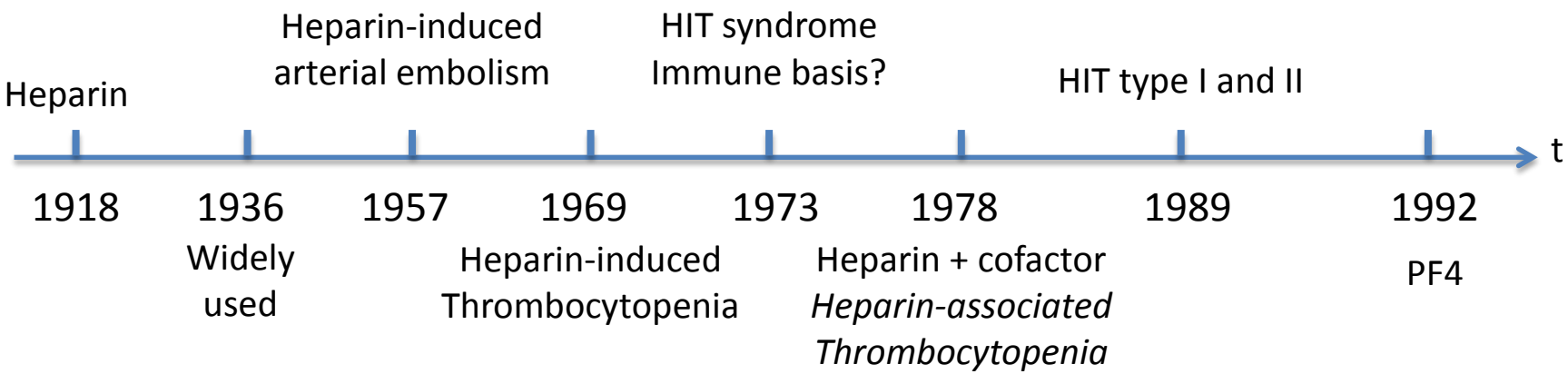
HIT in UZ Leuven

Steven Pauwels

11/5/2012

UZ LEUVEN



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Kelton J G , Warkentin T E Blood 2008;112:2607-2616.
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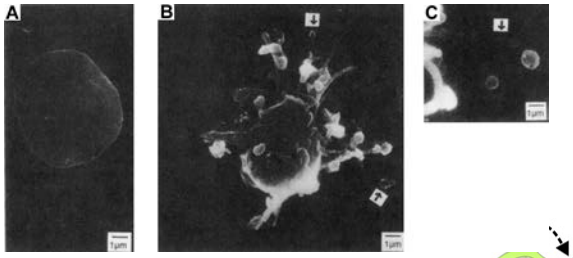
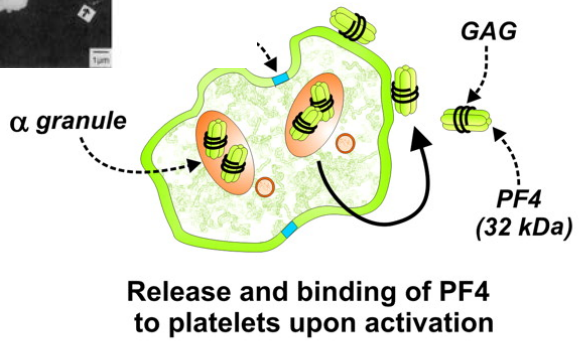
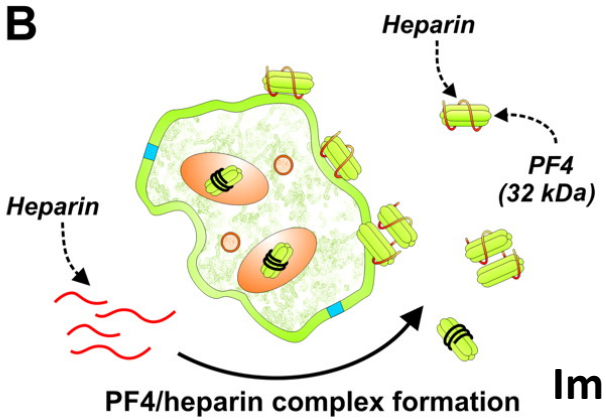


