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ILLUSTRATED REVIEW

rpth research & practice in thrombosis & haemostasis

An illustrated review of bleeding assessment tools and common coagulation tests

Carolyne Elbaz MDCM, FRCPC[1] | Michelle Sholzberg MDCM, MSc, FRCPC[2,3]

[1]Department of Medicine, University of Toronto, Toronto, ON, Canada

[2]Departments of Medicine and Laboratory Medicine & Pathobiology, St. Michael's Hospital, Toronto and University of Toronto, Toronto, ON, Canada

[3]Li Ka Shing Knowledge Institute, Toronto, ON, Canada

Correspondence
Carolyne Elbaz, Department of Medicine, University of Toronto, 1007 - 30 Roehampton, Toronto, ON M4P 0B9, Canada.
Email: carolyne.elbaz@mail.mcgill.ca

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Abstract

Recognizing the complexity of coagulation tests and currently used anticoagulants, we developed this illustrated review on bleeding assessment tools and common coagulation screening tests. Quantitative bleeding assessment tools (BATs) are available to standardize the bleeding history and improve the pretest probability prior to coagulation testing. We describe use of BATs and the principles, indications, and limitations of the prothrombin time (PT)/International Normalized Ratio, activated partial thromboplastin time (APTT), and 50:50 mix. Use of these tests to identify coagulation factor deficiencies, specific and nonspecific inhibitors, coagulopathy of liver disease, disseminated intravascular coagulation, and commonly used anticoagulant medications are reviewed. Current literature suggests that unnecessary coagulation testing is rampant. The PT and APTT have astoundingly low sensitivity (1.0%-2.1%) for detection of clinically significant bleeding disorders. Thus, current guidelines recommend against the use of screening PT and APTT in preoperative patients undergoing noncardiac/vascular surgery.

KEYWORDS

bleeding disorders, clinical laboratory techniques, hemorrhage, International Normalized Ratio, thrombosis

Essentials

- Quantitative bleeding assessment tools standardize the bleeding history and improve the pretest probability of bleeding disorders prior to coagulation testing.
- Unnecessary coagulation testing is rampant.
- Thorough understanding of common hemostatic tests is essential for appropriate selection and interpretation of tests.

Bleeding Assessment Tools (BAT)

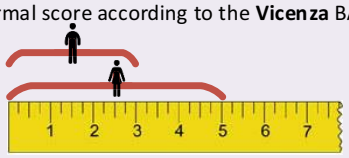
A bit about BATs...

The patient history is the most important tool in determining the pre-test probability of a bleeding disorder. Quantitative bleeding assessment tools (BATs) have thus been developed to standardize the bleeding history and guide appropriate testing to investigate bleeding disorders. Bleeding scores are based on symptom frequency and severity (i.e. need for surgical or medical attention).

The Vicenza BAT was validated in 2005 based on the ISTH provisional criteria for the diagnosis of Type 1 von Willebrand Disease (VWD).[13]

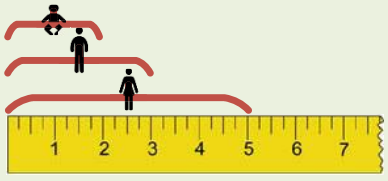
This BAT prioritizes bleeding symptoms that lead to medical attention and treatment of bleeding symptoms.

Normal score according to the **Vicenza** BAT



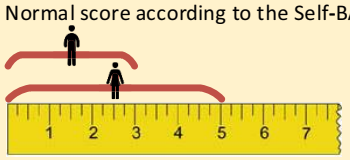
In 2010, the International Society of Thrombosis and Haemostasis (ISTH) BAT was developed.[7,14]

Normal score according to the **ISTH BAT**



BATs require expert administration (e.g. nurse or physician) Therefore, the **ISTH-BAT** was converted to a patient self administered BAT **(Self-BAT)**.[6]

Normal score according to the Self-BAT



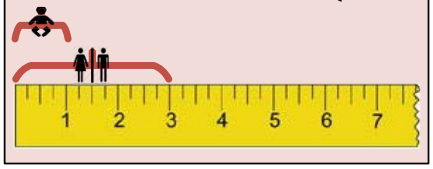
2005

2006

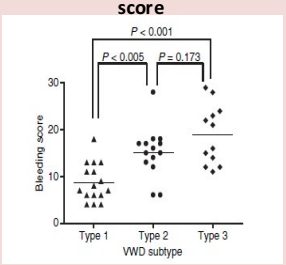
2010

The European Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD (**MCMDM-1 VWD BAT**)[2,17] was developed initially in 2006, and shortened in 2008 to allow for a short administration time. The Pediatric Bleeding Questionnaire (**PBQ**)[3] was then developed, adding pediatric-specific bleeding symptoms to the MCMDM1-VWD.

Normal score according to the **MCMDM-1 VWD** and **PBQ**



Condensed MCMDM-1 VWD BAT score



Bleeding score is higher with increasing VWD severity[2]

	Vicenza BAT[13]	Condensed MCMDM-1 VWD[2,17]	PBQ[3]	ISTH BAT[7,14]	Self BAT[6]
Sensitivity of a normal score to rule out the diagnosis of VWD (true positives/all positive tests)	69%	100%	83%	64%	78%
Specificity of an abnormal score to rule in the diagnosis of VWD(true negatives/all negative tests)	98%	87%	79%	99%	23%

