

Hemostatic disturbances and methods for their correction



Методическое пособие для подготовки к практическим занятиям
общая хирургия (3 курс)
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3. Methods for correction of hemostatic disturbances
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7. Perioperative management of antithrombotic drugs



Blood coagulation

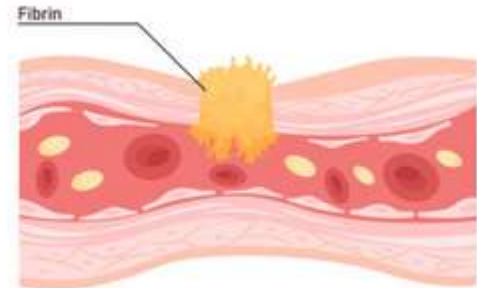
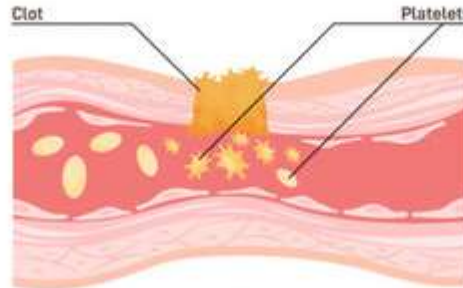
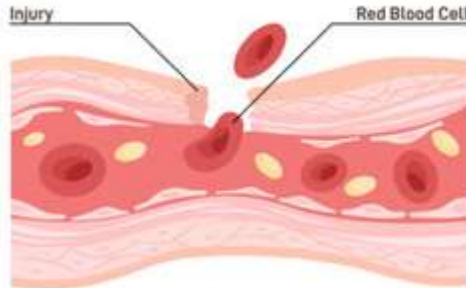
The blood coagulation system is a complex biological mechanism that protects the body from blood loss and systemic infection by forming a thrombus to stop bleeding from a damaged vessel and to prevent the hematogenous spread of infectious agents.

- **Cascade (classical) model of hemostasis:**

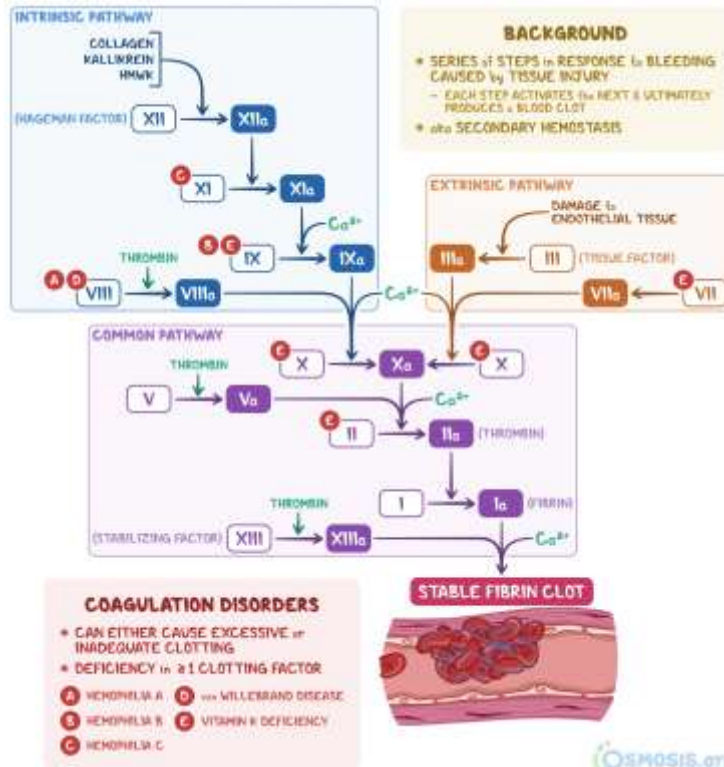
- Extrinsic pathway
- Intrinsic pathway
- Common pathway

- **Cell-based (modern) model of hemostasis:**

- Initiation
- Amplification
- Propagation
- Termination
- Lysis

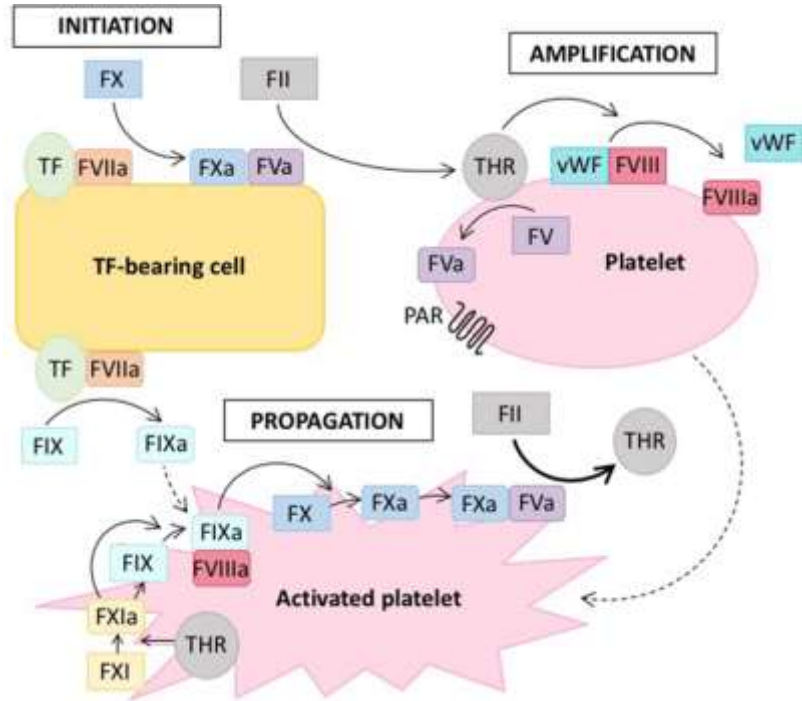


Cascade model of hemostasis



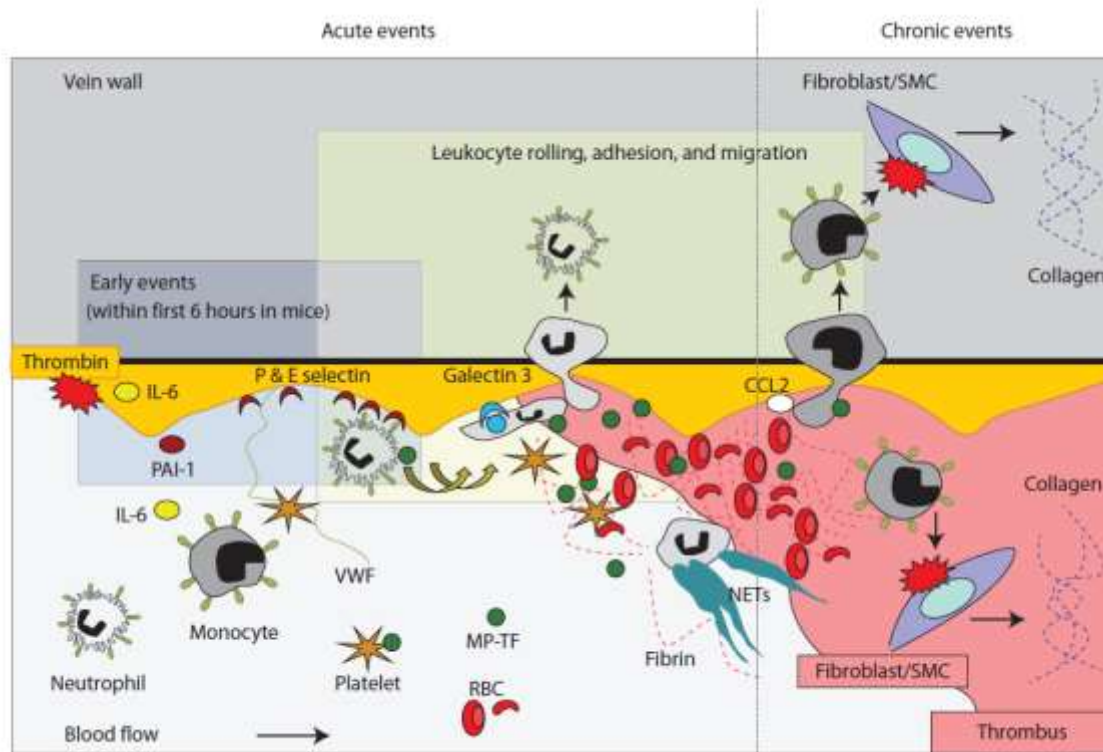
- Well reflects the process of clot formation in vitro and the deficiency of the corresponding coagulation factors
 - **Intrinsic pathway** (XII, XI, IX, VIII, high-molecular-weight kininogen, and prekallikrein) – **APTT**
 - **Extrinsic pathway** (II, V, VII, X, fibrinogen) – **PT**
 - **Common pathway** (fibrinogen) – **TT**
- Does not explain clinical phenomena:
 - Prolongation of APTT in the deficiency of FXII can increase the risk of both bleeding and thrombosis
 - Prekallikrein and high-molecular-weight kininogen deficiency do not increase the risk of bleeding
 - FXI deficiency does not increase the risk of bleeding
 - With a deficiency of FVIII and FIX, the extrinsic coagulation pathway does not compensate for the hemostatic system
 - With a deficiency of FVII, the intrinsic coagulation pathway does not compensate for the hemostatic system

Cell-based model of hemostasis



- Considers the interaction of cells during blood coagulation.
- Considers the role of platelets, their membranes, and receptors.
- Explains the clinical features of individual hemostatic disorders (deficiency of FXII and FXI).
- Explains changes reflected in global hemostasis tests.
- Key points:
 - **Tissue factor** is a transmembrane protein expressed by all cells except intact endothelial cells and activates FVII upon contact.
 - **FX** is a key player in all phases of coagulation.
 - **Thrombin** is produced at all stages, but its maximum production occurs during the propagation phase, when its amount exceeds that required for clot formation.
 - **Factor XI** is involved in the formation of the "thrombin burst," the propagation of thrombosis, and differentiates between physiological and pathological thrombus formation.
 - Tenase (FIXa + FVIIIa + Ca²⁺) and prothrombinase (FXa + FVa + Ca²⁺) complexes acquire the correct spatial organization on the membranes of activated platelets.

