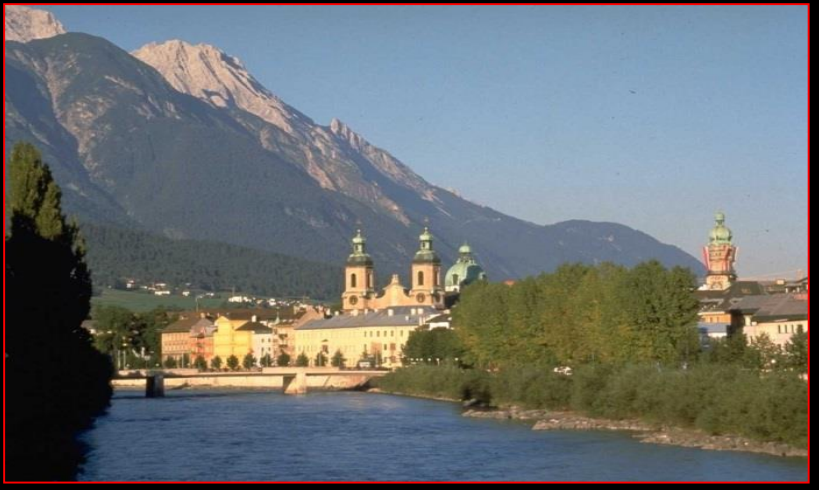

LABORATORY DIAGNOSTICS OF ANTICOAGULATION

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Anticoagulants - Definitions

„Indirect“ anticoagulants

Heparins: via Antithrombin ⌦ FXa / Thrombin

Vitamin K Antagonists: ⌦ Vitamin K epoxide reductase → ↓↓ gamma carboxylation of FII, FVII, FIX, FX, Protein S, Protein C

„Direct“ anticoagulants

Parenteral

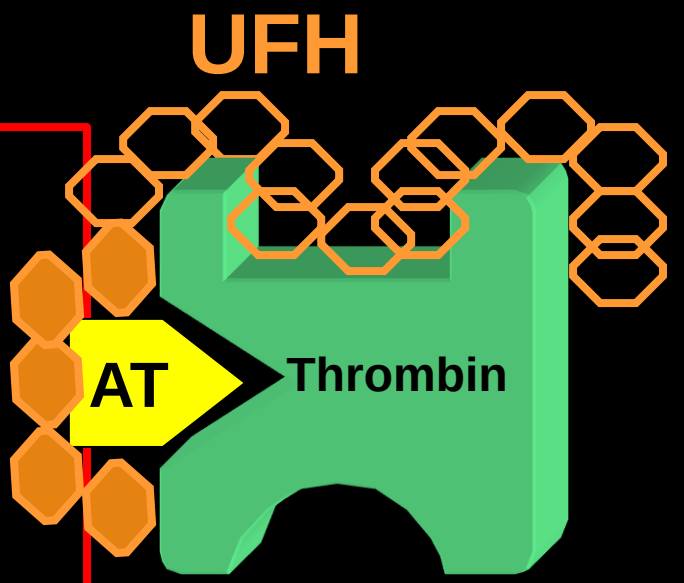
Thrombin inhibitors: Argatroban, Lepirudin, Bivalirudin, Desirudin

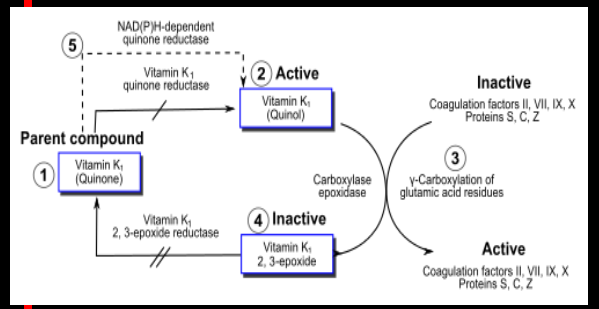
FXa inhibitor: Fondaparinux

Oral – Direct Oral Anticoagulants = **DOACs (NOACs)**

Direct oral thrombin inhibitor (DTI): Dabigatran (Pradaxa®)

Direct oral FXa inhibitors (DXI): Rivaroxaban (Xarelto®), Apixaban (Eliquis®), Edoxaban (Lixiana®), Betrixaban (Bevyxxa®)





VKAs interfere with the recycling of Vitamin K epoxide into Vitamin K (step 4 to 1). Source: Wikipedia 2019-04

Conway SE et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy. 2017.

Oral drugs (VKA vs. DOACs)

VKA

approved since 1954 → a lot of experience

lower costs

need for regular monitoring / INR testing → compliance ↑

DOACs

at least as effective as VKA and tendentially safer

therapeutic span ↑

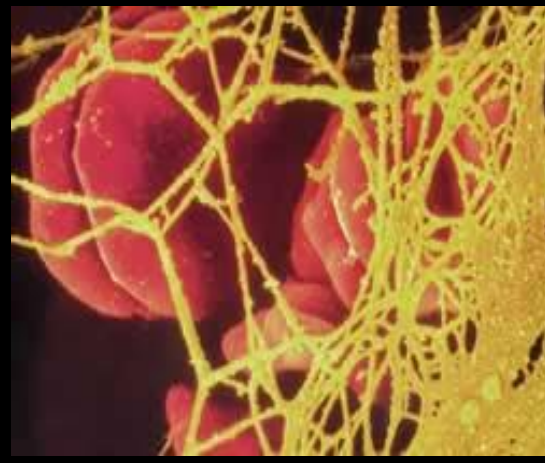
More comfortable for the patient:

