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How to approach a patient with bleeding?

ISTH Advanced training course, Portugal March 2014

Differential diagnosis

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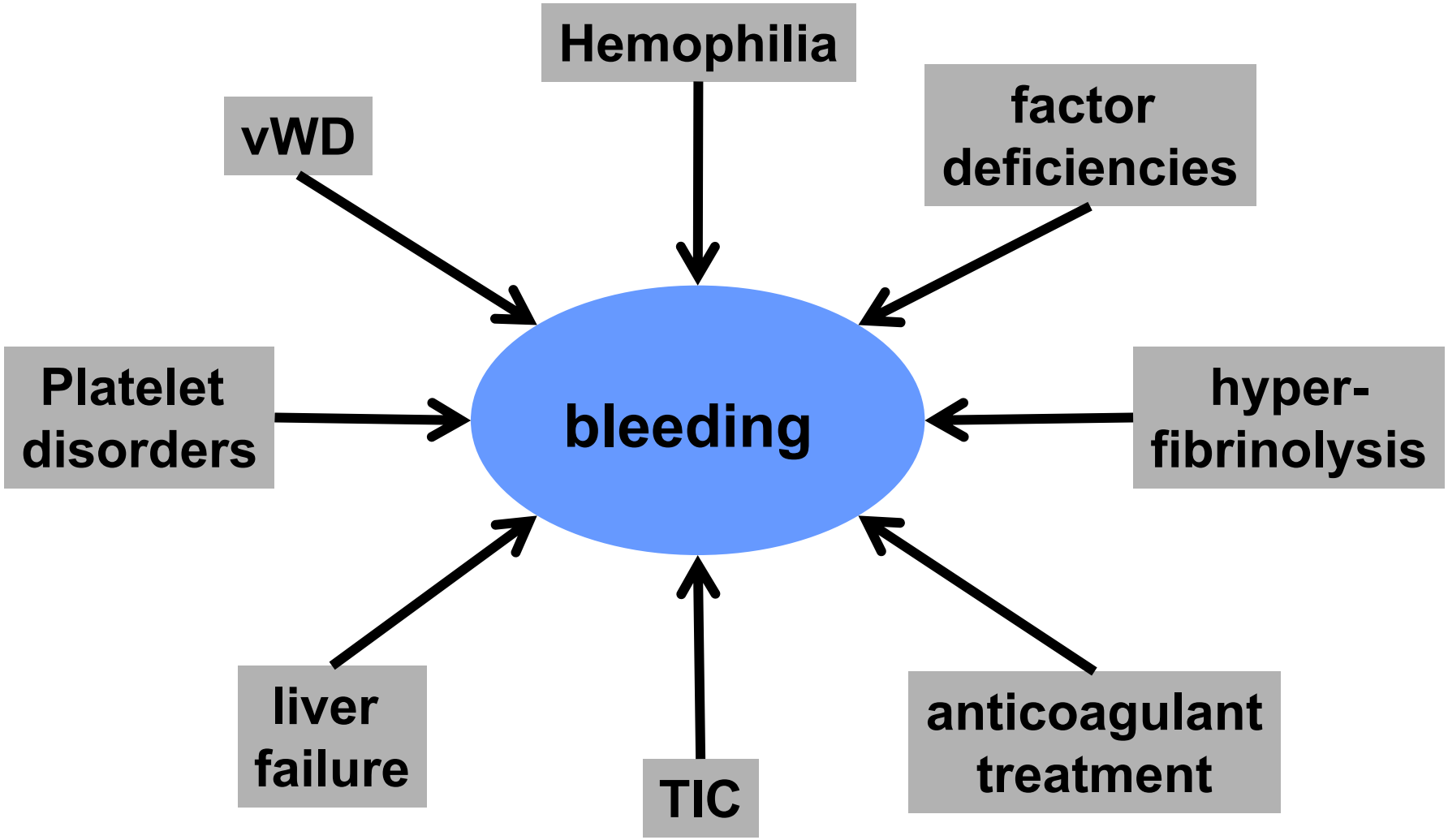

Clinical situations

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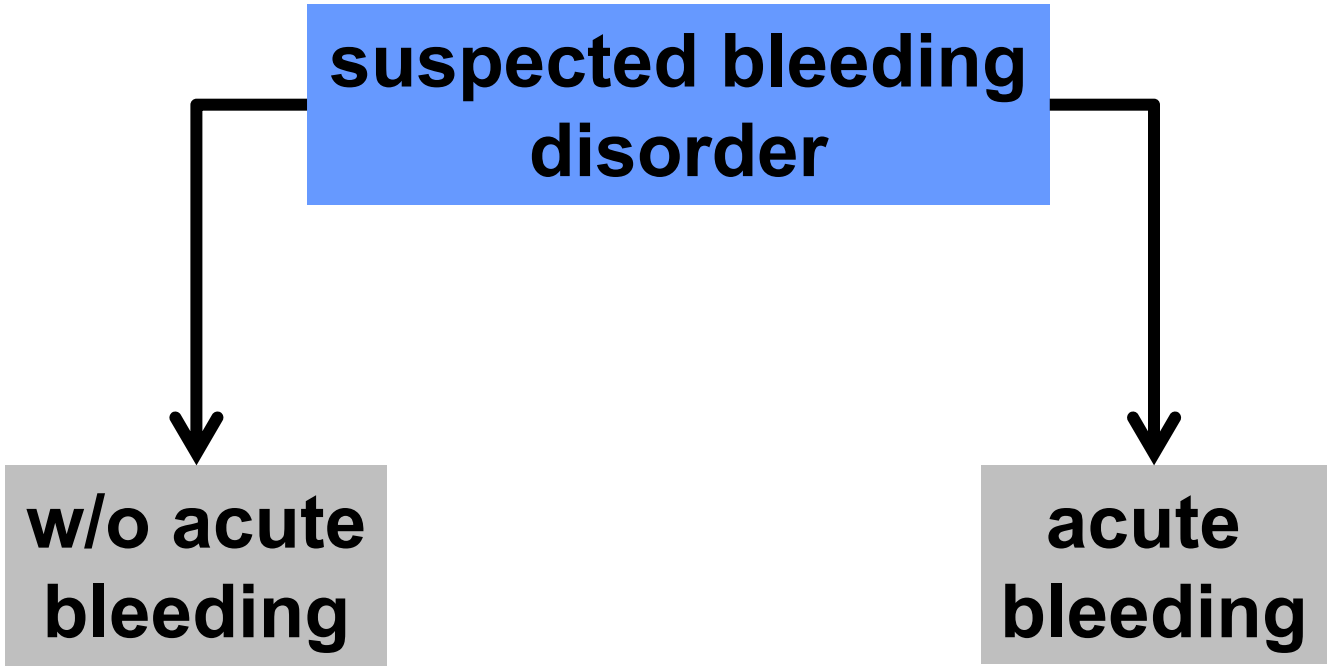

Clinical situations

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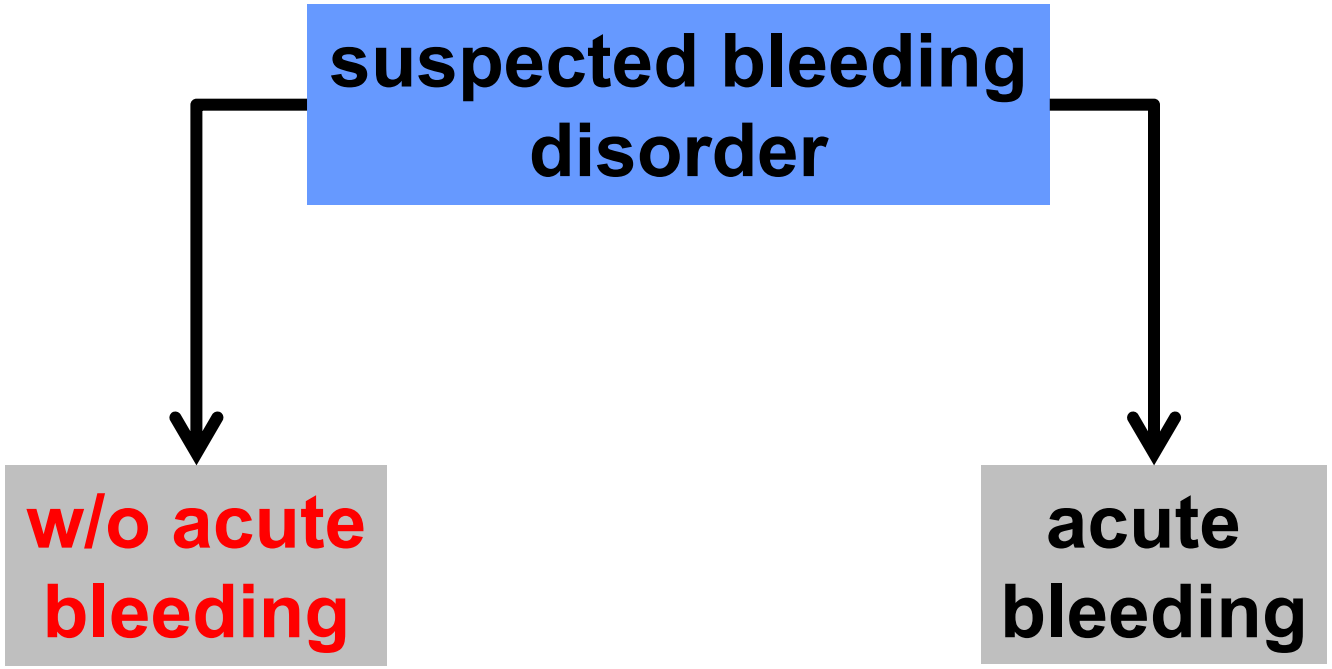

Initial question

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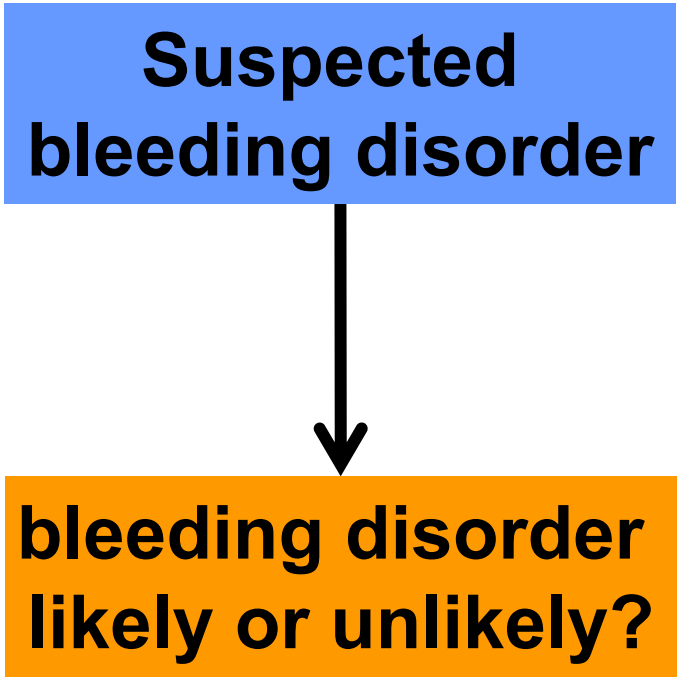
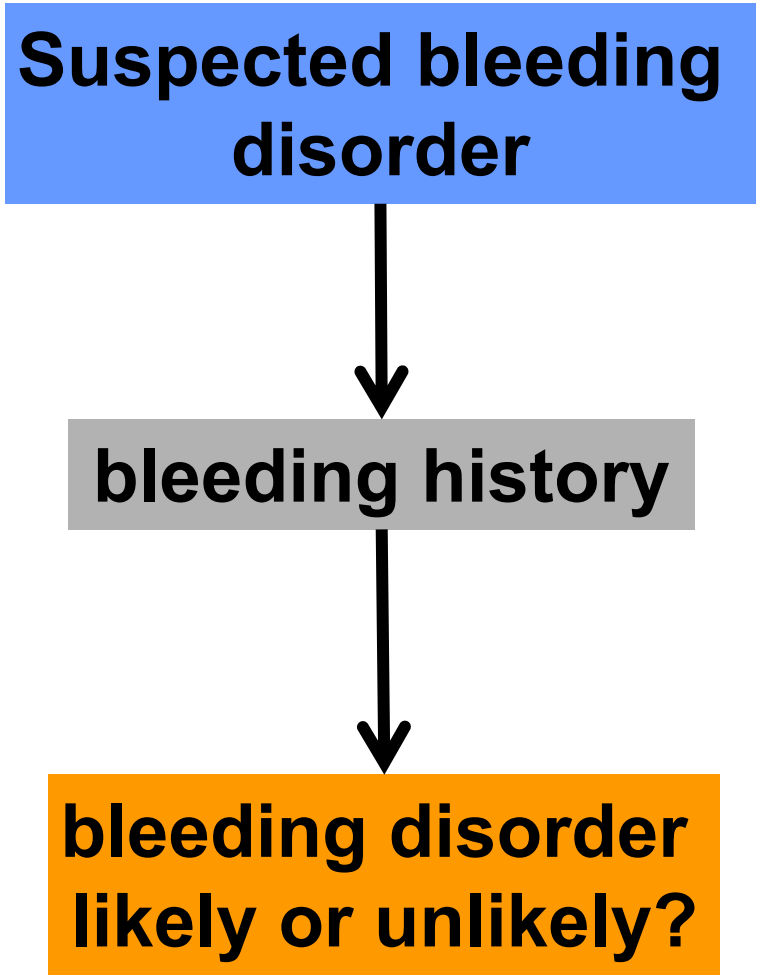


Initial work-up (I)



Bleeding history

- type and frequency of bleeding
- provoked or unprovoked
- type of treatment
- family history (family tree)
- drug history

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Bleeding history

- usually clear in patients with severe bleeding disorders

- in patients with mild/moderate bleeding symptoms a standardized questionnaire is helpful

- standardized scores to quantitate bleeding symptoms

Bleeding history: scoring key

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Symptom	0	1	2	3
Epistaxis	no/trivial < 5/y	> 5/y > 10 min	Packing/ cauterization	transfusion, replacement, DDAVP
Cutaneous	no/trivial < 1 cm	> 1 cm w/h trauma	-	-
Minor wounds	no/trivial < 5/y	> 5/y or > 5 min	Surgical hemostasis	Hemostatic treatment
Oral cavity	no	Reported at least 1	Surgical hemostasis	Hemostatic treatment
Gastro-intestinal tract	no	Identified cause	Surgical hemostasis	Hemostatic treatment

Bleeding history: scoring key

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Symptom	-1	0	1	2	3
Tooth extraction	No bleeding in 2	None done or no bleeding in 1	reported	Resuturing, repacking or antifibrinolytics	Transfusion, replacement, DDAVP
Surgery	No bleeding in 2	None done or no bleeding in 1	reported	Surgical hemostasis or antifibrinolytics	Transfusion, replacement, DDAVP
Muscle hematoma	-	never	Post-trauma, no therapy	Spontaneous, no therapy	Spontaneous requiring treatment
Hemarthrosis	-	never	Post-trauma, no therapy		Spontaneous
CNS	-	never	-	-	Subdural, intracerebral

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Validated questionnaire[1,2]

- includes 13 bleeding symptoms
- provides a summative score
- mean bleeding scores:
  in healthy individuals: 0.5
  abnormal: ≥ 2

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[1]Biss TT, et al. J Thromb Haemost 2010; 8: 950
[2]Biss TT, et al. J Thromb Haemost 2010; 8: 1416

Initial work up (II)

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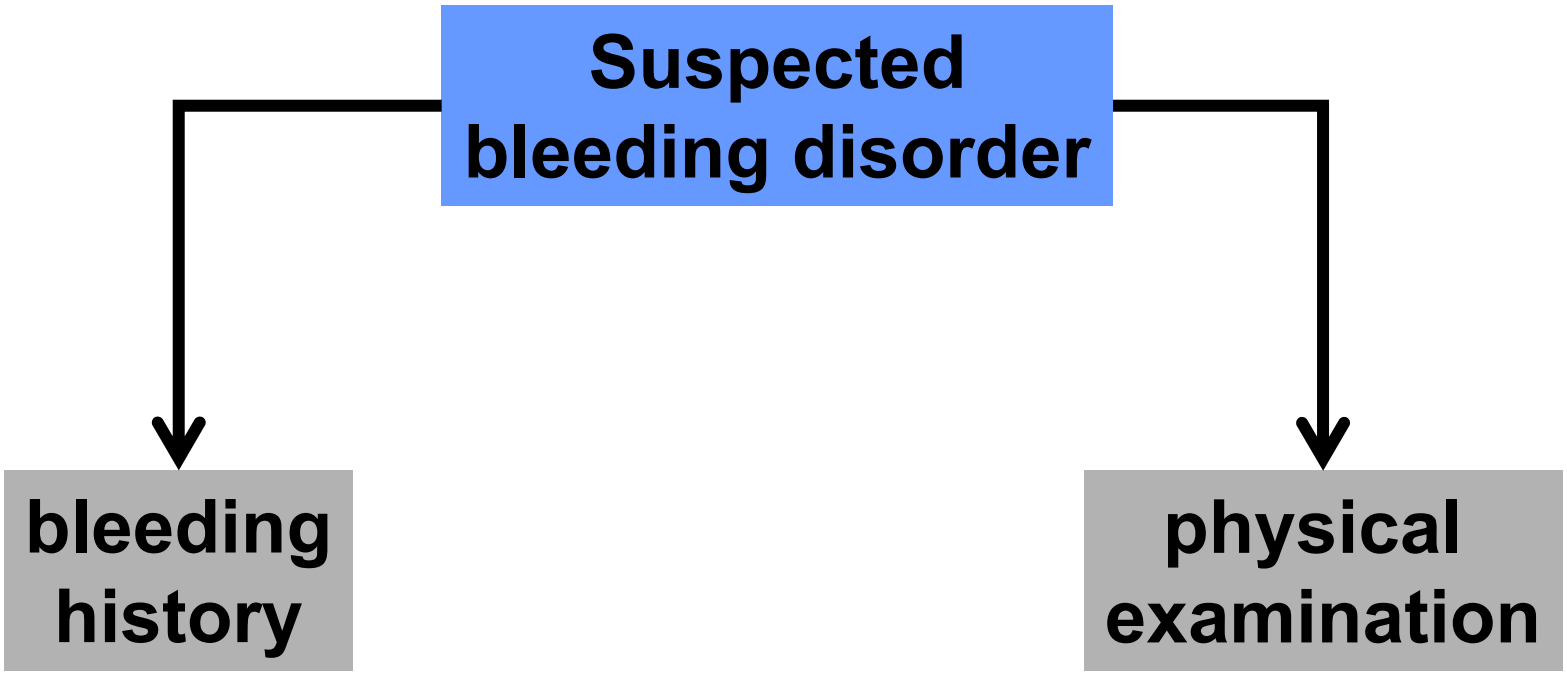

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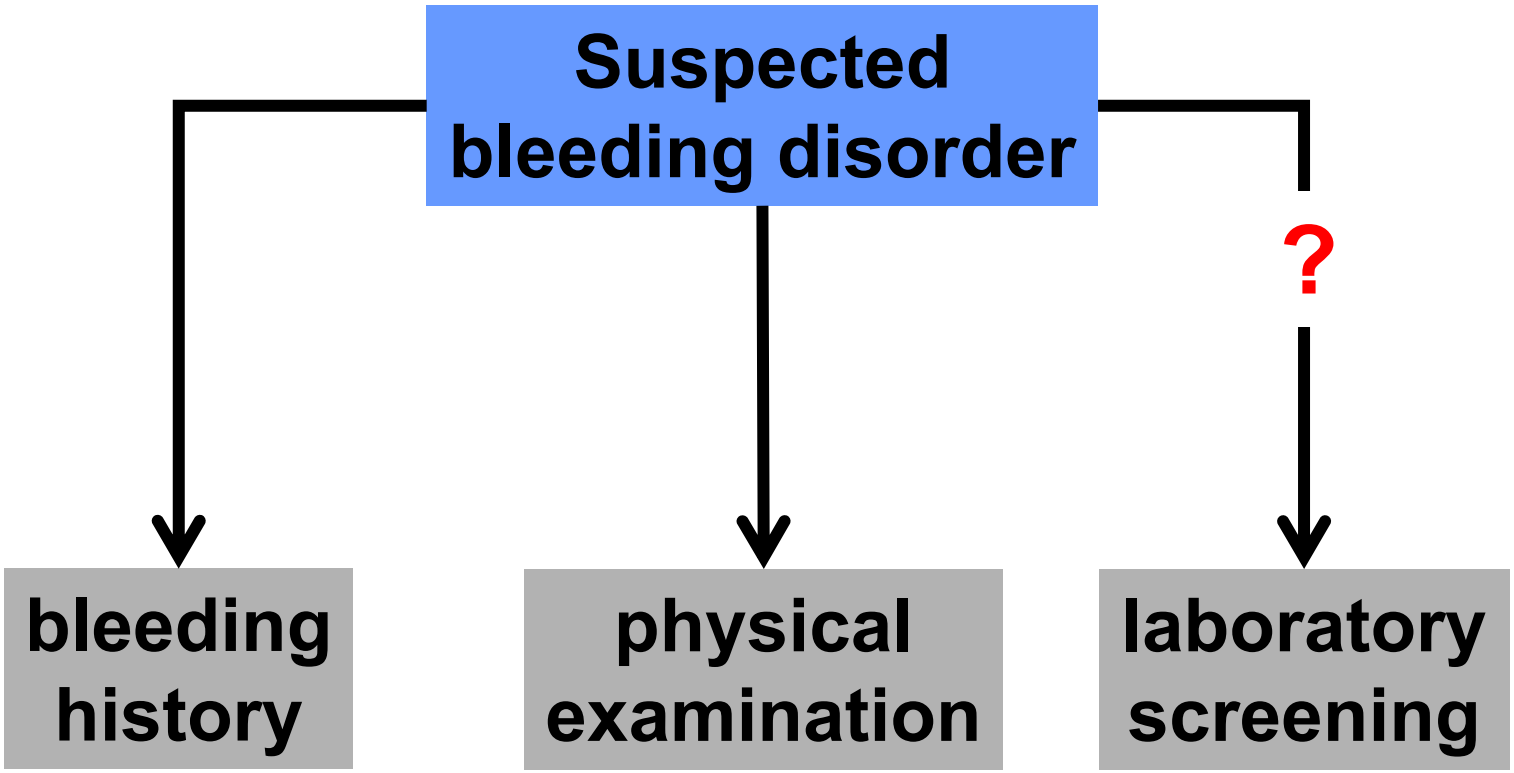
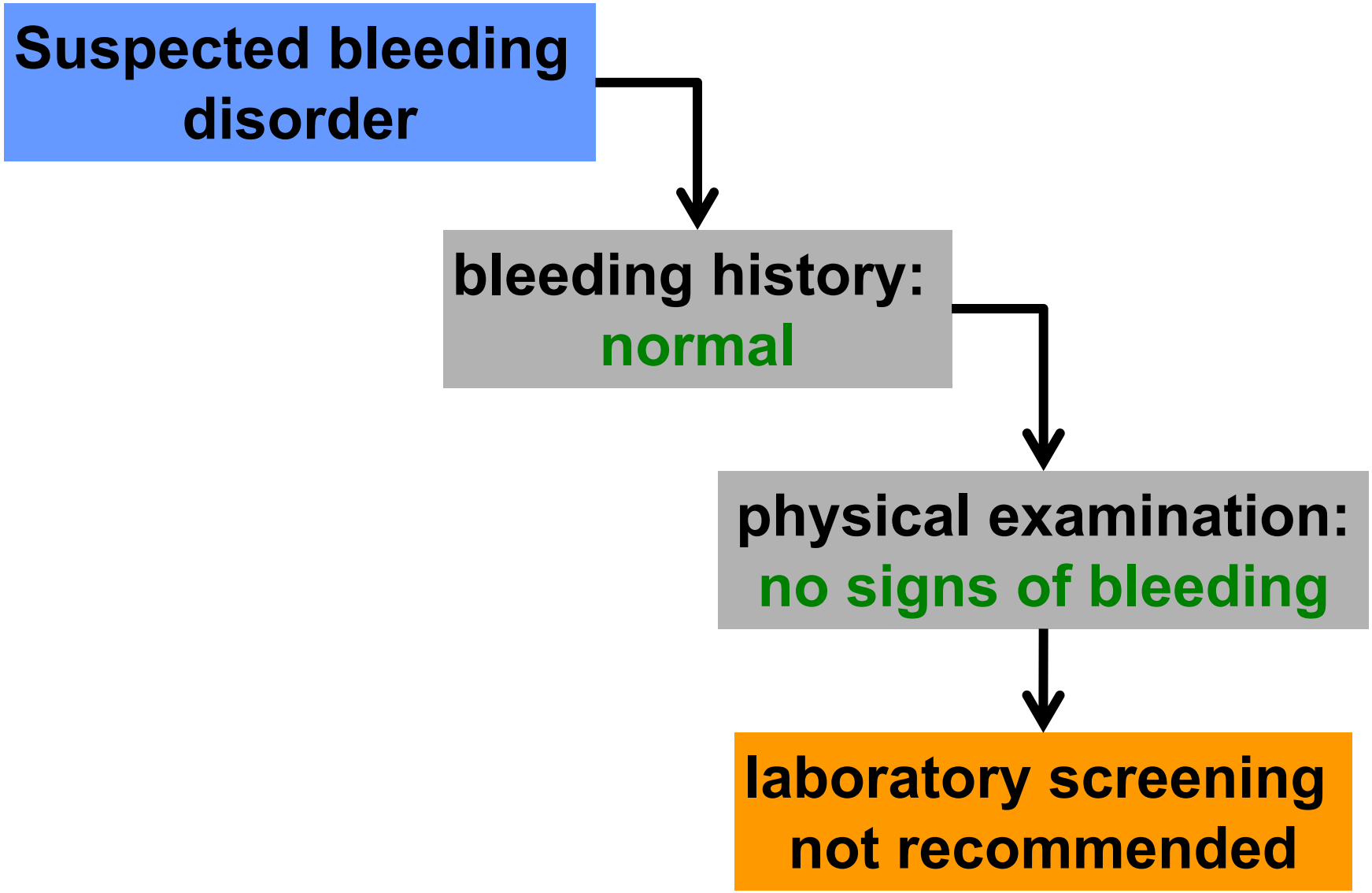
Physical examination

- inspection for any bleeding signs
- joint abnormalities
- lymphadenopathy
- organomegalies
- in children: signs of nonaccidental trauma!