Cell-based model of hemostasis



Other participants in thrombus formation and evolution:

- Endothelial cells
- Neutrophils
- Neutrophil Extracellular Traps
- Microparticles
- Monocytes and macrophages
- Mast cells
- T-lymphocytes
- Fibroblasts
- Smooth muscle cells



Methods of hemostasis assessment: a survey



- Do you bruise easily?
- How often do you get nosebleeds?
- Have you experienced significant bleeding after minor injuries or cuts?
- How often do your gums bleed?
- Have you ever had intramuscular hemorrhages? If so, what caused them?
- Have you had a tooth extraction? If so, how long did the bleeding last?
- Have you had any surgery? If so, what was the cause?
- Have you had significant bleeding in the postoperative period?
- Have you received a blood transfusion or blood component transfusion for this reason?
- Do you experience heavy menstrual bleeding?
- Have you ever been pregnant or given birth?
- Have you experienced heavy bleeding after childbirth or abortion? If so, have you received a blood or blood component transfusion for this reason?
- List the medications you are taking.
- Are you taking hormonal contraceptives or hormone replacement therapy?
- Do you have any liver, kidney, or blood diseases?
- Have you had thrombosis?
- Have any of your relatives experienced excessive bleeding after tooth extractions, surgeries, or childbirth?



Methods of assessing hemostasis: physical examination

- **Thrombotic syndrome:**

- **Arterial thrombosis** (ischemia)
 - Intense pain
 - Paleness, mottling
 - Hypothermia
 - Volume loss
 - Impaired function
 - Necrosis (rapid)
- **Venous thrombosis** (plethora)
 - Moderate pain (distension)
 - Cyanosis
 - Hyperthermia
 - Volume increase, edema
 - Impaired function
 - Necrosis (slow)
- **Microcirculatory thrombosis:**
 - Multiple organ failure

- **Hemorrhagic syndrome:**

- **Hematoma type** (subcutaneous, intramuscular, intermuscular, retroperitoneal hematomas, hemarthrosis, hemoperitoneum, hemothorax, hemopericardium, intracranial hematomas)
- **Petechial-purpuric type** (petechiae and ecchymoses on the skin and mucous membranes, bleeding from hollow organs: nosebleeds, gastrointestinal bleeding, uterine bleeding, hematuria)
- **Mixed type**
- **Vasculitic-purpuric type** (hemorrhagic papular rash with possible necrosis)



Methods of assessing hemostasis: physical examination

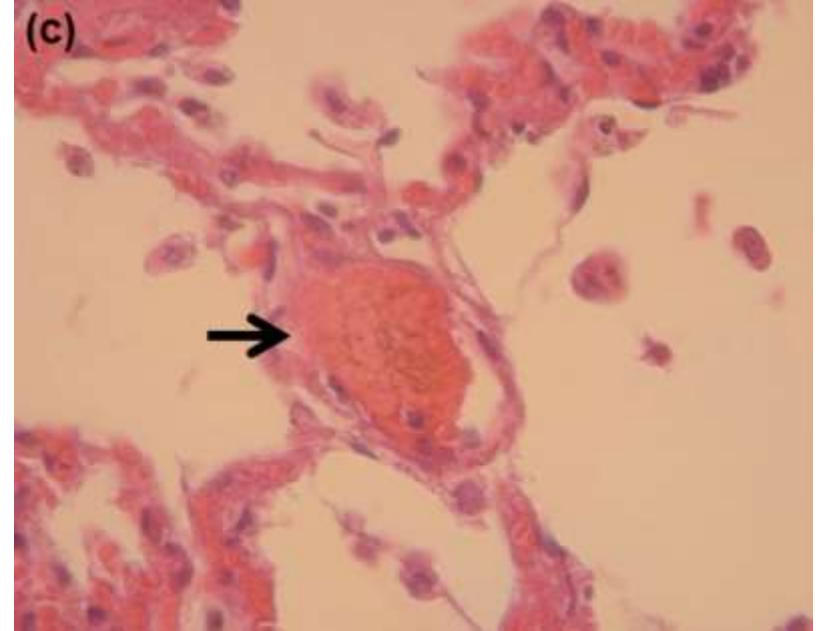
**Arterial thrombosis
with gangrene**



Venous thrombosis



Microvascular thrombosis in kidney



Methods of assessing hemostasis: physical examination

Hemarthrosis in hemophilia



Ecchymosis in thrombocytopenia



Purpura in vasculitis



Laboratory tests

- Screening tests:

- Activated partial thromboplastin time
 - Prothrombin time
 - International normalized ratio
 - Fibrinogen
 - D-dimer
 - Anti-Xa activity
 - Antothrombin-3 activity
- Show HYPO but not HYPER coagulation**

- Global tests:

- Thrombin generation test
 - Thromboelastography
 - Thrombodynamics
- Show HYPO and HYPER coagulation**

- Special tests:

- Factors V, VIII, IX, XI, XII, XIII, and vWF activity;
- Platelet function: spontaneous and induced platelet aggregation, detection of antibodies to the heparin/TF-4 complex;
- Fibrinolysis: plasminogen, antiplasmin, tissue plasminogen activator, plasminogen activator inhibitor-1;
- Proteins C and S;
- Coagulation inhibitors: antibodies to factors VIII and IX, antibodies to vWF, lupus anticoagulant;
- Coagulation system activation markers: thrombin-antithrombin complex, prothrombin fragments 1+2, fibrinopeptides A and B;
- Genetic defects: hemophilia A and B, von Willebrand disease, FVL, FIIG20210A, etc.



Prothrombin test

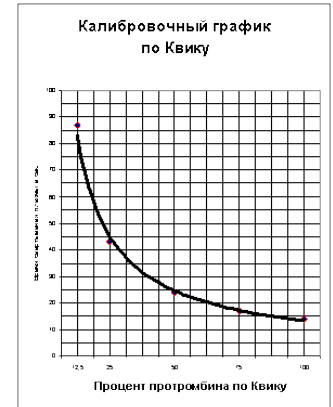
- Factors II, V, VII, X, and fibrinogen
- Extrinsic coagulation pathway
- Addition of excess tissue thromboplastin to citrated plasma
- Interpretation:

- Prothrombin time (11-14 sec): depends on the reagents' activity

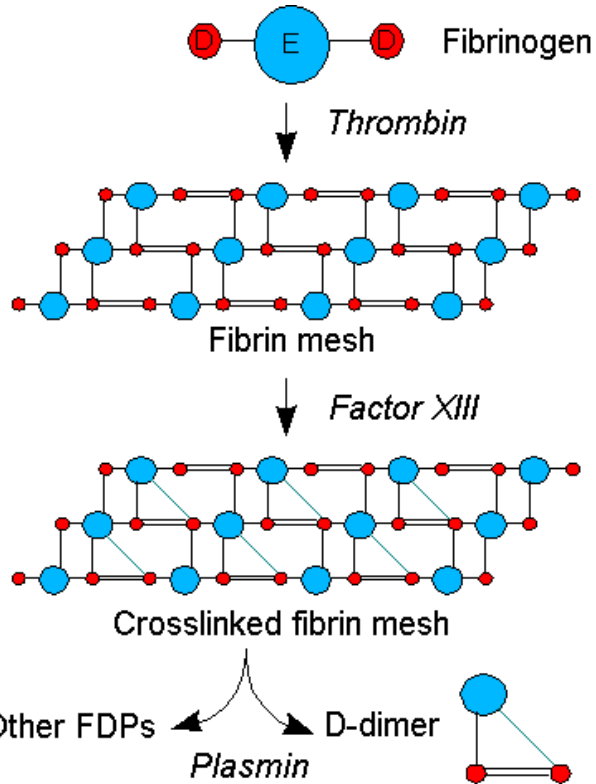
- Prothrombin (index) ratio (80-120%): $\frac{PT (control)}{PT (patient)} * 100\%$

