Heparin-induceret trombocytopeni type II

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Heparin-induceret trombocytopeni (HIT) type II

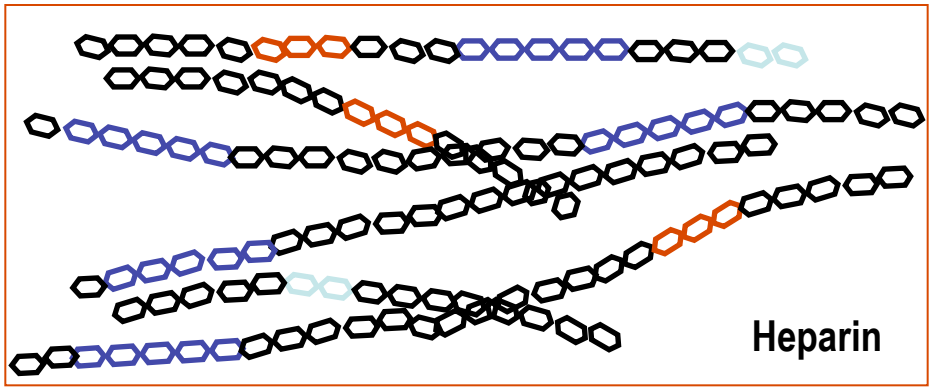
- **Første beskrivelse:**
  - Weismann RE, Tobin RW. Arterial embolism occurring during systemic heparin therapy. Arch Surg 1958; 76: 219–227.

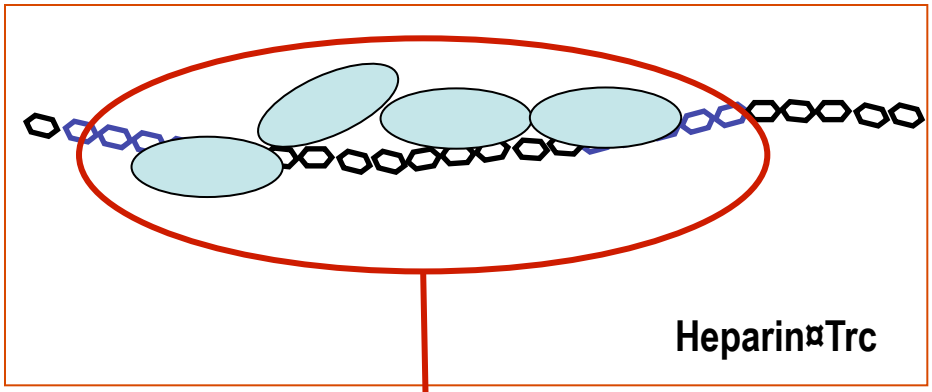
- **Første beskrivelse af HIT-antigen:**
  - Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. Thromb Haemost 1992; 68: 95–96.

Ufraktioneret heparin er lange kulhydratkæder (stærkt sulfaterede glukosaminoglykaner, 10-30 kD)

Bindes elektrostatisk til trombocytter

Agglutinationen medfører ofte 10-20% fald i trombocyttallet (HIT type 1)





Subunits

- β-L-glucuronic acid
- α-L-iduronic acid
- 2-O-sulfo-α-L-iduronic acid
- 2-deoxy-2-acetamido-α-D-glucopyranosyl
- 2-deoxy-2-sulfamido-α-D-glucopyranosyl
- 2-deoxy-2-sulfamido-α-D-glucopyranosyl-6-O-sulfate

Elimineres i milt og lever

HIT type I and type II

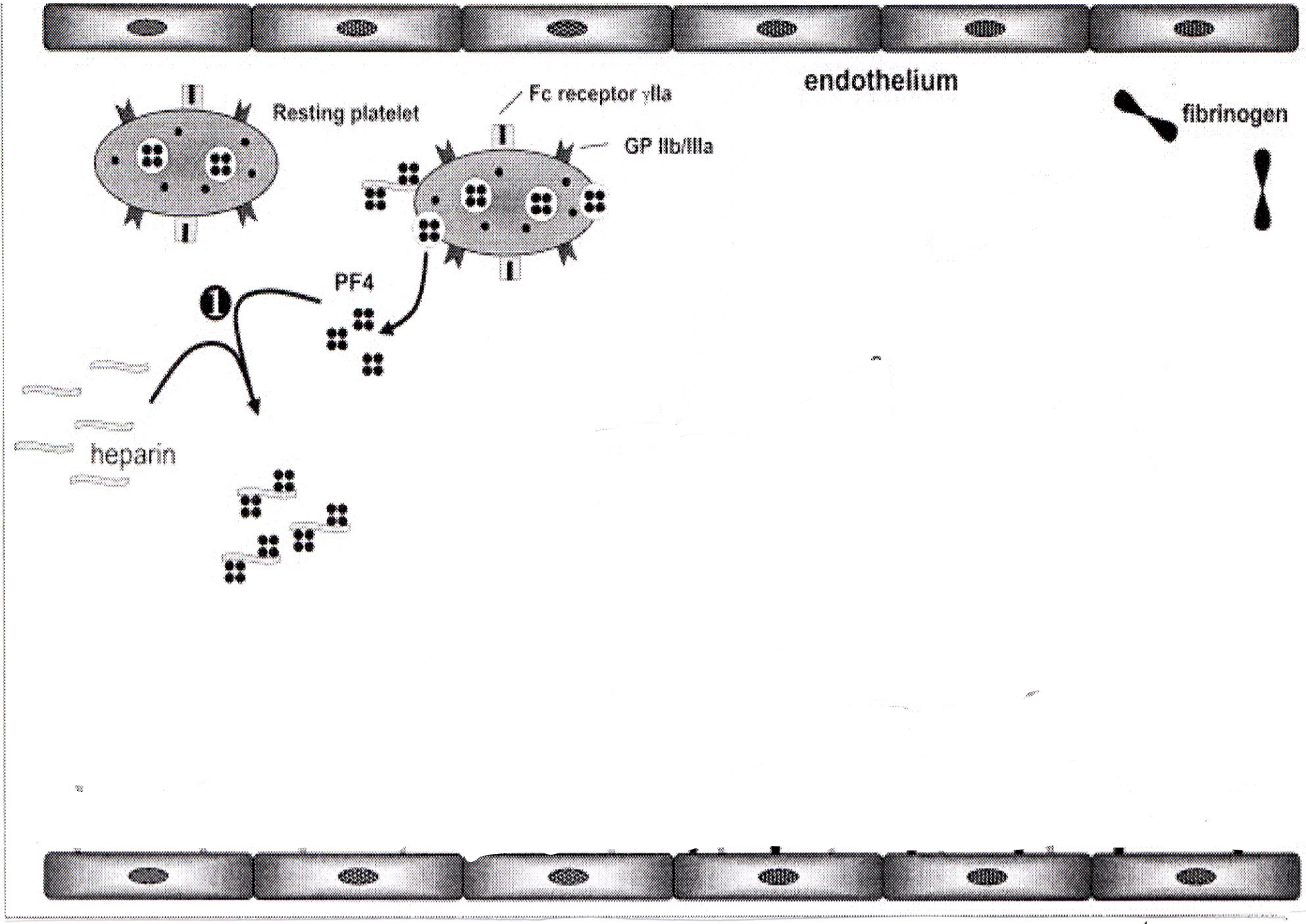
- HIT type I: Electrostatic agglutination of platelet causing mild thrombocytopenia shortly after onset of heparin treatment.
- HIT type II: Autoimmune heparin-induced thrombocytopenia occurring in 2-5% of patients treated with unfractionated heparin (UFH) and 0.1% of patients treated with low-molecular-weight heparin (LMWH).

