HIT
(Heparin-Induced Thrombocytopenia)

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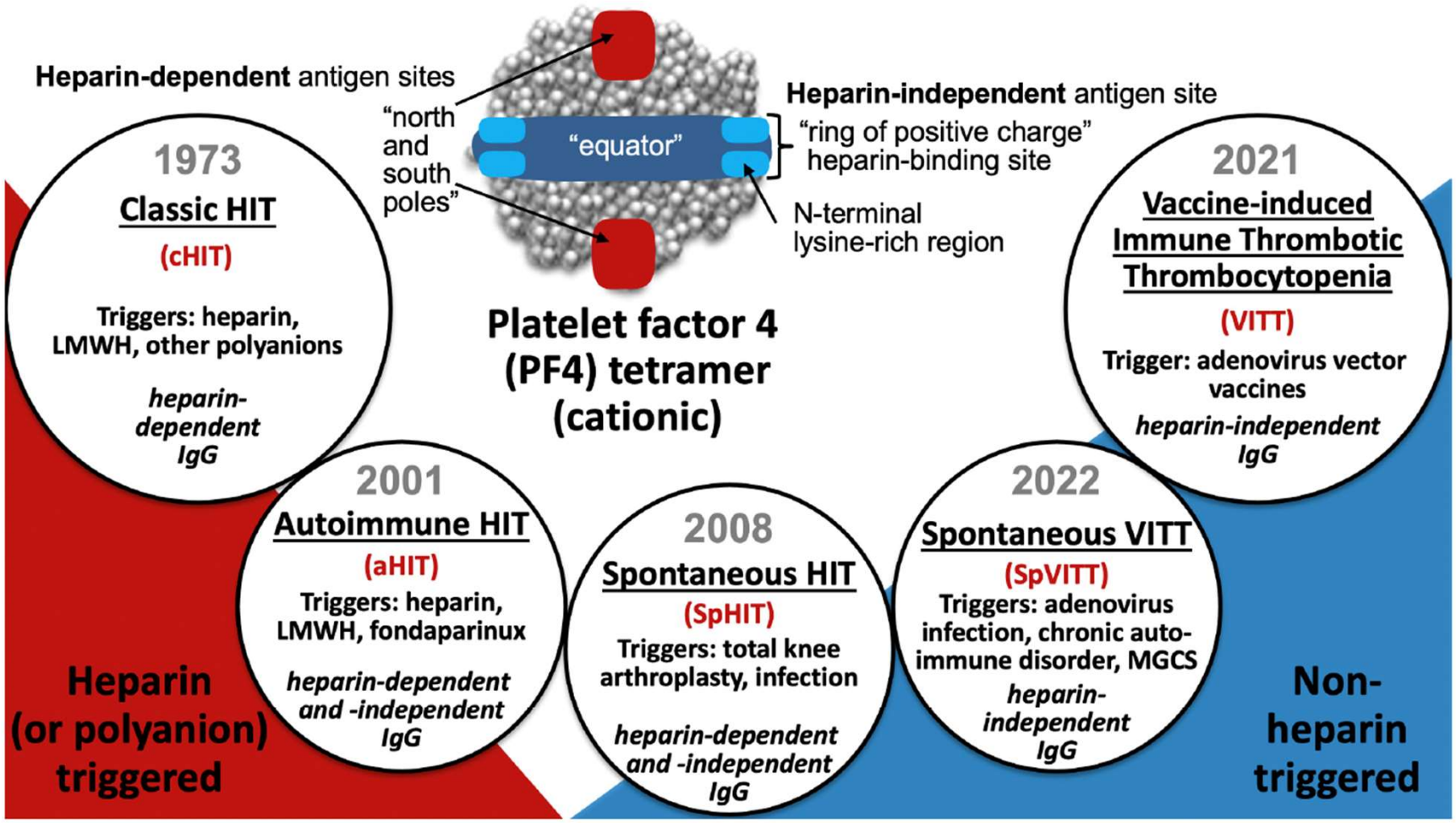
Outline

- ✓ Definition and epidemiology
- ✓ Clinical manifestations
- ✓ Clinical and laboratory diagnosis
- ✓ Therapy

HIT and VITT types



Trombocitopenia indotta da eparina (HIT)

✓ E' una reazione avversa all'eparina mediata da anticorpi IgG che attivano le piastrine in seguito al legame con i complessi fattore piastrinico 4 (PF4) - eparina

✓ È caratterizzata da una riduzione della conta piastrinica con complicanze trombotiche sia venose che arteriose, di difficile diagnosi e cura

L'eparina può indurre 2 tipi di trombocitopenia

Tipo I: non immunitaria, esordio precoce, senza complicanze trombotiche, regredisce nonostante il proseguimento della terapia eparinica

- conta plts raramente < 80 G/l
- compare nei primi due giorni di terapia eparinica
- nessuna conseguenza sul piano clinico

Tipo II (HIT): moderata o grave, insorgenza tardiva, IgG median survival 100 giorni, alto rischio di trombosi

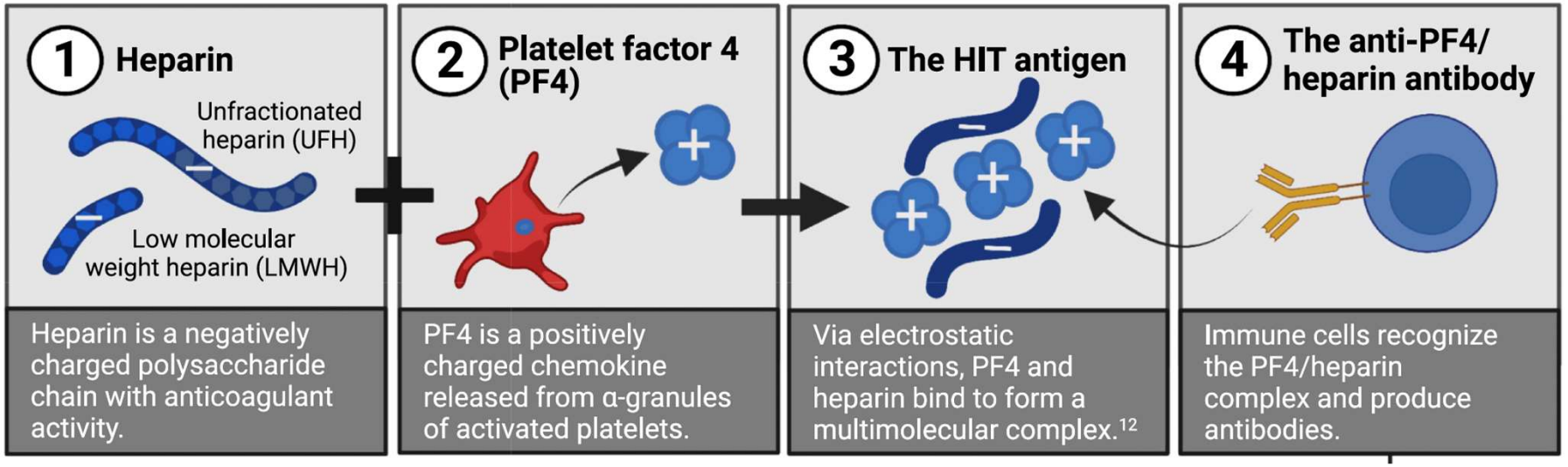
Presentazione clinica

- Trombocitopenia con **diminuzione del numero di piastrine** dopo l'esposizione all'eparina:
  - ≥50% del basale (tra il 30 e il 50% nel 10% dei casi)
  - generalmente non grave: tra 30 e $70x10^9/L$
- modalità di insorgenza:

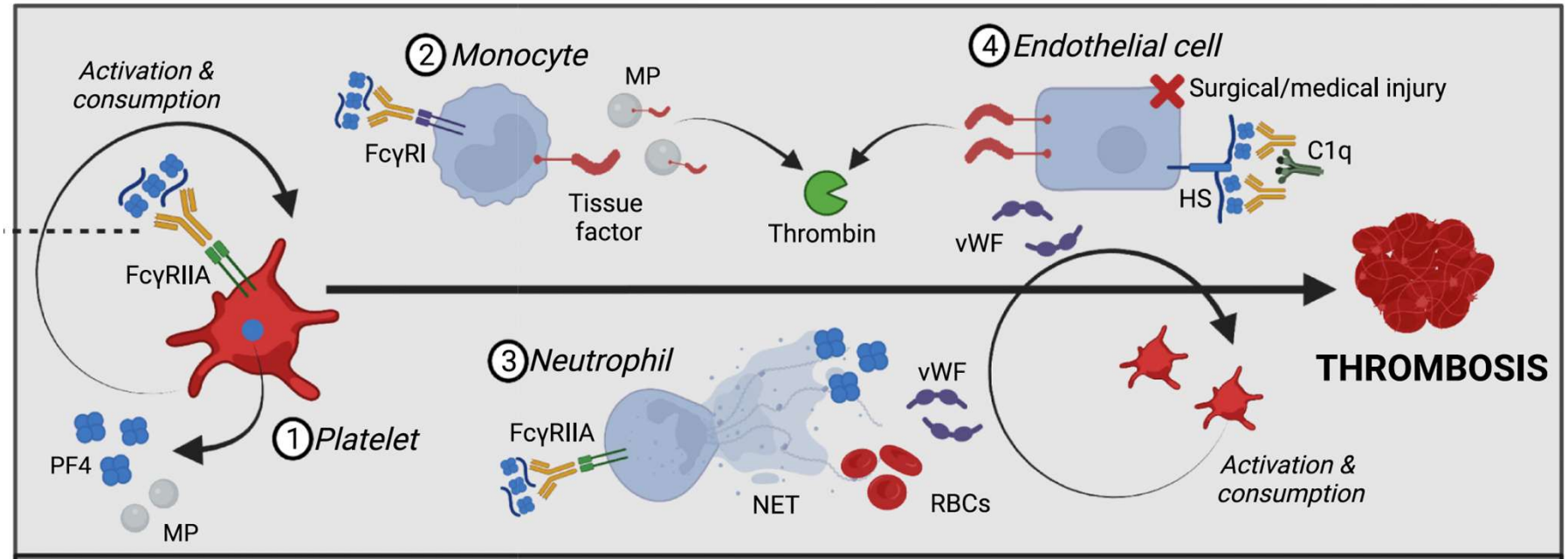
Insorgenza rapida	Insorgenza tipica	Insorgenza ritardata
Diminuzione della conta piastrinica entro 24 ore dall'esposizione all'eparina	Diminuzione della conta piastrinica 4-14 giorni dopo l'esposizione all'eparina	Diminuzione della conta piastrinica da giorni a settimane dopo la cessazione dell'eparina

Nei pazienti che hanno ricevuto eparina nei precedenti 90 giorni potrebbero persistere in circolo anticorpi anti PF4-Eparina,e la HIT potrebbe insorgere rapidamente in seguito a successiva somministrazione di eparina.

