

# Heparin-Induced Thrombocytopenia (HIT)

NMSHP 22<sup>nd</sup> Balloon Fiesta Symposium  
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## Learning Objectives

After the lecture, participants will be able to:

- Distinguish HIT from non-HIT thrombocytopenia
- Interpret lab tests for HIT antibodies
- List six treatment principles for HIT
- Describe pitfalls of PTT monitoring for DTIs
- Explore emerging therapies for HIT

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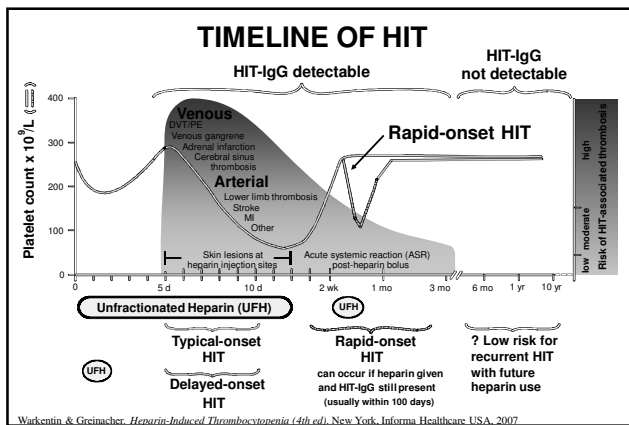
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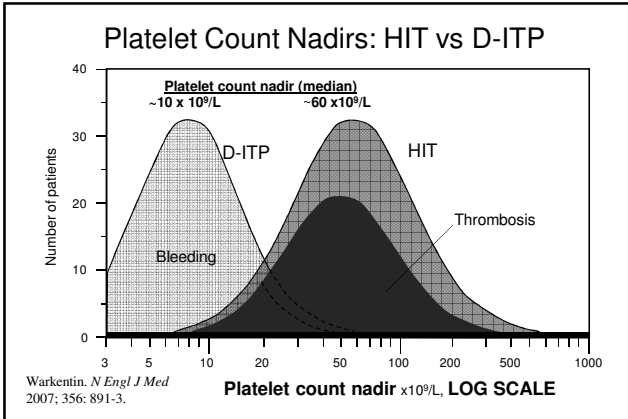
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- ### Complications of HIT
- **Venous thrombosis (50%)**
    - DVT ± PE > adrenal > cerebral > splanchnic
  - **Arterial thrombosis (10-15%)**
    - limb > stroke > MI > mesenteric > other
  - **Microvascular (5%), venous limb gangrene**
    - DIC ± warfarin
  - **Miscellaneous (5%)**
    - necrotizing skin lesions (injection sites)
    - anaphylactoid reactions (post-i.v. bolus/s.c. injection)

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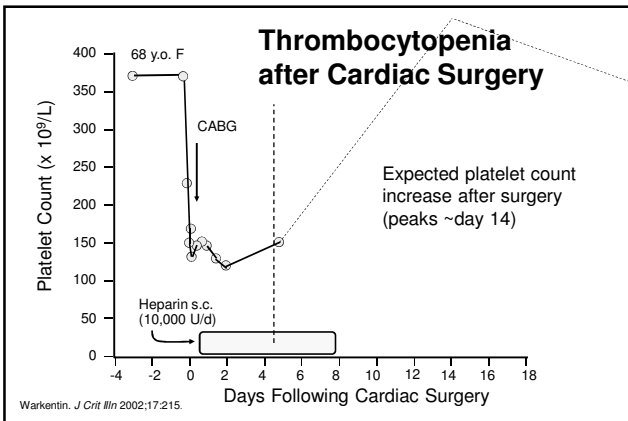
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## Risk Factors for HIT

- Heparin use > 1 week (vs <1 day)
- Unfractionated heparin (vs LMWH)
- Post-surgery (vs medical or obstetrical)
- Females (vs males)

Warkentin TE. Who is (still) getting HIT? *Chest* 2007

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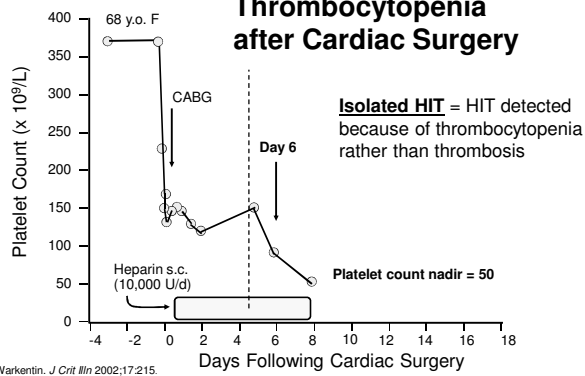
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## Thrombocytopenia after Cardiac Surgery