Characteristic of HIT type II

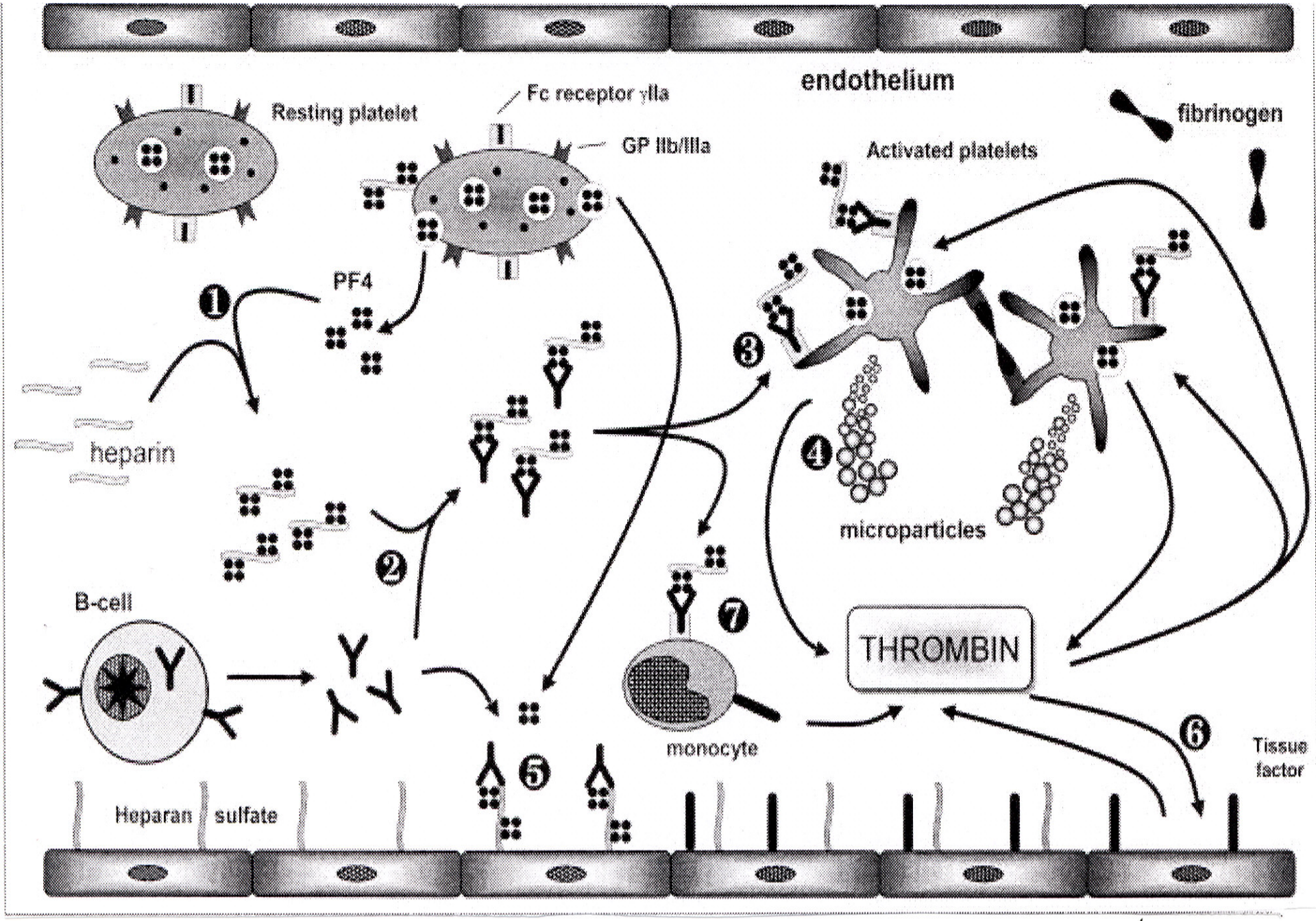
- High risk of thromboembolism
  - Art. or venous thrombosis: 50%
  - Limb amputation: 10%
  - Mortality: 20%
- Bleeding is rare, even at platelet counts of 20-30 x 10^9/L.
- In 2/3 of the patients HIT type II developes after major surgery.

Warkentin TE, Kelton JG. Am J Med 1996;101:502-7

The pathogenesis of HIT type II



The pathogenesis of HIT type II



Heparin-induced thrombocytopenia (HIT): laboratory tests

Assay	Sensitivity	Specificity	Weakness
Functional SRA HIPA	Moderate-High	High	Technically difficult.Results differ widely
Washed platelets HIPA	Moderate-High	High	
Citrated-PRP HIPA	Moderate	Moderate-High	
Antigen/ELISA	High	Poor-Moderate	False positives

Chong BH. *Br J Haematol.* 1995;89:431-439. Warkentin TE. *Drug Saf.* 1997;17:325-341. Warkentin TE, Greinacher A. In: Warkentin TE, Greinacher A, eds. *Heparin-Induced Thrombocytopenia.* 2nd ed. New York, NY:Marcel Dekker, Inc; 2001. Warkentin TE, Chong BH, Greinacher A. *Thromb Haemost.* 1998;79(1):1-7.

