Heparin-induzierte Thrombozytopenie

Wann daran denken?
Wie behandlen?

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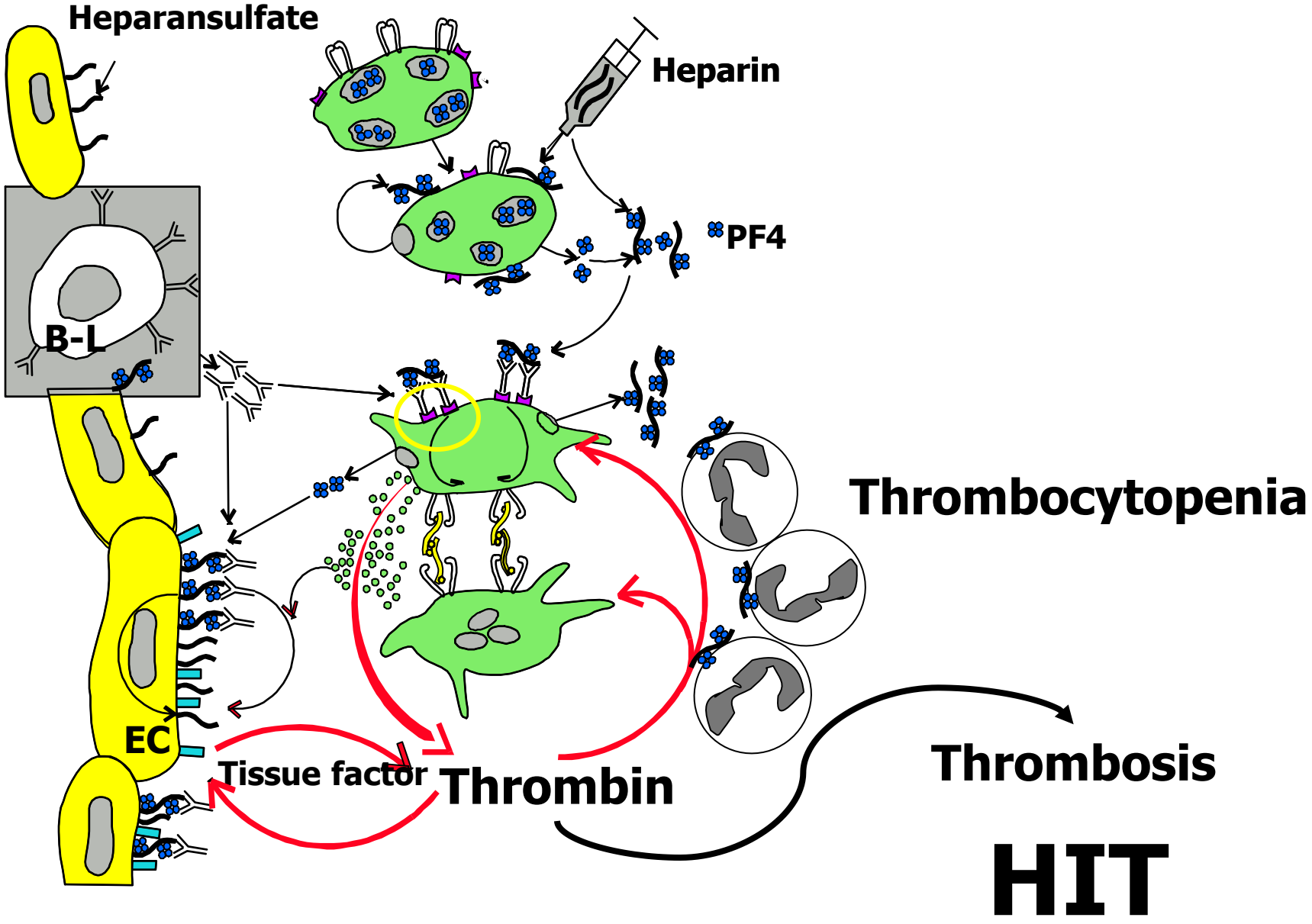
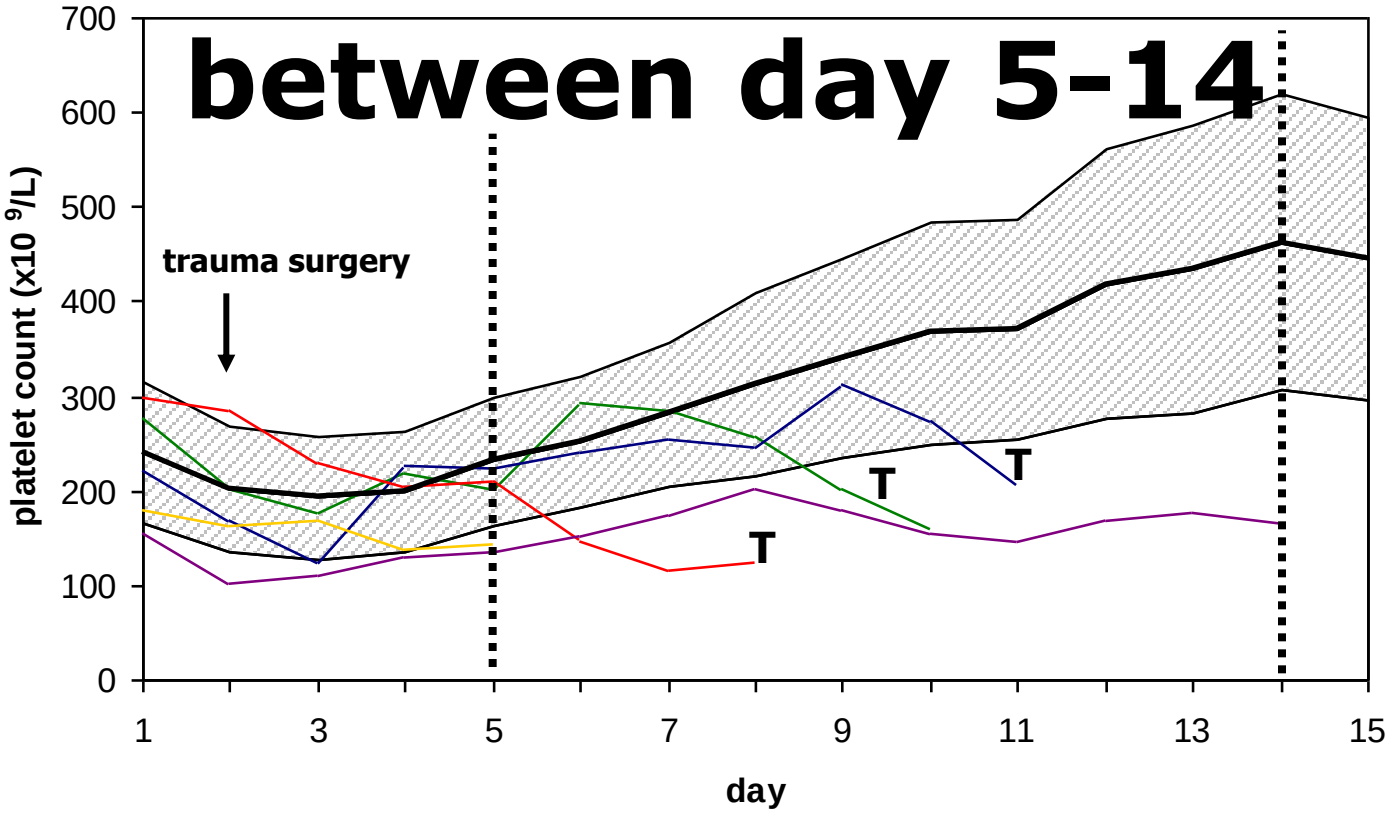


