

Heparin Induced Thrombocytopenia

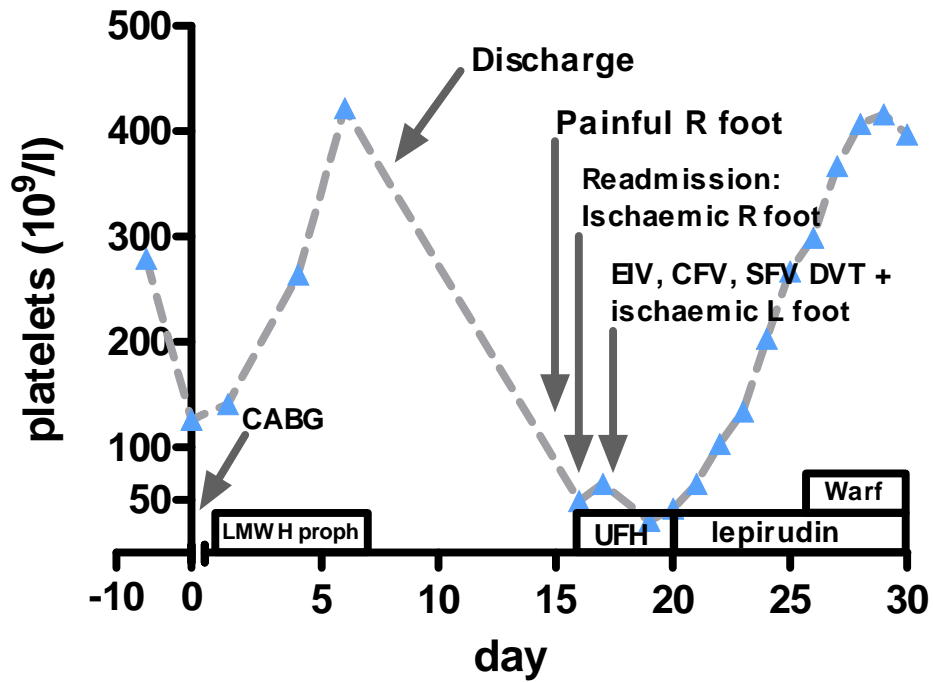
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Conclusion

- HIT can be excluded with a low clinical pre-test probability or negative immunoassay.
- IgG only assays improve specificity but still have a low PPV and significant risk of overdiagnosis.
- HIT is unlikely, but not excluded, at low OD. There may be a role for confirmatory steps.
- HIT is very likely with high optical density.
- Diagnosis remains uncertain in intermediate OD values and ideally needs functional assays.

Case



Introduction

- Immune mediated reaction to heparin.
- Life threatening thrombotic events if unrecognized.
- Alternative anticoagulants associated with higher risk of haemorrhagic complications.

Introduction

- **Clinicopathological syndrome. Diagnosis requires:**
 - Thrombocytopenia, arterial/venous thrombosis
 - Detection of pathogenic antibodies
- **Many potential causes for thrombocytopenia**
- **Detection of antibodies**
 - High negative predictive value
 - Poor positive predictive value (ELISA)
 - Gold standard: washed platelet assay
 - Non standardized , time consuming, few centers only

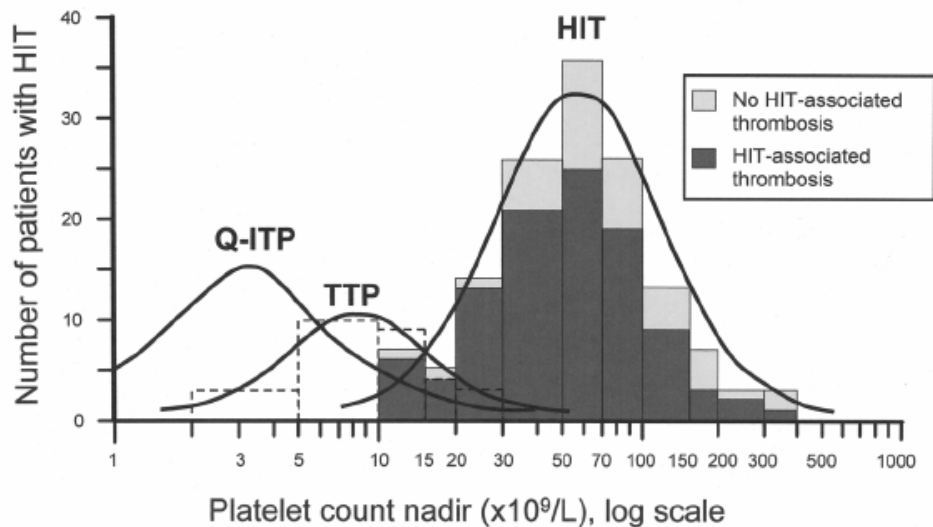
Pathogenesis

- HIT antigens: PF4 + heparin.
- Antibodies bind through F(ab) domain
- Antigens form multimolecular clusters binding several IgG molecules: large immune complexes
- Cross link with platelet Fc γ IIa receptors
 - coagulation activation and thrombin generation
 - Thrombocytopenia due to intravascular platelet activation with release of procoagulant platelet derived microparticles
- Antibodies also cause procoagulant endothelial changes and activate monocytes and neutrophils

Clinical presentation

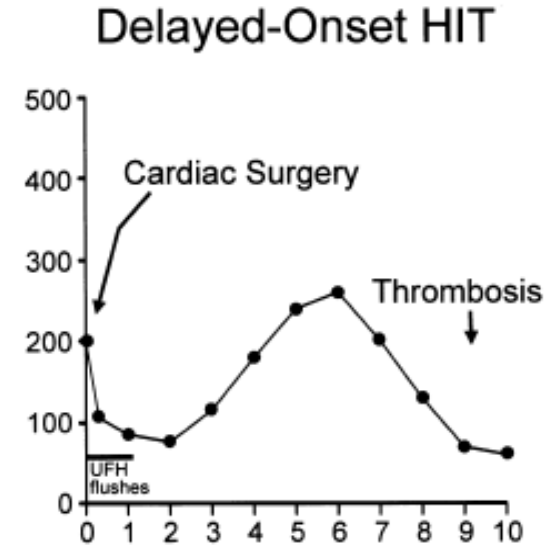
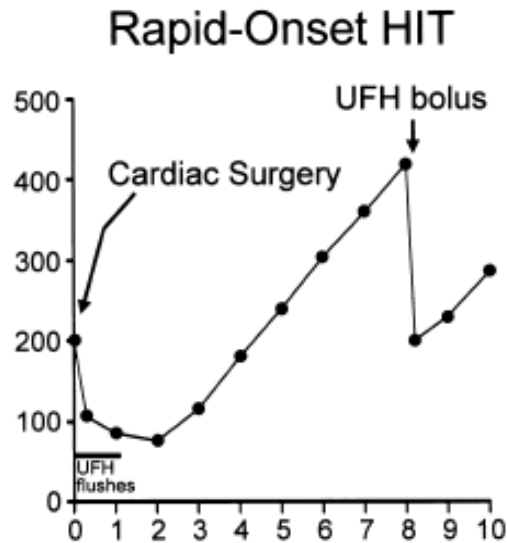
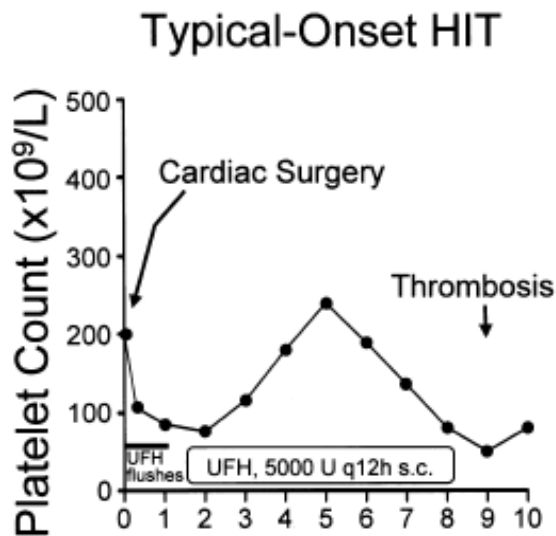
- Severity/magnitude of the thrombocytopenia
- Onset of thrombocytopenia in relation to heparin exposure
- Presence of thrombotic events
- Other causes of thrombocytopenia