The key players

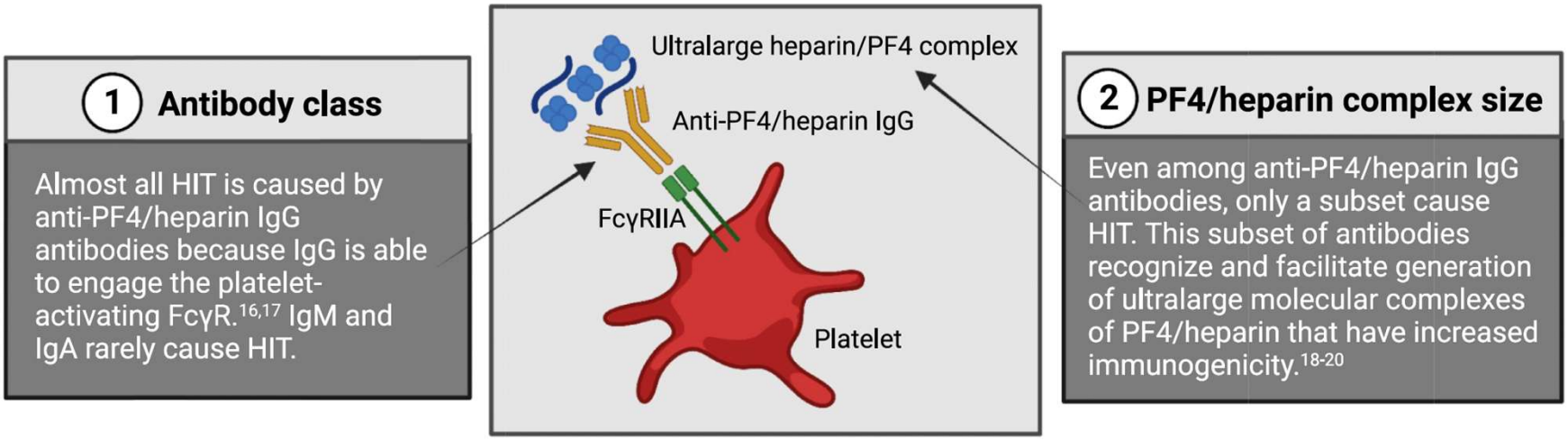


How the anti-PF4/heparin antibodies cause HIT?

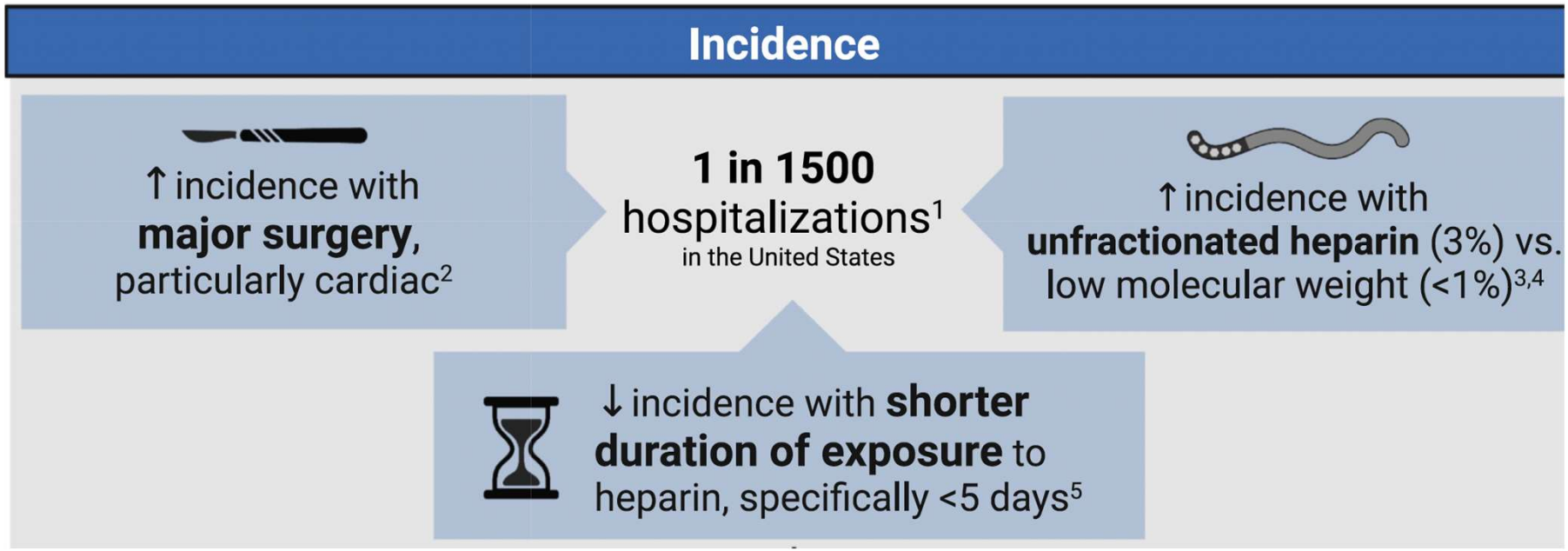


The anti-PF4/heparin IgG antibody binds Fc receptors (FcR), leading to FcR clustering which stimulates (1) platelet activation, consumption, and granule and microparticle (MP) release, (2) expression and release of tissue factor (TF) and TF-containing MPs by monocytes, generating thrombin, and (3) release of neutrophil extracellular traps (NETs) that engage platelets, red blood cells (RBCs), PF4, and von Willebrand factor (vWF).[9,13,14] There is also FcR-independent activation of (4) endothelial cells via direct injury causing TF expression and vWF release as well as binding of anti-PF4/heparin IgG to complexes of PF4 and surface heparan sulfate (HS), triggering complement activation via C1q.[9,15]

Why don't all anti-PF4/heparin antibodies cause HIT?



Incidence


Incidence
↑ incidence with **major surgery**, particularly cardiac[2]
1 in 1500 hospitalizations[1] in the United States
↑ incidence with **unfractionated heparin** (3%) vs. low molecular weight (<1%)[3,4]
↓ incidence with **shorter duration of exposure** to heparin, specifically <5 days[5]

Rischio di HIT

fattori legati al paziente e al farmaco

Esposizione prolungata alla terapia con eparina

- HIT nel 2-3% dei pazienti che ricevono ENF per 6 giorni o più

Tipo e dose di eparina somministrata

rischio di HIT 10 volte > con ENF rispetto a EBPM:

- ENF (~3%)
- EBPM (0,2%)

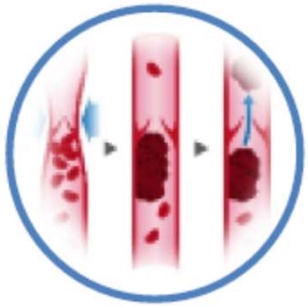
Indicazione per il trattamento

- pazienti chirurgici (cardiaci, ortopedici) o traumatizzati rischio compreso tra 1% e 5%.
- Pazienti medici o in terapia intensiva rischio < 2%

Sesso del paziente

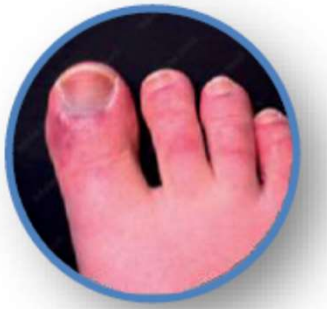
- Le donne hanno un rischio doppio rispetto agli uomini (aumento della risposta immunitaria)