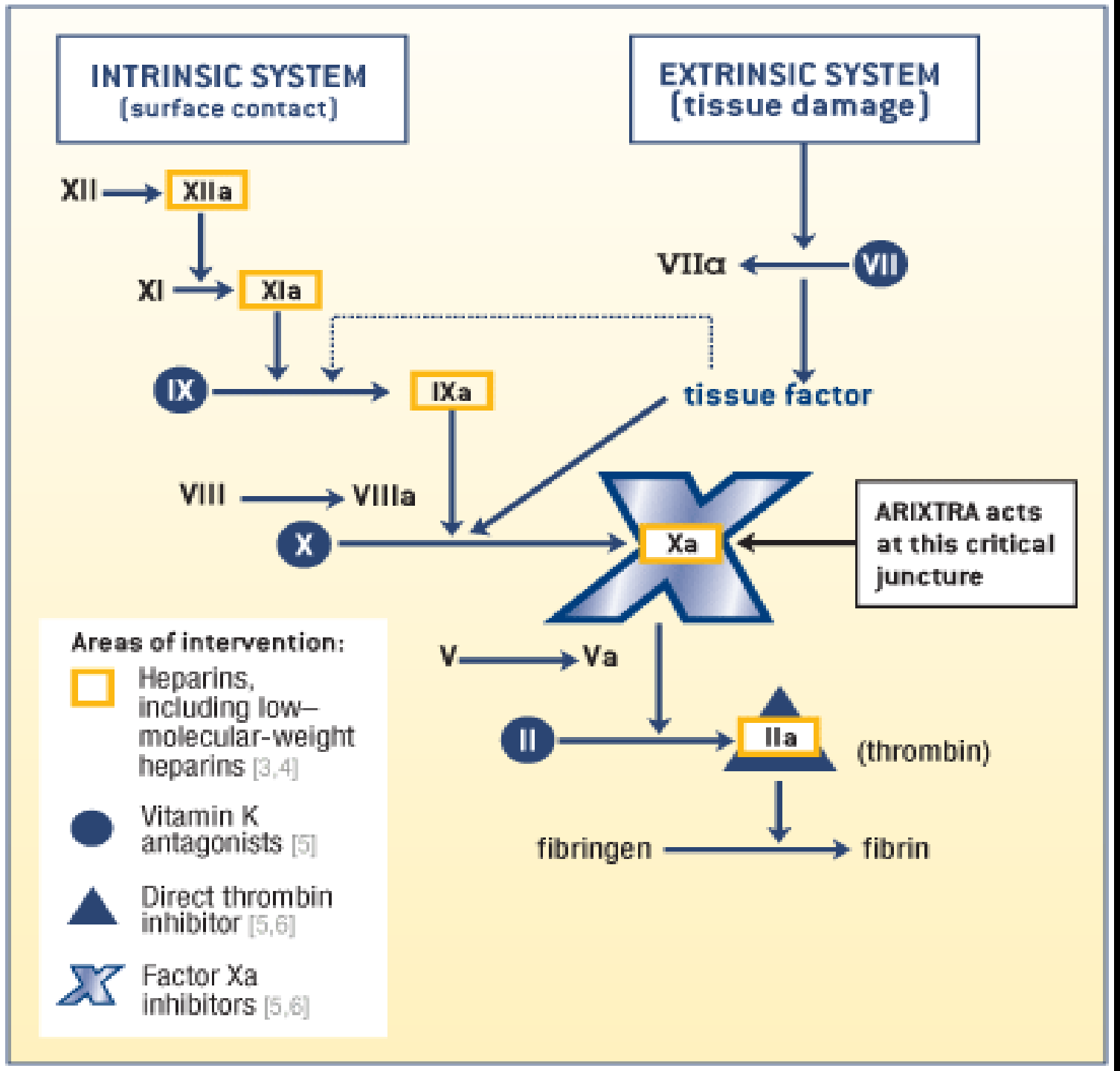
no routine monitoring recommended

Conway SE et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy. 2017.

Pharmakologie der DOACs

Substanz	**Apixaban** Handelsname **Eliquis**	**Edoxaban** Handelsname **Lixiana**	**Rivaroxaban** Handelsname **Xarelto**	**Dabigatran** Handelsname **Pradaxa**
Mechanismus	Dir. Xa Hemmer	Dir. Xa Hemmer	Dir. Xa Hemmer	Dir. IIa Hemmer
Absolute Verfügbarkeit	ca. 50 %	ca. 62 %	80 – 100 %	ca. 6,5%
Renal clearance	*ca. 27 %*	*ca. 35 %*	*ca. 33 %*	*85 %*
Halbwertszeit	ca. 12 h	ca. 10 bis 14 h	ca. 7 – 11 h	ca. 12 – 14 h
T_{max}	3 – 4 h	1 – 2 h	2 – 4 h	0.5 – 2 h




INTRINSIC SYSTEM
(surface contact)
EXTRINSIC SYSTEM
(tissue damage)
XII
XIIa
XI
XIa
VIIα
VII
IX
IXa
tissue factor
VIII
VIIIa
X
Xa
ARIXTRA acts at this critical juncture
V
Va
II
IIa
(thrombin)
fibringen
fibrin
Areas of intervention:
Heparins, including low–molecular-weight heparins [3,4]
Vitamin K antagonists [5]
Direct thrombin inhibitor [5,6]
Factor Xa inhibitors [5,6]

While monitoring of vitamin K antagonists and heparins is easily performed by prothrombin time (PT) and activated partial thromboplastin time (aPTT), respectively, testing for new anticoagulants is much more sophisticated.

