

Diagnosis of Heparin-induced Thrombocytopenia (HIT)

Meet the Hemostasis Experts III

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Conflict of Interest Statement

- In the past 5 years I have received honoraria for advisory boards and/or research support from the following company:
Axon Lab, Baxalta, Bayer, Boehringer Ingelheim, CSL Behring, Siemens, Glaxo Smith Kline, Novo Nordisk, Pfizer, Roche und Sanofi Aventis
- I was free regarding the choice of this presentation's content
- My activities follow GL of the SAMW and FAMH

Introduction: a voyage



1. View of the world

- Map of the world of Hekataios of Millet (6th century bc): world as disk
- Martin Waldseemüller and Matthias Ringmann: Worldmap, Globe und explaining text)

2. Starting point

- Where do I start from?

3. Goal

- Where do I want to go?

4. Tools

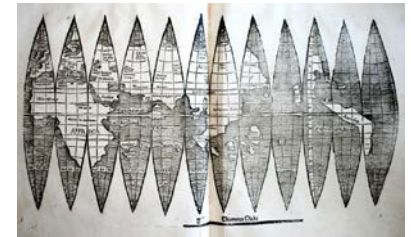
- which resources do I have available

5. The trip itinerary

- a predefined plan with starting- and endpoint that acknowledges available resources and timeline (and potential alternatives)

6. Motivation

- Why am I going on this voyage?



Introduction: HIT - a diagnostic journey



1. View of the world

"model"

- pathogenesis of HIT: an immune mediated drug-induced thrombocytopenia
- beware of overdiagnosis

2. Starting point

- **acquired thrombocytopenia**

3. Goal

- **positive patient outcome:** safe and efficient

4. Tools

4T score, antigenic and functional tests

- patient history, clinical findings, laboratory tests (screening and confirming)

5. The trip itinerary

- a comprehensive **algorithm** defined for an individual institution with a timeline

6. Motivation

- I will get back to this

7. Outlook

- What we need in the future?

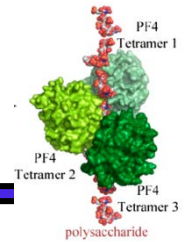


Aims of this talk:

- Provide useful information regarding HIT diagnosis
- Make you aware of (and fear) HIT **overdiagnosis**
- Convince you that you must establish your own **local algorithm**

*Warkentin TE , Seminars Thromb Hemost 2004; 30:273
HIT paradigms and paradoxes; JTH 2011; 9(Suppl 1): 105-17

1. Model (or world view)

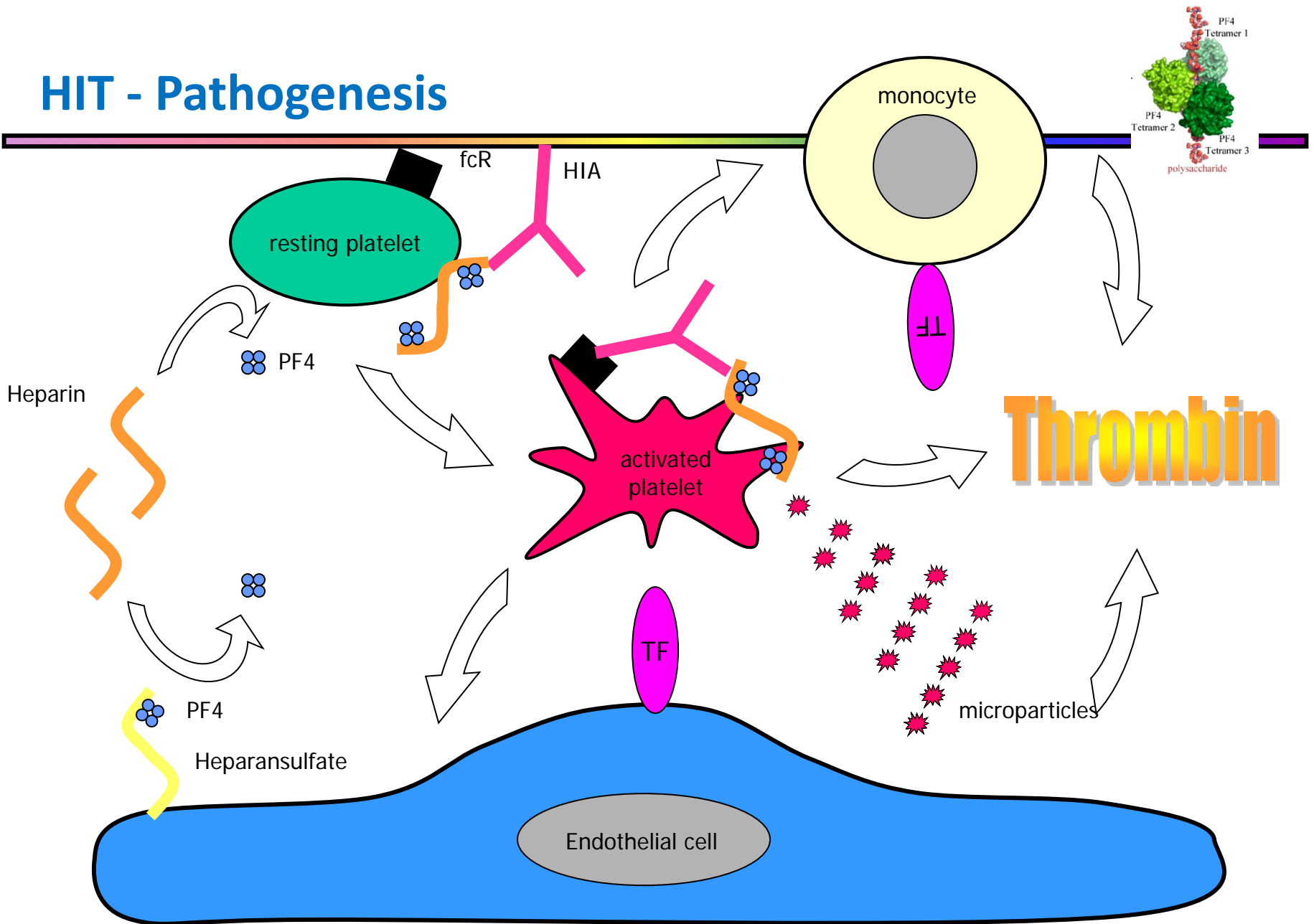


Definition:

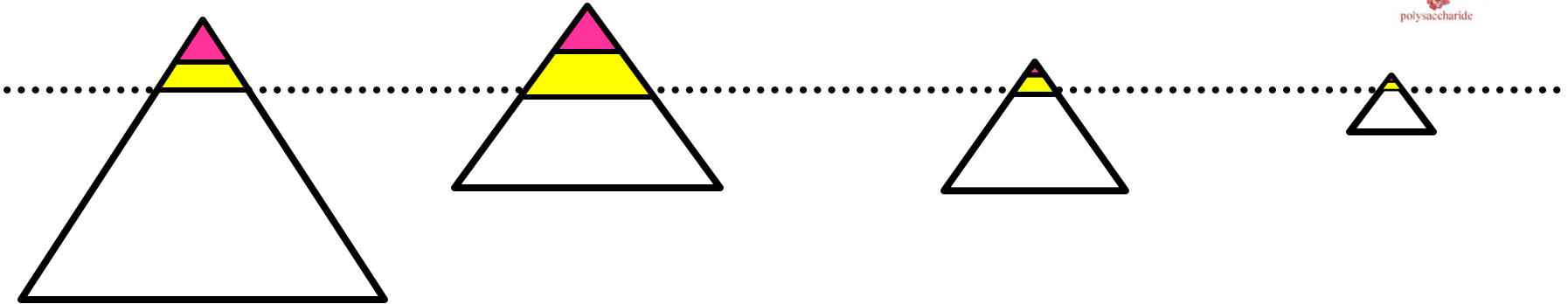
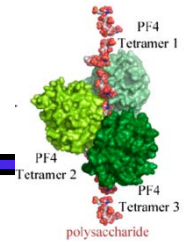
- “clinicopathologic syndrome” (T. Warkentin)
- Thrombocytopenia
 - absolute <math><150\text{ G/l od }150\,000/\mu\text{l}</math>
 - relative >50% drop in platelet count
- Exposure to heparin (in the last 100 days)
all heparins: UFH > LMWH; bovine > porcine
- Time course: platelet drop typically after 5-10 days
(but “early onset” and “delayed onset HIT”)

*Warkentin TE , Seminars Thromb Hemost 2004; 30:273
HIT paradigms and paradoxes; JTH 2011; 9(Suppl 1): 105-17

HIT - Pathogenesis



1. HIT Iceberg modell (~ Warkentin)



CardiacSx-UFH:
50%-2%-1%

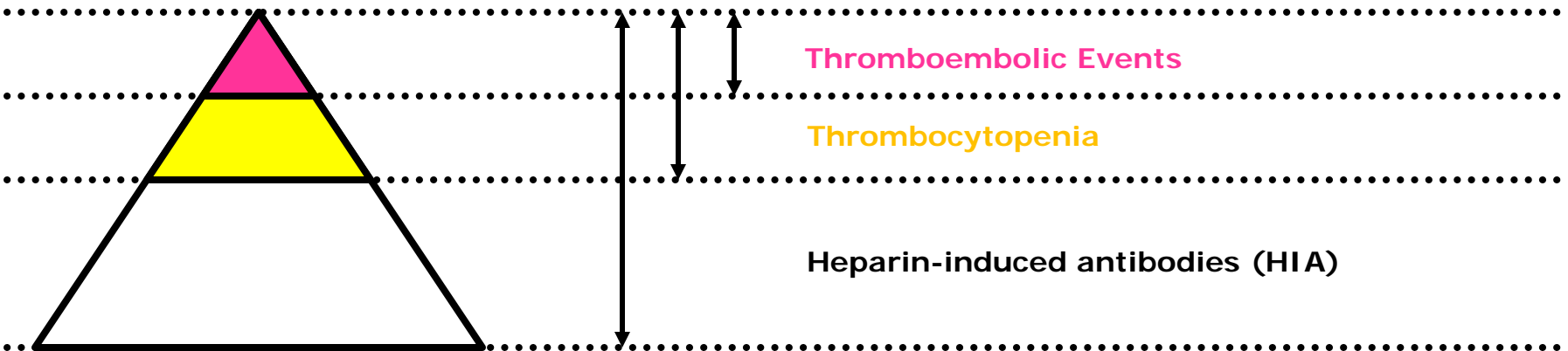
OrthoSx-UFH:
15%-5%-3%

OrthoSx-LMW:
8%-1%-0.5%

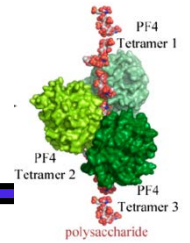
MedicalPt-UFH:
3%-0.5%-0.25%

Surgery (Sx)

Medical



1. Over-Diagnosis of HIT



Acquired TCP in ICU setting^{1,2,3}

- acquired TCP (HIT+/?/?): occurs in 30-50% of patients
- true positive HIT (HIT+/+/+): occurs in 0.3-0.5% of these patients

1:100!

