4 = platelet factor 4, EIA = enzyme immunoassay, UFH = unfractionated heparin  
Warkentin TE et al. Chest 2008; 133: 340-380.

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## Cardiac Surgery with Acute HIT ACCP Recommendations

Decreasing Order of Preference

- 1) Delay surgery until HIT resolves, antibody negative - Level 1 B
- 2) Bivalirudin for intra-op anticoagulation – Level 1 B
- 3) Lepirudin for intra-op anticoagulation – Level 2 C
  - ECT is available
  - Normal renal function
  - Low risk of post-op renal dysfunction
- 4) UFH + epoprostenol – Level 2 C
- 5) UFH + tirofiban – Level 2 C

Warkentin TE et al. Chest 2008; 133: 340-380.

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Which of the following best describes the status of HIT recognition and management at your institution?

- A. No formal protocol for recognition or management
- B. Pharmacy Protocol for DTI dosing & monitoring only
- C. Protocol for HIT recognition & comprehensive management (DTI dosing, monitoring, conversion to warfarin)
- D. None of the above

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### Why an HIT Management Protocol?

- Under diagnosis is a concern: CATCH registry
  - prospective observational study in 3,536 pts in 48 U.S. hospitals
  - infrequent recognition & evaluation of HIT
  - treatment often delayed
- Over diagnosis is also a concern

Frequency of  $\geq 50\%$  serotonin release by EIA optical density

		Optical Density units			
399	0/304 0%	1/37 2.7%	2/11 18.2%	5/10 50%	33/37 89.2

Crespo EM. *Am Heart J* 2009; 157: 651-657, *J Thromb Haemost* 2008; 6:1304-1312.

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### Why an HIT Management Protocol?

- Infrequent ADR, medications used to manage are costly and have risk
- Poor compliance with platelet count monitoring and DTI dosing recommendations
- National Patient Safety Goal 03.05.01 (former 3 E)
  - reduce the likelihood of patient harm associated with anticoagulation therapy

Saxer SB. *Am J Health Syst Pharm* 2003; 60: 2588-93., ten Berg MJ. *Ann Pharmacother* 2009; 43: 1405-12.

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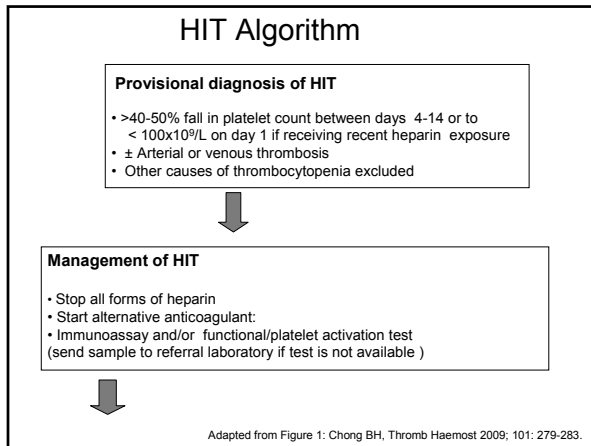
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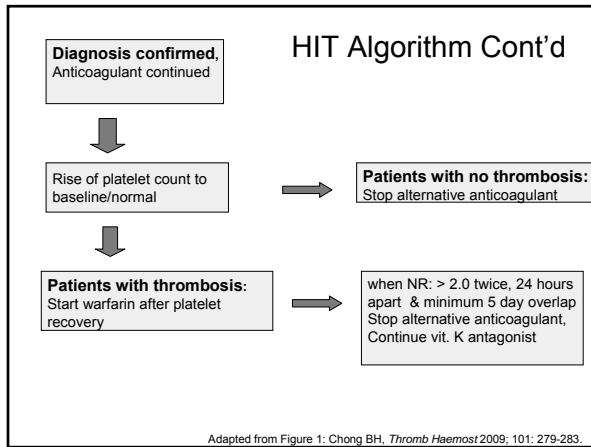
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- ### Components of an HIT Protocol
- When to suspect HIT
  - Laboratory testing for the heparin PF4 antibody
  - Removal of all sources of heparin
  - When to initiate DTI therapy
- Fugate S. *Am J Health-Syst Pharm* 2008; 65: 334-9.,  
Cooper T. *Am J Health-Syst Pharm* 2009; 66: 1297-303.