Initial work up (III)



Decision pathway (I)



Take home message (I)

- Thorough personal and family histories are the best screening tests for identifying potential hemostatic problems.

- Properly obtained histories eliminate the need for laboratory screening procedures.

Decision pathway (II)

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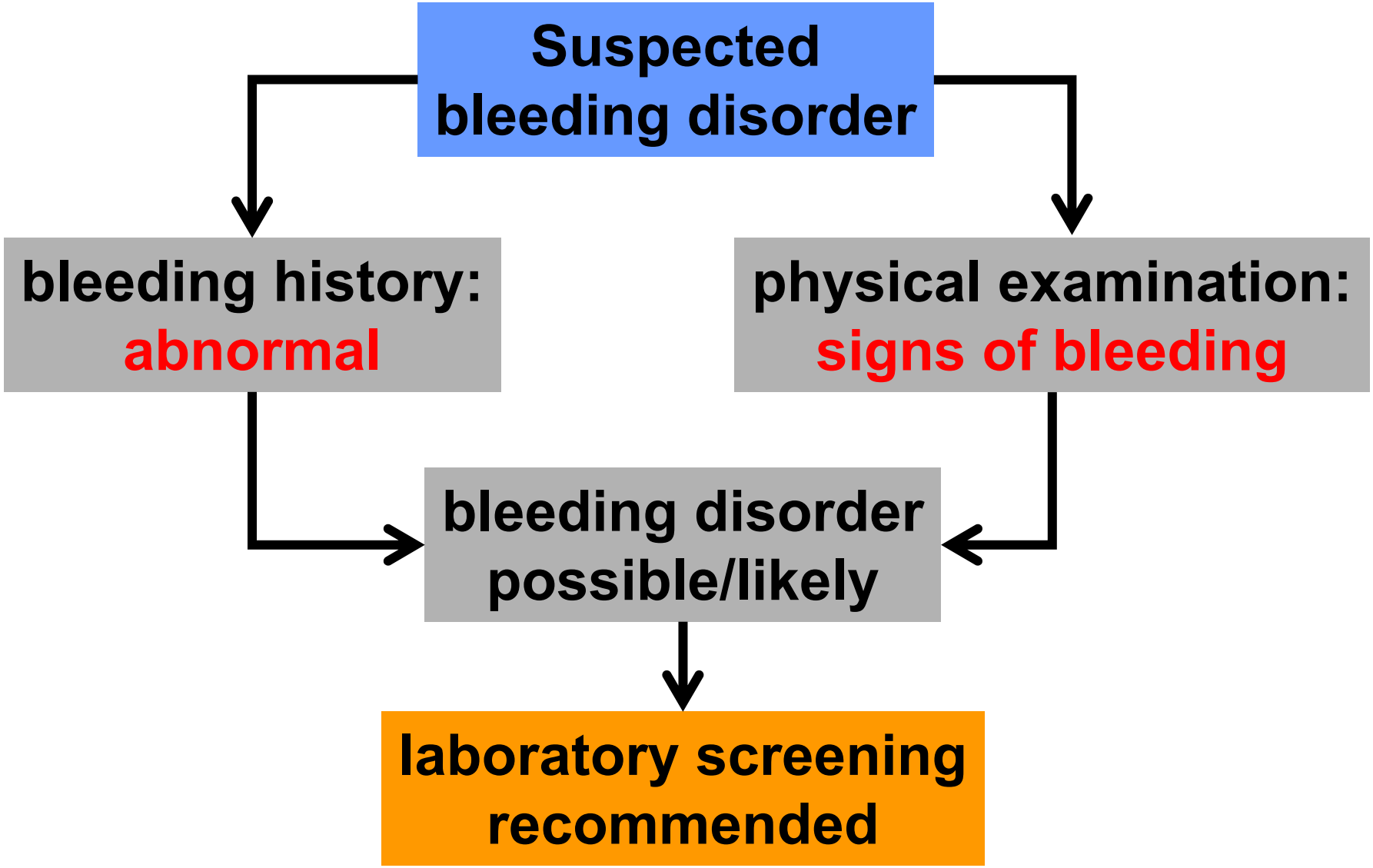
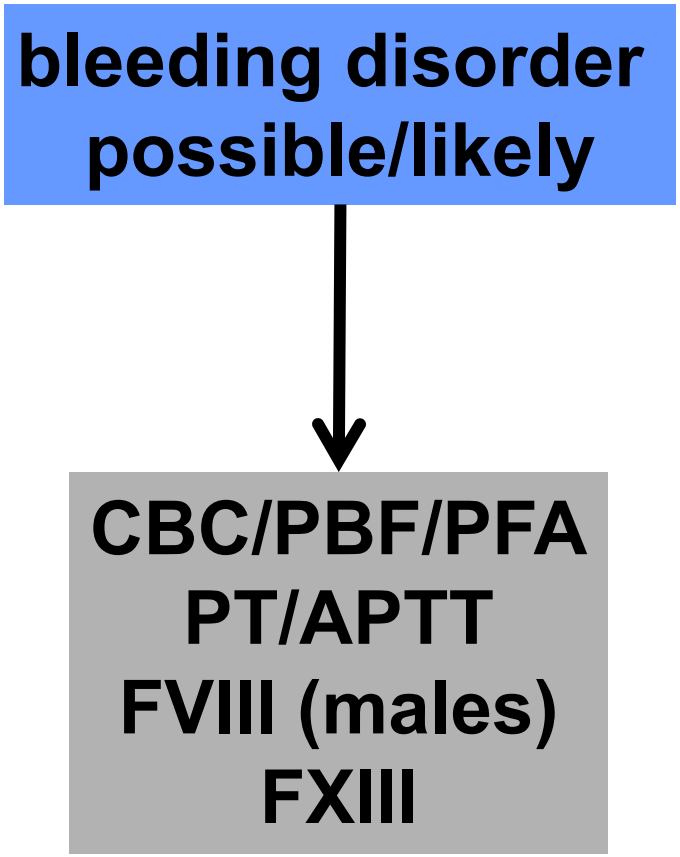


Screening parameters



CBC, complete blood count; PBF, peripheral blood film; PFA, platelet function analyser; PT, prothrombin time; APTT, activated partial thromboplastin time

Screening parameters

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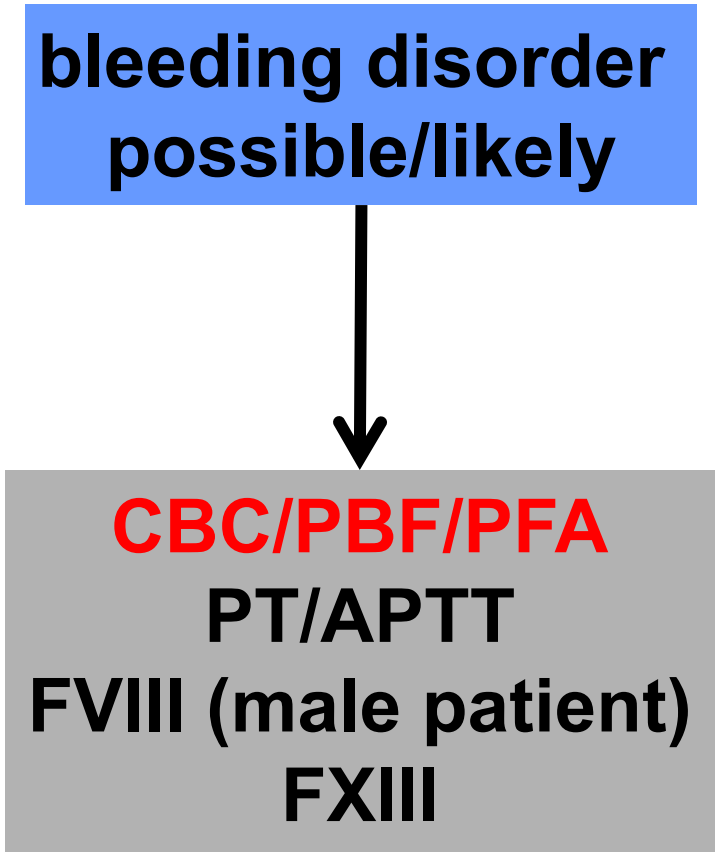

CBC/PBF/PFA

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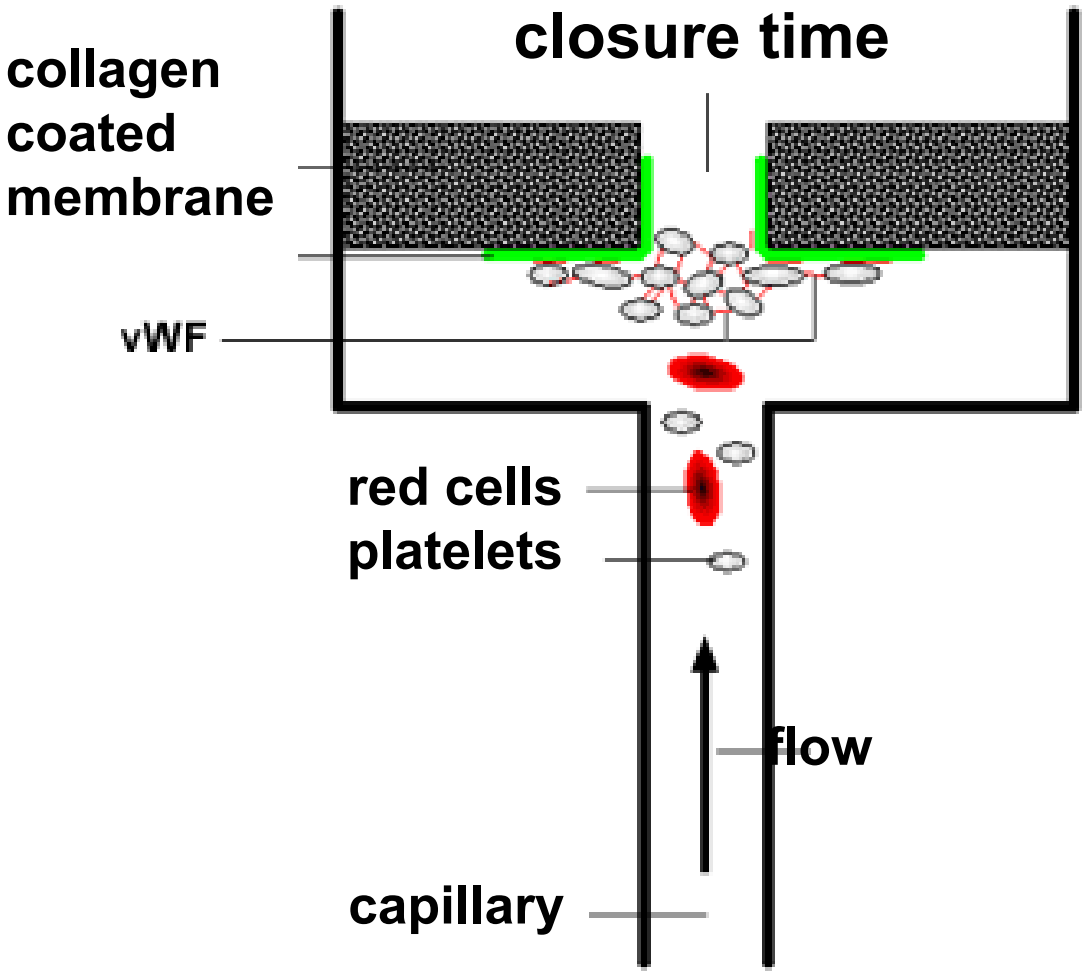
CBC/PBF:

- platelet count, size and morphology
- leukocyte morphology
- other cytopenias

PFA:

- axis subendothelium-vWF-platelet
- platelet-platelet interaction

Platelet function analyser (PFA)



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CBC/PBF/PFA: pitfalls

CBC:

- **pseudothrombocytopenia**

PFA:

- **hematocrit < 35**

Pseudothrombocytopenia

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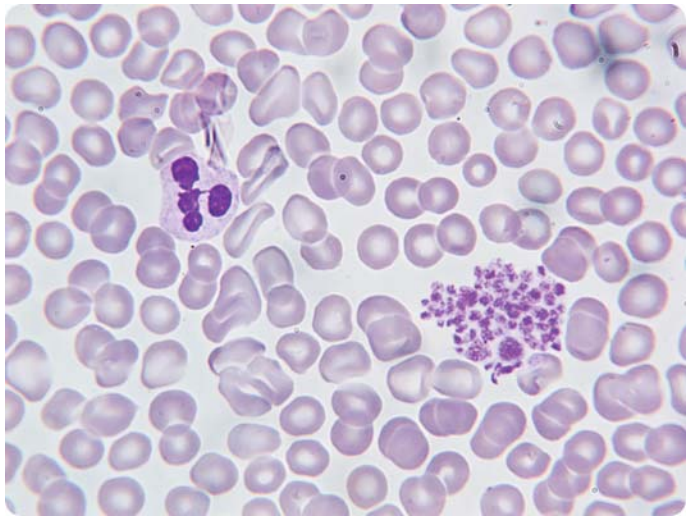
- EDTA-induced agglutination of platelets

- w/o clinical relevance



ASH et al. Blood 2011;117:4168-4168

- confirmed by platelet counting using citrate anticoagulated blood

Decision finding (III)

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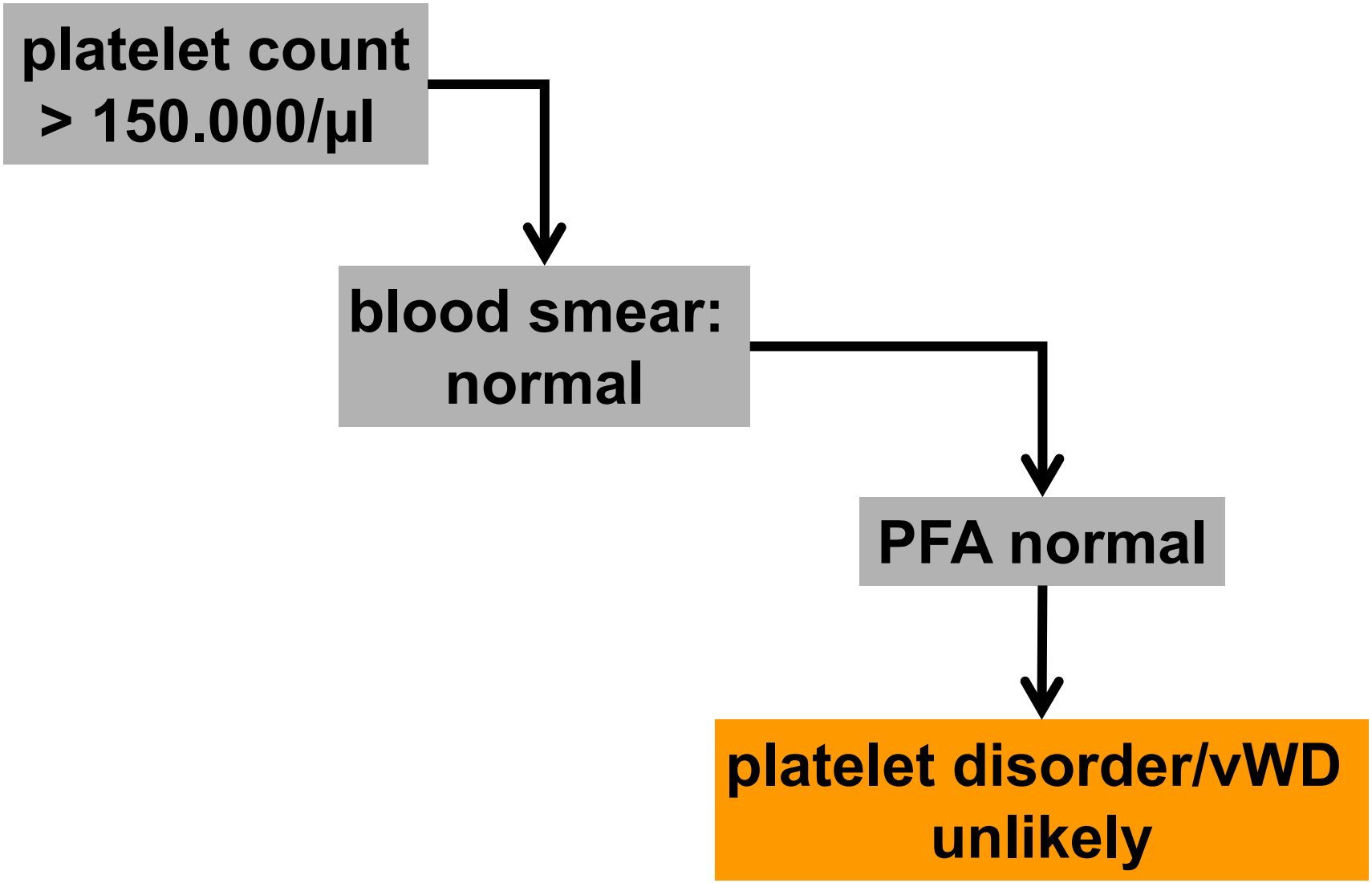

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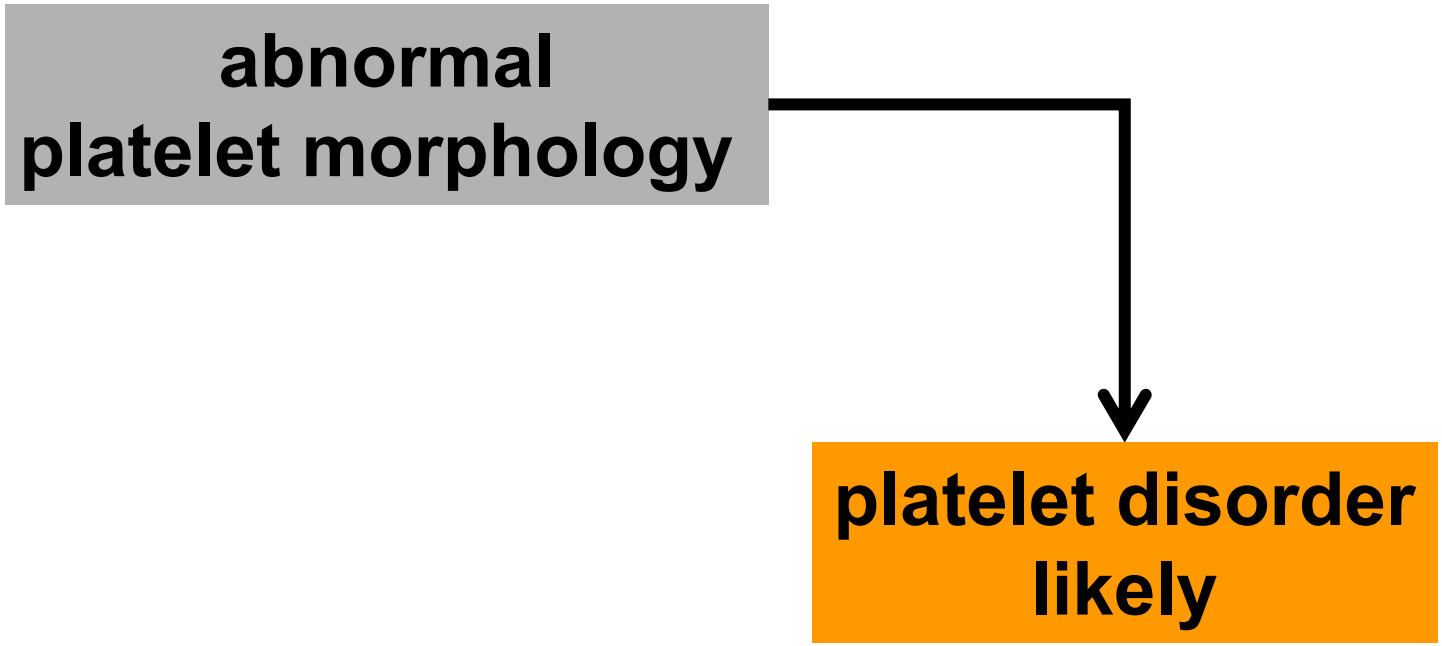
Decision finding (IV)



DD: Platelet disorder

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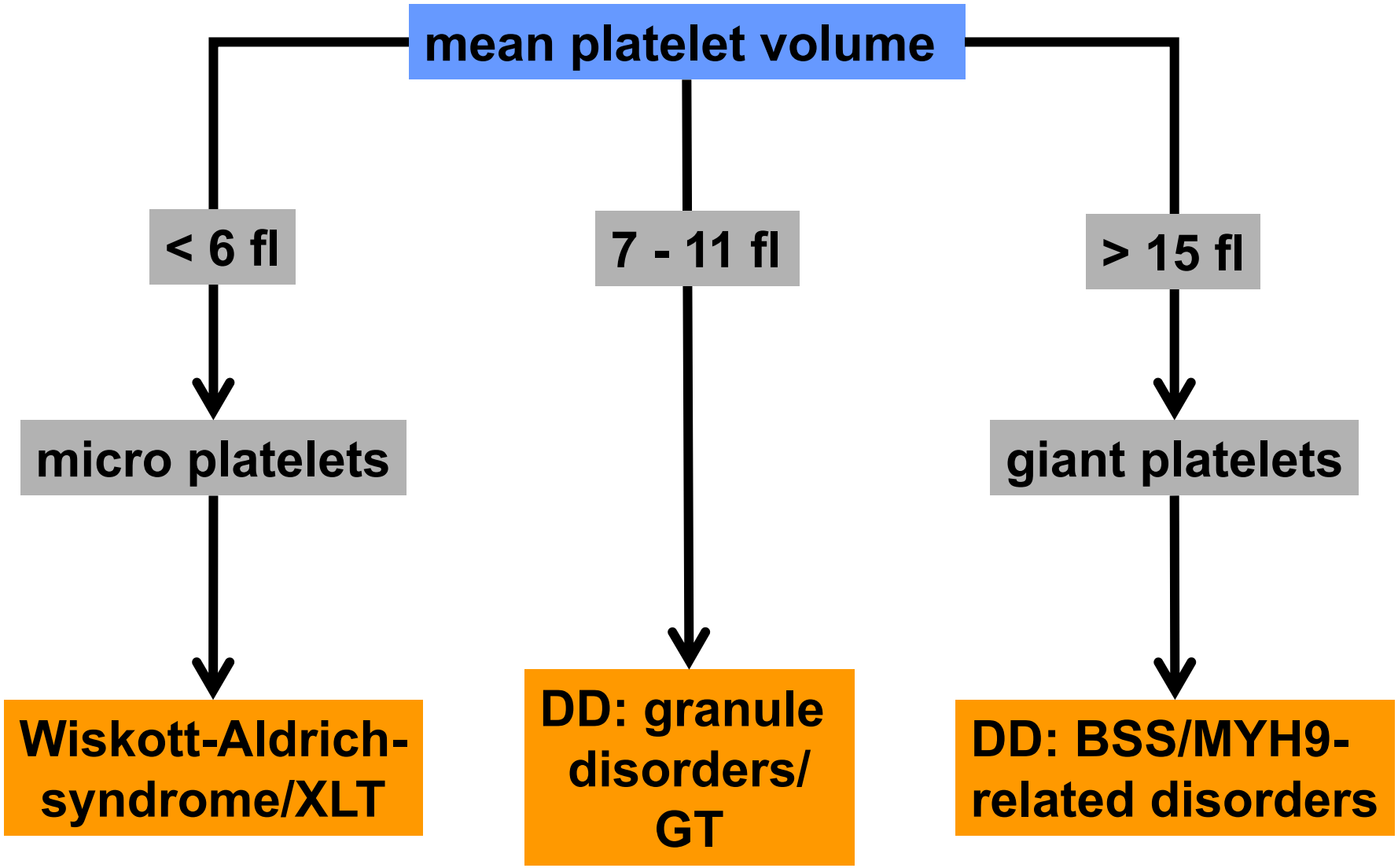