- Prothrombin by Quick (80-140%): corresponds to the calibrated curve

- INR (0,8-1,2): $\left[\frac{PT (patient)}{PT (control)} \right]^{ISI}$



D-dimer



- A product of lysis of cross-linked fibrin strands, resulting in:
 - Thrombinemia
 - Factor XIII activity
 - Plasmin activity
- Sensitivity for thrombosis at any location is high: 97%
- Specificity for thrombosis at any location is very low: 35%
- Increases in various conditions (inflammation, trauma, surgery, cancer, pregnancy, etc.)
- **An elevated value cannot confirm thrombosis and is therefore not used for screening or diagnosis**
- **A normal value can rule out thrombosis if there is clinical suspicion**



Standard coagulological tests



- APPT
- PT
- Prothrombin by Quick
- INR
- TT
- Fibrinogen

} Hypocoagulation

- D-dimer (optional)
- Antithrombin 3 activity (optional)
- Protein C and S activity (optional)

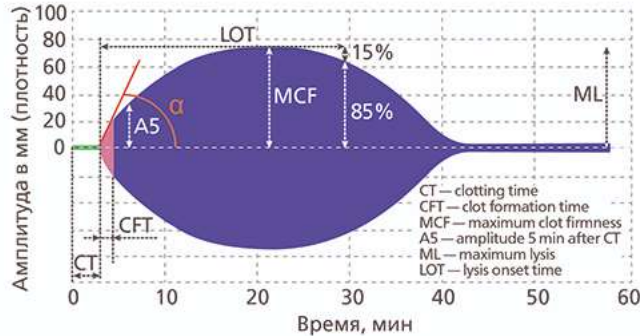
— Thrombosis
} Hypercoagulation



Global assays

Provide information on general changes in the hemostasis system (hypo-, normo-, hypercoagulation) without specifying the causes and mechanisms

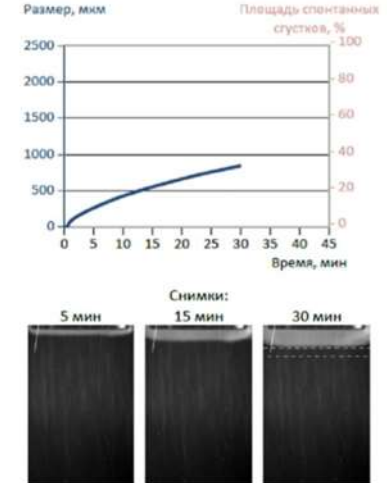
TEG, ROTEM (Viscoelastic tests)



Thrombin generation test



Thrombodynamic



Methods of hemostasis correction

• Hypercoagulation and thrombosis

- **Unfractionated heparin (UFH):** works via AT-3 and heparin cofactor-2
- **Low molecular weight heparins (LMWH):** work via AT-3 (enoxaparin, dalteparin, nadroparin, bemiparin, parnaparin)
- **Fondaparinux (synthetic pentasaccharide):** works via AT-3
- **Vitamin K antagonists:** disrupt the synthesis of active forms of vitamin K-dependent coagulation factors (II, VII, IX, X) and the anticoagulant system (proteins C and S) (warfarin)
- **Direct oral anticoagulants (DOACs):** directly block coagulation factors Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran)
- **Natural anticoagulants:** concentrate of AT-3, protein C, thrombomodulin (including recombinant)

• Hypocoagulation and bleeding

- **Fresh frozen plasma (FFP):** all coagulation and anticoagulation factors
- **Cryoprecipitate:** FVIII, FXIII, vWF, fibrinogen, fibronectin (hemophilia A, hypofibrinogenemia)
- **Prothrombin complex concentrate (PCC):** FII, FVII(a), FIX, FX (vitamin K-dependent coagulation factor deficiency, hemophilia B)
- **Recombinant FVIIa**
- **Individual coagulation factor concentrates**
- **Protamine sulfate:** antidote for UFH/LMWH
- **Phytomenadione (synthetic vitamin K1):** antidote for VKA
- **Idarucizumab:** antidote for dabigatran
- **Andexanet alfa:** antidote for rivaroxaban, apixaban, endoxaban
- **Cirrapantag:** universal antidote for anticoagulants
- **Platelet concentrate:** thrombocytopenia, thrombocytopathy



Hypocoagulation syndromes



- Thrombocytopenia – decreased platelet count $<150 \times 10^9$ cells/L
 - Abnormal production (aplastic, drug-induced, tumor-related, etc.)
 - Increased destruction (immune)
 - Abnormal distribution (splenomegaly)
 - Hereditary
- Petechial-purpuric type of bleeding
 - Asymptomatic: $>100 \times 10^9$ cells/L
 - Hemorrhagic syndrome: $50-100 \times 10^9$ cells/L
 - Spontaneous hemorrhage: $<50 \times 10^9$ cells/L
 - Threatened bleeding: $<20 \times 10^9$ cells/L
- Normal coagulation parameters
- Treatment: determined by etiology
 - Splenectomy
 - Platelet concentrate transfusion for non-immune causes



Target platelet levels for invasive interventions

Surgery or other invasive procedure	Target platelet count
Dental cleaning, dental calculus removal	$>20-30 \times 10^9/l$
Tooth extraction (simple)	$>30 \times 10^9/l$
Tooth extraction (complex, surgical, molar teeth)	$>50 \times 10^9/l$
Regional anesthetic nerve block for tooth extraction	$>30 \times 10^9/l$
Lumbar puncture (elective)	$>50 \times 10^9/l$
Lumbar puncture (emergency)	$>20 \times 10^9/l$
Spinal anesthesia	$>50 \times 10^9/l$
Epidural anesthesia	$>80 \times 10^9/l$
Central line placement	$>20 \times 10^9/l$
Gastrointestinal endoscopy without biopsy even with very low platelet counts possible.	
Gastrointestinal endoscopy with biopsy	$>20 \times 10^9/l$
Bronchoscopy, bronchial lavage	$>20 \times 10^9/l$
Bronchoscopy with transbronchial biopsy	$>50 \times 10^9/l$
Puncture of a joint	$>20 \times 10^9/l$
Liver biopsy, transjugular (preferred for thrombocytopenic patients)	$>10 \times 10^9/l$
Liver biopsy, transcutaneous	$>50 \times 10^9/l$
Bone marrow biopsy from iliac crest even with very low platelet counts possible.	
Other organ biopsies/punctures	$>50 \times 10^9/l$
Minor surgery ¹	$>50 \times 10^9/l$
Minor surgery at a location where compression can be applied to stop bleeding	$>20 \times 10^9/l$
Major surgery ²	$>80 \times 10^9/l$
Neurosurgery	$>70-100 \times 10^9/l$
Surgery at posterior segment of eyeball	$>70-100 \times 10^9/l$

¹Minor surgeries are operations with a low risk of bleeding, including the majority of extremity operations.

²Major surgeries include abdominal or thoracic surgery and operations in regions that cannot be compressed in the case of postoperative bleeding.

*These target values were developed from experience with patients with platelet production disorders (e.g. MDS). There is no corresponding data for TTP patients.

The individual bleeding history should also be considered, e.g. whether a patient has already bled with the indicated platelet counts in the past or not



Hypocoagulation syndromes



- Vitamin K-dependent coagulation factor deficiency:
 - Liver failure
 - Nutritional vitamin K deficiency
 - Obstructive jaundice (fat-soluble vitamin malabsorption)
 - VKA therapy (warfarin), including overdose
- Hematoma-type bleeding (intracranial hemorrhage, retroperitoneal hematoma)
- Prolonged INR
 - Target value for VKA therapy: 2.0-3.0
- Treatment:
 - Phytomenadione
 - PCC
 - FFP (if other options are unavailable)



Hypocoagulation syndromes



- DOAC overdose
- The risk increases with:
 - Renal impairment (CrCl <50 ml/min)
 - Elderly age (>75 years)
 - Low body weight (<50 kg)
- Hematoma-type bleeding (more often GI bleeding, less often ICH compared to VKA)
- Prolonged PT with rivaroxaban therapy
- Prolonged APTT and TT with dabigatran therapy
- Treatment
 - Antidotes:
 - Idarucizumab – dabigatran
 - Andexanet alfa – rivaroxaban, apixaban, edoxaban
 - PCC
 - FFP (if other options are unavailable)



Hypocoagulation syndromes



- Hereditary hemophilias
 - **Hemophilia A** – FVIII deficiency – is an X-linked recessive familial disorder that predominantly affects males
 - **Hemophilia B** – FIX deficiency – is an X-linked recessive familial disorder that predominantly affects males
 - **Hemophilia C** – FXI deficiency – is an autosomal recessive disorder
- Hematoma-like bleeding disorder (hemarthrosis)
- Prolonged APTT
- Treatment:
 - Replacement therapy with FVIII or FIX concentrate
 - Cryoprecipitate for type A
 - PCC for type B
 - Recombinant FVIIa for threatened bleeding
 - FFP (if other options are unavailable)



Hypocoagulation syndromes



- Von Willebrand Disease
 - Type 1 – Quantitative deficiency of vWF with preserved structure
 - Type 2 – Qualitative abnormalities of vWF
 - Type 3 – Total deficiency of vWF
- Mixed bleeding disorder (vWF + factor VIII complex)
- Prolonged APTT
- Treatment:
 - Replacement therapy with vWF concentrate
 - Cryoprecipitate
 - FFP (if other options are unavailable)
 - Desmopressin (stimulates vWF release from the endothelium)



