Heparin-Induced Thrombocytopenia (HIT)

ISTH Advanced Course, Cascais, Portugal
Sat 15 Mar 2014

Dr. Ted Warkentin

Professor, Depts. of Pathology & Molecular Medicine, and Medicine, McMaster University
Hematologist and Regional Director, Transfusion Medicine, Hamilton, Ontario, Canada
## Disclosures

<table>
<thead>
<tr>
<th>Organization</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GlaxoSmithKline</td>
<td>research funding</td>
</tr>
<tr>
<td>W. L. Gore</td>
<td>consulting, research funding</td>
</tr>
<tr>
<td>Taylor &amp; Francis</td>
<td>royalties</td>
</tr>
<tr>
<td>Instrumentation</td>
<td></td>
</tr>
<tr>
<td>Laboratory</td>
<td>lecture honoraria</td>
</tr>
<tr>
<td>Pfizer Canada</td>
<td>lecture honoraria</td>
</tr>
<tr>
<td>Law firms</td>
<td>medical-legal testimony</td>
</tr>
</tbody>
</table>

- Specific therapeutic recommendations that are **not** FDA-labeled indications ([treatment of HIT: danaparoid & fondaparinux](#))
Objectives

Learning Objectives-- Review:

THEME #1  Characteristic timing features of HIT
THEME #2  Strong reactivity at buffer control
THEME #3  Treatment of HIT: Indirect Xa inhibitors vs DTIs
Warkentin TE & Greinacher A. Heparin-Induced Thrombocytopenia. 5th edn. CRC Press, Boca Raton, FL, USA 2013.
HIT is Prothrombotic
HIT is Prothrombotic

- Both venous and arterial thrombosis
- ~50-70% of HIT patients develop thrombosis

<table>
<thead>
<tr>
<th></th>
<th>HIT</th>
<th>Non-HIT</th>
<th>RR (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prox DVT</td>
<td>8/18 (44%)</td>
<td>26/647 (4%)</td>
<td>11 (6, 21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulm emb</td>
<td>2/18 (11%)</td>
<td>2/647 (0.3%)</td>
<td>36 (5, 241)</td>
<td>0.004</td>
</tr>
<tr>
<td>VTE</td>
<td>9/18 (50%)</td>
<td>28/647 (4%)</td>
<td>12 (6, 21)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>


VTE = venous thromboembolism (proximal DVT and/or pulmonary embolism)
HIT “Paradox”
### Postoperative DVT: UFH vs Placebo

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Odds Ratio (&amp; 95% CI)</th>
<th>Risk Reduction (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td>67% ± 4</td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td>65% ± 7</td>
</tr>
<tr>
<td>Urologic</td>
<td></td>
<td>75% ± 15</td>
</tr>
<tr>
<td>ANY TYPE</td>
<td></td>
<td><strong>68% ± 3</strong></td>
</tr>
</tbody>
</table>

Heparin $\downarrow$ thrombosis $\sim 68\%$; but HIT $\uparrow$ thrombosis $\sim 12x$; THUS, HIT $\uparrow$ thrombosis $\sim 4x$ (vs never getting heparin)

UFH reduces clots

Baseline risk

HIT $\uparrow$ clots $\sim 4X$ vs no UFH given (+ unusually severe clots)
UFH reduces clots

Baseline risk

HIT \uparrow \text{clots} \approx 4X vs no UFH given (+ unusually severe clots)

5% limb loss in HIT!
HIT: a “Clinical-Pathologic” Syndrome

<table>
<thead>
<tr>
<th>“Clinical”</th>
<th>“Pathologic”</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <em>Thrombocytopenia</em></td>
<td></td>
</tr>
<tr>
<td>• <em>Thrombosis</em> (≥50%, ven &gt; art)</td>
<td></td>
</tr>
<tr>
<td>• <em>Timing</em> (proximate heparin)</td>
<td></td>
</tr>
<tr>
<td>• oTher cause(s) less likely</td>
<td></td>
</tr>
</tbody>
</table>