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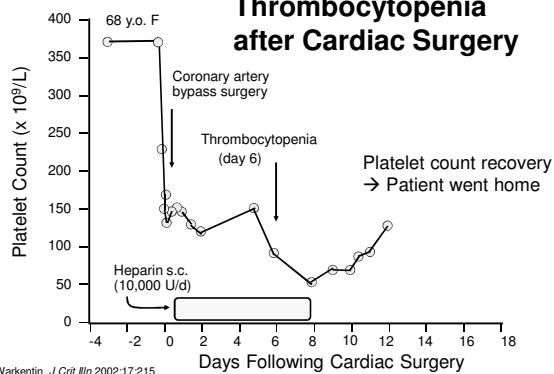
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## Thrombocytopenia after Cardiac Surgery




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# Natural History of Isolated HIT

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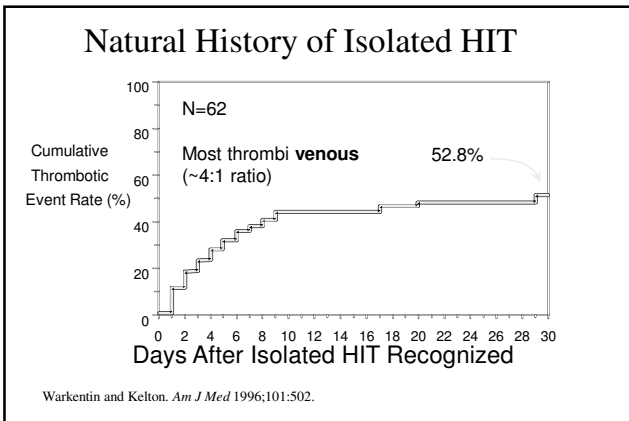
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## Unfavourable Natural History of HIT: Frequency of Symptomatic Thrombosis

- Positive serotonin release assay  
– 32/62 = 52%
- Positive Platelet Aggregation Assay  
– 43/113 = 38%
- Positive ELISA (OD > 1.0 units)  
– 5/14 = 36%

Warkentin and Kelton. *Am J Med* 1996;101:502.  
Wallis et al. *Am J Med* 1999; 106: 629-635.  
Zwicker et al. *J Thromb Haemost* 2005; 2: 2133-2137.

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### Treatment and Prevention of Heparin-Induced Thrombocytopenia

#### *Treatment of HIT*

- 2.1 Nonheparin Anticoagulants for Treating HIT (With or Without Thrombosis)
- 2.1.1. 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).

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## Why does Venous Thrombosis Predominate?

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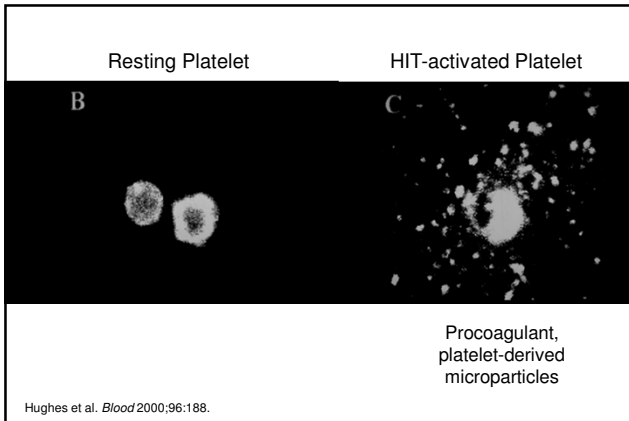
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**HIT = Clinical-Pathological**

<u>“Clinical”</u>	<u>“Pathological”</u>
<ul style="list-style-type: none"> <li>• <b>Thrombocytopenia</b></li> <li>• <b>Thrombosis, etc.</b> <ul style="list-style-type: none"> <li>— Venous (DVT, PE, <i>adr</i>)</li> <li>— Arterial (<i>limb</i>, CVA, MI)</li> <li>— Skin lesions (<i>inj. sites</i>)</li> <li>— Anaphylactoid (<i>post-iv</i>)</li> <li>— DIC (<i>decompensated</i>)</li> </ul> </li> <li>• <b>Timing fits</b></li> <li>• <b>No better non-HIT explanation</b></li> </ul>	<ul style="list-style-type: none"> <li>• <b>Heparin-dependent, platelet-activating IgG</b> <ul style="list-style-type: none"> <li>-Platelet activation assay (e.g., serotonin release assay)</li> <li>-Antigen assay (e.g., PF4/heparin-ELISA)</li> </ul> </li> </ul>
	<small>Warkentin et al. <i>Thromb Haemost</i> 1998;79:1-7</small>

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**Platelet Factor 4 (PF4)**

**Lys + Arg**

Amiral et al. *Thromb Haemost* 1992

Kelton et al. *Blood* 1994

Visentin et al. *J Clin Invest* 1994

Greinacher et al. *Thromb Haemost* 1994

Suh et al. *Blood* 1998

Ziporen et al. *Blood* 1998

Li et al. *Blood* 2002

Greinacher et al. *Arterioscler Thromb Vasc Biol* 2006

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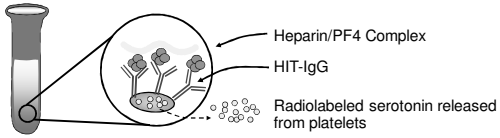
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## Platelet Serotonin Release Assay (Platelet Activation Assay)



Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin-induced thrombocytopenia. *Blood* 1986; 67: 27-30.