Greinacher A, Chong BH, Warkentin TE; in Michelson A; Platelets 3rd ed; 2012

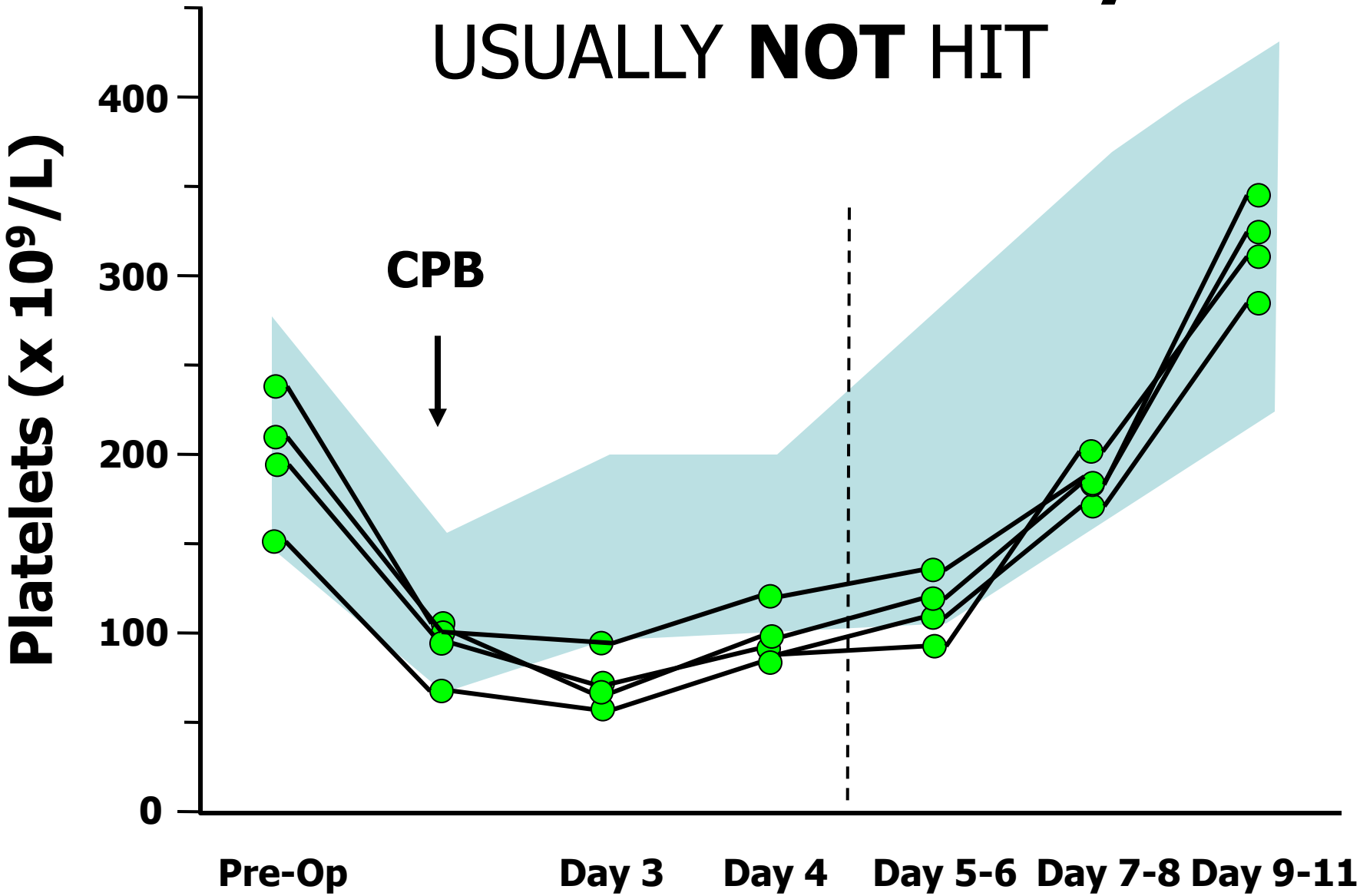
Platelet count decrease > 50%
and/or
new thrombotic complications



How to diagnose HIT?

HIT in surgical patients

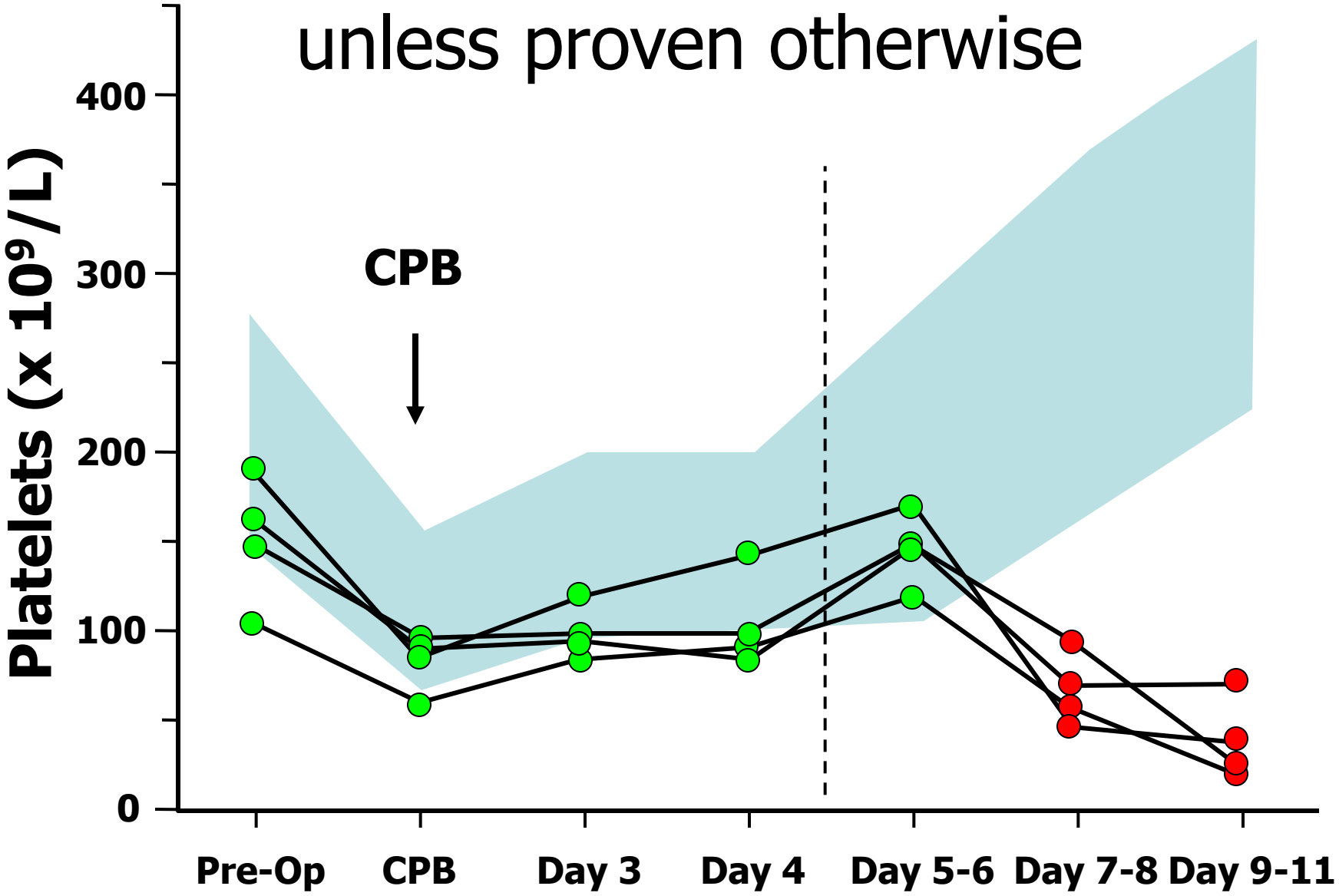
Platelet fall in first 4 days is USUALLY **NOT** HIT