_The 4 T’s_
_(pre-test scoring system)_

Warkentin, Chong, Greinacher. _Thromb Haemost_ 1998; 79: 1
4T’s
# 4Ts Scoring System for HIT

<table>
<thead>
<tr>
<th></th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td>Thrombocytopenia</td>
<td>&gt;50% fall (nadir &gt;20)</td>
<td>30-50% fall or nadir 10-19; or &gt;50% (surgery)</td>
</tr>
<tr>
<td><strong>T</strong></td>
<td>Timing c/w HIT</td>
<td>Yes (day 5-10); or &lt;d1 (hep 5-30d)</td>
<td>Yes (&gt;d10); or &lt;d1 (31-90d)</td>
</tr>
<tr>
<td><strong>T</strong></td>
<td>Thrombosis</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>Other Dx</td>
<td>No</td>
<td>Possible</td>
</tr>
</tbody>
</table>

High probability: 6 – 8 points  
Moderate probability: 4 – 5 points  
Low probability: 0 – 3 points → **HIGH NEG PREDICTIVE VALUE**

HIT: a “Clinical-Pathologic” Syndrome

“The 4 T’s”
(pre-test scoring system)

Two Types of Assays

Platelet Activation Assays

- SRA
- HIPA

PF4-dependent Immunoassays

- EIA (ELISA)
- PaGIA

instrumentation-based
Serotonin-Release Assay (SRA)

Washed platelet activation assay

Washed with apyrase (preserves reactivity to ADP)

Resuspended in buffer (physiological Ca++, Mg++)

↓ Inhibitors of HIT Ab-induced plt act’n (IgG, fibronectin)

PF4/heparin complexes

HIT-IgG antibodies

Radiolabeled $^{14}$C-serotonin released released from normal donor platelets

Sheridan D, Carter C, Kelton JG. A diagnostic test for HIT.

Polyspecific EIA systems detect all 3 classes: IgG, IgA, IgM. IgG-specific EIA systems generally provide higher specificity.

Higher ODs in the EIAs of SRA+ (or HIPA+) status increase the probability of SRA+ status.

EIA-IgG/A/M result (OD units):<0.4  0.4-1.0  1.0-1.5  1.5-2.0  >2.0
Probability of SRA+ status: <1%  ~5%  ~25%  ~50%  ~90%
EIA Optical Density (OD) Levels Strongly Predict for Platelet-activating Antibodies
Clinical Picture of HIT
Clinical Picture of HIT

VENOUS
- DVT
  - lower limb
  - upper limb (CVC)
- PE
- Adrenal vein (hemorrh.)
- Cerebral venous (dural sinus)

ARTERIAL
- Limb > CVA > MI

SKIN NECROSIS
- at sc injection sites

MICROVASCULAR
- Warfarin necrosis
- Venous limb gangrene
- Central skin necrosis
- DIC

ANAPHYLACTOID Rx
- Post-iv UFH bolus
- Post-sc LMWH
- Chills/rigors/fever
- Dyspnea/chest pain
- Flushing
- Transient global amnesia

Without thrombosis

Thrombosis

Nadir platelet count (x 10^-9/µL)

Number of cases (arbitrary scale)
Upper-limb DVT: role of vascular injury
### Upper-limb DVT Frequency in HIT

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Thrombosis</th>
<th>Thrombosis Rate in:</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with central line</td>
<td>Upper-limb DVT</td>
<td>14/145 (9.7%)</td>
<td>3/484 (0.6%)</td>
<td>17.1 (4.9-60.5)</td>
</tr>
<tr>
<td>Patients without central line</td>
<td>Upper-limb DVT</td>
<td>0/145 (0%)</td>
<td></td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

All 14 upper-limb DVTs occurred at site of central venous catheter:

- Right, n=12
- Left, n=2

P = 0.011

“We conclude that a localizing vascular injury (catheter use) and a systemic hypercoagulability state (HIT) **interact** to explain upper-limb DVT complicating HIT.”