	act. Partial Thromboplastin Time (aPTT)	Prothrombin Time (Quick)	Thrombotest (TT)*	Vit K-dependent
Factor	I (Fibrinogen)	I (Fibrinogen)		
Factor	II (Prothrombin)	II (Prothrombin)	II (Prothrombin)	II
Factor	V	V		
Factor		VII	VII	VII
Factor	VIII			
Factor	IX			IX
Factor	X	X	X	X
Factor	XI			
Factor	XII			
				Prot C
				Prot S

*Some reagents (e.g., NormoTest + ThromboTest) do not detect fibrinogen and FV cave different heparin sensitivity

DOACs - aPTT

DTI (Dabigatran)

Therapeutic level ca. 90-180 ng/ml → aPTT ca. 46-54 sec

qualitative statement

Moderate dosage correlation (coefficient of correlation: 0.8)

CAVE: a normal aPTT does not exclude a considerable Dabigatran effect

DXI (Rivaroxaban, Apixaban, Edoxaban)

DXIs prolong aPTT to a different extent (Riva/Edoxa > Apixa), high interindividual variation, low sensitivity

No statement about anticoagulant effectness

Conway SE et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy. 2017.

DOACs – PT / INR

PT / INR: activity of factors I, II, V, VII, X

~~INR is calculated based on the ISI correction factor; it was developed specifically for VKA and is thus diagnostically conclusive only for VKA monitoring~~

DTI (Dabigatran)

Only marginal reduction of PT%

DXI (Rivaroxaban, Apixaban, Edoxaban, Betrixaban)

The different DXI influence PT to different extent and is and additionally strongly depends on the thromboplastin used in the assay

Rivaroxaban: in most cases a qualitative statement is possible, but a normal PT does not exclude a Rivaroxaban effect

Apixaban, Edoxaban: no considerable effect on most PT assay

Conway SE et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy. 2017.

DOACs – thrombin time (TT)

DTI (Dabigatran)

Dabigatran prolongs thrombin time in a concentration-dependent and linear manner (CC: 0,86)

Highly (over)sensitive → a normal thrombin time excludes a relevant Dabigatran effect

No quantitative statements

DXI (Rivaroxaban, Apixaban, Edoxaban)

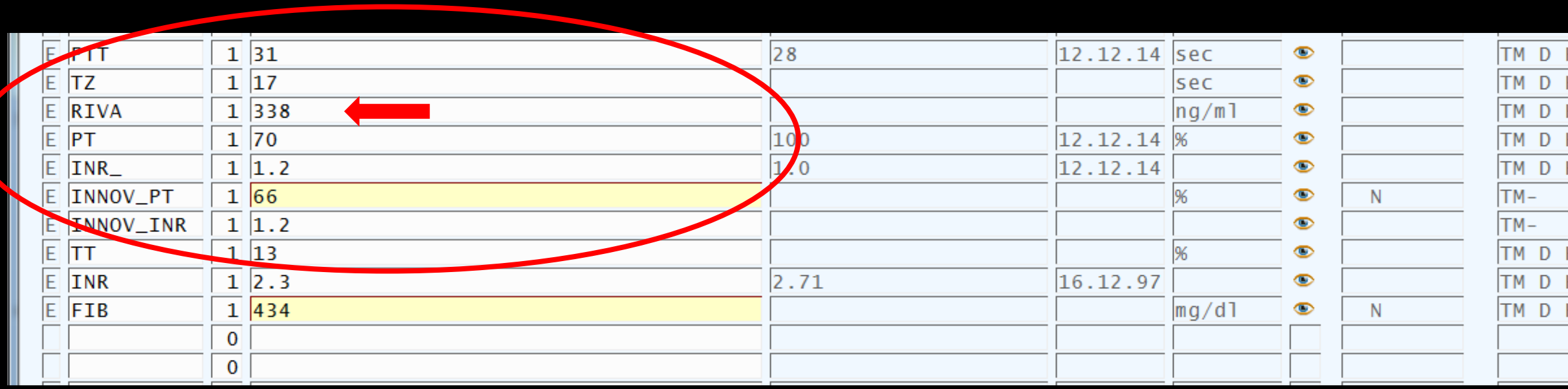
~~No effect on thrombin time~~

Conway SE et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy. 2017.

DOACs – overview of affected assays

	DTI	DXI
Coagulation factors II-XII via one stage assay	False low	False low
F XIII chromogenic	False low	OK
Thrombotest (PT Owren)	Established for VKA monitoring	
Heparin (UFH, LMWH) a-FXa	Gives a false UFH/LMWH-activity	
DRVVT lupus anticoagulant screening	Prolongation	Prolongation
Protein S activity (activation via RVV)	False low	False low
Antithrombin III activity via FIIa	False high	OK
Antithrombin III activity via Fxa	OK	False high
APC resistance via clotting	False low	False low

Rivaroxaban/Xarelto-Therapy



E	PTT	1	31	28	12.12.14	sec			TM D
E	TZ	1	17			sec			TM D
E	RIVA	1	338			ng/ml			TM D
E	PT	1	70	100	12.12.14	%			TM D
E	INR_	1	1.2	1.0	12.12.14				TM D
E	INNOV_PT	1	66			%		N	TM-
E	INNOV_INR	1	1.2						TM-
E	TT	1	13			%			TM D
E	INR	1	2.3	2.71	16.12.97				TM D
E	FIB	1	434			mg/dl		N	TM D
		0							
		0							

DOACs –monitoring (after 3 months)

Laboratory

- GFR/Creatinine (Dabigatran)
- LFP (Rivaroxaban, Apixaban, Edoxaban!): GPT, GOT, AP, bilirubin, INR
- Blood count

Clinically

- Compliance
- Drug interactions (Cytochrome P450-enzymes: CYP3A4, P-gp)
- Comorbidities

Conway SE et al. Laboratory and Clinical Monitoring of Direct Acting Oral Anticoagulants: What Clinicians Need to Know. Pharmacotherapy. 2017.