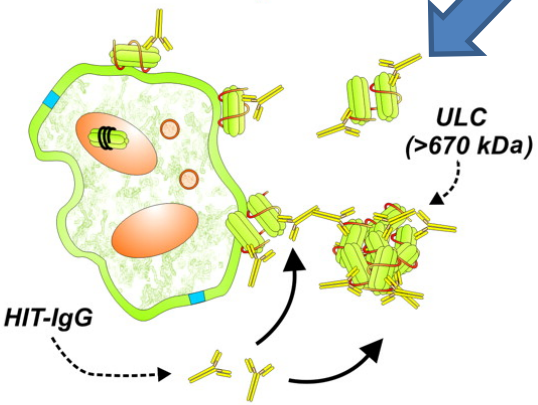


Release and binding of PF4
to platelets upon activation



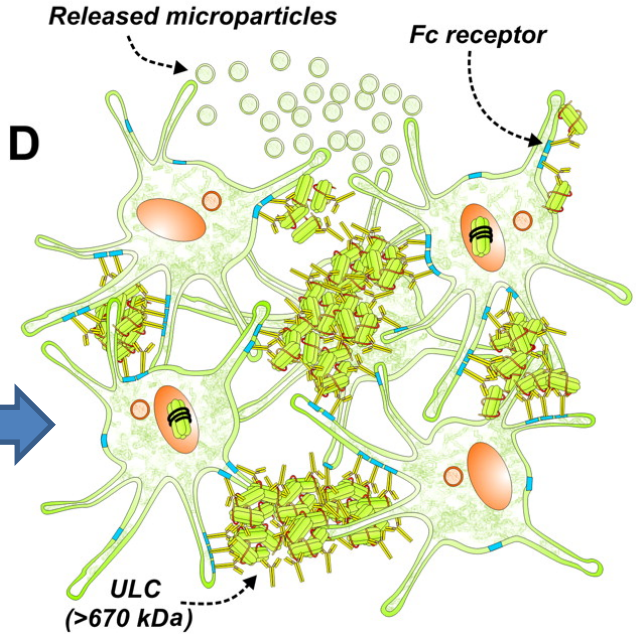
PF4/heparin complex formation

Immunoassay

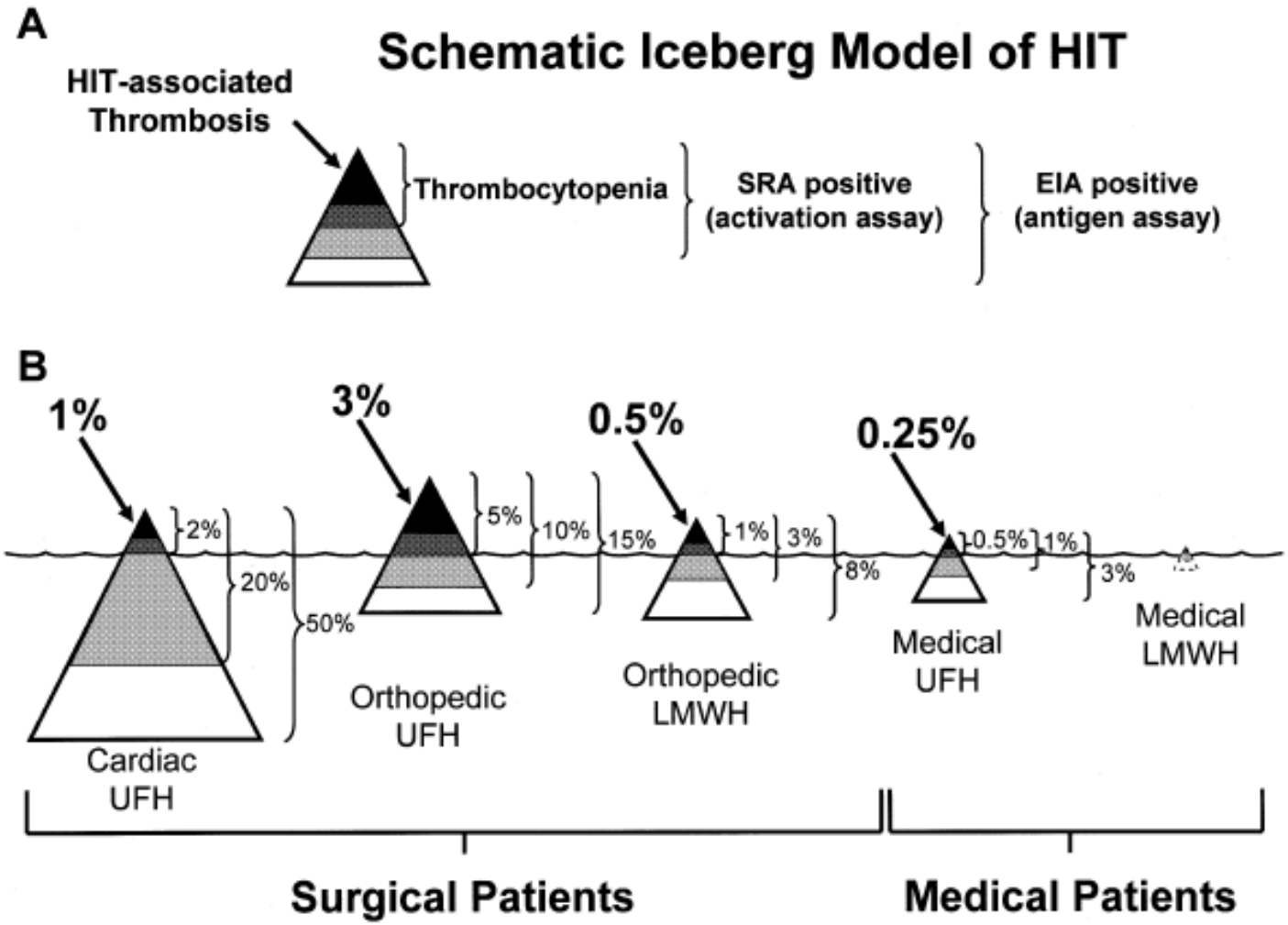


HIT-IgG binding to PF4/heparin complexes

Functional



Kelton J G , Warkentin T E Blood 2008;112:2607-2616



Warkentin TE. Br J Haematol. 2003;121(4):535-55.

Author: Marina Mukovnikova
Supervisor: Els Bailleul
Search/methodology verified by:
Date: 10/05/2011

CLINICAL BOTTOM LINE

Heparine-geïnduceerde trombocytopenie is een potentieel levensbedreigende complicatie van heparinetherapie die een snelle diagnose vereist. Om de diagnose van HIT te stellen moet er een gegronde klinische verdenking zijn, gebaseerd op het Warkentin pretest scoring systeem. Labotesten hebben de ondersteunende rol in de diagnose van HIT. Immunologische antigeentesten (ELISA) zijn zeer sensitief en een negatieve test sluit de diagnose uit bij lage of intermediaire score. Daar de specificiteit van immunoassays relatief laag is, moet een positieve test bevestigd worden met een functionele test. Functionele testen hebben een hoge specificiteit en worden als confirmatie testen beschouwd, maar ze zijn technisch ingewikkeld en niet geschikt voor gebruik in een routine-labo. Om deze reden willen wij een snelle en gemakkelijk uit te voeren functionele test op Multiplate® aggregometer implementeren.

Functional Assay

- In UZ leuven about 1 positive ELISA a week
- Functional assays
  - SRA, HIPA
    - Gold standard
    - Only in reference centres
  - FCM, HIMEA
    - Faster, easier
    - Position?