Complicanze trombotiche arteriose e venose



Trombosi venosa profonda
~50% dei pazienti

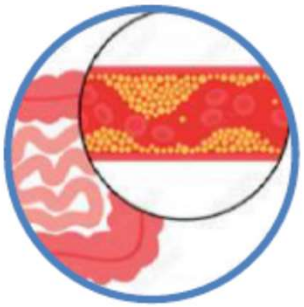
Embolia polmonare
10-25% dei pazienti



Necrosi ischemica degli arti 5%-10% dei pazienti

Infarto miocardico acuto
~3% dei pazienti

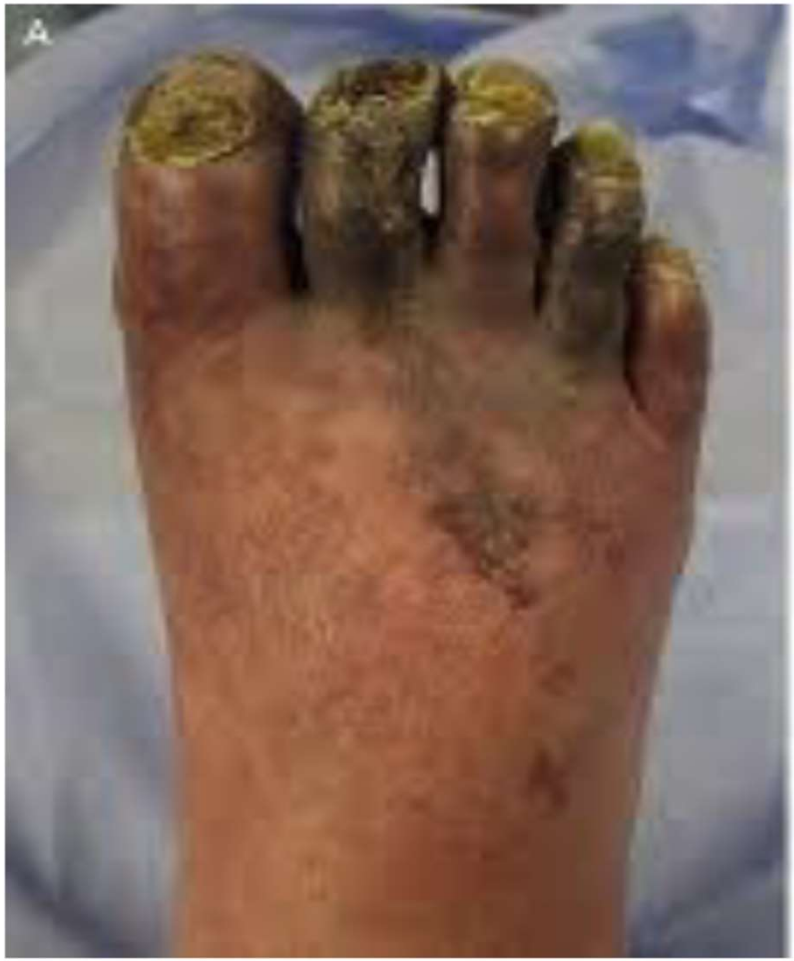
Ictus
~4% dei pazienti

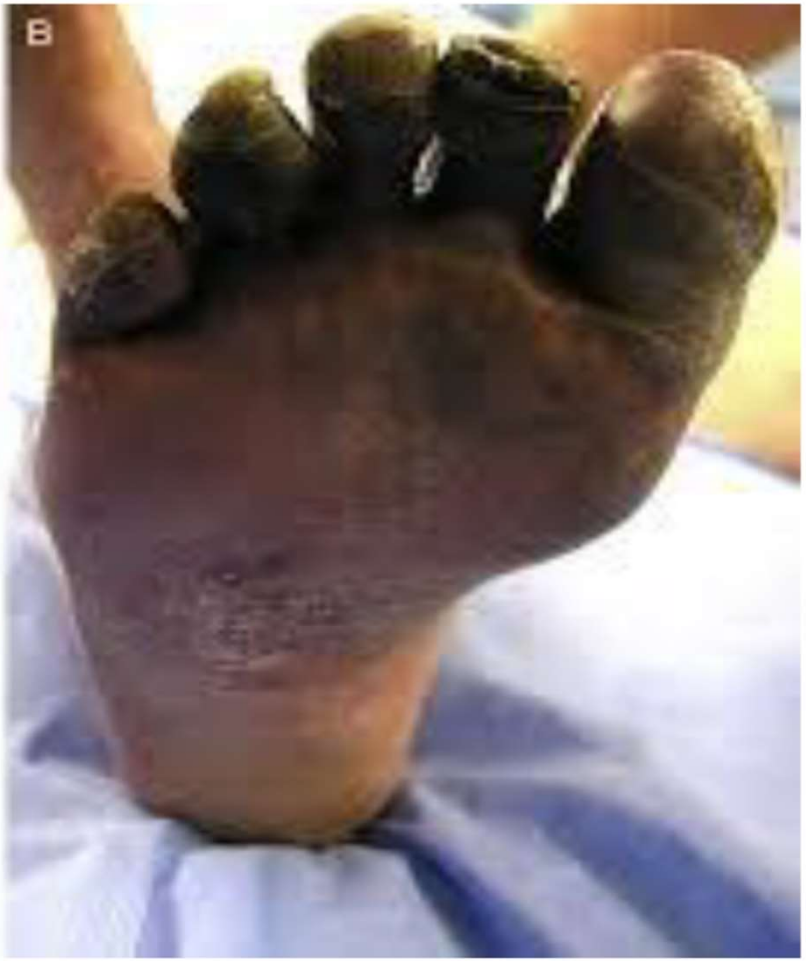


Ischemia mesenterica rara

Mortalità associata a HIT
Dal 5% al 30%

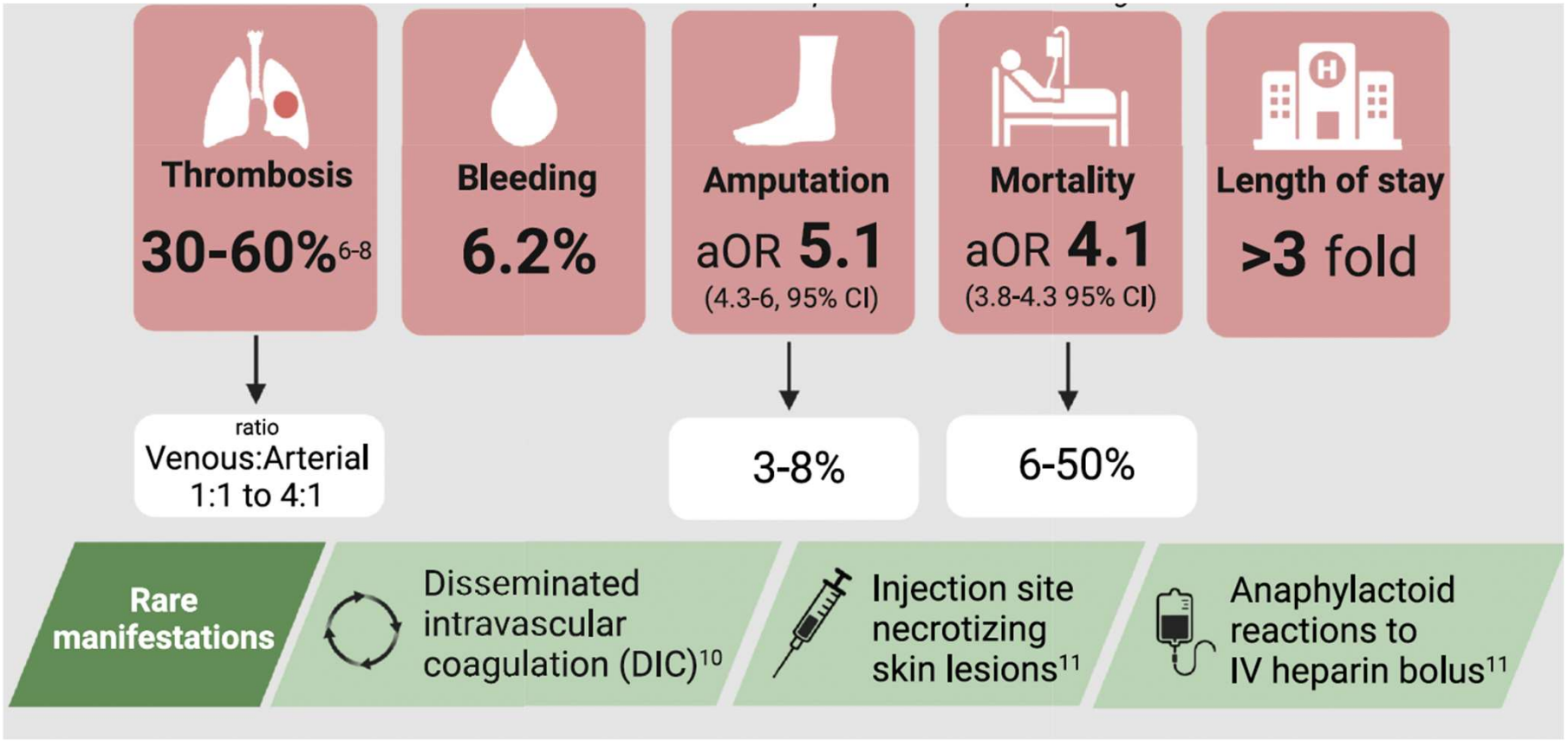
Necrosi ischemica periferica



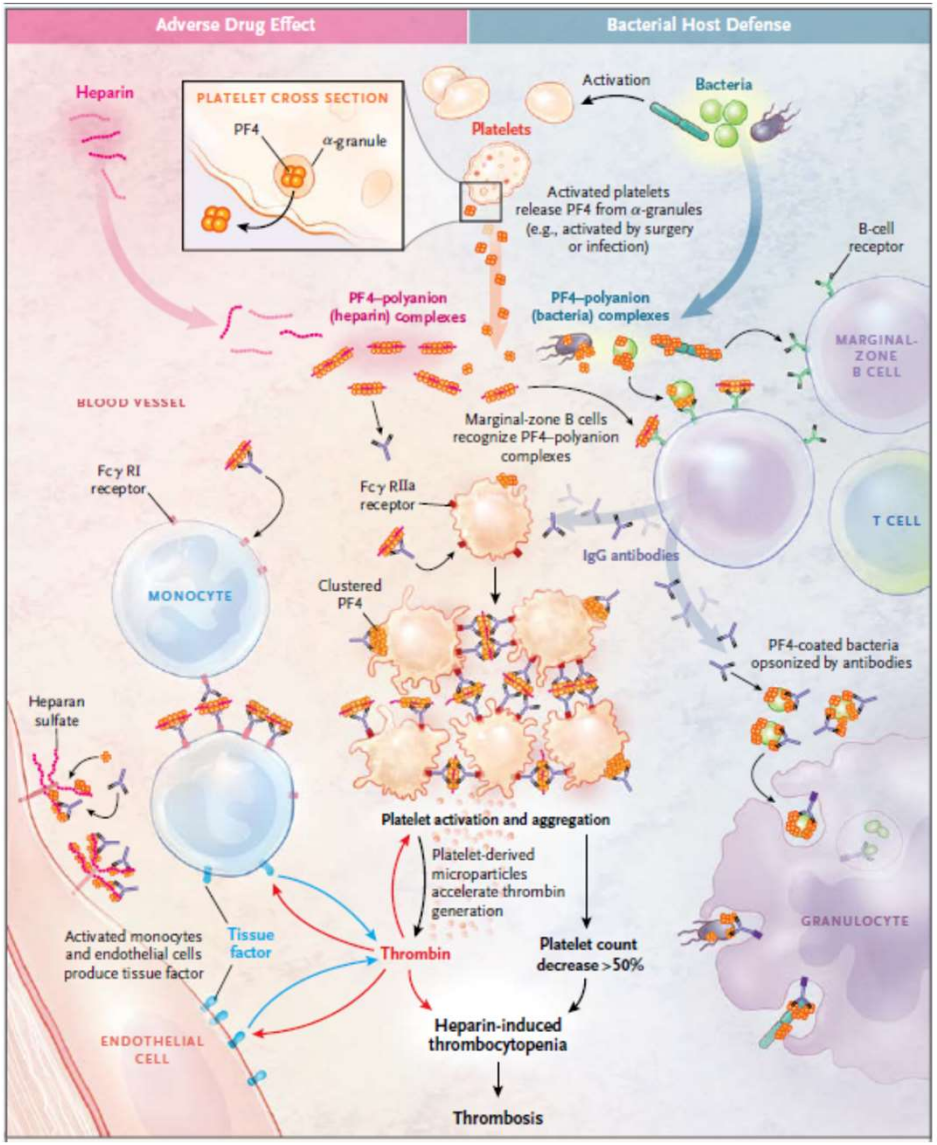


Tasso di amputazione
1% - 3%[1,5]

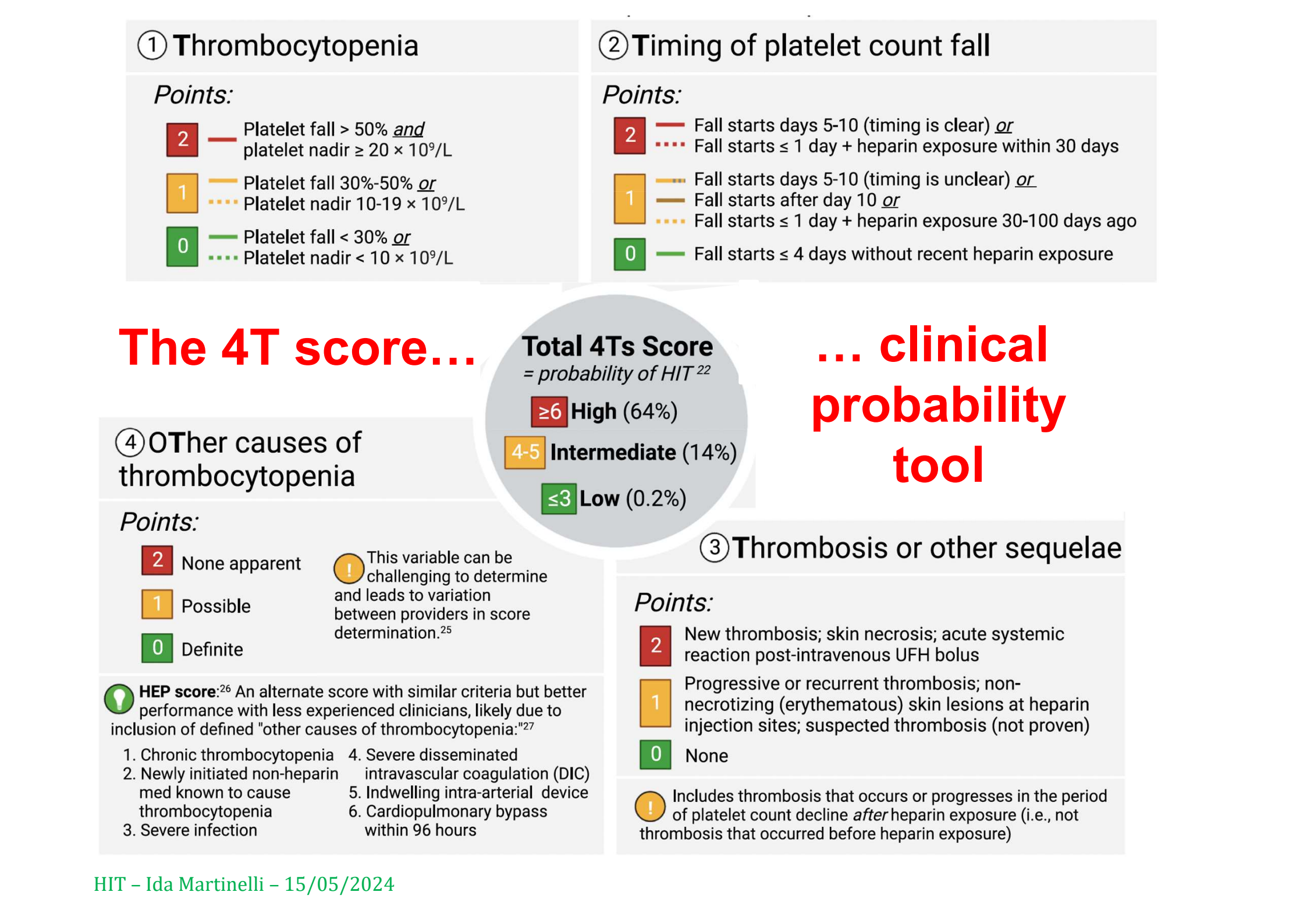
Clinical manifestations & outcomes



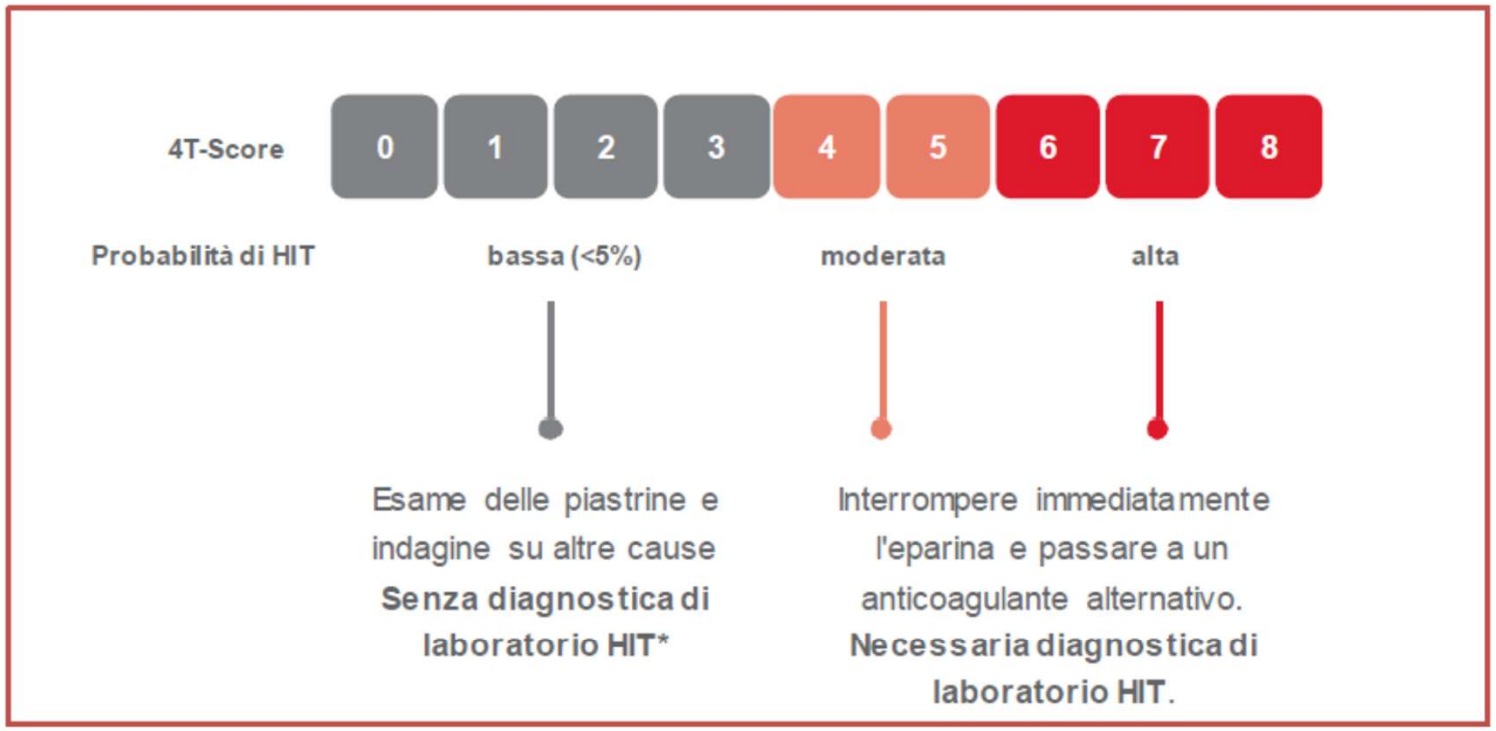
compared to hospital discharges without HIT



HIT - diagnosi clinica e di laboratorio


① Thrombocytopenia
Points:
2 Platelet fall > 50% and platelet nadir ≥ 20 × 10⁹/L
1 Platelet fall 30%-50% or Platelet nadir 10-19 × 10⁹/L
0 Platelet fall < 30% or Platelet nadir < 10 × 10⁹/L
② Timing of platelet count fall
Points:
2 Fall starts days 5-10 (timing is clear) or Fall starts ≤ 1 day + heparin exposure within 30 days
1 Fall starts days 5-10 (timing is unclear) or Fall starts after day 10 or Fall starts ≤ 1 day + heparin exposure 30-100 days ago
0 Fall starts ≤ 4 days without recent heparin exposure
The 4T score…
Total 4Ts Score
= probability of HIT [22]
≥6 High (64%)
4-5 Intermediate (14%)
≤3 Low (0.2%)
… clinical probability tool
④ OTher causes of thrombocytopenia
Points:
2 None apparent
1 Possible
0 Definite
This variable can be challenging to determine and leads to variation between providers in score determination.[25]
HEP score:[26] An alternate score with similar criteria but better performance with less experienced clinicians, likely due to inclusion of defined "other causes of thrombocytopenia:"[27]
1. Chronic thrombocytopenia
2. Newly initiated non-heparin med known to cause thrombocytopenia
3. Severe infection
4. Severe disseminated intravascular coagulation (DIC)
5. Indwelling intra-arterial device
6. Cardiopulmonary bypass within 96 hours
③ Thrombosis or other sequelae
Points:
2 New thrombosis; skin necrosis; acute systemic reaction post-intravenous UFH bolus
1 Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions at heparin injection sites; suspected thrombosis (not proven)
0 None
Includes thrombosis that occurs or progresses in the period of platelet count decline after heparin exposure (i.e., not thrombosis that occurred before heparin exposure)