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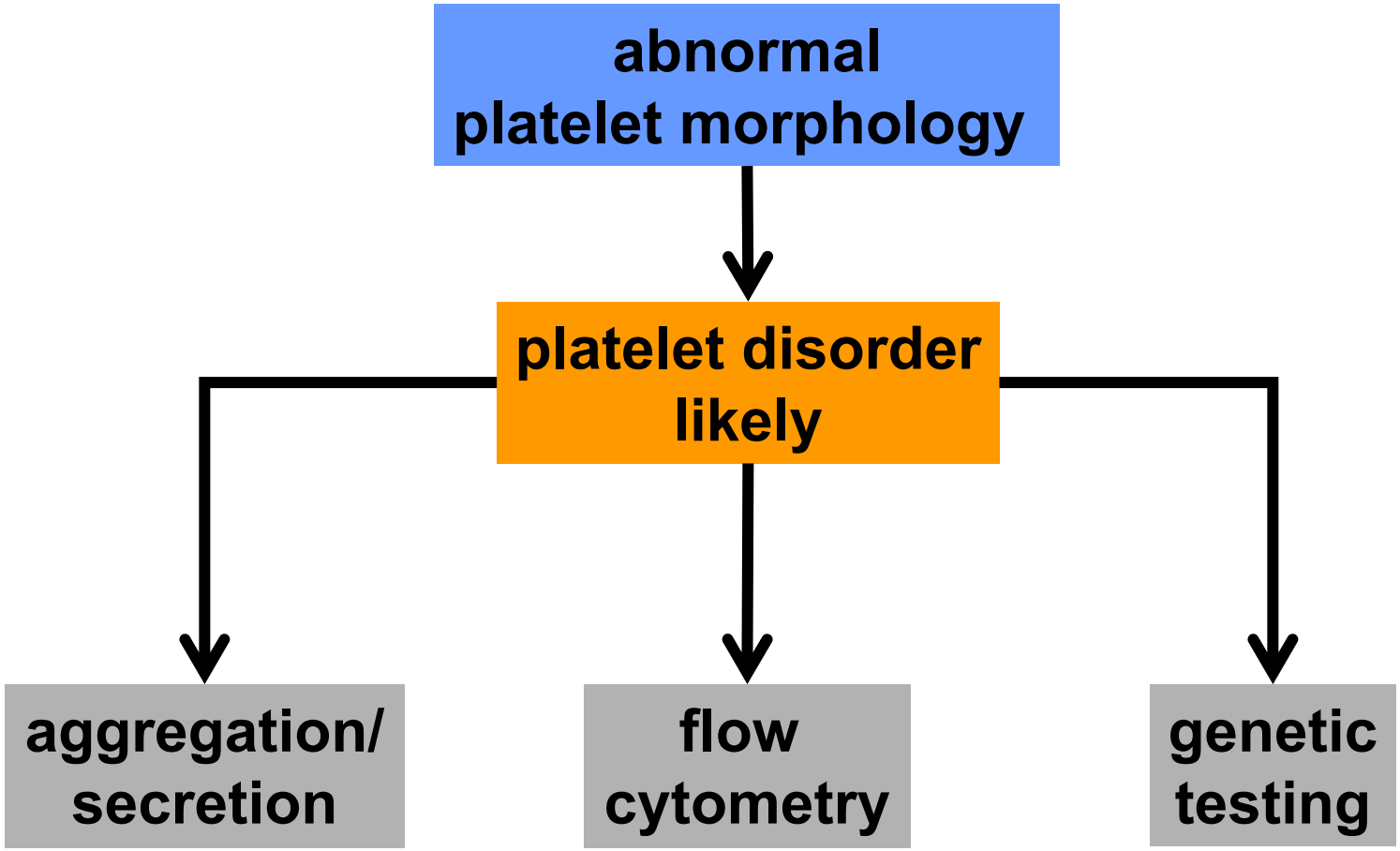
Confirmatory procedures



Decision finding (V)

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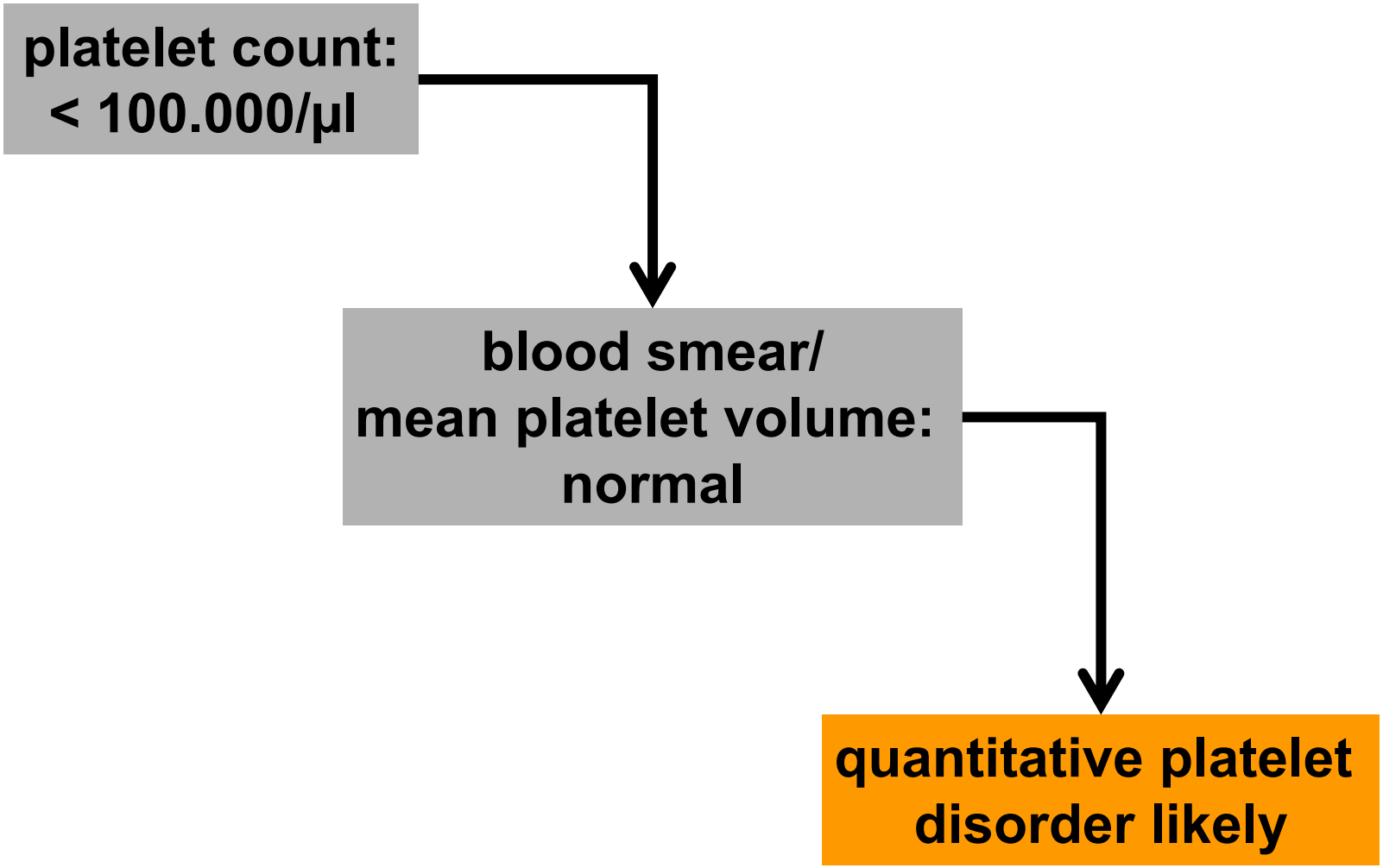

Isolated thrombocytopenia

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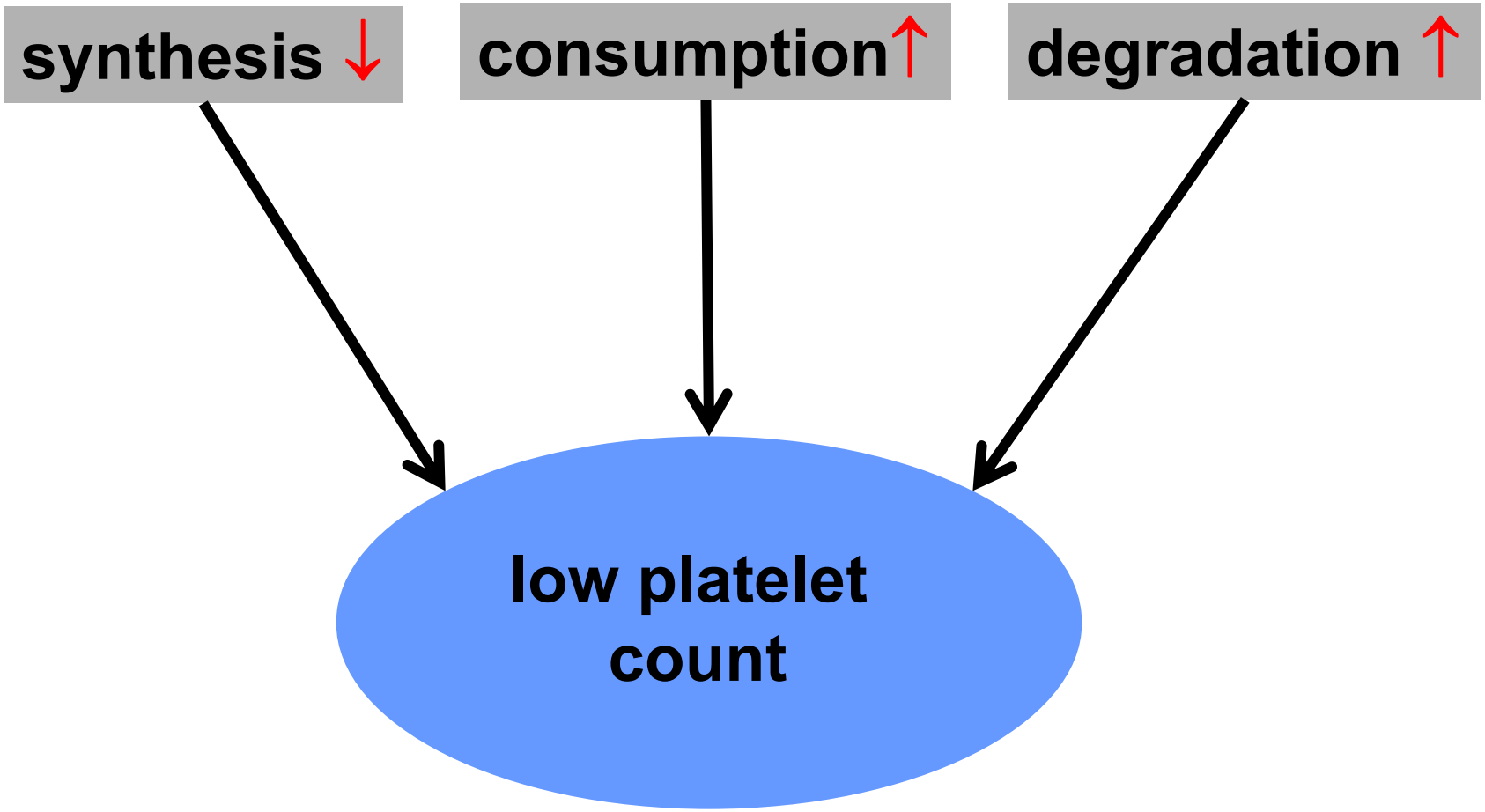
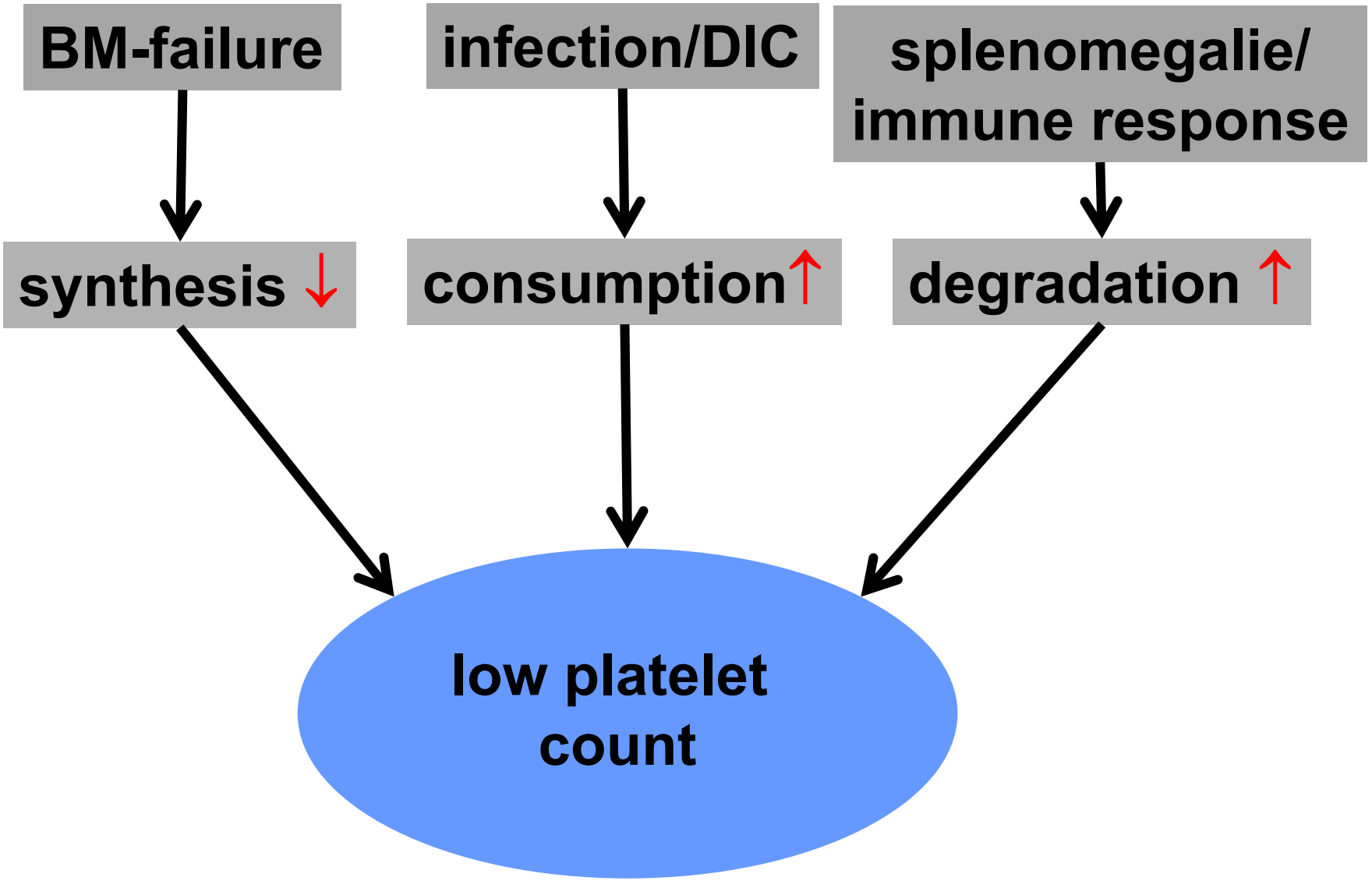


Isolated thrombocytopenia

universitäts klinikum bonn



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Additional information

- isolated versus combined
- new onset or chronic
- signs of organomegalie
- drug history
- previous infections

Additional information

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- **isolated versus combined**
- **new onset or chronic**
- **no signs of organomegalie**
- **no drug intake**
- **previous infections**

➔ **immune thrombocytopenia suspected**

Decision finding (VI)

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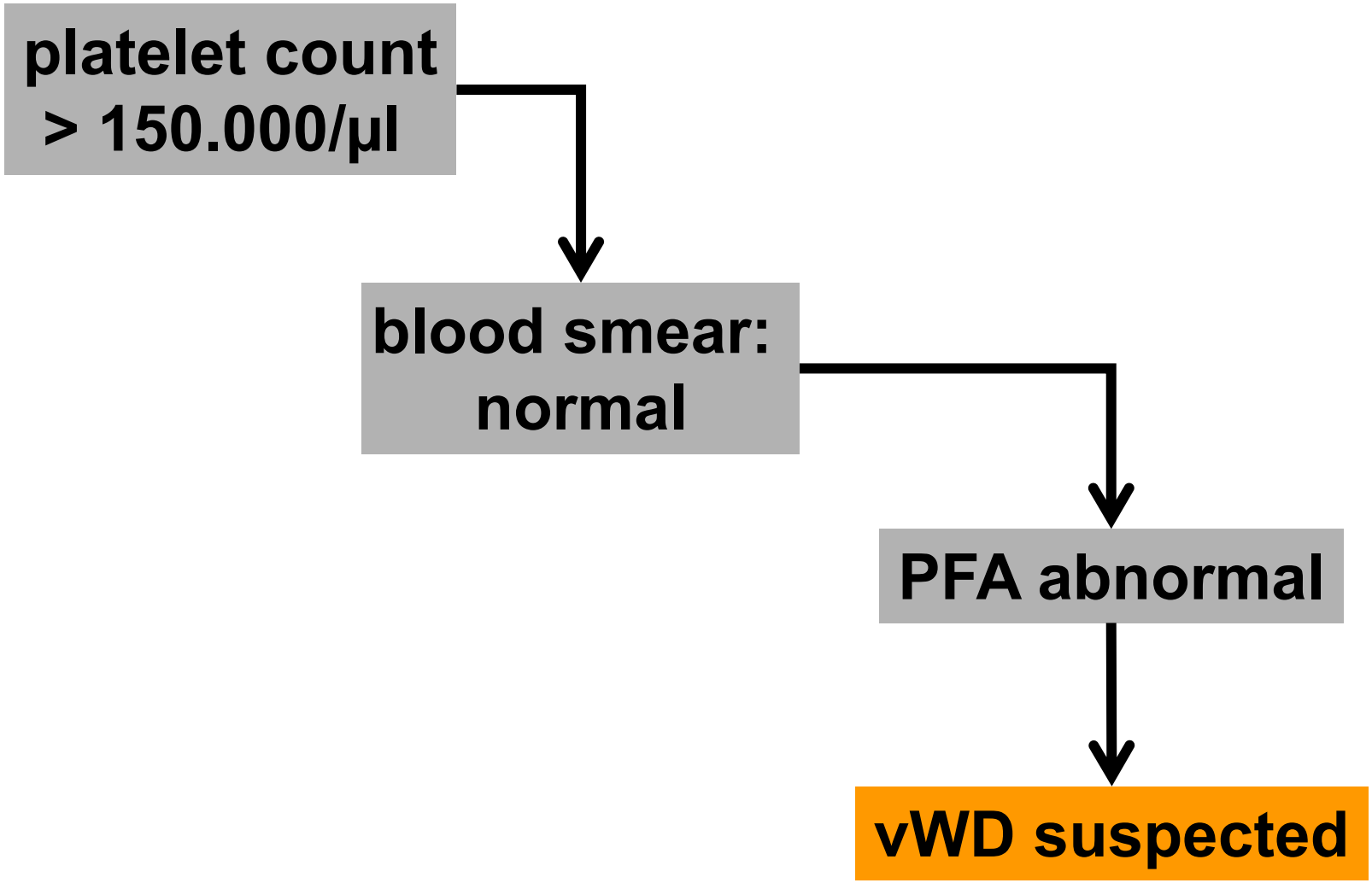

Confirmatory procedures

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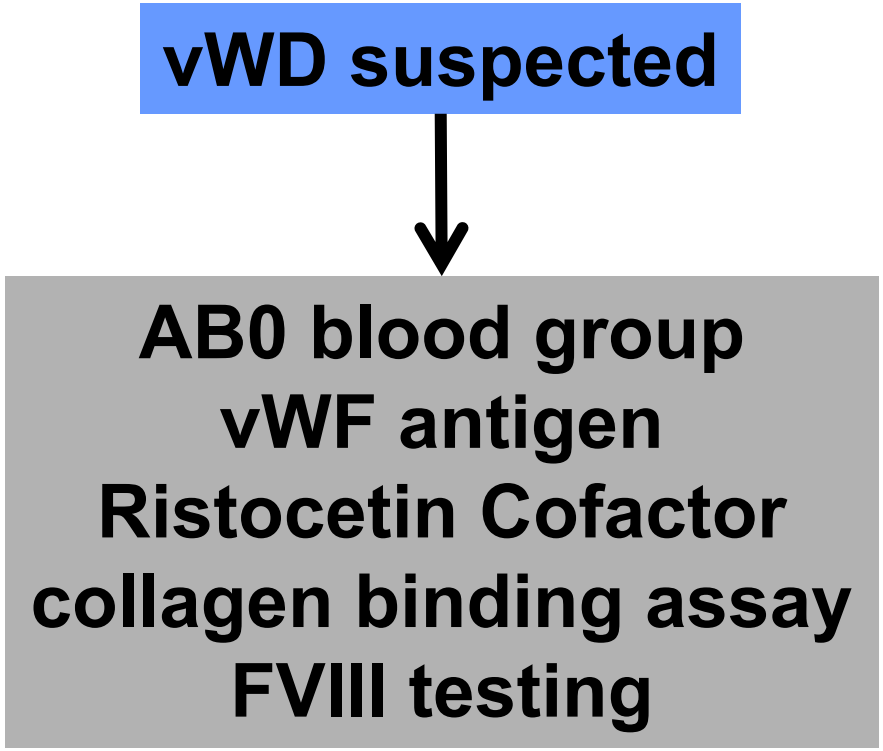

Confirmatory procedures

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vWD suspected

↓

AB0 blood group
vWF antigen
Ristocetin Cofactor
collagen binding assay
FVIII testing

genetic testing
vWF-multimeric analysis
propeptide analysis

Screening parameters

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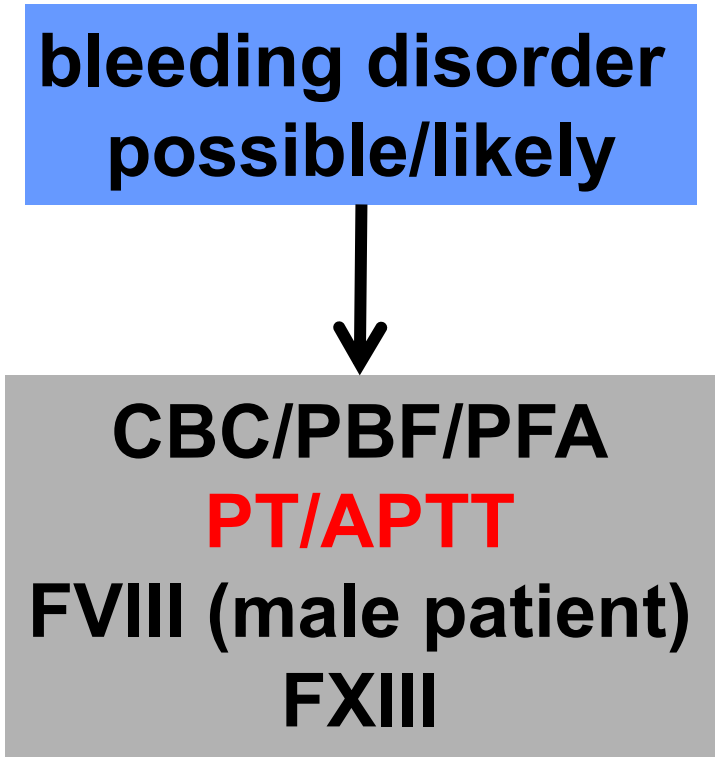