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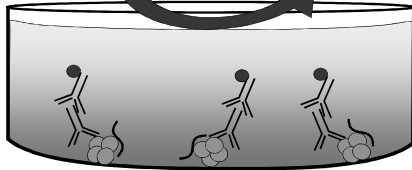
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## PF4/heparin-ELISA

Add substrate → COLOR

**Commercial EIAs detect 3 Ig classes: IgG, IgA, IgM**



Adapted from: Lee & Warkentin. In: Warkentin & Greinacher, eds. *Heparin-Induced Thrombocytopenia*, 3rd edn. New York: Marcel Dekker, 2004

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## Iceberg Model

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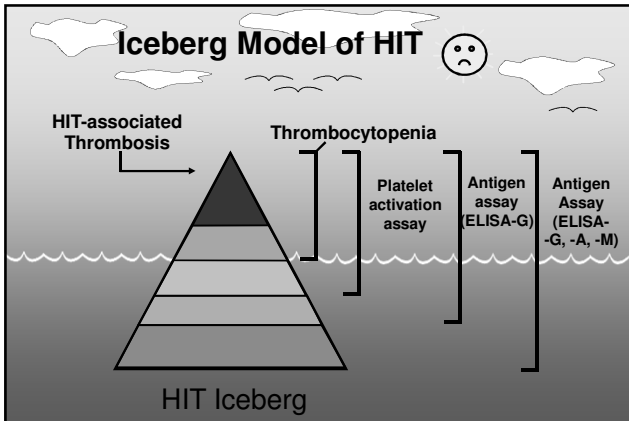
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# IgG-specific EIA's

Warkentin et al. *J Thromb Haemost* 2009 Oct 10 [Epub ahead of print]

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PF4-dependent ELISAs			
Assay	PF4 (source)	Polyanion	Ab classes
<b>Diagnostica Stago</b> Asserachrom HPIA	Recombinant	Heparin	IgG/A/M
<b>GTI Diagnostics</b> PF4 Enhanced PF4 IgG	Platelets (outdated)	Polyvinyl sulfonate	IgG/A/M <b>IgG</b>
<b>HYPHEN BioMed</b> Zymutest HIA IgGAM -IgG -IgA -IgM	Platelet lysate	Heparin bound to protamine	IgG/A/M <b>IgG, IgA, or IgM</b>
<b>Research ELISAs</b> e.g. McMaster	Platelets (outdated)	Heparin	IgG/A/M <b>IgG, IgA, or IgM</b>

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### 4T's Scoring System for HIT

- Thrombocytopenia
- Timing
- Thrombosis (or other sequelae)
- oTher cause for thrombocytopenia not evident

Lo GK et al. *J Thromb Haematol* 2006.

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### 4T's Scoring System: *Low: 0-3* *Intermediate: 4-5* *High: 6-8*

- Thrombocytopenia  
**0, 1, or 2**
- Timing  
**0, 1, or 2**
- Thrombosis (or other sequelae)  
**0, 1, or 2**
- oTher cause for thrombocytopenia not evident  
**0, 1, or 2**

Lo GK et al. *J Thromb Haematol* 2006.

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### 4T's Scoring System: Max = 8

- Thrombocytopenia  
**2 = >50% fall but nadir >20**
- Timing  
**2 = onset day 5-10, or <1 day (hep past 30d)**
- Thrombosis (or other sequelae)  
**2 = new thrombosis, skin necrosis,  
or anaphylactoid reaction**
- oTher cause for thrombocytopenia not evident  
**2 = no other cause evident**

Lo GK et al. *J Thromb Haematol* 2006.

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## What is HIT?

- Intermediate or High Score
- Heparin-dependent, platelet-activating antibodies (positive serotonin release assay)
- **NEGATIVE ELISA—rules out HIT**
- **STRONG POS ELISA (int/high)—likely HIT**

Lo GK et al. *J Thromb Haematomol* 2006.