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### Components of an HIT Protocol

- DTI dosing and monitoring recommendations
  - agent selection, who initiates and adjusts therapy?
  - starting doses, titration nomogram
  - Fondaparinux ?
- Interpretation of laboratory test results
- Warfarin reversal
- Lower limb ultrasonography

Fugate S. *Am J Health-Syst Pharm* 2008; 65: 334-9.  
 Cooper T. *Am J Health-Syst Pharm* 2009; 66: 1297-303.

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### Components of an HIT Protocol

- Transition to warfarin therapy
  - When, how, in whom?
- Medical record documentation
- Patient education if HIT confirmed

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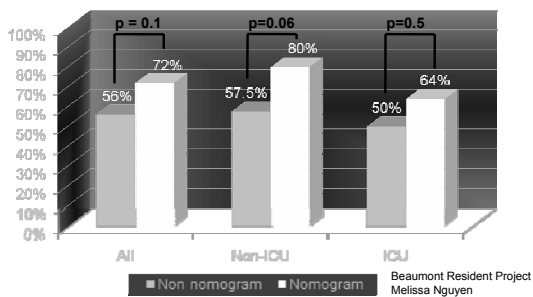
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### Nomogram Managed Argatroban Therapy vs Individualized Dosing (N = 100)

Therapeutic aPTT ratio with initial dose




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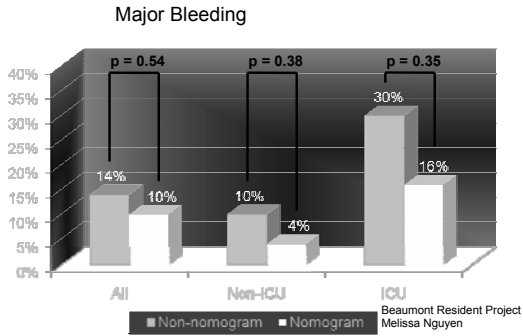
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### Nomogram Managed Argatroban Therapy vs Individualized Dosing (N = 100)




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### Concluding Remarks

- Reduce lepirudin dosing in renal dysfunction, dialysis, and in critical illness
- Reduce argatroban dosing in hepatic dysfunction, critical illness, post CV surgery, and anasarca
- When transitioning to warfarin, overlap DTI therapy with warfarin for at least 5 days
- The optimal duration of anticoagulant therapy in patients with isolated HIT is uncertain
- Avoid prolonged heparin exposure in those with a history of HIT
- A HIT management protocol can standardize care of an infrequent ADR

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# Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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## SELECTED REFERENCES AND RESOURCES

1. O'Connor ED, Fraser JF. Heparin induced thrombocytopenia without thrombosis: an evidenced based review of the literature. *Crit Care Resusc.* 2006; 8: 345-352.
2. Greinacher A. Heparin-induced thrombocytopenia. *J Thromb Haemost.* 2009; 7(Suppl 1):9-12.
3. Warkentin TE. Management of heparin induced thrombocytopenia: a critical comparison of lepirudin and argatroban. *Thromb Res.* 2003; 110: 73-82.
4. Greinacher A, Warkentin TE. The direct thrombin inhibitor hirudin. *Thromb Haemost* 2008; 99:819-829.
5. Rice L. Heparin-induced thrombocytopenia: myths and misconceptions that will cause trouble for you and your patient, *Arch Int Med* 2004; 164: 1961-1964.