Clinical presentation-Thrombocytopenia



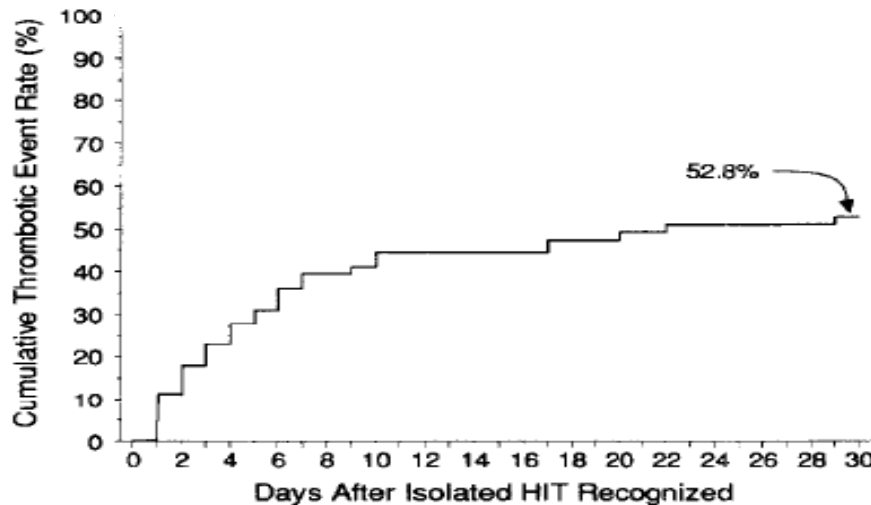
- Thrombocytopenia nadir 20 – 100 x 10⁹/l or fall in platelet count > 50% from peak post operative platelet count.
- Median time to recovery (plt > 150): 4 days, longer for plateau and in severe HIT.
- Generally does not recover unless heparin stopped.

Types of HIT



- **Typical HIT: 70%.**
- **Rapid onset: 25 – 30%**
- **Delayed onset: rare**
- **Median time to plt recovery 4 days, 90% recovery < 1 week.**

Clinical Presentation - Thrombosis

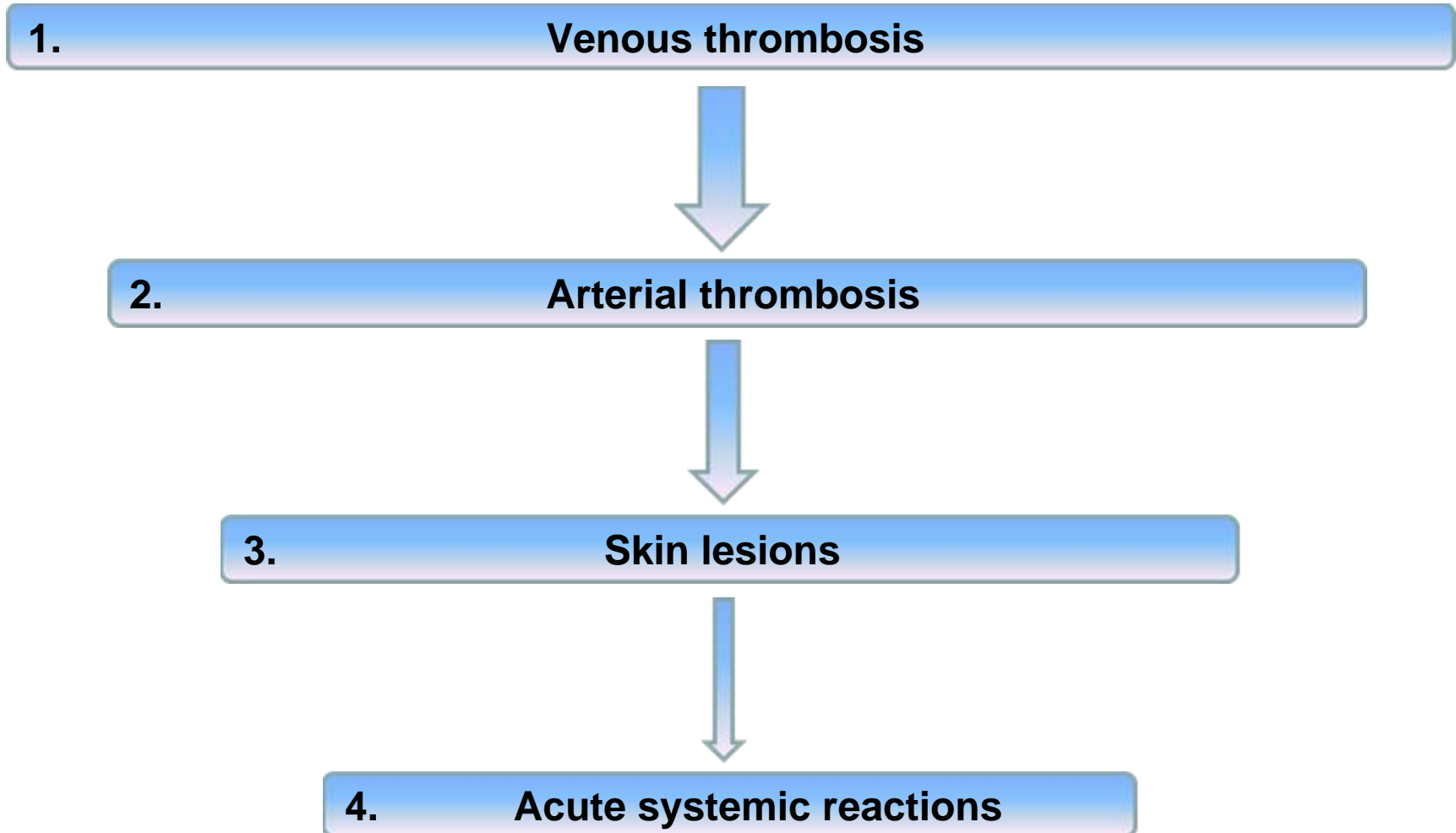


- Petechiae and other spontaneous bleedings are not signs of HIT even in severe thrombocytopenia.
- Thrombosis is presenting symptom in 50 - 60%.
- 36% in isolated HIT, most within the first week^{2,3}
 - *Irrespective of heparin discontinuation.*
- Estimated 1:8 with UFH thrombosis and 1:100 with LMWH thrombosis have HIT¹