Hypercoagulation syndromes

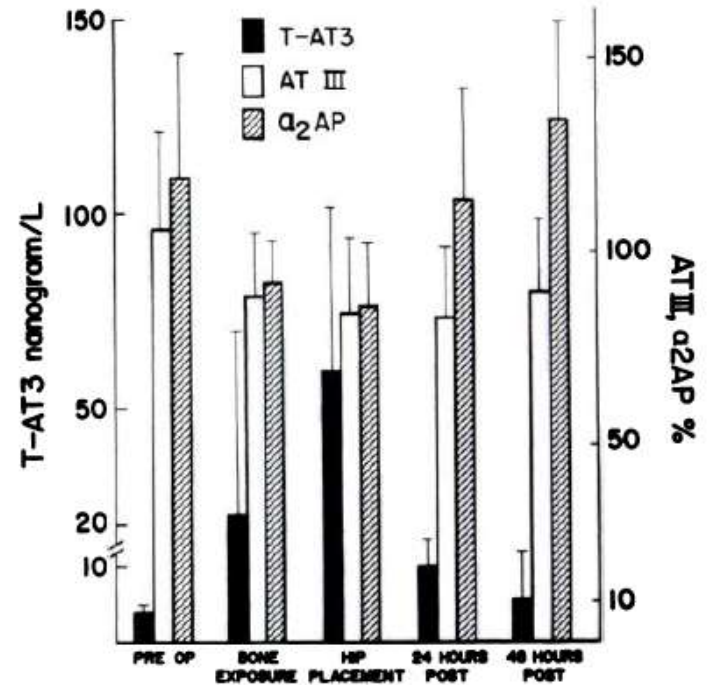


- Surgery
- Malignancy
- Pregnancy
- Combined oral contraceptives
- Infection, sepsis
- Autoimmune diseases
- Antiphospholipid syndrome
- Hereditary thrombophilia
- Hyperhomocysteinemia
- Heparin-induced thrombocytopenia

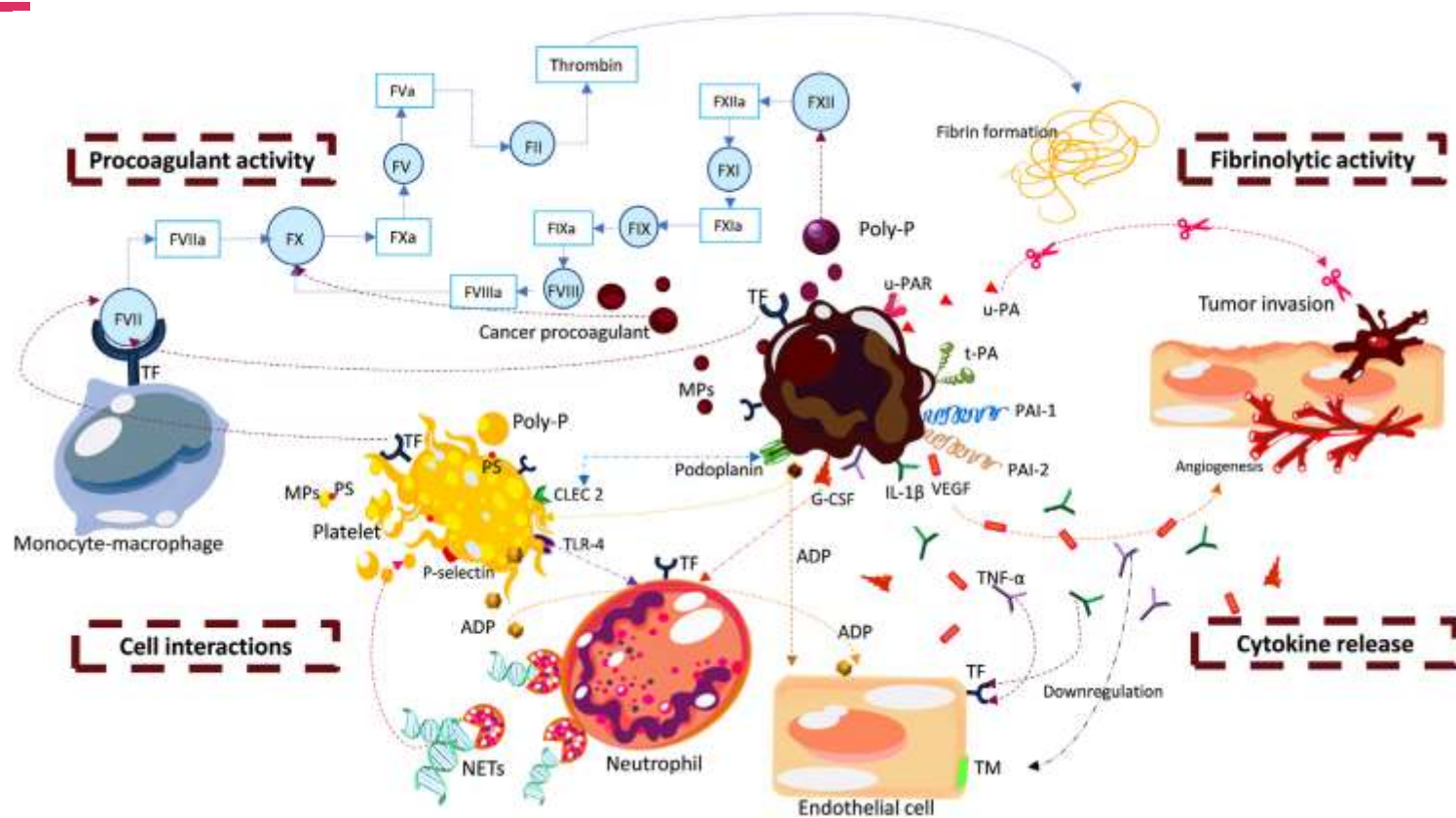


Surgery

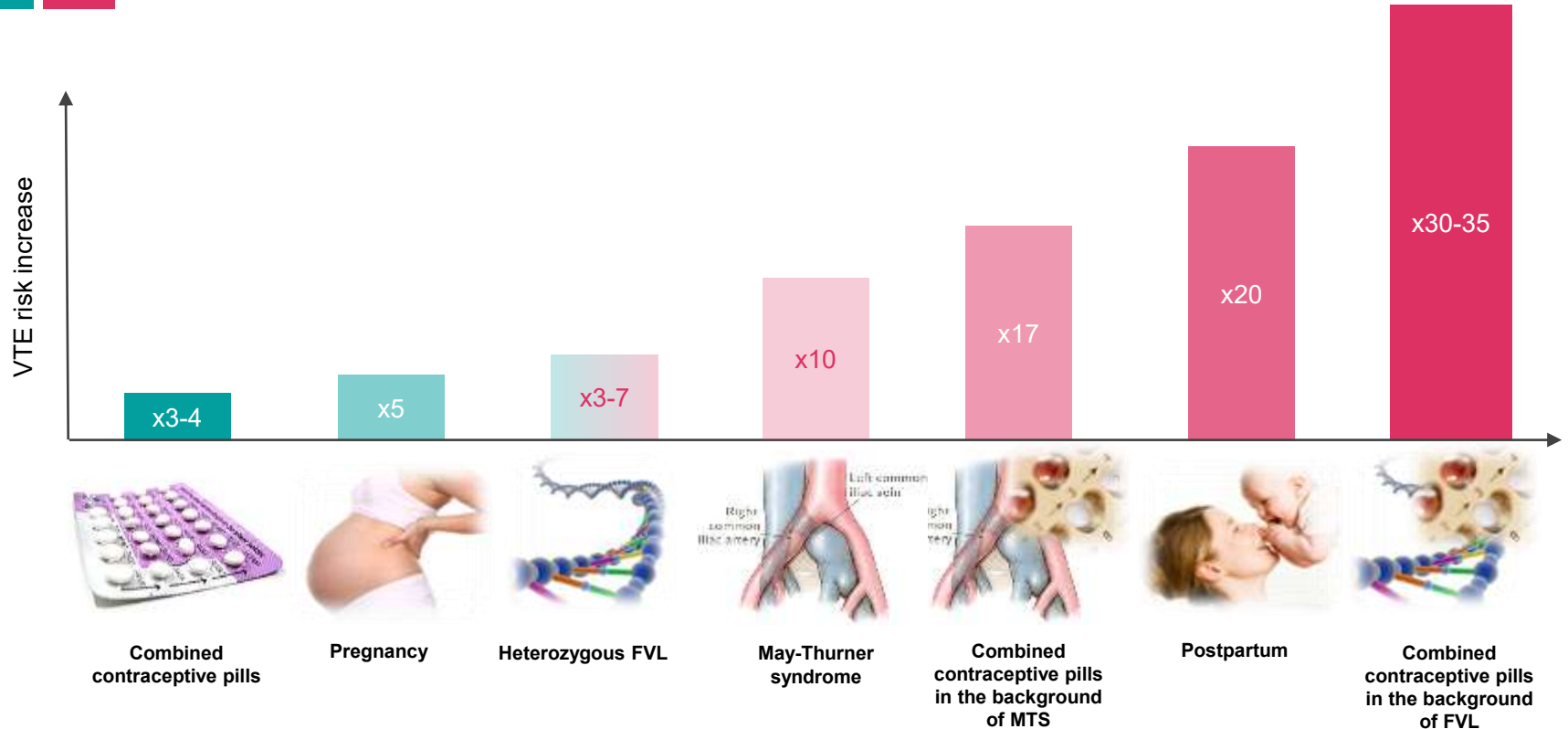
- Surgical trauma causes significant changes in the hemostasis system:
 - Increased levels of active coagulation factors: IX, X, XI, XII
 - Increased levels of thrombus formation markers: thrombin-antithrombin, plasmin-antiplasmin complexes, D-dimer, prothrombin fragments 1+2
 - Decreased activity of the anticoagulation and fibrinolytic system: AT-3, alpha-2-antiplasmin, tissue plasminogen activator, most likely due to their active consumption