Functional Assay

- Economic/organizational/clinical
  - Very few tests, costs, labour
  - Pooling of samples, long TATs, no use in acute settings, false negatives?
  - Technical issues (indeterminate, platelet donors)

- Clinical/strategical
  - ‘true’ HITs who should not receive heparin in next 100 days
  - Samples from other centres?
  - Doubtful benefits

HIT – UZ Leuven

- GTI polyspecific assay
  - ELISA
  - PF4/PVS
  - High-dose heparin step
- Analysed once a week
  - Urgent after discussion with coagulation specialist
- Positive or negative
- No confirmation
- Redesigning, rebuilding

Clinical probability

	Points		
	2	1	0
Thrombocytopenia	50% platelet fall to nadir >20	30–50% platelet fall, or nadir 10–19	<30% platelet fall, or nadir <10
Timing of onset of platelet fall	Days 5–10, or < 1 day with recent heparin (past 30 days)	> 10 days or timing unclear, or < 1 day with recent heparin (past 31–100 days)	< Day 4 (no recent heparin)
Thrombosis	Proven new thrombosis, skin necrosis, or acute systemic reaction after IV UFH bolus	Progressive or recurrent thrombosis, erythematous skin lesions, suspected thrombosis (unproven)	None
Other causes of platelet fall	None evident	Possible	Definite

Warkentin TE. Br J Haematol. 2003;121(4):535-55.

Clinical probability

Location	HIT definition	Low		Intermediate		High	
		HIT	Total	HIT	Total	HIT	Total
Hamilton	SRA	0	64	8	28	8	8
Greifswald	HIPA	0	55	11	139	9	42

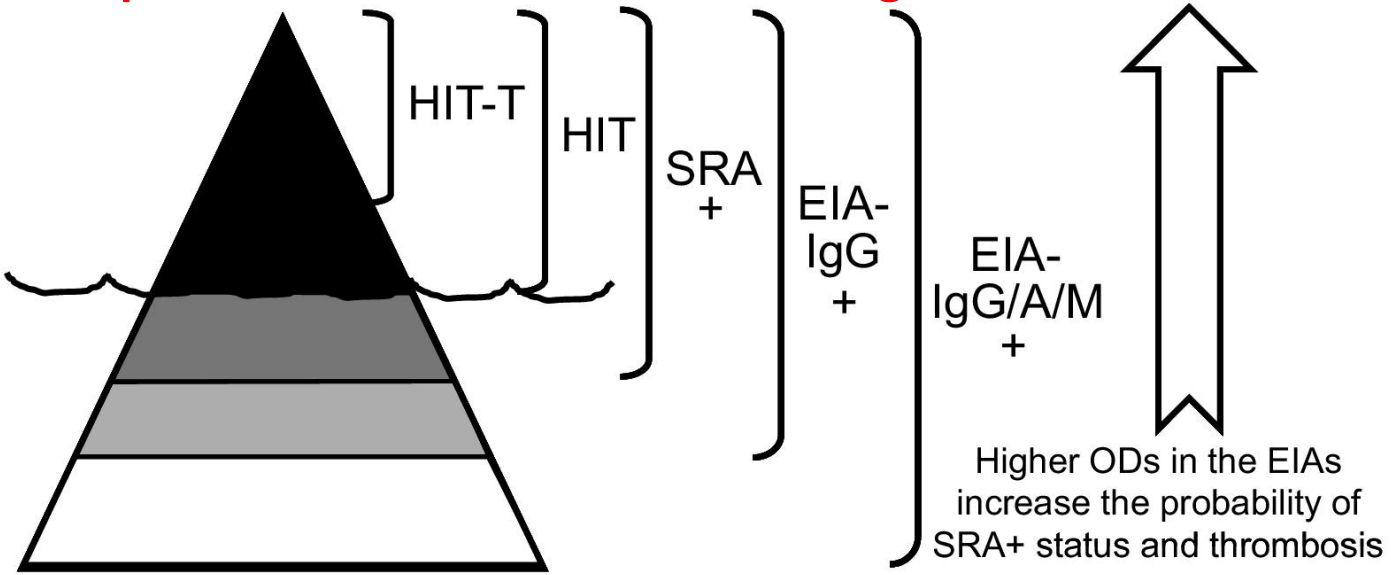
Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. J Thromb Haemost 2006 ;4(4):759-65.