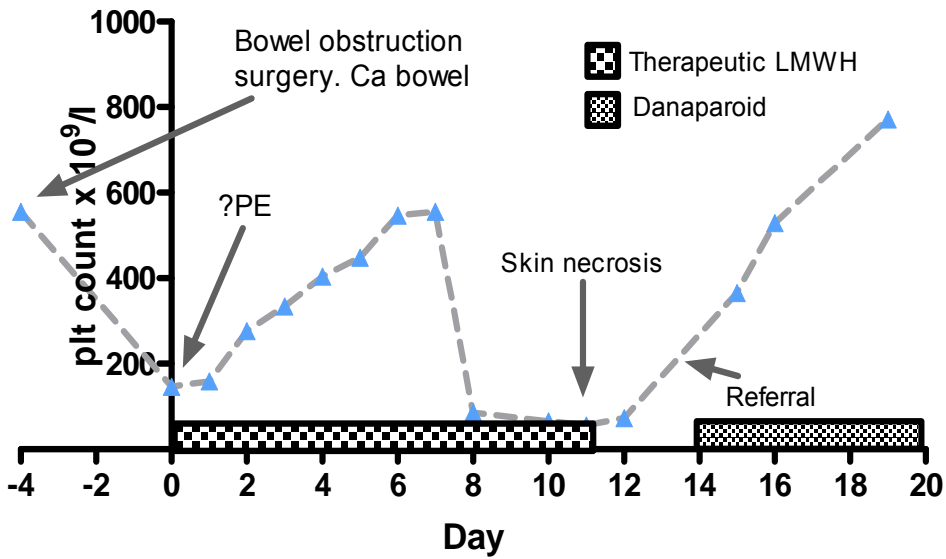
1. T. Warkentin, American Society for Hematology, Hematology 2006, 408-416
2. A. Greinacher, Blood 2000;96:846-851
3. T.E. Warkentin, American Journal of Medicine 1996;101;502-507



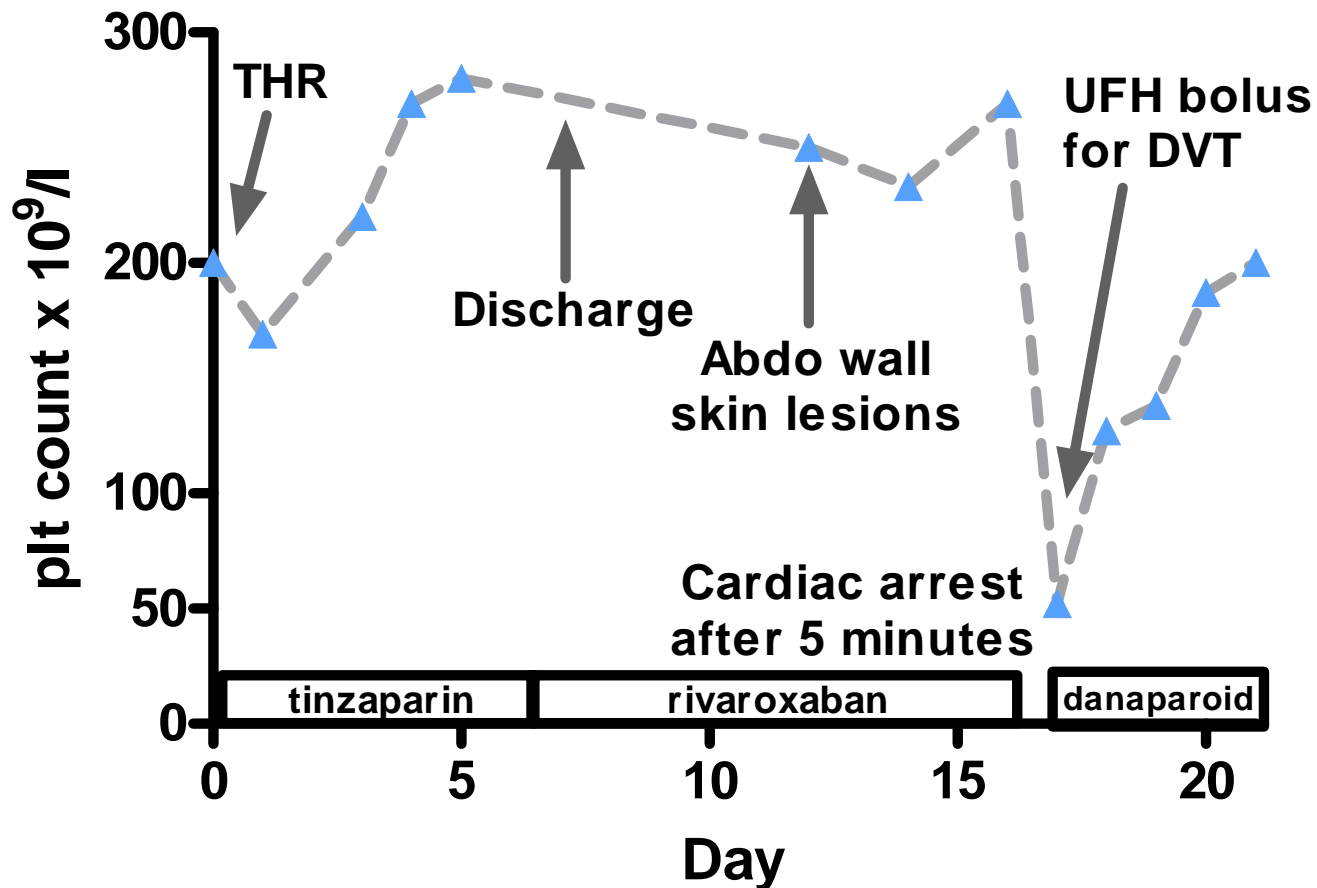
Clinical Presentation - Thrombosis



3. Skin lesions



4. Acute systemic reactions



Clinical Pretest probability (4T's)

	Points (0,1, or 2 for each of 4 categories, maximum possible score = 8)		
	2	1	0
Thrombocytopenia	>50% fall or platelet nadir 20-100 x10 ⁹ /L (usually day 7 -14)	30-50% fall or platelet nadir 10-19x10 ⁹ /L	Fall <30% or platelet nadir <10x10 ⁹ /L
Timing of platelet count fall	Clear onset days 5-10 or <1 day (if heparin exposure within past 100 days)	Consistent with immunisation but timing not clear (ie missing platelet counts or onset >day 10)	Platelet count fall too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin necrosis)	New thrombosis; skin necrosis; post heparin bolus acute systemic reaction	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
Other causes for thrombocytopenia?	No other cause evident	Possible alternative explanation/ cause	Definite other cause present

Low probability 0 -3, intermediate probability 4 – 5, high probability 6 - 8

Diagnosis

- **Clinical pretest probability**
 - Clinical scoring system
 - Score ≤ 3 : $< 5\%$ risk of HIT^{1,2,3}
- **Laboratory testing**
 - Immunoassays
 - Platelet activation assay