Pouplard C et al. Br J Haematol. 2005;128:837-41

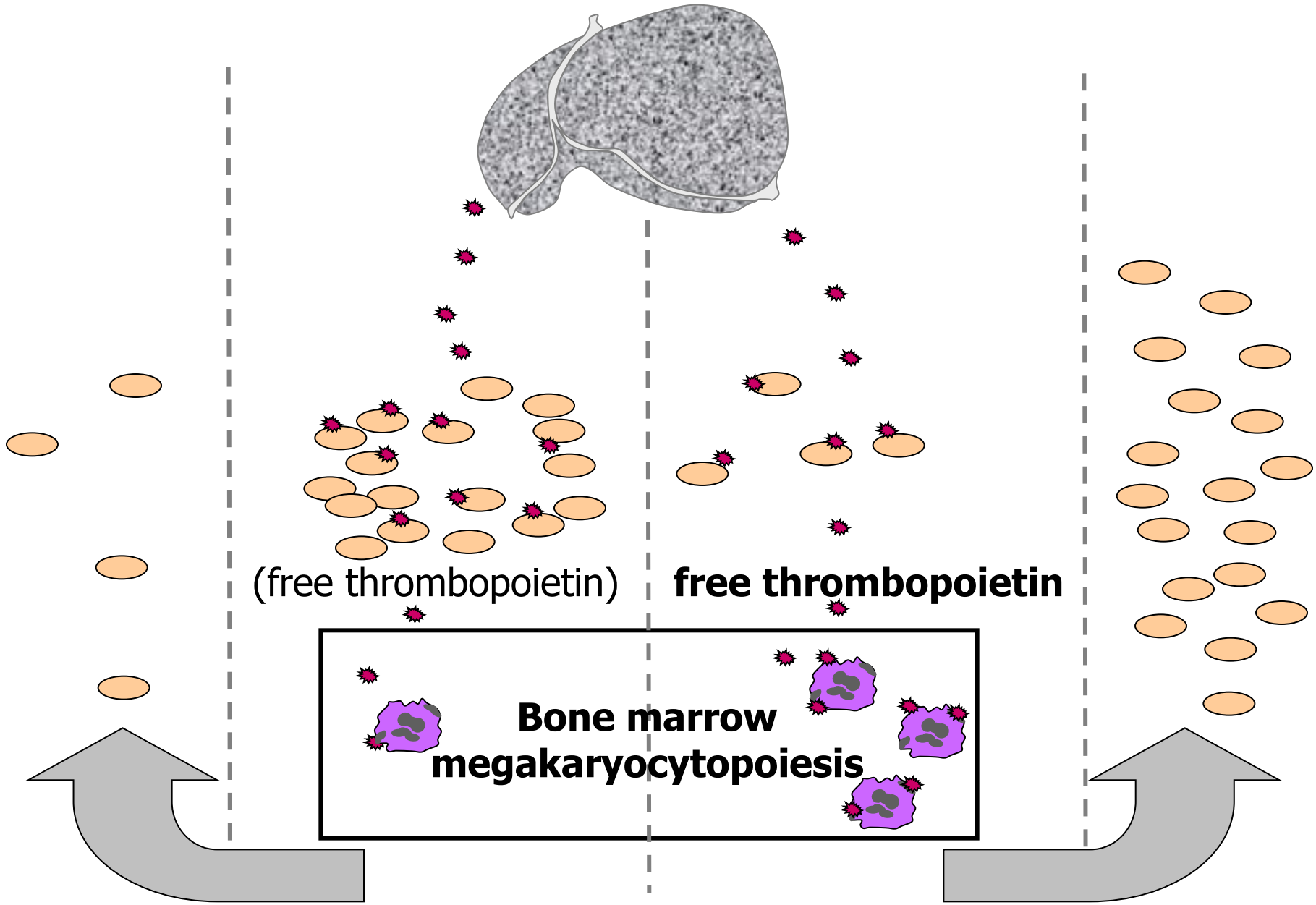
Platelet fall on day 5-10 = HIT

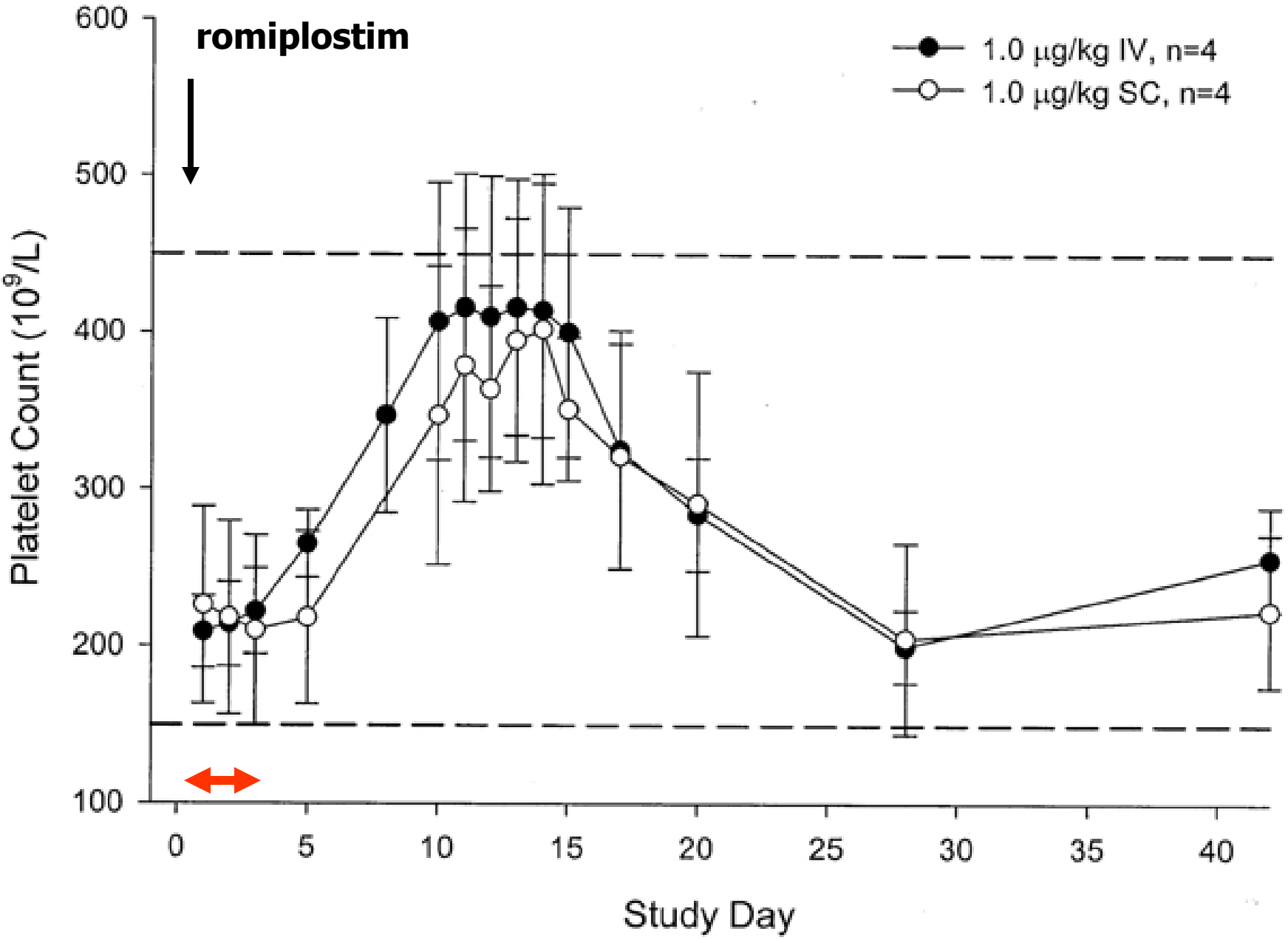
unless proven otherwise



Pouplard C et al. Br J Haematol. 2005;128:837-41

Constant production of thrombopoietin in the liver





Wang B, et al. Clin Pharmacol Ther. 2004;76:628-38

An early fall in platelet counts to 60,000 – 100,000/µL until day 4 after major surgery is normal

Major surgery "resets the clock" for the 5-14 day time window

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

		Scoring points: 2	1	0
A	**T**hrombocytopenia	>50% nadir ≥ 20 G/L	30-50% nadir 10-19 G/L	<30% nadir ≤ 10 G/L
B	**T**iming (onset)	day 5-10 (d1 if recent heparin)	> day 10, or unclear	before day 4
C	**T**hrombosis	new thrombosis	progressive thrombosis	None
D	o**T**her cause for thrombocytopenia	no other cause	possible	definite

0-3 low score	4-6 medium score	7-8 high score

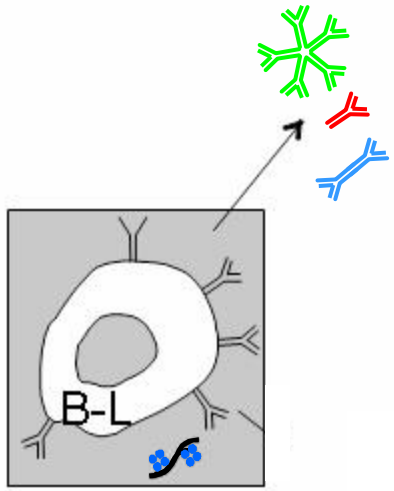
Lo et al. J Thromb Haemost 2006;4:759-65