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## HIT Overdiagnosis

- **PF4-dependent immunoassays and inferential detection of HIT antibodies.**

Warkentin TE. *J Thromb Haemost* 2007

- **What is the potential for overdiagnosis of HIT?**

Lo GK, Sigouin CS, Warkentin TE.  
*Am J Hematol* 2007

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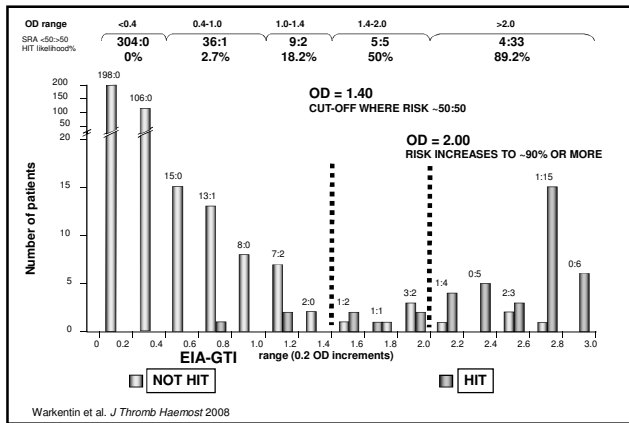
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## REPORTING OF EIA's

- OD <0.40  
~0%
- OD 0.40-1.0  
~5%
- OD 1.0-1.4  
~20%
- OD 1.4-2.0  
~50%
- OD >2.0  
~90%

**Predictivity  
for +SRA  
increases  
as the optical  
density (OD)  
levels increase**

Warkentin et al. *J Thromb Haemost* 2008

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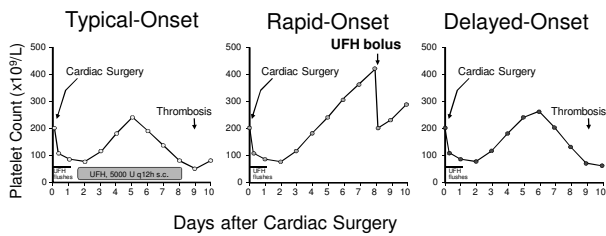
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## 3 Presentations of HIT



Warkentin *Br J Haematol* 2003; 121: 535

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## Delayed-onset HIT

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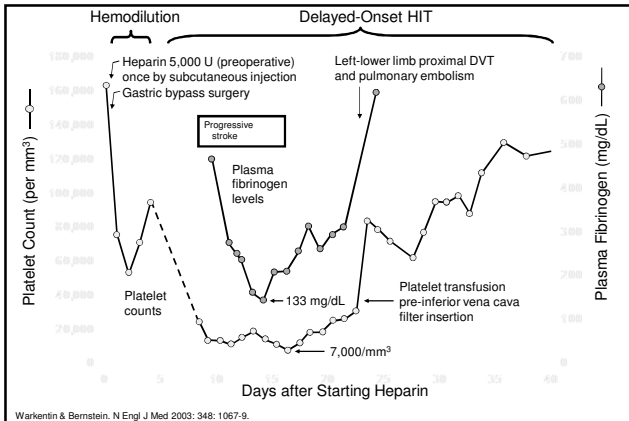
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# Treating HIT

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- ## Six HIT Treatment Principles
- **Do's**
    - Stop Heparin
    - Switch to alternate anticoagulant
      - (Danaparoid\*)
      - Lepirudin
      - Argatroban (Fondaparinux\*)
      - (Bivalirudin\*)
  - **Don'ts**
    - No warfarin (Vit K if warfarin given)
    - No prophylactic platelets
  - **Diagnostics**
    - HIT antibodies
    - Ultrasound for lower-limb DVT
- \* not approved for treatment of HIT in the U.S.

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# Limb Loss in HIT

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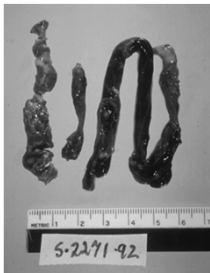
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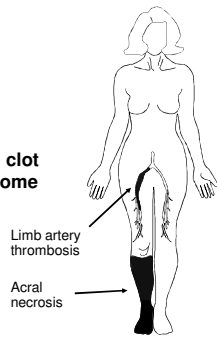
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## Limb Artery Thrombosis in HIT



White clot syndrome



Warkentin *J Crit Illn* 2002

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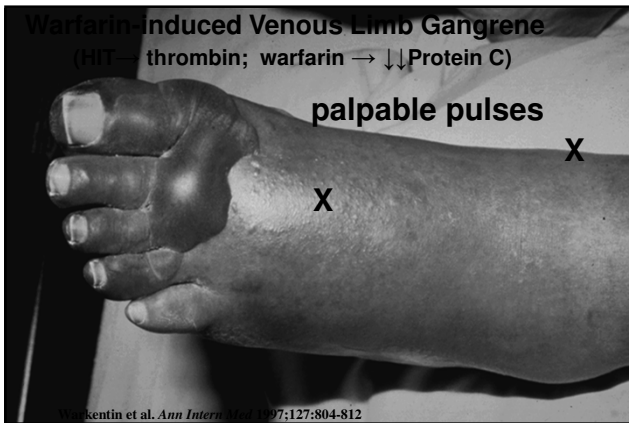
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## Warfarin-Induced Venous Limb Gangrene (HIT → thrombin; warfarin → ↓↓Protein C)