1. High score ≠ HIT
2. Intermediate = large, least informative → Experience required
3. Interrater agreement moderate

Preferred Assay

SRA + = platelet-activating antibodies

High- dose heparin confirmation? Cave false negatives for OD> 1.0



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:	~0%	~5%	~25%	~50%	~90%
Probability of thrombosis:	-----	~15%	~20%	~30%	~50%

Warkentin TE. Am J Med. 2012; 125(1):44-9 (figure)
Greinacher A, Ittermann T, Bagemuhl J, Althaus K, Furll B, Selleng S, et al. J Thromb Haemost 2010;8(9):2025-31.
Warkentin TE, Sheppard JI, Moore, JC Sigouin CS, Kelton JG. J Thromb Haemost 2008;6(8):1304-12.

Althaus K, Strobel U, Warkentin TE, Greinacher A. Thromb Res. 2011; 128(3):256-60
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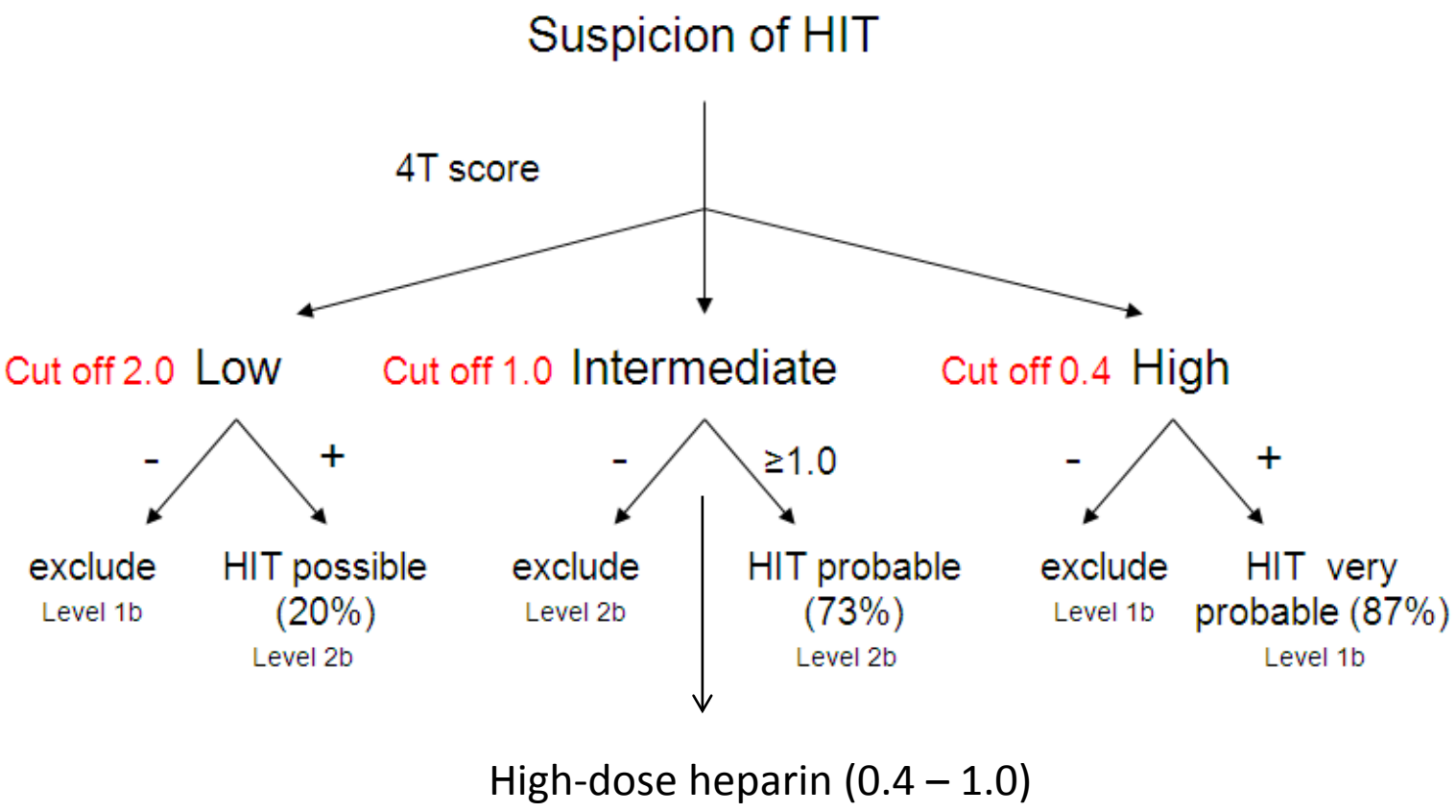
Post-test probability scheme