## Emerging Therapies in the Treatment of Heparin-Induced Thrombocytopenia

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### SELF-ASSESSMENT QUESTIONS

1. The initial dose of argatroban must be reduced in patients with multiple organ failure.
2. A HIT management protocol is not recommended since most clinicians are familiar with the management of HIT.
  - a. True.
  - b. False.
3. BG is a 45 year old male in the hospital with HIT and thrombosis. BG is on lepirudin therapy with a therapeutic aPTT of 60 seconds (45 – 90 seconds). BG's baseline platelet count was  $230 \times 10^9/L$ . BG's current platelet count is  $79 \times 10^9/L$ . The medical resident wishes to transition BG to warfarin therapy at this time. Which of the following is true?
  - a. BG should receive an initial warfarin dose of 10 mg.
  - b. Warfarin therapy should be delayed until BG's platelet count rises to  $> 100 \times 10^9/L$ .
  - c. Warfarin therapy should be delayed until BG's platelet count rises to  $> 150 \times 10^9/L$ .
  - d. Warfarin therapy should be overlapped with lepirudin therapy for 3 days.
4. ML is a 65 year old female with a history of HIT with thrombosis 1 year ago. ML is scheduled to undergo coronary artery bypass graft surgery in 7 days. ML has been tested for the heparin platelet factor 4 antibody with both an antigen test and a functional assay. Both have returned negative. What is the recommended approach for intraoperative anticoagulation in ML?
  - a. Unfractionated heparin.
  - b. Bivalirudin.
  - c. Lepirudin.
  - d. Argatroban.

### Answers

1. a
2. b
3. c
4. a

## Heparin-Induced Thrombocytopenia (HIT) Clinical Pearls



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## Clinical Pearl

### The 4Ts of HIT

Edith Nutescu, Pharm.D., FCCP



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## Patient Case

- 70 year-old 4 weeks s/p St. Jude's mitral mechanical heart valve placement now hospitalized heart failure and *staph aureus* endocarditis. Started on vancomycin, rifampin and gentamicin
- Admitted on warfarin INR 3.0; heparin started on Hospital Day 3 for INR 2.6
- Now hospital day 5 WBC 28K, Temp 102.1, BP 90/70 mmHg,
- No signs of embolization



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## Platelet Count

- Discharge 4 weeks ago      210K
  - Admit Hospital Day 1        180K
  - Hospital Day 2                175K
  - Hospital Day 3                178K
  - Hospital Day 4                130K
  - Hospital Day 5 (Monday)    98K
- } 2 days of heparin therapy
- 46% reduction from admission




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## Establishing the Diagnosis

- 4 T's bedside scoring system:
  - Thrombocytopenia; Timing; Thrombosis, Other causes for TCY
  - Each scored 0-2 points
  - High probability 6-8; low 0-3 points
- Scores 0-3: < 2% chance of + HPF4 antibody
- Scores 6-8: 21 – 100% chance of + HPF4 antibody

*Circulation 2004; 110: e454-e458, J Thromb Haemost 2006; 4: 894-896.*




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### Diagnosis - Pretest Probability: the 4 T's

Points: Score 0, 1 or 2 for each of 4 categories:

	2	1	0
Thrombocytopenia	> 50% platelet count fall or nadir 20-100K	30-50% platelet count fall or nadir 10-19K	<30% platelet count fall or nadir ≤ 10K
Timing of fall in platelet count or other sequelae	Onset d 5-10 or < 1 d (if heparin exposure within 30 d)	> d 10, or timing unclear, or < d 1 with recent heparin 31-100 d or consistent with immunization	Platelet count fall < d 4 (without recent heparin exposure)
Thrombosis or other sequelae	New thrombosis; skin necrosis; post-heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis – not confirmed	None
Other cause for thrombocytopenia	No other cause for platelet count fall is evident	Possible other cause is evident	Definite other cause is present
<b>Total Point Score = 2</b>			

*Warkentin TE and Heddle NM. Current Hematology Reports 2003;2:148-57*




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## Clinical Diagnosis of HIT Pretest Probability: the 4 Ts Score

- **Score 0-3:**  
very unlikely to be HIT (<5%)
- **Score 4 - 5:**  
a minority have HIT (10-30%)
- **Score 6 – 8:**  
20 to >80% have HIT, depending on the clinical setting and scorer's experience



Warkentin TE and Heddie NM. *Current Hematology Reports*. 2003;2:148-57.  
Pouplard C, et al. *J Thromb Haemost* 2007;5:1373-9.

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## Management of Suspected HIT

- **Interpret 4T score**
  - Low risk for HIT
    - Continue therapeutic heparin
    - Switch to either fondaparinux or lepirudin for prophylaxis
  - For moderate to high-risk for HIT, start DTI
- **Confirm with laboratory diagnosis**



Hirsh J, et al. *Arch Intern Med*. 2004;164:361-369.  
Warkentin TE, et al. *Chest*. 2008;133 (Suppl):340S-380S.