Malignancy



Estrogen-related conditions



Antiphospholipid syndrome

Clinical Criteria	Laboratory Criteria
<u>1. Vascular thrombosis</u> - Venous, arterial or microvascular; - Confirmed by objective validated criteria; - No evidence of inflammation in vessel wall.	1. Lupus anticoagulant present in plasma on ≥ 2 occasions, at least 12 weeks apart.
and/or	and/or
<u>2. Pregnancy morbidity</u> - ≥ 1 unexplained fetal death ≥ 10 th week of gestation or; - ≥ 1 premature birth < 34 th week of gestation because of: ° Eclampsia or severe pre-eclampsia ° Features of placental insufficiency; - ≥ 3 unexplained consecutive abortions < 10 th week of gestation.	2. Anticardiolipin antibody IgG and/or IgM in serum or plasma, present in medium or high titer (> 40 GPL or MPL, or > 99 th percentile), measured by a standardized ELISA on ≥ 2 occasions, at least 12 weeks apart.
	and/or
	<u>3. Anti-$\beta 2$-glycoprotein I antibody IgG and/or IgM in serum or plasma, present in titer > 99th percentile, measured by a standardized ELISA on ≥ 2 occasions, at least 12 weeks apart.</u>

Abbreviations: ELISA, enzyme-linked immunosorbent assay; GPL, IgG phospholipid units; MPL, IgM phospholipid units.

- **Screen:** prolonged APTT/dRVVT
- **Confirm:** shortened by phospholipid excess
- **Mix:** no changes with pooled normal plasma

APS = 1 clinical + 1 laboratory (confirmed with interval of 12 weeks)



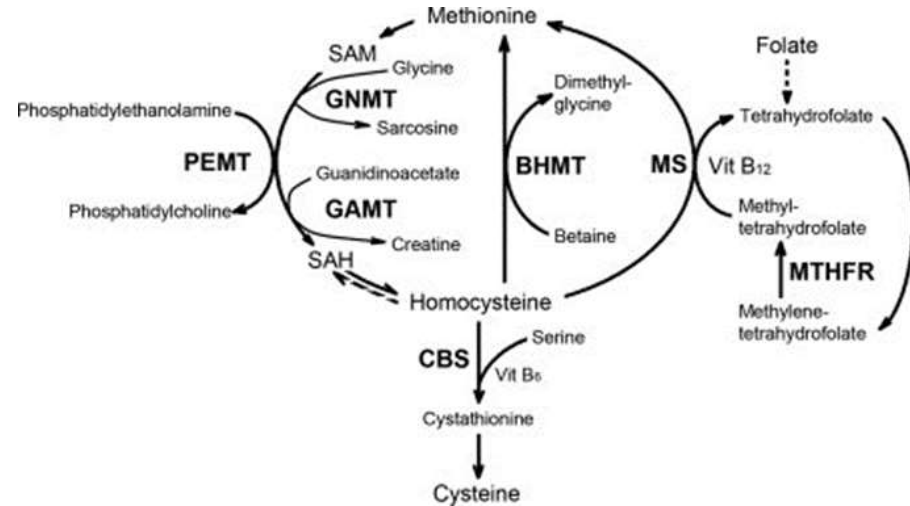
Hereditary thrombophilia

Type	% in population	% among VTE patients	VTE risk increase
AT-3 deficiency (heterozygous)	0,02	1	10-30
Protein C deficiency (heterozygous)	0,2-0,5	1-3	10
Protein C deficiency (homozygous)	-	-	Very high
Protein S deficiency (heterozygous)	0,1-0,7	1-2	8
Protein S deficiency (homozygous)	-	-	Very high
FVL (heterozygous)	2-15	10-20	3-7
FVL (homozygous)	0,06-0,25	-	80
FII G20210A (heterozygous)	1-2	3-5	3-7
FII G20210A (homozygous)	Rare	Rare	10-20
FVL + FII G20210A (heterozygous)	Rare	Rare	10-20
Non-0 blood group	55-57	75	2



Hyperhomocysteinemia

- Homocysteine is an intermediate product of the amino acid metabolism of cysteine and methionine:
 - Hereditary defect of enzyme systems
 - Deficiency of vitamins B6, B12, and folate
- Hyperhomocysteinemia increases the risk of arterial and venous thrombosis by 2-4 times, especially in individuals under 69 years old:
 - Toxic effects on the endothelium,
 - Impaired synthesis of vasodilators and prostacyclin,
 - Increased platelet aggregation,
 - Activation of TF, FV, and inactivation of tPA.
- MTHFR is a key enzyme in homocysteine metabolism.
 - The C677T polymorphism results in the synthesis of a heat-labile form with reduced activity, leading to increased homocysteine levels.
 - C677T MTHFR does not significantly increase the risk of venous thromboembolism: 1.38 (95% CI, 0.98–1.93)



Degree by Kang (1992)

Mild: 15-30 mmol/L

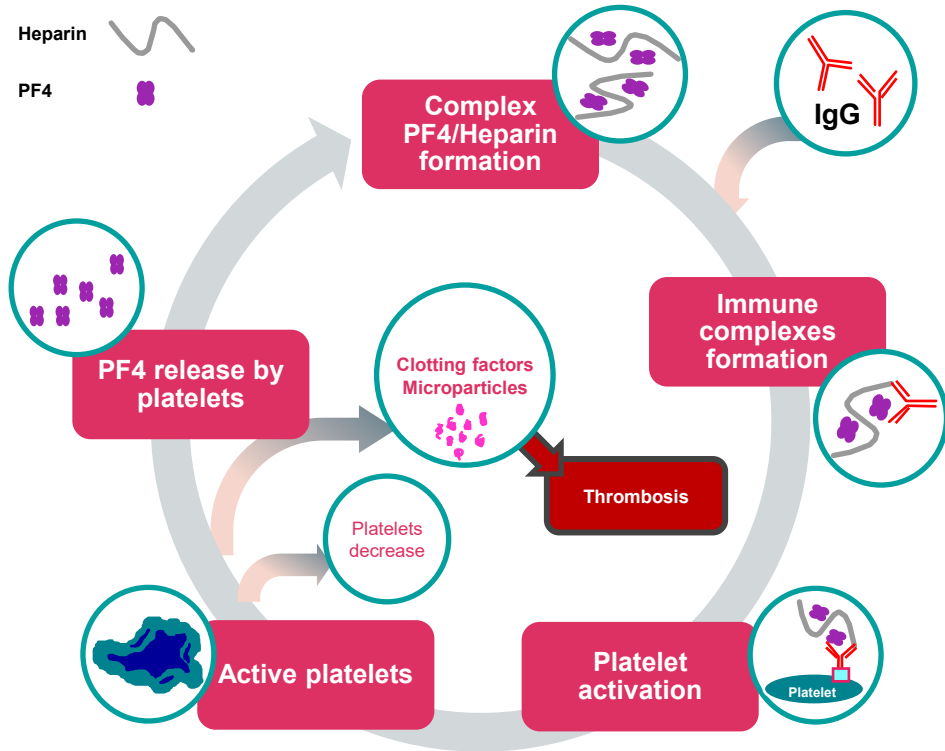
Moderate: 30-100 mmol/L

Severe: >100 mmol/L



Heparin-induced thrombocytopenia

- **Type 1 (non-immune):** a benign drug-induced reduction in platelet count in response to heparin administration.
- **Type 2 (immune):** production of antibodies to the heparin/PF4 complex, which activate platelets, leading to uncontrolled aggregation, thrombocytopenia, and the development of progressive thrombotic syndrome.
 - The thrombotic process is triggered and intensified in response to anticoagulant use.
 - With heparin administration, the primary concern is thrombosis, not bleeding.
 - The thrombotic process affects both venous and arterial blood vessels and often has an atypical location.
 - Platelet transfusion significantly increases the risk of thrombosis.
 - Discontinuation of heparin not only fails to reduce the risk of thrombosis but also provokes its further progression.