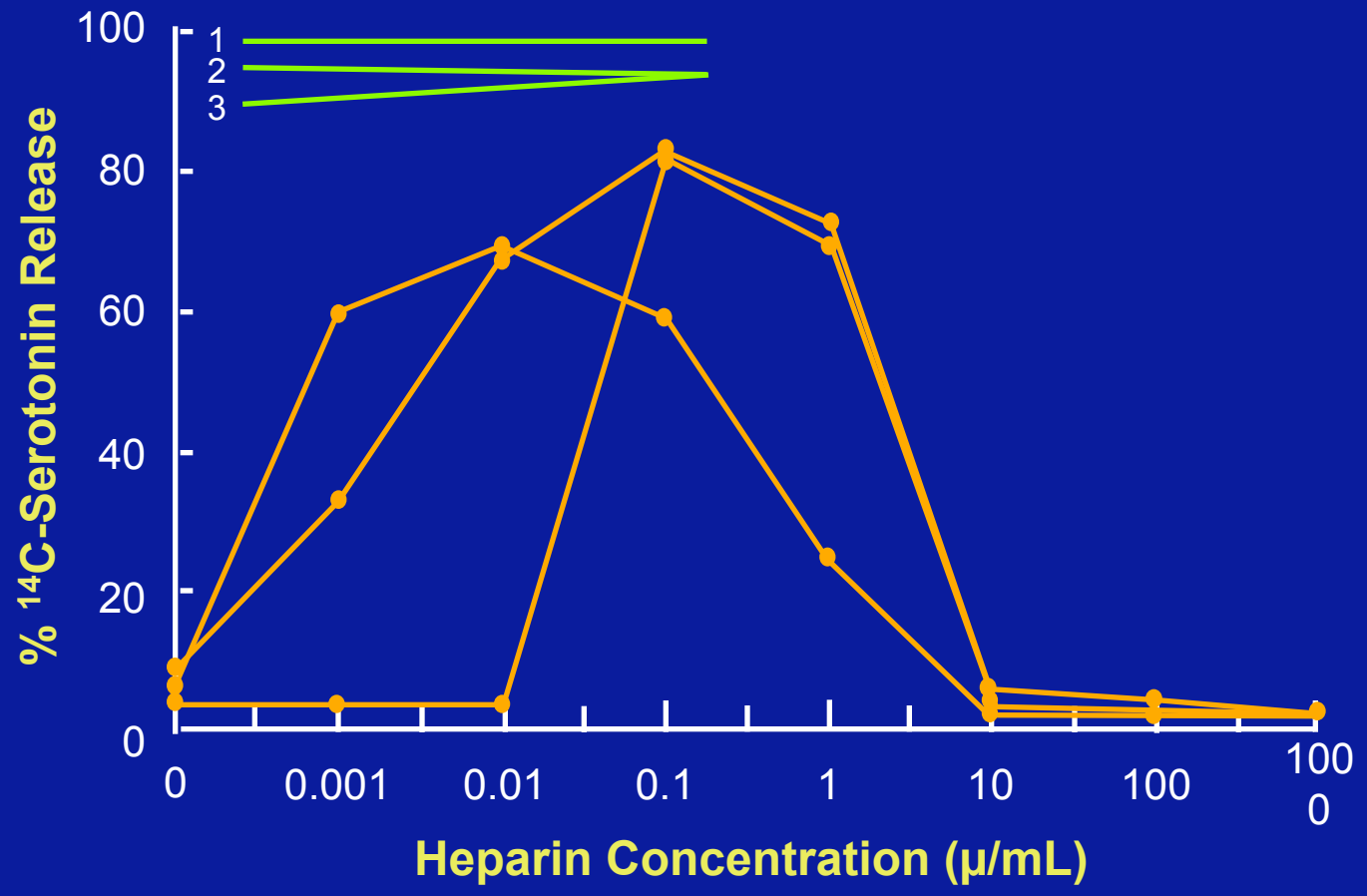
Serotonin Release Assay

- Whole blood from healthy individuals is collected into ACD (acid-citrate-dextrose, 1:6, v:v).
- The platelet-rich plasma (PRP) is obtained by centrifugation for 5 min. at 250 g.
- The PRP is incubated with ^{14}C-serotonin for 45 min. at 37 °C (50 μCi ^{14}C-serotonin/ml PRP).
- Approximately 50% of the ^{14}C-serotonin is bound to the washed platelets, giving a final specific activity of 1.84 x 10^{-4}μCi of serotonin per 10^{6} platelets.
- The platelets are then washed resuspended in albumin-free Tyrode's solution and the final platelet count is adjusted to 300,000/μl.
- 20 μl of test serum is mixed with 5 ml of various heparin concentrations (0.1 to 100 IU/ml, final) and 75 μl of ^{14}C-serotonin-labeled platelets.
- The platelet mixture is incubated in microtiter wells containing a magnetic stir bar.
- Following a 60-minute incubation at 22 °C, 100 μl of 0.5% EDTA in saline is added to each well to terminate the release reaction.
- The platelets are centrifuged for five minutes at 1,500 g, and 50 μl of the supernatant fluid is added to 10 ml scintillation fluid and counted in a liquid scintillation counter.

Serotonin Release Assay

- The percent release is calculated as follows:
- Percent release = $\frac{\text{release of test sample – background}}{\text{total radioactivity - background}}$ **x 100**

Relationship Between Release of ^{14}C-Serotonin and Final Concentration of Heparin in HIT Patients



Sheridan D, Carter C, Kelton JG. *Blood*. 1986;67:27–30.

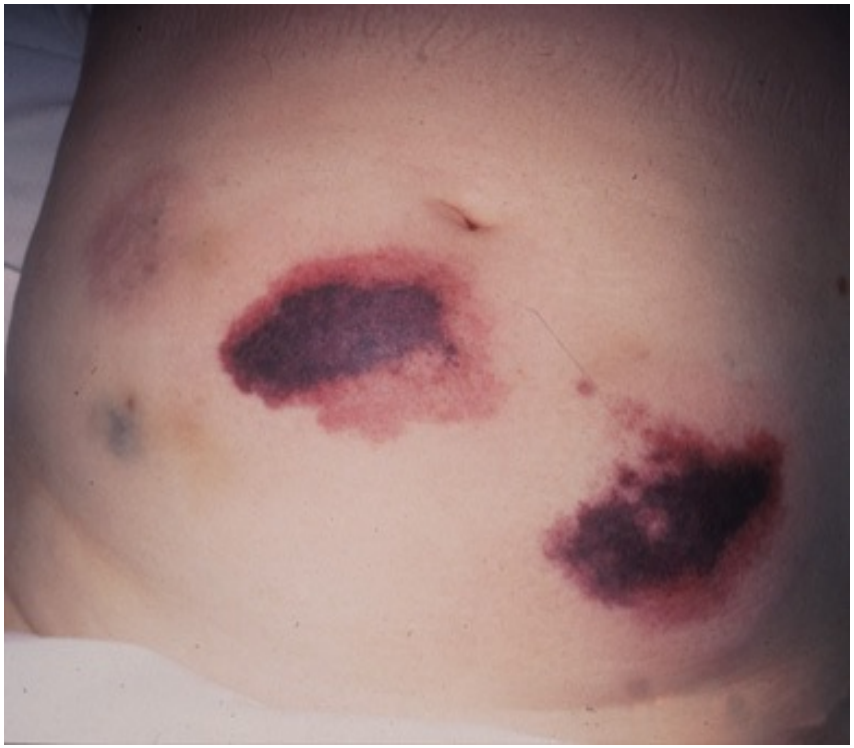
Estimating probability of HIT: The 4 T's

Points	2 points	1 point	0 point
Thrombocytopenia	50% fall or platelet nadir of 20,000–100,000/µL	30%–50% fall or platelet nadir of 10,000–19,000/µL	Fall < 30% or platelet nadir < 10,000/µL
Timing of platelet count	Clear onset between days 5 and 10 or less than 1 day if exposed to heparin within past 100 days	Consistent with day 5-10 fall but not clear (e.g. missing platelet counts) or onset after day 10	Fall in platelet count is too early (without recent heparin exposure)
Thrombosis or other sequelae (e.g. skin lesions)	New thrombosis; skin necrosis; acute systemic reaction following heparin bolus	Progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis not yet proven	None
OTher cause of thrombocytopenia	No other cause for fall in platelet count is evident	Possible other cause is evident	Definite other cause is present

*A patient's pretest probability equals the total points in all four categories:
0–3 points = low (0 - 1,6%)
4–5 points = intermediate (7,9 – 28,6%)
6–8 points = high (21,4 – 100%)

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

Heparin-inducerede hudreaktioner



Subkutan infiltration eller nekrose efter heparin-injektioner kan være første tegn på HIT type II

Warkentin TE. Br J Haematol. 1996; 92: 494–7

Clinical Diagnosis of HIT and initial therapeutic considerations

Platelet count drop occurs during or after heparin therapy

Platelet count drops to <50% of baseline **or** **Platelet count <100 x 10^9/L**

No other cause of thrombocytopenia identified

Clinical diagnosis of HIT

Discontinue all types of heparin

- including LMW heparin and heparin-coated catheters

?