Warkentin et al. *Ann Intern Med* 2007;127:804-812

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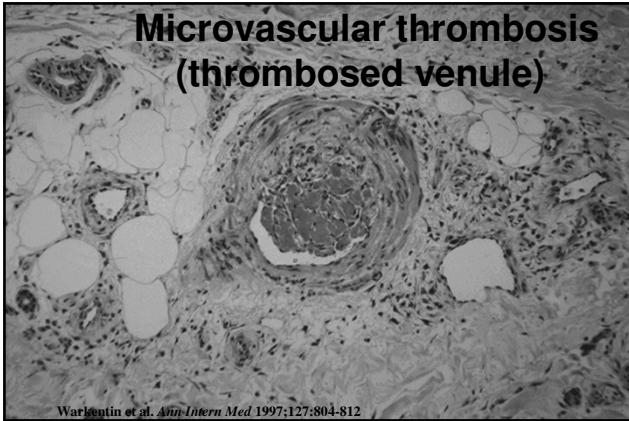
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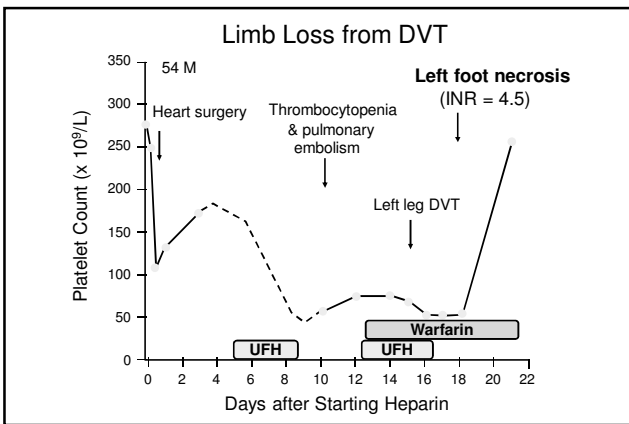
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**Warfarin is ineffective and even deleterious in HIT**

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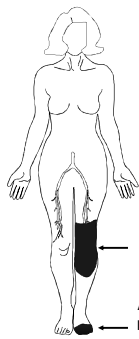
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### Limb Loss from Venous Limb Gangrene

**Elevated INR  
(> 3.5)**  
**Surrogate marker  
for very low  
Protein C levels**



DVT  
Acral necrosis  
**Coumarin-induced venous limb gangrene**

Modified from: Warkentin. *Transfus Med Rev* 1996

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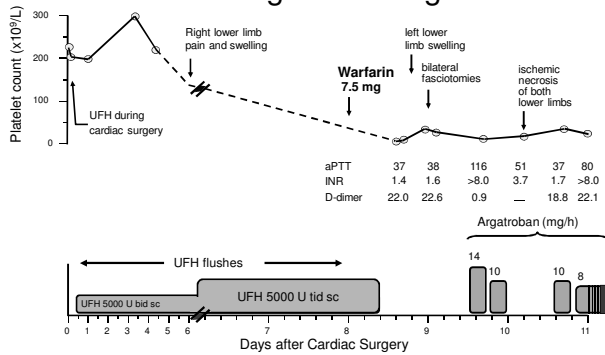
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### Limb Gangrene during DTI



Warkentin. *J Thromb Haemost* 2006; 4: 894-6.

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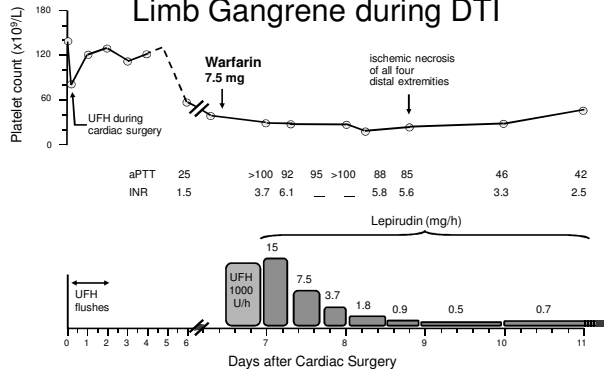
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### Limb Gangrene during DTI



Warkentin. *J Thromb Haemost* 2006; 4: 894-6.