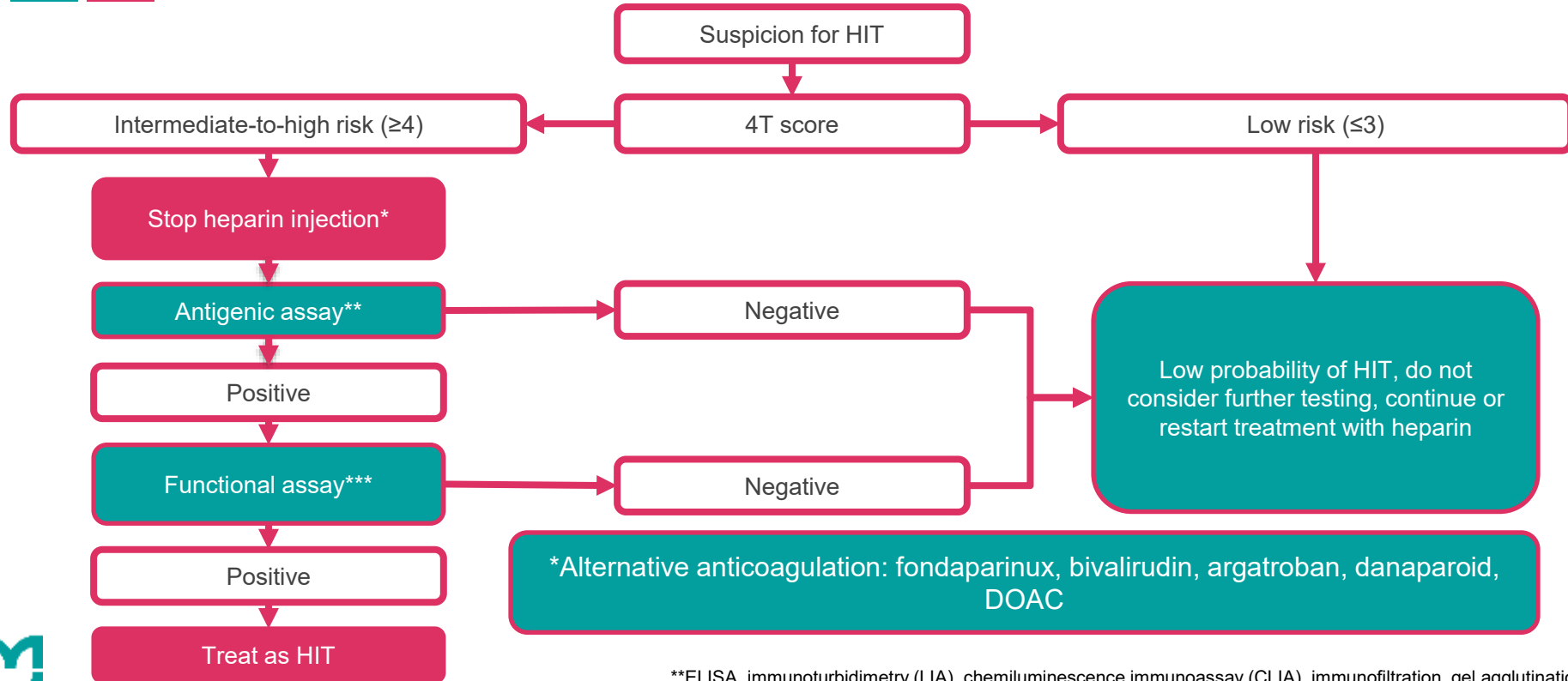


4T score

Variable	Score		
	2	1	0
Acute Thrombocytopenia	Platelet count decrease of >50% and nadir $\geq$ 20,000/mm ³	Platelet count decrease of 30-50% or nadir 10,000-19,000/mm ³	Platelet count decrease of <30% or nadir of $\leq$ 10,000/ mm ³
Timing of onset	Day 5-10 or day 1 if recent heparin exposure	> Day 10 or unclear exposure	$\leq$ Day 4 with no recent heparin exposure
Thrombosis	New thrombosis of anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis	None
Other cause of Thrombocytopenia	None	Possible	Definite
Total score	High risk (6-8)	Intermediate risk (4-5)	Low risk (0-3)
Probability of HIT	64%	14%	<1%
* adapted from Cuker et al Blood 2012			



The approach for diagnosis and treatment

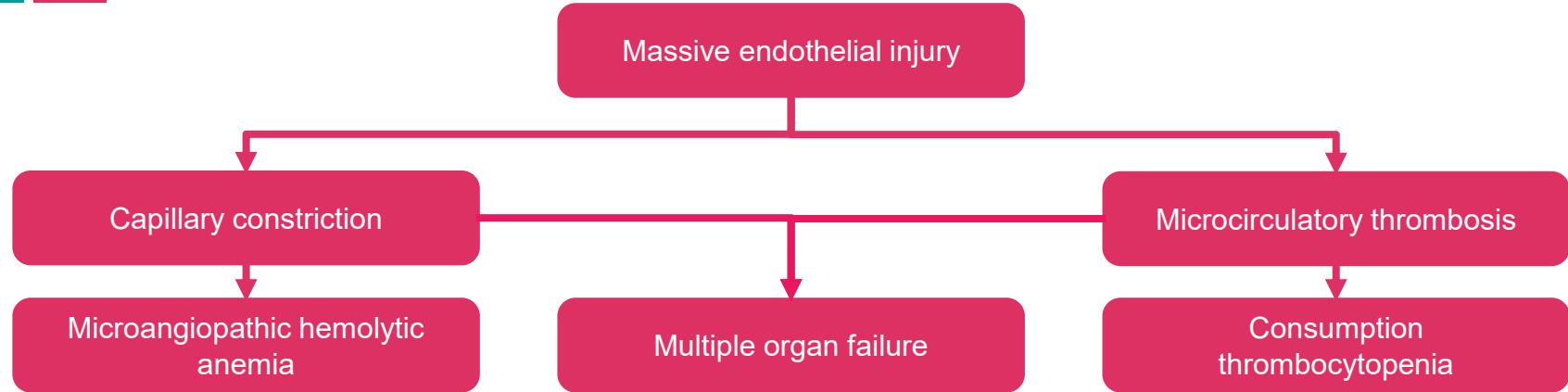


**ELISA, immunoturbidimetry (LIA), chemiluminescence immunoassay (CLIA), immunofiltration, gel agglutination

***serotonin release assay (SRA), heparin-induced platelet aggregation (HIPA), platelet aggregation, flow cytometry



TMA-associated syndromes



- **Thrombotic thrombocytopenic purpura (TTP):** congenital or acquired deficiency of the ADAMTS13 enzyme, responsible for the breakdown of vWF
- **Typical hemolytic uremic syndrome (HUS):** endothelial damage caused by Shiga toxin from Escherichia coli
- **Atypical hemolytic uremic syndrome (aHUS):** a heterogeneous group of disorders associated with genetic defects in proteins that limit complement activation via the alternative pathway
- **HELLP syndrome in pregnancy:** hemolysis, liver damage, and thrombocytopenia
- **DIC syndrome**
- **Catastrophic APS**



Disseminated Intravascular Coagulation syndrome



- A nonspecific pathological process characterized by widespread thrombus formation in the microcirculation with the development of organ and tissue hypoperfusion, manifested by multiple organ failure, and secondary depletion of the coagulation system (consumptive coagulopathy), which can lead to bleeding.
- Main causes:
 - Sepsis caused by various pathogens (bacterial, fungal, viral, parasitic);
 - All types of shock and terminal conditions;
 - Malignancy, especially acute promyelocytic leukemia, mucinous tumors (e.g., pancreatic, gastric, and ovarian cancer), and brain tumors;
 - Extensive trauma, including surgical trauma, especially with damage to the central nervous system;
 - Obstetric complications, including preeclampsia, retained stillbirth, acute fatty liver disease of pregnancy, and amniotic fluid embolism;
 - Intravascular hemolysis, including transfusion of incompatible blood.



DIC syndrome pathogenesis



- Exposure of procoagulants
- Coagulation
- Fibrinolysis
- Compensatory changes
 - Acute (decompensated) DIC syndrome
 - Chronic (compensated) DIC syndrome
- Target organ damage (TOD)



DIC-syndrome stages



- **Stage 1 (hypercoagulation)** includes activated blood coagulation, thrombus formation in the microcirculation, and impaired tissue perfusion;
- **Stage 2 (consumptive coagulopathy)** is characterized by a decrease in platelet count, decreased fibrinogen concentration, and depletion of coagulation factors;
- **Stage 3 (hypocoagulation and activated fibrinolysis)** is characterized by generalized fibrinolysis, accompanied by the formation of fibrin degradation products (FDP) and soluble fibrin-monomer complexes (SFMC), a critical decrease in fibrinogen levels (blood defibrination), and restoration of vascular patency;
- **Stage 4 (restorative)** includes the development of degenerative and necrotic changes in organs as part of multiple organ failure syndrome.