Hong et al. *Blood* 2003;101:3049-51
Adrenal hemorrhage (hemorrhagic necrosis)

Adrenal vein thrombosis $\rightarrow$ secondary hemorrhage

Hematologist $\rightarrow$ 3 causes of adrenal hemorrhage

1. HIT $\rightarrow$ 2-3% of HIT; 50% are unilateral
   50% are bilateral (adrenal failure)
2. APS $\rightarrow$ can be a feature of CAPS
3. Sepsis $\rightarrow$ Waterhouse-Friderichsen syndrome
Warfarin-induced Venous Limb Gangrene
(HIT → thrombin; warfarin → ↓↓ Protein C)

- palpable pulses
- Macrothrombosis (DVT) + microthrombosis (venules)

Profound Disturbance in Procoagulant-Anticoagulant Balance

1. HIT: ↑↑ Thrombin
2. Warfarin: ↓↓ PC
67-year-old Female with Respiratory Arrest Post-Heparin Bolus

Aortic valve replacement surgery

Sternal wound infection

PICC line heparin flush followed by respiratory arrest and bleeding (accidental heparin overdose)

Resp. arrest

Nadir = 32 x 10⁹/L

S.C. UFH 5000 U BID

Danaparoid

Acute Systemic (Anaphylactoid) Reactions to iv Bolus Heparin

- Onset within 5 - 30 minutes
- Chills, rigors, fever
- Tachycardia, hypertension
- Tachypnea, dyspnea
- Chest pain or tightness
- Diaphoresis, flushing
- Nausea, vomiting, diarrhea
- Sudden death
- Transient global amnesia

**Death in ICU Trial**

**TIMELINE OF POST-UFH BOLUS CARDIAC ARREST**

- **0518h** platelet count = 427
- **1050h** UFH 5000 U i.v. bolus given
- **1100h** UFH 1600 U/hr i.v. given x 30min
- **1105h** Onset bradycardia, severe ↓BP, ECG changes of acute MI;
- **1126h** CPR for cardiac arrest
- **1131h** Death

[No repeat platelet count performed]  
[No post-mortem examination performed]

**“fatal presumed anaphylactoid reaction”**

---

Interpreting Platelet Counts Post-Surgery
Interpreting Platelet Counts

81 F

Previous Hx of DVT 10y ago

Colon resection

Day 3 platelet count ~95
IS THIS HIT?

Heparin s.c. 5000 U bid
Platelet Counts After Surgery

Preoperative Platelet Counts

Postoperative Platelet Counts (mean ± 2 SD)

Mean ±2 SD

Postoperative thrombocytosis

Early postoperative thrombocytopenia

>50% ↓

e.g., d8

500 → 200

Day of Postoperative Platelet Count Nadir

Orthopedic surgery data

Day of Platelet Count Nadir (Surgery = Day 0)

Potentially abnormal on/after day 5

32%
55%
13%
<1%
0%
0%

Day of Postoperative Platelet Count Nadir

Day of Postoperative Platelet Count Nadir

Comparison: orthopedic vs cardiac

Potentially abnormal on/after day 5

Interpreting Platelet Counts

81 F

Colon resection

Day 3

nadir

Platelet count fall on **day 5** of heparin (first day of heparin = day 0)

Day 9 platelet count ~20

IS THIS HIT?

Heparin s.c. 5000 U bid

Days after surgery

Platelet count (x10⁹/L)
Timing of HIT
All had previous heparin exposure within last 100 days

Timing of Typical-Onset HIT

HIT Antibodies are Transient

Enzyme-immunoassay

Serotonin release assay

Platelet count fall began on day 6 of heparin treatment. Platelet count nadir on day 11 (60 x 10⁹/L).

Abrupt fall in platelet count from 179 to 49 x 10⁹/L with repeat use of heparin (day 30).

Typical onset of HIT:
- Platelet count fall began on day 6 of heparin treatment.
- Platelet count nadir on day 11 (60 x 10⁹/L).