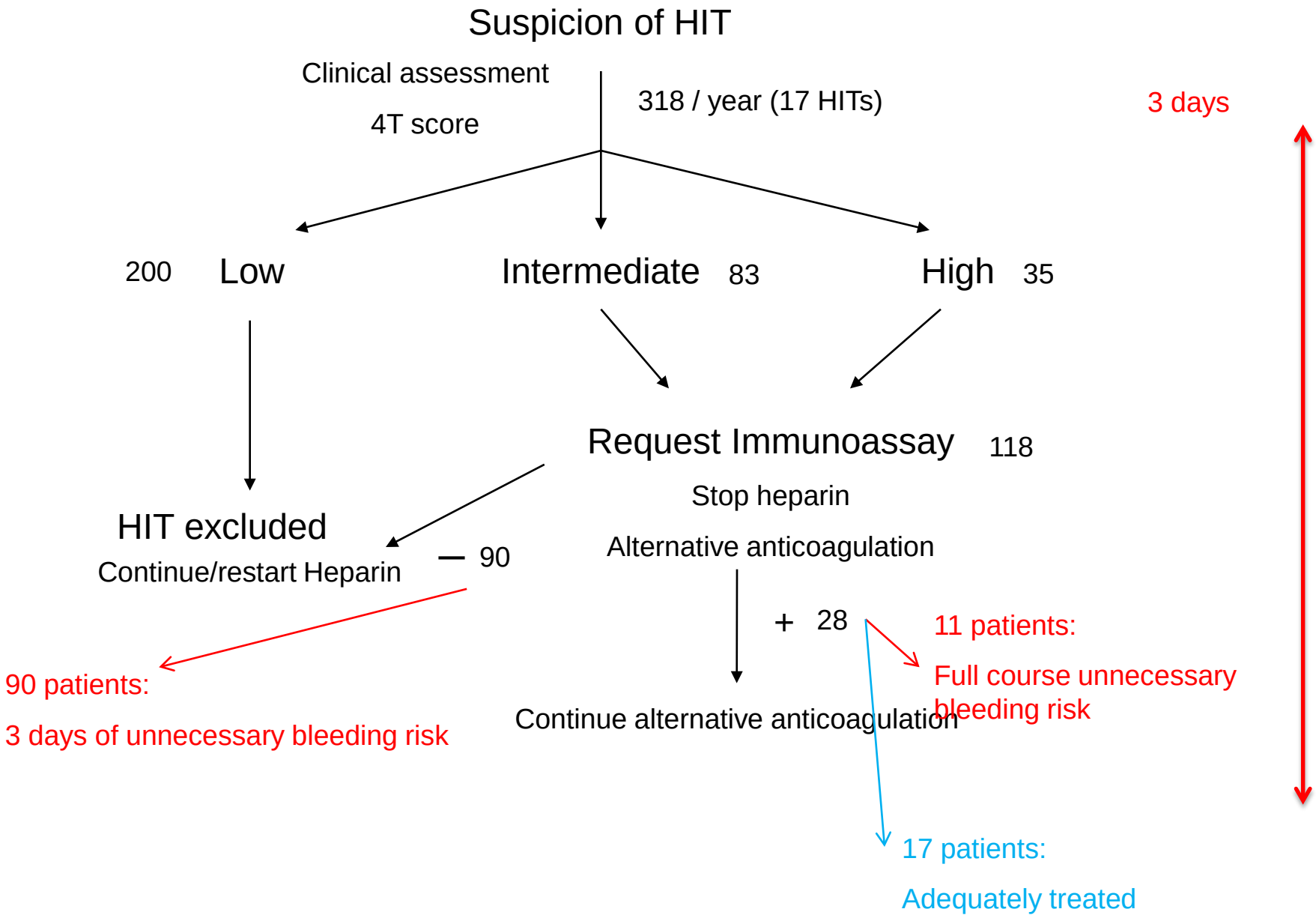
GTI polyspecific Cut off (OD)	**4T score (% pre-test probability)**					
	Low (0.3%; 3/911)		**Intermediate** (12%; 90/750)		**High** (51%; 83/163)	
	Negative % [95% CI]	**Positive %** [95% CI]	**Negative %** [95% CI]	**Positive %** [95% CI]	**Negative %** [95% CI]	**Positive %** [95% CI]
0.40	**0** [0-1]	**2** [1-3]	**0** [0-2]	**48** [41 53]	**0** [0-4]	**87** [83-90]
1.00	**0** [0-1]	**6** [3-9]	**0** [0-2]	**73** [64-81]	**2** [1-5]	**95** [92-97]
1.40	**0** [0-1]	**12** [6-24]	**1** [0-3]	**86** [76-93]	**7** [4-11]	**97** [95-99]
2.00	**0** [0-2]	**20** [6-47]	**3** [1-4]	**92** [80-97]	**17** [14-21]	**99** [96-100]