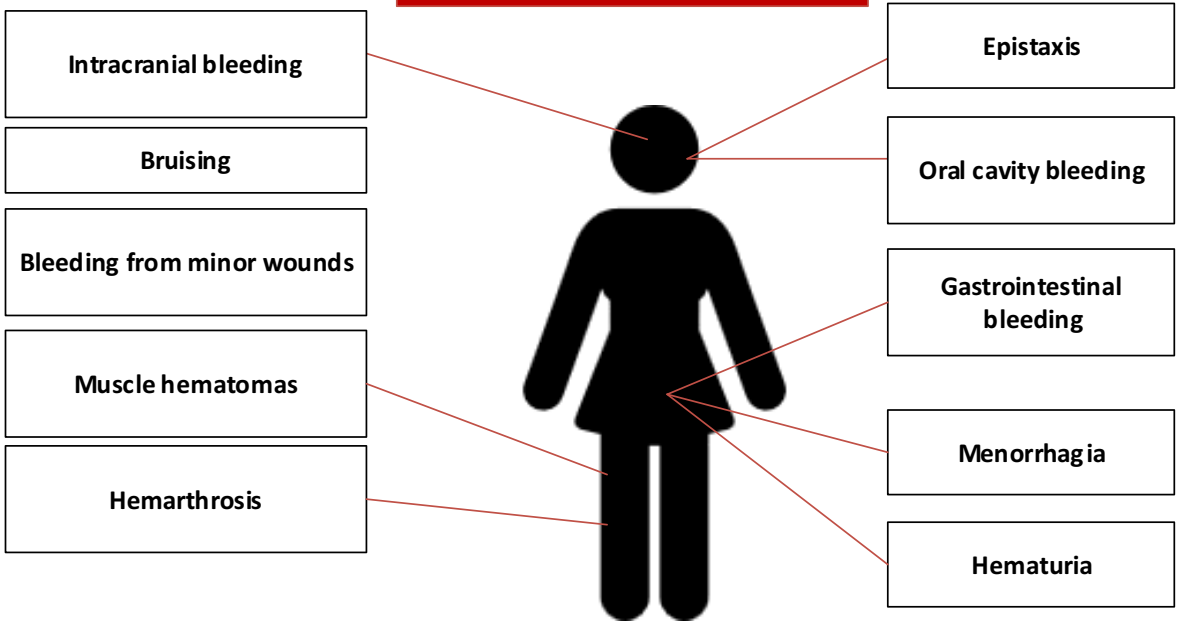
How to use the BAT

How BATs differ

There are many validated BATs. The following are some key distinctive features:
- The MCMDM-1 VWD and PBQ assign negative points for hemostatic challenges without bleeding complications (i.e. surgeries, deliveries, dental extractions).
- The ISTH BAT and PBQ evaluate pediatric bleeding symptoms in the "other bleeding" category (i.e. cephalohematoma, umbilical stump bleeding, cheek hematoma and conjunctival hemorrhage)
- The ISTH BAT assesses menorrhagia more comprehensively and is the only BAT that evaluates hematuria.

Bleeding symptom categories in the ISTH BAT

Spontaneous bleeding



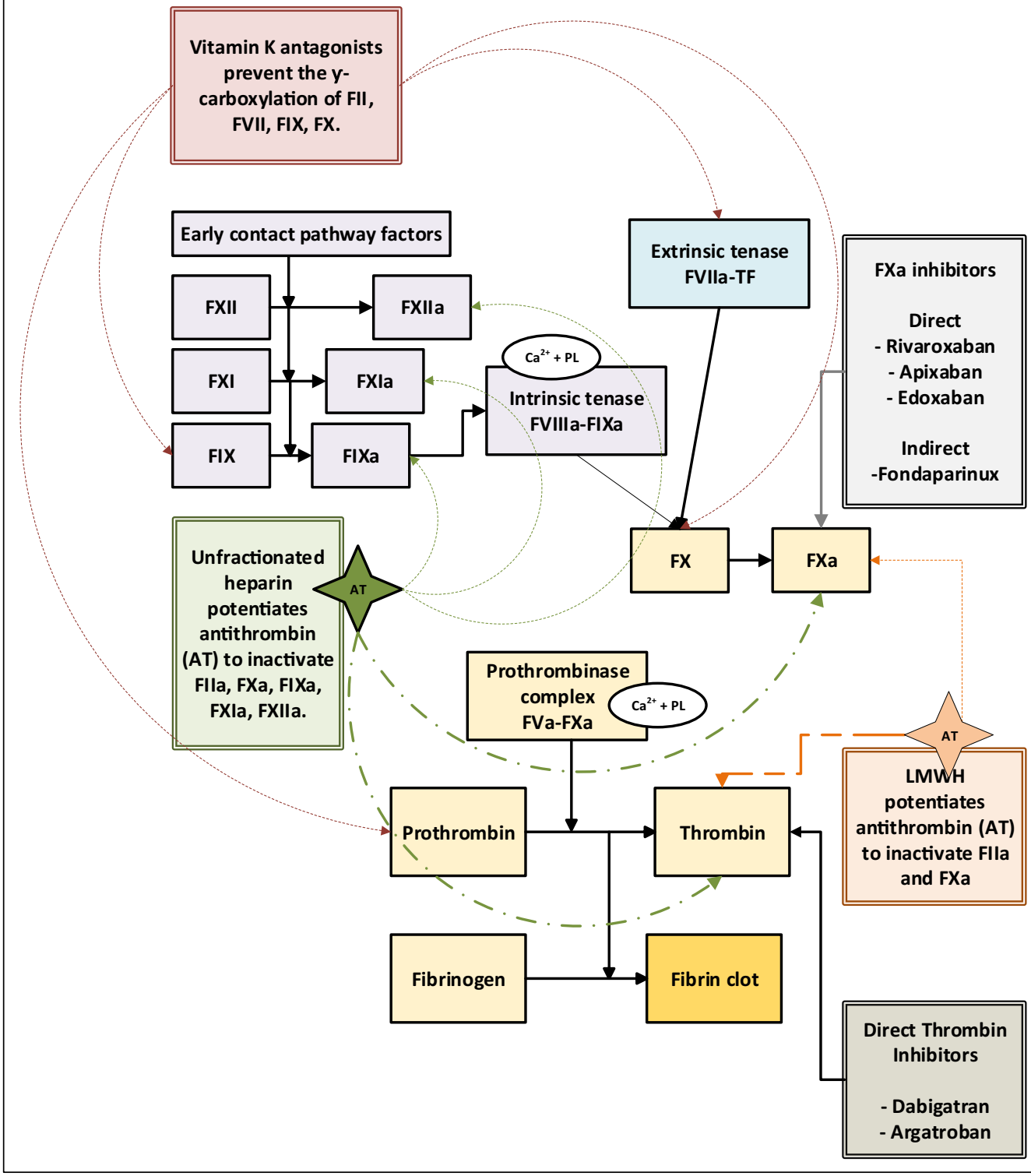
Bleeding after hemostatic challenges:

Tooth extraction | Post partum hemorrhage | Surgery

Did you know?