Rapid onset of HIT:
- Abrupt fall in platelet count from 179 to 49 x 10⁹/L with repeat use of heparin (day 30).

## Timing of Onset of HIT

<table>
<thead>
<tr>
<th>Typical</th>
<th>Rapid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibodies newly formed</td>
<td>Antibodies already present</td>
</tr>
<tr>
<td>Timing day 5 to 10</td>
<td>Timing immediate (&lt;24 h)</td>
</tr>
<tr>
<td>irrespective of history</td>
<td>Recent heparin (past 100 days) crucial</td>
</tr>
<tr>
<td>of previous heparin</td>
<td></td>
</tr>
</tbody>
</table>

What is the explanation for this speedy (5d) “primary” immunization?
HIT is a misdirected host defense

One antibody specificity recognizes a large variety of bacteria = innate humoral immune defense

HIT is a misdirected host defense
Why do Platelets Fall After Stopping UFH?

Day 9 platelet count ~20
IF THIS IS HIT, why are platelets falling off heparin?

Colon resection

Heparin s.c.
5000 U bid
Delayed-Onset HIT
Delayed-onset HIT:

Definition

platelet count begins to fall,$^1$ or continues to fall,$^2$ despite stopping all heparin


**Immunizing heparin exposure**

**Postoperative thrombocytopenia, day 1-4 (hemodilution, platelet consumption)**

**UFH (intra- or peri-op)**

± UFH or LMWH prophylaxis ("delayed-onset HIT" if off heparin)

**Macrovascular to Microvascular Thrombosis**

**Consumptive coagulopathy intensifies during 2nd week**

INR ↑, PTT ↑, fibrinogen ↓

Progressive platelet activation and PF4 release (vicious cycle)

Protein C pathway activation

Hemodilution

Platelet Count (per mm$^3$)

Days after Starting Heparin

Delayed-Onset HIT

Platelet counts

Plasma fibrinogen levels

Platelet transfusion pre-inferior vena cava filter insertion

Heparin 5,000 U (preoperative) once by subcutaneous injection

Gastric bypass surgery

Left-lower limb proximal DVT and pulmonary embolism

Progressive stroke

Plasma fibrinogen levels

Heparin Rechallenge (Previous HIT)
Heparin Rechallenge

• **N=20 patients with previous HIT**
  — 0/3 medical pts formed Abs (despite full course of hep!)
  — 11/17 (65%) surgical pts formed anti-PF4/H Abs

• **8/11 (73%) anti-PF4/H Ab+ pts became +SRA**
  — high SRA+ frequency (? memory for plt-activating Abs)
  — 1/8 pts → recurrent HIT (despite no postop heparin!)
  HOW IS THIS POSSIBLE?

• **Thus, reasonable to consider heparin re-exposure, especially for cardiac or vascular surgery**
  (caveat: delayed-onset HIT remains possible)

Two Episodes of HIT

A

Cardiac surgery (heparin) exposure

Onset of HIT, day 7
DVT and PE

Nadir = 26 (day 10)

1st Episode of HIT (1998)

Danaparoid, therapeutic-dose with transition to warfarin therapy

B

Cardiac surgery (heparin re-exposure)

Onset of HIT, day 7
DVT by US

Nadir = 20 (day 10)

2nd Episode of HIT (2009)

Fondaparinux, therapeutic-dose (2.5 mg per day)

Fondaparinux, therapeutic-dose (7.5 mg per day)

SRA+ on Day 6, Delayed-onset HIT Abs, No Fx X-Reactivity

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Previous HIT Episode</th>
<th>Weeks to rechallenge</th>
<th>Heparin Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>G: **</td>
<td>132</td>
<td>G: **</td>
</tr>
<tr>
<td>8</td>
<td>A: **</td>
<td>180</td>
<td>A: **</td>
</tr>
<tr>
<td>15</td>
<td>M: *</td>
<td>515</td>
<td>M: *</td>
</tr>
<tr>
<td>16</td>
<td>G: •</td>
<td>422</td>
<td>G: •</td>
</tr>
<tr>
<td>20</td>
<td>A: •</td>
<td>20</td>
<td>A: •</td>
</tr>
<tr>
<td>10</td>
<td>M: •</td>
<td>37</td>
<td>M: •</td>
</tr>
<tr>
<td>11</td>
<td>A: *</td>
<td>47</td>
<td>A: *</td>
</tr>
</tbody>
</table>