1. Pouplard J Thromb Haemost 2007; 5: 1373–9

2. Lo J Thromb Haemost 2006; 4: 759–65.

3. Denys Thromb Res 123, 137–145.

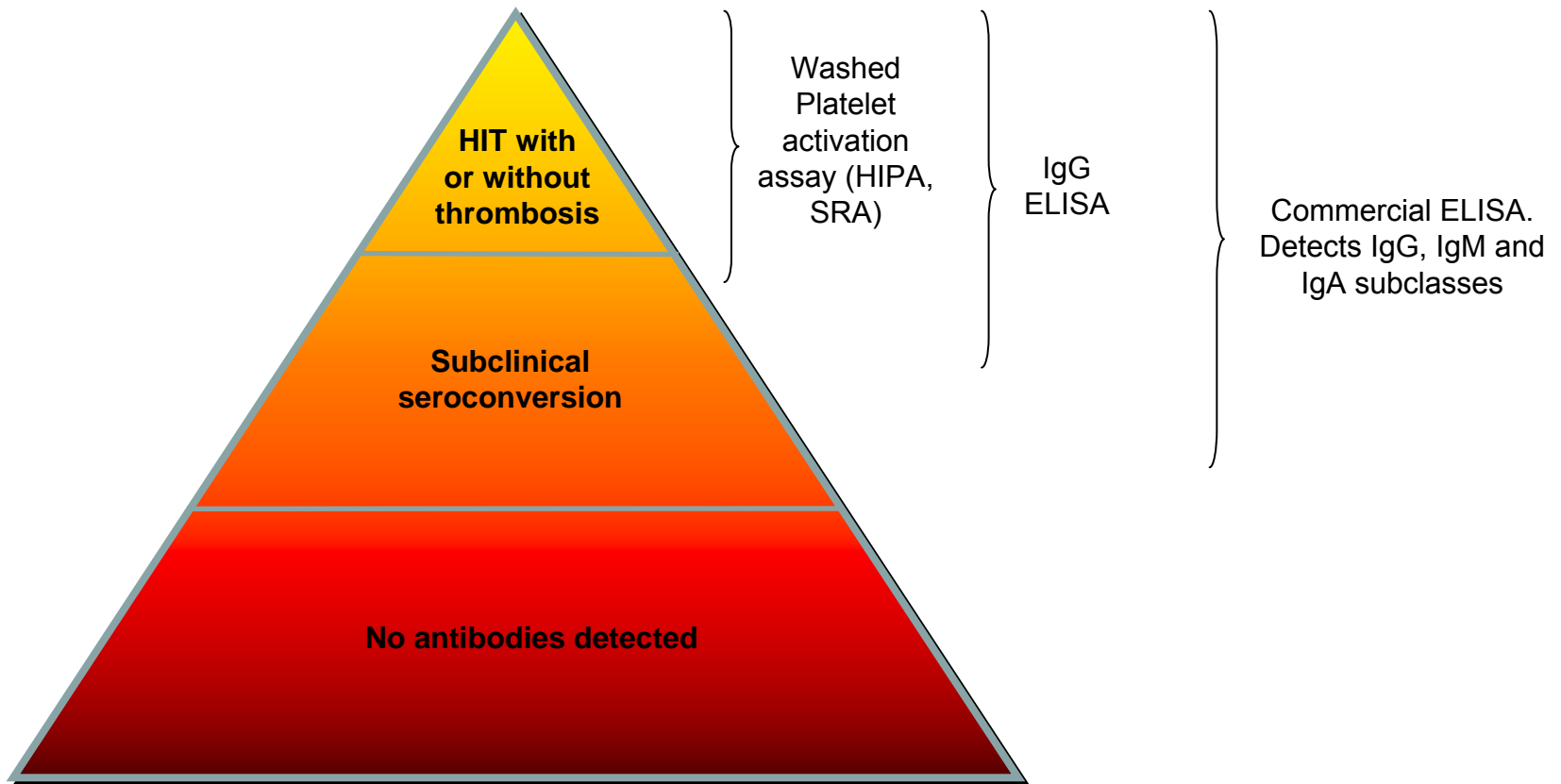


Diagnosis – laboratory testing

- Platelet activation assays
 - Test for presence of platelet activating IgG antibodies.
 - Heparin induced platelet aggregation assay
 - Serotonin release assay (SRA)
 - Specificity 95 – 99%
 - Very limited availability



How to improve antigen test specificity?



Adapted from T.E Warkentin, JTH 2007:5;232-234

Laboratory testing – IgG vs IgG/M/A

HIT is caused by IgG antibodies¹⁻³

Do IgM/A antibodies produce procoagulant changes?

Does Ig class switching occur?

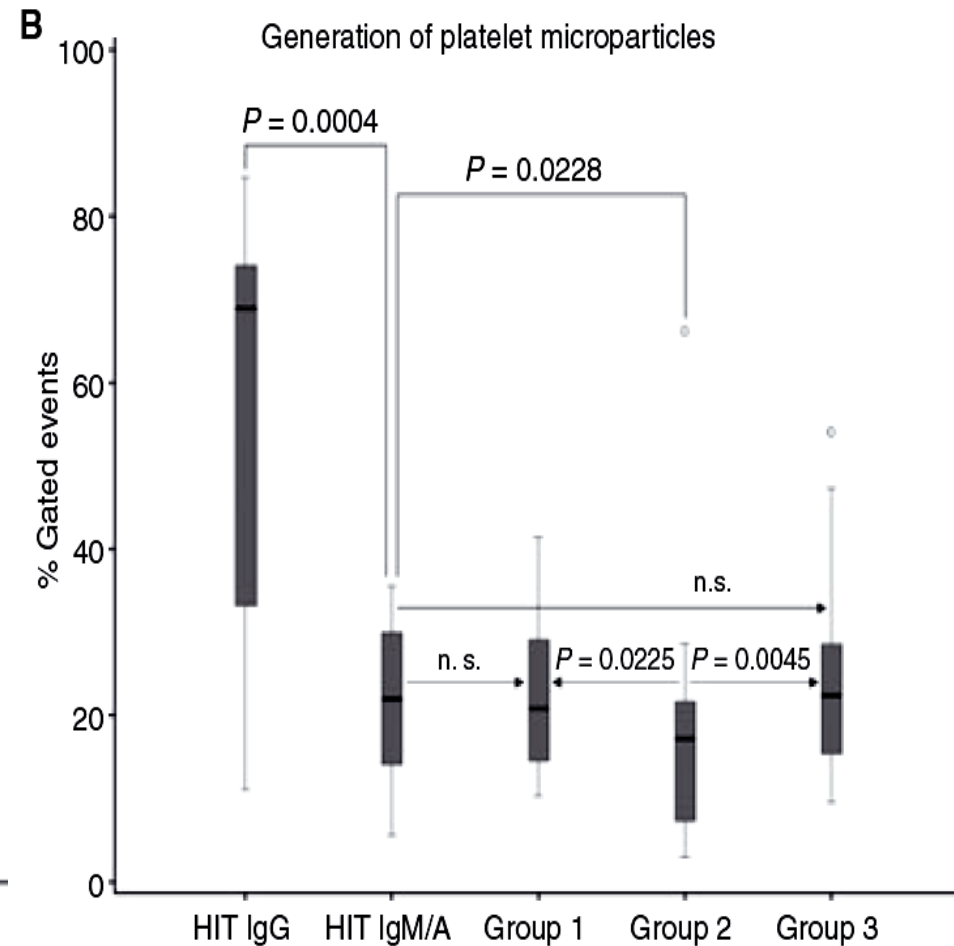
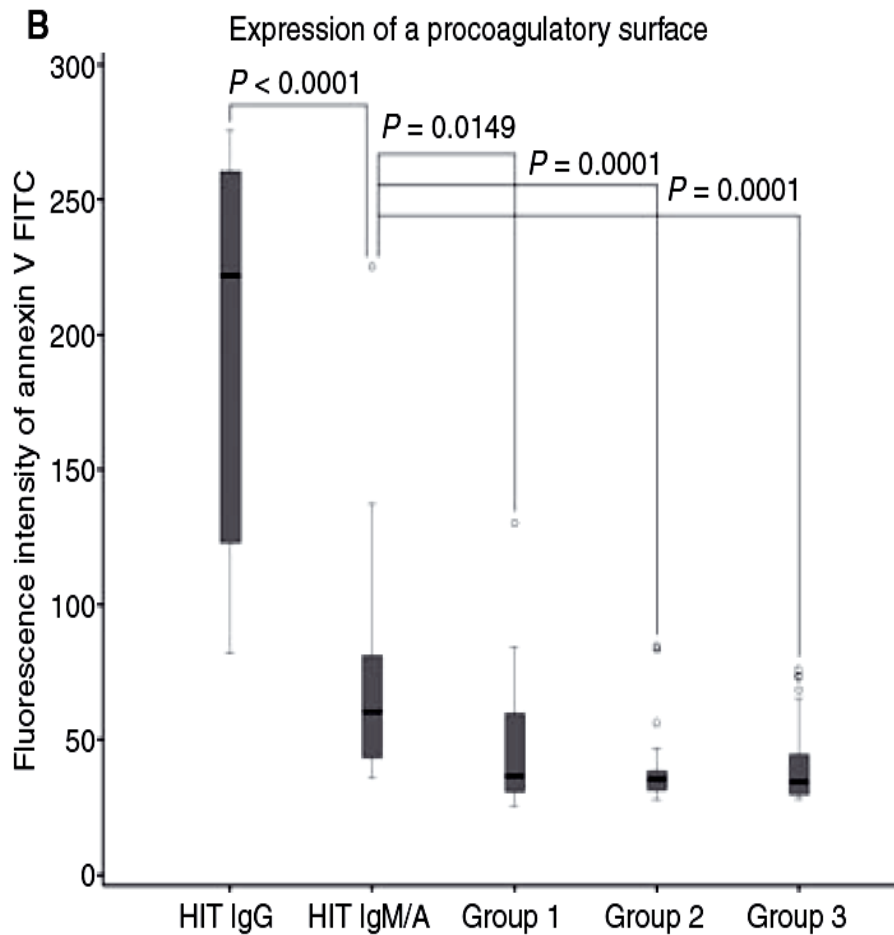
Does IgG testing only improve the specificity?

