

HEPARIN-INDUCED **THROMBOCYTOPENIA:**

Management and Challenges

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GOALS

- Identify the main diagnostic criteria for heparin-induced thrombocytopenia (HIT)
- Understand the BWH strategy for therapeutic management
- Identify the main points of controversy

HEPARIN-INDUCED THROMBOCYTOPENIA

- A serious complication of unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) therapy
- Antibody-mediated decrease in platelets
- Paradoxically associated with thrombosis

TERMINOLOGY

Type I HIT

- Non-immune mechanism
- Mild platelet decrease
- Benign
- 1-4 day onset
- No treatment indicated
- No need to stop heparin

Type II HIT

- Immune-mediated mechanism
- Significant platelet decrease
- Significant sequelae
- 5-14 day onset
- Treatment indicated?
- Must stop heparin
- HITT

MALIGNANT HITT

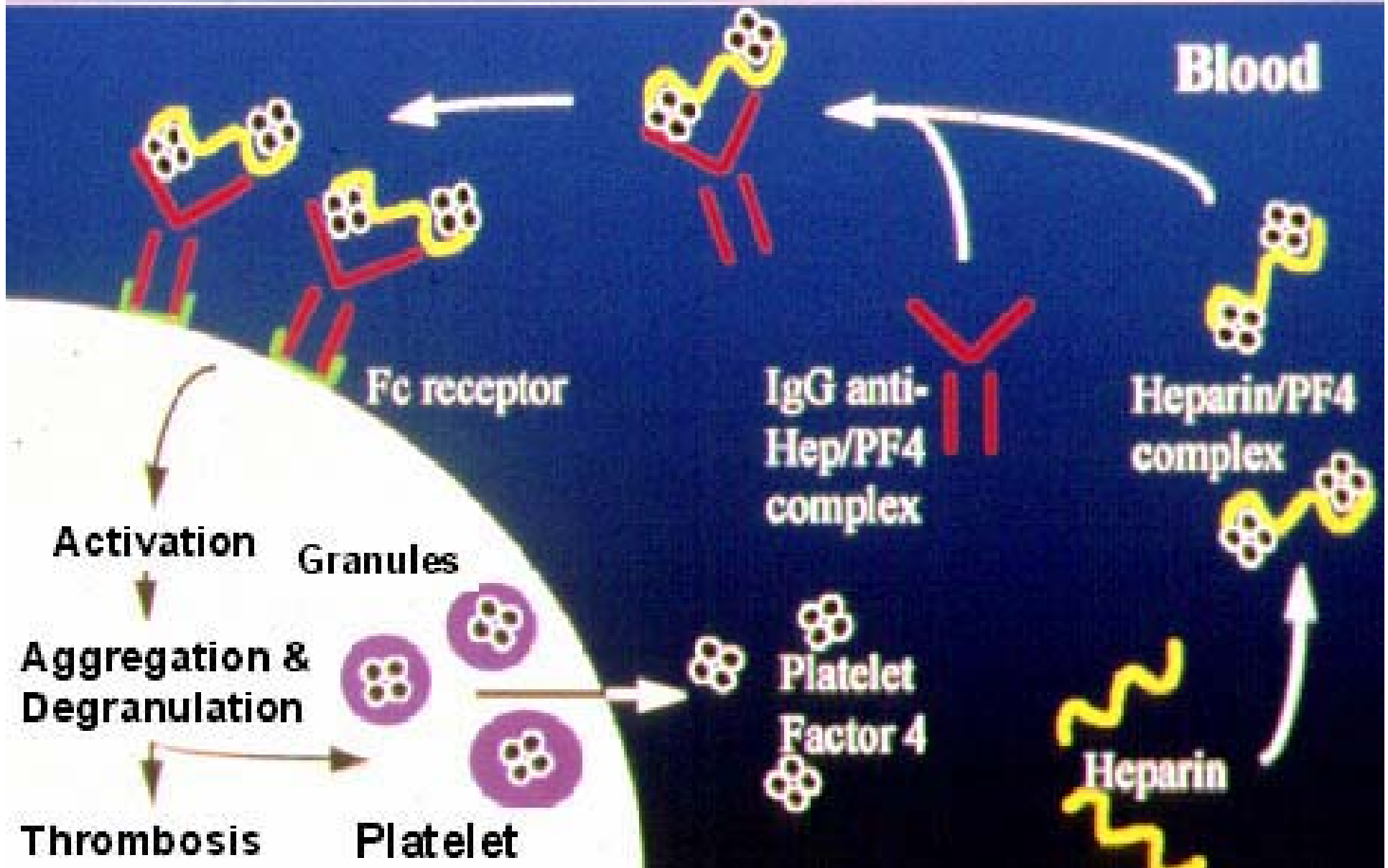
- 1) High morbidity and mortality:
 - $\frac{3}{4}$ venous catastrophes
 - $\frac{1}{4}$ arterial catastrophes
- 2) Paradoxical massive PE, bilateral or 3-limb DVT; mesenteric arterial thrombosis; MI, stroke
- 3) Venous gangrene, especially fingers, toes, penis, nipples