PT versus APTT

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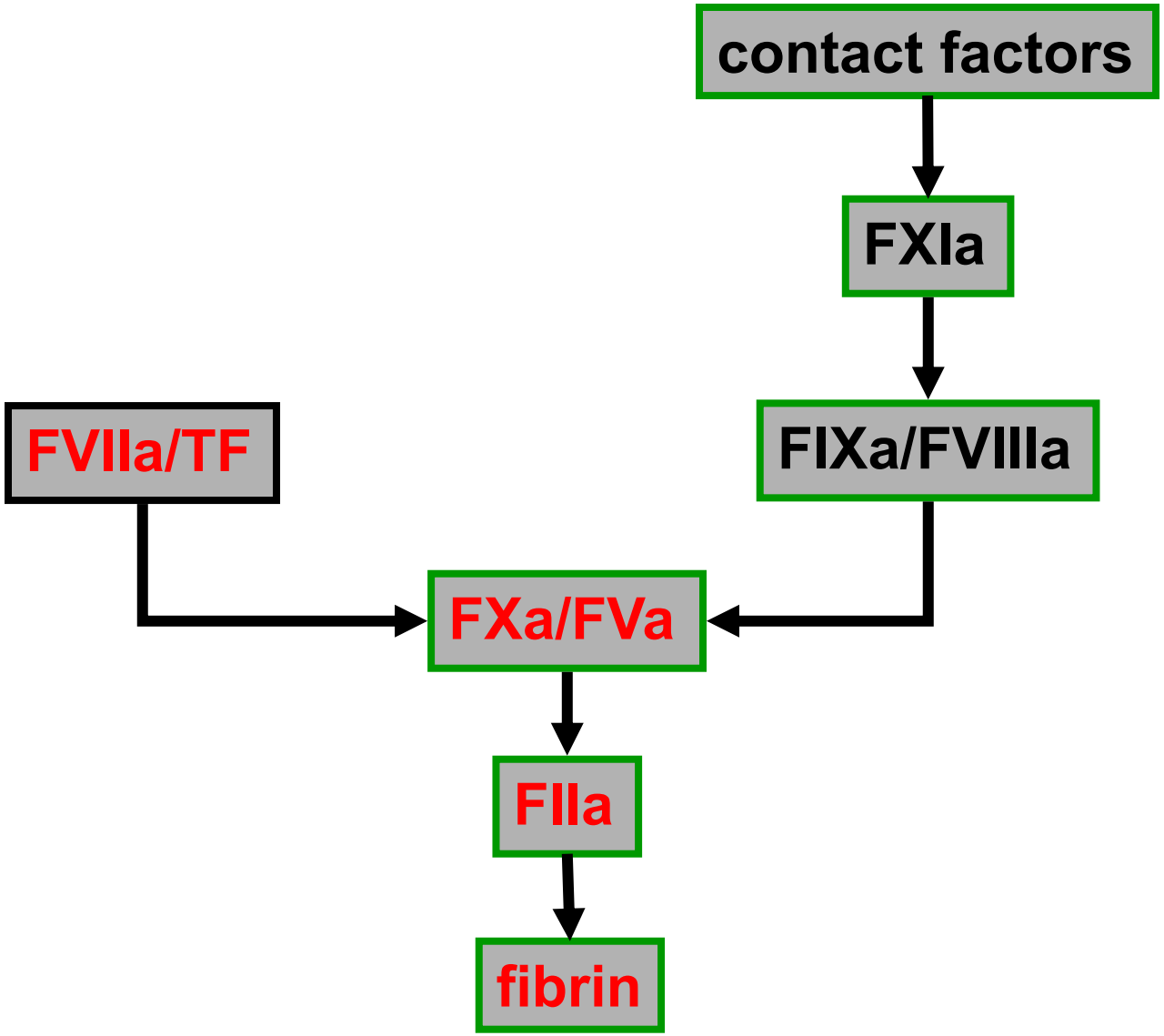
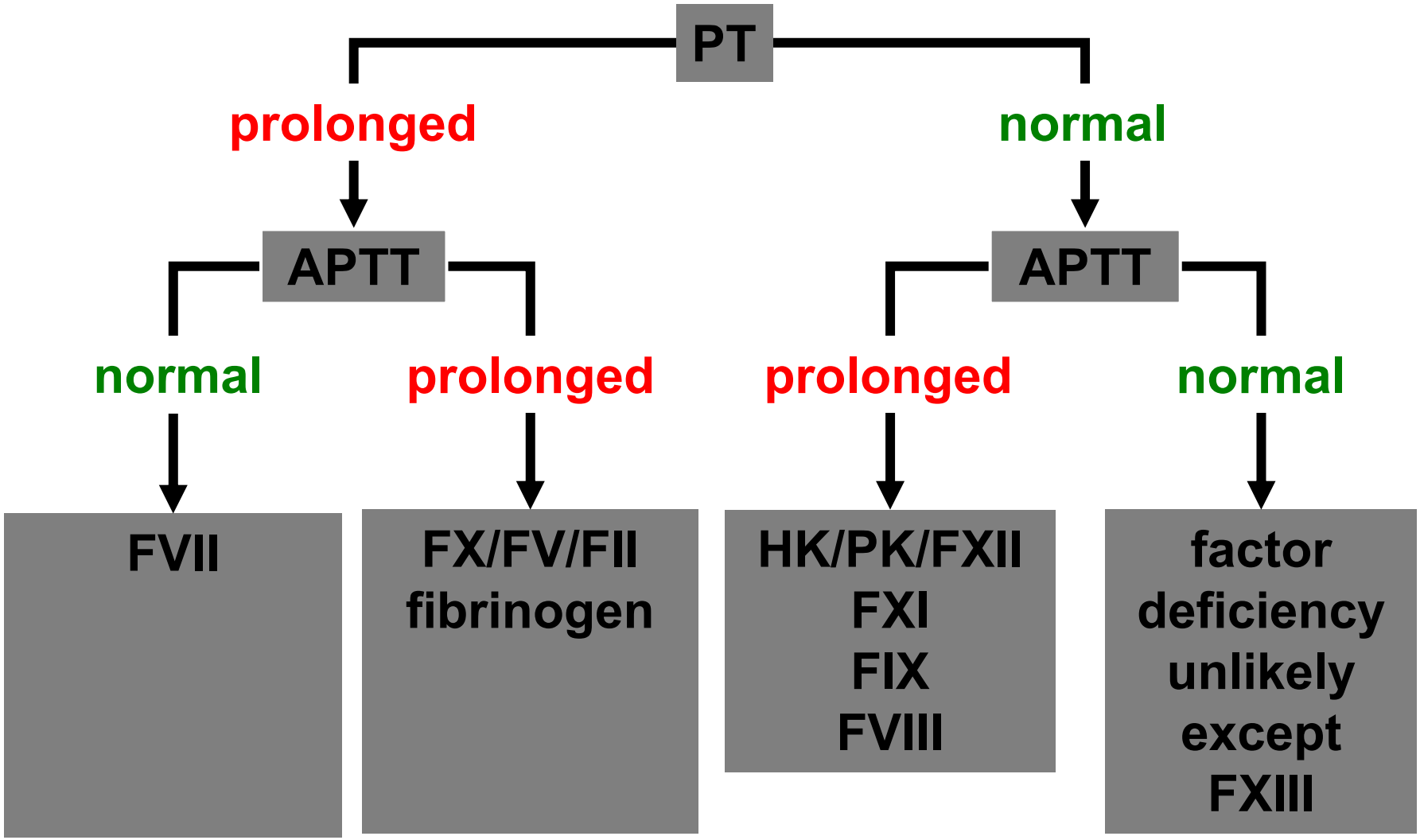


DD: single factor deficiencies



Screening parameters

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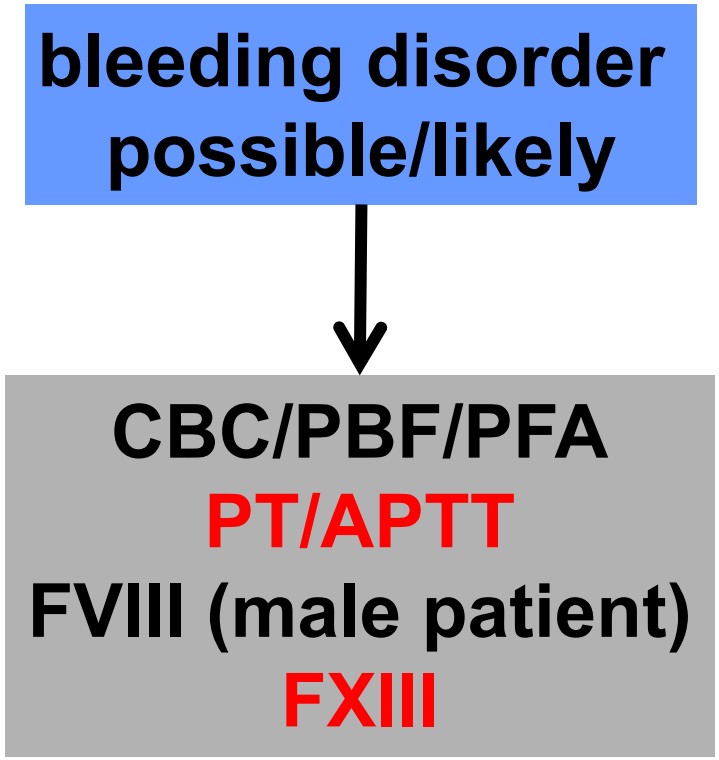
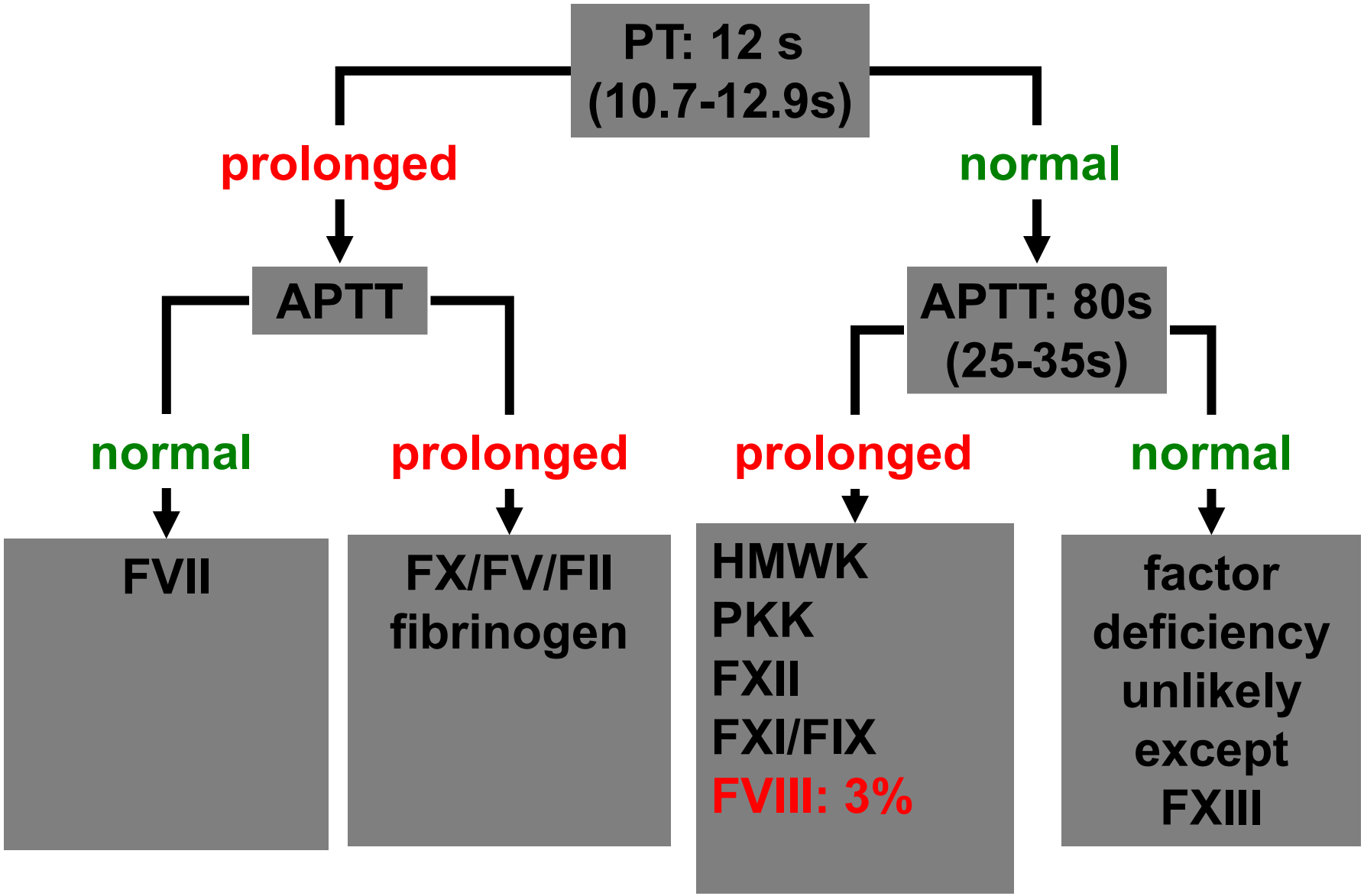


Hemophilia A pattern



APTT versus FVIII (one stage)

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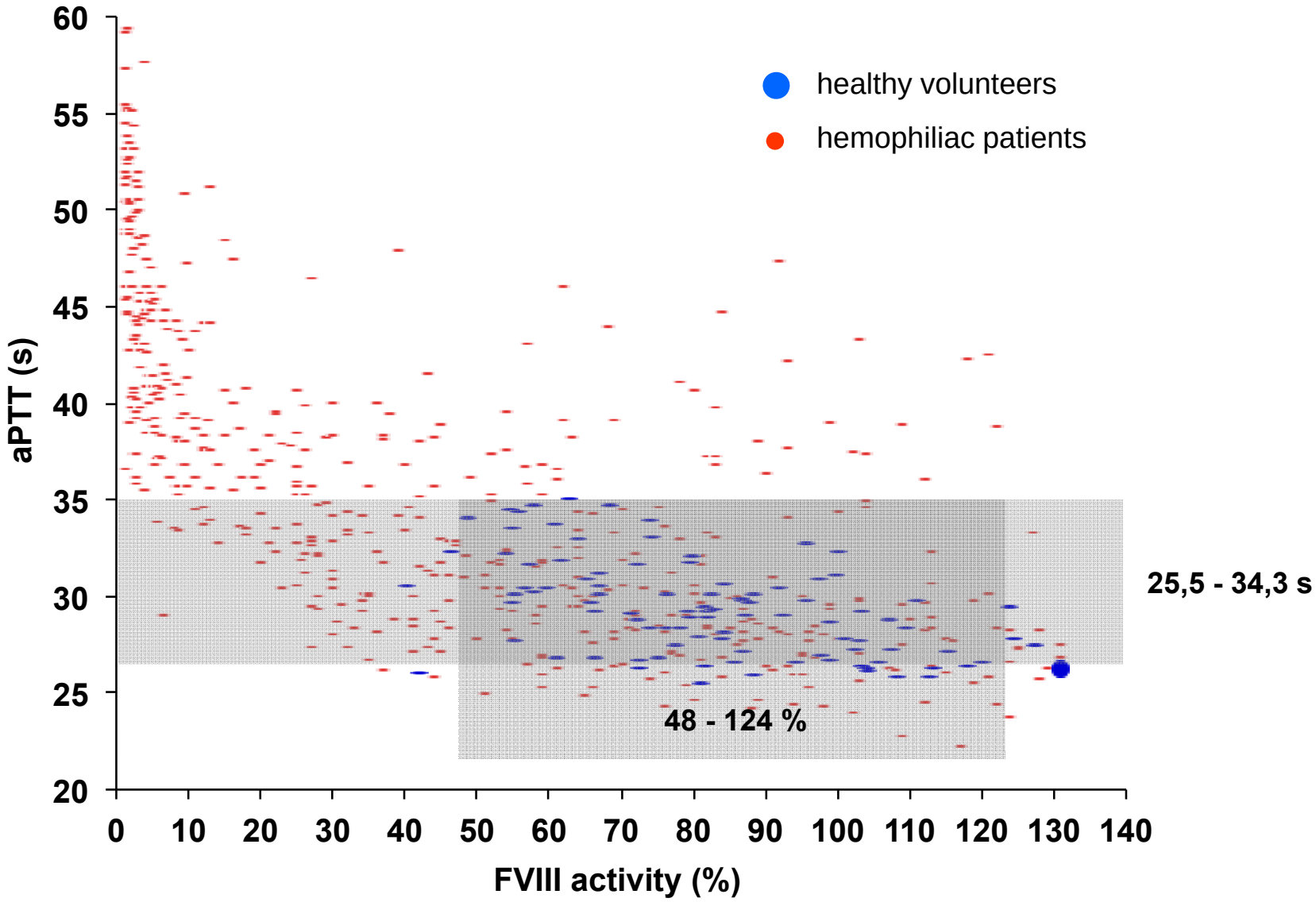

Screening parameters

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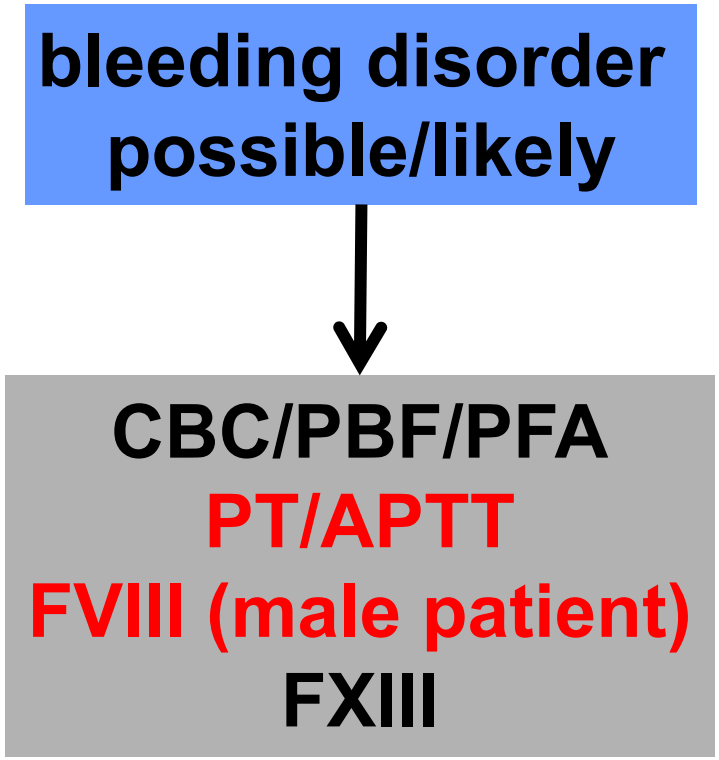

Confirmatory procedures

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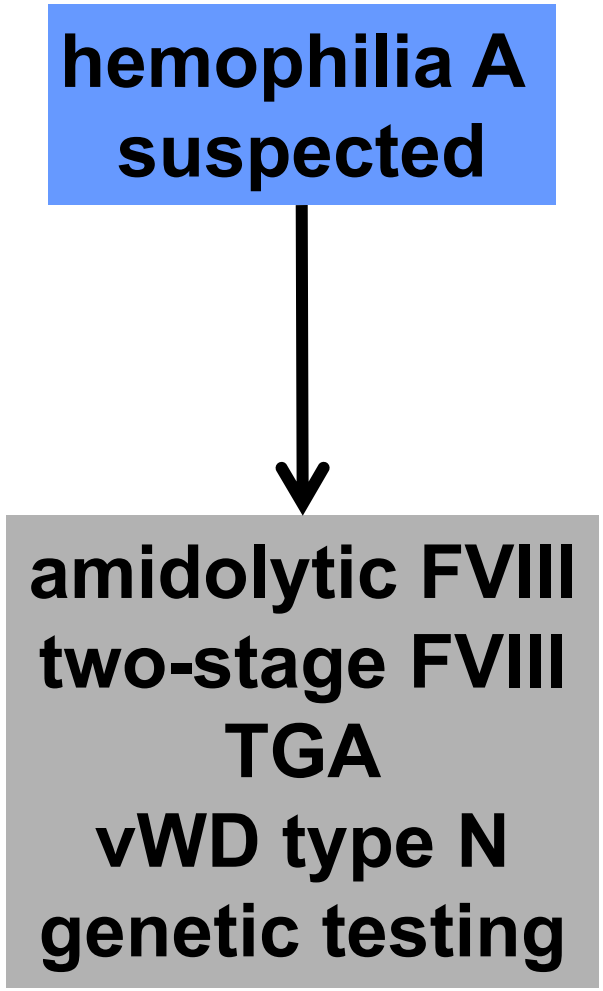

DD: single factor deficiencies

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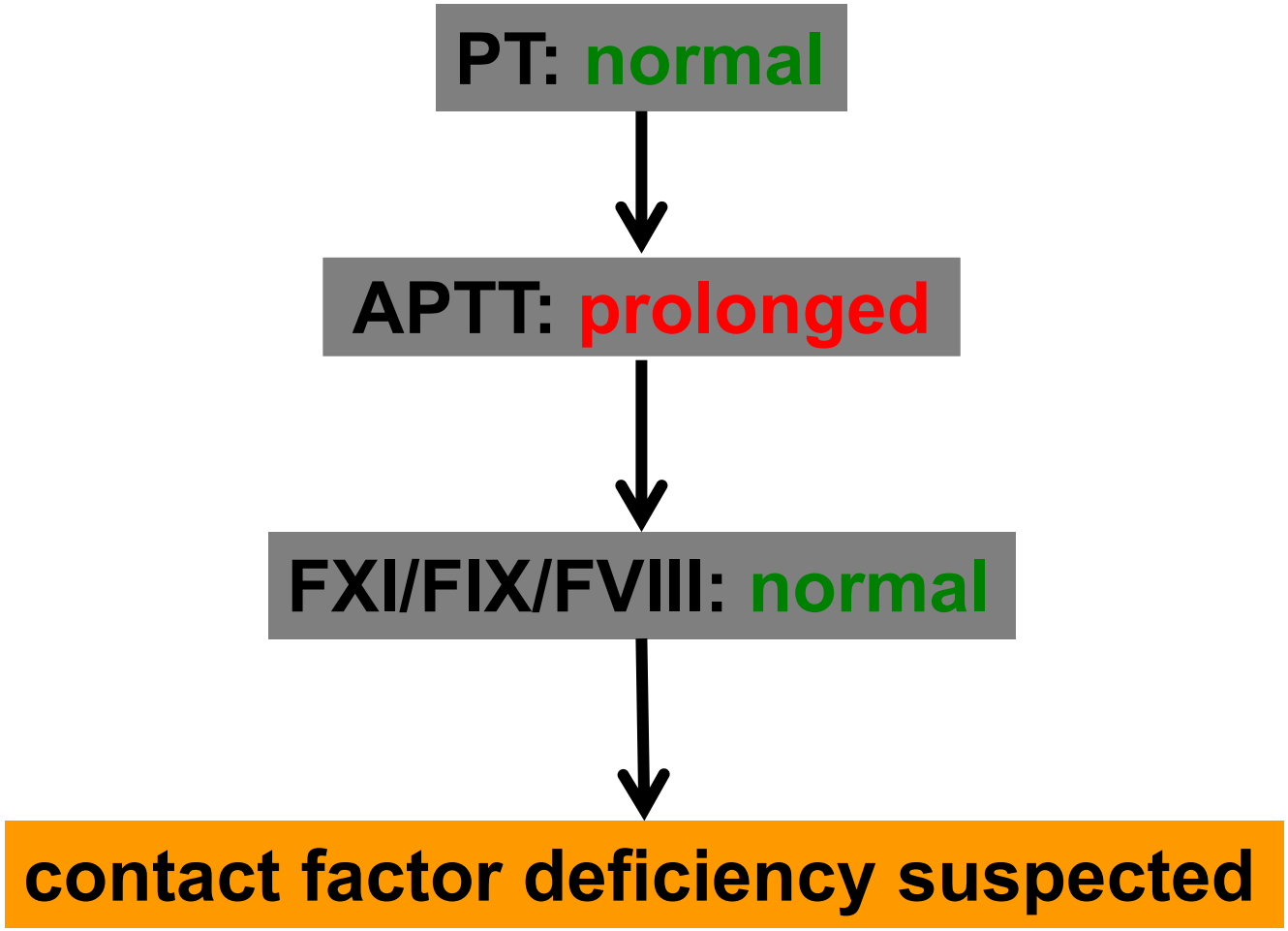