1. Suh Am J Hematol.1997;54;196-201

2. Vun Br J Haematol.2001;112;69-75

3. Lindhoff Last Br J Haematol. 2001;113;886-890.

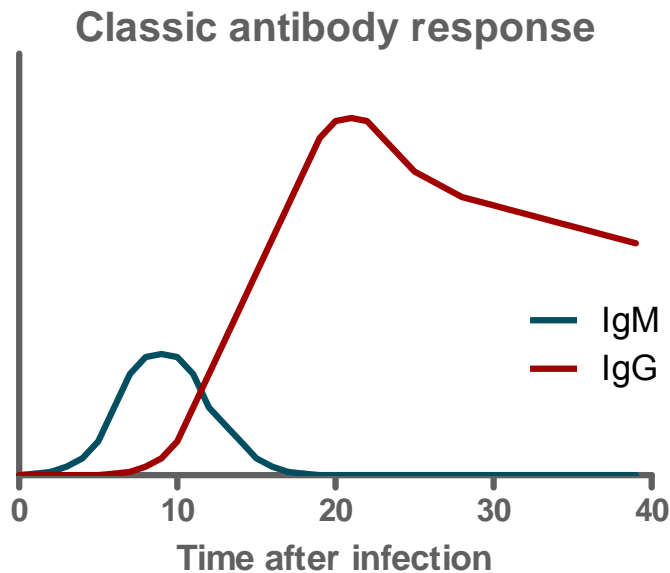
Do IgM/A antibodies produce procoagulant platelet changes?



How many thrombotic events occur with IgM/A only?

- 13 of 14 IgM/A + patients had – HIPA
 - No thrombotic events.
 - All thrombocytopenic with good other reasons than HIT.
 - 1 patient with + HIPA had low clinical probability for HIT.

Does Ig class switching occur?



- In HIT IgG/A/M appear simultaneously and transiently without IgM precedence even without previous pharmacologic heparin exposure¹.



How many of + EIA caused by IgM/A only?

- 10 – 30%^{1–5} IgM/A only
- PPV IgG/M/A vs IgG: 28 – 50: vs 40 – 57%
- Only 40 – 50% of IgG + samples also + on platelet activation assay.
- Different patient populations and definitions of HIT
- Review⁶:

	Sensitivity %	Specificity %	PPV %	NPV %	LR +	LR -
Polyspecific ELISA	98.1	89.4	38.7	99.9	9.29	0.021
IgG specific ELISA	95.8	93.5	49.6	99.7	14.64	0.045

1. Greinacher J Thromb Haemost 2007; 5: 1666–73.

2. Bakchoul J Thromb Haemost 2009; 7: 12605.

3. Warkentin J Lab Clin Med 2005;146:341–6

4. Lo Am J Hematol. 2007;82:1037-1043

5. Juhl Eur J Haematol. 2006;76:420-426.

6. Cuker Hematology 2009; 250 - 252

Laboratory testing - seroconversion

Table 2. Type of injury/surgical procedure related to outcome

Surgical procedures	Number of patients	Seroconversion		HIT cases	
		UFH	LMWH	UFH	LMWH
Major surgical procedures					
Fracture humerus	63	5	1	—	—
Fracture hip/pelvis	54	3	2	—	—
Fracture femur	59	5	2	2	1
Knee endoprosthesis	3	1	—	1	—
Fracture head of tibia	15	2	—	1	—
Fracture tibia	30	1	—	—	—
Total major surgical procedures (95% CI)	224	17/100, 17.0% (9.6-24.4)	5/124, 4.0% (0.6-7.4)	4/100, 4.0% (0.2-7.8)	1/124, 0.8% (0.0-2.4)
		<i>P</i> = .001		<i>P</i> = .18	
Minor surgical procedures					
Lower arm/hand	123	1	—	—	—
Shoulder	21	—	—	—	—
Knee (eg, cruciate ligament rupture)	23	—	—	—	—
Fracture ankle joint	57	2	—	—	—
Foot	19	—	—	—	—
Removal of metal	35	—	—	—	—
Fracture spine	14	—	—	—	—
Tendon injury	26	—	—	—	—
Others	19	—	—	—	—
Total minor surgical procedures	337	3/189 (1.6%)	0/148 (0.0%)	0/189 (0.0%)	0/148 (0.0%)
Total no surgical procedures	53	1/27 (3.7%)	0/26 (0.0%)	0/27 (0.0%)	0/26 (0.0%)
Total (95% CI)	614	21/316, 6.6% (3.9-9.3)	5/298, 1.7% (0.2-3.2)	4/316, 1.3% (0.1-2.5)	1/298, 0.3% (0.0-0.9)
		<i>P</i> = .002		<i>P</i> = .37	