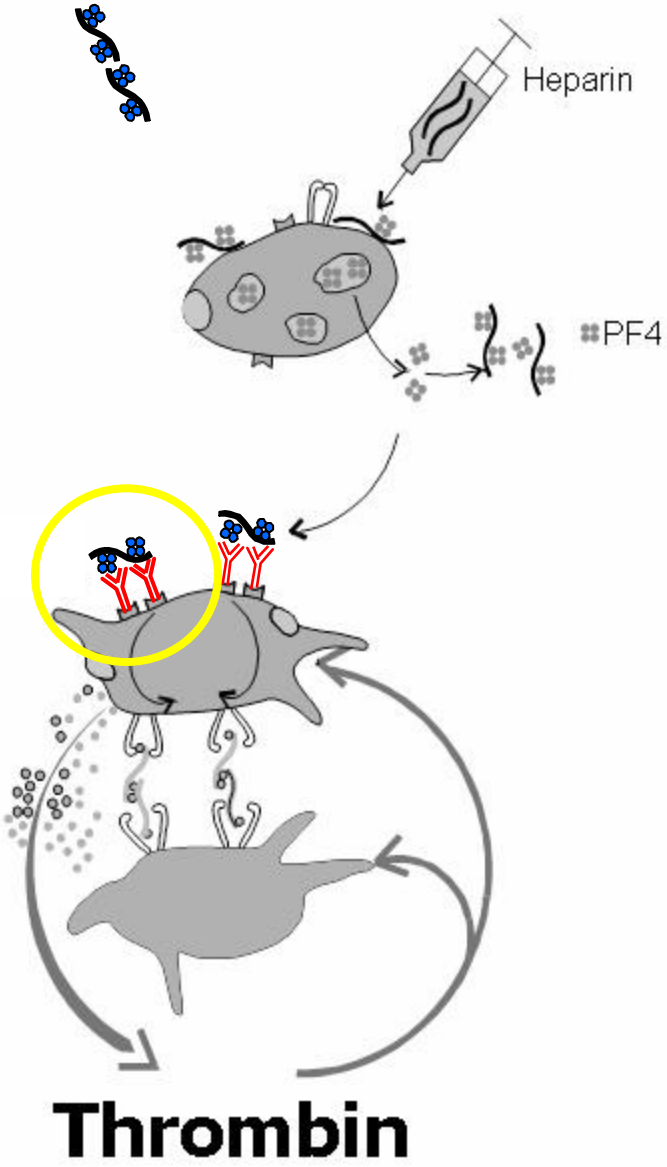
Antigen tests

detect IgG, IgM, IgA

Functional test

detect IgG

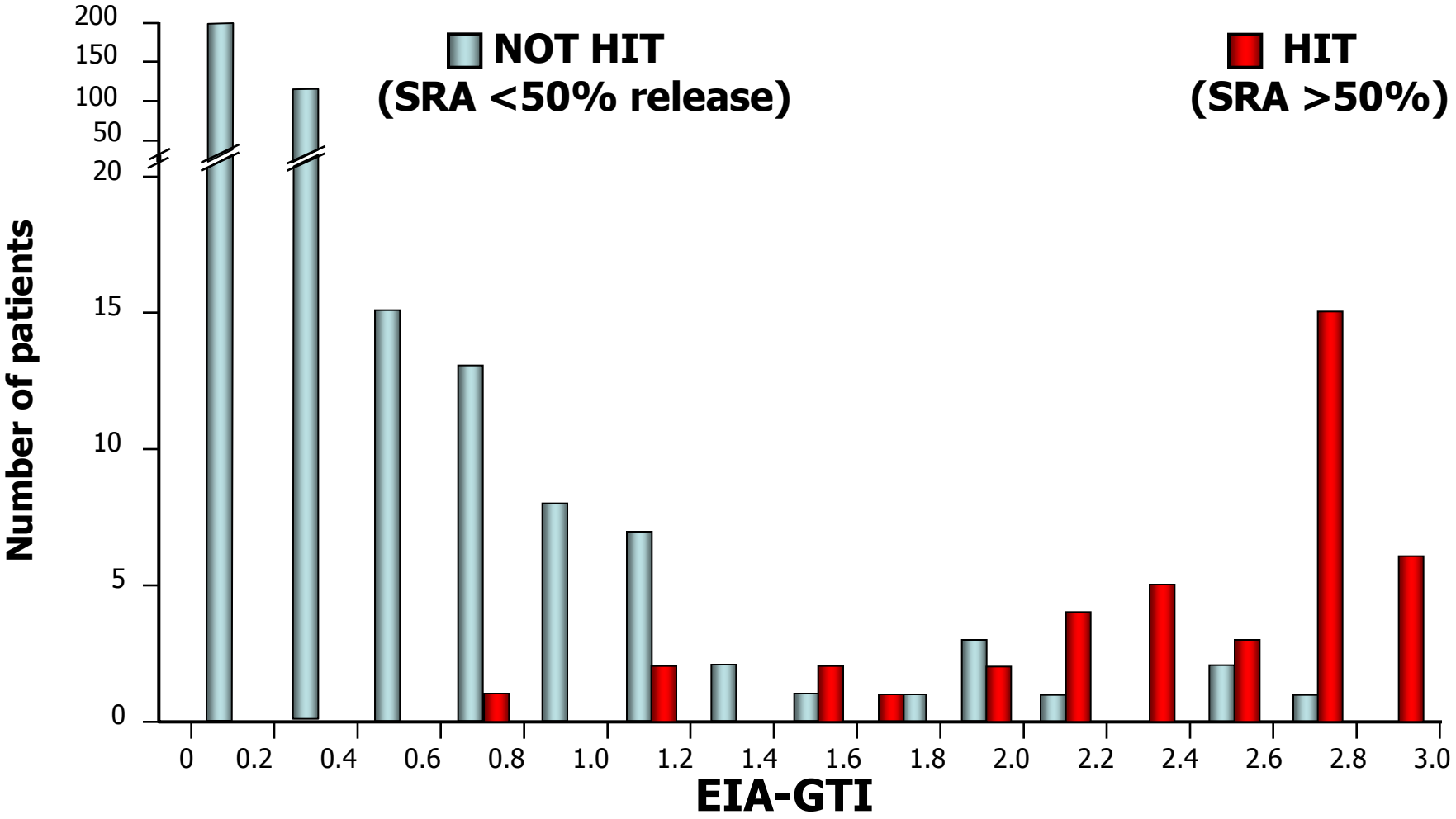




Optimal is a combination of both tests

EIA-SRA Relationship

N = 405



Warkentin et al. J Thromb Haemost 2008;6:1304-12

PF4/heparin antigen tests have a high negative predictive value

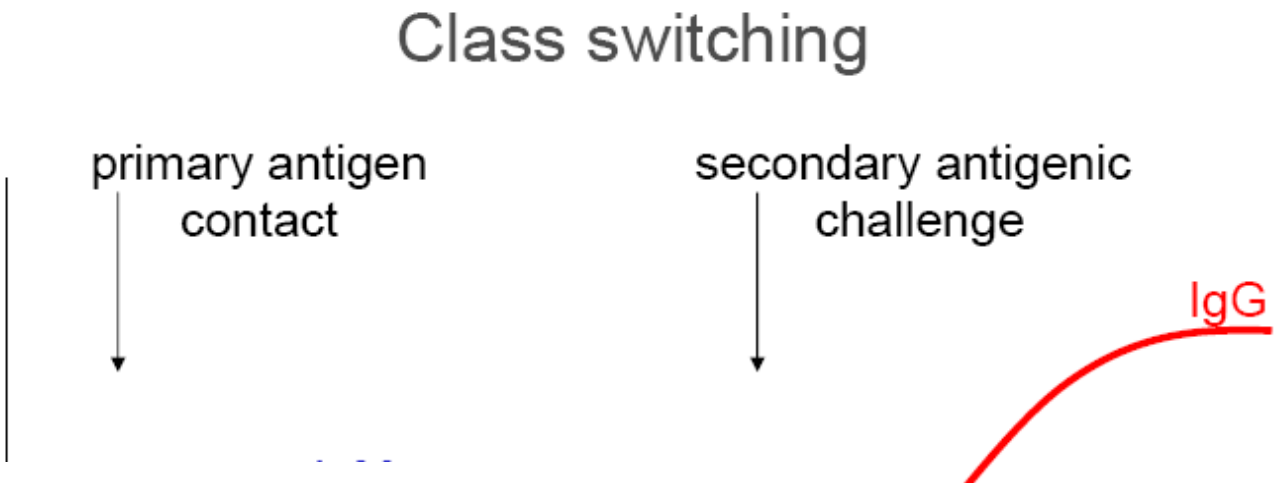
There is no substitute for a functional washed platelet assay to confirm the diagnosis of HIT

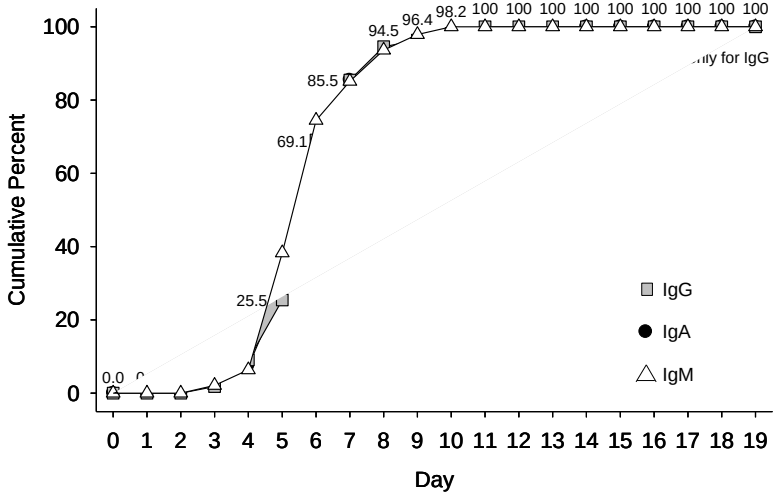
HIPA test or ^{14}C-SRA

How to diagnose HIT?