In a study using the Condensed MCMDM-1, ISTH BAT and PBQ to evaluate bleeding symptoms in 927 patients with excessive bleeding, the investigators found that history of hemarthrosis, post surgical bleeding and menorrhagia increased the likelihood of laboratory confirmed VWD. In addition, the number of bleeding symptoms increased the odds ratio for a VWD diagnosis.[16]

Coagulation cascade with sites of action of commonly used anticoagulants

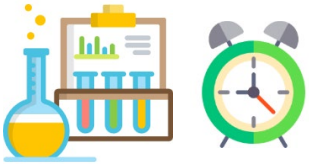


Prothrombin time (PT)
Quick's Time

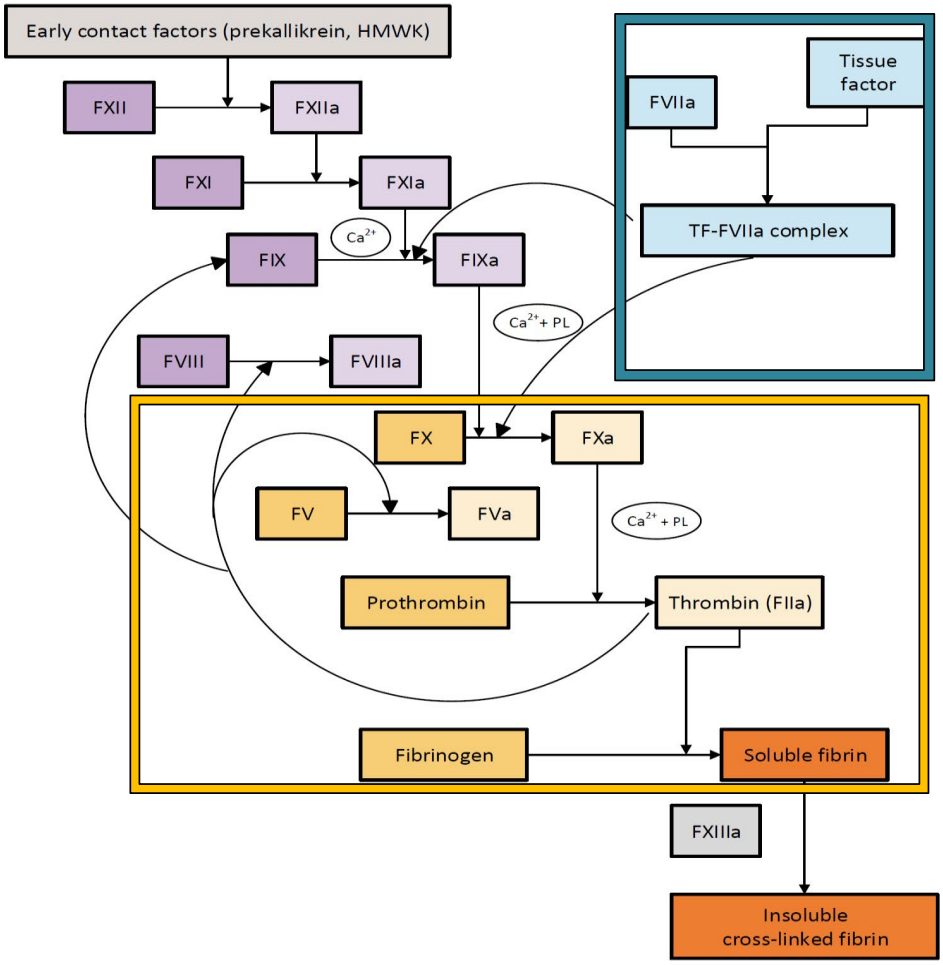
Collect sodium citrate tube

Centrifuge to obtain platelet poor plasma (PPP) and warm at 37°C

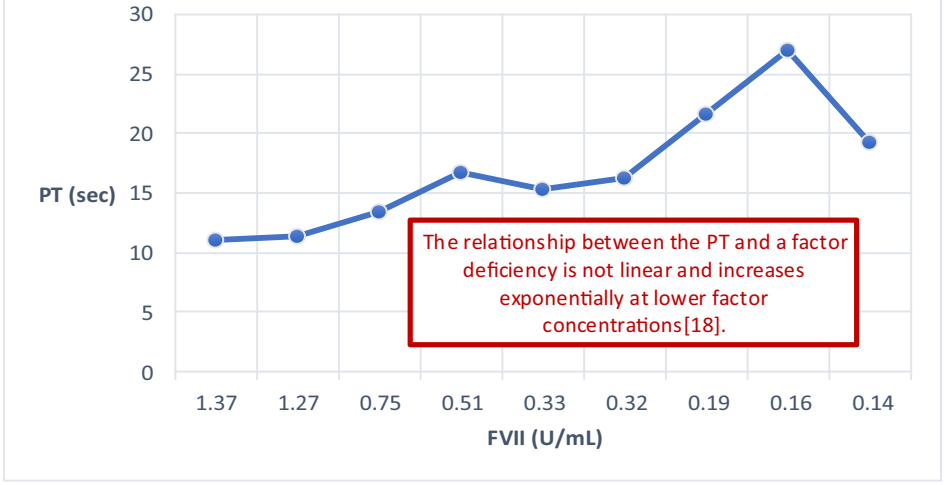
Combine with thromboplastin (contains phospholipids) and calcium chloride



Once fibrin strands are detected, the timer stops and the PT is reported in seconds.