Conclusion

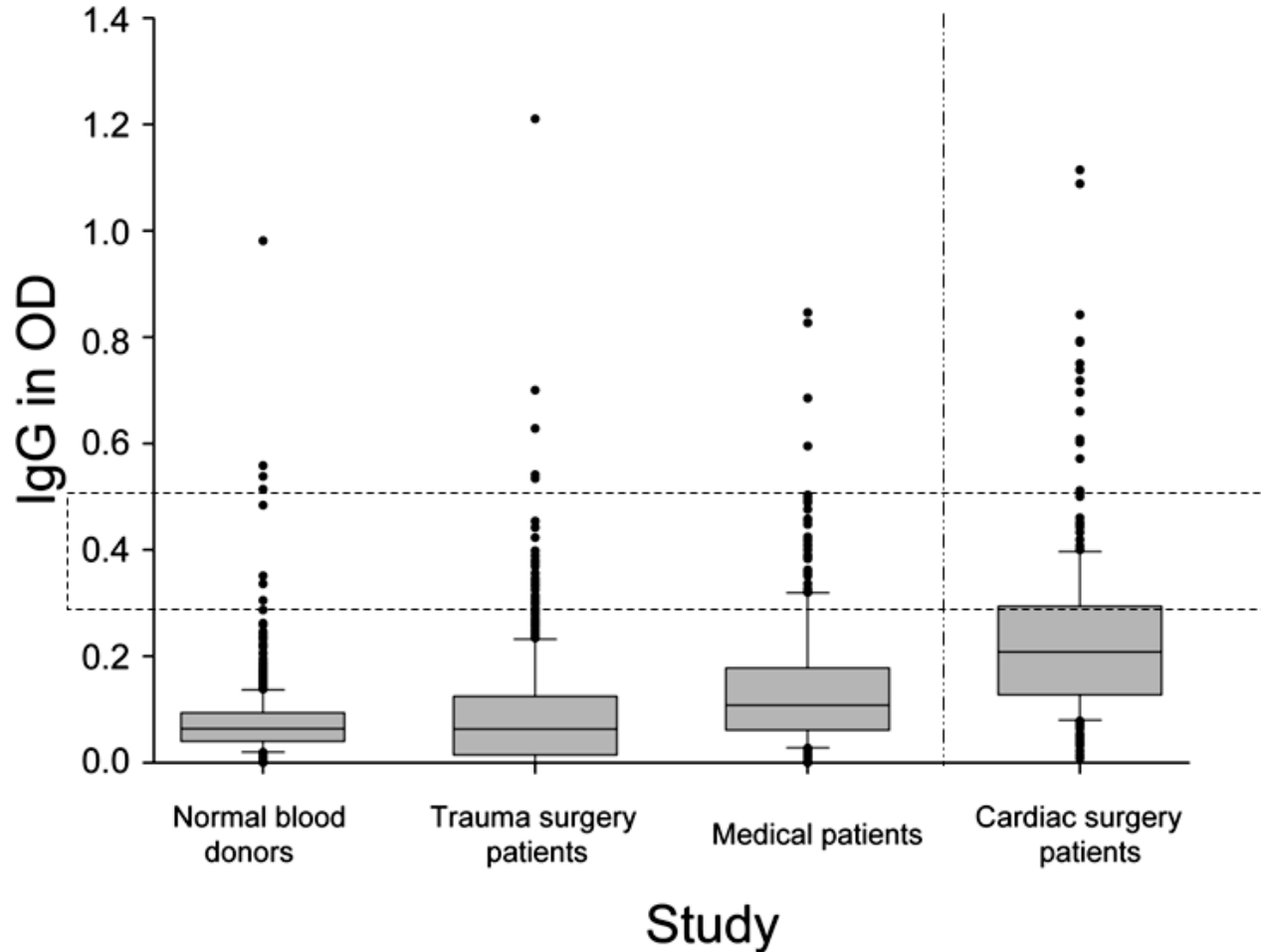
- High sensitivity of IgG/A/M EIA: can rule out HIT.
- Cannot fully exclude possibility that IgM/A can contribute to some degree of platelet activation and thrombocytopenia but clinically seems not important.
- IgG has higher specificity but still poor PPV

Optical density and risk of HIT

- Can the specificity be improved upon by:
 - Higher cut off values?
 - degree of positivity?
 - Confirmation procedure with excess heparin?



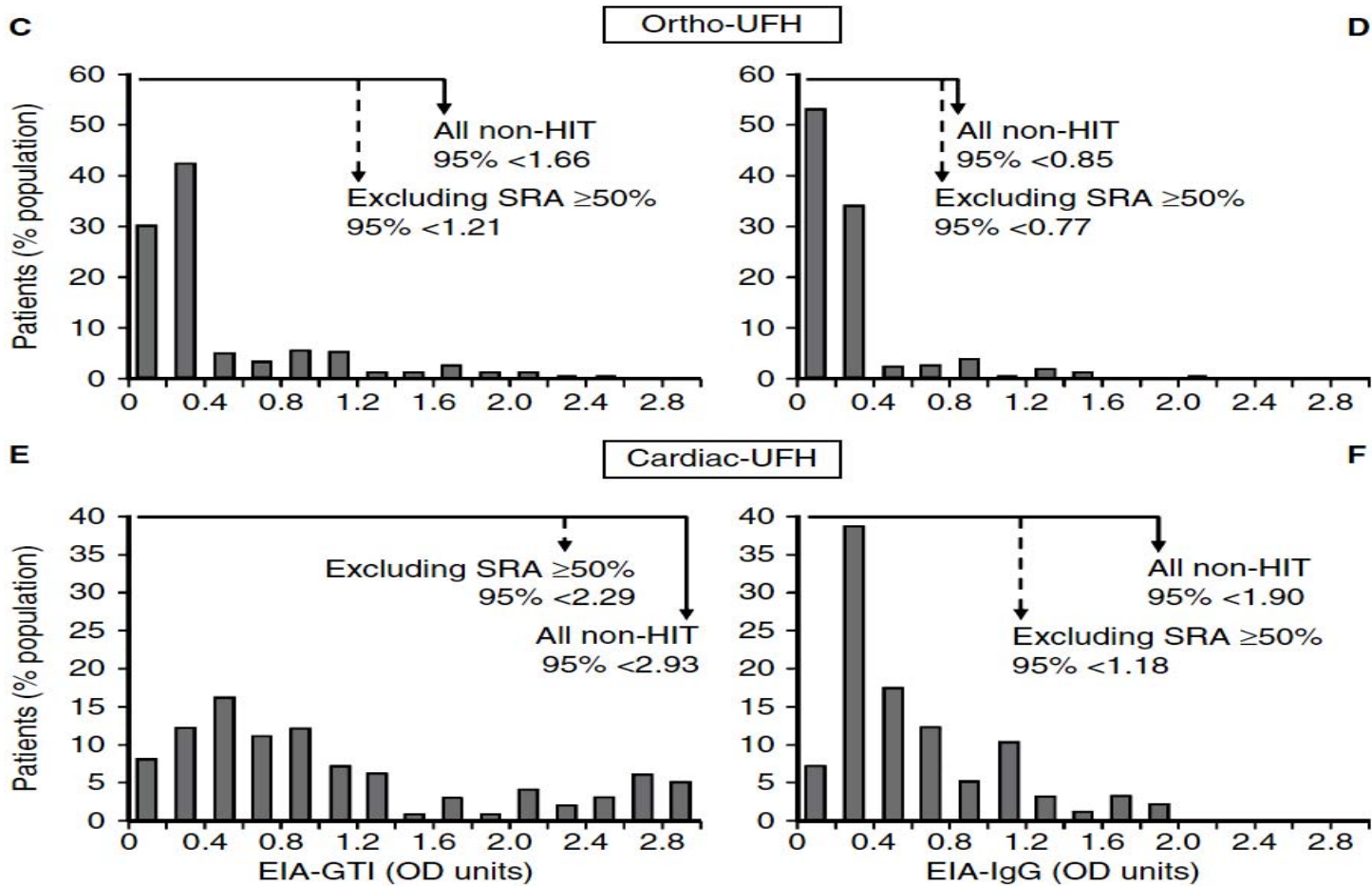
OD in different groups before heparin prophylaxis¹