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**Warfarin: inimical to successful HIT Rx**

**Warfarin is not an inhibitor**

HIT is a hypercoagulability state

**Warfarin causes protein C depletion**

PC protects small vessels from thrombin

**Warfarin prolongs the APTT**

Underdosing of lepirudin and argatroban

Important reasons to give vitamin K

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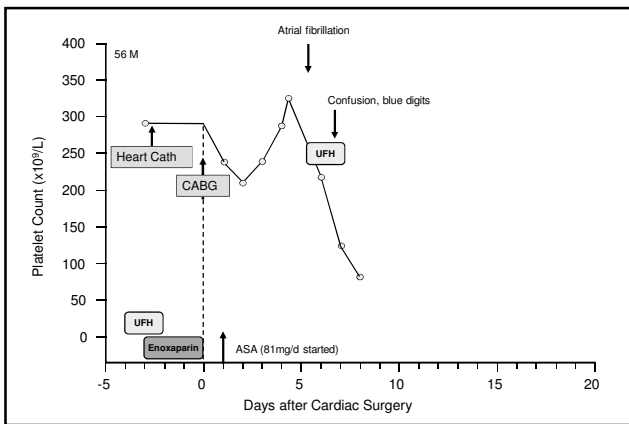
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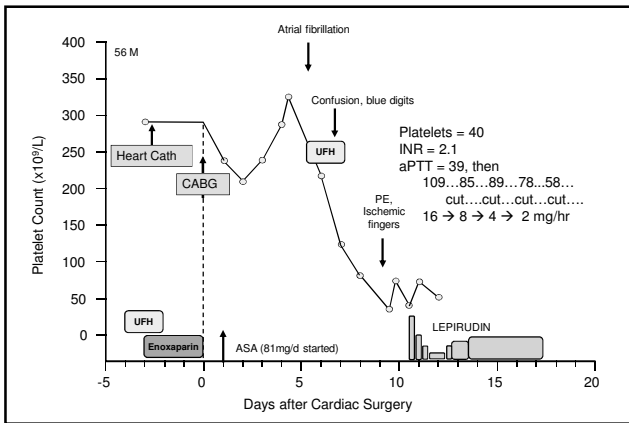
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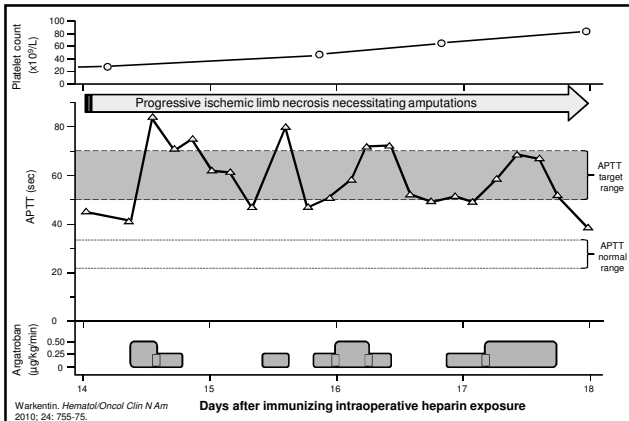
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### HIT Paradoxes

- Clinical
  - Thrombosis 'caused' by anticoagulant
  - Thrombosis despite thrombocytopenia
  - Adrenal hemorrhage = adrenal vein thrombosis
- Diagnosis
  - Overdiagnosis (many "HIT" patients are not)
- Treatment
  - Stop heparin → thrombosis risk persists/increases?
  - Warfarin → microthrombosis in HIT
  - Heparin re-exposure after Abs gone → okay
  - Bad HIT hard to treat with DTIs (PTT confounding)

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### Fondaparinux for HIT Studies with ≥5 Patients and + Lab Testing

	N (% with HIT-thrombosis)	New Thrombosis	Major Bleeding
Kuo & Kovacs <i>Thromb Haemost</i> 2005	N=5 (100%)	0/5 (0%)	0/5 (0%)
Lobo et al. <i>Thromb Haemost</i> 2007	N=7 (86%)	0/7 (0%)	0/7 (0%)
Grouzi et al. <i>Clin Appl Thromb Haemost</i> 2009	N=24 (58%)	0/36 (0%)	0/36 (0%)
<b>Pooled data</b>	<b>N=36 (69%)</b>	<b>0/36 (0%)</b>	<b>0/36 (0%)</b>

35/36 patients had thrombosis; 25/36 (69%) had HIT-associated thrombosis, i.e., in 10 thrombosis preceded HIT

Warkentin. *Hematol/Oncol Clin N Am* 2010; 24: 755-75.

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**Fondaparinux  
Paradox:  
Can it cause HIT?  
Can it treat HIT?**

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**HIT Prevention:  
Do Heparin  
Preparations Differ  
in their Risk of HIT?**

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**Frequency of HIT (Platelets < 150 x 10<sup>9</sup>/L)**

	<u>UFH</u>	<u>Enoxaparin</u>	<i>P</i>
<b>HIT</b>	<b>9/332 (2.7%)</b>	<b>0/333 (0%)</b>	<b>&lt;0.001</b>
+ SRA*	19/192 (10%)	5/170 (3%)	0.010

• UFH more immunogenic than LMWH

\* SRA = serotonin release assay

Warkentin et al. *N Engl J Med* 1995;332:1330 (see also Warkentin et al. *J Lab Clin Med* 2005;146:341-346)