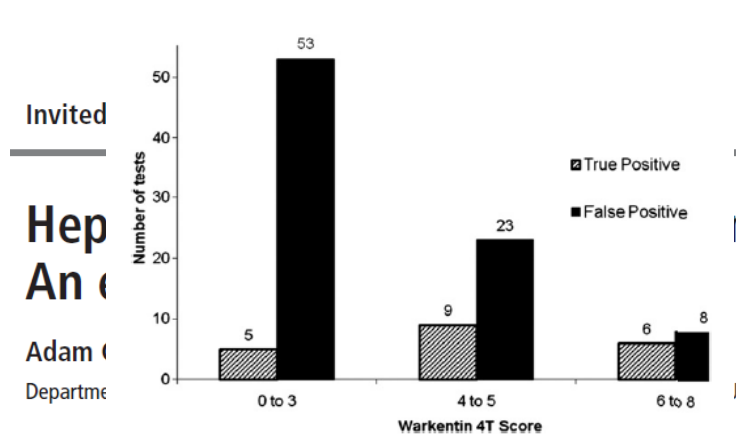


Figure 2. Heparin-induced thrombocytopenia (HIT) results, grouped by Warkentin score (0 to 3, HIT unlikely; 4 to 5, intermediate suspicion; 6 to 8, high suspicion) (x-axis), from 104 Warkentin tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with SRA \geq 20%. False positive, black bar, patients with a serotonin releasing assay < 20%.

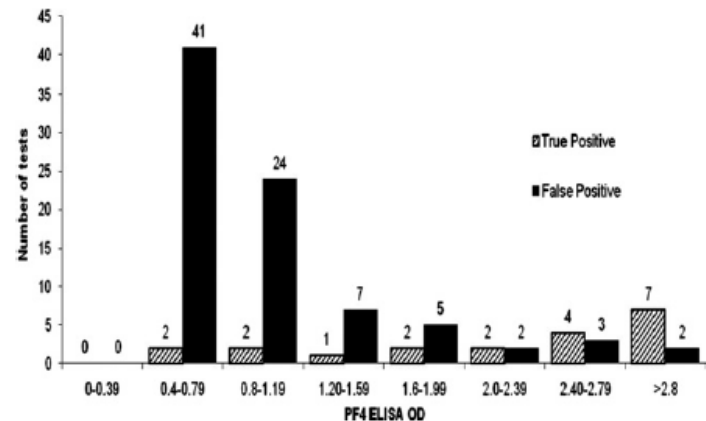


Figure 3. Heparin-induced thrombocytopenia (HIT) results, grouped by 0.4 optical density (OD) (x-axis), from 104 PF4 ELISA tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with serotonin releasing assay (SRA) \geq 20%. False positive, black bar, patients with a SRA < 20%.

2011 993

- lack of specificity of diagnostic tests
(many positives: true and false positives)
- tests can be very sensitive (to rule out disease)

1. Warkentin HIT in critically ill patients. Critical Care 2011; 805-23 2. Berry et al JAMCollSurg 2011; 213;10-17. 3. Demma LJ Anasth Analg 2011; 113:697.

2. Where do I start from?

DD of acquired thrombocytopenia



1. Consumption TCP

- SIRS, Sepsis
- DIC (PT, aPTT, Fibrinogen, D-Dimere, Tc)
- Medications
- uncontrolled bleeding
- hemofilters, dialysis
- IABP
- TTP/HUS
- ITP

2. Production TCP

- Medications (chemo therapy)
- Toxins (alcohol)
- BM infiltration a/o necrosis
- (ITP)

3. Pooling TCP

- Splenomegaly (portal hypertension)

LoE: Low

Lars' rule of thumb (not-evidence based):

consider a HIT test (4T and ELISA/EIA),

when HIT is in #1 or #2 position of your DD

2. Where do I start from?

Severity of acquired thrombocytopenia

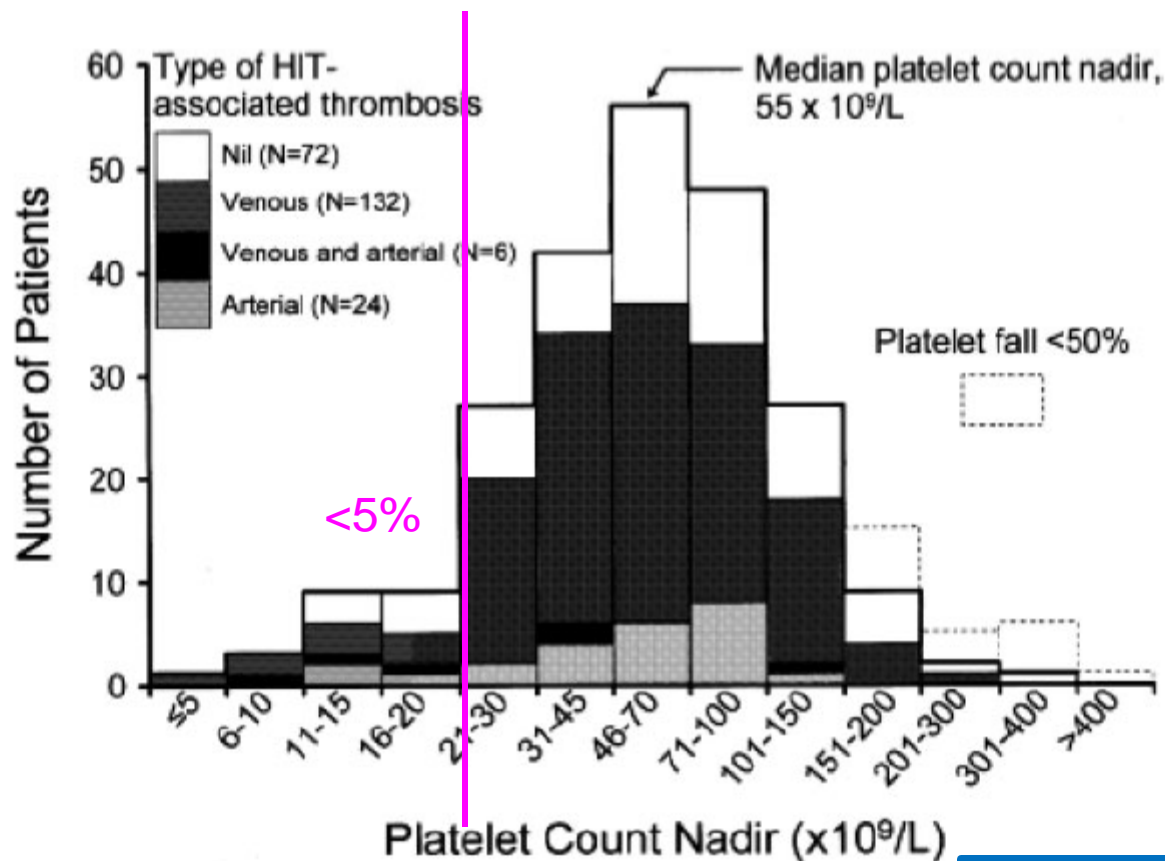


Fig. 1. Platelet counts at the time of diagnosis in 234 patients with heparin-induced thrombocytopenia.

LoE: Med

Lars' rule of thumb (partially-evidence based):

if you have acquired TCP <20 G/l HIT is unprobable
(unless you have HIT plus another etiology)

3. Where do I want to go?



1. Fast and adequate diagnosis

- true positives **HIT+//+//+** functionally active HIA
- false positives **HIT+//+/-**
- true negatives **HIT+/-/- or nd**
- false negatives **HIT+/-/+**

2. Efficient and safe treatment

- true positives require alternative anticoagulation
- false positives – cave: anticoagulation in acquired TCP
- true negatives continue heparin
- false negatives – cave: thromboembolic risk

HIT status: 3 parameters, each + or -
HITacquired thrombopenia/HIA status/functional status

4. Tools



Methods of diagnosis

- HIT definitions have varied over time
 - 1958 clinical “pale soft salmon colored” emboli or white (arterial) clots under heparin therapy
 - 1980’s functional tests (heparin-induced antibodies that clot with normal platelets)
 - 1990’s antigenic tests (heparin/PF4/HIA complexes)

Weismann RE Tobin RW Arch surg 1958; 76:219-27.

Silver D. Annals Surg 1983 198:301-6.

Amiral J. J Thromb Haemost 1992; 68:95-6.