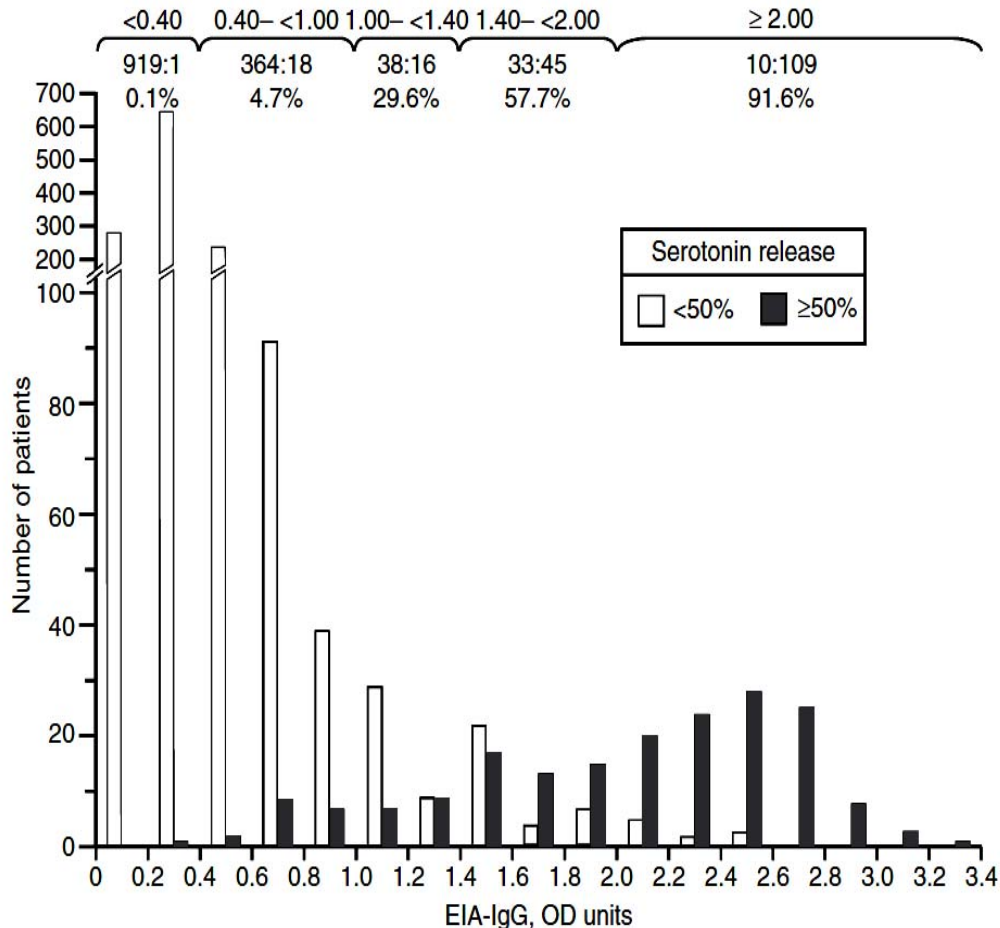
1. Greinacher J thromb Haemost 2010 online. doi: 10.1111/j.1538-7836.2010.03974.x