Confirmatory procedures

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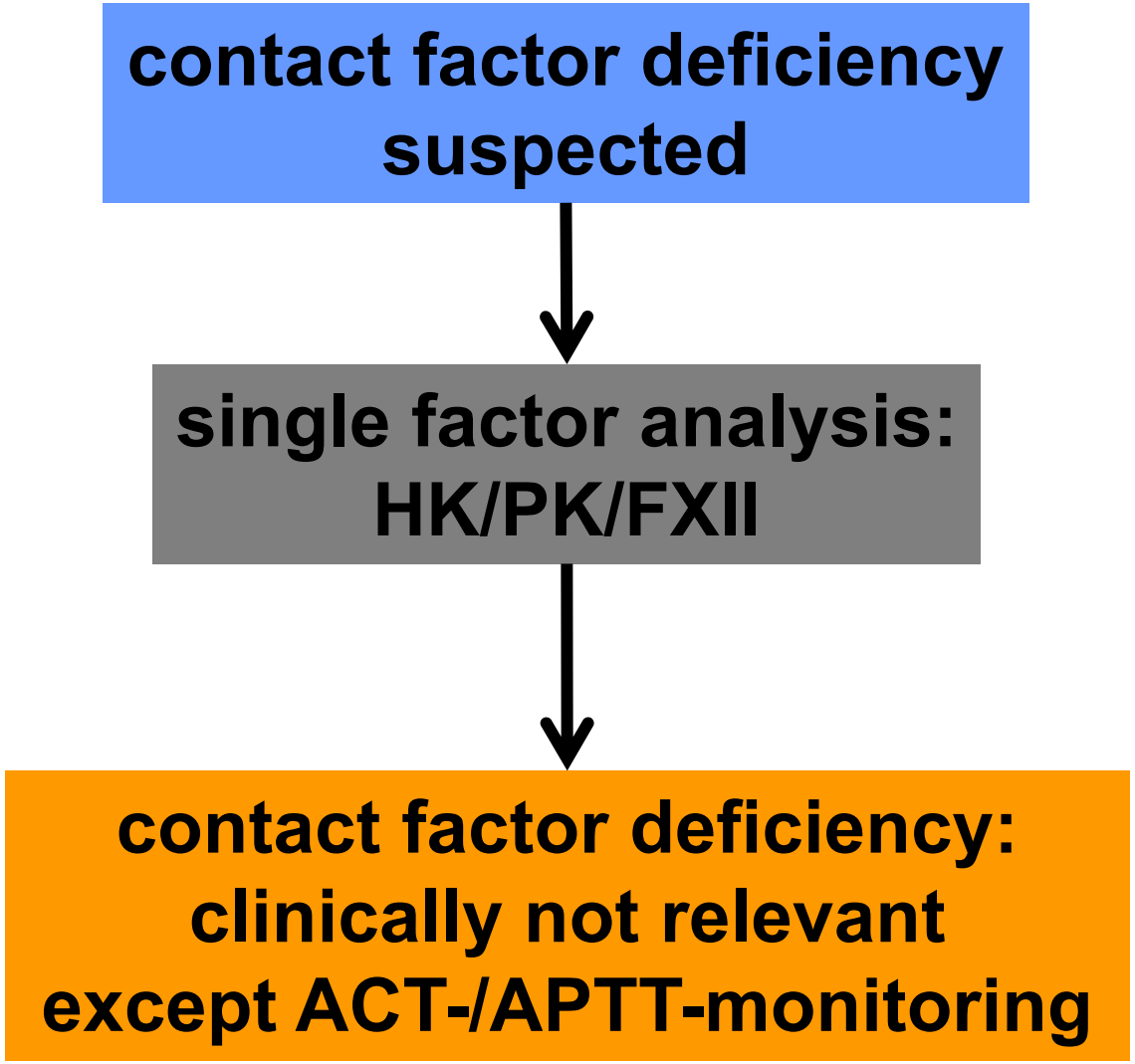

Patients : initial screens

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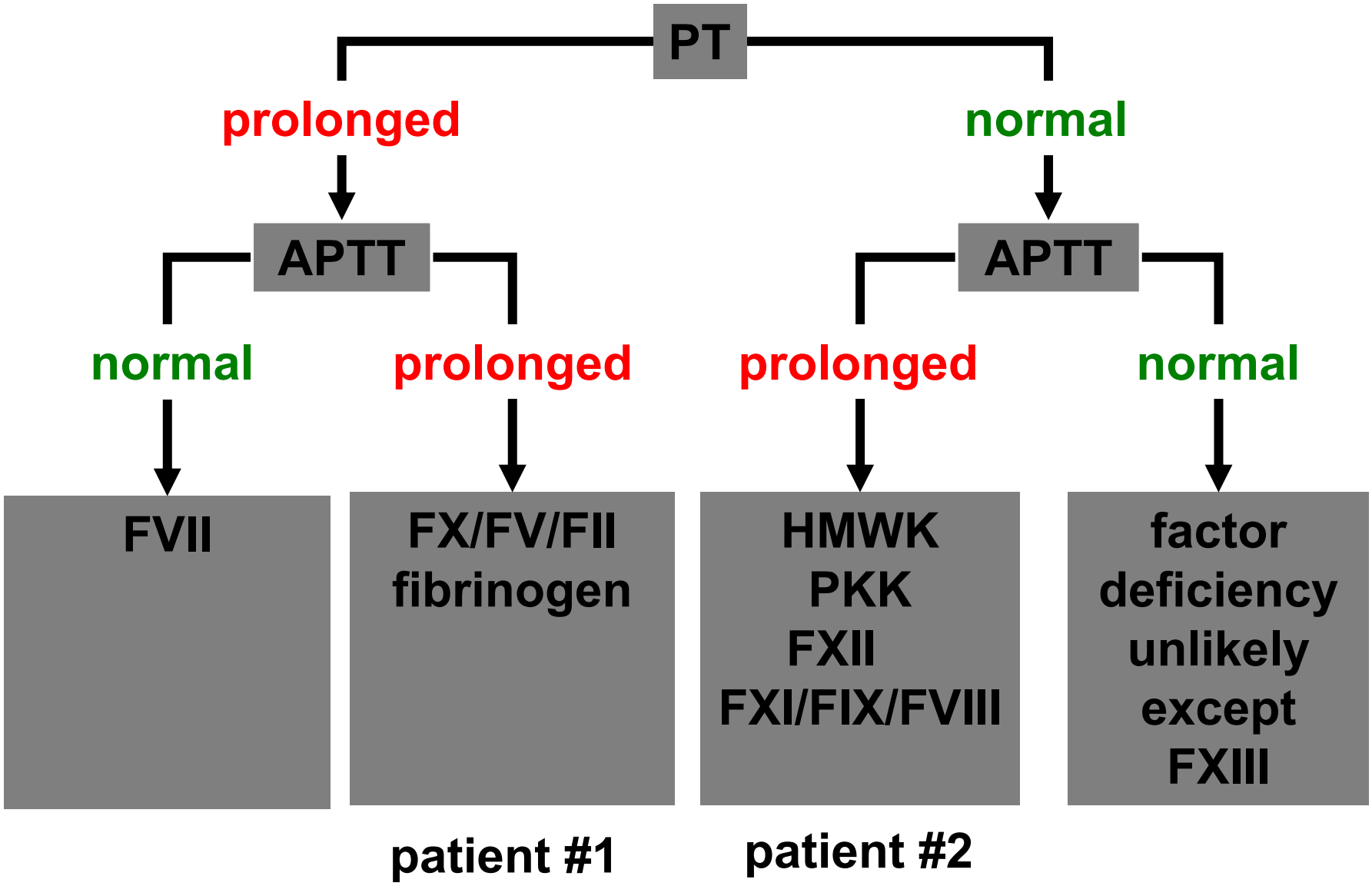
Patient	Platelet count (/µl)	PT (s)	APTT (s)	FXIII (%)
#1	234,000	61	> 150	89
#2	172,000	11	> 150	91

DD: single factor deficiencies



Patients: single factor analysis

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Patient	FII (%)	FX (%)	FV (%)	FIX (%)	FVIII (%)	FXI (%)
#1	87	2	89	-	-	-
#2	-	-	-	83	< 1	91

Suspected diagnosis:
Patient #1: FX deficiency
Patient #2: FVIII deficiency (severe hemophilia)

Patient #1: 68-y old male

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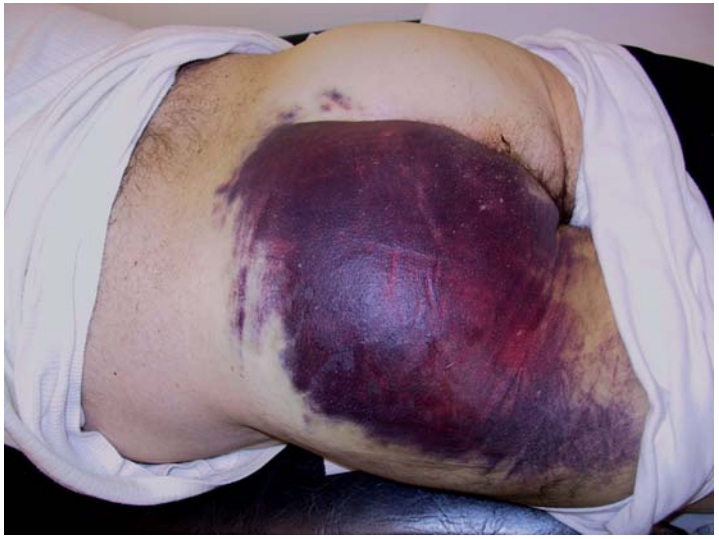

- severe hematoma after minimal trauma

- he reported no personal or familial history of bleeding

Patient #2: 56-y old male

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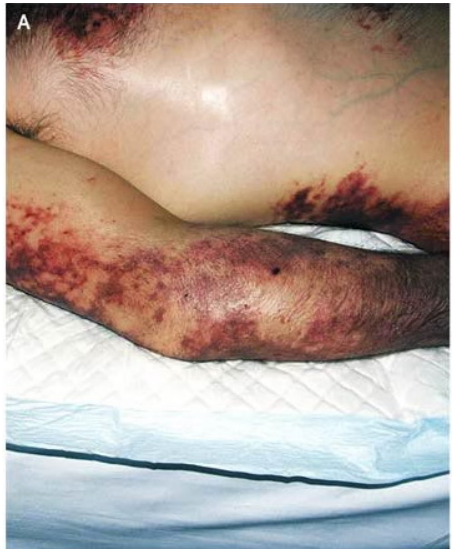
- severe postoperative bleeding after hernia operation

- haematothorax after central venous support

- massive transfusion
  24 RBC, 32 FFP
  4 platelet conc.



- referred to Bonn via helicopter

Acquired hemophilia

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- large hematomas
- extensive ecchymoses
- severe mucosal bleeding
- gastrointestinal bleeding
- gross hematuria
- w/o a bleeding history

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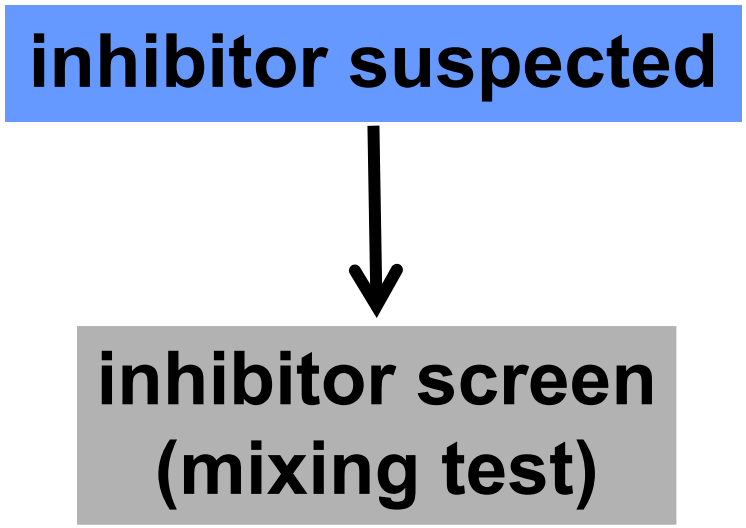
Laboratory approach



Inhibitor screen

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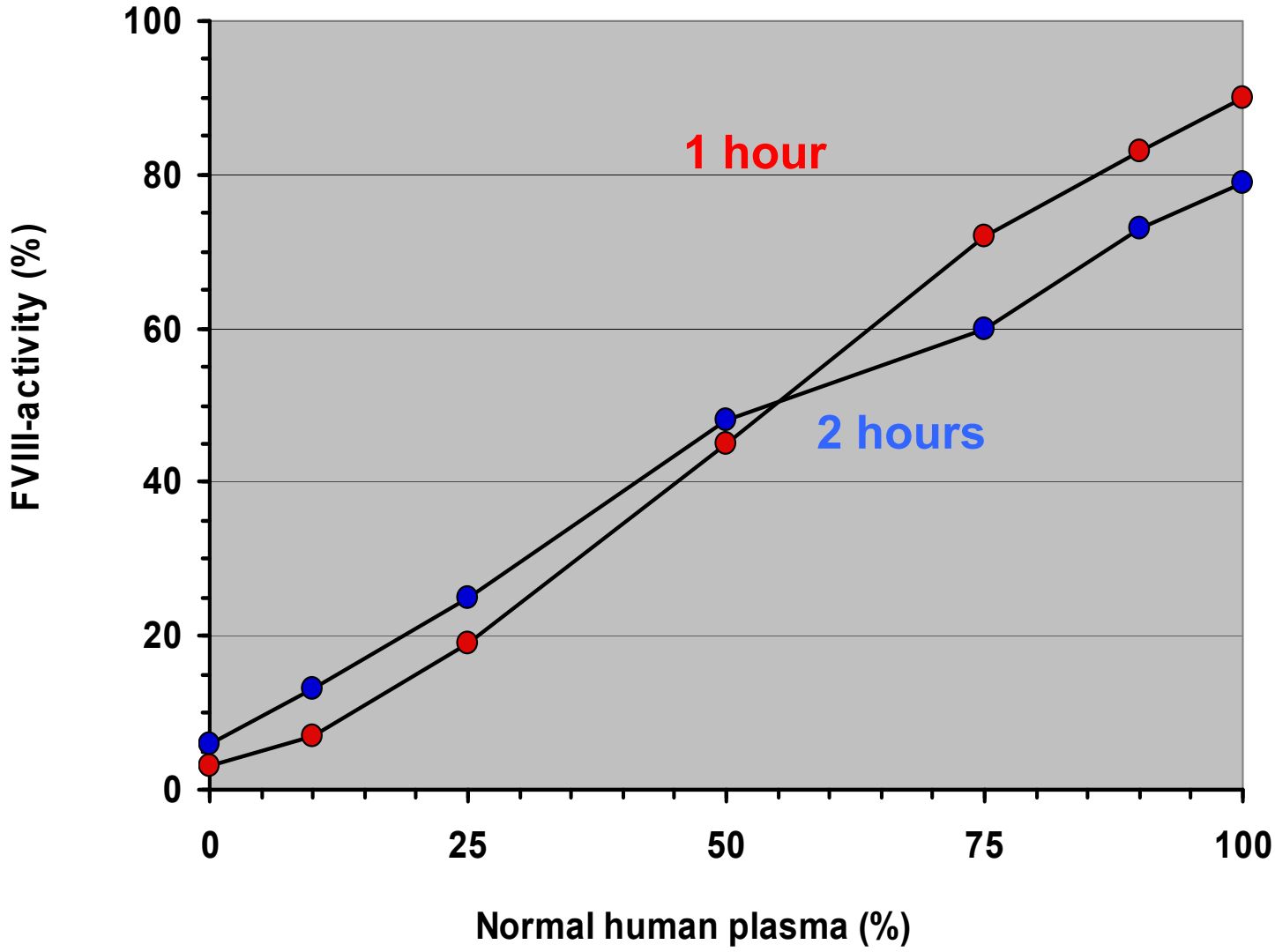
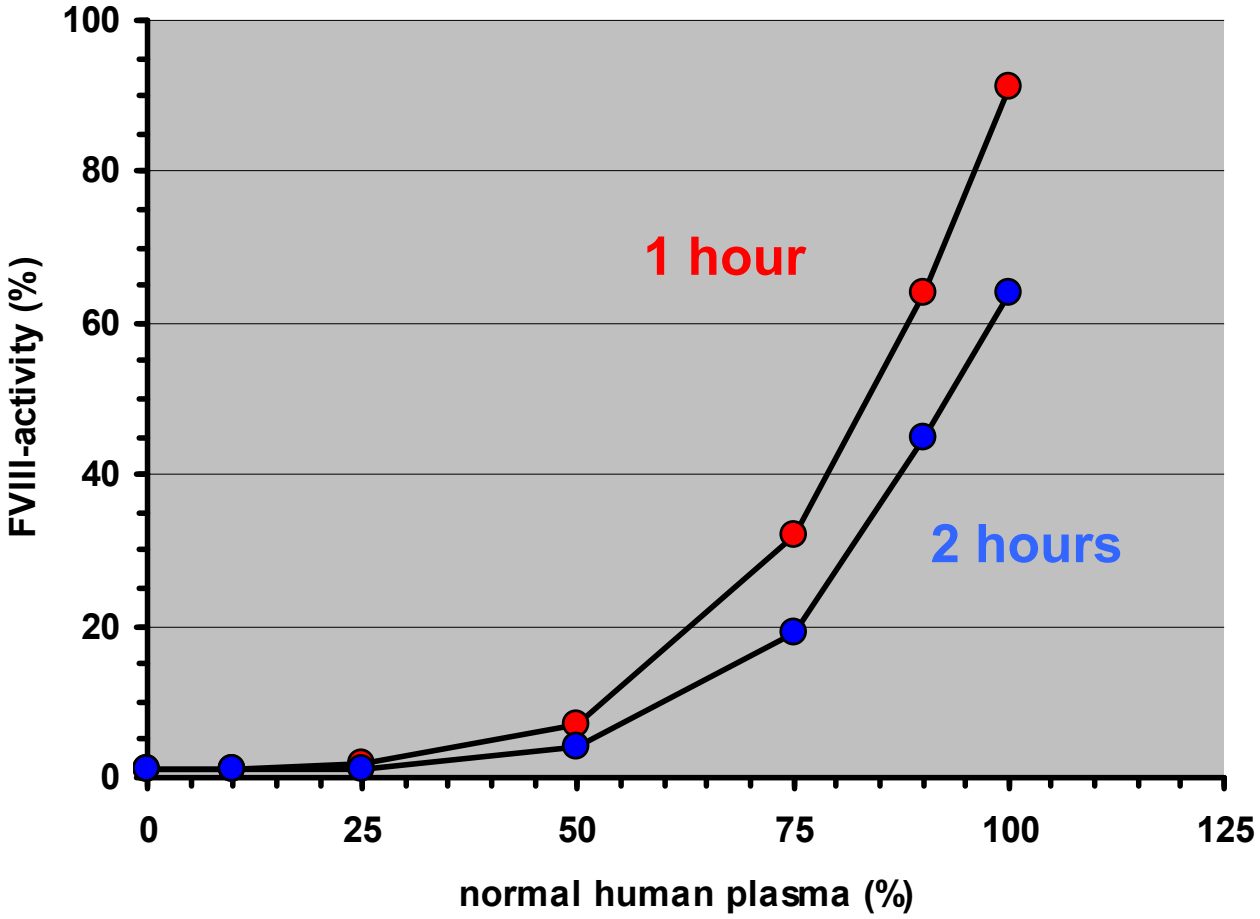
- patient plasma is mixed with increasing concentrations of normal human plasma

- clotting factor activity measured after incubation for 1 and 2 hours at 37° C

Inhibitor screen: negative



Inhibitor screen: positive



Patients: inhibitor screen

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Patient	FX (%)	FV (%)	FVIII (%)	Mixing test
#1	2	89	-	neg
#2	-	-	< 1	pos

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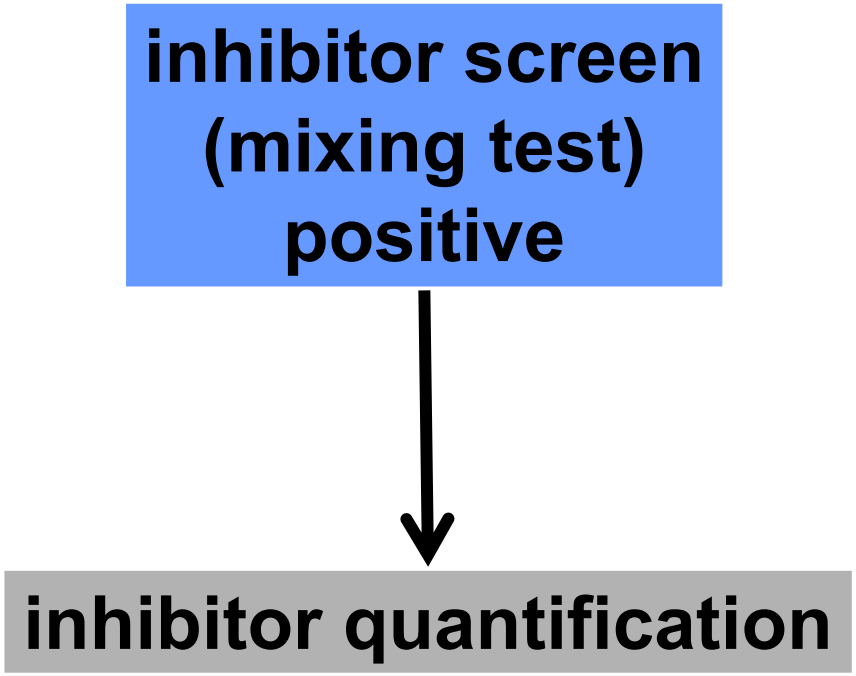
Laboratory approach



Bethesda assay

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- serial dilutions of patient plasma are incubated for two hours at 37° C with normal human plasma

- factor activity is then measured using a clotting assay

- 1 Bethesda unit (BU) is defined to reduce the activity of a clotting factor in normal human plasma to 50%

Bethesda units (BU)

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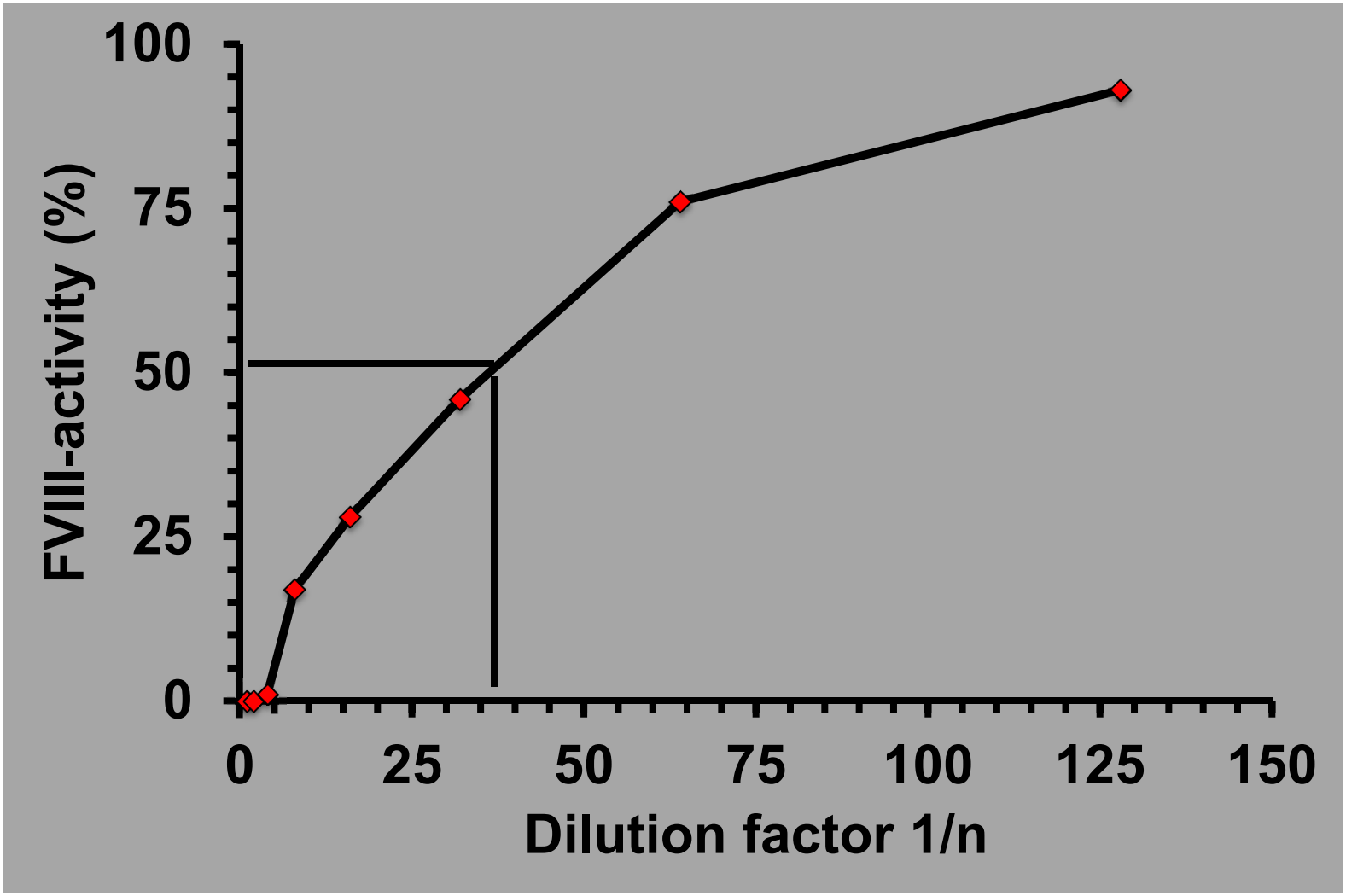

Patients: Bethesda units (BU)

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Patient	FX (%)	FV (%)	FVIII (%)	Mixing test	BU
#1	2	89	-	neg	-
#2	-	-	< 1	pos	37

Patient #2: 56-y old male

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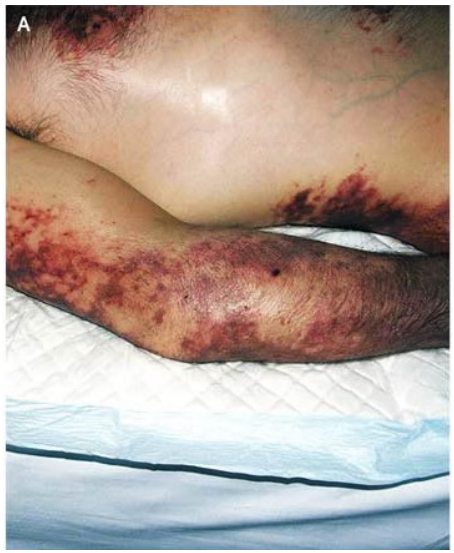
- severe postoperative bleeding after hernia operation

- haematothorax after central venous support



➔ acquired hemophilia A caused by high titer FVIII-autoantibodies

Acquired inhibitors: frequencies

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Molecular target	Estimated frequency
Factor VIII	1 – 1.5 x 10^6 in non-hemophiliacs
Factor II	few case reports only
Factor V	~ 105 cases described
Factors VII, IX, X, XI	few case reports only
Factor XIII	~ 20 cases described

Patients: inhibitor screen

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Patient	FX (%)	FV (%)	FVIII (%)	Mixing test
#1	2	89	-	neg
#2	-	-	< 1	pos

Acquired inhibitors

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- The majority of acquired inhibitors are antibodies that either inhibit the activity or increase the clearance of a clotting factor.