4. Tools: Sec

Table 1 Bayesian diagnostic algorithm for HIT that employs the 4Ts score and stratified interpretation of HIT ELISA, with recommendations for reasonable clinical actions based on post-test probability of HIT

Four-T score	Pretest probability of HIT	Anti PF4/H ELISA (OD)	Post-test probability of HIT	Recommendation
0-3	1%	≥ 2.000	42%	Order SRA*
		1.500-1.999	7%	Order SRA*
		0.600-1.499	1%	HIT ruled out†
		< 0.600	0	
4-5	10%	≥ 2.000	91%	HIT ruled in‡
		1.500-1.999	44%	Order SRA*
		0.600-1.499	11%	Order SRA*
		< 0.600	0	HIT ruled out†
6-8	50%	> 2.000	99%	HIT ruled in‡
		1.500-1.999	87%	HIT ruled in
		0.600-1.499	54%	Order SRA*
		< 0.600	0	HIT ruled out/ Order SRA***

“Gut feel

- f.e. low/
- few pub
- works a

HIT Experi

- 8 clinical sens: 95

Simple sc

- low or pl

4T Score

- <4 low, < sens 97.

anti-PF4/H, anti-platelet factor 4/heparin; ELISA, enzyme-linked immunosorbent assay; HIT, heparin-induced thrombocytopenia; SRA, serotonin release assay; OD, optical density. We suggest that the final recommendation in this algorithm should be modified to ‘Order SRA’ (see Discussion). *Stop heparin and start alternative antithrombotic therapy for HIT pending SRA results. †No need for SRA. ‡Stop heparin, begin treatment, no need for SRA. *** Original algorithm recommendation: HIT ruled in, modified algorithm recommendation: Order SRA (see discussion).

bability)

LoE: Med

LoE: Hi

4. Tools: 4T S

Suspicion of HIT based upon the "4 T's"	Score	Pre-test Probability Score Criteria		
		2	1	0
Thrombocytopenia	<input type="checkbox"/>	nadir 20-100, or >50% platelet fall	nadir 10-19, or 30-50% platelet fall	nadir <10, or <30% platelet fall
Timing of onset of platelet fall	<input type="checkbox"/>	day 5-10, or ≤day 1 with recent heparin*	>day 10 or timing unclear (but fits with HIT)	≤day 1 (no recent heparin)
Thrombosis or other sequelae	<input type="checkbox"/>	proven thrombosis, skin necrosis, or ASR†	progressive, recurrent, or silent thrombosis; erythematous skin lesions	none
Other cause of platelet fall	<input type="checkbox"/>	none evident	possible	definite



Bitte bestimmen Sie bei HIT-Verdacht den Score. Wir wollen diesen Score prospektiv evaluieren, um die Diagnose einer HIT an Hand klinischer Symptome zu vereinfachen.

der HIT-Verdacht basiert auf folgenden Kriterien	Score	Wahrscheinlichkeitskriterien		
		2	1	0
Thrombozytopenie	<input type="checkbox"/>	niedrigster Wert ≥20 GPT und >50% Abfall	niedrigster Wert 10-19 GPT oder 30-50% Abfall	niedrigster Wert <10 GPT oder <30% Abfall
Tag des Auftretens des Thrombozyten-Abfalls	<input type="checkbox"/>	Tag 5-10 oder ≤1 bei früherer Heparintherapie (innerhalb der letzten 30 Tage)	unbekannt, aber könnte zur HIT passen bzw. >Tag 10 bzw. ≤Tag 1 bei früherer Heparintherapie (innerhalb der letzten 30 bis 90 Tage)	Tag <4 (keine frühere Heparintherapie)
Thrombosen oder andere Komplikationen	<input type="checkbox"/>	gesicherte neue Thrombose, Hautnekrosen, anaphylaktische Reaktion (anaph. Reaktion nach Heparinbolus)	Fortschreitende oder rezidivierende Thrombose, Verdacht auf Thrombose (noch nicht bestätigt) oder nicht nekrotisierende Hautläsionen	keine Komplikationen
andere Gründe für Thrombozytenabfall	<input type="checkbox"/>	keine	denkbar	definitiv
Wahrscheinlichkeits-Score	<input type="checkbox"/>			

*Warkentin TE, Seminars
Thromb Hemost 2004; 30:273

treat isolated HIT (0.1 mg/kg/h, adjusted by aPTT); to avoid overdosing and anaphylaxis, it may be preferable to omit the bolus, and begin as i.v. infusion (except when facing life-or limb-threatening thrombosis); reduce dose for renal insufficiency

heparinoid: usual i.v. bolus, 2,250 U (body weight 60-75 kg) followed by infusion (400 U/hr for 4 h, then 300 U/h for 4 h, then 200 U/h, adjusted by anti-factor Xa levels); this therapeutic-dose regimen is appropriate both for isolated HIT and for HIT complicated by thrombosis (though higher than approved dose in some jurisdictions); withdrawn from U.S. market (2002)

†† bivalirudin: no bolus, i.v. infusion 0.15 mg/kg/h adjusted by aPTT; limited experience (off-label)

††† fondaparinux: dosing for HIT not established; limited experience (off-label)

†††† delay coumarin pending substantial platelet count recovery (at least >100, preferably >150); begin coumarin in low doses, with at least 4-5 day overlap, stopping alternative anticoagulant when INR therapeutic for 2 days and platelets recovered

depending on physician confidence in the laboratory's ability to rule out HIT antibodies (usually, negative PF4-dependent enzyme-immunoassay and/or washed platelet activation assay performed by an experienced laboratory)

*** some thrombi may require special treatment, e.g., thrombectomy for large limb artery thrombosis

††††† routine ultrasound of lower-limb veins recommended, since many HIT patients have subclinical deep-vein thrombosis (DVT)

4. Tools: Third step – antigenic tests



Table 2. Pooled diagnostic accuracy measures of different classes of immunoassays for diagnosis of HIT

Type of test	No. studies; no. patients*	Statistical model	Sens. (%)	Spec. (%)	LR		Posttest probability of pos. test result			Posttest probability of neg. test result		
					Pos. (95% CI)	Neg. (95% CI)	1% Prev.	7% Prev.	15% Prev.	1% Prev.	7% Prev.	15% Prev.
Polyspecific ELISA												
LT ^{16,19,20,28,30,41,43,44,46,47,49,54,59,61,63,64,68,69,71,74,75,77,79}	31; 8933	Unified†	96.7 (89.7, 99.0)	86.8 (82.0, 90.5)	7.3 (5.4-10.0)	0.04 (0.01- 0.12)	6.9 (5.1, 9.2)	35.5 (28.9, 42.9)	56.3 (48.9, 63.8)	0.0 (0.0, 0.1)	0.3 (0.1, 0.9)	0.7 (0.2, 2.1)
IT ^{19,47,61,65,77}	5; 2334	Unified†	98.4 (90.8, 99.7)	94.9 (90.5, 97.3)	19.3 (10.4-36.0)	0.02 (0.00-0.1)	16.3 (9.5, 26.7)	59.2 (43.9, 73.0)	77.3 (64.7, 86.4)	0.0 (0.0, 0.1)	0.1 (0.0, 0.7)	0.4 (0.0, 1.7)
HT ^{19,30,47}	3; 1014	Fixed effects‡	15.0 (14.5, 15.5)	100 (99.3, 100)	73.4 (28.2-190.9)	0.3 (0.2-0.5)	42.6 (22.2, 65.9)	84.7 (68.0, 93.5)	92.8 (83.3, 97.1)	0.3 (0.2, 0.5)	2.2 (1.5, 3.6)	5.0 (3.4, 8.1)
IgG-specific ELISA												
LT ^{19,20,44,55,63,64,66,69,72,77}	12; 3116	Unified†	98.3 (95.1, 99.4)	85.4 (78.2, 90.6)	6.7 (4.5-10.2)	0.02 (0.01-0.05)	6.3 (4.3, 9.3)	33.5 (25.3, 43.4)	54.2 (44.3, 64.3)	0.0 (0.0, 0.1)	0.2 (0.1, 0.4)	0.4 (0.2, 0.9)
IT ^{19,20,77}	4; 2545	Unified†	91.2 (86.2, 94.5)	93.5 (89.1-96.2)	14.1 (8.1-24.5)	0.09 (0.05-0.15)	12.5 (7.6, 19.8)	51.5 (38.0, 64.8)	71.3 (58.9, 81.2)	0.1 (0.1, 0.2)	0.7 (0.4, 1.1)	1.6 (1.0, 2.6)
HT ¹⁹	2; 1958	Fixed effects‡	60.9 (59.7, 62.1)	99.4 (97.6-100)	97.0 (53.0-177.6)	0.4 (0.3-0.5)	49.5 (34.9, 64.2)	88.0 (80.0, 93.0)	94.5 (90.3, 96.9)	0.4 (0.3, 0.5)	2.9 (2.2, 3.6)	6.6 (5.0, 8.1)
PaGIA												
LT ^{20,36,42,45,46,53,58,64,68,70,72,75,79}	12; 2205	Unified†	96.5 (89.8, 98.9)	93.7 (83.1, 97.8)	15.3 (5.5, 42.3)	0.04 (0.01, 0.11)	13.4 (5.3, 29.9)	53.5 (29.3, 76.1)	73.0 (49.3, 88.2)	0.0 (0.0, 0.1)	0.3 (0.1, 0.8)	0.7 (0.2, 1.8)
IT ⁶⁵	1; 1291	None§	98.9	95.9	24.1	0.01	19.6	64.5	81.0	0.0	0.1	0.2
Lateral flow immunoassay ^{54,56,58,66,70,72}	7; 1163	Unified†	98.4 (85.3, 99.9)	90.3 (84.4, 94.1)	10.1 (6.2, 16.5)	0.02 (0.00, 0.18)	9.3 (5.9, 14.3)	43.3 (31.9, 55.4)	64.2 (52.4, 74.5)	0.0 (0.0, 0.2)	0.1 (0.0, 1.3)	0.3 (0.0, 3.0)
PIFA ²⁸	1; 88	None§	0.0	70.1	2.3	0.5	2.3	14.8	28.9	0.5	3.6	8.1
Latex agglutination assay ³⁷	1; 119	None§	100.0	84.3	3.7	0.0	3.6	21.8	39.5	0.0	0.0	0.0
Polyspecific CLIA												
LT ^{37,38,57,61,62,77}	7; 1008	Unified†	98.9 (92.7, 99.8)	85.6 (79.3, 90.3)	6.9 (4.7-10.0)	0.01 (0.00-0.09)	6.5 (4.5, 9.2)	34.2 (26.1, 42.9)	54.9 (45.4, 63.8)	0.0 (0.0, 0.1)	0.1 (0.0, 0.7)	0.2 (0.0, 1.6)
IT ³⁷	2; 448	Fixed effects‡	97.9 (94.6, 100.0)	93.1 (90.4, 95.8)	13.5 (9.5-18.9)	0.0 (0.0-0.1)	12.0 (8.8, 16.0)	50.4 (41.7, 58.7)	70.4 (62.6, 76.9)	0.0 (0.0, 0.1)	0.0 (0.0, 0.7)	0.0 (0.0, 1.7)
HT ^{37,61,62,77}	5; 755	Unified†	98.3 (69.5, 99.9)	97.5 (94.4, 98.9)	39.5 (17.5-89.2)	0.0 (0.0-0.40)	28.5 (15.0, 47.6)	74.8 (56.8, 87.1)	87.5 (75.5, 94.1)	0.0 (0.0, 0.4)	0.1 (0.0, 2.9)	0.2 (0.0, 6.6)
IgG-specific CLIA												
LT ^{37,57,61,77}	5; 741	Unified†	98.8 (69.2, 100.0)	94.6 (90.7, 96.9)	18.3 (10.6-31.5)	0.01 (0.00- 0.40)	15.6 (9.7, 24.1)	57.9 (44.4, 70.3)	76.3 (65.2, 84.8)	0.0 (0.0, 0.4)	0.1 (0.0, 3.2)	0.2 (0.0, 7.2)
IT ³⁷	2; 448	Fixed effects‡	78.6 (75.9, 81.2)	98.7 (94.6, 100)	42.3 (20.1-88.7)	0.2 (0.1-0.3)	29.9 (16.9, 47.3)	76.1 (60.2, 87.0)	88.2 (78.0, 94.0)	0.2 (0.1, 0.3)	1.5 (0.7, 2.2)	3.4 (1.7, 5.0)
HT ^{37,61}	3; 552	Fixed effects‡	74.2 (71.9, 76.5)	99.1 (96.4, 100)	47.8 (23.2-98.7)	0.2 (0.1-0.4)	32.6 (19.0, 49.9)	78.3 (63.6, 88.1)	89.4 (80.4, 94.6)	0.2 (0.1, 0.4)	1.5 (0.7, 2.9)	3.4 (1.7, 6.6)