DIC syndrome signs

	Acute DIC-syndrome	Chronic DIC-syndrome
Underlying disease	Trauma, sepsis, malignancy, bleeding, transfusion of incompatible blood, any other procoagulant effects	A malignant neoplasm, especially a tumor of the pancreas, stomach, ovaries, or brain
Hemostatic changes	• Thrombocytopenia • Prolonged PT, APTT, TT • Decreased fibrinogen • Increased D-dimer, FDP, and SFMC • Decreased levels of FVII, FX, FV, and FII • Decreased levels of AT-3, proteins C, and S	• Mild or absent thrombocytopenia • Normal or slightly prolonged PT and APTT • Normal or slightly elevated fibrinogen levels • Elevated D-dimer levels
Complications	Bleeding more often	Thrombosis more often



DIC syndrome criteria

Criteria	Non-overt DIC syndrome		Overt DIC syndrome	
	Result	Score	Result	Score
Presence of a disease associated with DIC syndrome	Yes	2	-	-
Platelet count (cells x10 ⁹ /L)	<100	1	≥100	0
			50-100	1
			<50	2
Prolonged PT (sec)	>3	1	<3	0
			3-6	1
			≥6	2
Fibrinogen (g/L)	-	-	≥1	0
			<1	1
Elevated levels of a fibrin-related marker (e.g. D-dimer, FDPs). Use lab-specific cutoff values.	Increase	1	No increase	0
			Moderate increase	2
			Severe increase	3
Protein C activity	Decrease (<70%)	1	-	-
Antithrombin-3 activity	Decrease (<80%)	1	-	-
Thrombin-antithrombin complex	Increase	1	-	-
Plasmin-antiplasmin complex	Increase	1	-	-

≥5 scores: non-overt DIC syndrome, treatment should be started, and the calculation should be repeated daily to assess the dynamics

- <5 points: no overt DIC syndrome, but non-overt DIC syndrome cannot be ruled out. If there is clinical suspicion, it is advisable to repeat the calculation in 1-2 days.
- ≥5 points: overt DIC syndrome, treatment should be initiated, and the calculation should be repeated daily to assess the dynamics.



DIC syndrome treatment



- Eliminating the triggering factor;
- Anticoagulants to stop thrombus formation (non-overt DIC syndrome);
- Replenishment of hemostatic component deficiencies through blood transfusions (overt DIC syndrome);
- Inhibition of fibrinolysis according to strict indications (hyperfibrinolytic variant);
- Intensive care, correction of fluid-electrolyte and acid-base imbalances, gas exchange and hemodynamic disorders, anemia, hypoproteinemia, and maintenance of nutritional status.



Sepsis-induced coagulopathy

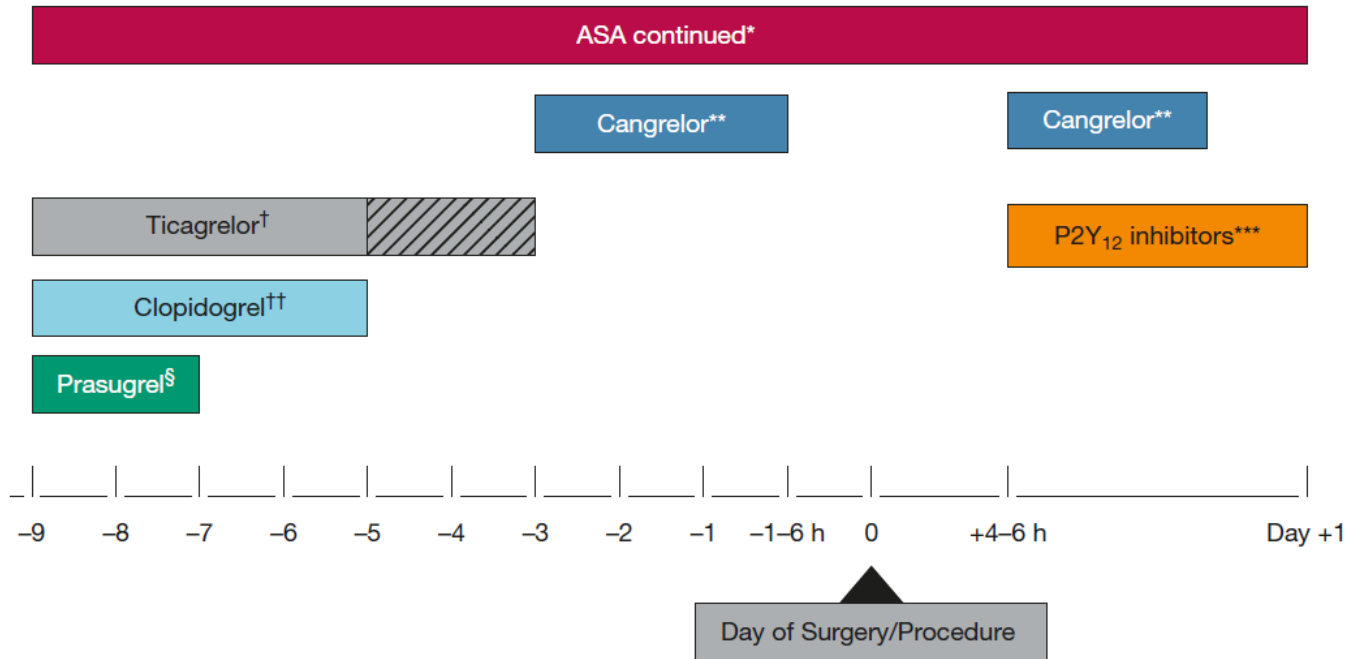
- Non-overt (laboratory) DIC syndrome in sepsis, reflecting microvascular thrombosis as the basis of multiple organ failure
- A short phase, when antithrombotic drugs may be useful: UFH, LMWH, AT-3 concentrate, protein C, thrombomodulin

Criteria	Result	Score
INR	$\leq 1,2$	0
	$>1,2$ до 1,4	1
	$>1,4$	2
Platelet count (cells $\times 10^9/L$)	≥ 150	0
	<150 до 100	1
	<100	2
SOFA score (Respiratory, Cardiovascular, Hepatic, and Renal components)	0	0
	1	1
	≥ 2	2

SIC: ≥ 4 scores AND ≥ 3 scores of INR and platelet count



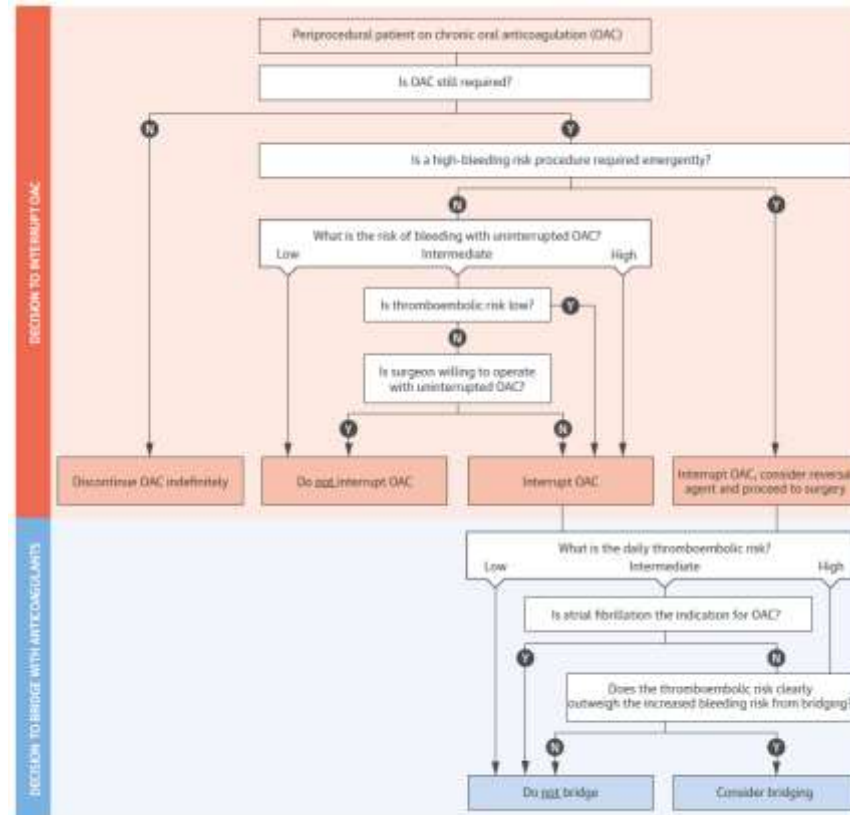
Perioperative management of antithrombotic drugs



*Based on surgery/procedure bleed risk assessment. **Routine use not suggested. If used, initiate within 72 hours from P2Y₁₂ inhibitor discontinuation at dose of 0.75 mg/kg/min; resume within 6 hours post-procedure for minimum of 48 hours and maximum of 7 days total. Very low quality data for antiplatelet bridging with glycoprotein IIb/IIIa inhibitors (e.g., eptifibatide, tirofiban). ***P2Y₁₂ inhibitors can be resumed within 24 hours post-procedure at a maintenance dose. †For ticagrelor, 3-5 day interruption ††For clopidogrel, 5 day interruption §For prasugrel, 7-10 day interruption.