Antibody OD:
- 0.45 - 0.99
- 1.00 - 1.99
- ≥2.00
Re-exposure to heparin in uremic patients requiring hemodialysis with heparin-induced thrombocytopenia


*Kobe Research Projects on Thrombosis and Haemostasis, Kobe; †Hyogo Prefectural Awaji Hospital, Sumoto; ‡Hyogo Cancer Center, Akashi; and §Kobe City Medical Center West Hospital, Kobe, Japan

Wanaka et al. J Thromb Haemost 2010
Typical-onset HIT
Rapid-onset HIT
Delayed-onset HIT
Persisting HIT
Spontaneous HIT
PERSISTING HIT, i.e., Duration of HIT >30 days

Cardiac surgery

Onset of HIT, d6

Platelet count nadir = 13, d11

UFH (70,000 IU)

Kopolovic & Warkentin. CMAJ 2014 in press.
Results of SRA (d8 serum)

Onset of HIT, d6

Platelet count nadir = 13
d11

Kopolovic & Warkentin. CMAJ 2014 in press.
Spontaneous HIT (or Autoimmune HIT) 
DEFINITION 
disorder mimicking HIT both clinically and serologically except for no proximate heparin

62-y.o. male admitted for acute thrombotic stroke
Platelet count = 65 x 10^9/L
No recent hospitalizations, no previous heparin

Platelet transfusions
1U 1U 1U 2U

Serotonin-release assay and enzyme-immunoassays (3 assays):
POSITIVE on day 0 and day 14

Platelet count nadir, 27 x 10^9/L

Mechanical thrombectomy
Intra-arterial t-PA (15 mg)
UFH 1000 IU
Complicated by multiple rethromboses requiring multiple thrombectomies

ASA 325 mg daily x 5
Warfarin
Fondaparinux 7.5 mg SC daily x 3
Argatroban IV target 2-times baseline APTT

Spontaneous HIT Syndrome

Treatment of HIT
Six HIT Treatment Principles

• 2 Do’s
  Stop Heparin (LMWH, flushes, ...)
  Give alternative anticoagulant

• 2 Don’ts
  No warfarin (vit K if warfarin given)
  No prophylactic platelet transfusions

• 2 Diagnostics
  Test for HIT antibodies
  Ultrasound for lower-limb DVT

Adapted from Warkentin TE. Circulation. 2004; Warkentin et al. Chest 2008
## AT3-Dependent Anti-FXa Inhibitors vs DTIs

<table>
<thead>
<tr>
<th></th>
<th>Anti-FXa Inhibitors (Danaparoid, Fondaparinux)</th>
<th>DTIs* (Argatroban, Lepirudin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-HIT indications</strong></td>
<td>√ Numerous</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>√ Long (fonda ~17h)</td>
<td>Short (&lt;1h)</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>√ Prophylactic/therapeutic</td>
<td>Therapeutic only</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>√ Direct (anti-FXa levels)</td>
<td>Indirect (PTT)</td>
</tr>
<tr>
<td><strong>Effect on INR</strong></td>
<td>√ No effect</td>
<td>↑INR (esp. arg)</td>
</tr>
<tr>
<td><strong>Protein C pathway</strong></td>
<td>√ No effect</td>
<td>? Inhibit APC gen’n</td>
</tr>
<tr>
<td><strong>Reversibility</strong></td>
<td>√ No (covalent AT3-Xa)</td>
<td>Yes (non-covalent)</td>
</tr>
<tr>
<td><strong>Platelet activation</strong></td>
<td>√ Inhibits (danap only)</td>
<td>No effect</td>
</tr>
<tr>
<td><strong>Drug clearance</strong></td>
<td>Renal</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Inhibit clot-bound IIa</strong></td>
<td>No</td>
<td>√ Yes</td>
</tr>
<tr>
<td><strong>Approved for HIT</strong></td>
<td>√ Yes (danaparoid)</td>
<td>√ Yes</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>√ Low (fondaparinux)</td>
<td>High</td>
</tr>
</tbody>
</table>