4. Toc



Table 2: Continued

Chemiluminescent Assays†					
Althaus 2013 (14)	Italy, England, Germany (448)	Surgical and Medical (NR)	NR	NR	HIPA (loss of turbidity in 30 min)
Legnani 2010 (24)	Italy (102)	Medical (49) Cardiac surgical (10) General surgical (32) Thrombosis treatment (29)	73	47 (46)	PAT > 20% aggregation AND 4T score ≥ 4
Minet 2013 (2)					
Van Hoecke 2013 (2)					
Table 4: Predictive values of rapid immunoassays for HIT.					
Assay		PPV (95 % CI)	NPV (95 % CI)		
PaGIA		0.45 (0.33–0.57)	1.00 (0.99–1.00)		
IgG-CA		0.71 (0.49–0.93)	0.99 (0.98–1.00)		
Poly-CA		0.42 (0.30–0.53)	1.00 (0.98–1.00)		
LFIA		0.66 (0.41–0.90)	1.00 (0.99–1.00)		
NPV, negative predictive value; PPV, positive predictive value; PaGIA, particle gel immunoassay; IgG-CA, IgG-specific chemiluminescent assay; Poly-CA, polyspecific chemiluminescent assay; LFIA, lateral flow immunoassay.					
		Orthopedic (7) Cardiac surgical (20) ICU (17) Other (7)	62.2* (M)		4T score ≥ 4
Latex Particle Enhanced Assay					
Althaus 2013 (14)	Italy and England (119)	Surgical and Medical (NR)	NR	NR	HIPA (loss of turbidity in 30 min)
Jourdy 2015 (20)	France (100)	NR	69 (F) 73 (M)	42 (35)	+/- HIPA (≥ 30% aggregation between spontaneous curve and 0.5 or 11IU/mL curve and inhibited with 100 IU/ml UFH) +/- SRA > 20% release ‡
Particle Immunofiltration Assay					
Andrews 2013 (15)	United States (92)	MICU (100)	54 *	34 (37)	SRA > 20% release

Assay classes used	Regulatory approval
	Asia Australia Canada Europe
	Europe
IgM	Europe
	Europe
IgM	Europe

	n	Quadas-2	Sensitivity	Specificity	NPV
Althaus	119	Hi: 6/7	1.00 (0.83-1.00)	0.76 (0.66-0.84)	0.99
Jourdy	110	Hi: 6/7	1.00 (0.66-1.00)	0.91 (0.83-0.96)	0.99

4. Tools: Third step – antigenic tests



Which test to use?

- Study 1850 patients, single center, divided in 2 periods
period 1: PaGIA (particle gel immune assay) and ELISA (IgG only)
period 2 CLIA (lateral flow immune assay)

➤	test	n	pos	%	cost/test
	PaGIA	892	281	31.5%	12.27
	ELISA	901	83	9.2%	26.17
	CLIA	1174	71	6.0%	37.51

LoE: Low

Lars' rule of thumb (not-evidence based):

you want to choose an antigenic HIA test

that produces few positive results (<10%)

(less positives result in less false positives)

4. Tools: Third step – antigenic tests



IgG (specific) vs IgGAM (polyspecific)

Table 2 Study quality assessment by QUADAS-2 criteria

References	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Warkentin* 2013 [19]	Low	Unclear	Low	Low	Low	High	High
Cuker 2013 [20]	High	Unclear	High	Low	Low	Low	High
Galea 2013 [21]	Low	Unclear	Unclear	Low	Low	Low	High
McFarland 2012 [22]	High	Unclear	High	High	Low	High	High
Van Hoecke 2012 [13]	Low	Unclear	High	Low	Low	Low	High
Morel-Kopp 2010 [23]	Low	Low	High	High	Low	Low	High
Pouplard 2010 [24]	High	Unclear	Low	Low	Low	Low	High
Bakchoul 2009 [25]	Low	Unclear	Unclear	Low	Low	High	High
Warkentin 2008 [15]	Low	Unclear	High	High	Low	High	High

*Determined from data reported in original article, the PROTECT trial, and discussions with Dr. Theodore Warkentin.

Lars' rule of thumb (not-evidence based): 2 alternatives

only one test:

then use IgG specific test

if more than one test

then use IgGAM unspecific test next to IgG

LoE: Hi

LoE: Low

4. Tools: Third step – antigenic tests



LoE: Low

What is a good antigenic (or immunological) test

- sensitivity >99 (98)%
negative predictive value (NPV) >99 (98)%
- Low absolute and relative number of positive tests
few positives = few to follow up on with a functional test
my view: should be below 10%
- Rapid turn around time (20-30 minutes! vs hours to days)
- Low absolute and relative number of false positive tests

4. Tools: Fourth step – functional tests



Serotonin release assay

- Functionally active HIA induce secretory response in healthy donor platelets
- Considered one of two gold standards

Heparin-induced platelet activation

A positive functional test is sufficient condition to prove the HIA's "danger"

- functional HIA (HIT+ / + / +) require alternative anticoagulation (in therapeutic dose)

PS: the presence of an acquired TCP and HIA positivity (HIT+ / + / ?) are the necessary condition

- n.b: platelet count should normalize after 3-5 days, same goes for D-dimers
- Not considered to be “gold standard”

5. The plan



Algorithm*:

- “unambiguous specifications for performing a task”*
- Common features
 - background
 - starting point
 - end point or goal
 - equipment and tools
 - periodic reevaluation!
 - motivation
- abundance of examples/data from other fields indicating things start improving once you define a plan/algorithm

*wikipedia

5. The Algorithm



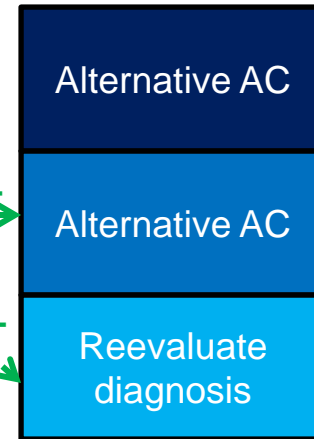
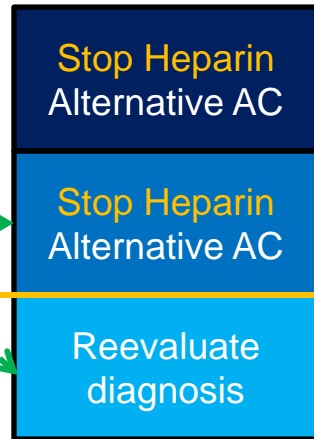
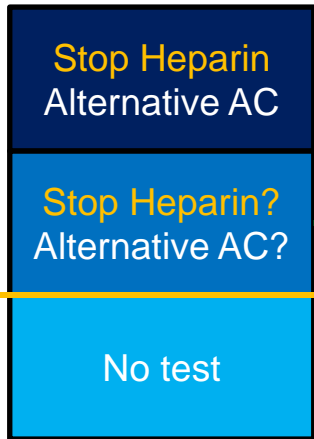
< Day 1!