Argatroban

Direct *intravenous* thrombin inhibitor

Dosage: initially 2µg/kg/min

Screening: thrombin time (extremely sensitive)

Monitoring:

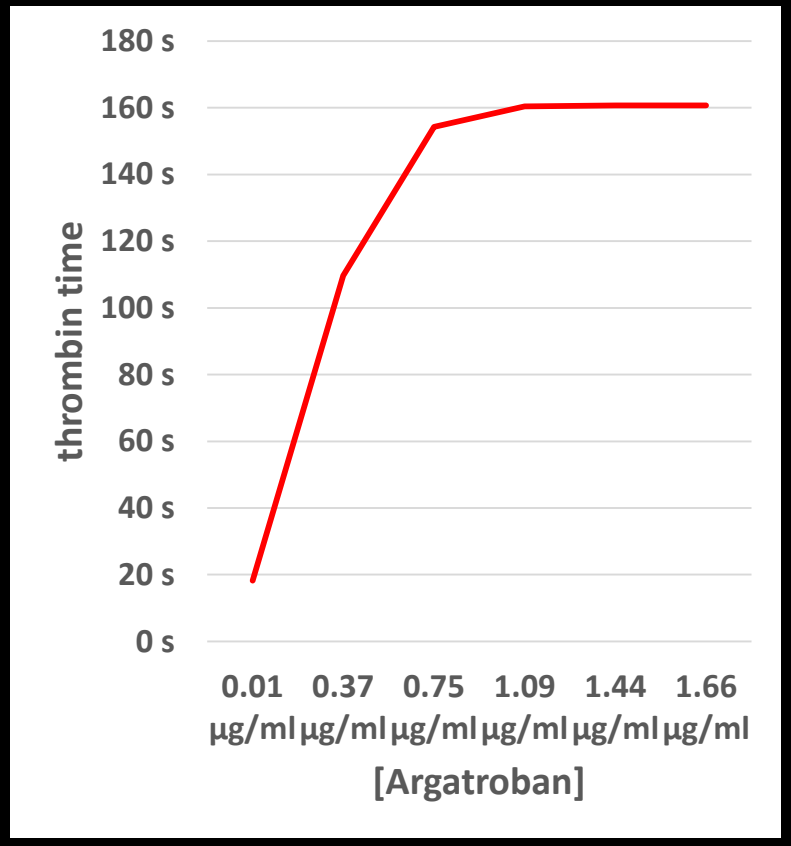
Argatroban-calibrated diluted thrombin time (→ 0,5 µg/ml Argatroban)

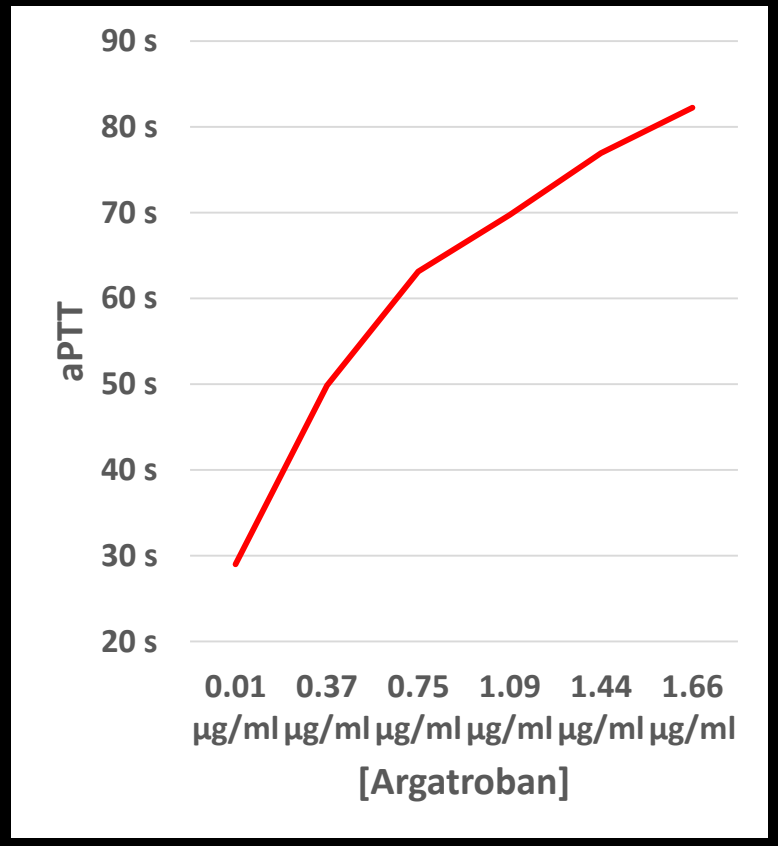
aPTT (1,5-3x)