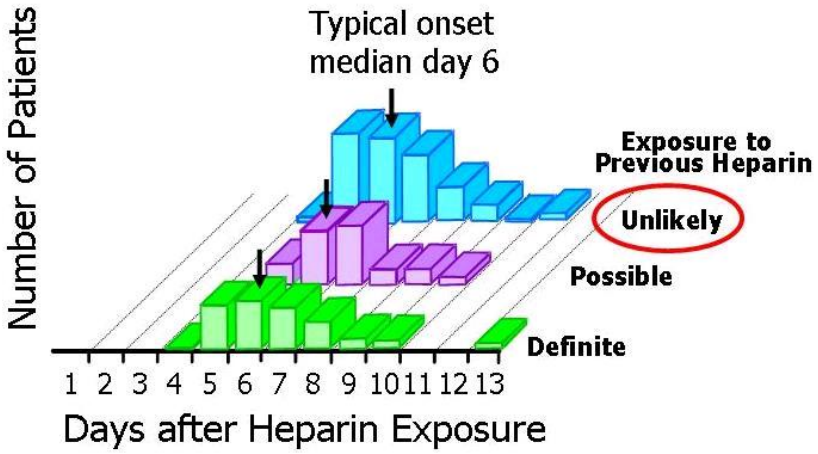
HIT for the medical expert

HIT differs from Classical Antibody Responses



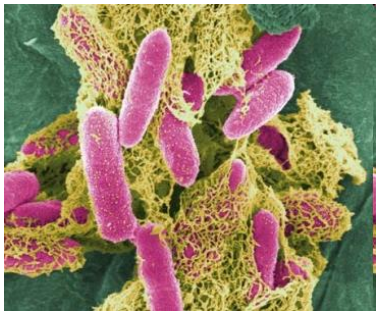


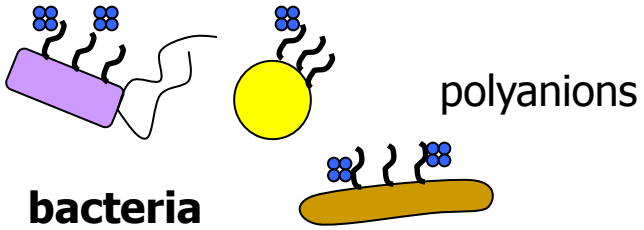
Greinacher A et al Blood. 2009;113:4970-6

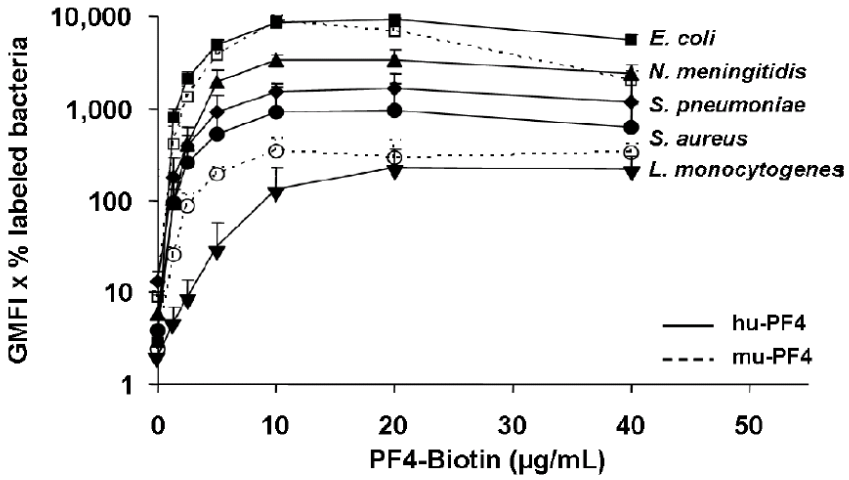


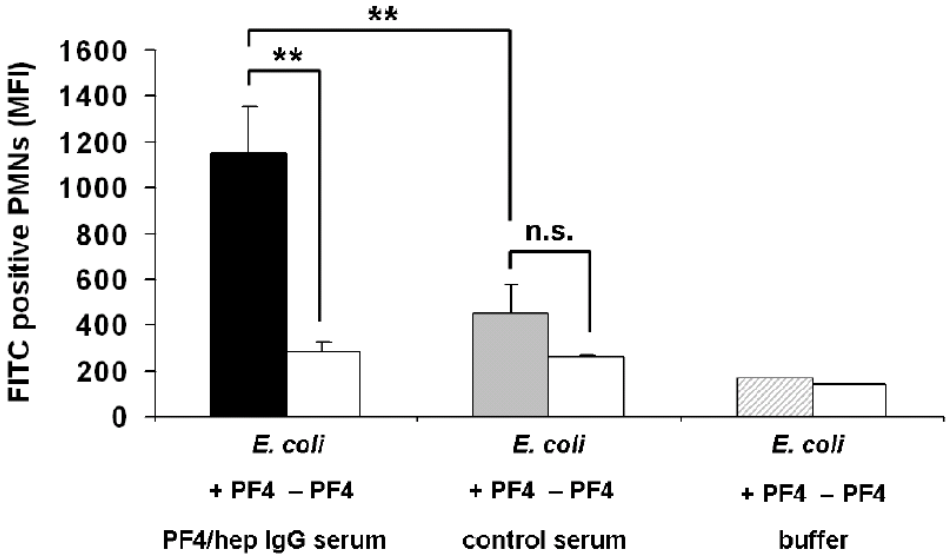
Warkentin & Kelton. N Engl J Med 2001;344:1286-1292