Pre Test Pb
- 4T score
- Other scores

Post Test 1
- EIA Test
- other Ag Tests

Post Test 2
- HIPA / SRA
- Tc evolution, D-Dimers

High



Medium

Low

5. The Algorithm

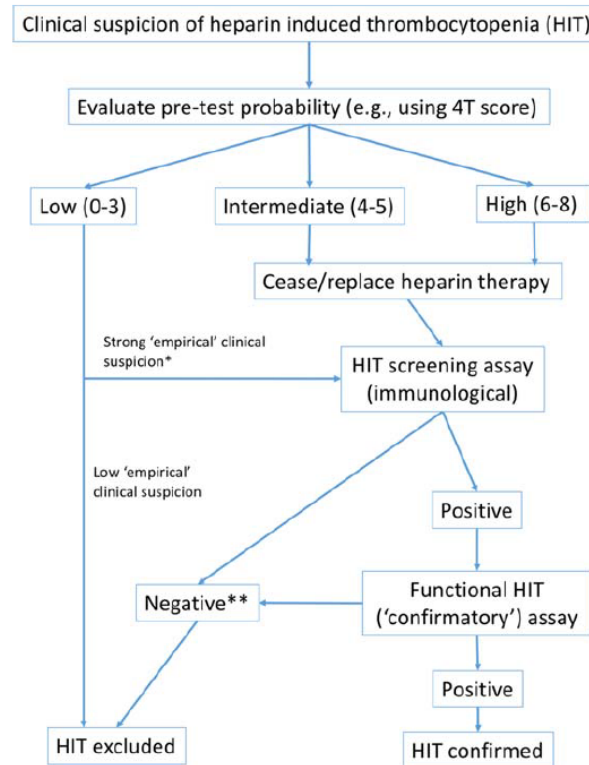


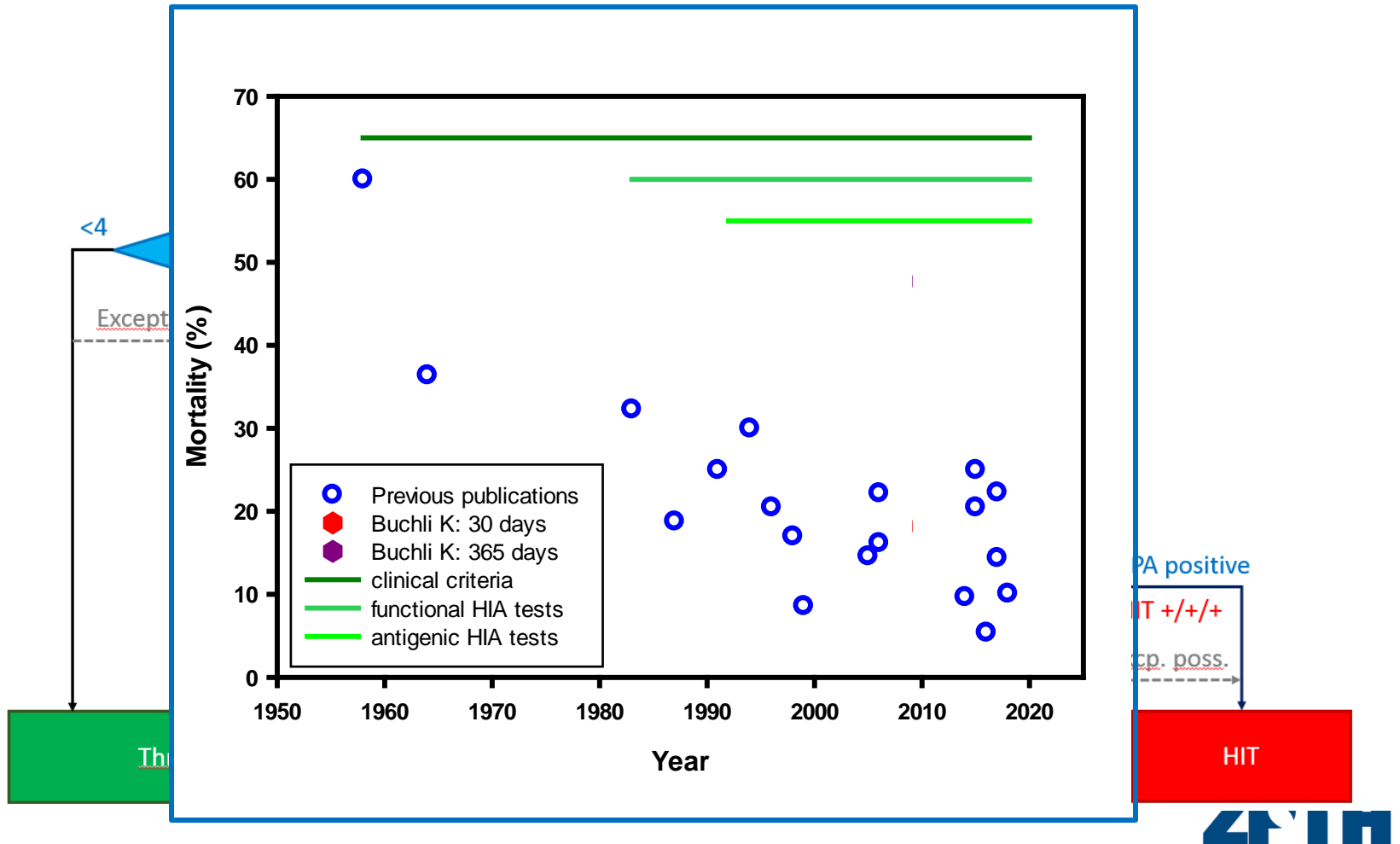
FIGURE 1 An algorithm that reflects a recommended approach to the investigation of individuals with potential heparin induced thrombocytopenia (HIT), based on local^{3,9} and other published experience. Notes: *Strongly recommended that the decision to perform HIT testing in cases with low 4Ts only progress after consultation with a local hematology expert. **Be aware that

6. The Motivation



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A 4 year case-control study at a tertiary hospital:

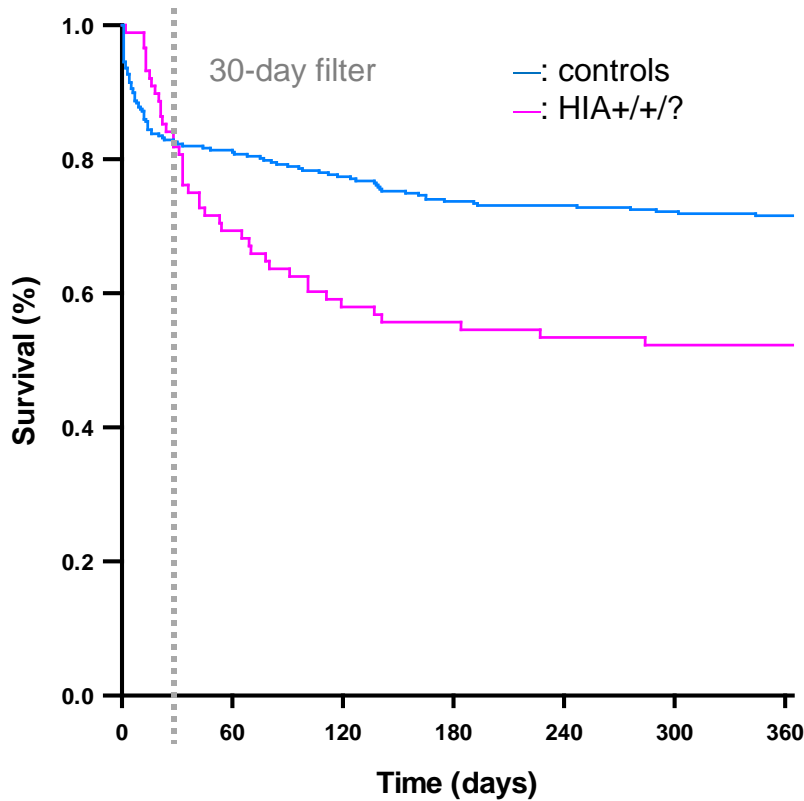


6. The Motivation

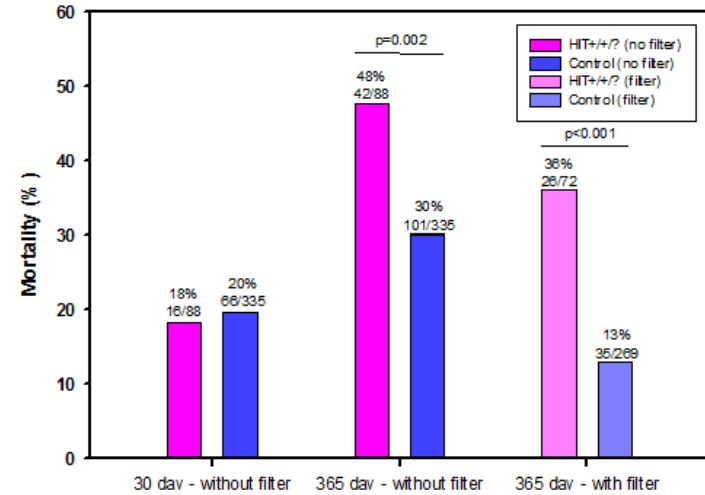


352

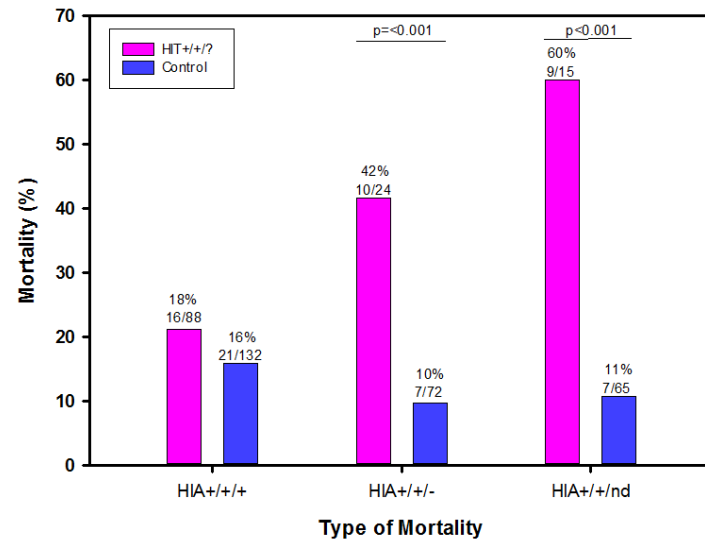
Kaplan-Meier survival: Buchli K et al.



Mortality: without and with 30 day filter

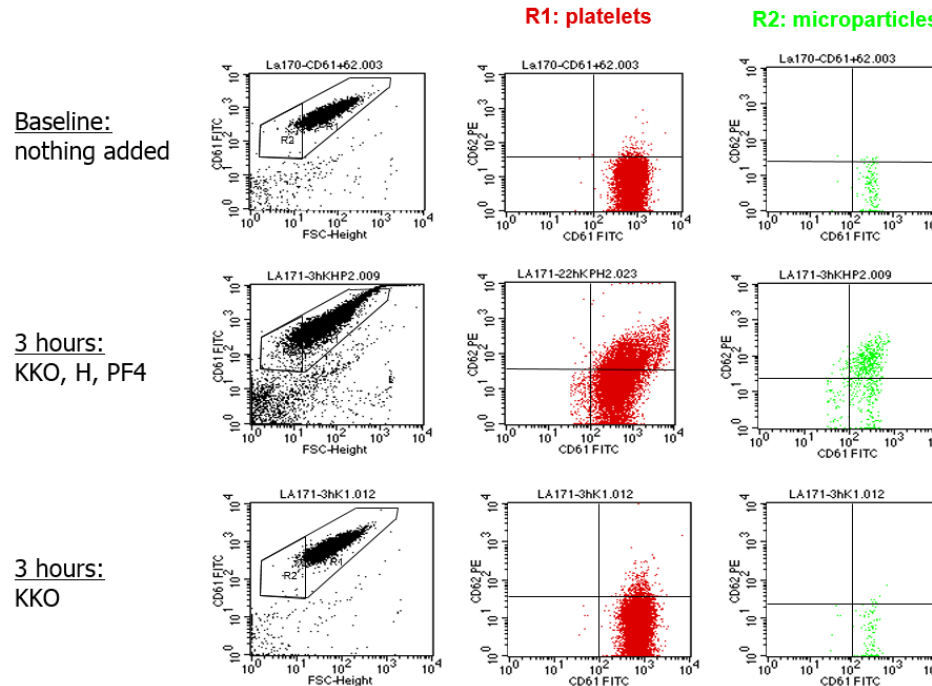


Mortality: without and with 30 day filter





7. Outlook – what we need?



Time limiting factor: functional tests:

- (1) or 3 to 5 days: this needs to be improved
- shorter delays might decrease mortality

Conclusions: HIT - a diagnostic journey



1. View of the world

"model"

- pathogenesis of HIT: an immune mediated drug-induced thrombocytopenia
- beware of overdiagnosis

2. Starting point

- **acquired thrombocytopenia** (median plt count 55 G/l)

3. Goal

- positive

4. Tools

- patient

**Thank you,
for Your attention!**

5. The trip itinerary

- a comprehensive **algorithm** defined for an individual institution with a timeline

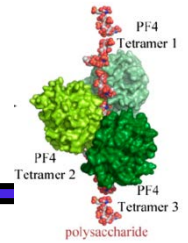
6. Motivation

- 365 day mortality ↑; HIT+/+/+ vs con: ≈, HIT+/+/- and HIT+/+/nd vs con: ↑

7. Future

- we need quicker confirmation!