Discontinuation of heparin is not enough

- The risk of thrombosis in the days following discontinuation of heparin is still high: 19-52%.
- High risk persists even when the platelet counts return to normal values.

Warkentin et al. Am J Med 1996;101:502-7.
Wallis et al. Semin Thromb Hemost 1999;25 Suppl 1:3-7.
Chong et al. Thromb Haemost 2001;86:1170-5.
Lewis et al. Arch Intern Med 2003;163:1849-56.
Hirsh J et al. Arch Intern Med. 2004;164:361-9.

Alternatives to heparin

HEPARINOIDS	DIRECT THROMBIN INHIBITORS	PENTASACCHARIDES
Danaparoid (Orgaran®)	Argatroban (Novastan®) Bivalirudin (Angiox®) Lepirudin (Refludan®)	Fondaparinux (Arixtra®)

Danaparoid (Orgaran®)

- A mixture of heparan sulfate, dermatan sulfate and chondroitin sulphate derived from porcine gut mucosa.
- Suggested dosage: Bolus 2500 U iv. followed by 400 U/h for 4 h, 300 U/h for 4 h, and 200 U/h for 5 days.
- Monitoring (usually unnecessary): anti-Xa 0.5-0.8 U/mL
- Elimination: Renal.
- Half-life: 25 hours.

Danaparoid (Orgaran®)

- Data on 1418 HIT patients treated with danaparoid (Chong et al. Thromb Haemost 2001;86:1170-5):
- Rate of new thrombosis: 9.7%
- Rate of haemorrhage: 8.1%
- Rate of cross-reactivity with heparin-induced antibodies: 3.2%

- Due to the observed cross-reactivity with heparin-induced antibodies and introduction of new potent anticoagulant drugs without this problem, danaparoid has been withdrawn in some countries.

Kodityal et al. Eur J Haematol 2003;71:109–13.

Fondaparinux (Arixtra®)

- A synthetic pentasaccharide
- Suggested dosage: 2.5 mg sc once daily
- Monitoring (usually unnecessary): anti-Xa 0.5-0.8 U/mL
- Elimination: Renal.
- Half-life: 17 hours.

Problem: Most patients with HIT-2 have renal dysfunction

Wester et al. Netherlands J Med 2007;65:101-8

Fondaparinux (Arixtra®)

- Limited experience in the treatment of HIT.
- Like with danaparoid, cross-reactivity with heparin-induced antibodies has been observed.

Warkentin et al. N Engl J Med 2007;356:2653-4

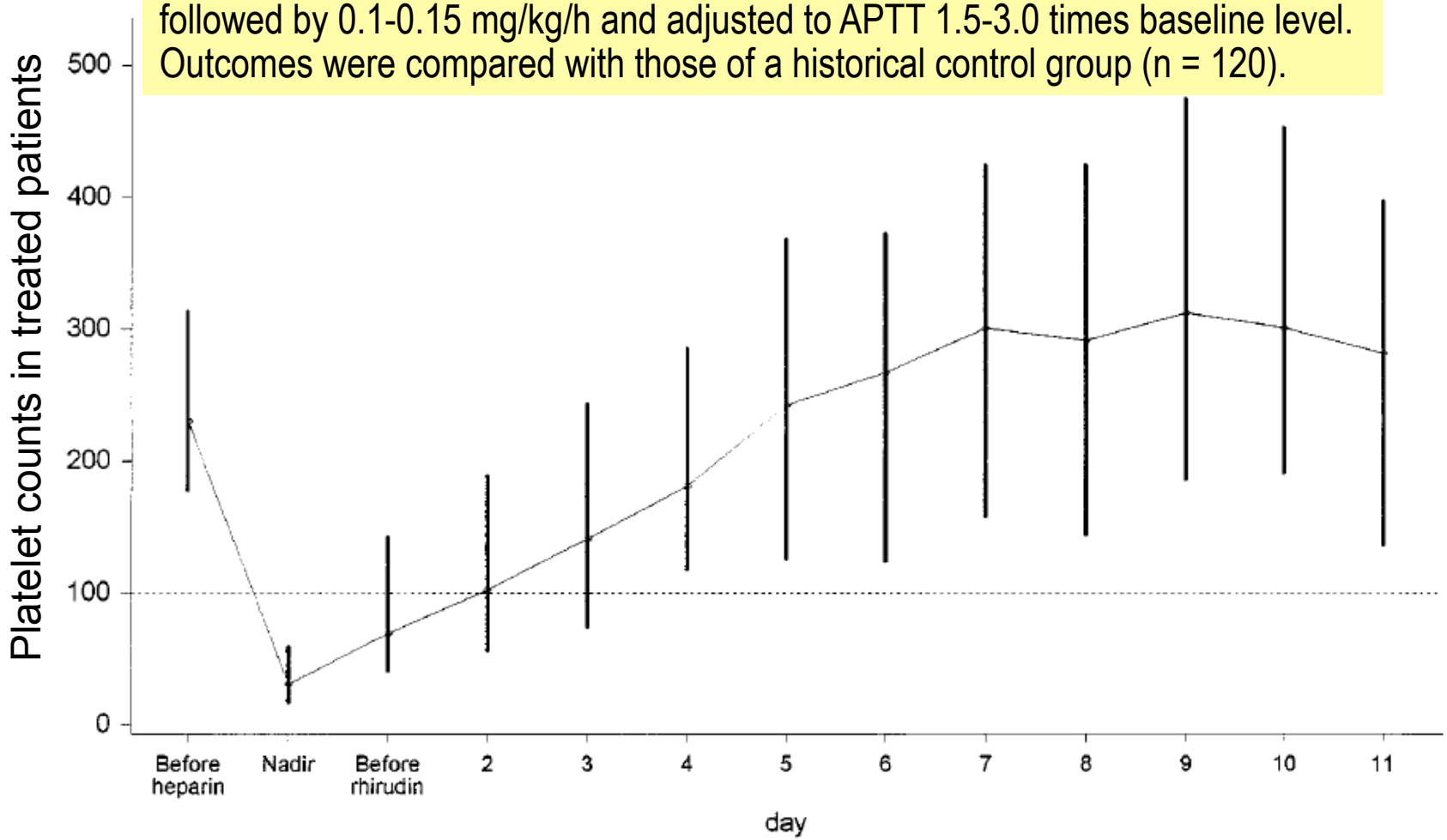
Direct thrombin inhibitors (DTI)

	Lepirudin (Refludan)	Bivalirudin (Angiox)	Argatroban (Novastan)
Molecule	Recombinant hirudin	Synthetic hirudin analogue	Synthetic L-arginine derivative
Administration	iv	iv	iv
Thrombin binding	Irreversible	Strong	Reversible
Elimination	Renal	Renal	Hepatic
Half-life	100 min	40 min	50 min
Monitoring	APTT*	APTT*	APTT*
Increase in INR	+++	+++	++
Experience in HIT	+++	+(PCI)	+++

*Increase to 1,5-3,0 times baseline level

A prospective study of recombinant hirudin (lepirudin) in patients with HIT

Multicenter study: 82 patients with HIT were treated with lepirudin, 0.1-0.4 mg/kg followed by 0.1-0.15 mg/kg/h and adjusted to APTT 1.5-3.0 times baseline level. Outcomes were compared with those of a historical control group (n = 120).