The PT can assess for deficiencies or inhibitors of the **extrinsic pathway factors** (FVII) and **common pathway factors** (FX, FV, FII, fibrinogen)



Prothrombin time (PT)
International Normalized Ratio (INR)

If the PT is prolonged but the aPTT is not, consider :

1. Acquired deficiency of FVII
   - Early warfarin therapy
   - Early vitamin K deficiency
   - Early liver disease

2. Drugs : Direct Xa inhibitors (e.g., rivaroxaban, apixaban, edoxban, but typically prolong the aPTT too)[15]

3. Congenital deficiency of FVII

4. Specific inhibitors to FVII (exceptionally rare)

Did you know?

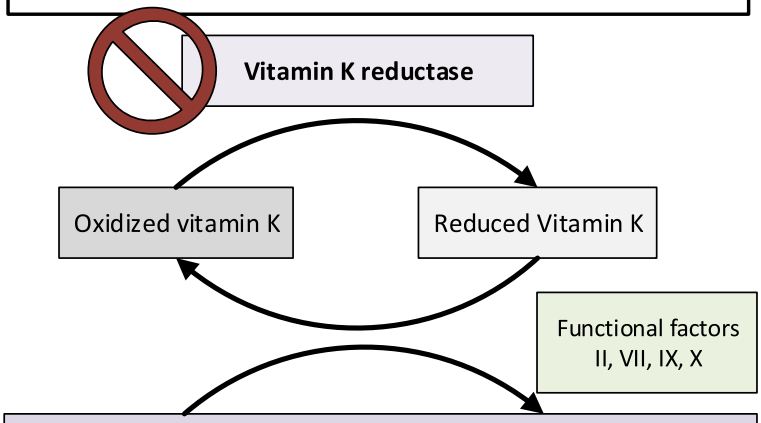
The INR does not correlate with the bleeding risk in patients with liver disease

The INR was developed in the 1980s to standardize the PT which allowed for the monitoring of **oral vitamin K antagonist** therapy (e.g. warfarin, acenocoumarol) across different labs.[11,12]

Each lot of PT reagent has an International Sensitivity Index (ISI) which indicates the sensitivity of the reagent to deficiencies of the Vitamin K dependent factors compared with the WHO reference standard.

$$\text{INR} = \left(\frac{\text{Patient PT}}{\text{Geometric mean of normal PT}} \right)^{\text{ISI}}$$

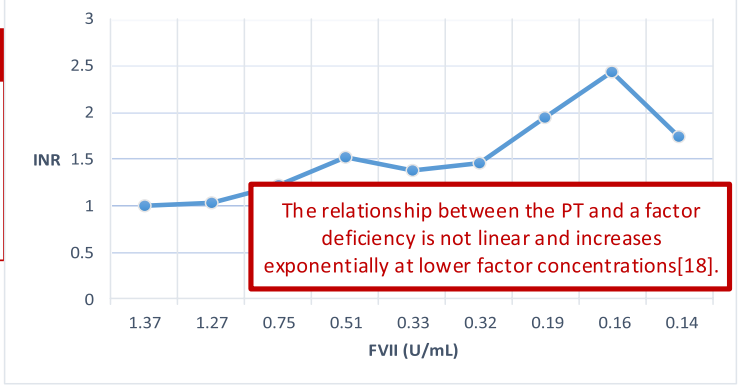
Warfarin is a competitive inhibitor of oxidized vitamin K and interferes with its reduction, making Vitamin K unavailable for the vitamin K dependent caboxylase enzyme to y-carboxylate FII, VII, IX, X.



Vitamin-K-dependent carboxylase
is a vitamin-K-dependent enzyme responsible for the y-carboxylation of factors II, VII, IX, X. Factors are then capable of interacting with other components of coagulation.

Caution

The PT/INR can be NORMAL with mild single factor deficiencies due to differential reagent sensitivity.

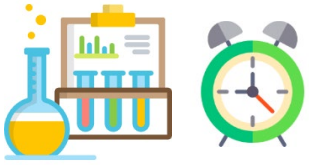


Activated Partial Thromboplastin Time (aPTT)