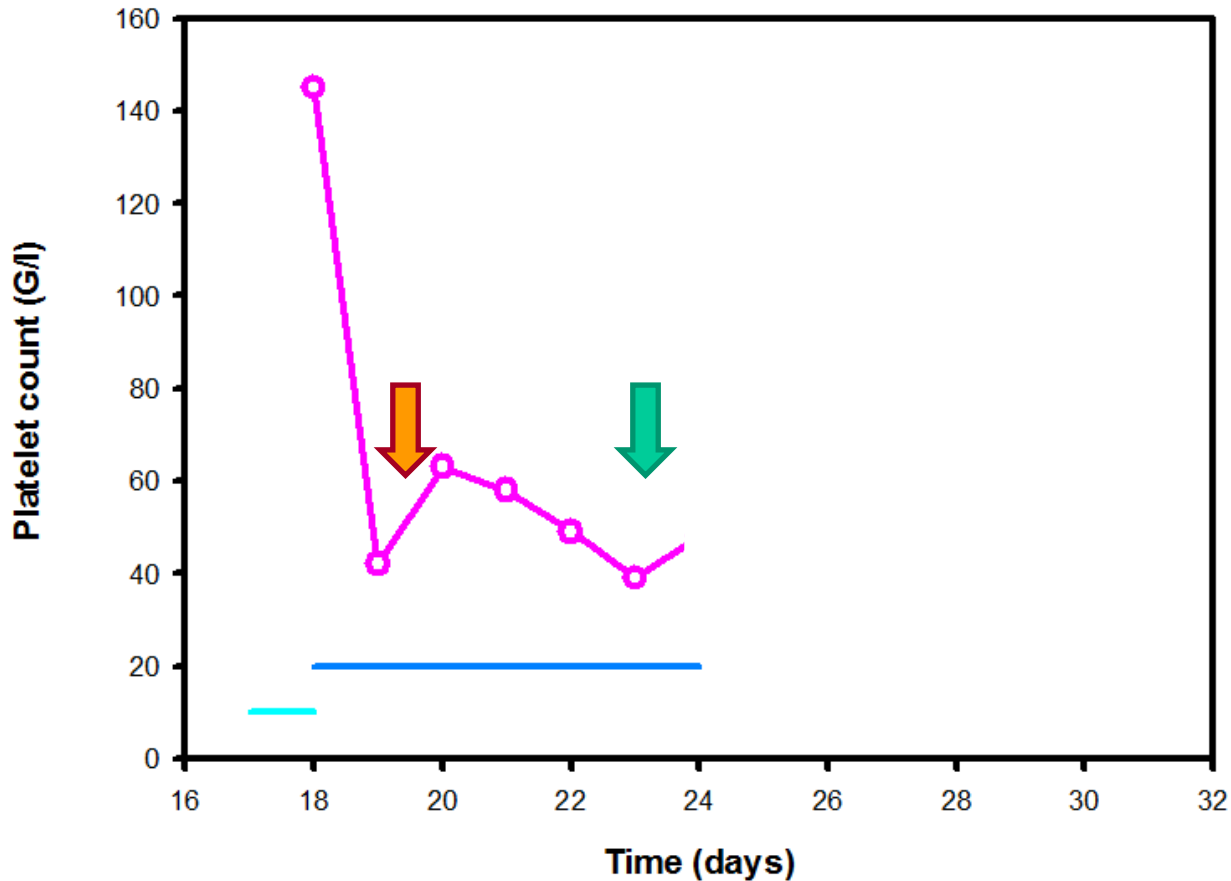
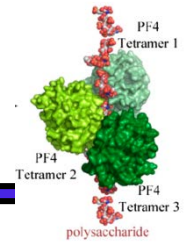
79yo Mrs Cucinelli



Severe mitral insufficiency, AFIB, hypertensive and valvular heart disease, COPD, PAD

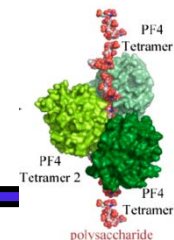
- TEE 30.3.2017: PFO, mitral insufficiency
- Mitra Clip, PFO occlusion (Amplatzer), PM (DDDRP) 30.3.2017
- Electroconversion 30.3.2017
- Electrophysiologic exploration: av node ablation (bled into M psoas under VKA 8/2016)
- Electroconversion 14.4.
- ad cardiac rehab
- Emergency retransfer to ICU 19.5.: severest mitral insufficiency **Plt 145**
- Mitral valve replacement, tricuspid valve reconstruction (Physio Ring), left atrial resection, intraatriale fixation atrial electrode 19.5
- Severe postoperative bleeding, acute renal insufficiency

79yo Mrs Cucinelli



- Heparin pretreated (<100 days!)
- 4T Score: $2 + 2 + 1 + 0 = 5$ (medium pretest probability)

HIT: Monitoring of therapy (argatroban)



aPTT

- Depending on test: prolongation 1.5-2.5 (3)x

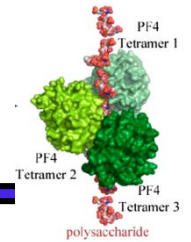
POCT (Table 1 Example nomogram for argatroban²⁸)

➤ aPTT	A. Initial dose of 0.5 µg/kg/min
➤ ACT	If aPTT is ≤39, increase rate by 0.2 µg/kg/min
➤ (ECT	If aPTT is 40 to 49, increase rate by 0.1 µg/kg/min
	If aPTT is 50 to 70, no change
	If aPTT is 71 to 84, decrease rate by 0.1 µg/kg/min
	If aPTT is 85 to 99, decrease rate by 0.2 µg/kg/min
	If aPTT is ≥100, hold and call responding clinician for new order

Anti FIIa

- eQK
- Anti-FIIa target: 0.5.-1.0 µg/ml (not clinically validated; personal op.)

HIT: Therapy



Anti FIIa

	Herst.	Appl	Elimination	t1/2	Reg. appr.
➤ Argatroban	synth	iv	hepatic	kurz	+
➤ Bivalirudin	synth	iv	renal	kurz.	-

Anti FXa

➤ Danaparoid	synth	sc/iv	renal	lang	+
➤ Fondaparinux	synth	sc/(iv)	renal	lang	-

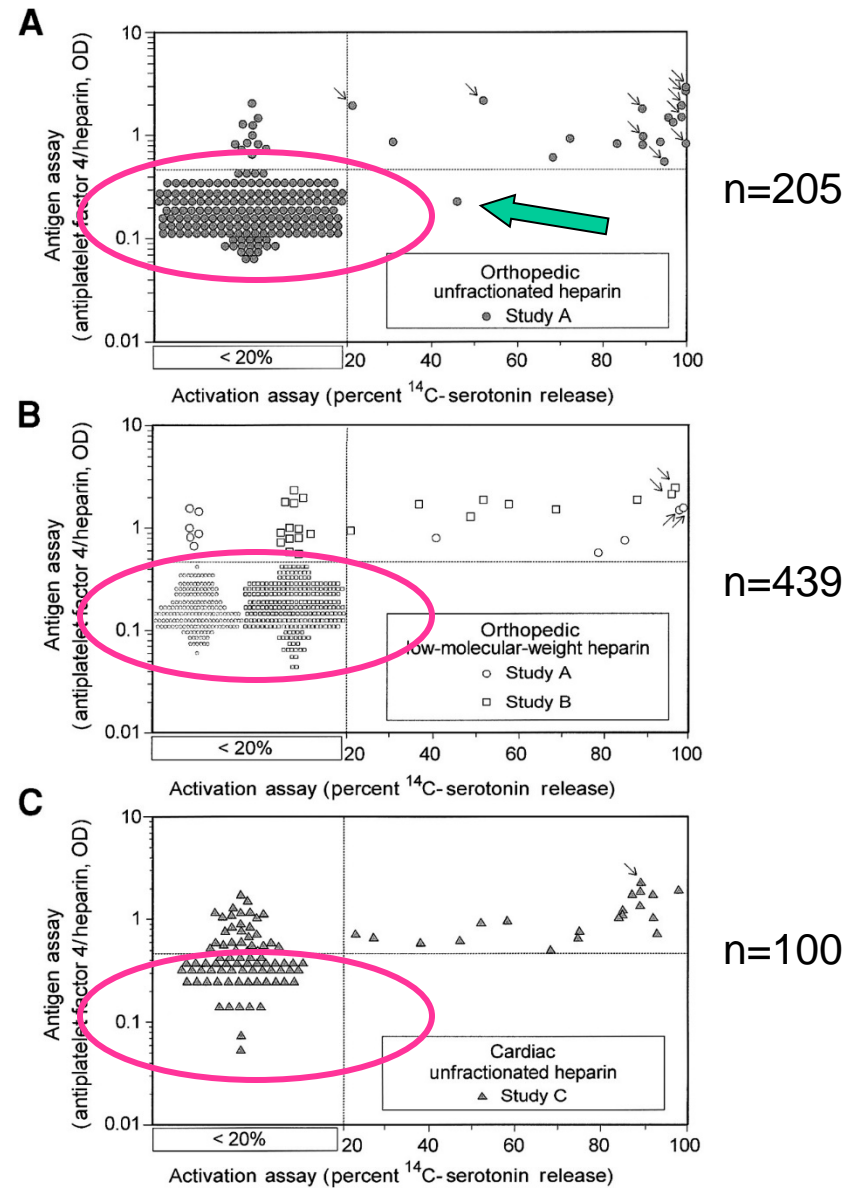
DOAC

➤ Anti FIIa	synth	oral	renal	lang	-
➤ Anti FXa	synth	oral	renal	lang	-

HIT: NPV of ELISA

$$NPV = \frac{\text{Test neg without dz (TN)}}{\text{Test neg (TN+FN)}}$$

$$= >99\% \\ (1/179, 0/406, 0/50)$$



HIT: Klinische Manifestationen

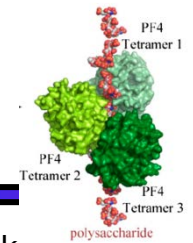


Tabelle 1: Klinische Manifestationen der HIT und deren geschätzte relative Häufigkeit