PF4 binds to bacteria and PF4/H abs enhance phagocytoses



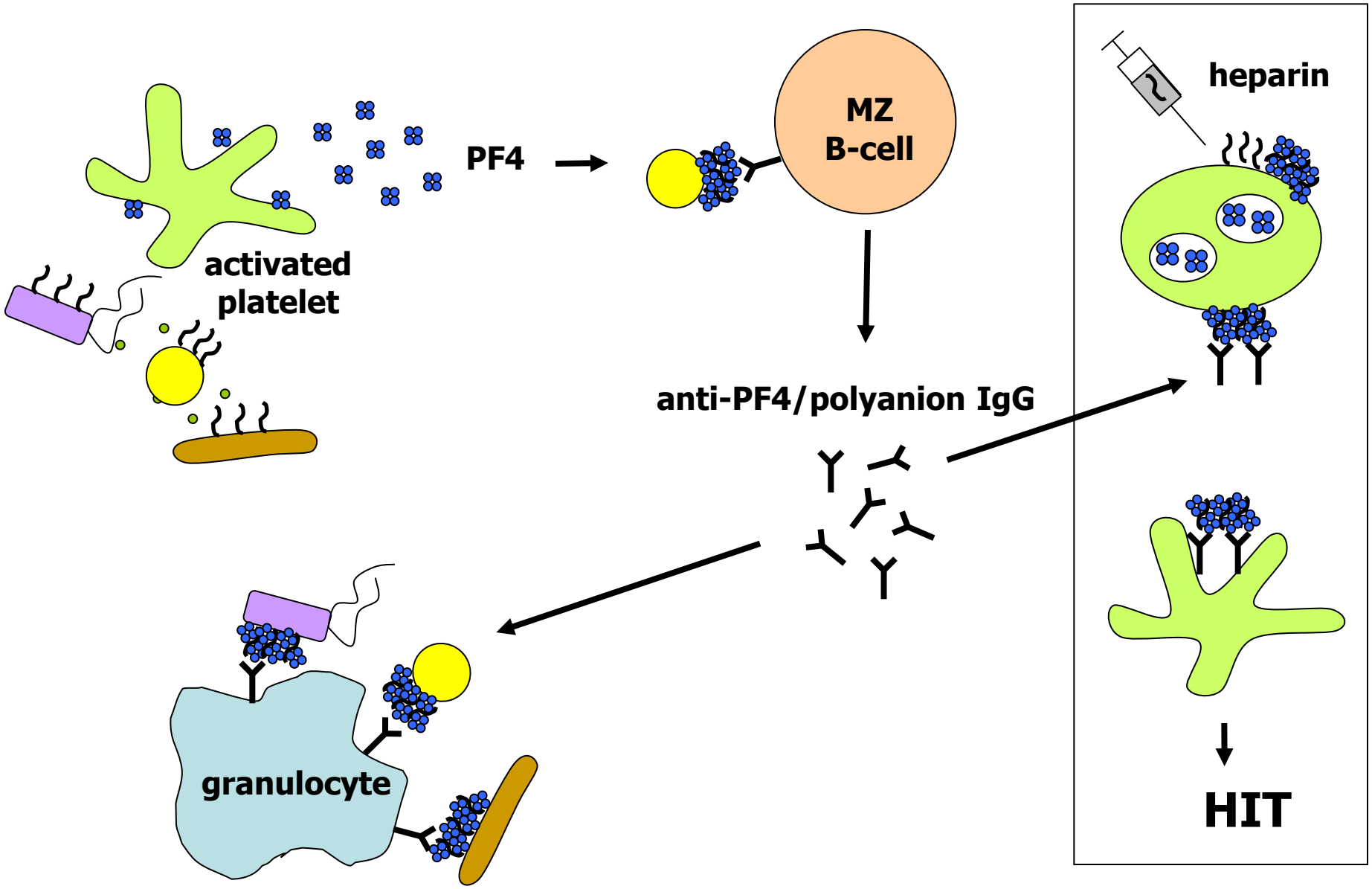




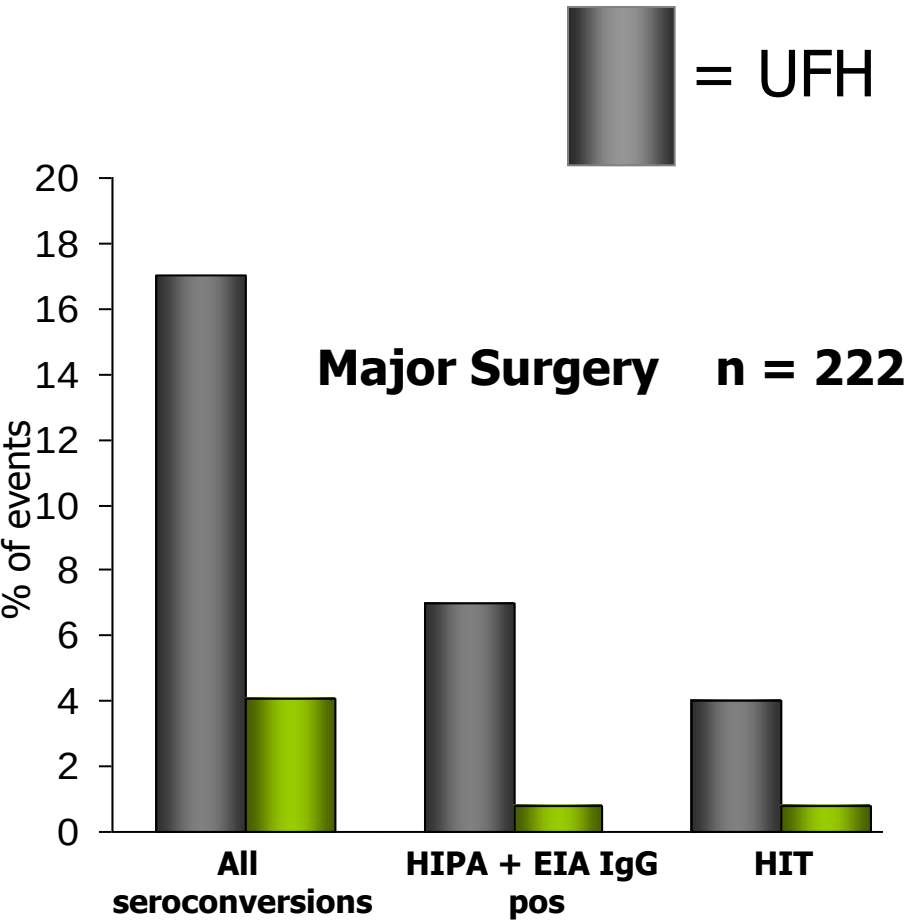


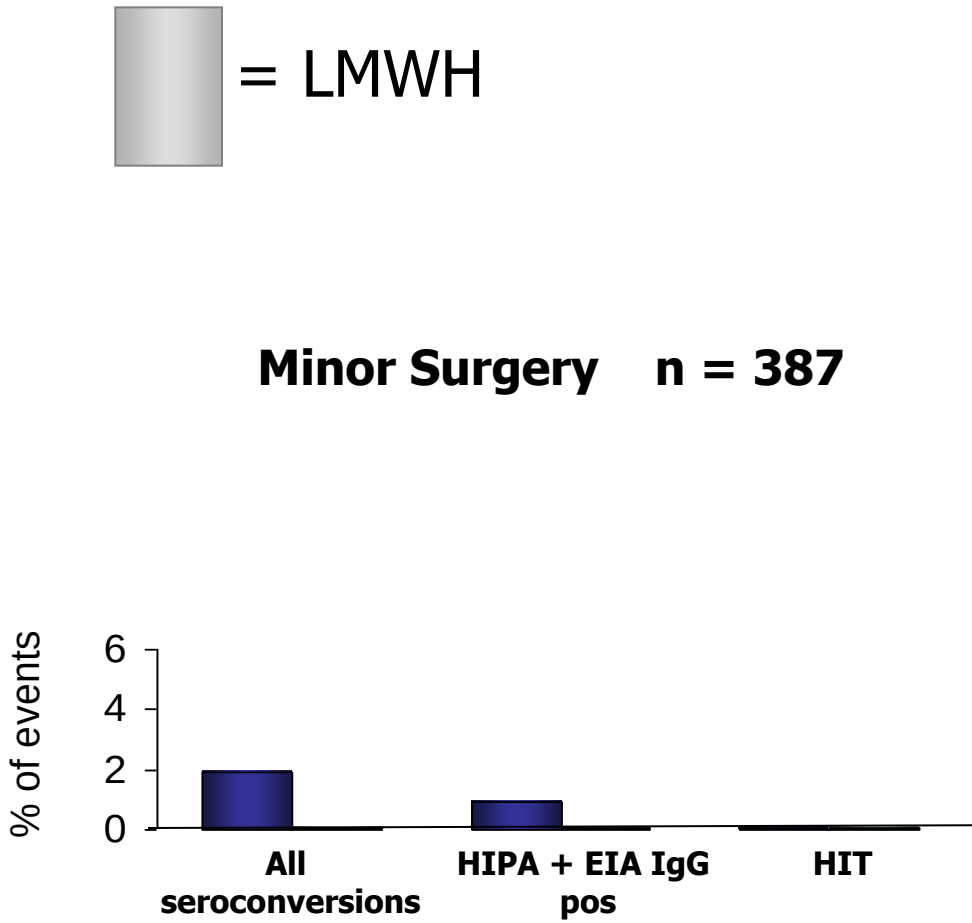
Krauel K, et al. Blood 2011

HIT is a misdirected host defense



Anti-PF4/heparin Immune Response requires additional signals





Lubenow et al. BLOOD 2010

- 31 year old female admitted with severe head ache.
- Upper respiratory tract infection that began 10 days earlier.
- Otherwise healthy, no medications.
- INR 1.4, aPTT 34s, fibrinogen 0.6 g/L, D-dimer >35mg/L (<0.5), platelets 31,000/µL, no bleeding, no signs of infection
- normal CT head scan (to exclude sinus vein thrombosis).

Greinacher A, BLOOD 2014

- 4 g fibrinogen and LMWH thrombosis prophylaxis.
- Next day: platelet count 15,000/μL
- New DVT; persistent headache

- Although HIT seemed implausible, platelet decrease and new thrombosis during LMWH prompted HIT testing

Greinacher A, BLOOD 2014

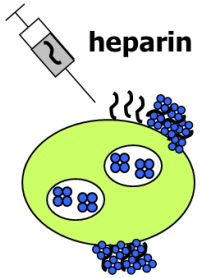
- Anti-PF4/heparin IgG ELISA strongly positive OD >2.5
- HIPA test strongly positive also in the sample without addition of heparin.
- Pre-LMWH admission sample: same results
- Immediate start of therapeutic-dose danaparoid anticoagulation
- she deteriorated neurologically the same day, and massive sinus vein thrombosis associated with intracerebral bleeding was demonstrated by repeat CT imaging.