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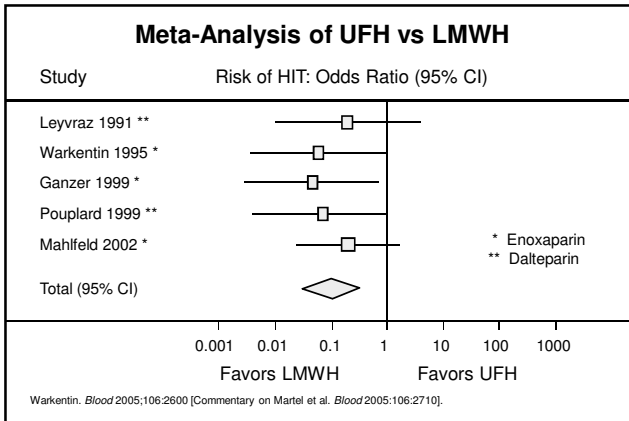
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**Risk of HIT:  
UFH >> LMWH  
(OR = 0.10)**

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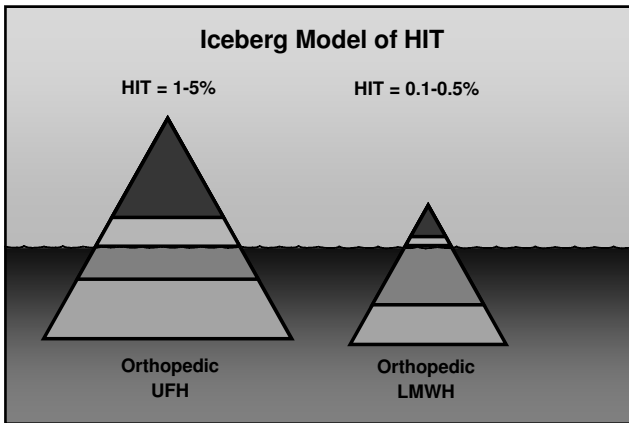
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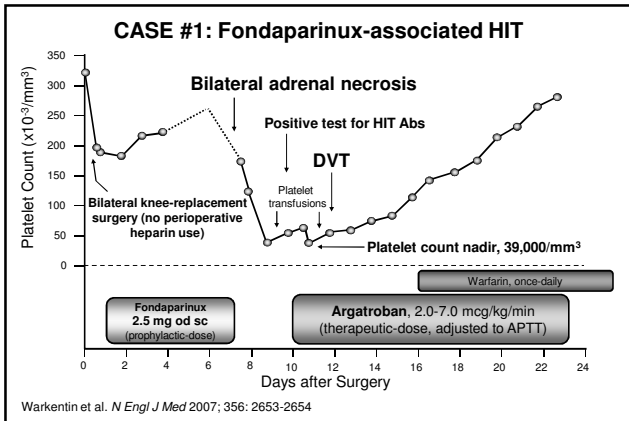
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**Fondaparinux-associated HIT: 4 Cases**

- 3 cases (“delayed-onset” HIT mechanism)
  - 2006<sup>1</sup> (U.S.A.)
  - 2007<sup>2</sup> (Italy)
  - 2010<sup>3</sup> (U.S.A)
- 1 case (“cross-reactivity” HIT mechanism)
  - 2008<sup>4</sup> (Canada)

<sup>1</sup> Warkentin et al. *N Engl J Med* 2007; 356: 2653-4.  
<sup>2</sup> Rota et al. *Thromb Haemost* 2008; 99: 779-81.  
<sup>3</sup> Salem et al. *Thromb Haemost* 2010; in press.  
<sup>4</sup> Alsaleh et al. *Am J Hematol* 2008 Aug 19. [Epub ahead of print]

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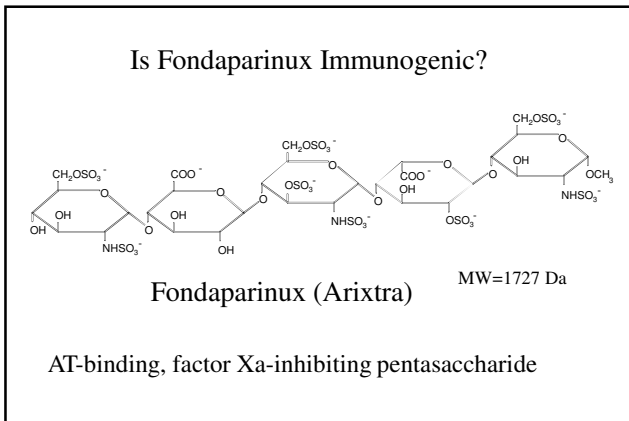
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## Is There Evidence that Fondaparinux is Potentially Immunogenic?

Warkentin et al. *Blood* 2005; 106: 3791-6.  
Pouplard et al. *J Thrombo Haemost* 2005; 3: 2813-5.