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## Clinical Pearl

How should argatroban infusions be adjusted?

Sarah A. Spinler, Pharm.D., FCCP, FAHA, BCPS (AQ  
Cardiology)

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## Case

- A 64 year-old patient hospitalized with ischemic stroke and given LMWH DVT prophylaxis has suspected HIT was started on argatroban 2 mcg/kg/min while awaiting results of confirmatory testing.
- The patient has no significant renal disease
- The upper limit of the hospital normal range for aPTT is 30 sec
- The patient's initial aPTT drawn 4 hrs after the infusion started is 110 sec
- What should the new argatroban dose be?

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## Argatroban Dosing Adjustment

**Table 1. Standard Nomogram**

Initial infusion rate: 2 µg/kg/min; check aPTT 3 h after start of infusion. Adjust rate of infusion as follows:

aPTT (sec)	infusion rate change	next aPTT
≤44	increase by 0.5 µg/kg/min	3 h after rate change
45-90 (target)	none	3 h from last aPTT; after 2 consecutive aPTTs within target range, check aPTT every 12 h
91-120	decrease by 0.5 µg/kg/min	3 h after rate change
121-140	hold infusion 1 h, resume at 1/2 rate	3 h after rate change
≥150	hold infusion 1 h, resume at 1/2 rate when aPTT <90 sec	repeat every hour until aPTT <90 sec

aPTT = activated partial thromboplastin time.

Ansara AJ et al. *Ann Pharmacother.* 2008;43:9-18.

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## Argatroban Dosing Adjustment

**Table 2. Hepatic/Critically Ill Nomogram**

Initial infusion rate: 0.5 µg/kg/min; check aPTT 4 h after start of infusion. Adjust rate of infusion as follows:

aPTT (sec)	infusion rate change	next aPTT
≤44	increase by 0.1 µg/kg/min	4 h after rate change
45-90 (target)	none	repeat 4 h from last aPTT; after 2 consecutive aPTTs within target range, check aPTT every 12 h
91-120	decrease by 0.1 µg/kg/min	4 h after rate change
121-140	hold infusion 2 h, resume infusion at 1/2 rate	4 h after rate change
≥150	hold infusion 2 h, resume at 1/2 rate when aPTT <90 sec	repeat every 2 h until aPTT <90 sec

aPTT = activated partial thromboplastin time.

Ansara AJ et al. *Ann Pharmacother.* 2008;43:9-18.

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## Ansara et al. Argatroban Nomograms

- N=51 patients
- Therapeutic range derived from median of range (22-36 sec in this case)
- aPTTs measured every 3 hrs. until in range in standard nomogram and every 4 hrs. in hepatic/critically ill nomogram
- Dose adjustments of 50% were used if patients required doses lower than 0.2 mcg/kg/min
- Can move between dosing nomograms if more than 3 dosage adjustments up or down in a row
- Caution if using hepatic/critically ill nomogram as only 11.8% therapeutic at 24 hrs. with most (76.5%) supratherapeutic



Ansara AJ et al. *Ann Pharmacother.* 2008;43:9-18.

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## Clinical Pearl

Why administer Vitamin K if warfarin is on board at the time HIT is diagnosed?

Maureen Ann Smythe, Pharm.D.

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1) Warfarin does not inhibit activated clotting factors and does not inhibit thrombin generation

2) Avoid under- dosing of DTI as warfarin  $\uparrow$  aPTT

Warfarin induced protein C depletion and subtherapeutic DTI dosing can be a set up for venous limb gangrene (VLG)



Warkentin TE. *Chest* 2008; 133: 340s-380s.  
Warkentin TE. *J Thromb Haemost* 2006; 4: 894-96.

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- 3) ↓ potential for warfarin induced VLG
- progression to necrosis in limb affected by DVT
  - palpable or doppler identified pulses
  - elevated INR (marker of severe protein C deficiency)



Smythe MA. *Am J Hematol* 2002; 71: 50-52.

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