For operating characteristics: *Warkentin TE, Sheppard JI, Moore JC, Sigouin CS, Kelton JG. J Thromb Haemost. 2008;6(8):1304-12*

Algorithm



Own scheme, based on *Ruf KM, Bensadoun ES, Davis GA, Flynn JD, Lewis DA. Thromb Haemost. 2011;105(3):553-9.*



For operating characteristics: *Bakchoul Y, Giptner A, Najaoui A, Bein G, Santoso S, Sachs UJ. J Thromb Haemost. 2009;7(8):1260-5*

All Intermediate/High risk treated

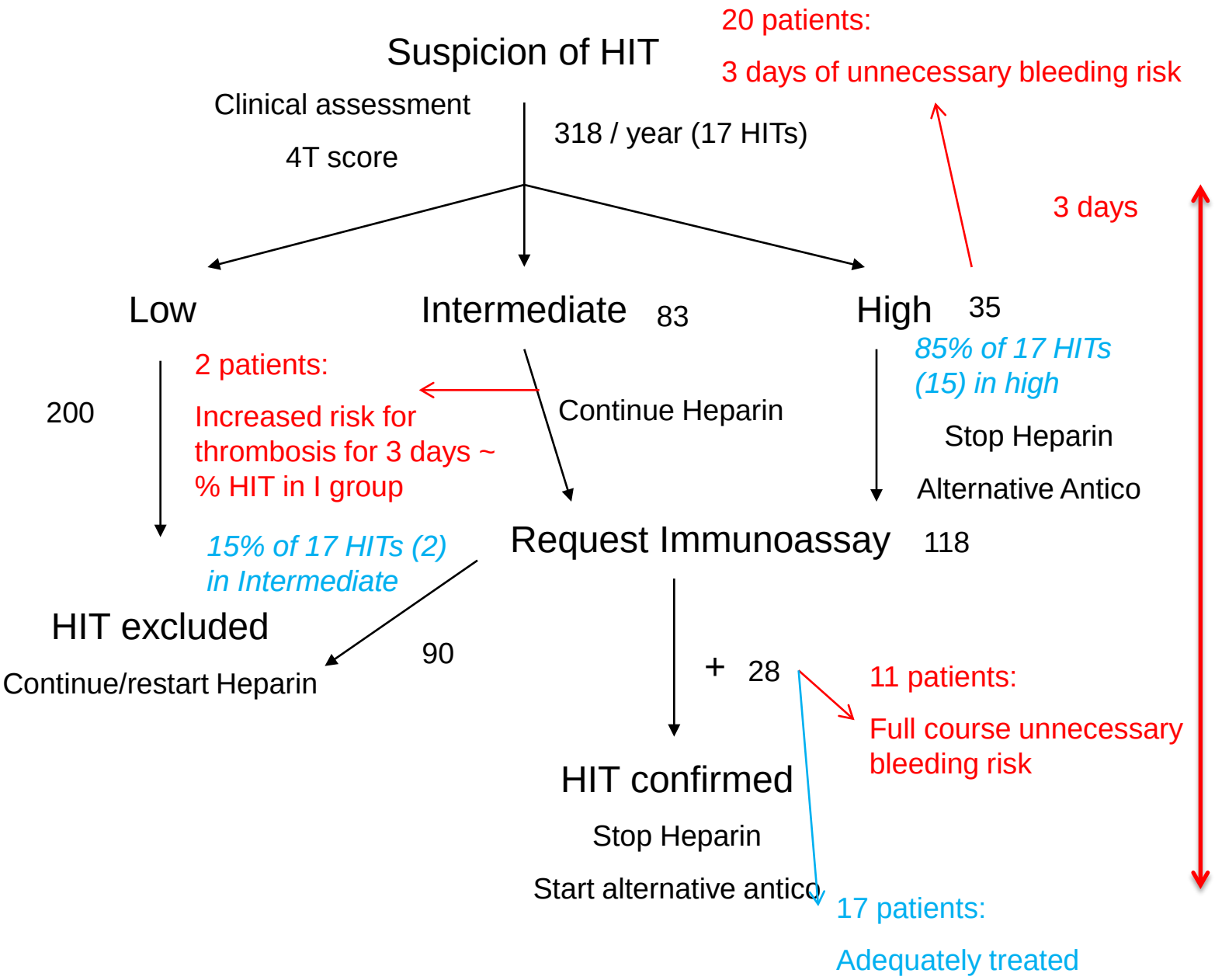
Cut off 0.4

Intermediate + High risk (% of 318)	Increased bleeding risk pre-test (n)	Increased bleeding risk post-test (n)	Increased thrombosis risk pre-test (n)	Increased thrombosis risk post-test (n)	Gain/loss (€)
10	15	2	0	0	- 34 972
30	78	9	0	0	+ 50 010
50	142	16	0	0	+ 136 991
70	204	23	0	0	+ 222 973

Cut off 1.0

Intermediate + High risk (% of 318)	Increased bleeding risk pre-test (n)	Increased bleeding risk post-test (n)	Increased thrombosis risk pre-test (n)	Increased thrombosis risk post-test (n)	Gain/loss (€)
10	15	1	0	2	- 33 642
30	78	4	0	2	+ 58 136
50	142	7	0	2	+ 149 914
70	204	10	0	2	+ 241 692

For operating characteristics: *Bakchoul Y, Giptner A, Najaoui A, Bein G, Santoso S, Sachs UJ. J Thromb Haemost. 2009;7(8):1260-5*