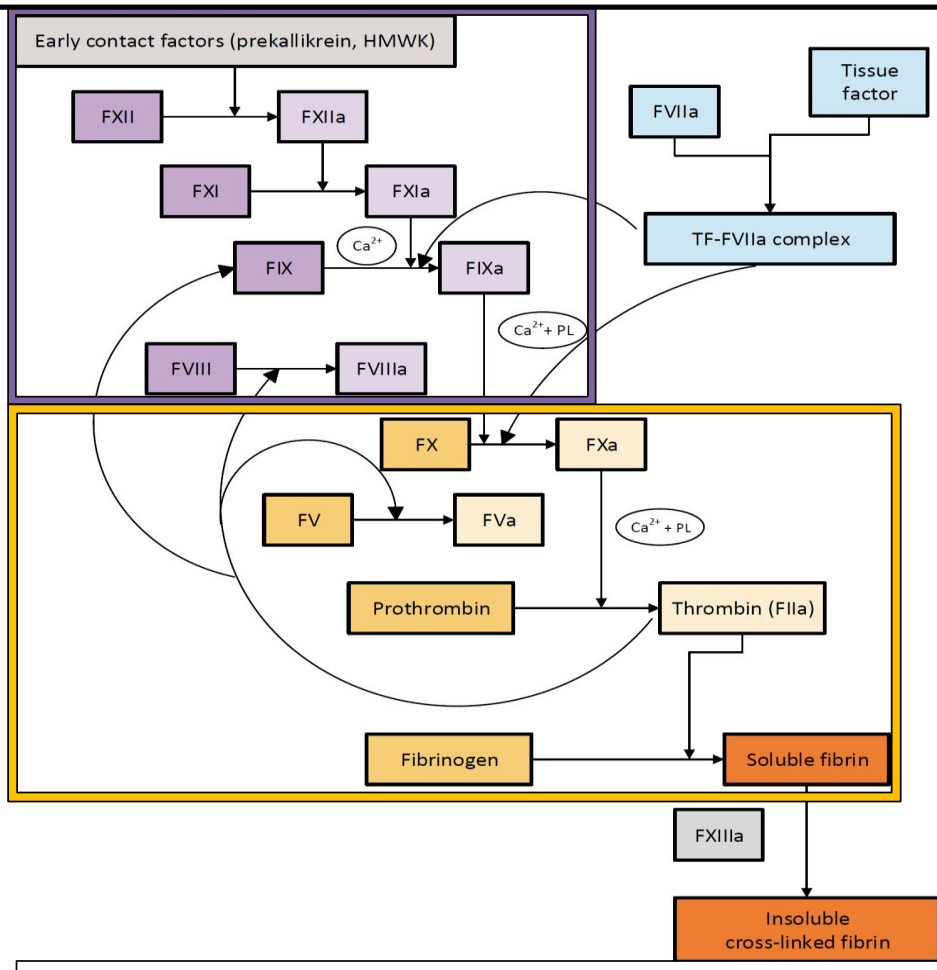
Collect sodium citrate tube

Centrifuge to obtain platelet poor plasma (PPP) and warm at 37°C

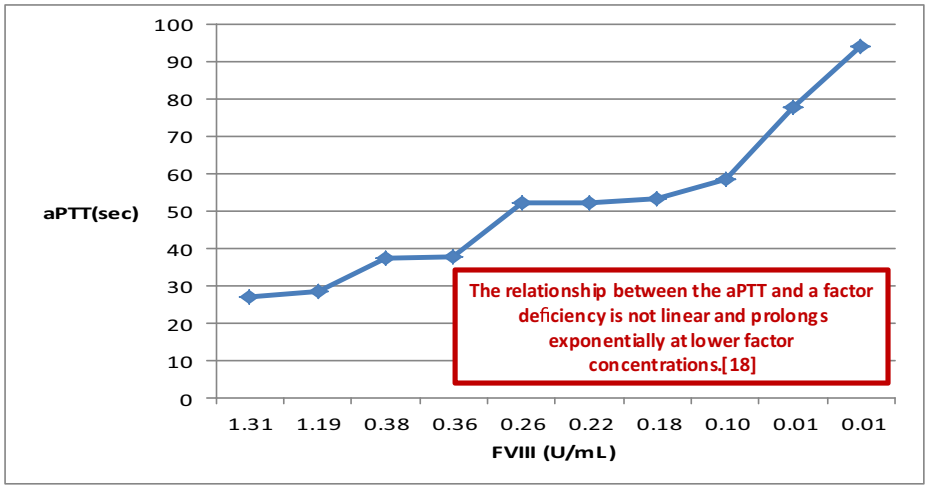
Combine contact activator (ellagic acid, silica, kaolin or glass beads), phopholipids and calcium chloride



Once fibrin strands are detected, the timer stops and the aPTT is reported in seconds.



The aPTT can assess for deficiencies or inhibitors of the **intrinsic pathway factors (early contact factors, FXII, FXI, FIX, FVIII)** and **common pathway factors (FX, FV, FII, fibrinogen)**



Activated Partial Thromboplastin Time (aPTT)

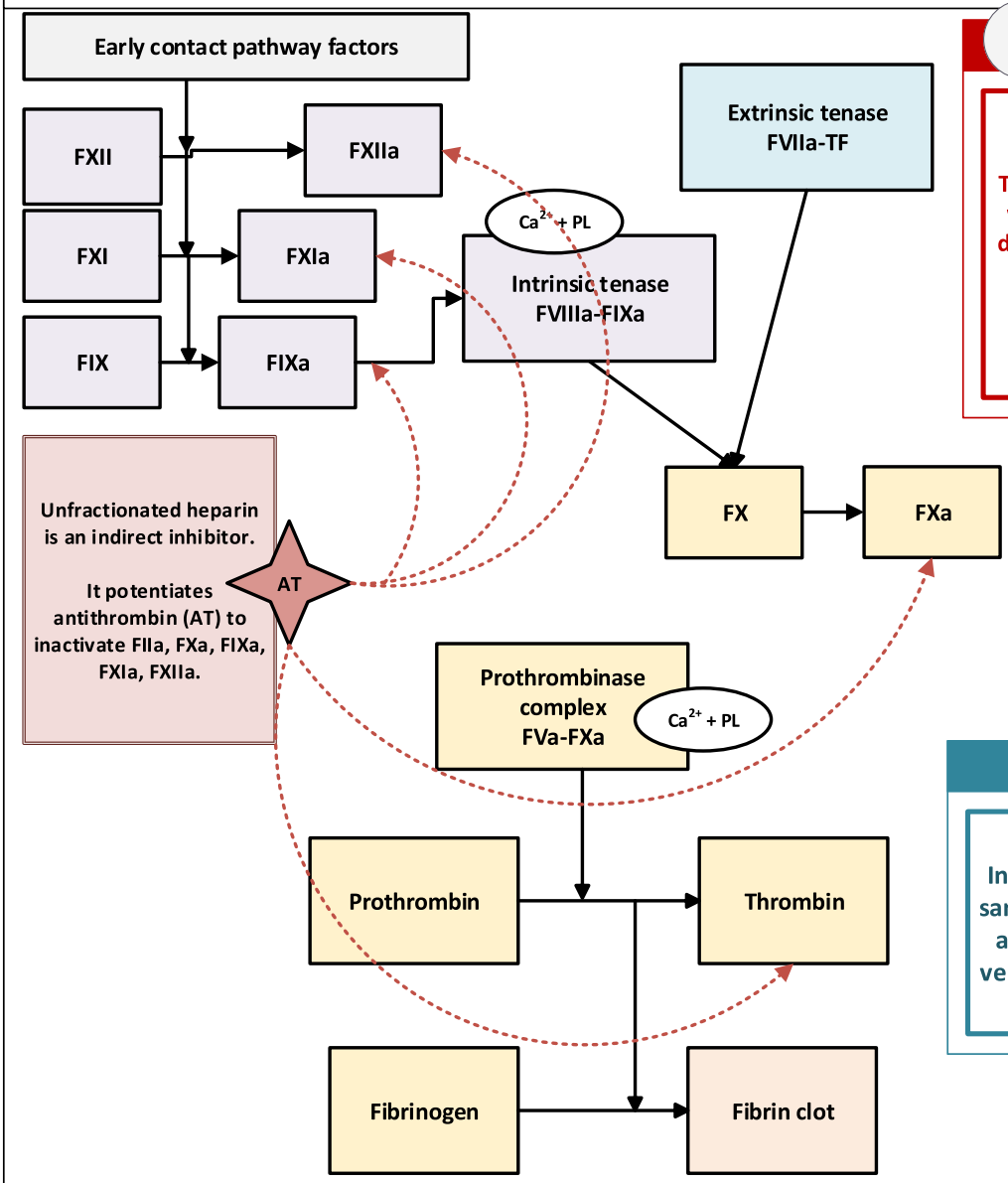
If the aPTT is prolonged but the PT is not, consider:

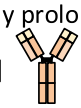
1. Therapeutic unfractionated heparin
(other anticoagulants may prolong the aPTT alone but typically prolong the PT too)

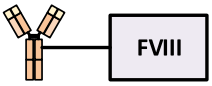
2. Non specific inhibitors (e.g. antiphospholipid antibodies)[8]

3. Congenital intrinsic coagulation factors deficiencies: contact pathway factors
(prekallikrein, kallikrein, HMWK), FXII, FXI, FIX, FVIII)

4. Specific inhibitors to one factor (e.g. FVIII antibody)







Caution

The aPTT can be normal with mild single factor deficiencies and is often normal in von Willebrand disease

Did you know?

In a study reviewing 100 samples with a prolonged aPTT, 14% were due to venipuncture artifact [10]

Differential Diagnosis for a Prolonged PT and aPTT

If the PT and the aPTT are both prolonged, there could be multiple factors affected in the intrinsic and extrinsic pathways or a single factor deficiency in the common pathway : FX, FV, FII or severe fibrinogen deficiency.

Causes include :

1. Pre-analytical cause
(e.g. heparin contamination, under filling of tube)

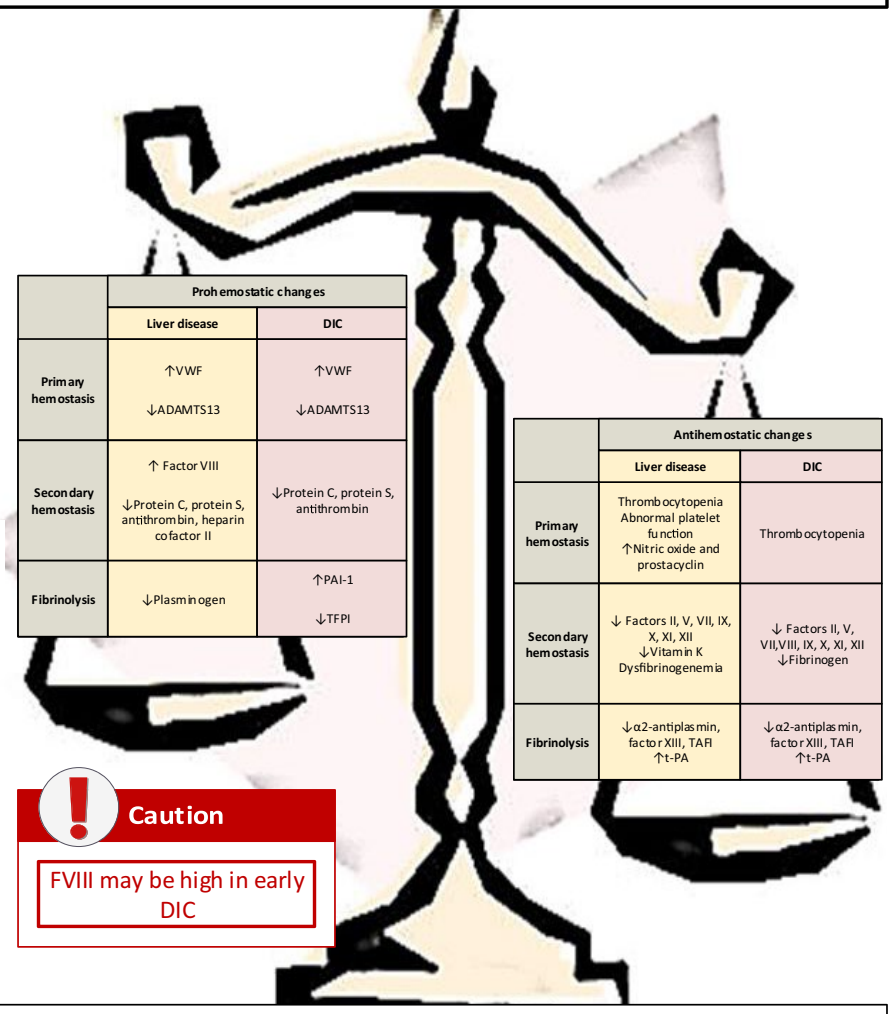
2. Drugs :
Direct or indirect inhibitory drugs (e.g. direct thrombin inhibitors, heparin)
Supratherapeutic warfarin effect (FII, FVII, FIX, FX <30%)

3. Inhibitors
Non specific inhibitor (e.g. antiphospholipid antibodies)
Specific inhibitors to the common pathway factors (rare)

4. Decreased factor synthesis :
- Congenital deficiency
- Reduced liver synthesis (impaired production FII, FV, FVII, FIX, FX, FXI, FXII, FXIII, dysfibrinogenemia)
- Severe vitamin K deficiency (↓FII, FVII, FIX, FX)

5. Factor consumption or binding
- Massive hemorrhage
- Disseminated intravascular coagulation (DIC)
- Factor X deficiency associated with systemic amyloidosis

Changes in hemostasis in DIC and liver disease



	Prohemostatic changes	
	Liver disease	DIC
Primary hemostasis	↑VWF ↓ADAMTS13	↑VWF ↓ADAMTS13
Secondary hemostasis	↑ Factor VIII ↓Protein C, protein S, antithrombin, heparin cofactor II	↓Protein C, protein S, antithrombin
Fibrinolysis	↓Plasminogen	↑PAI-1 ↓TFPI