Laboratory approach

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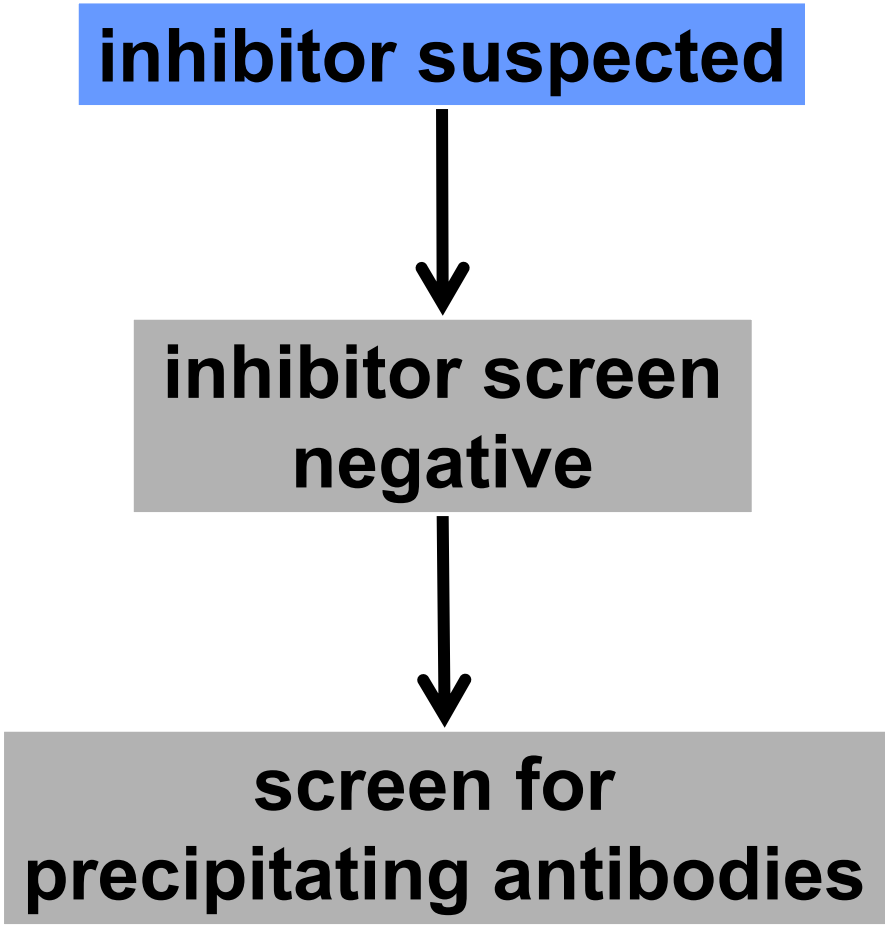
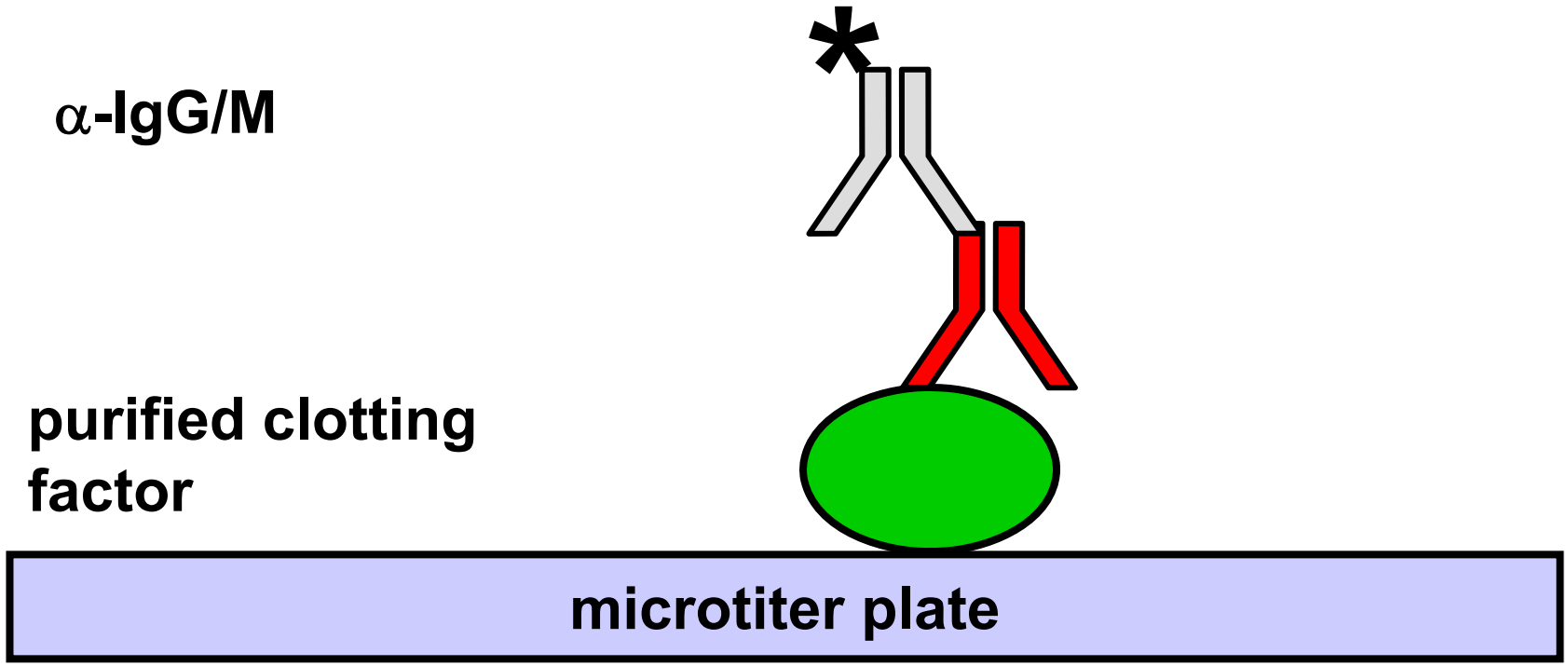


Acquired inhibitor: ELISA



Patients: laboratory data

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Patient	FX (%)	FV (%)	Mixing test	BU	APA	ELISA
#1	2	89	neg	-	neg	neg
#2	-	-	pos	37	neg	-

Patient #1: 68-y old male

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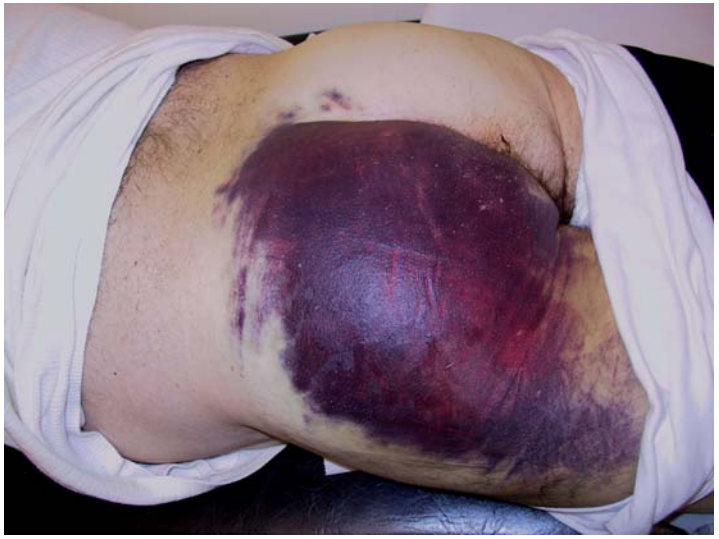

- severe hematoma after minimal trauma
- skin biopsy reveals amyloidosis
- ➔ amyloid-associated FX-deficiency

Screening parameters

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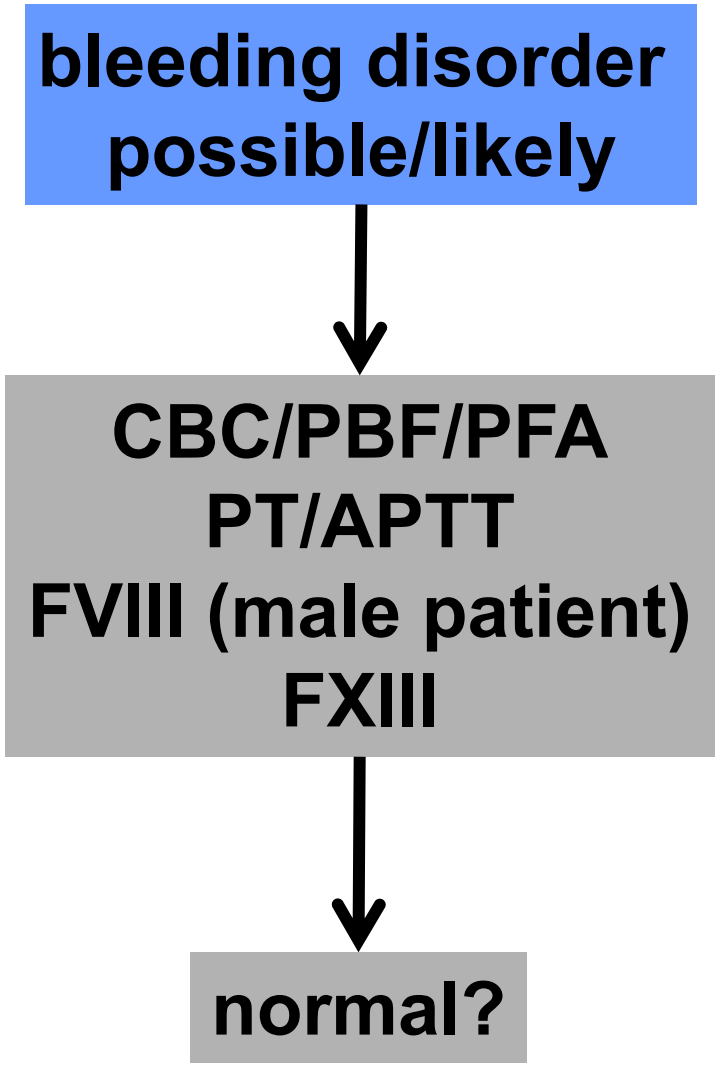

Extended screening

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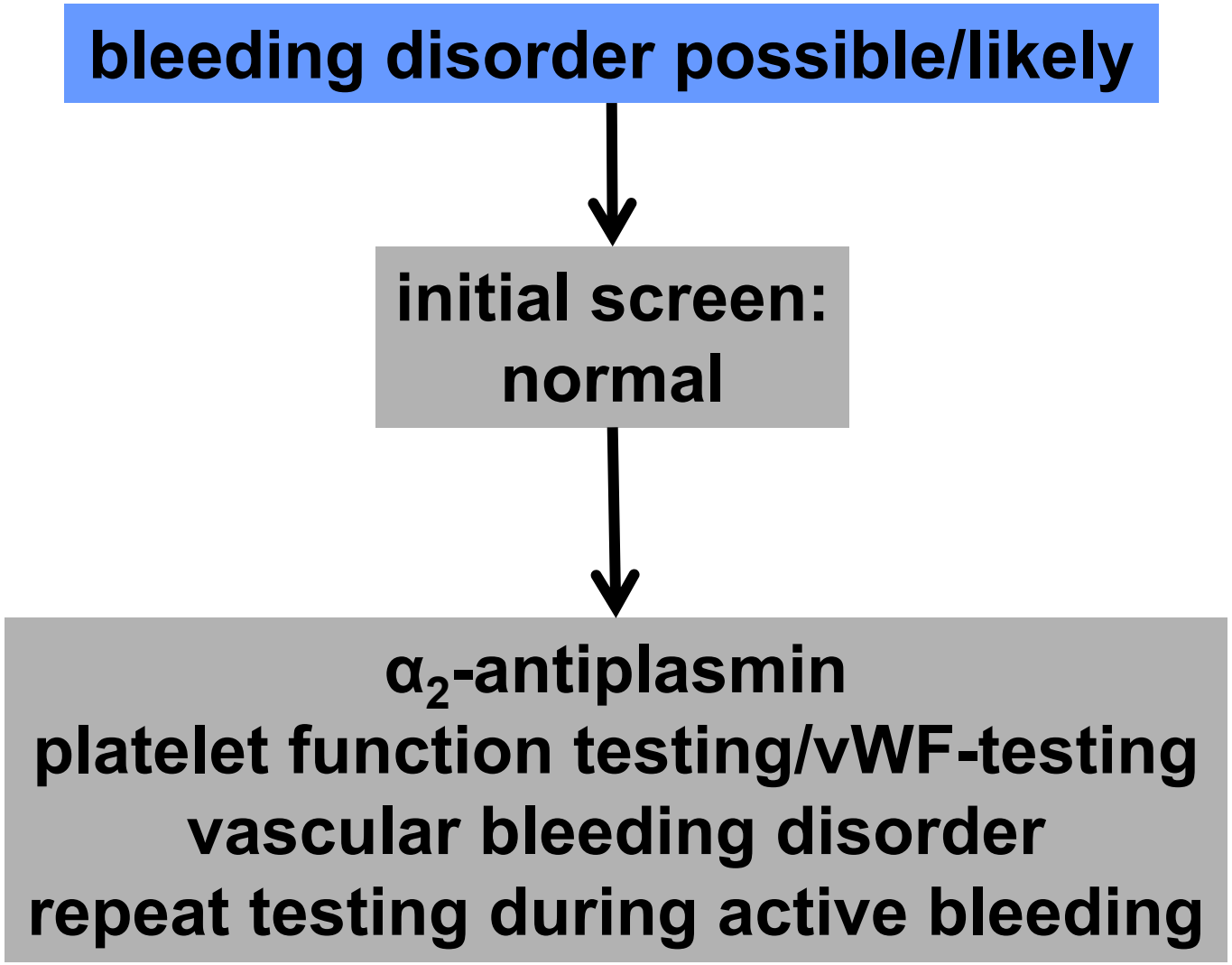

Clinical decision finding

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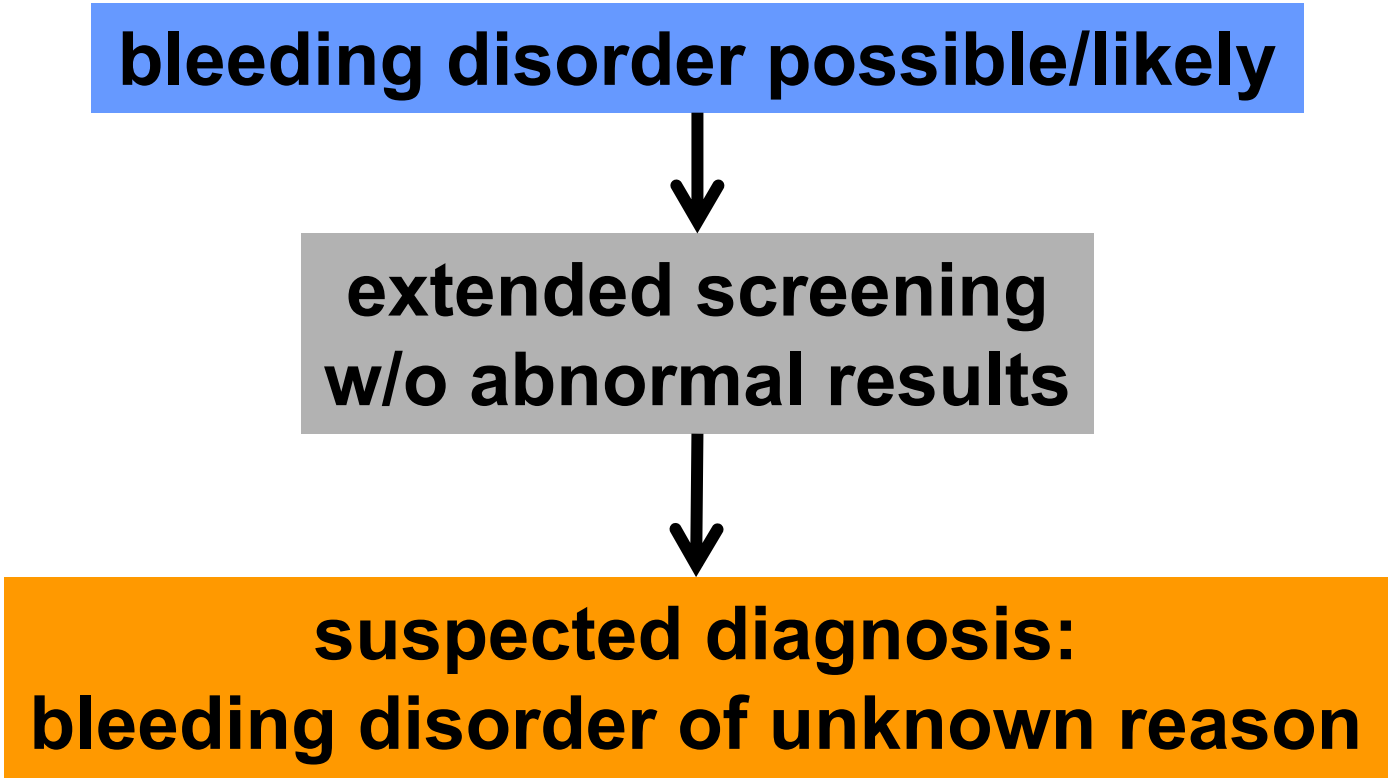

Take home message (II)

- If relatively simple screening procedures are used, the vast majority of hemorrhagic problems can be identified.

- Confirmatory tests are subsequently used to establish an appropriate differential diagnosis.

Clinical situations

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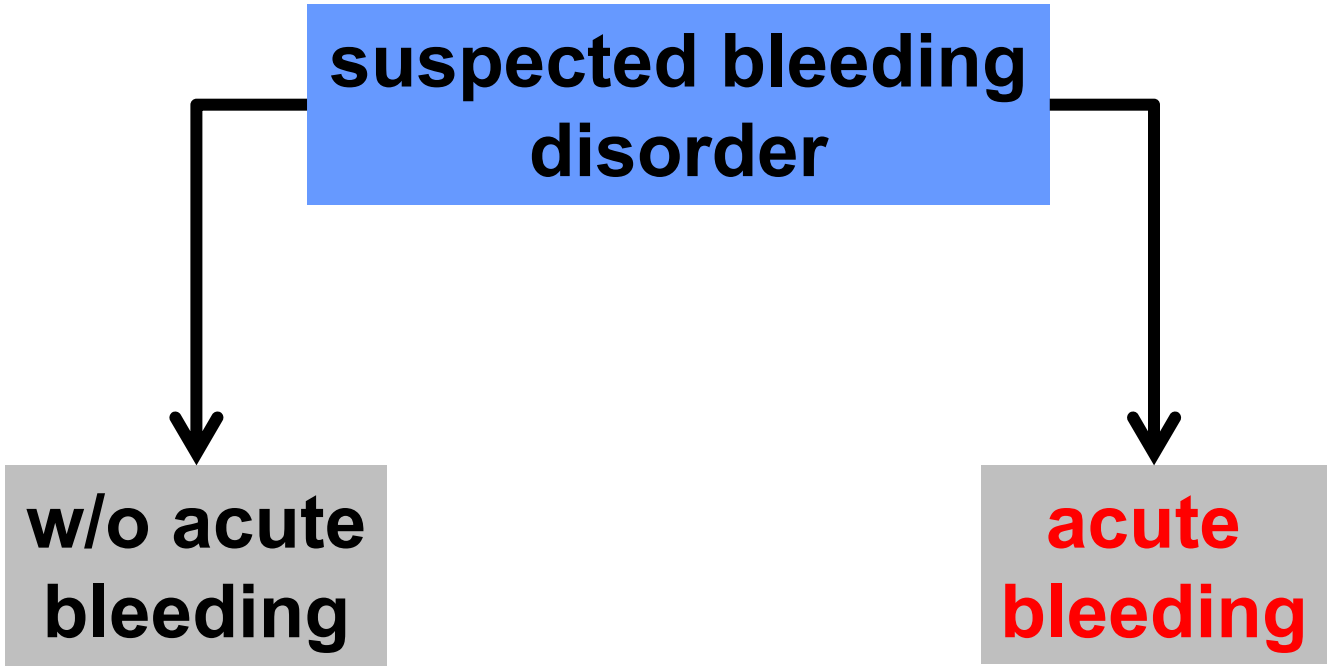

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Acute Bleeding: Grading

- **Life-threatening (WHO grade 4)**
  Trauma or critical organ bleeding

- **Severe (WHO grade 3)**
  gross blood loss, requires transfusion

- **Mild blood loss but clinically significant (WHO grade 2)**

TIC-cascade (I)