For operating characteristics: *Bakchoul Y, Giptner A, Najaoui A, Bein G, Santoso S, Sachs UJ. J Thromb Haemost. 2009;7(8):1260-5*

Only High risk treated

15% of HIT in intermediate

Intermediate /High risk (% of 318)	Increased bleeding risk pre-test (n)	Increased bleeding risk post-test (n)	Increased thrombosis risk pre-test (n)	Increased thrombosis risk post-test (n)	Gain/loss (€)
20/10	17	9	2	0	- 23 171
35/15	33	16	2	0	+ 3 716
40/20	49	19	2	0	+ 30 603
20/40	113	19	2	0	+ 138 150

50% of HIT in intermediate

Intermediate/ High risk (% of 318)	Increased bleeding risk pre-test (n)	Increased bleeding risk post-test (n)	Increased thrombosis risk pre-test (n)	Increased thrombosis risk post-test (n)	Gain/loss (€)
20/10	23	9	9	0	- 13 993
35/15	39	16	9	0	+ 12 894
40/20	55	19	9	0	+ 39 780
20/40	119	19	9	0	+ 147 328

For operating characteristics: *Bakchoul Y, Giptner A, Najaoui A, Bein G, Santoso S, Sachs UJ. J Thromb Haemost. 2009;7(8):1260-5*

Rapid assays

- PaGIA
- HemosIL Acustar HIT-IgG or Ab
  - Chemiluminiscent
- HemosIL HIT Ab on ACL TOP
  - Latex particle enhanced immunoturbidometry

Conclusions

1. Quantitative, IgG specific immunoassay combined with ‘experienced’ 4T scoring

2. No functional assay for UZ Leuven at the moment

3. Evaluation of HemosIL ab on ACL TOP platform linked to track