	Antihemostatic changes	
	Liver disease	DIC
Primary hemostasis	Thrombocytopenia Abnormal platelet function ↑Nitric oxide and prostacyclin	Thrombocytopenia
Secondary hemostasis	↓ Factors II, V, VII, IX, X, XI, XII ↓Vitamin K Dysfibrinogenemia	↓ Factors II, V, VII,VIII, IX, X, XI, XII ↓Fibrinogen
Fibrinolysis	↓α2-antiplasmin, factor XIII, TAFI ↑t-PA	↓α2-antiplasmin, factor XIII, TAFI ↑t-PA

Caution

FVIII may be high in early DIC

ADAMTS13: A Disintegrin and Metalloproteinase with a ThromboSpondin type 1 motif, member 13; PAI-1: Plasminogen Activator Inhibitor type 1; t-PA: Tissue Plasminogen Activator; TAFI : Thrombin Activatable Fibrinolysis Inhibitor; TFPI: Tissue Factor Pathway Inhibitor; VWF: Von Willebrand Factor.

The ISTH DIC scoring system was developed in 2001 and uses widely available coagulation assays[1]

Points	0	1	2	3
Platelet count (10^9/L)	> 100	50-100	< 50	
Level of fibrin markers (e.g. D-dimer)	No increase		Increased but < 5x upper limit of normal	Strong increase, ≥ 5x upper limit of normal
Prolonged prothrombin time (seconds)	< 3	≥ 3 and < 6	≥ 6	
Fibrinogen(g/L)	> 1.0	≤ 1.0		

A score ≥ 5 is has a sensitivity of 93% and specificity of 98% for the diagnosis of DIC.

The severity of this score is a strong predictor for mortality in sepsis.

Workup of a Prolonged PT or aPTT

Investigations

To distinguish between a single factor deficiency and inhibitor, an immediate 50:50 mix is performed when the prolongation is greater than 4 seconds from the upper limit of normal .

Control plasma

Patient plasma

This test is performed by combining one part patient's plasma with one part normal plasma.

An aPTT or a PT is then performed on the 50:50 mix

Interpretation

The mixture "corrects" if the aPTT is within 3-4 seconds of normal and the PT is within 2 seconds of normal.

50:50 mix

- Does not correct
  - Specific inhibitor
  - Non-specific inhibitor
  - Multiple factor deficiencies
- Corrects
  - Suggests single factor deficiency

Caution

The 50:50 mix may not completely correct in the case of multiple factor deficiencies

Caution

Autoimmune FVIII inhibitors cause acquired hemophilia A. Alloimune FVIII inhibitors occur in patients with congential hemopiliha A and render the replaced FVIII less or not effective. These are the most common specific factor inhibitors.

Control plasma

Patient plasma

37°C

2 hours

Acquired hemophilia: the autoantibodies are temperature and time sensitive.

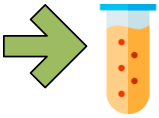
When the mix is incubated at 37° Celsius for two hours, the 50:50 aPTT remains prolonged (i.e. does not correct)

Specific factor levels are more informative than the 50:50 mix.

Specific factor levels are performed by combining one part patient's sample with commercial factor deficient plasma.

Factor deficient plasma: Commercial plasma completely deficient in a factor relevant to the PT (e.g. FVII, X) or aPTT (e.g. FVIII, IX, XI, XII).

Patient plasma



An aPTT or PT is performed on the mix and factor levels are derived from a calibration curve

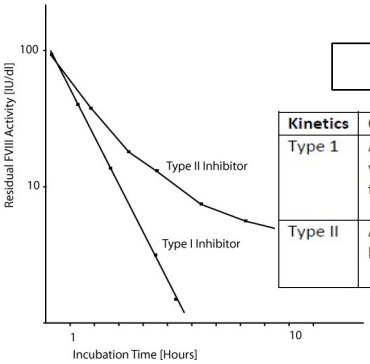
The Bethesda assay is used to quantitate specific factor inhibitors.

One Bethesda unit is defined as that amount of inhibitor that results in 50% residual FVIII:C activity after incubation at 37° Celsius for two hours.

No incubation is needed for factor inhibitors that are not time sensitive (i.e. FIX)

The inhibitor concentration is derived from a graph depicting factor VIII (Y axis) activity versus inhibitor units (x axis).

When defining a patient's inhibitor titer, derive the inhibitor titer from the graph and multiply by the dilution to obtain the final titer.



Types of inhibitors

Kinetics	Clinical syndrome
Type 1	Alloantibodies arising in a person with congenital haemophilia treated with FVIII concentrates
Type II	Autoantibodies as seen in acquired haemophilia A

Do not order baseline coagulation tests for asymptomatic patients having low-risk non-cardiac surgery.

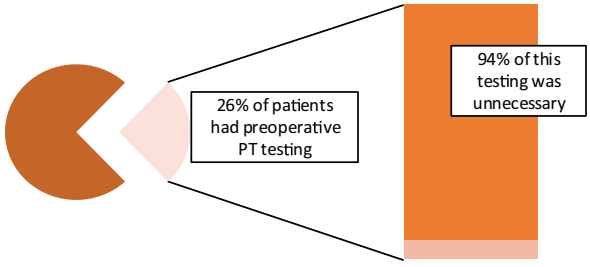
Choosing Wisely Canada

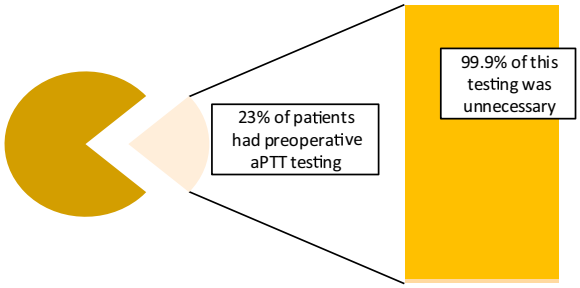
Canadian Anesthesiologists' Society, Choosing Wisely Canada recommendation #1.