Greinacher et al. Circulation 1999;99;73-80.

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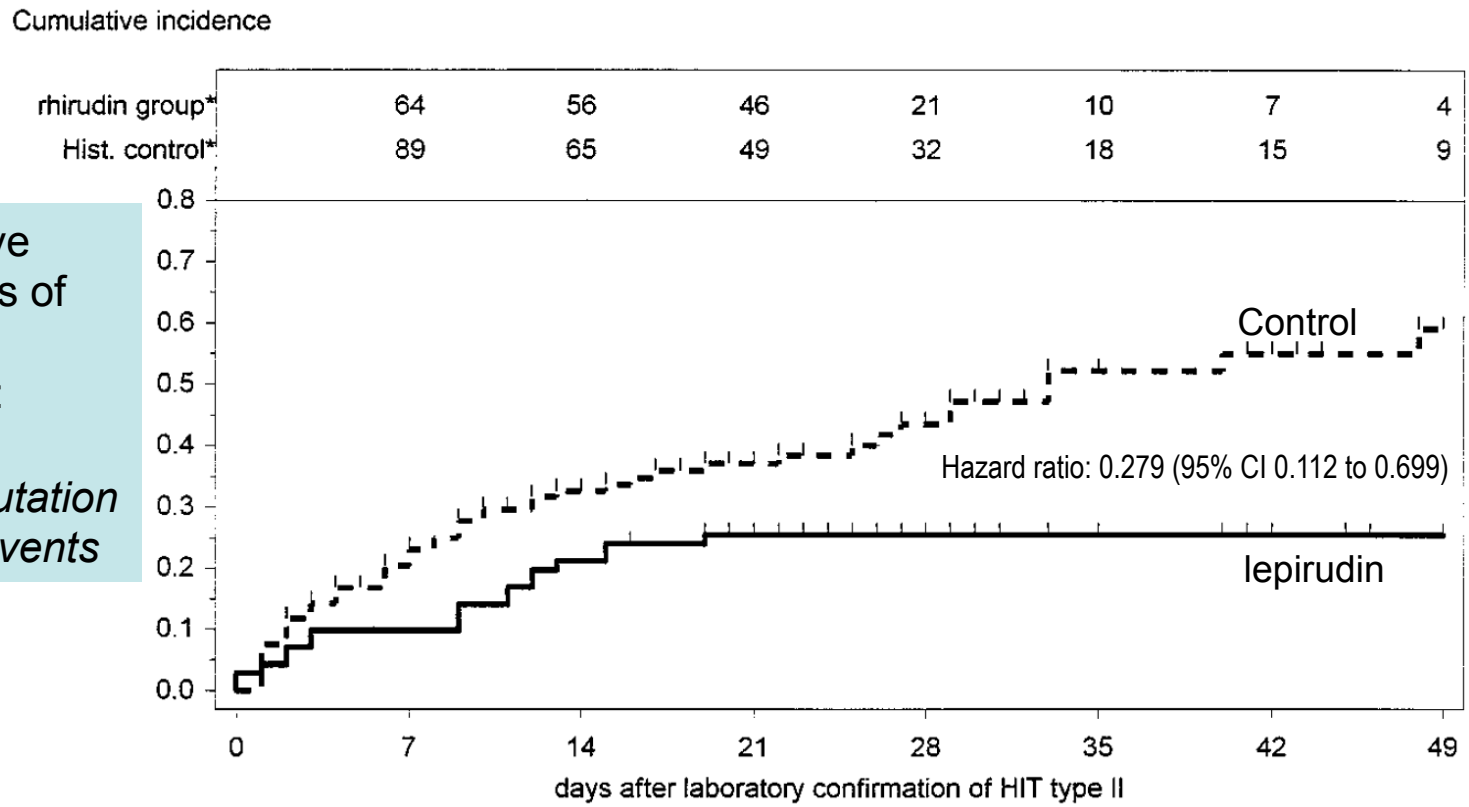
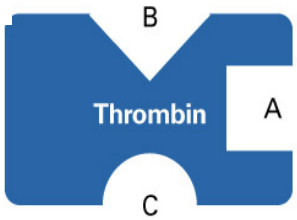
Cumulative incidences of combined end point:
death
limb amputation
new TE events

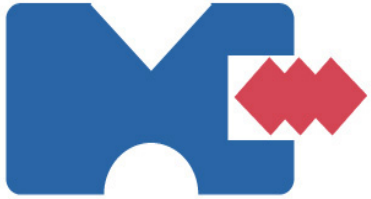


Greinacher et al. Circulation 1999;99;73-80.

Argatroban (Novastan®) is a Direct Thrombin Inhibitor (DTI)



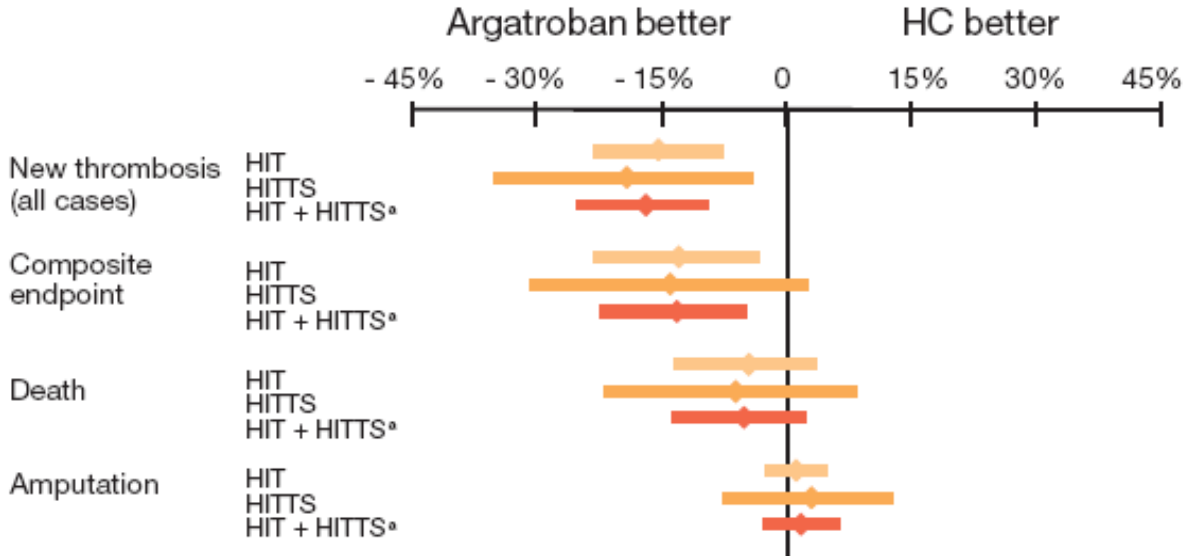
A. Active catalytic site
B. Exosite 1 (fibrinogen binding site)
C. Exosite 2 (heparin binding site)



Argatroban

Monovalent DTI

Pooled analysis of argatroban trials



Mean ± 95% CI. [a]Adjusted using Cochran-Mantel-Haenszel

Lewis BE. Thromb Haemost 2004: 92 (Suppl); 37–41.