OD in non HIT patients after > 5 days heparin prophylaxis¹



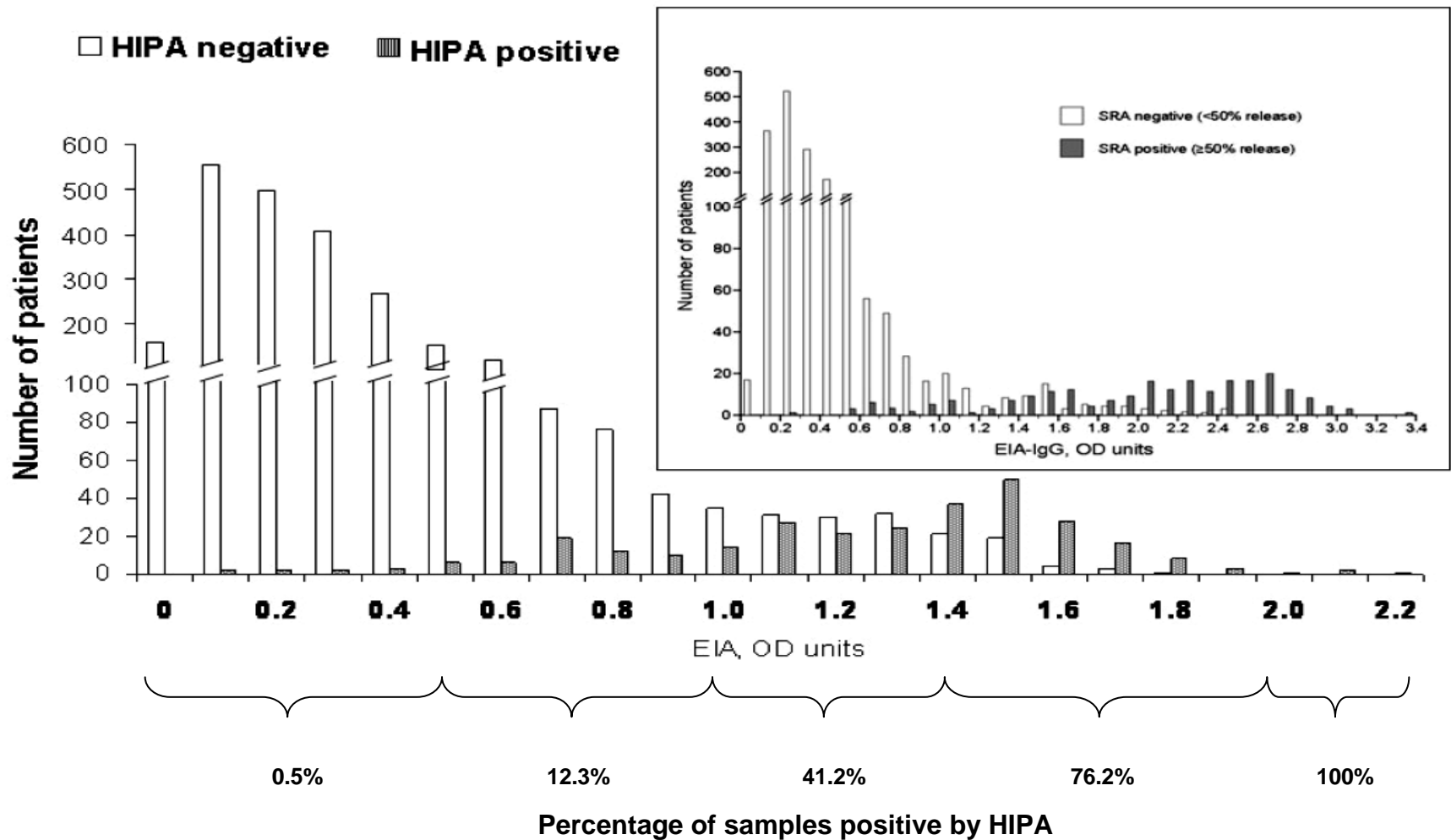
Laboratory testing - OD



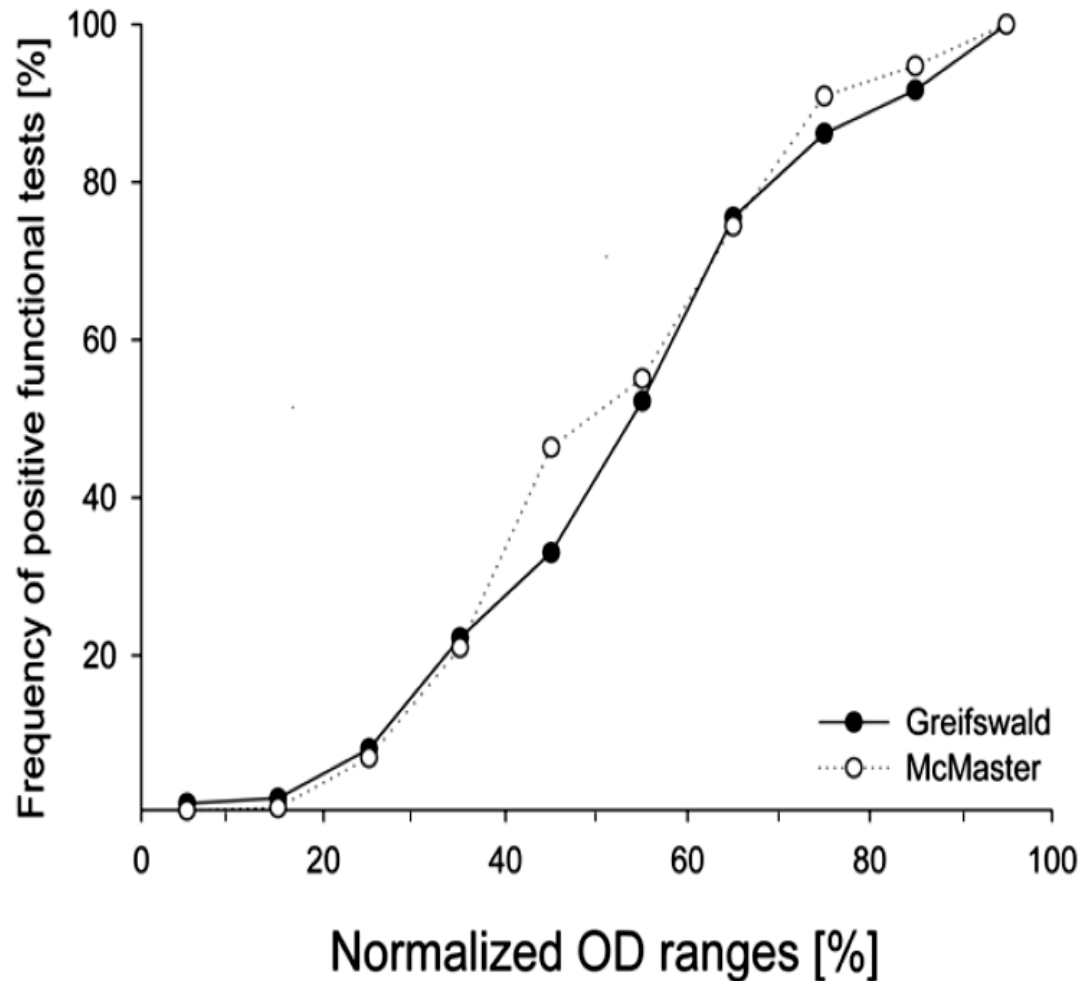
- Increase of 0.50 OD units EIA-IgG, risk of strong positive SRA increased by OR = 6.39
- Increase of 1.00 OD units EIA-IgG, risk increased by OR = 40.81.
- At OD 1.4 diagnosis HIT is more likely than not.
- Weak positive test (OD 0.40 -1.0) is strong evidence against HIT.
- Reporting in ranges allows risk stratification.

Is this reproducible between laboratories?

Predictivity of platelet activating antibodies by OD in 2 laboratories



Predictivity of platelet activating antibodies by OD in 2 laboratories



- Normalization of OD *may* make risk assessment generalizable.
- Does not replace functional assay.
- Positive functional assay does not mean clinical HIT.
- Needs clinical risk score.

Greifswald OD:	0-<0.22	<0.44	<0.66	<0.88	<1.1	<1.32	<1.54	<1.76	<2.0	<2.2
McMaster OD:	0-<0.3	<0.6	<0.9	<1.2	<1.5	<1.8	<2.1	<2.4	<2.7	<3.0

Confirmatory procedures for heparin dependent antibodies

- Inhibition of + ELISA result by >50% in the presence of excess heparin considered confirmatory of heparin dependent antibodies¹.
- Recommended by
 - BCSH guidelines for HIT²
 - In patients with low OD measurements (<1.0)³

Does this enhance specificity without loss of sensitivity?

1. Package insert, 'PF4 Enhanced®', GTI, Waukesha, WI
2. Keeling Br J Haematol 2006; 133, 259–269
3. Greinacher J Thromb Haemost 2009; 7 (Suppl. 1): 9–12

Confirmatory procedures for heparin dependent antibodies

- 98 post cardiac surgery samples¹:
 - 78 + with IgG/A/M
 - 76 “confirmed”
 - 20 SRA +
 - 1 Clinical HIT
 - 2 “not confirmed”
 - 1 strongly SRA and IgG +

“Procedure does little to improve diagnostic specificity in post cardiac surgery patients but doubles the cost¹.”

Confirmatory procedures for heparin dependent antibodies

- 1194 samples, 115 ELISA + patients (\approx 50% surgical, 50% medical)¹
 - 98 “confirmed” (56 met ACCP clinical criteria for HIT).
 - 17 “not confirmed” (2 met ACCP criteria for HIT and 1 ?HIT)
 - OD 1.1, 2.2, 3.3: ? Risk of misclassification and reduced sensitivity.
 - 72% vs 18% met clinical criteria for HIT in “confirmed group”

Confirmatory procedures for heparin dependent antibodies

- Highly SRA reactive sera and/or high antibody sera may fail confirmatory procedures¹.
- Overall OD levels better predictor than confirmatory procedure.
- Confirmatory procedure may have a role at low OD's^{1,2} as an unconfirmed test would make HIT very unlikely.

1. Warkentin Thromb Haemost 2008; 100: 523-524

2. Greinacher J Thromb Haemost 2009; 7 (Suppl. 1): 9–12

Conclusion

- HIT can be excluded with a low clinical pre-test probability or negative immunoassay.
- IgG only assays improve specificity but still have a low PPV and significant risk of overdiagnosis.
- HIT is unlikely, but not excluded, at low OD. There may be a role for confirmatory steps.
- HIT is very likely with high optical density.
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