HIT: CAUSE

Pathogenic platelet-activating IgG:

- Recognizes a heparin/PF4 complex
- Interacts with platelet receptors
- Triggers formation of procoagulant platelet-derived microparticles

PATHOGENESIS OF HIT



DIAGNOSIS OF HIT

- Significant Thrombocytopenia
- Onset
- Presence of thrombosis during anticoagulation
- Differential diagnosis ruled out

THROMBOCYTOPENIA

- Platelet count $<100,000$ while receiving UFH or LMWH
- Platelet drop of $> 50\%$ drop from baseline

ONSET

- Typical Onset HIT:
 - No previous recent exposure
 - 5-14 days after exposure
- Rapid Onset HIT:
 - Prior exposure within 100 previous day
 - Platelet count decreases rapidly after re-exposure

ALTERNATIVE CAUSES

- Sepsis
- Hemodilution
- DIC, TTP, ITP
- Intra-aortic balloon pumps
- CVVH
- Post-transfusion purpura
- Drug-Induced: linezolid, sulfa antibiotics, rifampin, NSAIDs

HIT: DIAGNOSTIC PEARLS

- Requires heparin exposure, within 5-14 days
- Not related to heparin dose or route
- Beware platelet count $< 50\%$ baseline, or platelet count $< 100,000$
- 40,000 to 70,000 is usual platelet count.
- Not reported in pregnant women
- Distinguish HIT from HITT

DIAGNOSTIC TESTS FOR HIT

HIPA Test:

Patient serum (HIT) +
Normal donor platelets +
Heparin (UFH or LMWH)

→

Positive Test

Platelet
aggregation

ELISA:

Patient serum (HIT) +
UFH/PF4 coated assay wells +
Anti-IG/ peroxidase conjugate

→

Colorimetric
change indicating
bound antibody

Good Sensitivity, Poor Specificity

HIT: HOW TO MAKE THINGS WORSE

- Overdiagnose and deny heparin
- Underdiagnose and continue heparin
- Transfuse platelets
- Order LMWH in lieu of UFH
- Give warfarin monotherapy

THERAPEUTIC MANAGEMENT

FDA Approved

- Lepirudin
- Argatroban

Non-FDA Approved

- Bivalirudin
- Fondaparinux

FDA APPROVED: Lepirudin

Approved for treatment of
HIT-associated thrombosis (HITT)

- Dosing:
 - Bolus: 0.4mg/kg
 - Infusion: start at 0.15mg/kg/hr,
Target PTT 2-3 X Control
- Renal excretion
- Anaphylaxis

FDA-APPROVED: Argatroban

Approved for both prophylaxis & treatment of HIT-associated thrombosis

- Dosing:
 - No bolus
 - Infusion- starts at 2ug/kg/min,
Target PTT 2-3 X Control
- Hepato-biliary excretion
- Expect an INR of at 4 without warfarin

NON-FDA APPROVED

Bivalirudin

- Published data are limited
- IV Administration
- Reports of use in HIT positive patients requiring open heart surgery

Fondaparinux

- Published data are limited
- SC Administration
- Renal Excretion
- Longer lasting anticoagulation