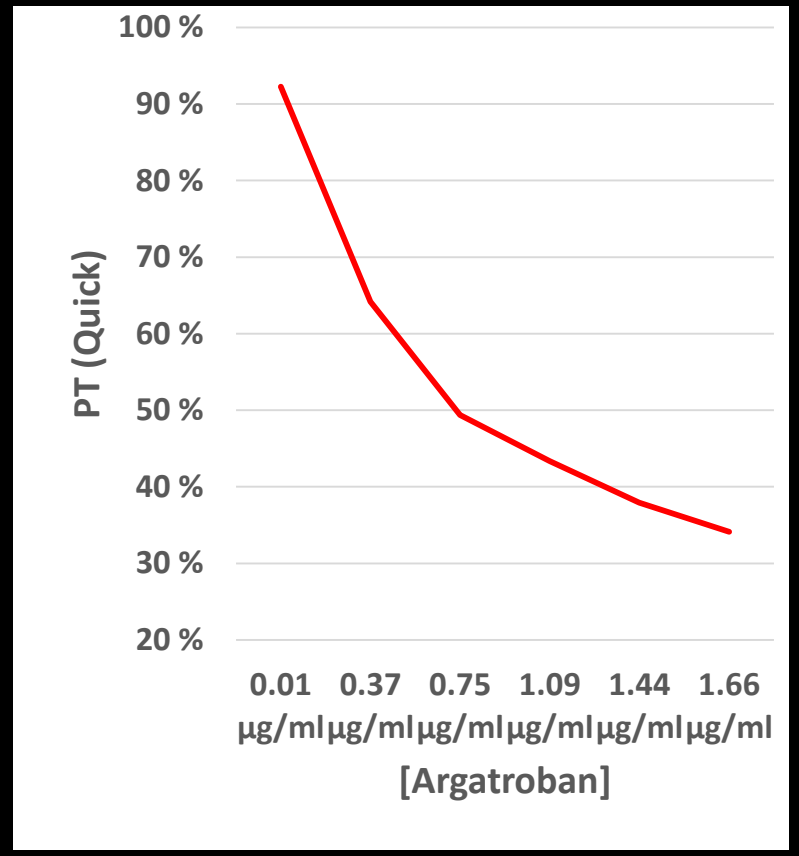
Half life in healthy people: 50 min

Renal elimination: 20 %

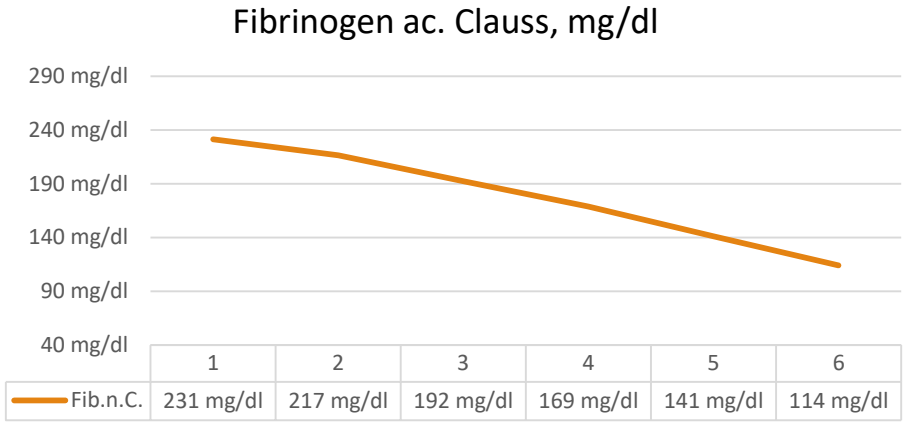
Argatroban (iv FII-Inhibitor)

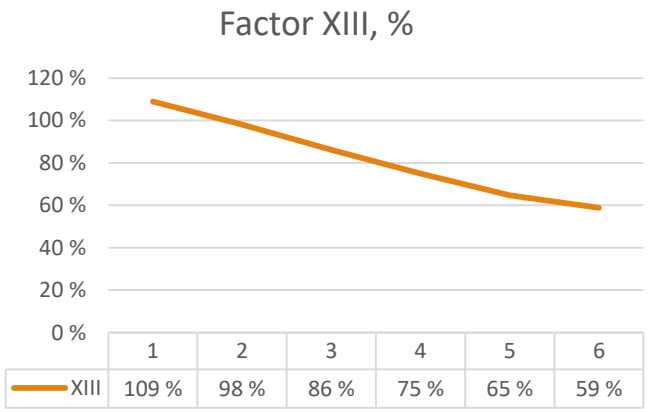




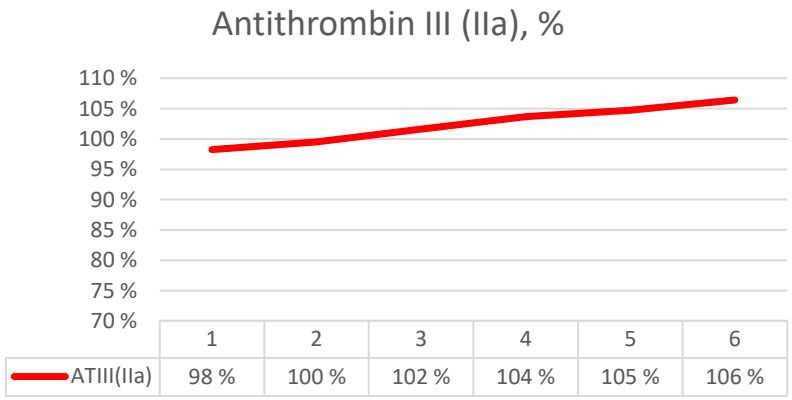


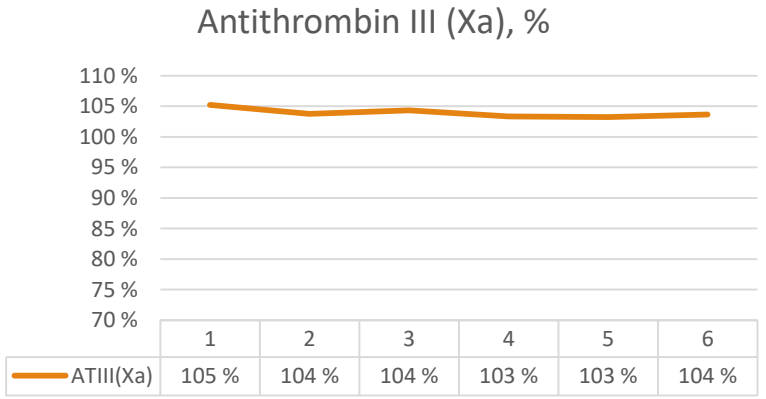
Argatroban-Fib/FXIII/ATIII





Spiking Step	[Arg]
Step 0	**0,01 µg/ml**
Step 1	**0,37 µg/ml**
Step 2	**0,75 µg/ml**
Step 3	**1,09 µg/ml**
Step 4	**1,44 µg/ml**
Step 5	**1,66 µg/ml**