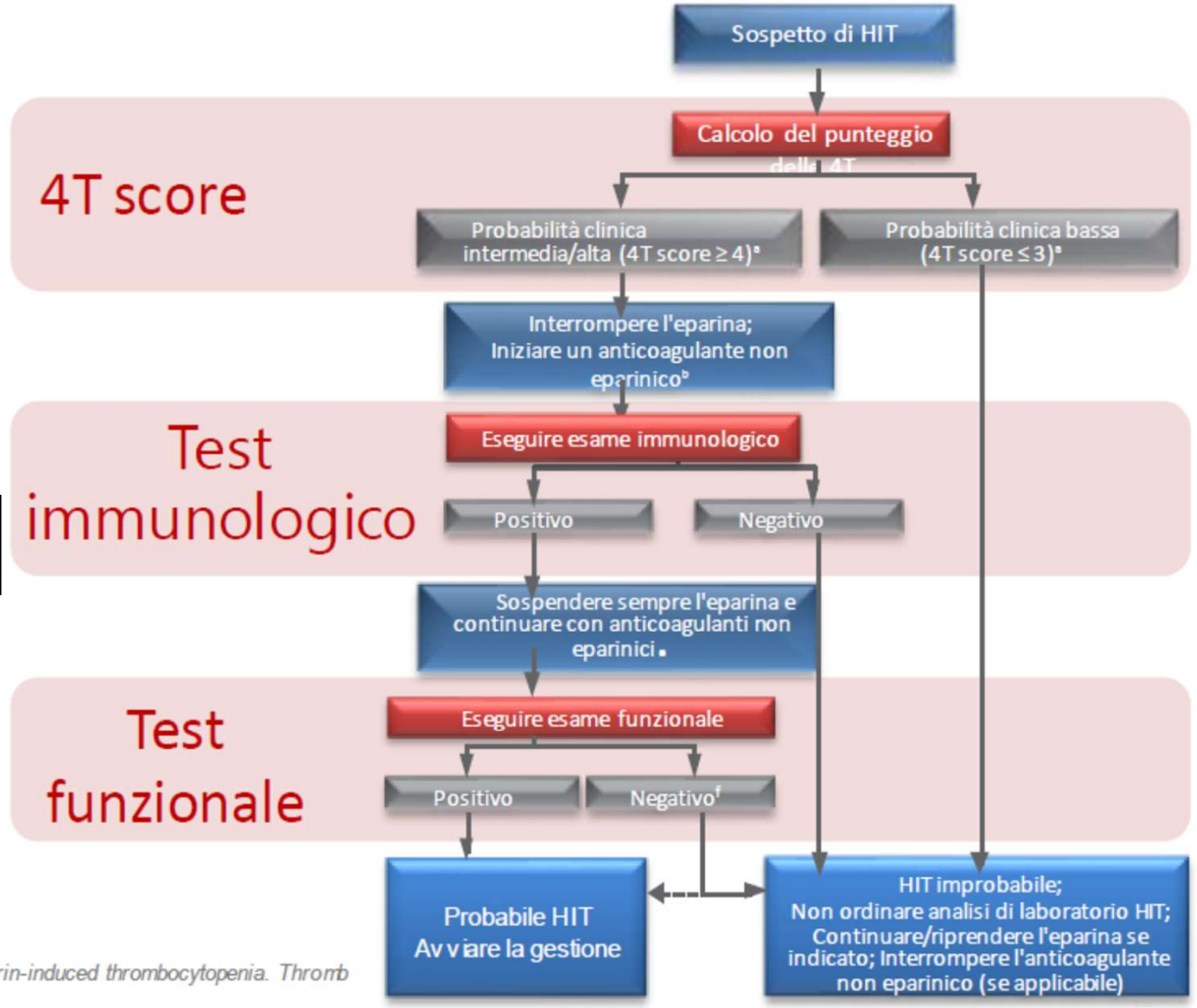
4T score - interpretazione del risultato



- Il 4T score è uno strumento di valutazione clinica e permette di escludere la HIT in molti pazienti
- Il suo utilizzo richiede esperienza ed è soggetto a una rilevante variabilità tra gli osservatori

Algoritmo per la diagnosi e la gestione iniziale dei pazienti con sospetta HIT

Sensibilità > 99%



Nagler M & Bakchoul T. Clinical and laboratory tests for the diagnosis of heparin-induced thrombocytopenia. Thromb Haemost 2016; 116: 823-834

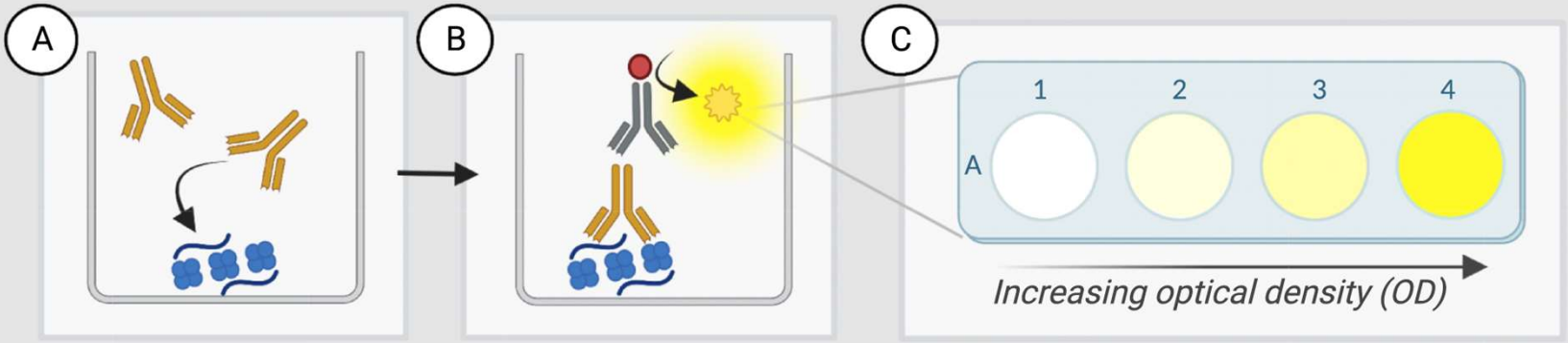
Enzyme Immunoassay (EIA)

The EIA is the prototypical immunoassay, and is used as the standard immunoassay throughout this manuscript

Purpose: Determine if anti-PF4/heparin antibodies are *present*, and if so, their abundance

Performance: High sensitivity (0.97, 95% CI 0.95-0.99), limited specificity (0.82, 95% CI 0.90-0.84)[28]

Specificity varies based on assay used, increasing with IgG-specific assays[28,29] and higher OD thresholds.[30]



Higher OD correlates with higher HIT likelihood[30] and thrombotic risk.[31]

How it works: (A) The plate well is coated with multimolecular complexes of PF4/heparin (or PF4/heparin-like polyanions). Patient serum or plasma is added and anti-PF4/heparin antibodies bind to the complex. (B) Tagged anti-human antibody is added and binds anti-PF4/heparin antibodies. A substrate is added to elicit color change. (C) Degree of color change (optical density, OD) increases with increasing concentration of anti-PF4/heparin antibodies.

Rapid Immunoassays (additional)

Multiple types of immunoassays exist, all with different performance characteristics and different international availability. Selected examples of rapid immunoassays are included below.