Adapted from: Warkentin TE. *Hematology Am Soc Hematol Educ Program 2011*

*Desirudin & bivalirudin are potential options
Macrovascular to Microvascular Thrombosis

Postoperative thrombocytopenia, day 1-4 (hemodilution, platelet consumption)

Platelet Count (x10^9/L)

UFH (intra- or peri-op)

± UFH or LMWH prophylaxis ("delayed-onset HIT" if off heparin)

Days after Heparin Exposure

Consumptive coagulopathy intensifies during 2nd week
INR ↑, PTT ↑, ↓ fibrinogen
Progressive platelet activation and PF4 release (vicious cycle)
Protein C pathway activation

Immune heparin exposure

HIT-Ab (OD)

Progressive ischemic limb necrosis necessitating amputations

PTT Confounding Argatroban for HIT

Pre-argatroban ↑PTT

Argatroban

Days after immunizing intraoperative heparin exposure

HIT-Associated DIC and “PTT Confounding” of Direct Thrombin Inhibitor (DTI) Therapy of HIT
Simple Rule:
If “baseline” (pre-treatment) PTT is $\uparrow$, PTT-based nomogram is unlikely to be successful ("PTT confounding")
PtT Confounding of DTI Therapy

- Hip fracture
- Surgery
- Admission to ICU
- Profound hypotension (adrenal crisis)
- Bilateral DVT
- Onset of HIT
- PTT = 35 s (ULN)
- 18 = Platelet count nadir

- UFH 5000 U bid sc
- Dalteparin 2500 U once sc then 5000 sc OD
- Arg dosing, mcg/kg/min

Warkentin: “[For] those patients with severe HIT who evince concomitant DIC, their hypercoagulability state can be ‘untreatable’ with the approved DTIs, at least when employing standard PTT monitoring regimens.”

Avoiding Treatment Failure Due to PTT Confounding
Days after starting heparin

DIC → 42
PTT → 42
Fbgn 2.8 → 1.0
PSO₄ neg- >4+

Warfarin given

1. Low platelets
2. Procedure

Danaparoid sodium...adjusted by anti-Xa levels

Platelet count x 10⁹/L ( ) Anti-Xa u/mL ( )

Days after starting heparin

DIC
PTT
27 → 42
Fbgn
2.8 → 1.0
PSO₄
neg- >4+

Ischemic feet

Plt = 17 (falling)

Danaparoid held

0.8
0.6
0.4
0.2

1.0
0.8
0.6
0.4
0.2

1.0
0.8
0.6
0.4
0.2
Fondaparinux for HIT
Studies with ≥5 Patients and +EIA

<table>
<thead>
<tr>
<th></th>
<th>N (% with HIT-thrombosis)</th>
<th>New Thrombosis</th>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kuo &amp; Kovacs 2005</td>
<td>N=5 (100%)</td>
<td>0/5 (0%)</td>
<td>0/5 (0%)</td>
</tr>
<tr>
<td>Lobo et al. 2007</td>
<td>N=7 (86%)</td>
<td>0/7 (0%)</td>
<td>0/7 (0%)</td>
</tr>
<tr>
<td>Grouzi et al. 2009</td>
<td>N=24 (58%)</td>
<td>0/24 (0%)</td>
<td>0/24 (0%)</td>
</tr>
<tr>
<td>Goldfarb &amp; Blostein 2011*</td>
<td>N=8 (75%)</td>
<td>0/8 (0%)</td>
<td>0/8 (0%)</td>
</tr>
<tr>
<td>Warkentin et al. 2011**</td>
<td>N=16 (56%)</td>
<td>0/16 (0%)</td>
<td>1/16 (6%)</td>
</tr>
<tr>
<td><strong>Pooled data</strong></td>
<td>N=60 (67%)</td>
<td>0/60 (0%)</td>
<td>1/60 (1.7%)</td>
</tr>
</tbody>
</table>