1. Venös

Tiefe Venenthrombose	+++++
Lungenembolie	++++
Cumarin-induzierte Extremitäten Gangrän	(+)
Zerebrale (Sinus) Venenthrombose	(+)
Hämorrhagischer Nebenniereninfarkt (thrombotisch)	(+)
Andere Venenthrombosen	(+)

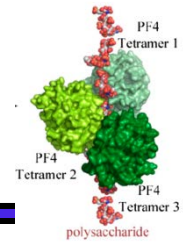
2. Arteriell

Akute Ischämie der (unteren) Extremitäten	+++
Zerebrovaskulärer Insult	++
Myokardinfarkt	+
Thrombosen anderer Arterien	(+)

3. Andere

Hautnekrosen bzw. -ulzera (auch ohne gleichzeitige Thrombopenie)	+
Akute systemische Reaktionen nach Bolus-Injektion	(+)
Dekompensierte intravaskuläre Gerinnung	(+)
Verschluss von Hämodialyse Fisteln	(?)

HIT: Monitoring



How to titrate? Nomogramm

- Case series shows, that a nomogram is faster and safer

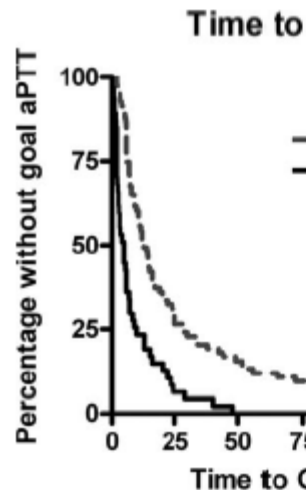


Figure 1. Time to goal aPTT for hist ratio 2.40 (95% CI 2.10–5.23); $P < 0.0$ (95% CI 1.16–3.46); $P = 0.01$. [Color which is available at wileyonlinelibrary.c

APPENDIX B. University of Colorado Hospital Direct Thrombin Inhibitor Protocol Initial Dosage Recommendations and Titration Nomogram

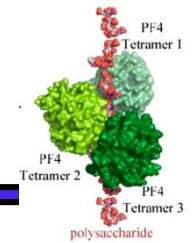
Argatroban ^a	Initial dosage recommendation
Normal hepatic function	1.5 mcg kg ⁻¹ min ⁻¹
Moderate hepatic dysfunction (child pugh B, total bilirubin >2 mg dL ⁻¹)	0.5 mcg kg ⁻¹ min ⁻¹
Severe hepatic insufficiency (child pugh C)	0.25 mcg kg ⁻¹ min ⁻¹
Bivalirudin ^b	Initial dosage recommendation
CrCl >60 mL min ⁻¹	0.15 mg kg ⁻¹ hr ⁻¹
CrCl 45–60 mL min ⁻¹	0.075 mg kg ⁻¹ hr ⁻¹
CrCl 30–44 mL min ⁻¹	0.05 mg kg ⁻¹ hr ⁻¹
CrCl <30 or renal replacement therapy	0.025 mg kg ⁻¹ hr ⁻¹
Standard aPTT goal (seconds) ^c	Dosage adjustment
Less than 35	Increase dose by 50%
35–44	Increase dose by 25%
45–49	Increase dose by 10%
50–80	Goal range. No change
81–90	Decrease dose by 10%
91–100	Hold infusion × 1 hr, decrease dose by 25%
Greater than 100	Hold infusion × 2 hr, decrease dose by 50%

^a Argatroban is preferred over bivalirudin in patients with renal insufficiency.

^b Bivalirudin is preferred over argatroban in patients with hepatic insufficiency or combined hepatic and renal insufficiency.

^c aPTT monitoring schedule: Baseline; 2 hr after DTI initiation; then every 4 hr; then every morning after two consecutive aPTTs in goal on stable DTI dose. Return to monitoring aPTT every 4 hr after any dose modification or aPTT result outside of goal range.

Cardiac Surgery: evolution of platelet count



C. Pouplard *et al*

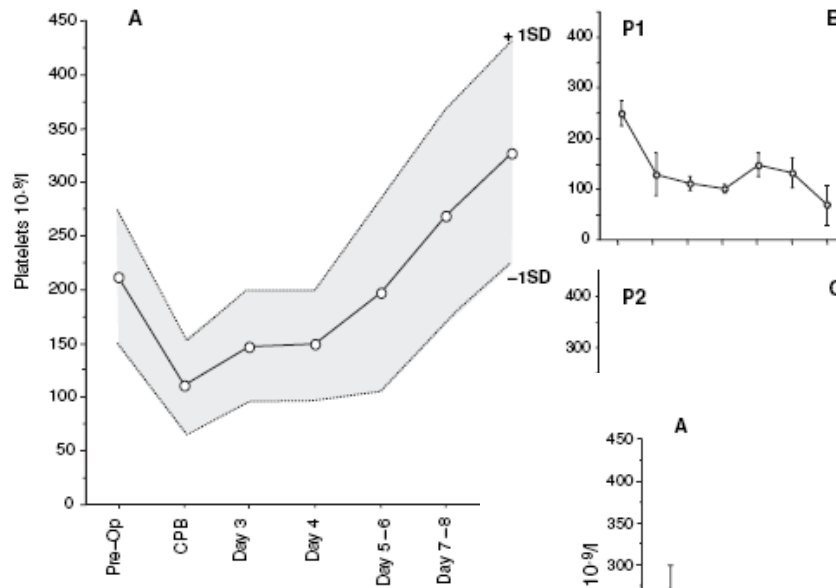


Fig 1. Retrospective cohort. (A) Normal changes in PC after CPB in patients patterns associated with HIT. Patterns P1 and P2 were defined according to t1 respectively.

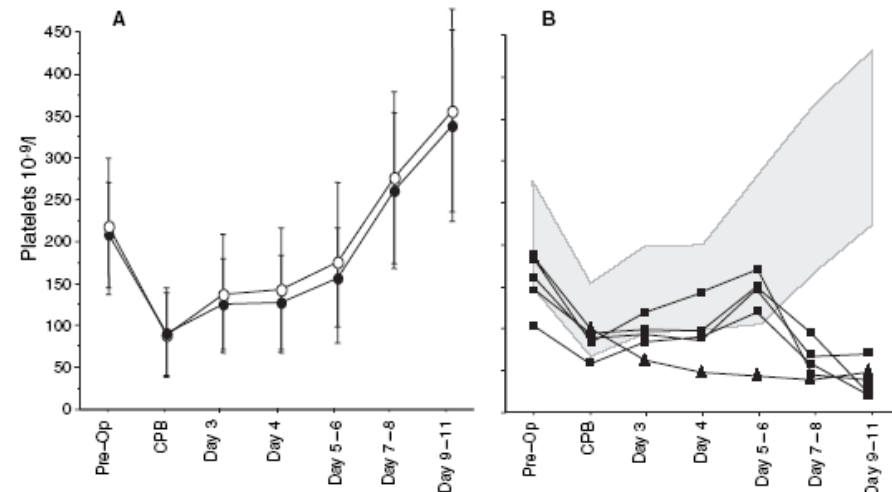
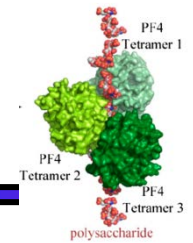


Fig 2. Prospective cohort. (A) Evolution of PC (mean \pm 1 SD) in 300 cardiac patients without HIT (O, negative H-PF4 ELISA; ●, positive H-PF4 ELISA). (B) Evolution of PC in five patients with suspected HIT (■, pattern P1; ▲, pattern P2).

Pouplard BJH 2005; 128:837-841



HIT overdiagnosis



Cave!!!

- erworbene Thrombopenie auf IPS
HIT auf IPS
dh 30-50%
0.3-0.5% HIT,
1:100¹
- Overdiagnosis²:

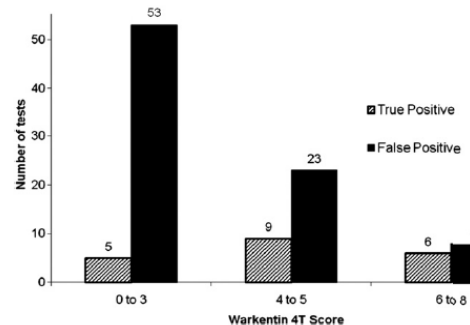


Figure 2. Heparin-induced thrombocytopenia (HIT) results, grouped by Warkentin score (0 to 3, HIT unlikely; 4 to 5, intermediate suspicion; 6 to 8, high suspicion) (x-axis), from 104 Warkentin tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with SRA \geq 20%. False positive, black bar, patients with a serotonin releasing assay < 20%.