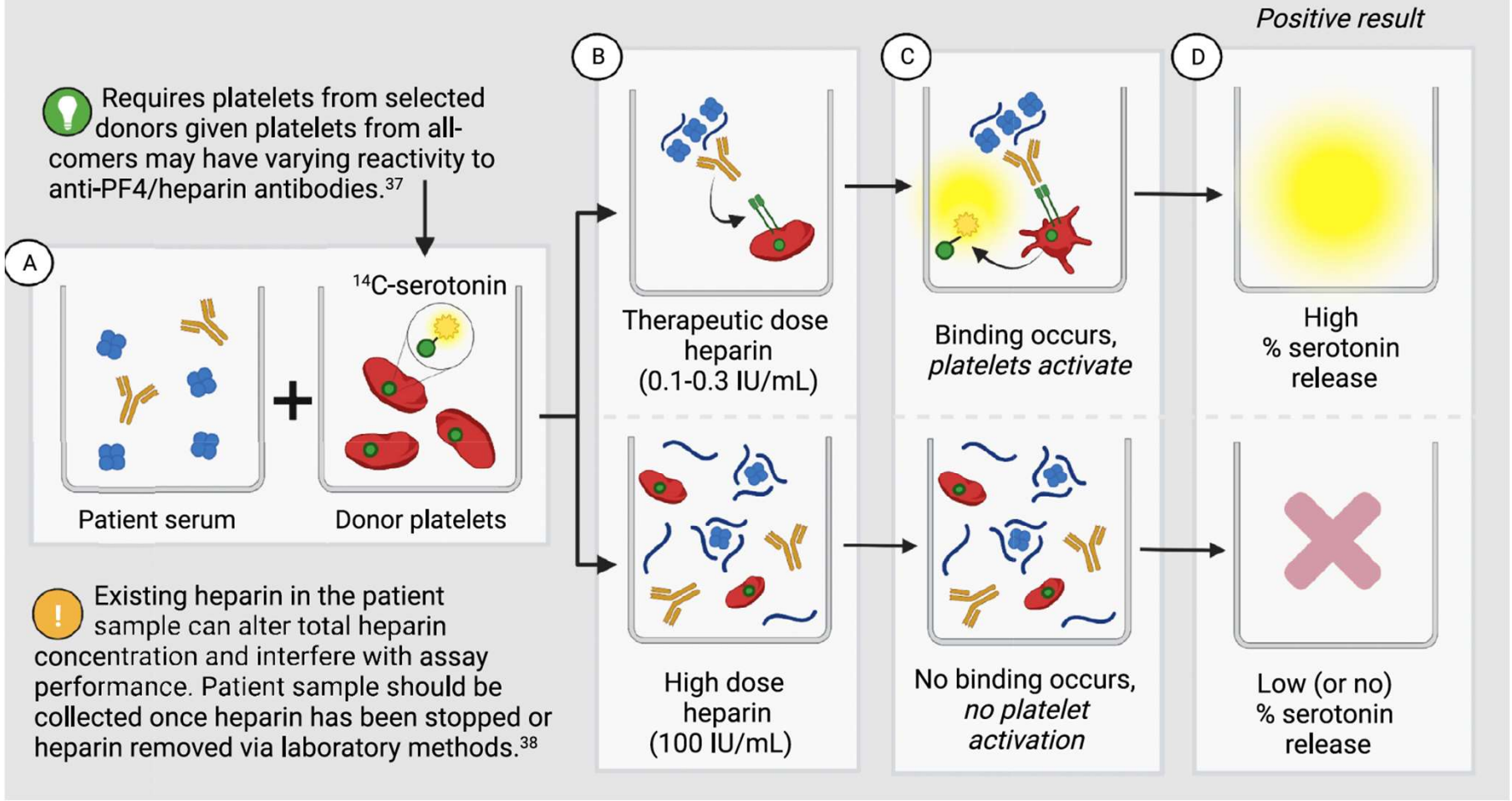
Purpose: Similar to EIA but provide results in ≤30 minutes (EIA is often batched, takes hours to perform)
Performance: Varies by assay

		Sensitivity (95% CI)	Specificity (95% CI)	How it works: Method of anti-PF4/heparin detection	Ab class detected
Particle gel immunoassay[32]	PaGIA	0.98 (0.94-1.00)	0.88 (0.91-0.96)	 Polymers coated with PF4/heparin complexes	IgG1
IgG-specific chemiluminescence assay[32]	IgG CIA	0.95 (0.90-1.00)	0.94 (0.89-0.99)	 Magnetic particles coated with PF4/polyvinyl sulfonate	IgG
Lateral flow immunoassay[32]	LFIA	0.97 (0.92-1.00)	0.91 (0.86-0.96)	 PF4-polyanion complexes	IgG
Latex immunoturbidimetric assay[33]	LIA	0.974	0.94	 Competitive inhibition of nanoparticles coated with HIT-like antibodies	IgG, IgA, IgM

Functional assays
C-serotonin release assay (SRA)

Purpose: Determine if anti-PF4/heparin antibodies are *pathogenic* (i.e. activate platelets)
Performance: High sensitivity (~0.95), high specificity (~0.95)[35]

Due to variation in assay performance and reporting practices,[36] real-world performance may vary from literature reports.

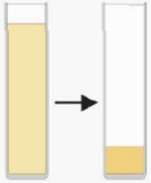


Additional functional assays

Multiple functional assays exist that differ by the method used for measuring platelet activation:

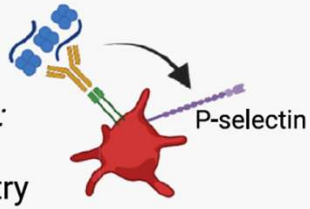
Heparin-induced platelet activation assay (HIPA)[40]

Measurement of activation:
Visual assessment of decreased turbidity with platelet activation

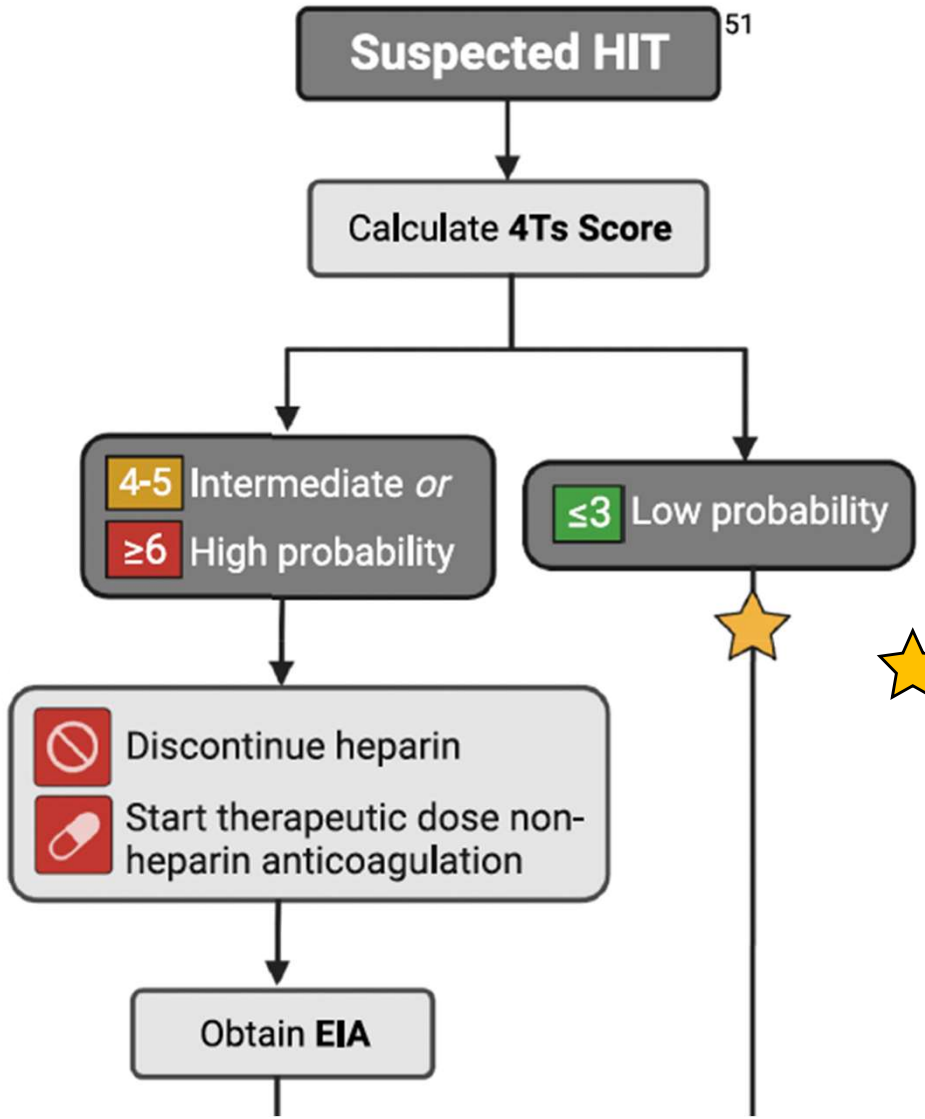


P-selectin expression assay (PEA)[41-43]

Measurement of activation:
Platelet P-selectin (CD62p) expression by flow cytometry