Spontaneous HIT or Autoimmune HIT

- 10 patients reported in the literature
- 6 after orthopedic surgery (no heparin)
- 3 after infection
- 1 no obvious trigger

Warkentin et al. BLOOD 2014
Greinacher BLOOD 2014

- HALLMARK: positive HIPA without heparin
- "HIT" during fondaparinux, rivaroxaban, dabigatran

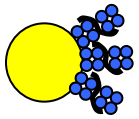


danger

PF4/heparin complexes on heparin-coated platelets

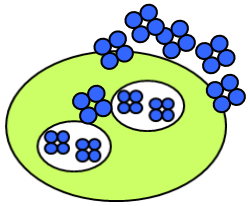
PF4/polyanion complexes

PF4/polyanion complexes on bacteria



danger

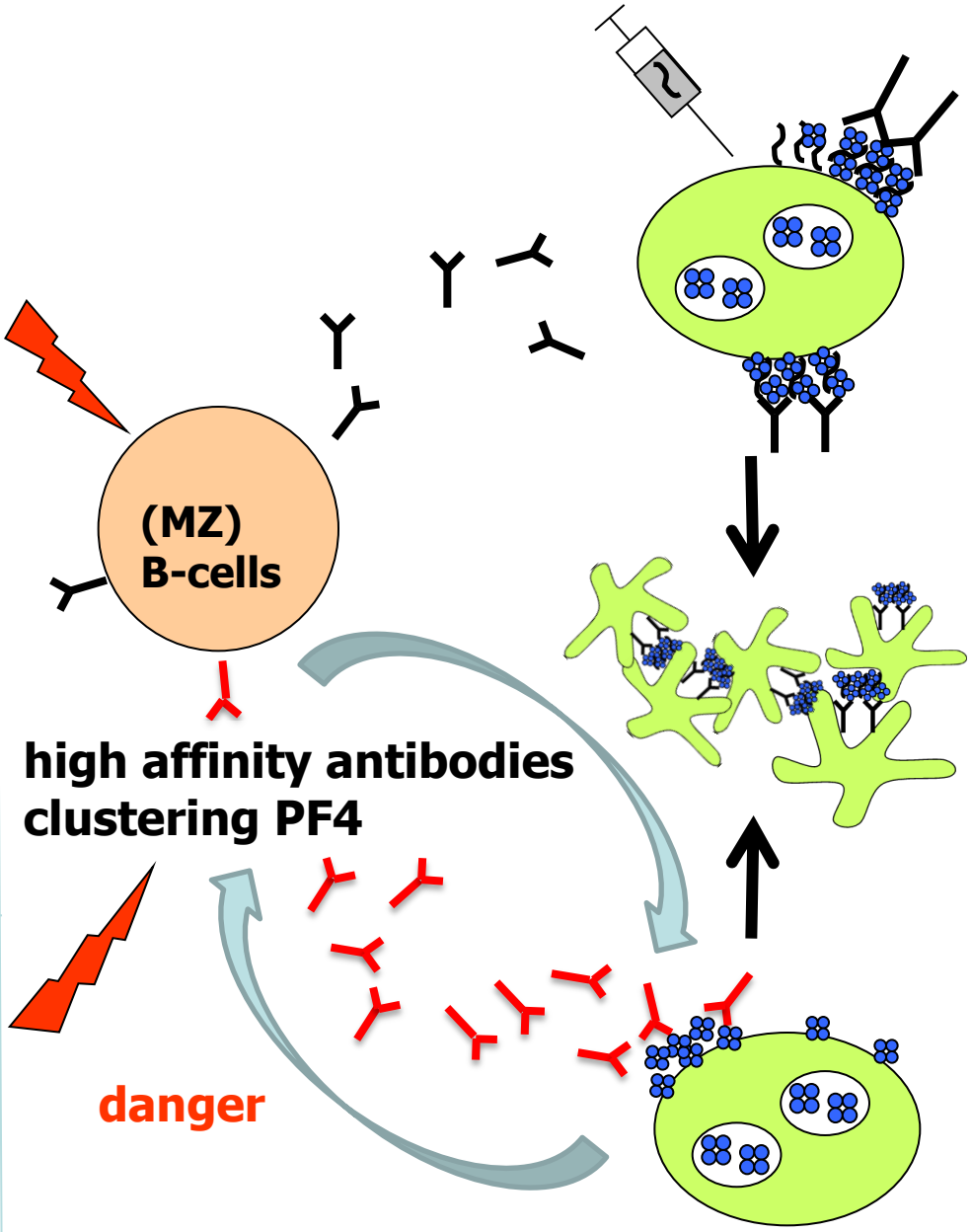
PF4 complexes formed by poorly-defined non-heparin triggers



danger

Greinacher A, BLOOD 2014

heparin-dependent HIT

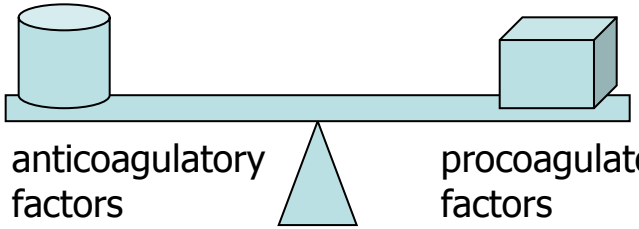


heparin-independent HIT

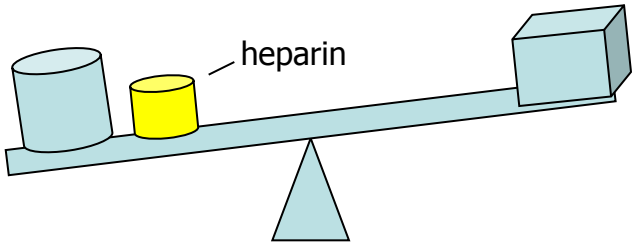
Platelet-activating anti-PF4/heparin IgG antibodies

	Heparin treatment	Platelet-activating IgG antibodies	
		with heparin	without heparin
Typical HIT	**yes**	**100%**	**acute phase (day 1-5) ~30%**
Delayed onset HIT	**5-14 days before**	**100%**	**100%**
Spontaneous HIT or Autoimmune HIT	**No (often, infection or major surgery 5-14 days prior)**	**100%**	**100%**

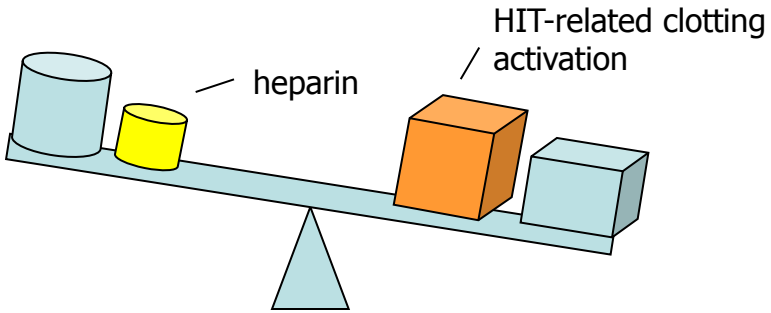
How to treat patients with HIT?



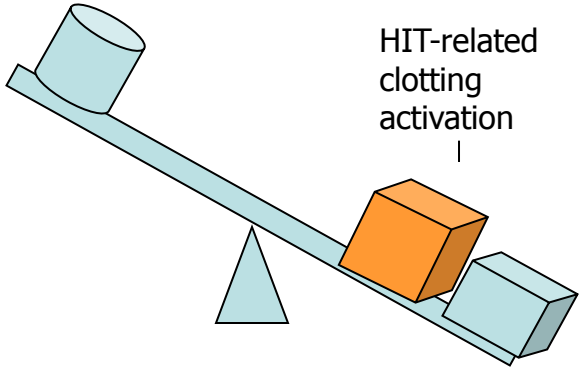
1. steady state of haemostasis



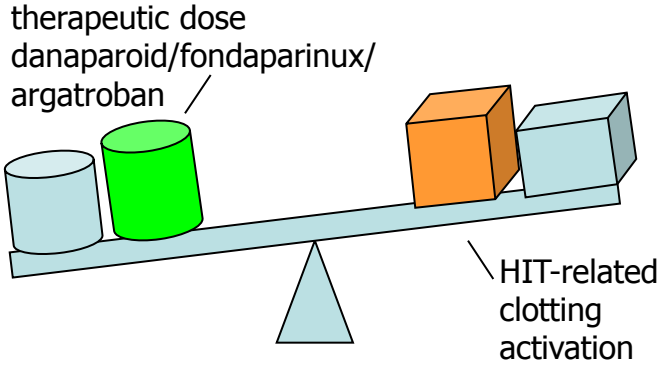
2. heparinized patient



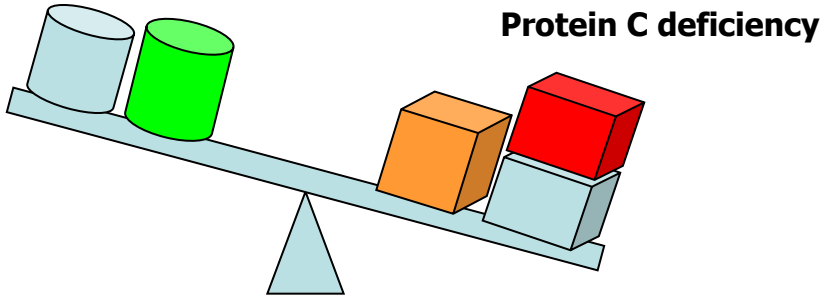
3. HIT-patient (still on heparin)



4. HIT-patient heparin stop



5. acute HIT-patient
(on compatible anticoagulant)



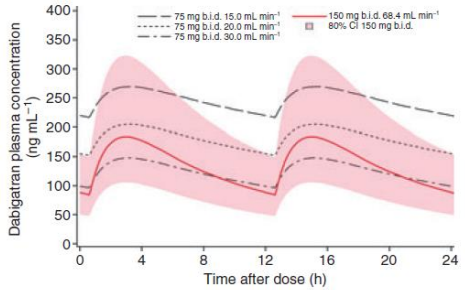
6. acute HIT-patient
avoid early start of VKA