Perioperative management of antithrombotic drugs



Thromboembolism risk assessment

Risk Category	Mechanical Heart Valve	Atrial Fibrillation	VTE
High (> 10%/y risk of ATE or > 10%/mo risk of VTE)	Mitral valve with major risk factors for stroke ^b Caged ball or tilting-disc valve in mitral/aortic position Recent (< 3 mo) stroke or TIA or other high-risk stroke situations ^c	CHA ₂ DS ₂ VASc score ≥ 7 or CHADS ₂ score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo and especially 1 mo) VTE Severe thrombophilia (deficiency of protein C, protein S or antithrombin; homozygous factor V Leiden or prothrombin gene G20210A mutation or double heterozygous for each mutation, multiple thrombophilias) Antiphospholipid antibodies Active cancer associated with high VTE risk ^a
Moderate (4%-10%/y risk of ATE or 4%-10%/mo risk of VTE)	Bileaflet AVR <i>with</i> major risk factors for stroke ^b	CHA ₂ DS ₂ VASc score of 5 or 6 or CHADS ₂ score of 3 or 4	VTE within past 3-12 mo Recurrent VTE Non-severe thrombophilia (heterozygous factor V Leiden or prothrombin gene G20210A mutation) Active cancer or recent history of cancer ^c
Low (< 4%/y risk of ATE or < 2%/mo risk of VTE)	Bileaflet AVR <i>without</i> major risk factors for stroke ^b	CHA ₂ DS ₂ VASc score of 1-4 or CHADS ₂ score of 0-2 (and no prior stroke or TIA)	VTE > 12 mo ago

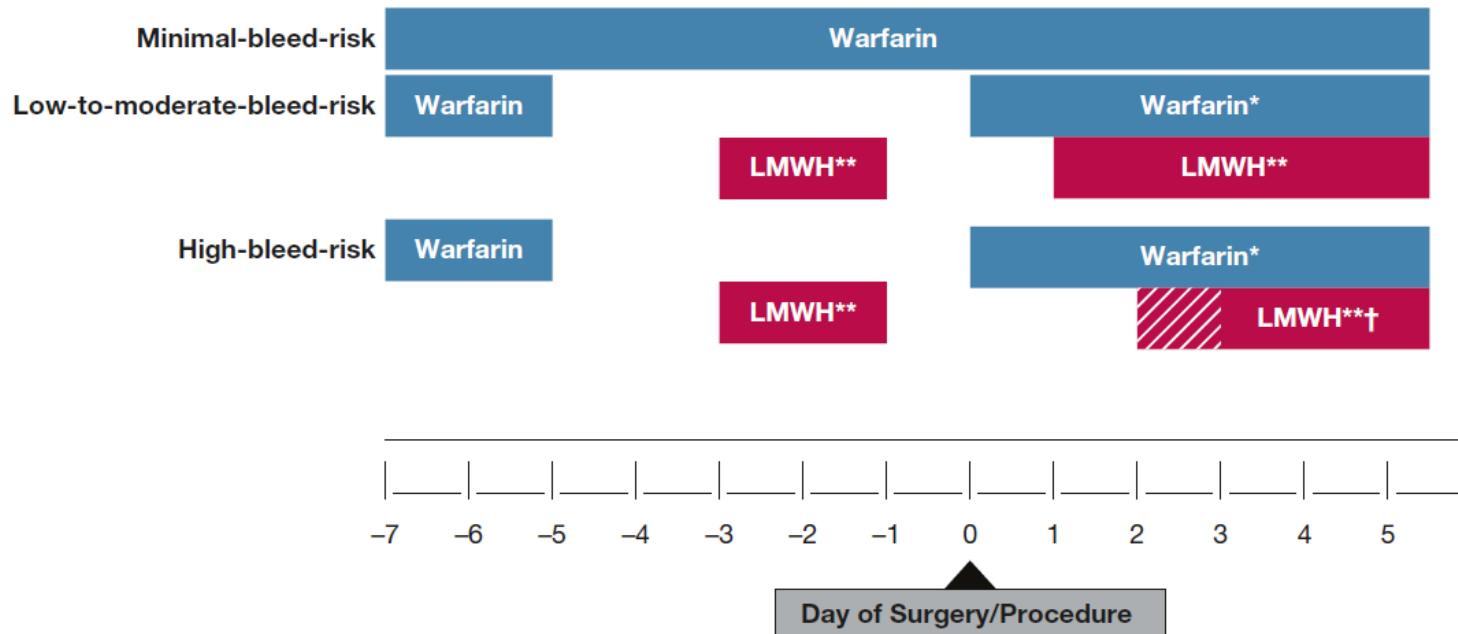


Bleeding risk assessment

High-bleed-risk surgery/procedure ^a (30-d risk of major bleed $\geq 2\%$)	Major surgery with extensive tissue injury Cancer surgery, especially solid tumor resection (lung, esophagus, gastric, colon, hepatobiliary, pancreatic) Major orthopedic surgery, including shoulder replacement surgery Reconstructive plastic surgery Major thoracic surgery Urologic or GI surgery, especially anastomosis surgery Transurethral prostate resection, bladder resection, or tumor ablation Nephrectomy, kidney biopsy Colonic polyp resection Bowel resection Percutaneous endoscopic gastrostomy placement, endoscopic retrograde cholangiopancreatography Surgery in highly vascular organs (kidneys, liver, spleen) Cardiac, intracranial, or spinal surgery Any major operation (procedure duration > 45 min) Neuraxial anesthesia^c Epidural injections
Low-to-moderate-bleed-risk surgery/procedure ^c (30-d risk of major bleed 0%-2%)	Arthroscopy Cutaneous/lymph node biopsies Foot/hand surgery Coronary angiography^d GI endoscopy $\pm$ biopsy Colonoscopy $\pm$ biopsy Abdominal hysterectomy Laparoscopic cholecystectomy Abdominal hernia repair Hemorrhoidal surgery Bronchoscopy $\pm$ biopsy
Minimal-bleed-risk surgery/procedure ^e (30-d risk of major bleed approximately 0%)	Minor dermatologic procedures (excision of basal and squamous cell skin cancers, actinic keratoses, and premalignant or cancerous skin nevi) Ophthalmologic (cataract) procedures Minor dental procedures (dental extractions, restorations, prosthetics, endodontics), dental cleanings, fillings Pacemaker or cardioverter-defibrillator device implantation



Warfarin bridging



*Warfarin can be resumed on the evening of procedure (D0) for most patients, or the day after procedure (i.e., D1) at the patient's usual maintenance dose.

**Bridging suggested for high thrombotic risk populations with full-dose, subcutaneous LMWH (e.g., enoxaparin, 1 mg/kg bid or 1.5 mg/kg daily or dalteparin, 100 IU/kg bid or 200 IU/kg daily), with the last dose given the AM of the day prior to the procedure (i.e., D-1) at half the total daily dose. †Low-dose LMWH (e.g., enoxaparin, 40 mg daily or dalteparin 5,000 IU daily) can be used for VTE prophylaxis for first 24-72 hours post-procedure, with full dose LMWH resumed 2-3 days post-procedure.



DOAC management

Direct Oral Anticoagulant	Procedure Bleeding Risk	Pre-Procedure DOAC Interruption						Surgery/Procedure (Day 0)	Post-Procedure Resumption*			
		Day -6	Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
Apixaban	High											
	Low/Mod											
Dabigatran (CrCl ≥ 50 ml/min)	High											
	Low/Mod											
Dabigatran (CrCl < 50 ml/min)	High											
	Low/Mod											
Edoxaban	High											
	Low/Mod											
Rivaroxaban	High											
	Low/Mod											

 No DOAC administered that day

*DOAC can be resumed ~24 hours after low/moderate-bleed-risk procedures, and 48-72 hours after high-bleed-risk procedures. In selected patients at high risk for VTE, low-dose anticoagulants (i.e., enoxaparin, 40 mg daily or dalteparin, 5,000 IU daily) can be given for the first 48-72 hours post-procedure.



List of abbreviations

ADP – adenosine diphosphate
AF - atrial fibrillation
APS – antiphospholipid syndrome
APTT – activated partial thromboplastin time
ASA – acetylsalicylic acid
AT-3 – antithrombin-3
DAMPs - damage-associated molecular patterns
DDU - D-dimer equivalent unit
DIC – disseminated intravascular coagulation
DNA – deoxyribonucleic acid
DOAC – direct oral anticoagulants
DVT - deep vein thrombosis
FDP – fibrin degradation products
FEU - fibrinogen equivalent unit
FFP – fresh frozen plasma
GPIb - glycoprotein Ib
GPVI - glycoprotein VI
HIT – heparin-induced thrombocytopenia
HK – high-molecular-weight kininogen
INR – international normalized ratio
ISS – international sensitivity index
LMWH – low molecular weight heparin
MCP-1 - monocyte chemotactic protein-1
MOD – multiple organ dysfunction
NET – neutrophil extracellular trap
NSAIDs – nonsteroidal anti-inflammatory drugs
PAI – plasminogen activator inhibitor
PAR - protease-activated receptors

PE - pulmonary embolism
PF4 - platelet factor 4
PL – phospholipids
PT – prothrombin time
PTI – prothrombin index
RNA - ribonucleic acid
SFMC - soluble fibrin-monomer complexes
SIC - sepsis-induced coagulopathy
SOFA - sequential organ failure assessment
TAFI – thrombin-activatable fibrinolysis inhibitor
TD – thrombodynamics
TEG – thromboelastography
TF - tissue factor
TF-MP – tissue factor-bearing microparticles
TFPI – tissue factor pathway inhibitor
TGT - thrombin generation test
TMA - thrombotic microangiopathy
TNF - tumor necrosis factor
tPA - tissue plasminogen activator
TT - thrombin time
TxA2 - thromboxane A2
UFH – unfractionated heparin
uPA - urokinase-like plasminogen activator
VKA – vitamin K antagonists
VTE – venous thromboembolism
vWF - von Willebrand factor
WHO – World Health Organization