* All 8 patients had positive SRA or strong positive EIA (>2.00 OD units)
** All 16 patients had positive SRA (mean EIA = 2.53 OD units)

Prevention of HIT
Meta-Analysis of UFH vs LMWH

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of HIT: Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leyvraz 1991 **</td>
<td></td>
</tr>
<tr>
<td>Warkentin 1995 *</td>
<td></td>
</tr>
<tr>
<td>Ganzer 1999 *</td>
<td></td>
</tr>
<tr>
<td>Pouplard 1999 **</td>
<td></td>
</tr>
<tr>
<td>Mahlfeld 2002 *</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>Common odds ratio = 0.10 (95% CI, 0.03-0.30)</td>
</tr>
</tbody>
</table>

Preventing HIT in the ICU with LMWH (Dalteparin)
Dalteparin versus Unfractionated Heparin in Critically Ill Patients

The PROTECT Investigators for the Canadian Critical Care Trials Group and the Australian and New Zealand Intensive Care Society Clinical Trials Group
PROTECT Trial: main findings
(“as-treated”\(^a\) analysis)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dalteparin (N = 1827)</th>
<th>UFH (N = 1832)</th>
<th>Hazard ratio (95% CI)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal DVT</td>
<td>94 (5.1%)</td>
<td>108 (5.9%)</td>
<td>0.91 (0.68, 1.23)</td>
<td>0.54</td>
</tr>
<tr>
<td>PE (any)(^b)</td>
<td>22 (1.2%)</td>
<td>42 (2.3%)</td>
<td>0.48 (0.27, 0.84)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death (in-hosp.)</td>
<td>396 (21.7%)</td>
<td>446 (24.3%)</td>
<td>0.90 (0.78, 1.04)</td>
<td>0.15</td>
</tr>
<tr>
<td>Bleeding (major)</td>
<td>100 (5.5%)</td>
<td>105 (5.7%)</td>
<td>0.98 (0.73, 1.31)</td>
<td>0.88</td>
</tr>
<tr>
<td>HIT</td>
<td>5 (0.3%)</td>
<td>12 (0.7%)</td>
<td>0.47 (0.16, 1.37)</td>
<td>0.17</td>
</tr>
<tr>
<td>HIT (per-protocol(^c))</td>
<td>3/1566 (0.2%)</td>
<td>12/1561 (0.8%)</td>
<td>0.27 (0.08, 0.98)</td>
<td>0.046</td>
</tr>
</tbody>
</table>

\(^a\) Excludes patients where consent withdrawn, incorrectly randomized, or study drug not given.
\(^b\) Includes all PE’s classified as: “definite”, “probable” or “possible”
\(^c\) Excludes patients with VTE on study entry; includes patients who received study drug \(\geq 2\) d; and who had \(\geq\) technically-adequate noninvasive imaging for DVT.

Heparin Use and HIT Post-Cardiac Surgery

<table>
<thead>
<tr>
<th>Year</th>
<th>UFH (0/171, 0.0%)</th>
<th>UFH (6/157, 3.8%)</th>
<th>UFH (3/104, 2.9%)</th>
<th>UFH (2/176, 1.1%)</th>
<th>LMWH (1/201, 0.5%)</th>
<th>LMWH (7/1502, 0.5%)</th>
<th>LMWH (8/1703, 0.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

80% reduction
Objectives

Learning Objectives-- Review:

THEME #1  Characteristic timing features of HIT
THEME #2  Strong reactivity at buffer control
THEME #3  Treatment of HIT: Indirect Xa inhibitors vs DTIs