ANTICOAGULANT MEDICATION ERRORS

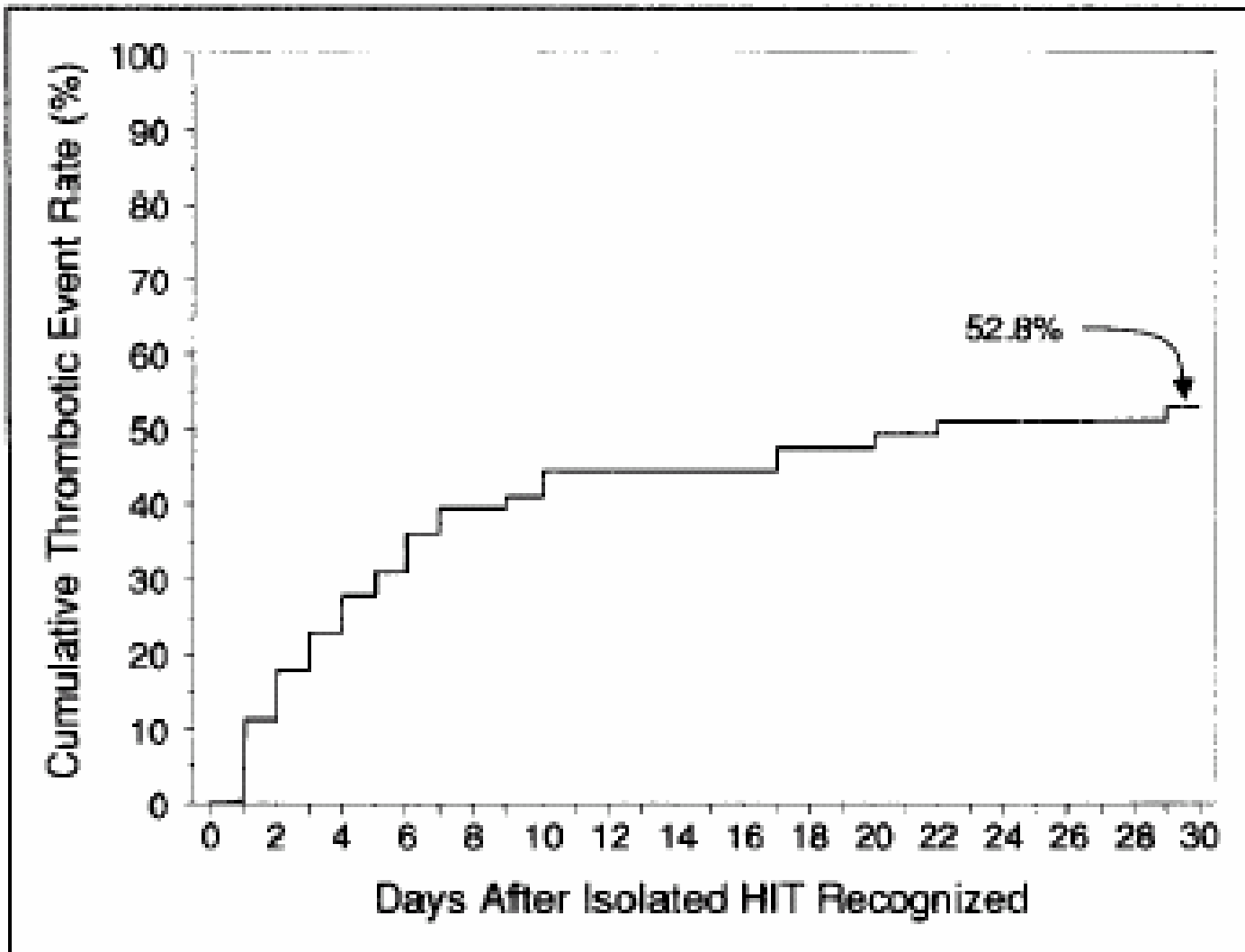
	UFH	Warfarin	LMWH	Argatroban
Event Rate per 1000 pts	1.3	1.0	1.2	31
Event Rate per 100,000 doses dispensed	20.0	24	16	429

Fanikos. Am J Cardiol 2004;94:532-535

A 14-Year Study of Heparin-Induced Thrombocytopenia

- Population: HITT (n= 65) or HIT (n= 62) treated with d/c of heparin or **Rx with oral anticoagulants**
- Interventions: Retrospective chart review of 127 patients over 14 years
- Endpoints: New thrombotic events

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



Am J Med 1996; 101: 502-507

BWH APPROACH TO HIT

- A summary of evidence-based strategies for the diagnosis and management of HIT and HITT
- Involvement of a multidisciplinary team

SCENARIO 1

New unexpected thrombotic event



Presume HITT



Stop ALL heparin

Measure but do not wait for antibody test



Treat immediately with DTI

SCENARIO 2

**Platelet count < 100,000 or > 50%
decrease from baseline**



If suspicion of HIT is high



Stop ALL heparin

Measure but do not wait for antibody test



Treat immediately with DTI

SCENARIO 3

Platelet count $< 100,000$ or $> 50\%$
decrease from baseline



Suspicion for HIT is low



Continue Heparin



Evaluate other causes of thrombocytopenia

Obtain PF4-antibody test



Positive PF4 Test

Negative PF4 Test



Presume HIT

R/O HIT

DISCUSSION

Should a PF4 antibody test be ordered in all patients,

- 1) Prior to starting heparin? **NO**
- 2) Following past heparin exposure? **NO**
- 3) Following recent heparin exposure? **NO**

DISCUSSION

4) What is the platelet threshold for obtaining a PF4 antibody test?

Platelet count < 100,000 or > 50% decrease from baseline

5a) In the absence of thrombosis, should all patients with a positive PF4 antibody test, be treated with a DTI or fondaparinux?

NO

DISCUSSION

5b) How long should the patient be treated for HIT?

For 3-5 days or until platelet recovers to at least $> 100,000$

CONCLUSIONS

- **HIT requires prompt recognition and management**
- **We have some answers, but many questions remain**
- **Collaborative discussion is essential**