Safety Results: ARG911 and ARG915

Number of patients (%) with major and minor bleeding events

	ARG-911 (n=304)	ARG-915 (n=264)	Total Argatroban (n=568)	Historical control group (n=193)
Major bleed events	21 (6.9)	10 (3.8)	31 (5.5)	13 (6.7)
Minor bleed events	124 (40.8)	97 (36.7)	221 (38.9)	79 (40.9)

Recommended Dosing Guidelines for argatroban (Novastan®)

HIT Patients

Initial dose:
2 µg/kg/min

Titrate until steady-state aPTT is 1.5–3.0 times baseline value*

HIT Patients with Renal Impairment

Same as:

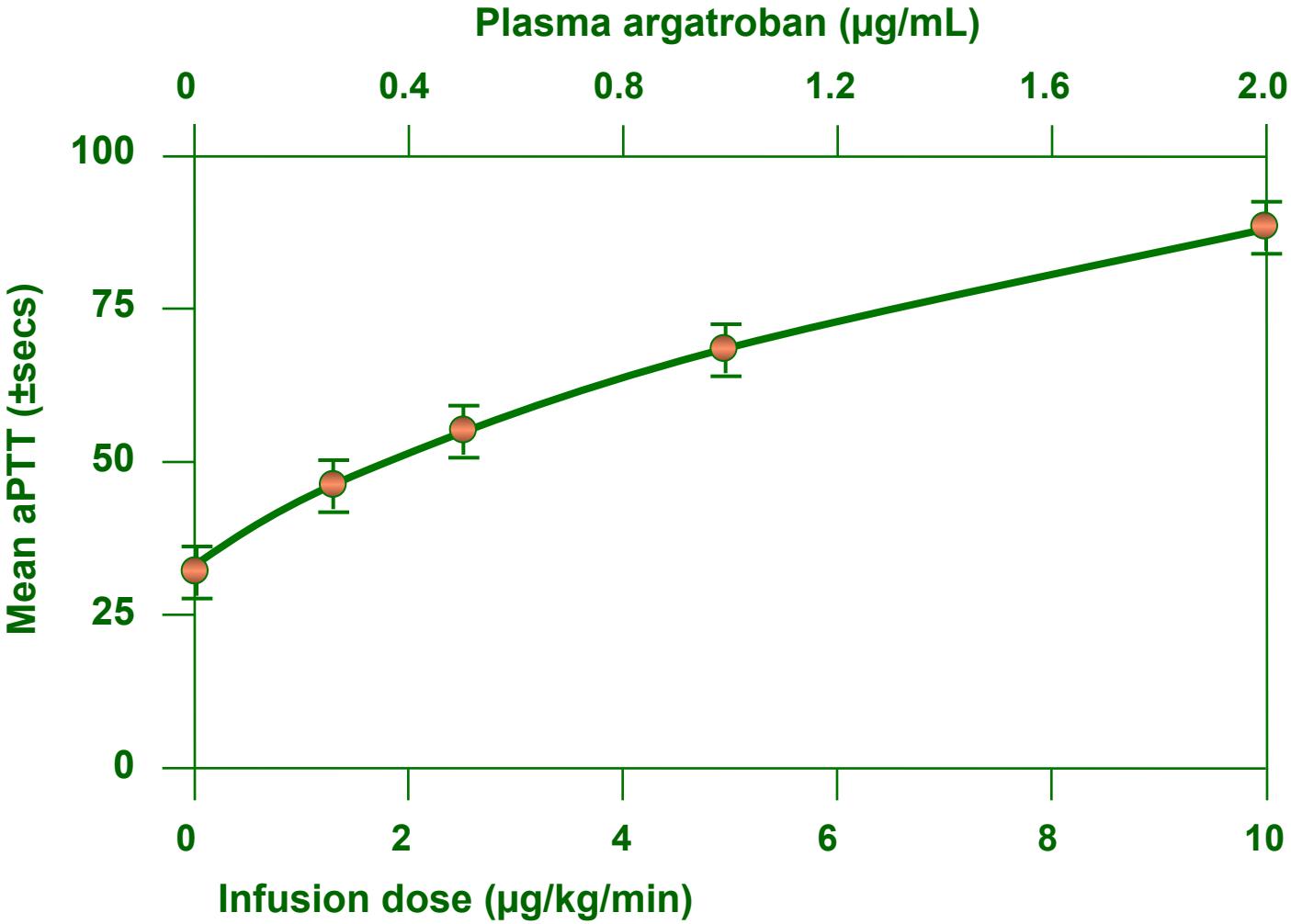
HIT Patients with Hepatic Impairment

Initial dose
0.5 µg/kg/min

Titrate until steady-state aPTT is 1.5–3.0 times baseline value*

*Not to exceed a dose of 10 µg/kg/min or aPTT of 100 seconds

Relationship at Steady-State Between Argatroban Dose, Plasma Argatroban Concentration and aPTT



Monitoring by aPTT

- Using the activated partial thromboplastin time (aPTT) to monitor anticoagulant effect
- **Target range:** 1.5 -3.0 times initial baseline value, (not exceeding 100 seconds)
- Check aPTT **2 hours after start** of infusion or each dose change, and daily
- In case of elevated aPTT (greater than three times baseline or 100 seconds) the infusion should be discontinued until the aPTT returns to the therapeutic range (typically within 2 hours of discontinuation of infusion). The infusion should then be restarted at one half of the previous infusion rate and the aPTT checked again after 2 hours.

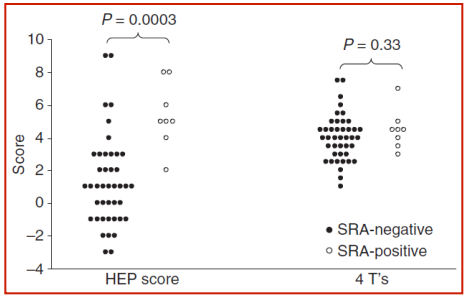
Argatroban → vitamin K antagonist

- Argatroban interferers with INR when the analysis is performed a.m. Quick (e.g. point-of-care instruments) but not when Owrens method is used.
- If Quicks method is used, argatroban should be continued until INR >4.0.
- If Owrens method is used, argatroban treatment can be stopped when INR >2.0.