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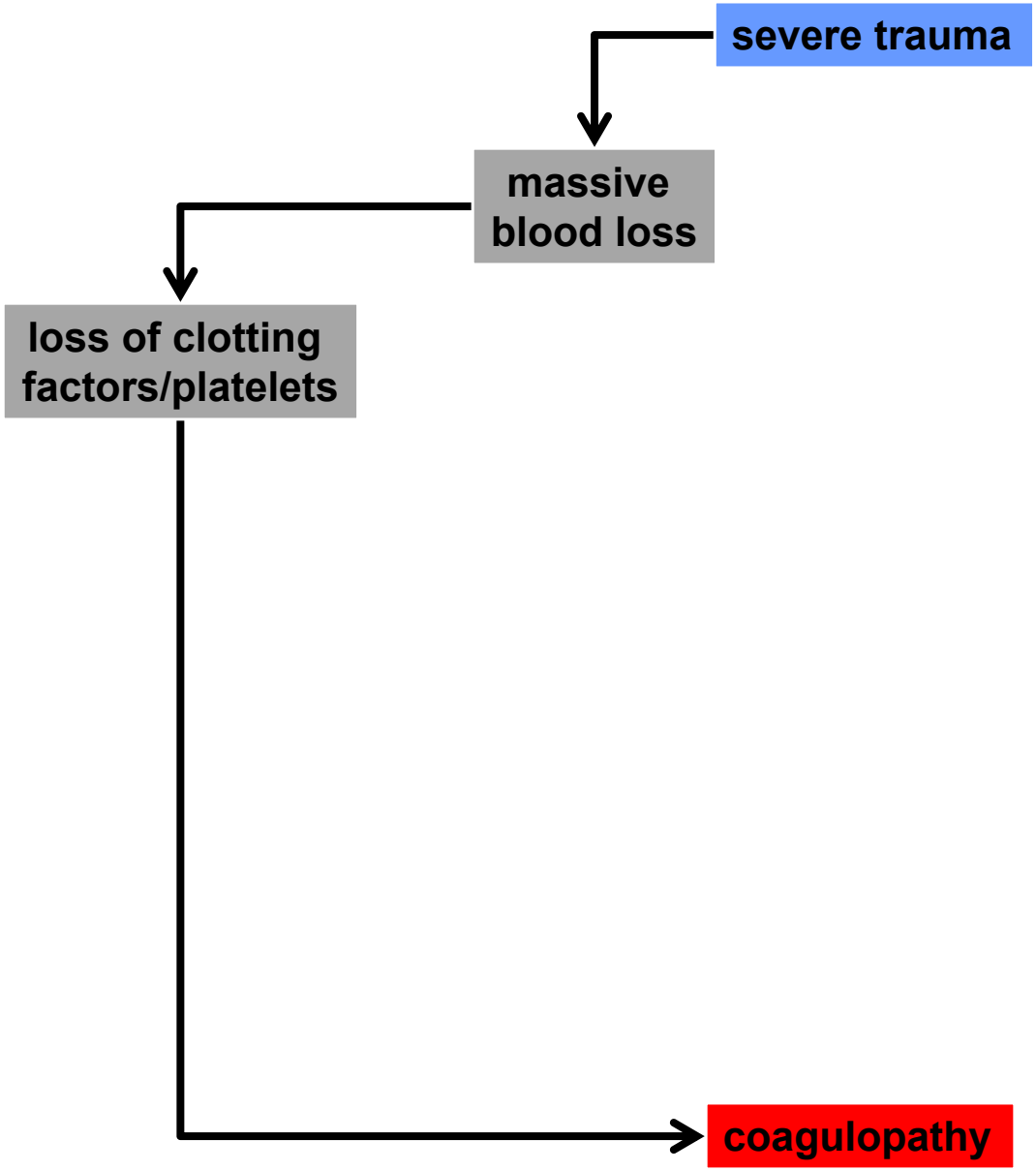

TIC-cascade (II)

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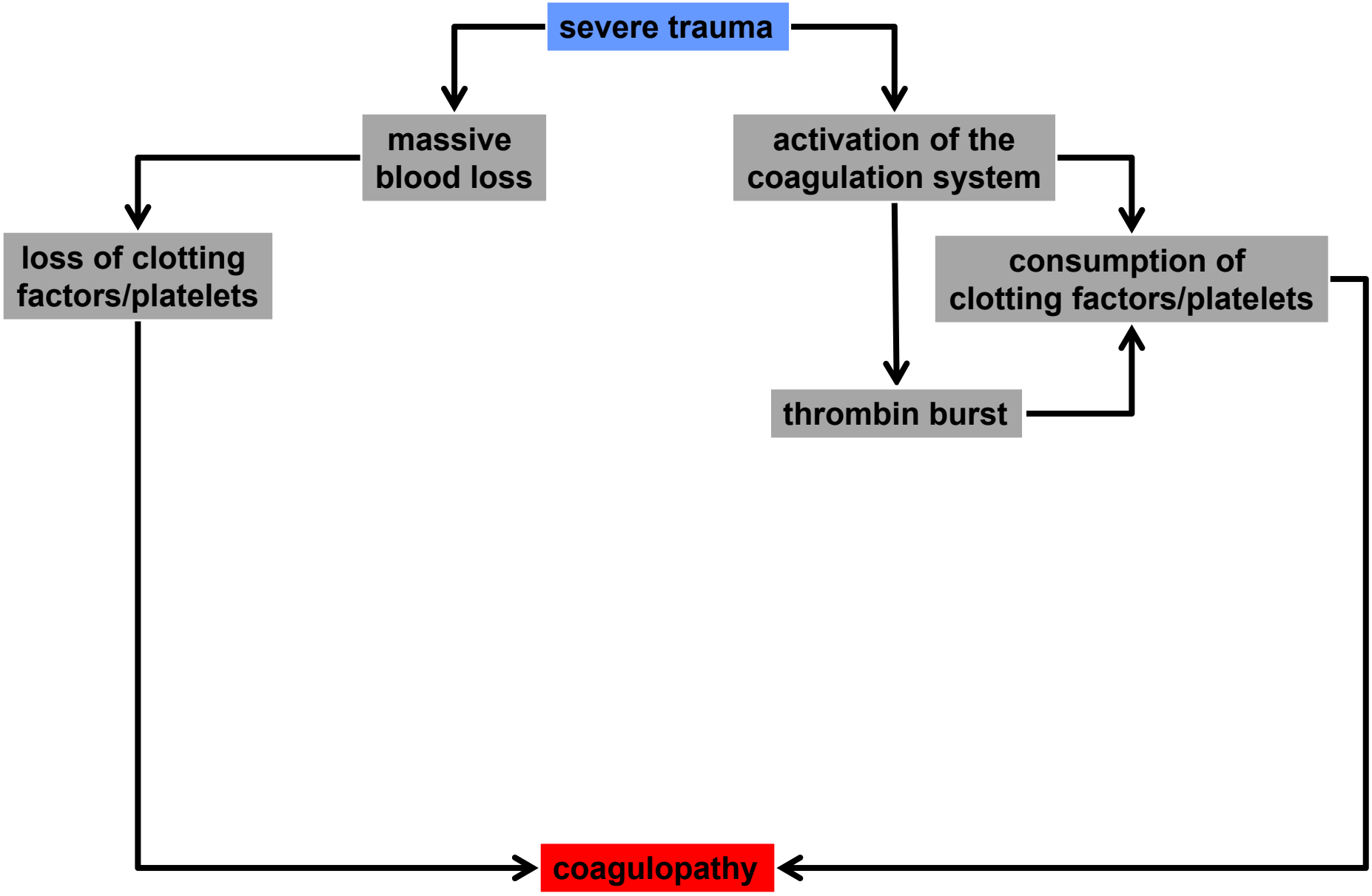

TIC-cascade (III)

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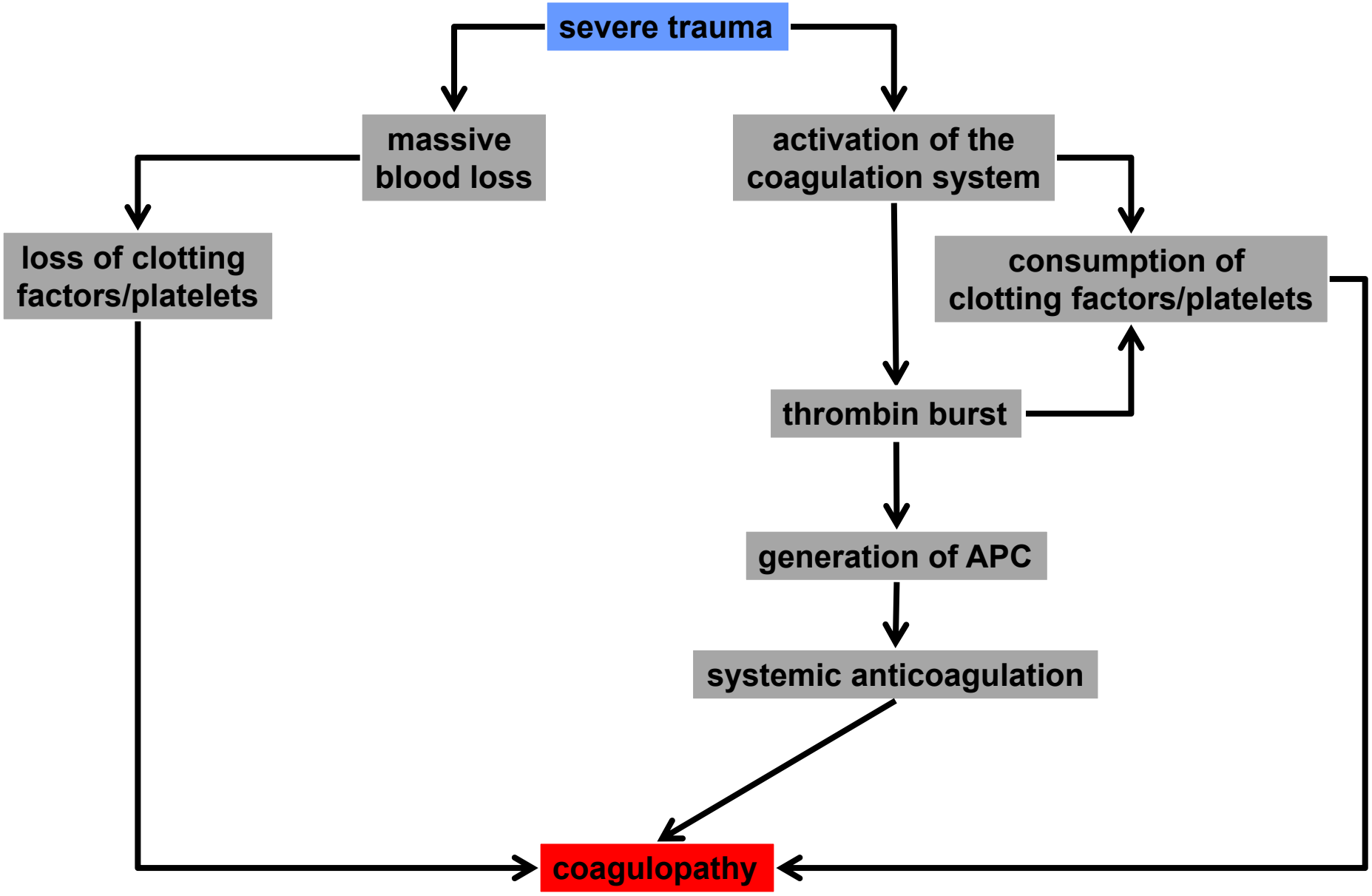
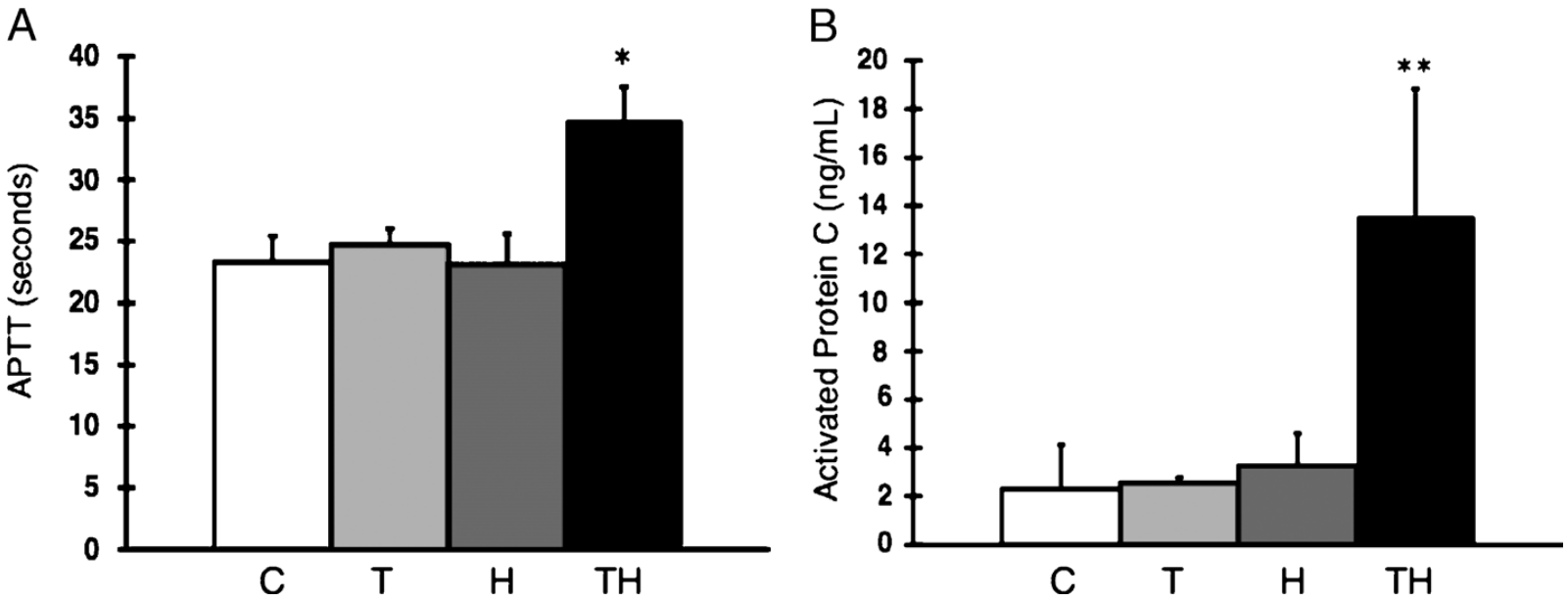


TIC: APC-formation



C = control, T = trauma, H = hemorrhage, TH = trauma + hemorrhage

Chesebro BB, et al. Shock 2009; 32: 659-665

TIC-cascade (IV)

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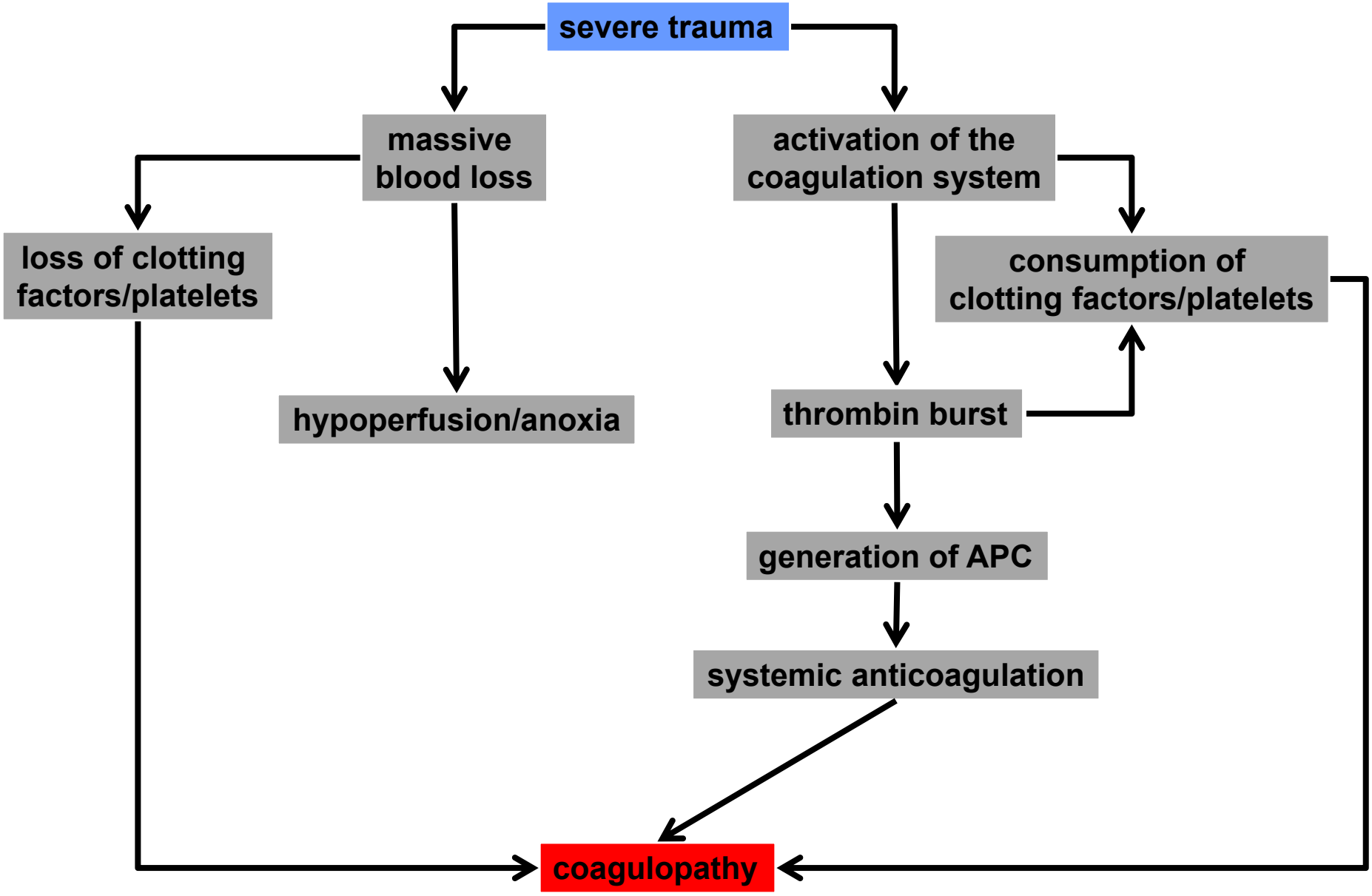
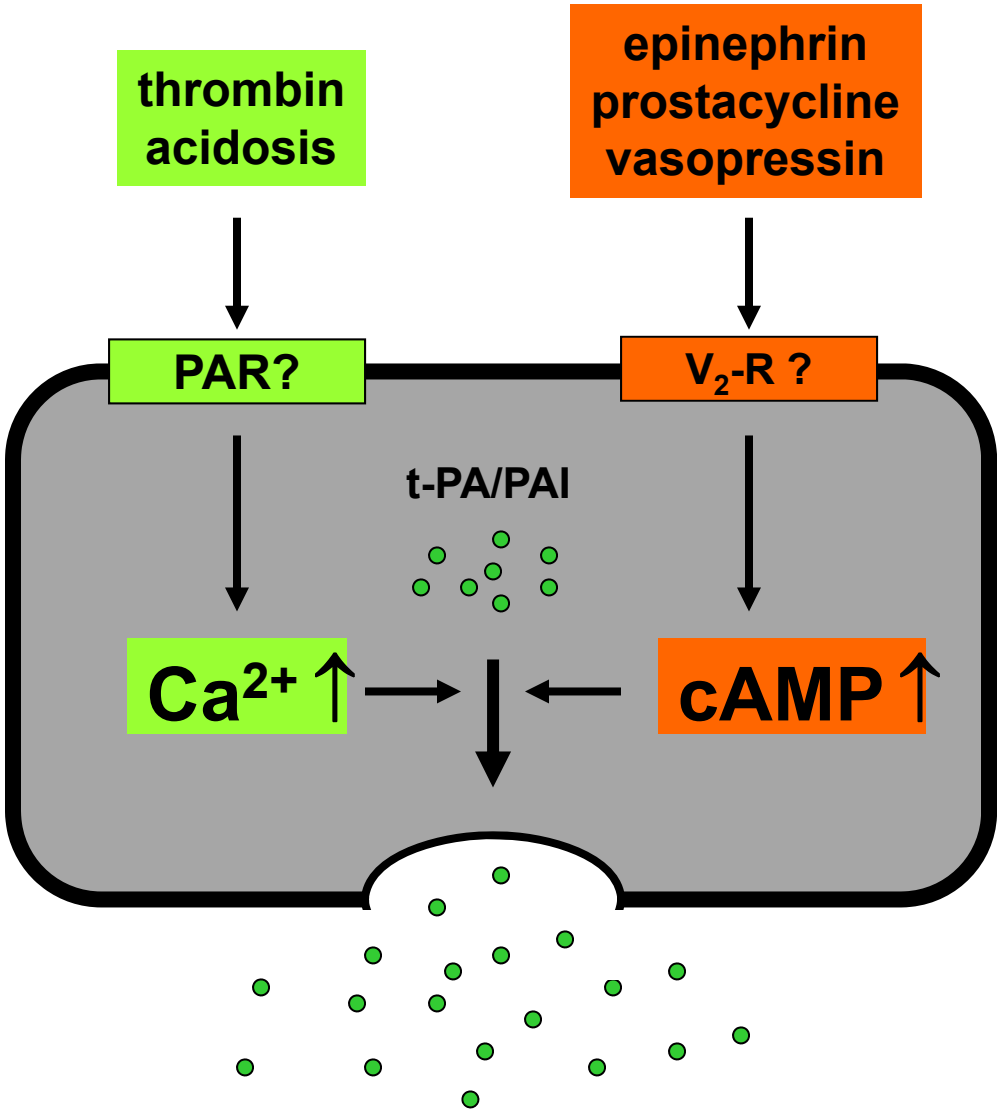


t-PA-secretion



t-PA: tissue-type plasminogen activator

TIC-cascade (V)

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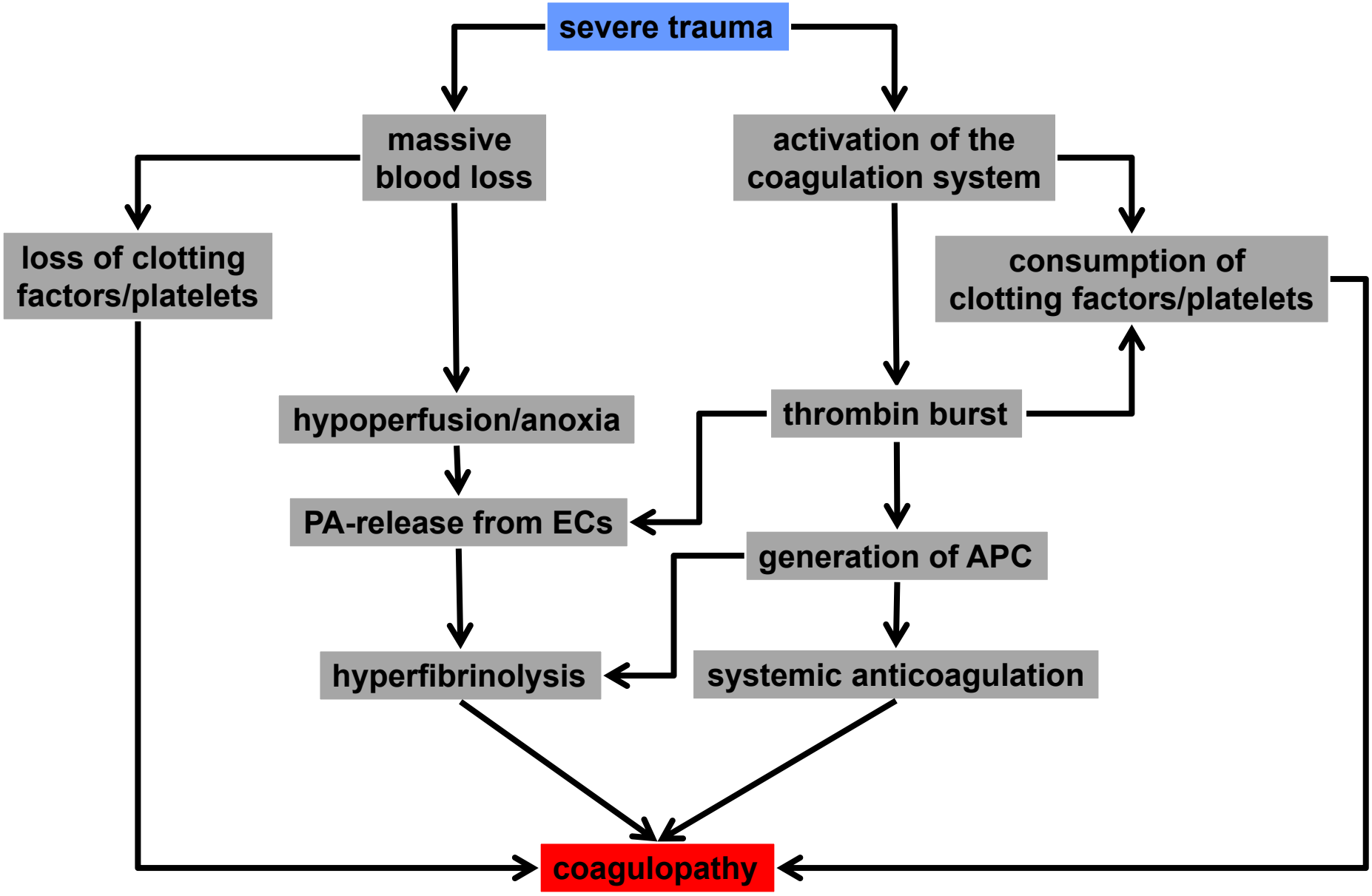