Did you know?

In a study evaluating subjects referred to hematologists for bleeding disorder assessment, PT and PTT had a sensitivity of 1.0-2.1% for ruling out bleeding disorders[9]
Therefore, a normal PT and PTT does not rule out the presence of a bleeding disorder.

In a retropective study of ~ 1 million preoperative patients [4]





Conclusion

The majority of preoperative PT and PTT tests are **unnecessary**.

When to order coagulation tests (PT/INR and aPTT) in a preoperative patient

Consider PT/INR

- Vitamin K antagonist (warfarin)
- Liver disease
- Patients at risk for Vitamin K deficiency (e.g. malnutrition, fat soluble vitamins, cholestasis, prolonged antibiotics)

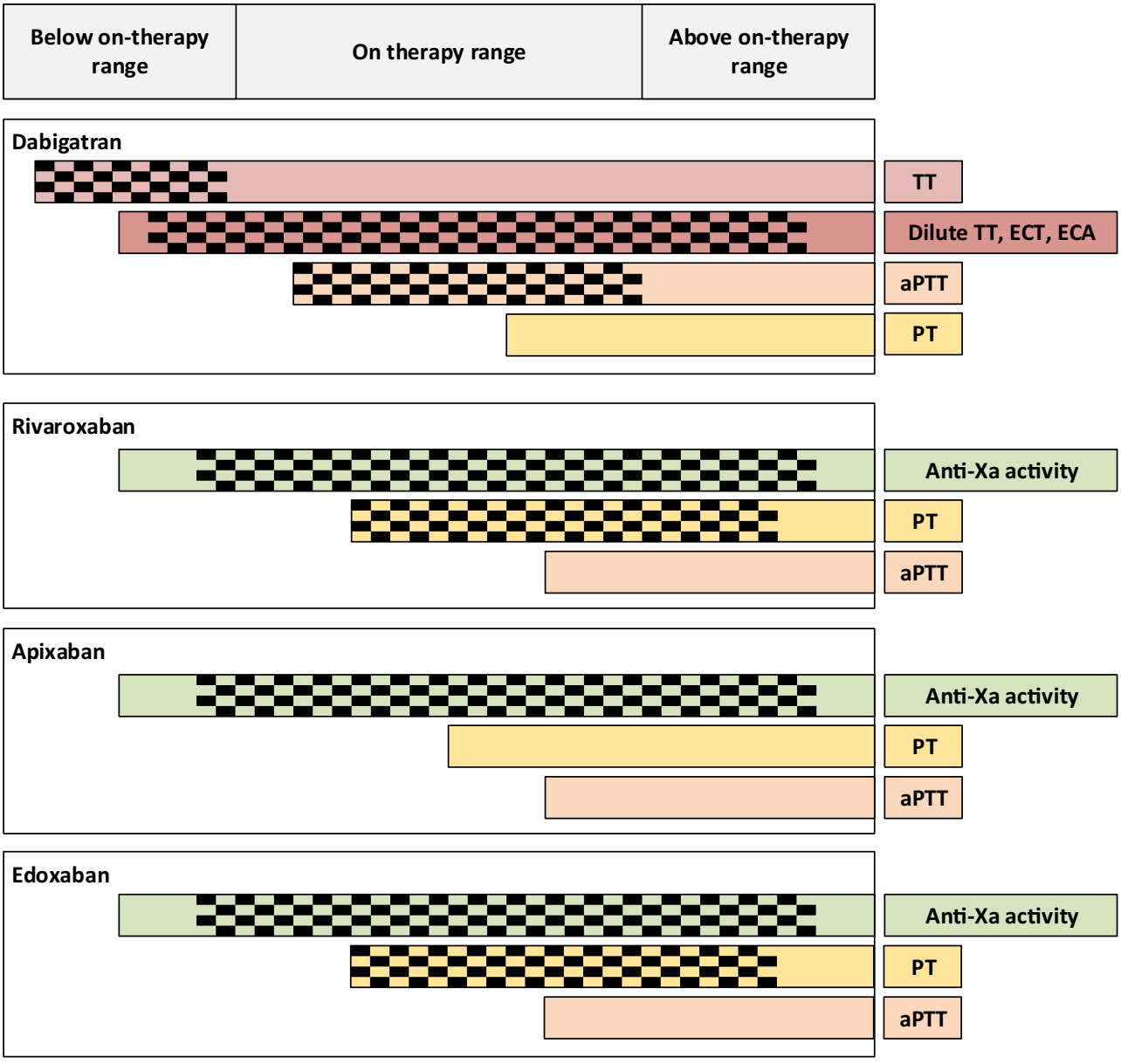
Consider aPTT

- Planned intraoperative IV heparin (e.g. cardiac or vascular surgery)
- Suspected hemophilia A/B, factor XI deficiency, severe von Willebrand disease
- Suspected antiphospholipid syndrome

Top five reasons NOT to order PT/INR or aPTT

1. Routine blood work
2. Routine pre-op screen in a low risk non-cardiovascular surgery patient
3. Monitoring of direct oral anticoagulants (DOAC)
4. Monitoring of low molecular weight heparin (LMWH)
5. Monitoring of thromboprophylaxis

Effect of Direct Oral Anticoagulants on Hemostatic Tests



Horizontal bars correspond to the approximate range of detectability (sensitivity) and checkered area corresponds to linearity of each assay at below, within and above typical on therapy concentrations of dabigatran, rixaroxaban, apixaban and edoxaban. Ranges are approximations and may vary depending on the choice of reagent.

ECA = ecarin chromogenic assay; ECT = ecarin clotting time; TT = thrombin time

Adapted from Cuker et al. with permission[5,15]

RELATIONSHIP DISCLOSURE

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

CE and MS developed the concepts and images, wrote the manuscript, and approved the final content.

TWITTER

Carolyne Elbaz @ElbCarolyne
Michelle Sholzberg @sholzberg

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