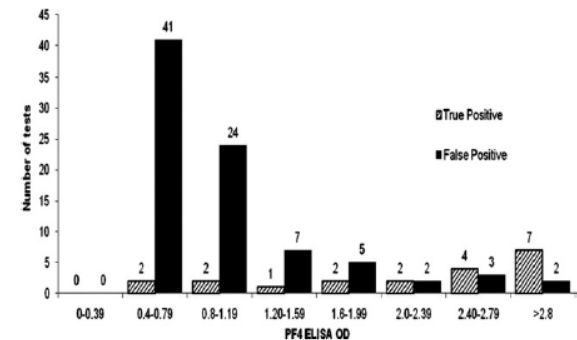
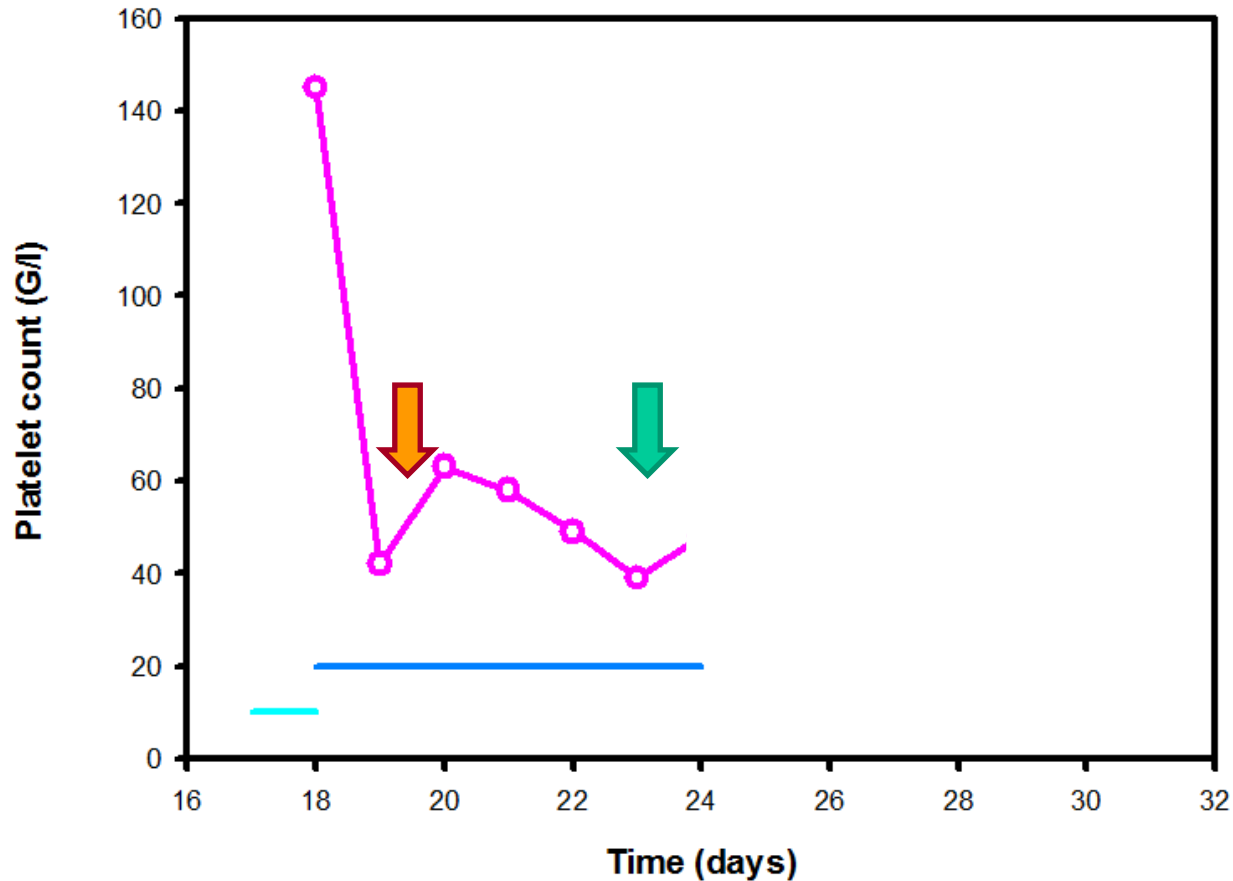
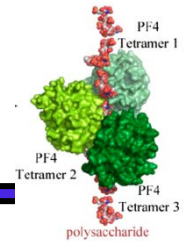


Figure 3. Heparin-induced thrombocytopenia (HIT) results, grouped by 0.4 optical density (OD) (x-axis), from 104 PF4 ELISA tests ordered (y-axis) based on a clinical suspicion of HIT. True positive, lined bar, patients with serotonin releasing assay (SRA) \geq 20%. False positive, black bar, patients with a SRA < 20%.

- man darf nicht nur auf ELISA schauen, sondern ELISA plus³
(ELISA und funktionellen Test)

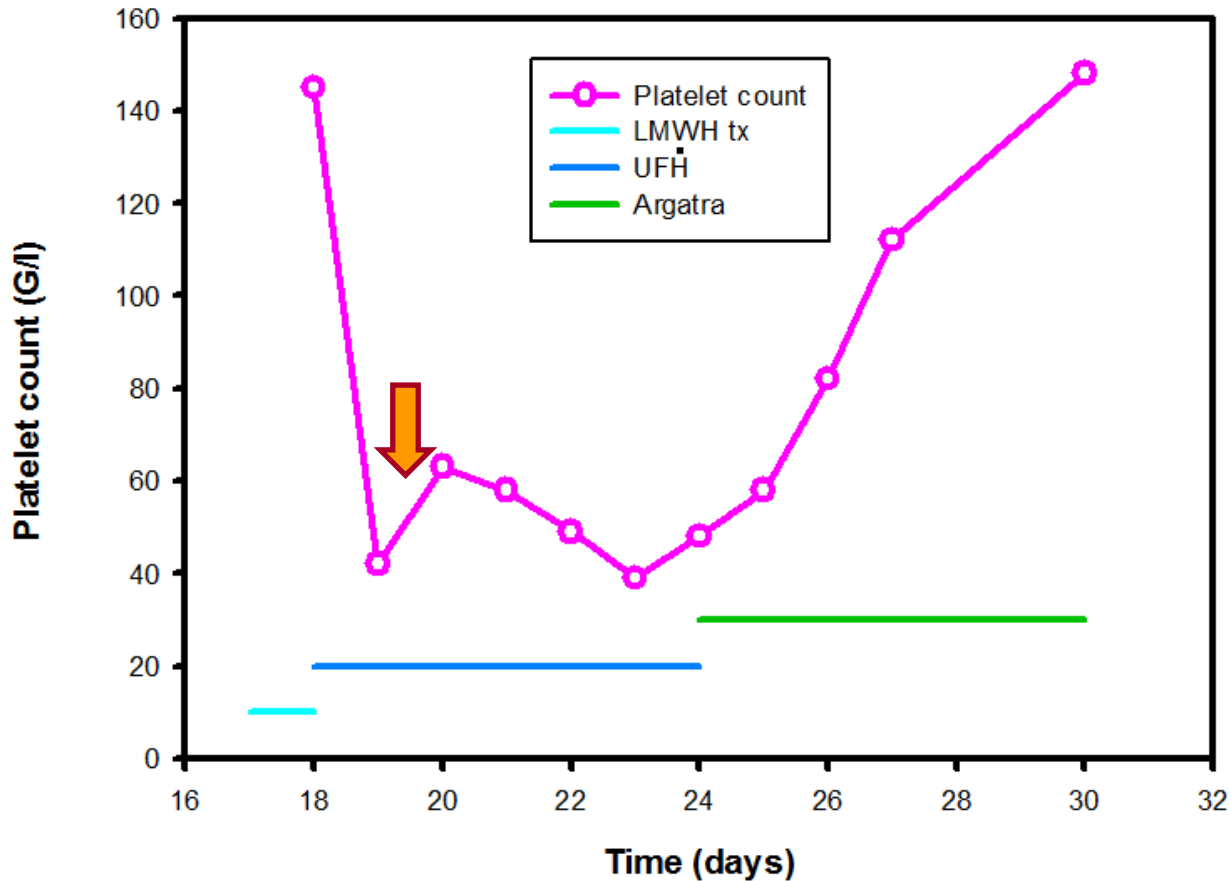
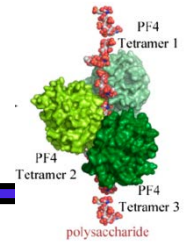
1. Warkentin HIT in critically ill patients. Critical Care 2011; 805-23
2. Berry et al JAMCollSurg 2011; 213;10-17.
3. Demma LJ Anasth Analg 2011; 113:697.

Frau I.B. 79jg



- Heparin vorbehandelt (<100 Tage!)
- 4T Score: $2 + 2 + 1 + 0 = 5$ (mittlere PTWS)

Frau I.B. 79jg



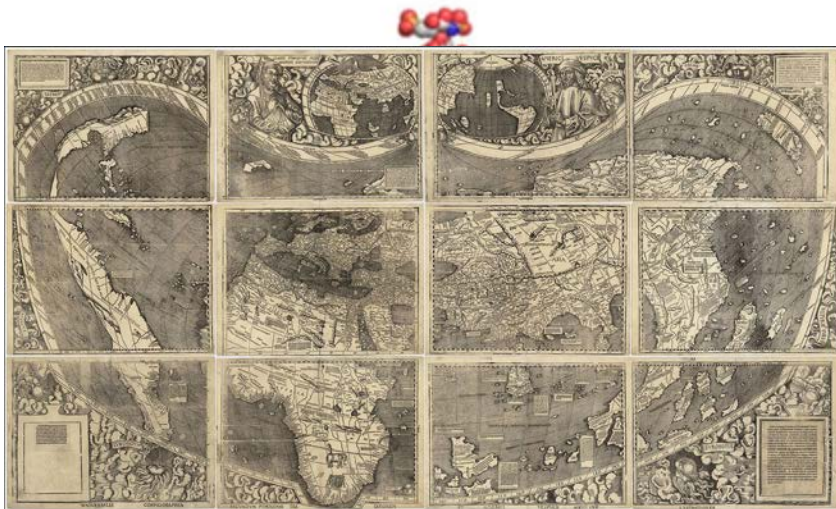
- Heparin vorbehandelt (<100 Tage!)
- 4T Score: 2 + 2 + 1 + 0 = 5 (mittlere PTWS)

“Arterial embolism occurring during systemic heparin therapy”

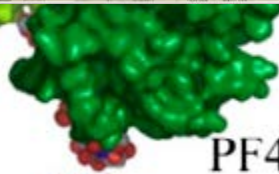
- 10 Fälle
- arterielle Emboli
- 6/10 verstorben
- “pale, soft, salmon colored emboli”
“comprised mostly of fibrin, platelet and leukocytes”

Lars M. Asmis

- Medical School in Bern, Switzerland 1984-1990
- Course in experimental medicine and biology 1990-1992
- Clinical and experimental training Univ. Hospital Bern & Geneva 1992-1995 resp 1995-2002
- Johns Hopkins University Baltimore MD 2002-04
- Head Coagulation Lab, Univ. Hospital Zurich 2004-2010
- Head Hematology CH, Private Lab Company 2010-2017
- Head ZPTH since 2010
- Accredited as “Privatdozent” at University of Zurich
- Certified internal medicine (clin) and hematology (clin+lab)
- 54 publications on PUBMED



PF4
Tetramer 2



PF4
Tetramer 3



polysaccharide