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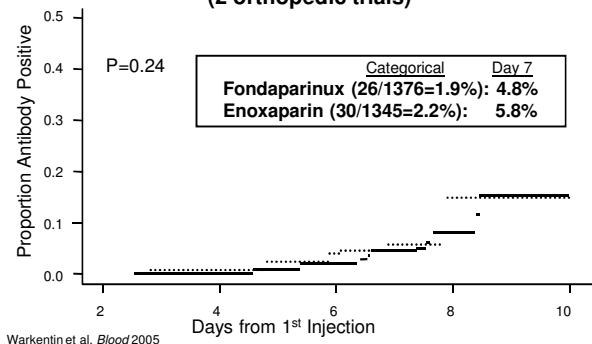
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### Anti-PF4/heparin antibodies (2 orthopedic trials)



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## Do Antibodies that are Generated during Fondaparinux Therapy Increase Binding of PF4 to Platelets?

“Cross-reactivity”– when a polyanion increases binding of HIT antibodies to PF4 or increases platelet activation induced by HIT antibodies

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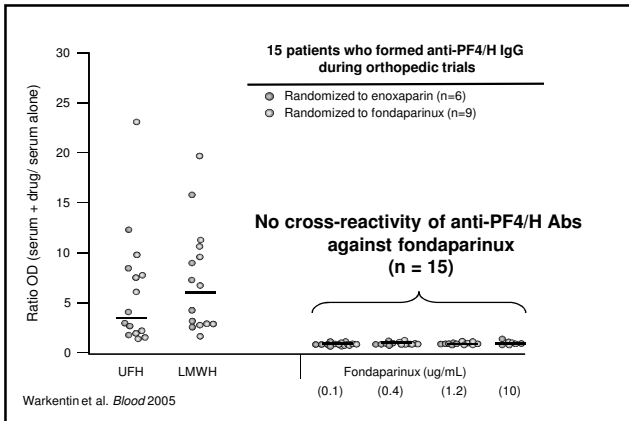
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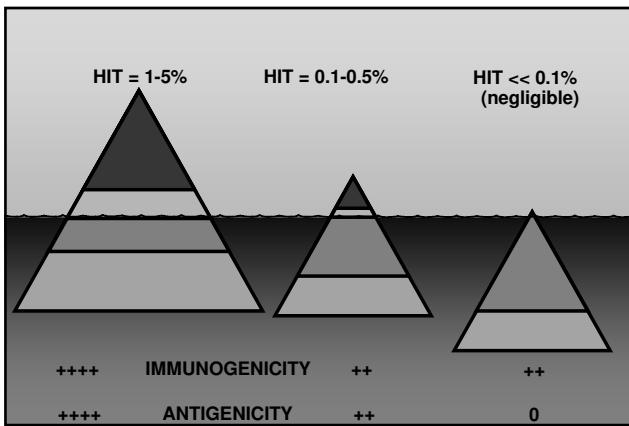
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### Hierarchy of Risks

Immuno- genicity	Antigen- icity	↓	
++++	++++	UFH	Risk of HIT ~ 1/100
++	++	LMWH	Risk of HIT ~ 1/1,000
++	-	Fondaparinux	Risk of HIT very low (perhaps only by delayed-HIT mechanism) ? ~1/10,000

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Question #1

HIT is associated with which of the following:

- (1) Pulmonary embolism
  - (2) Adrenal hemorrhagic infarction
  - (3) Arterial thrombosis
  - (4) Petechial hemorrhage
  - (5) Family history of HIT
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- (A) 1 and 3
  - (B) 1, 2, and 3
  - (C) 4
  - (D) all of the above
  - (E) none of the above

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Question #2

A critically-ill patient develops thrombocytopenia 2 days after admission, and while receiving UFH prophylaxis. There was heparin exposure 2 months earlier, and so a test for HIT antibodies is performed (negative). Three days later the platelet count remains the same. There is no evidence for thrombosis. Should a repeat test for HIT antibodies be done?

- (A) No: the patient likely has persistence of non-HIT thrombocytopenia and a subsequent positive test is most likely to represent a "false-positive".
- (B) Yes: the platelet count should have started rising, and so this is a high pre-test probability situation for HIT.

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Question #3

Which statement is not true about warfarin as a treatment for HIT?

- (1) Warfarin blocks thrombin generation in HIT.
- (2) Warfarin lowers protein C levels in HIT.
- (3) Warfarin lowers factor II levels in HIT.
- (4) Warfarin should be avoided/postponed in a patient with acute HIT.
- (5) Warfarin can be cautiously given once HIT has resolved.

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Question #4

Danaparoid (mixture of anticoagulant glycosaminoglycans) is used in many countries to treat HIT, but is not available in the U.S. and has never been FDA-approved for treatment of HIT.

What drug most resembles danaparoid in terms of: (a) relatively long half-life; (b) predominant anti-factor Xa effect; (c) lack of INR or APTT prolongation?

- (A) Lepirudin
- (B) Argatroban
- (C) Bivalirudin
- (D) Fondaparinux
- (E) Rivaroxaban

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