Heparin-induceret trombocytopeni

HEP score

(HIT Expert Probability Score)

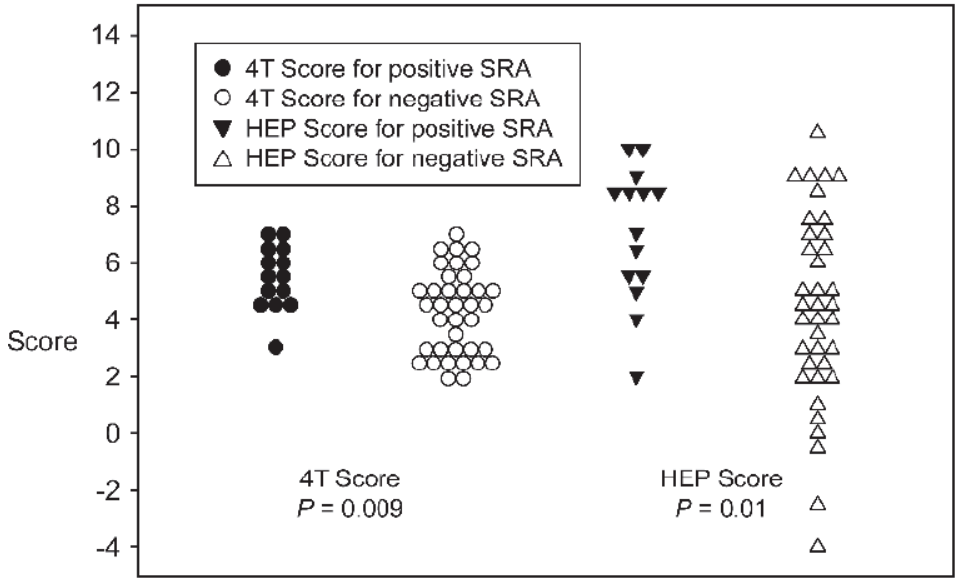


Clinical feature	Score
1. **Magnitude of fall in platelet count (measured from peak platelet count to nadir platelet count since heparin exposure)**	
a. < 30%	−1
b. 30%–50%	1
c. > 50%	3
2. **Timing of fall in platelet count**	
For patients in whom typical onset HIT is suspected	
a. Fall begins < 4 days after heparin exposure	−2
b. Fall begins 4 days after heparin exposure	2
c. Fall begins 5–10 days after heparin exposure	3
d. Fall begins 11–14 days after heparin exposure	2
e. Fall begins > 14 days after heparin exposure	−1
For patients with previous heparin exposure in last 100 days in whom rapid onset HIT is suspected	
f. Fall begins < 48 h after heparin re-exposure	2
g. Fall begins > 48 h after heparin re-exposure	−1
3. **Nadir platelet count**	
a. $\leq 20 \times 10^9$ L^{-1}	−2
b. $> 20 \times 10^9$ L^{-1}	2
4. **Thrombosis (Select no more than one)**	
For patients in whom typical onset HIT is suspected	
a. New VTE or ATE ≥ 4 days after heparin exposure	3
b. Progression of pre-existing VTE or ATE while receiving heparin	2
For patients in whom rapid onset HIT is suspected	
c. New VTE or ATE after heparin exposure	3
d. Progression of pre-existing VTE or ATE while receiving heparin	2
5. **Skin necrosis**	
a. Skin necrosis at subcutaneous heparin injection sites	3
6. **Acute systemic reaction**	
a. Acute systemic reaction after intravenous heparin bolus	2
7. **Bleeding**	
a. Presence of bleeding, petechiae or extensive bruising	−1
8. **Other causes of thrombocytopenia (Select all that apply)**	
a. Presence of a chronic thrombocytopenic disorder	−1
b. Newly initiated non-heparin medication known to cause thrombocytopenia	−2
c. Severe infection	−2
d. Severe DIC (defined as fibrinogen < 100 mg dL^{-1} and D-dimer > 5.0 μg mL^{-1})	−2
e. Indwelling intra-arterial device (e.g. IABP, VAD, ECMO)	−2
f. Cardiopulmonary bypass within previous 96 h	−1
g. No other apparent cause	3

VTE, venous thromboembolism; ATE, arterial thromboembolism; DIC, disseminated intravascular coagulation; IABP, intra-aortic balloon pump; VAD, ventricular assist device; ECMO, extracorporeal membrane oxygenation.

Cuker et al. J Thromb Haemost 2010; 8: 2642–50.

External validation of the HIT Expert Probability (HEP) score



- In this prospective validation study, test characteristics for the diagnosis of HIT based on confirmatory laboratory testing and expert opinion are similar.
- Given the complexity of the HEP scoring model compared to that of the 4T score, further validation of the HEP score is warranted prior to widespread clinical acceptance.

Joseph et al. Thromb Haemost 2015; 113: 633–40

HIT today

- The major clinical problem today is no longer *under-recognition of HIT,* but *over-diagnosis and over-treatment.*

- Among a recently reported cohort of patients managed with a direct thrombin inhibitor (DTI) for HIT at the University of Pennsylvania, 41% received treatment despite a very low clinical probability of disease as judged *post hoc by a panel of expert adjudicators.*

- 91 of 100 DTI-treated patients were ultimately determined to have a negative result by serotonin release assay

Adam Cuker. Thromb Haemost 2011; 106: 993–94

Requirements for immunoassays for the exclusion of HIT

- High negative predictive value (NPV: ~100%)
- Positive predictive value (PPV): >50%
- Simple assay, readily available
- Short turnaound time

New nanoparticle-based lateral-flow immunoassay for the exclusion of HIT

Milenia® QuickLine HIT
Einfacher und schneller Nachweis von
IgG-Antikörpern gegen PF4 / Polyanion-Komplexe

Einfache und schnelle Durchführung

5 µl Probe

1

2 Tropfen Puffer

2

Ergebnis nach 10 min

3

Sachs et al. Thromb Haemost 2011;106:1197–1202

Milenia® QuickLine HIT LFIA-assay

	LFIA –Assay	PaGIA	PF4 Enhanced GTI IgG ELISA	Zymutest HIA IgG ELISA
Sensitivität (%)	100	91,2	100	100
Spezifität (%)	**93**	86,8	89,2	87,3
NPV (%)	100	99,2	100	100
PPV (%)	54	36	43	39

Alternatives to heparin

NOAK ?

NOACs as Emerging Treatment Options for HIT

Trial	Study Type	n	Indication for Anticoagulation	Diagnostic Test/ Diagnosis	Treatment Regimen	HIT Phase DOAC Initiated	Outcomes
Fieland and Taylor[18]	Case report	1	Nonvalvular atrial fibrillation status post-CABG	PF4 antibody/HIT	Dabigatran 150 mg twice daily	Acute	No thrombotic or bleeding events reported
Mirdamadi[19]	Case report	1	Status post–orthopedic surgery	Clinical findings and lab results/HIT with thrombosis	Dabigatran 110 mg twice daily	Acute	Recanalization of thrombosis reported
Hantson et al[21]	Case report	1	Status post–orthopedic surgery	PF4 antibody/HIT with thrombosis	Rivaroxaban 15 mg twice daily ×21 days; 20 mg daily thereafter	Acute	Recanalization of thrombus reported
Ng et al[22]	Case series	3	Hemodialysis; status post–embolectomy for critical limb ischemia; pulmonary embolism, and deep-vein thrombosis	PF4 antibody/HIT with thrombosis (2); isolated HIT (1)	Rivaroxaban 10 mg daily transitioned to warfarin; rivaroxaban 15 mg twice daily ×3 weeks followed by 20 mg daily; 15 mg twice daily	Acute	No thrombotic or bleeding events reported
Sharifi et al[25]	Case series	12	Not specified	Not specified	Apixaban 5 mg twice daily (n = 3); dabigatran 150 mg twice daily (n = 2); rivaroxaban 20 mg daily (n = 7)	Subacute	No thrombotic or bleeding events reported