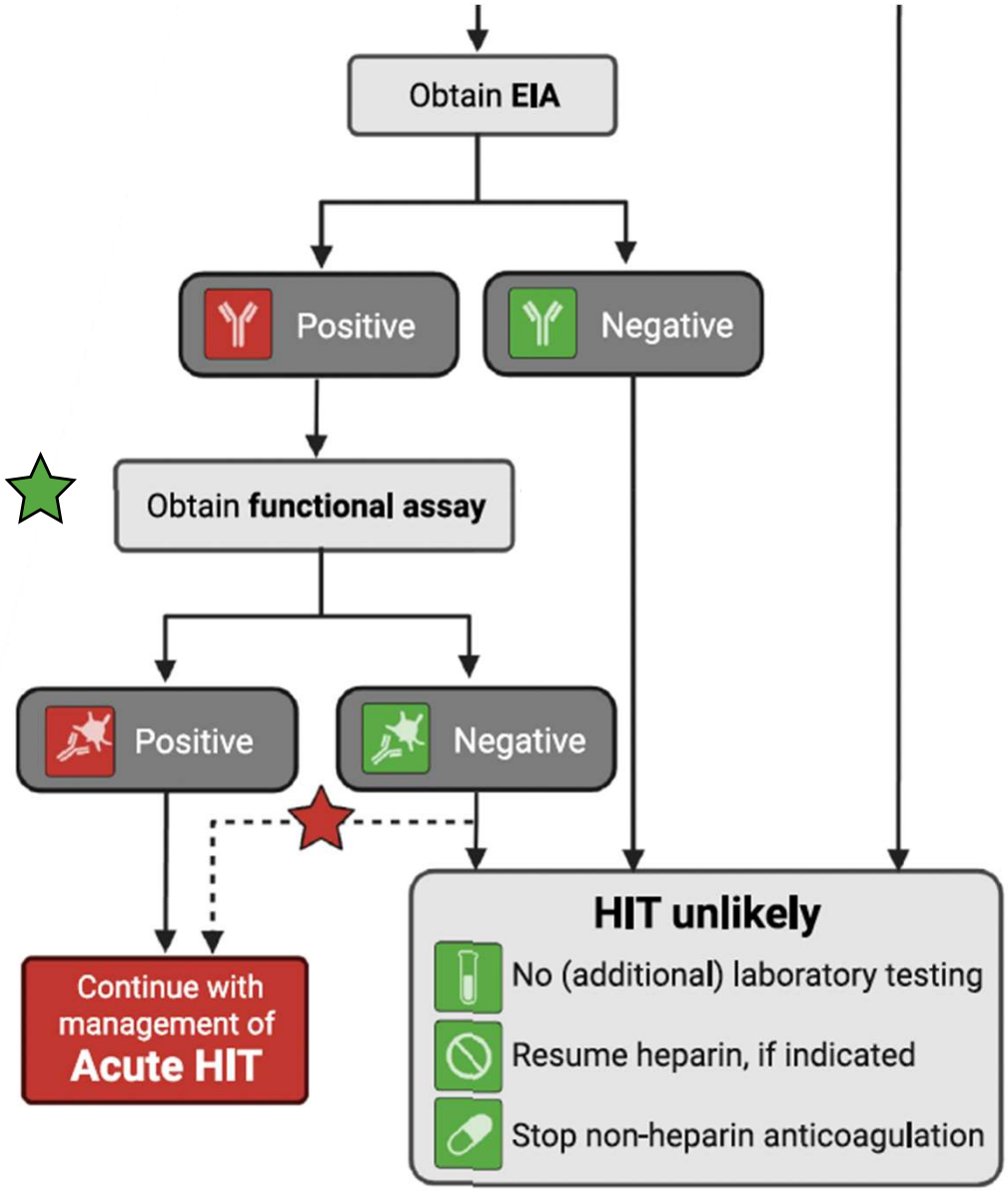
Summarizing HIT diagnosis



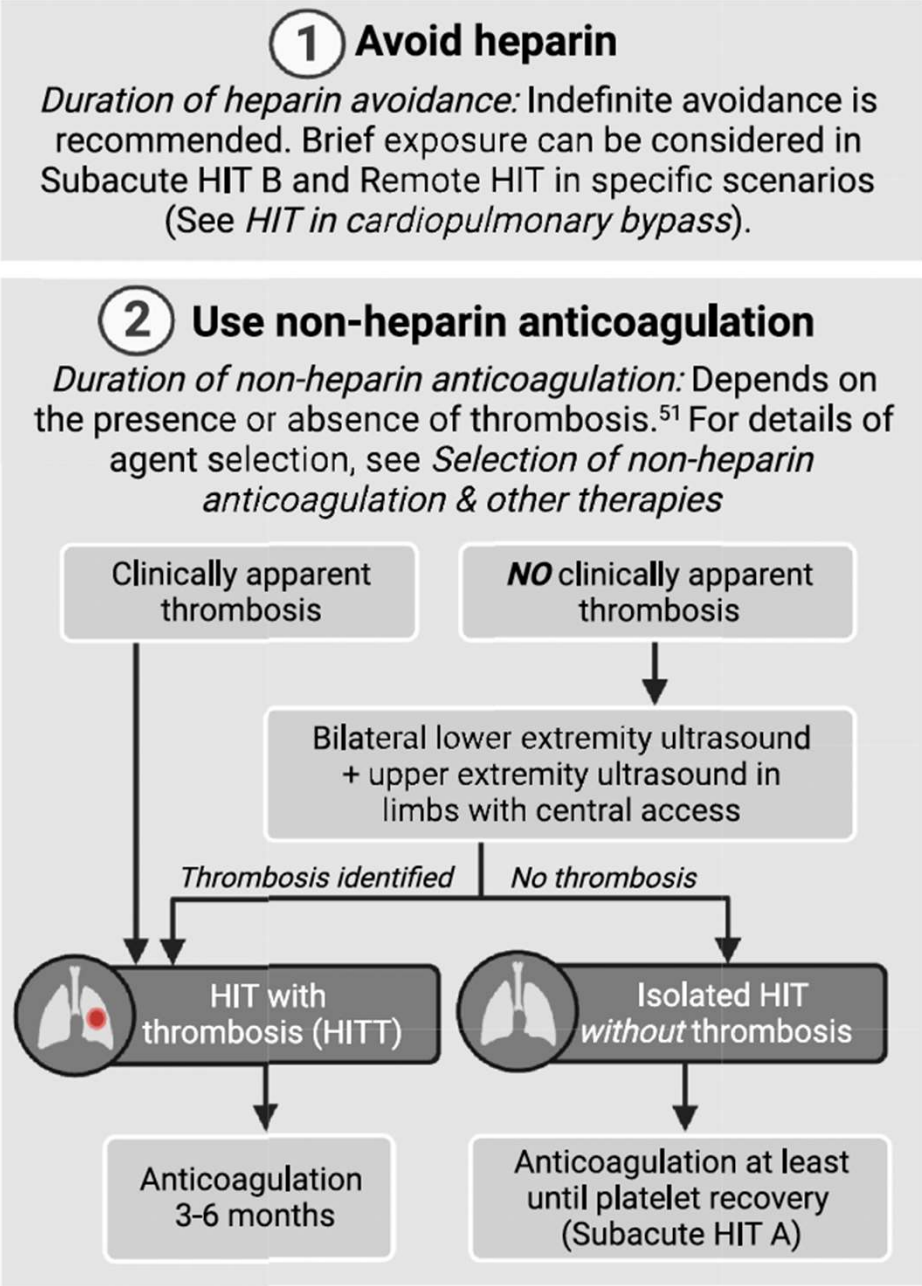
Avoid laboratory testing

In patients with high 4Ts and a strongly positive EIA, a functional assay may be avoided

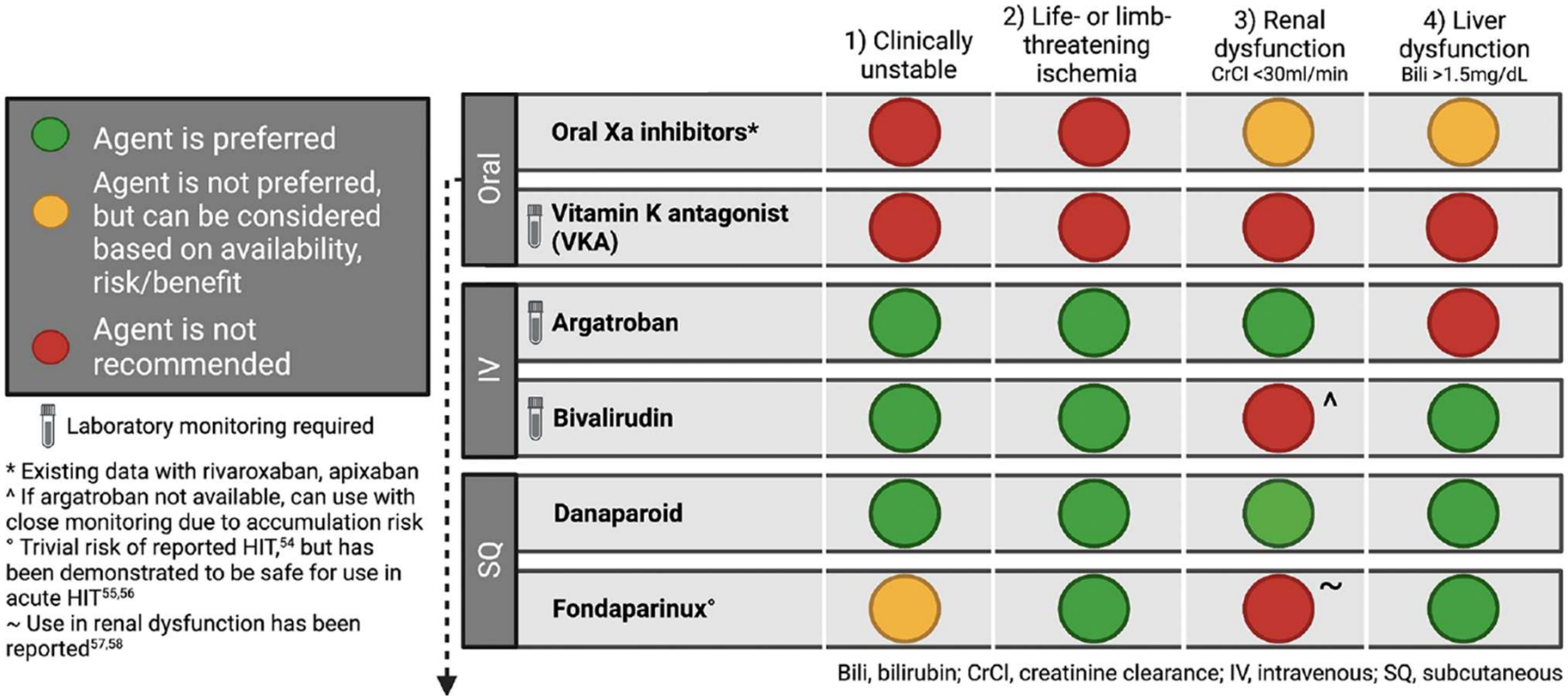
Rarely funtional asays are falsely negative. Patients with high 4Ts and high density EIA should be treated for HIT despite a negative functional assay