TIC: treatment options

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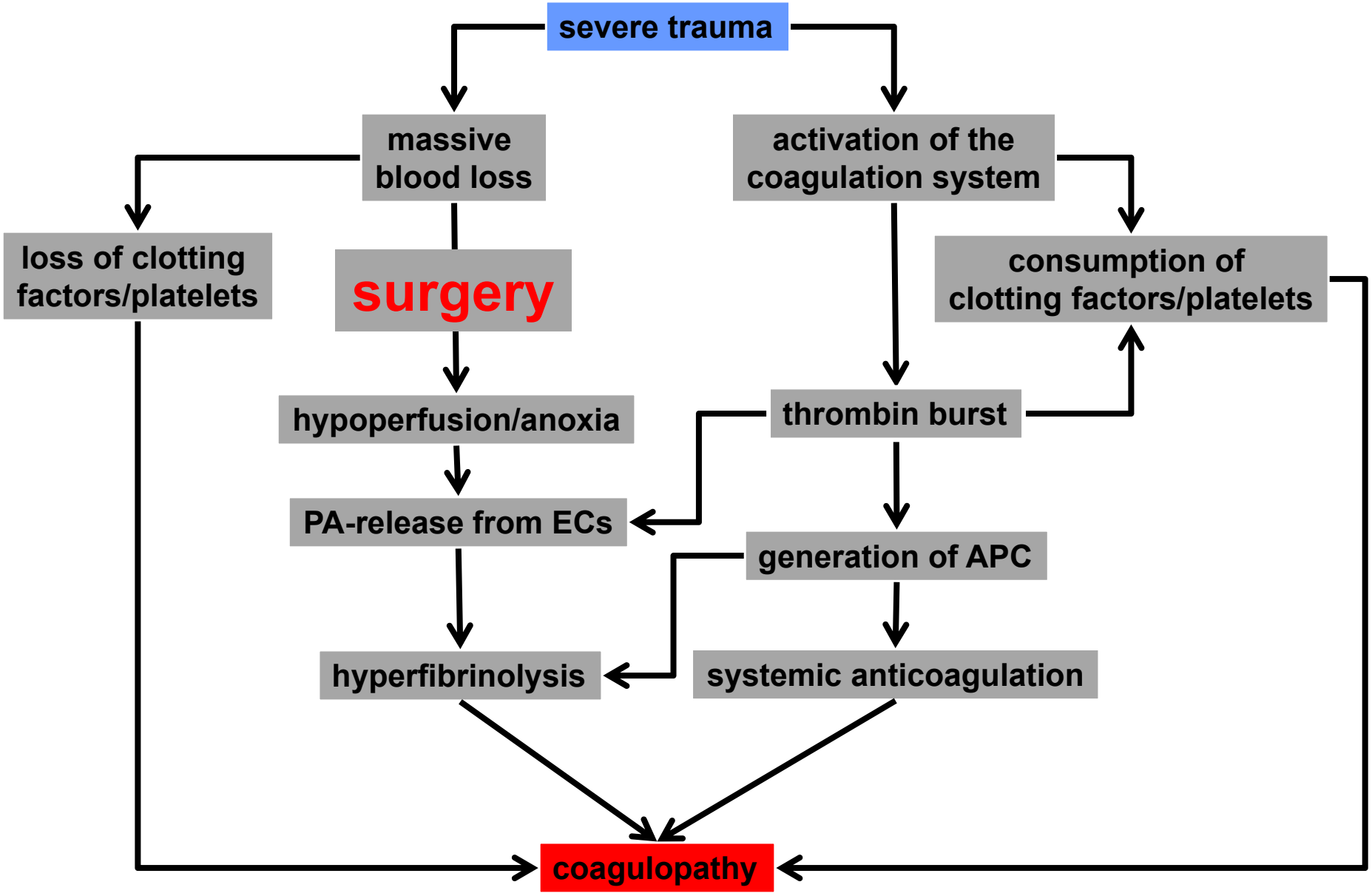

TIC: treatment options

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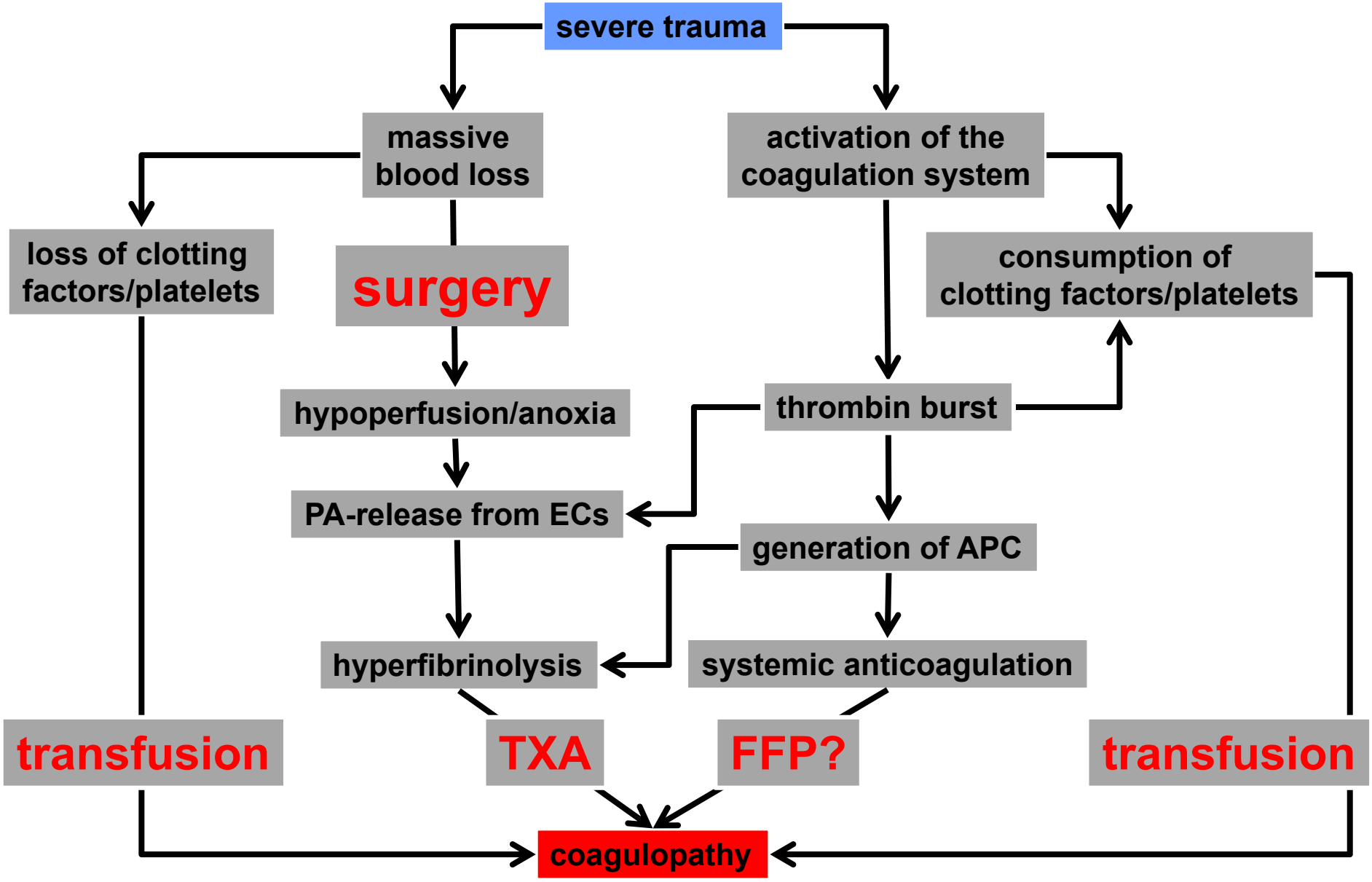

Tranexamic acid (TXA)

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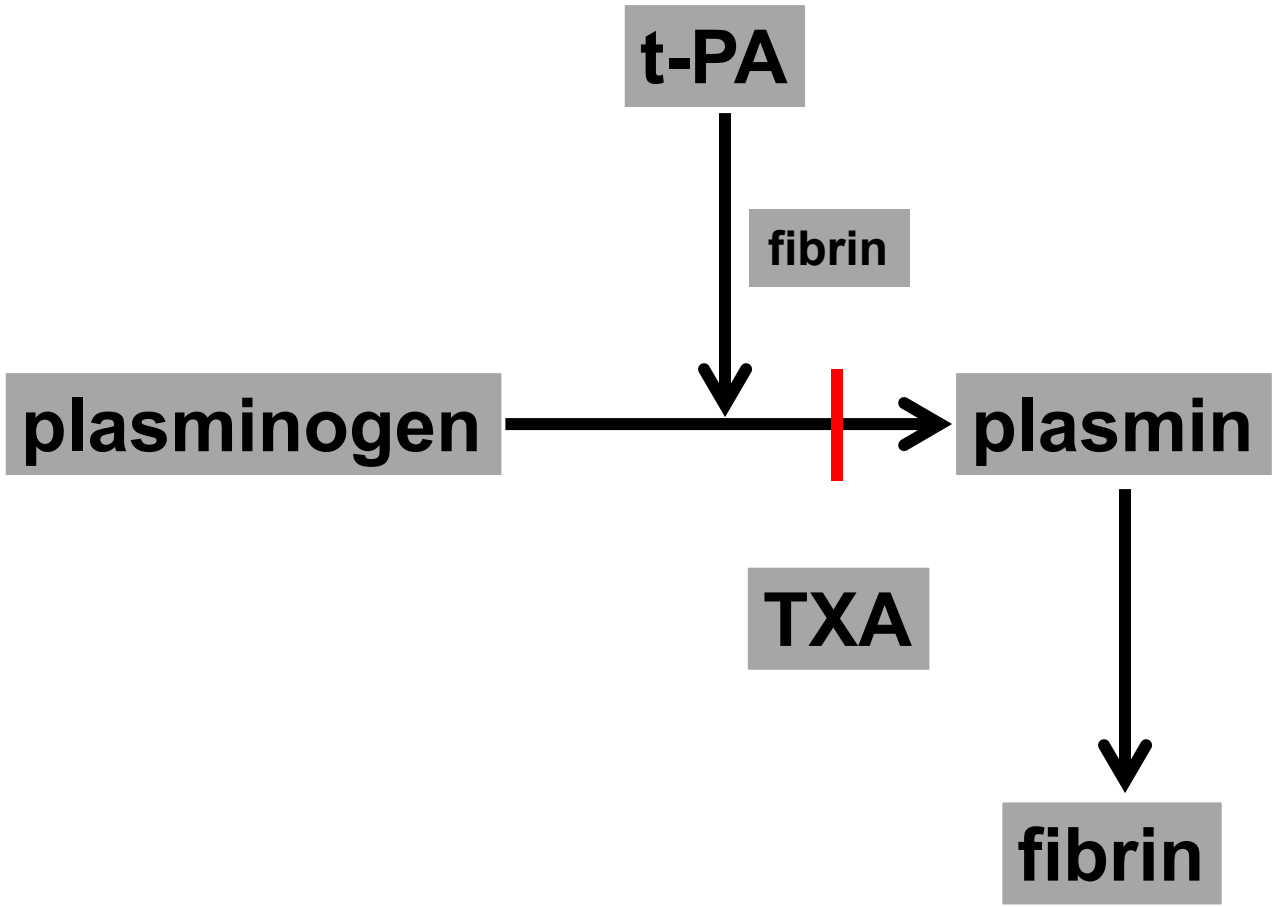

CRASH-2 trial

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Study population:	**20,211 trauma patients**
Treatment group:	**1 g TXA bolus/1 g over 8 h**
Control group:	**Placebo**
All-cause mortality:	**14.5% vs. 16% (p = 0.0035)**
Bleeding related mortality:	**4.9% vs. 5.7%**

[1]CRASH-2 trial. Lancet 2010; 376: 23-32, TXA: tranexamic acid

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TIC: treatment triggers

1. Clinical probability of TIC

1. Laboratory values

High TIC risk: indicators*

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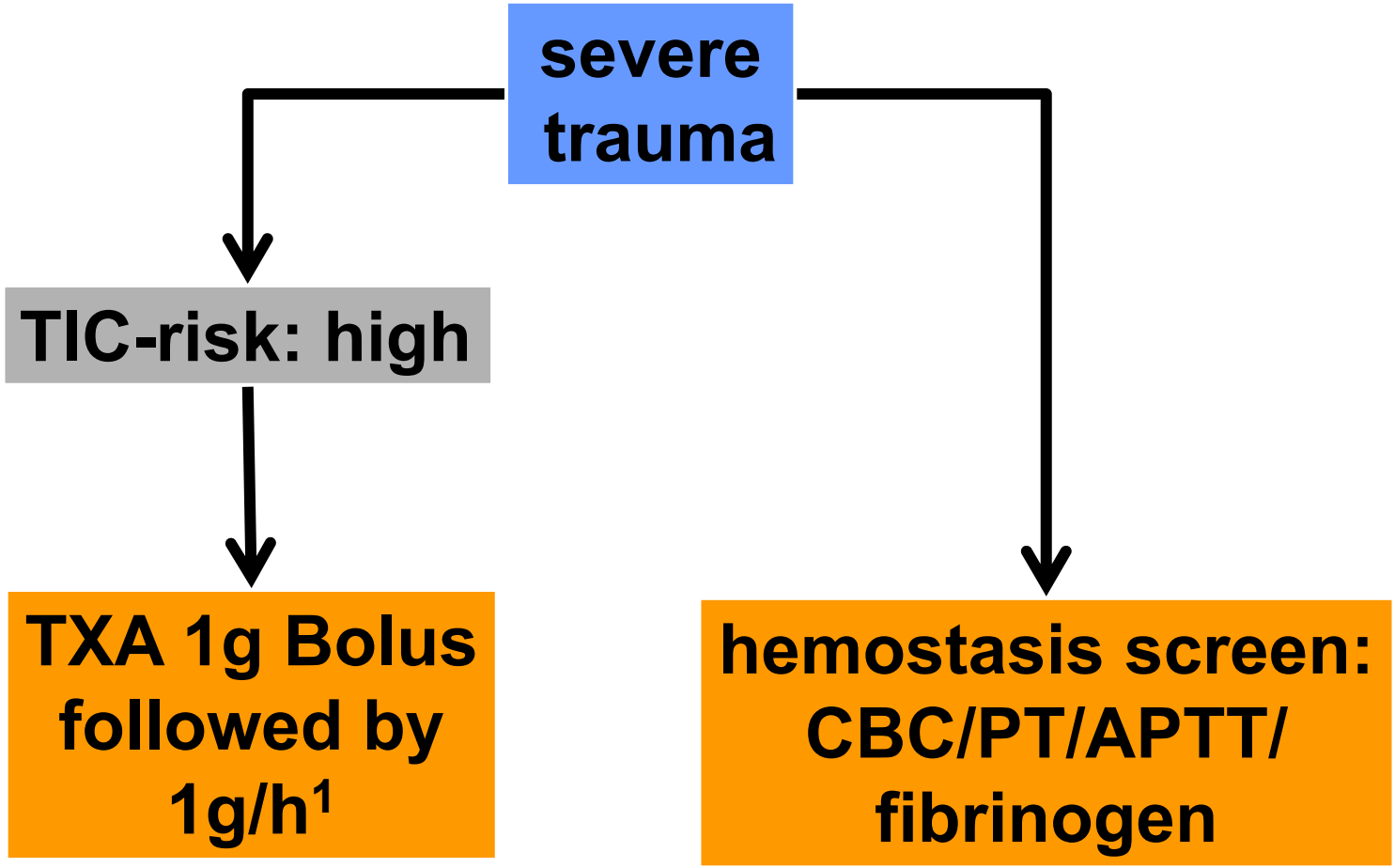
- hemorrhagic shock on admission
- pelvic fracture/multiple bone fractures
- rupture of liver/spleen/positive FAST
- brain damage
- BE < -6
- use of antithrombotic drugs

** TASH-Score, German Society of Trauma Surgeons*

TIC: hemostatic support (I)



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TIC: hemostatic support (II)

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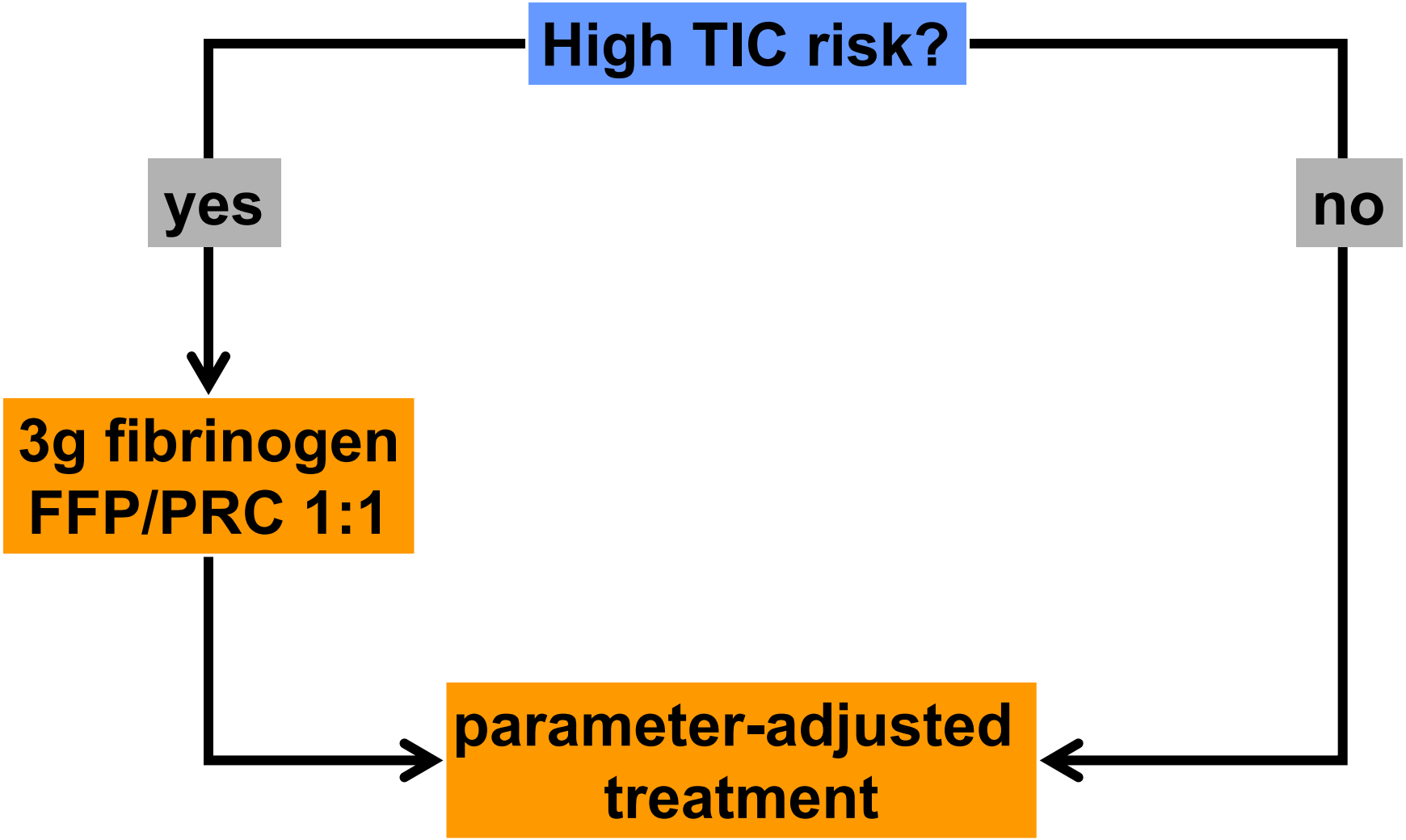

Parameter-adjusted treatment

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Fibrinogen:

- **< 1.5 g/dl with ongoing blood loss/ICB**
- **< 0.5 g/dl**

→ **3 g fibrinogen concentrate**

Prothrombin time:

- **> 25s with ongoing blood loss/ICB**
- **< 50s**

→ **50 IE/kg b.w. PCC**

ICB, intracranial bleeding;

Parameter-adjusted treatment

→ **platelet transfusion, if platelet count:**

- **< 100.000/µl with ongoing bleeding/ICB**
- **< 50.000/µl with coagulopathy**
- **< 30.000/µl**

ICB, intracranial bleeding

Parameter-adjusted treatment

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Signs of hyperfibrinolysis

→ **bolus injection of 1 g TXA followed by 20 mg/kg b.w./h**

→ **3 g fibrinogen concentrate**

TEG: fibrinolysis

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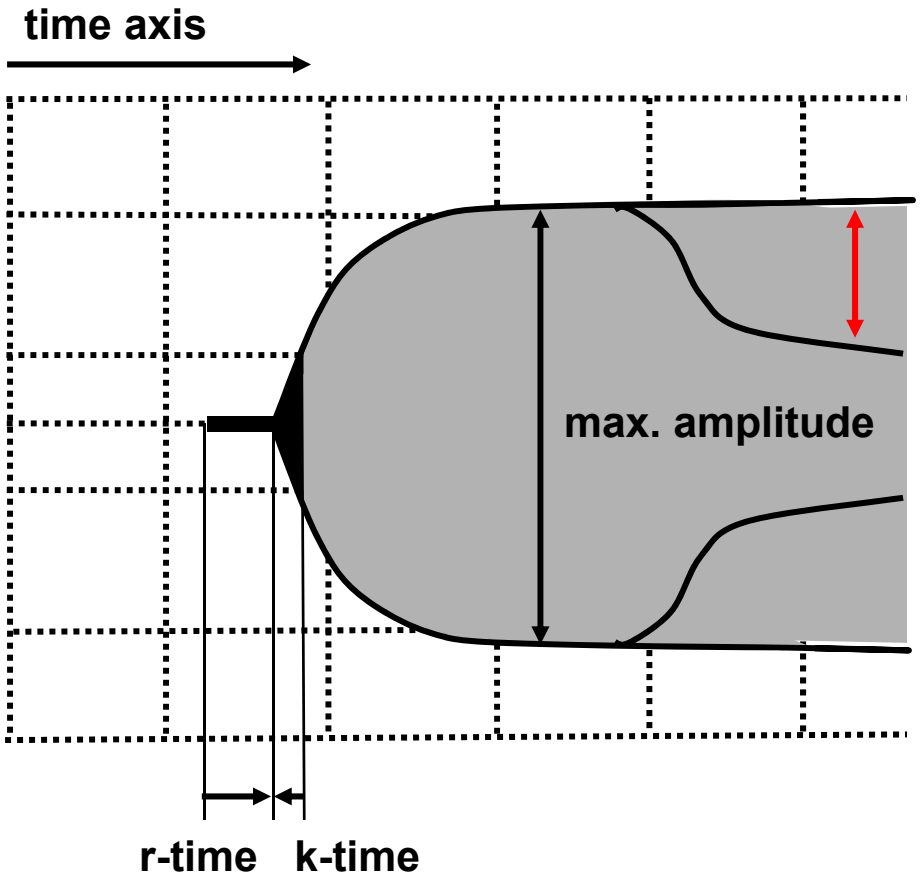

Take home message (III)

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- TIC is frequent in severe trauma patients.

- TIC is caused by consumption and loss of coagulation factors and platelets and by secondary hyperfibrinolysis and APC formation.

- TIC can be successfully treated by TXA treatment and transfusion of blood products including fibrinogen, fresh frozen plasma and platelets.

Acute Bleeding: Grading

- **Life-threatening (WHO grade 4)**
  Trauma or critical organ bleeding

- **Severe (WHO grade 3)**
  gross blood loss, requires transfusion

- **Mild blood loss but clinically significant (WHO grade 2)**

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Critical organ bleeding

Suspected anticoagulant treatment

antithrombotic screen: APTT/INR/TT/BT/aFXa/TTI

APTT, activated partial thromboplastin time; INR, international normalized ratio; TT, thrombin time; BT, batroxabin time; aFXa, anti-FXa-activity; TTI, thrombin inhibition time

Anticoagulant screen

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Parameter	Result indicating a clinically relevant anticoagulant activity				Reference range
	LMWH/ Fonda-parinux	Argatroban Bivalirudin Dabigatran	VKA	Rivaroxaban Apixaban	
APTT	normal	prolonged	prolonged	prolonged	< 35s
INR	normal	increased	increased	increased	< 1,2
TT	normal	prolonged	normal	normal	< 21 s
BT	normal	normal	normal	normal	< 21 s
aFXa	detectable	not detectable	not detectable	detectable	< 0,1
TTI	no inhibition	inhibition	no inhibition	no inhibition	

Anticoagulant screen

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Parameter	Result indicating a clinically relevant anticoagulant activity				Reference range
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Anticoagulant screen

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TT	normal	prolonged	normal	normal	< 21 s
BT	normal	normal	normal	normal	< 21 s
aFXa	detectable	not detectable	not detectable	detectable	< 0,1
TTI	no inhibition	inhibition	no inhibition	no inhibition	

Take home message (IV)

- If six relatively simple screening procedures are used, patients showing clinically relevant plasma levels of anticoagulants can be identified.