Miyares et al. Ann Pharmacother 2015;49:735-9

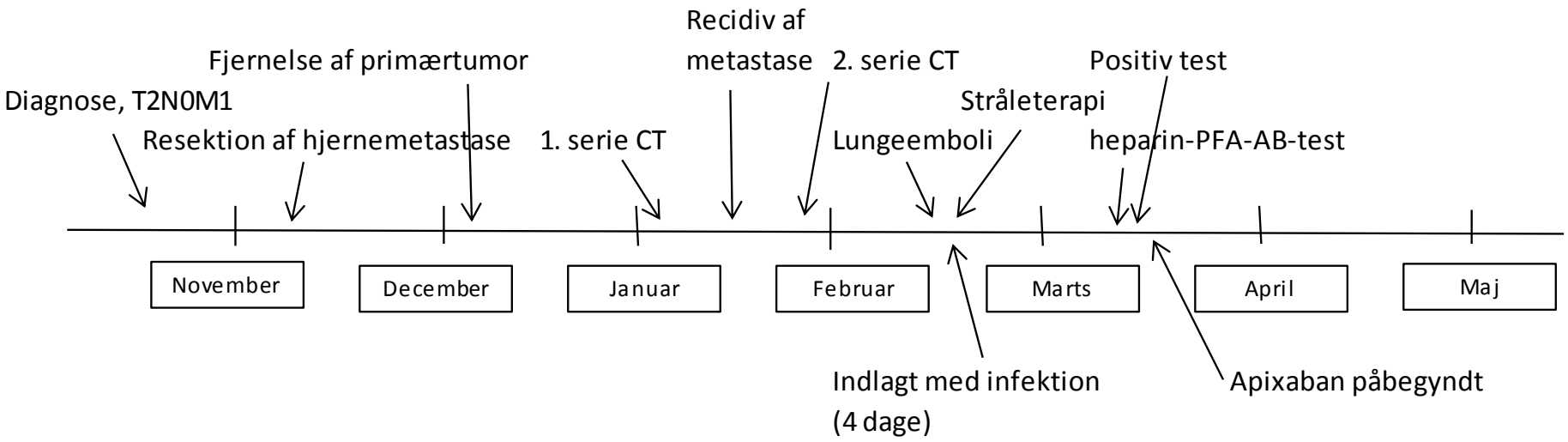
Sikker anvendelse af apixaban til behandling af HIT hos en 72-årig kvinde med lungecancer

Pia Bükmann Larsen, MD
Klinisk Biokemisk Afdeling

Næstved-Slagelse-Ringsted Sygehuse

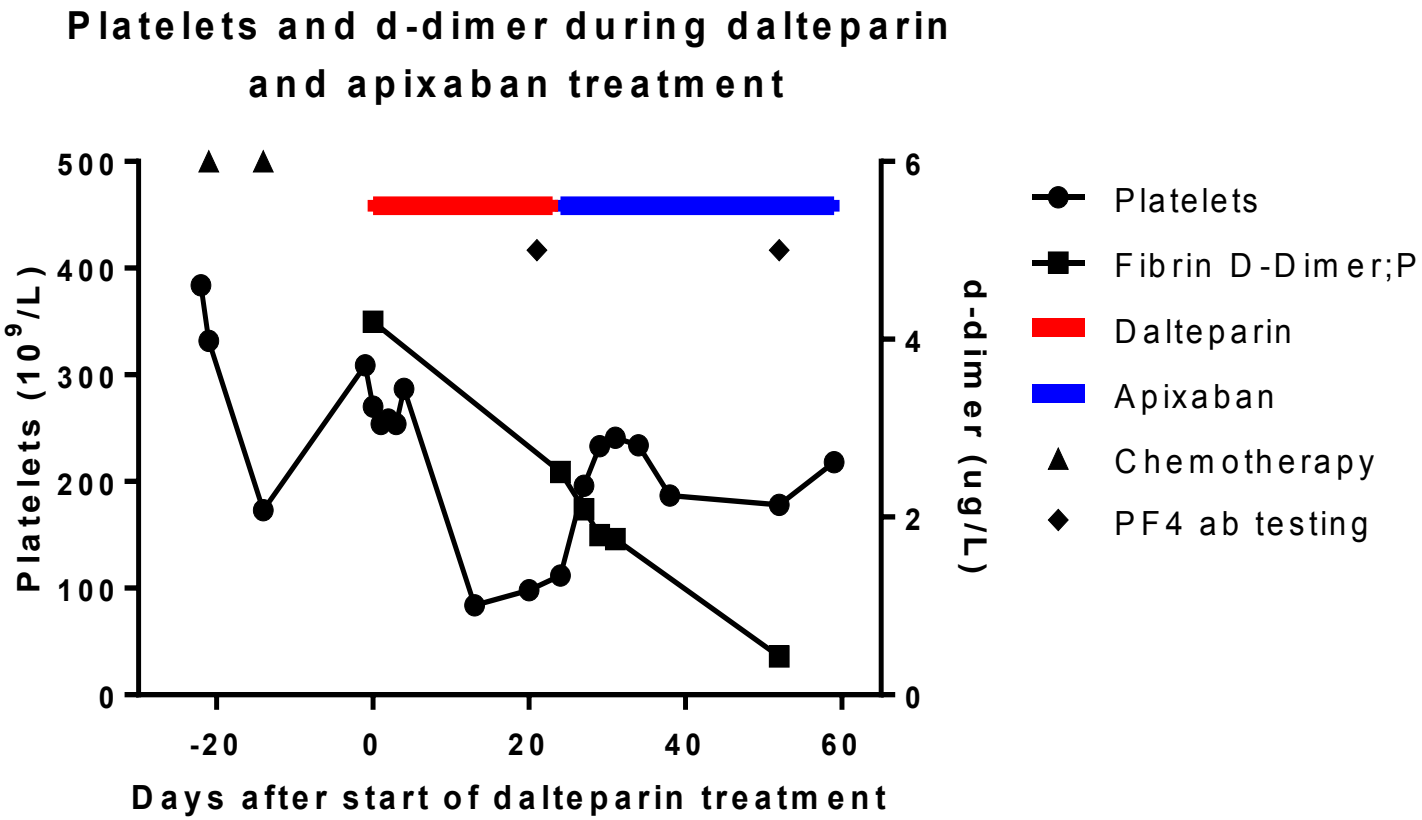
REGION SJÆLLAND
– vi er til for dig

Sygehistorie



- 72-årig kvinde
- NSCLC, T2N0M1

Hæmatologiske parametre



4Ts score = 5 points:

2 points: Thrombocytopenia: platelet count fall >50 % and platelet nadir >= 20 x 10^9/L

2 points: Timing of platelet count fall: Clear onset 13 days after exposure

0 points: Thrombosis or other sequelae: None (not progressive or recurrent)

1 point: Other causes of thrombocytopenia: Possible

Konklusion

REGION SJÆLLAND
– vi er til for dig

- Vi har succesfuldt behandlet HIT med apixaban som monoterapi

- Apixaban kan være en sikker peroral behandling af HIT hos patienter hvor der ikke er øvrige kontraindikationer mod NOAC.

Tak til

- Lennart Friis-Hansen
- Steen Ingeberg
- Maja Jørgensen
- Alice Anker
- Susanne Sigvard