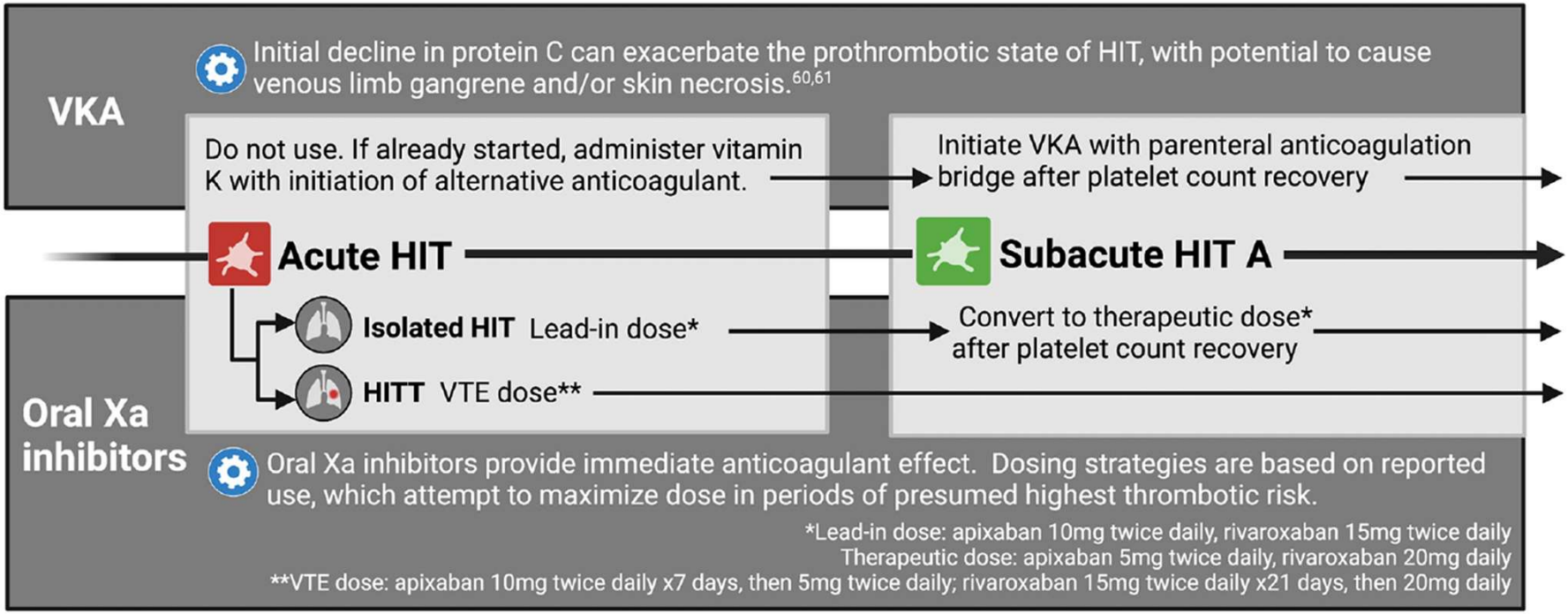
HIT - treatment



Non-heparin anticoagulation



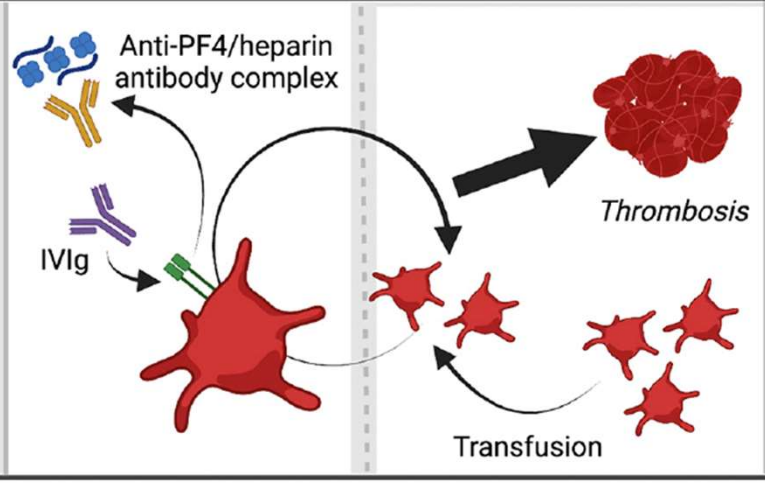
Oral anticoagulants



Additional treatments

Intravenous immunoglobulin (IVIg)

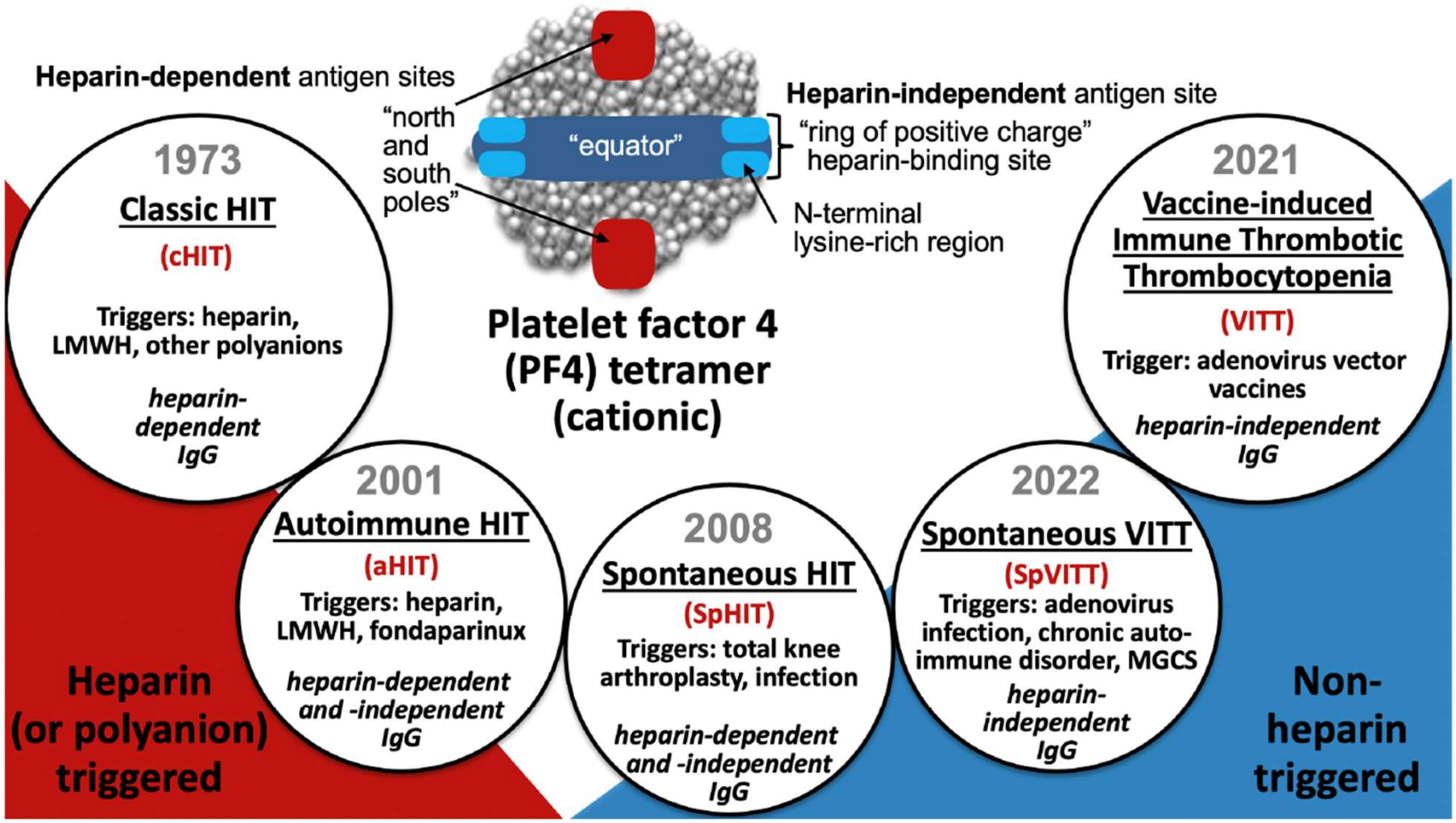
- Hypothesized to competitively inhibit binding of anti-PF4/heparin antibody to platelet FcR.[62]
- Can be considered in cases of **severe and/or refractory thrombosis or thrombocytopenia**.



Platelet transfusion?

- Routine use **NOT** recommended due to concern it may "fuel the fire" and increase thrombotic risk, particularly arterial
- Can be considered in patients with active bleeding or prior to urgent procedures.[51,5]

HIT and VITT types



Autoimmune HIT

- ✓ Severe subtype of HIT
- ✓ Highly pathological IgG Ab («aHIT Ab»)
- ✓ Platelet activation even in the absence of heparin

Types:

- ✓ Delay-onset HIT = worsening platelet count despite stopping heparin
- ✓ Persisting or refractory HIT = peristence despite stopping heparin
- ✓ Flush HIT = triggered by small amounts of heparin or fondaparinux

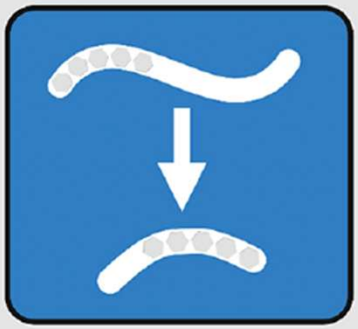
Symptoms:

- ✓ Multi-site or microvascular thrombosis
- ✓ DIC

High dose IVIG

Quality improvement in diagnosis & management

heparin exposure

Goal	Intervention	Impact
 Decrease exposure to unfractionated heparin (UFH) to decrease incidence of HIT	 **The Avoid Heparin Initiative:**[72] Replacement of UFH with LMWH for prophylactic and therapeutic indications	↓ **total HIT incidence** by 79% (10.7 to 2.2 per 10,000 admission) ↓ **HITT incidence** by 91% (4.6 to 0.4 cases per 10,000 admissions) ↓ **HIT-related costs** by $266,938 per year

Quality improvement in diagnosis & management

suspected HIT

Goal	Intervention	Impact
 Decrease unnecessary testing for HIT	 **Clinical decision support** requiring 4Ts Score calculation with all HIT assay[73,74]	↓ proportion of tested patients with **low 4Ts scores** from 66% to 56%[73] ↓ screening and functional assay **testing** by 37.5% and 85%, respectively[74]

Quality improvement in diagnosis & management

acute HIT

Goal	Intervention	Impact
 Increase appropriate use of non-heparin anticoagulants	 Creation of an **anticoagulation stewardship program**,[75] with a focus on anticoagulation in HIT	↓ median duration of **IV direct thrombin inhibitor use** from 9.9 days to 7.3 days ↓ **time from diagnosis to discharge** in acute HIT from 12.8 days to 9.2 days ↑ **fondaparinux and oral Xa inhibitor prescribing** rates in acute HIT from 40.7% to 62.2%

Grazie per l'attenzione!