Alternative Anticoagulants in HIT

- ~~Lepirudin~~
- ~~Danaparoid~~ North America, intermittendly in Europe
- Argatroban

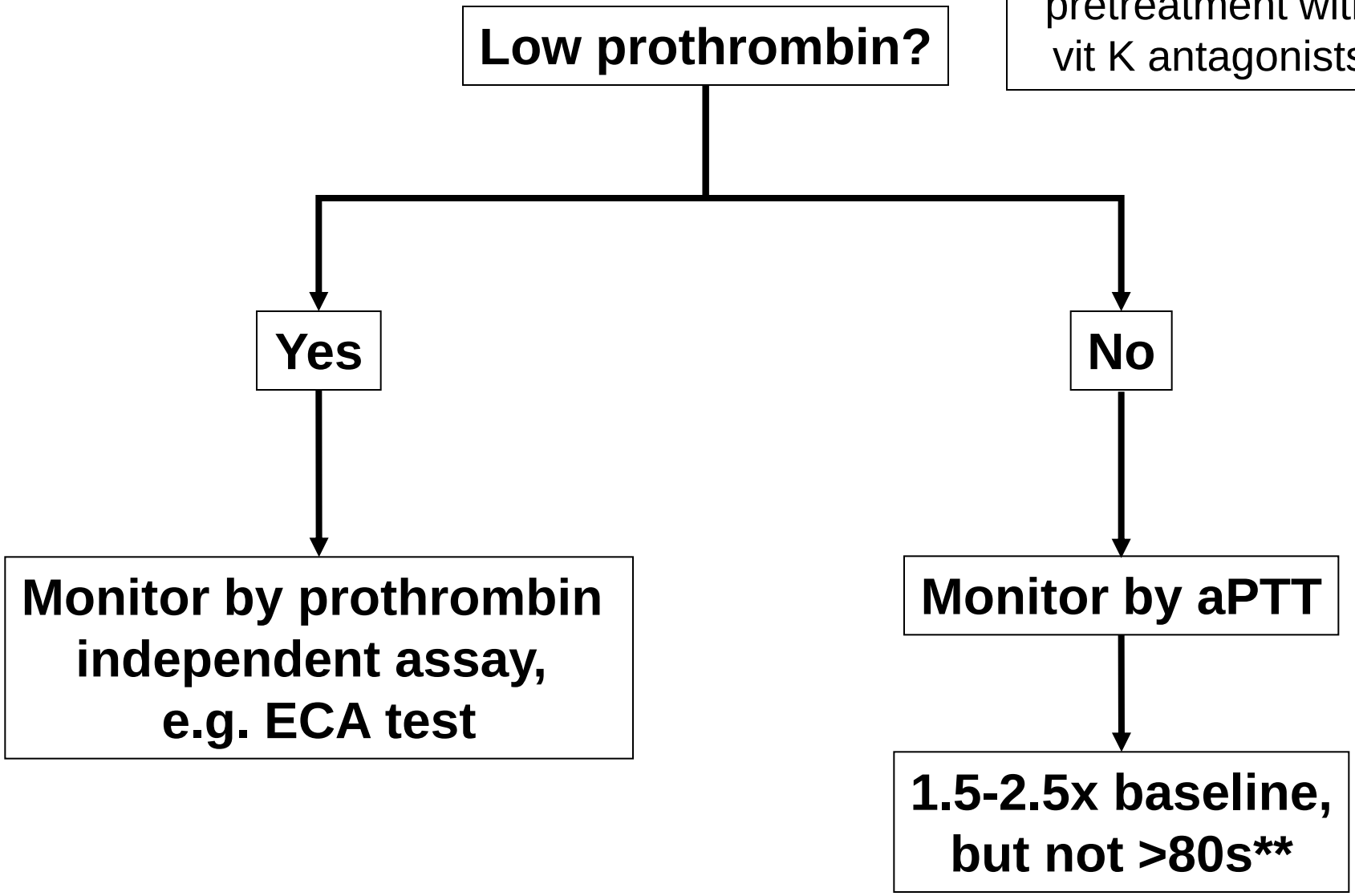
- Fondaparinux
- Bivalirudin

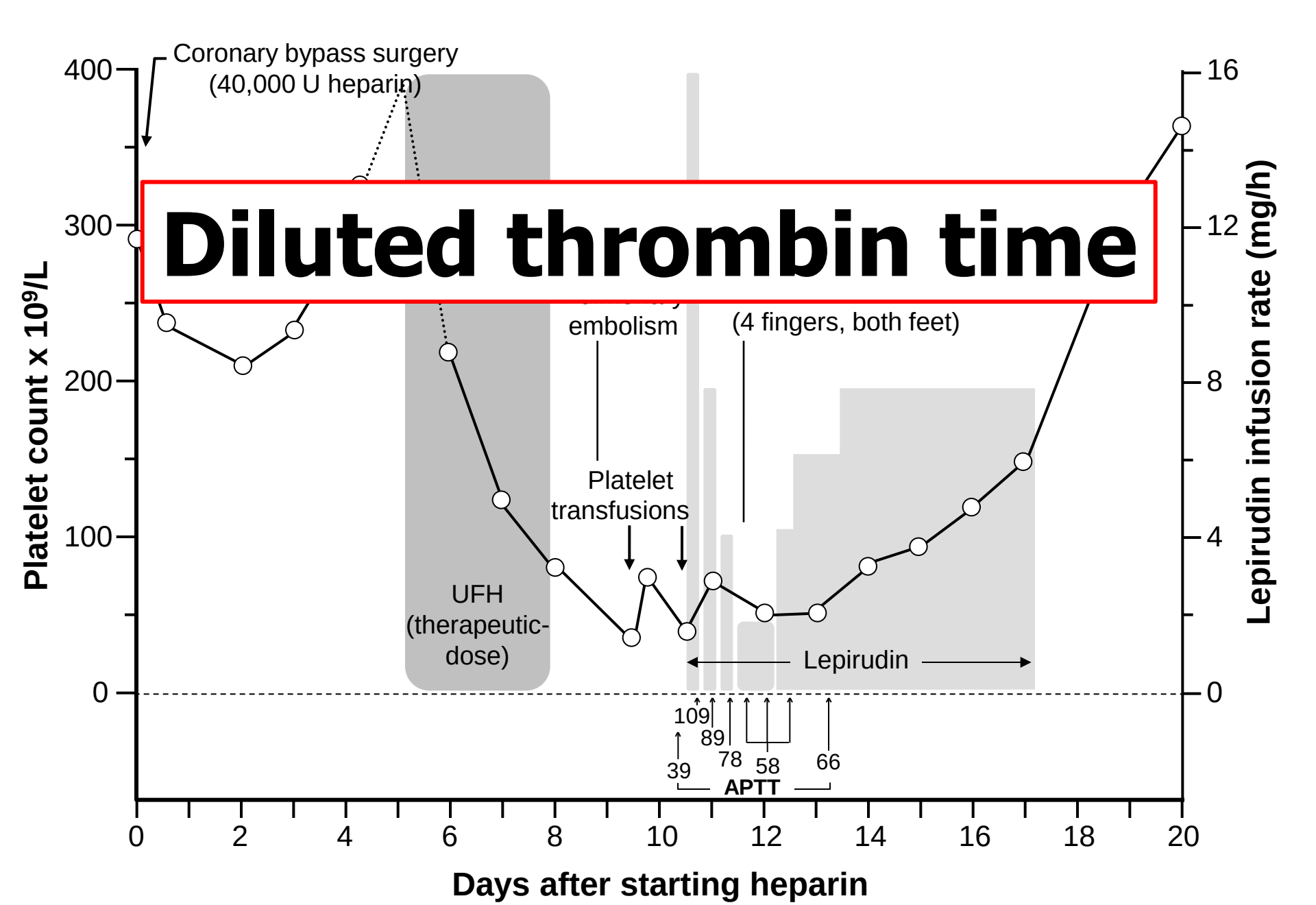
- Dabigatran
- Rivaroxaban
- Apixaban
- Edoxaban



Monitoring of DTIs

liver impairment, DIC; pretreatment with vit K antagonists





Greinacher A and Warkentin TE; Thromb Haemost 2008; 99: 819–829

Heparin-induced Thrombocytopenia in 2014

- HIT still exists
- Major surgery, cardiac surgery
- Medical intensive care patients

- **New: Autoimmune HIT/Spontaneous HIT**

- Treatment: argatroban, danaparoid, fondaparinux, bivalirudin,
  (rivaroxaban, apixaban, dabigatran)

T. Thiele
T. Bakchoul
K. Selleng
A. Sümnig
K. Althaus
S. Czekay