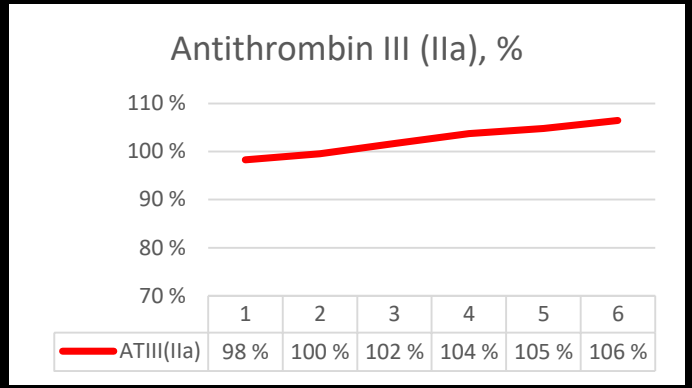


ATIII Assay (via FIIa) and Argatroban

AT (sample) + Thrombin (surplus) —Heparin→ [AT*Thrombin] + residual Thrombin

Tos-Gly-Pro-Arg-ANBA-IPA —residual Thrombin→ Tos-Gly-Pro-Arg-OH + ANBA-IPA

(405nm, indir.prop. to ATIII act.)

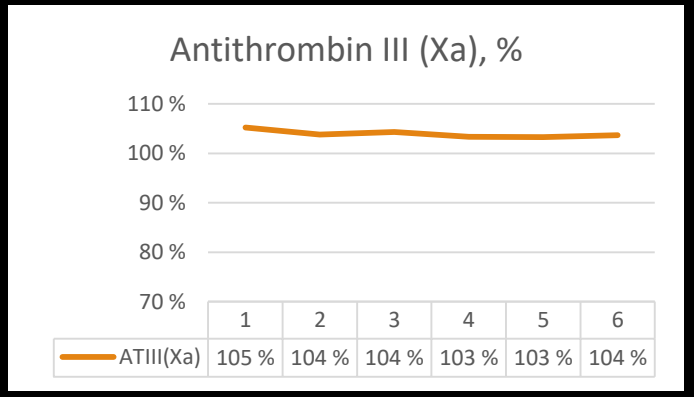


ATIII Assay (via FXa)

AT (Patient) + Heparin → [AT*Heparin]

[AT*Heparin] + FXa (surplus) → [AT*Heparin*FXa] + residual FXa

chromogenic FXa-substrate —Residual FXa→ Tripeptide + Dye (indir. prop. to ATIII act.%)



Case presentations

Emergency dept., 30.10.18

Coagulation screening

- PTT: 78 sec (26-37)
- PT: <10 % (70-130), INR >6

Anticoagulant screening

- antiFXa (calibrated against UFH): >1,3 IU/ml
- **antiFXa_Direct (calibrated against Rivaroxaban): >490 ng/ml**
- antiIFIIa (diluted thrombin time, calibrated against Argatroban): <0,18 IU/ml

☏ → **RIVAROXABAN 20 mg daily**

The most likely reasons for high rivaroxaban level

1. **The patient took more than the prescribed 20 mg daily**
2. Analytical error in the lab
3. **Drug interaction (e.g. Azole antimycotics, HIV protease inhibitors)**
4. **Renal impairment**
5. Heart failure
6. Hypothyreosis

Delayed elimination of Rivaroxaban due to impaired renal function

30.10.18:

Crea: 2,1 mg/dl

Riva: >490 ng/ml, PTT 78 sec, PT <10 %

31.10.18:

Crea: 1,9 mg/dl, *CHE: 2,37 kU/l (5,3-12,9)*

Riva: >490 ng/ml

RIVA PAUSE

01.11.18:

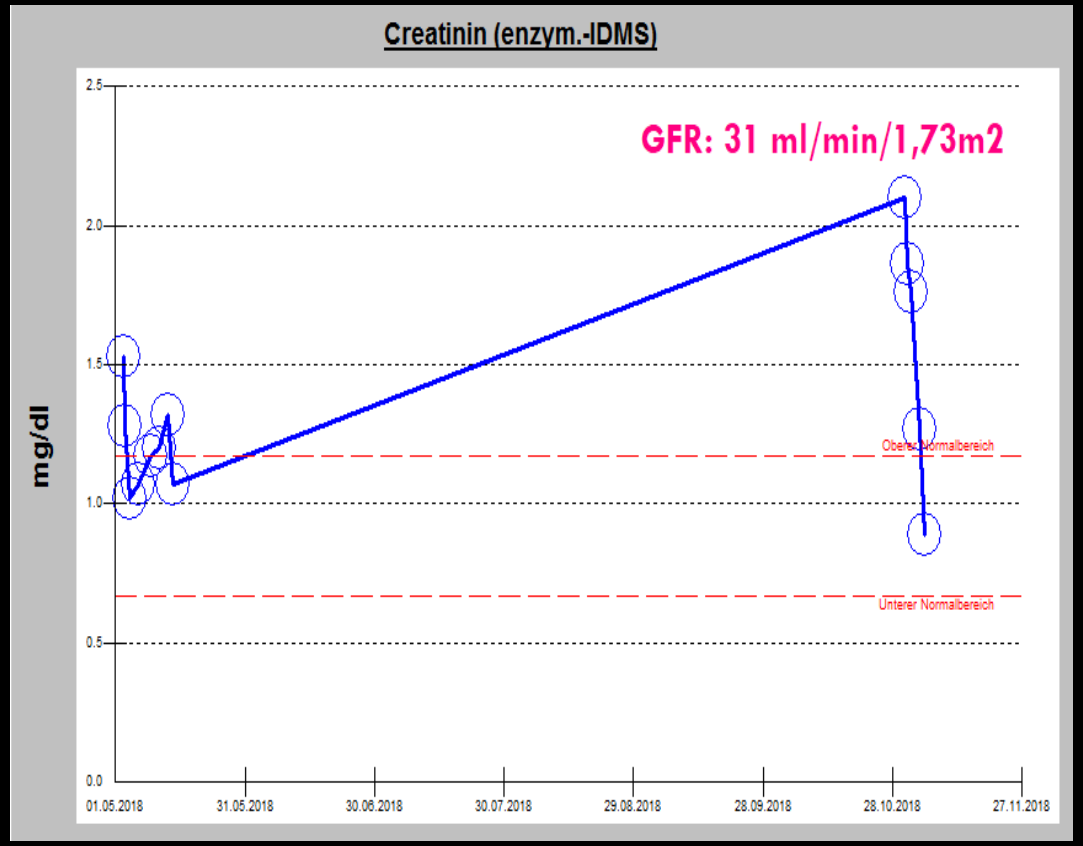
Crea: 1,8 mg/dl

Riva: >490 ng/ml

04.11.18:

Crea: 0,9 mg/dl

Riva: <20 ng/ml, PTT 33 sec, PT 100%



DOAC-STOP (activated carbon) binds low molecular weight substances, including direct oral anticoagulants such as rivaroxaban → coagulation tests are possible

History: Known steatosis hepatis (DD liver synthesis disorder, see single factors, AT3, CHE)

Parameter	30.10.18 before DOAC-STOP	30.10.18 after DOAC-STOP	4.11.18
PT –Quick (Thromborel S)	**<10 %**	**31 %**	**100 % (Vit. K!)**
PTT	**75 sec.**	**32 sec**	**33 sec**
RIVA	**> 490 ng/ml**	**< 20 ng/ml**	**< 20 ng/ml**
antiFXa	**>1.30 IU/ml**	**<0.30 IU/ml**	
FII (Vit K dep)		**44 %**	
FV		24 %	
FVII (Vit K dep)		**23 %**	
FX (Vit K dep)		**27 %**	
FVIII		131 %	
FIX (Vit K dep)		**37 %**	
FXI		46 %	
FXII		61 %	
FXIII		46 %	
AT3 (via IIa)	**40 %**	**36 %**	109 %
AT3 (via Xa)	**>140 %**	**45 %**	

Cholinesterase: 2,37 kU/L
(5,3-12,9)

Patient H.V., emergency dept.

Principal diagnosis: cardial decompensation; acute chronic renal failure; cardiorenal syndrome

Further diagnoses:

- Heart failure NYHA III – IV
- Intermittent tachycardic atrial fibrillation
- Chronic renal impairment
- Dabigatran – blood-levels >500 ng/ml

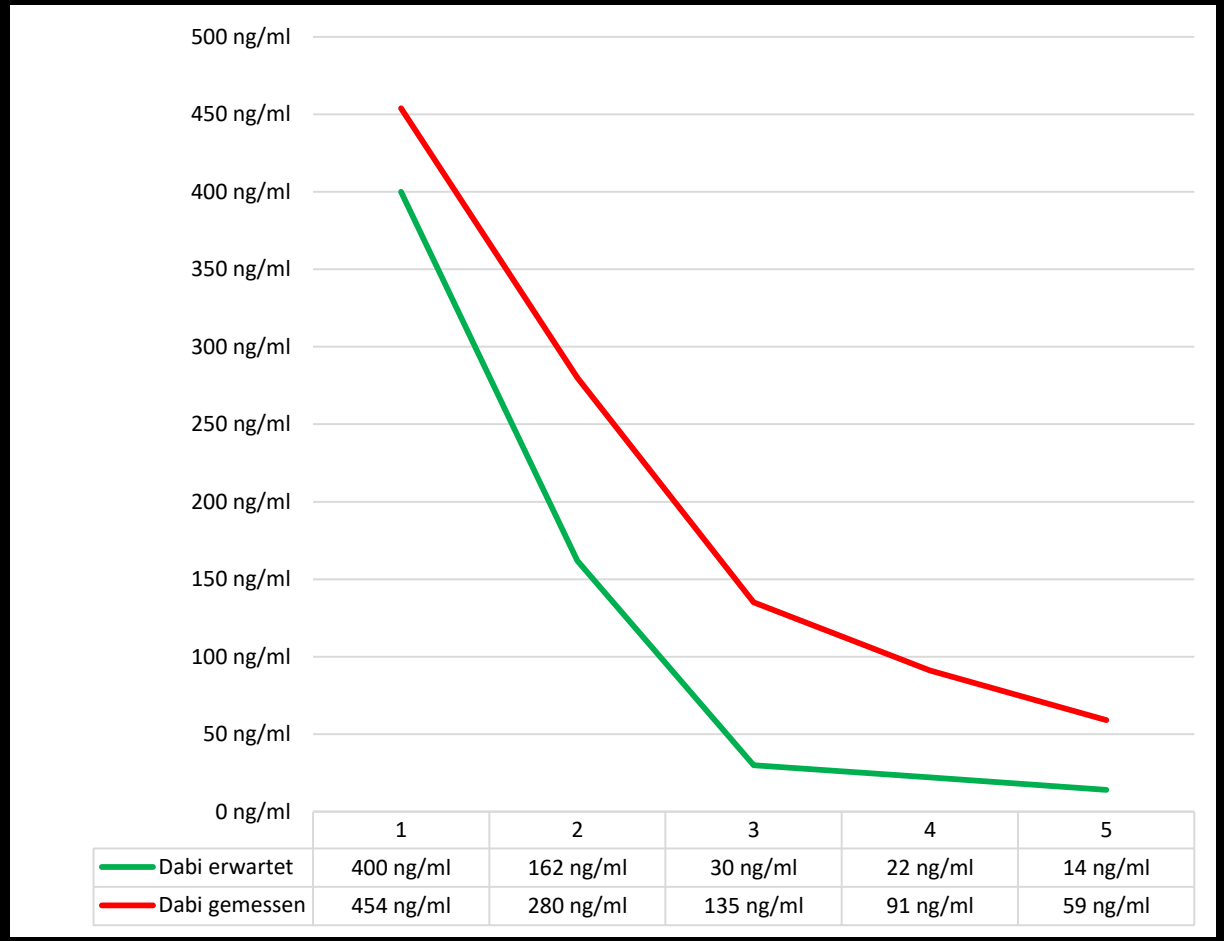
Premedication:

- Among others: Pradaxa (DABIGATRAN) 110 mg 1-0-1 (reduced dose) → discontinued

Delayed elimination of Dabigatran

	Inhibitoren des plasmatisch			
Wirkstoff	**Aragtroban**	**Dabigatranetexilat**	**Rivaroxaban**	**Apixaban**
Handelsname	Argatra®	Pradaxa®	Xarelto®	Eliquis®
Wirkmechanismus	Parenteraler direkter, reversibler Thrombin (IIa)-Inhibitor	Prodrug v. Dabigatran: Oraler direkter Thrombin (IIa)-Inhibitor	Oraler direkter Faktor Xa-Inhibitor	Oraler direkter Faktor Xa-Inhibitor
Indikationen (2018)	Antikoagulation bei Pat. mit HIT-II	Proph. Nach Knie/Hüft-TEP; NV-VHF, TVT + PE (Therapie + Prophylaxe)	NV-VHF, TVT + PE (Therapie + Prophylaxe), nach ACS (2x2.5 mg tgl.)	Proph. Nach Knie/Hüft-TEP; NV-VHF, TVT + PE (Therapie + Prophylaxe)
Standard-Dosierung	Initial 2,0 µg/kg/min	150 mg, 2 x tgl.	20 mg, 1 x tgl.	5 mg, 2 x tgl.
Wirkungseintritt	umgehend	C_{max} innerhalb 0.5 - 2 h	C_{max} innerhalb 2 - 4 h	C_{max} innerhalb 3 - 4 h
Ter.HWZ (Gesunde)	50 min	12 - 14 h	5 - 13 h	13 h
Wirkdauer	aPTT wird ca. 2 h nach absetzen normal	< 48 h*	< 48 h*	< 48 h*
Labor-Monitoring	aPTT (Ziel: 1,5-3x) verdünnte Thrombinzeit (Argatroban-kalibriert)	Thrombinzeit verdünnte Thrombinzeit (Dabigatran-kalibriert)	Anti-Faktor Xa-Aktivität (Rivaroxaban-kalibriert)	Anti-Faktor Xa-Aktivität (Apixaban-kalibriert)
Antidot (AD)	kein spez.AD, (FFP,PPSB)	Praxbind® 5 g i.v.	kein spez.AD, (FFP,PPSB)	kein spez.AD, (FFP,PPSB)
Renale Elimination	20 %	85 %	66 %	27 %
Einfluss der Nierenfunktion	keine Dosisnpassung	<30ml/min → KI	15-30 ml/min: Vorsicht <15ml/min: KI	15-30 ml/min: Vorsicht <15ml/min: KI
Leberfunktions-störung (LFS)	-Dosisanpassung bei mäßiger LFS -KI bei schwerer LFS	KI bei schwerer LFS	KI bei schwerer LFS	KI bei schwerer LFS

Date	Time	Delta time	Dabi expected (half life 14 h)	Dabi, measured
21.Jul	11:11	-	-	>500 ng/ml
21.Jul	12:33	01:22	-	>500 ng/ml
22.Jul	06:44	18:11	-	467 ng/ml
22.Jul	11:21	04:37	400 ng/ml	454 ng/ml
23.Jul	05:38	18:17	162 ng/ml	280 ng/ml
24.Jul	06:35	00:57	30 ng/ml	135 ng/ml
25.Jul	05:13	23:38	22 ng/ml	91 ng/ml
26.Jul	04:57	23:44	14 ng/ml	59 ng/ml



CAVE: inconspicuous coagulation screening under Apixaban

Patient 1:

aPTT: 29 sec (26-37 sec)

PT: 98 % (70-130 %)

TZ: 16 sec (15-21 sec)

APIXABAN (anti-FXa): 101 ng/ml

Patient 2:

PTT 36 sec (26-37 sec)

PT: 80 % (70-130 %)

TZ: 18 sec (15-21 sec)

APIXABAN (anti-FXa): 113 ng/ml

Surgery ambulance

- Patient with acute lower gastrointestinal bleeding
- Premedication: Lixiana® (Edoxaban) 60 mg 1-0-0
- Coagulation state:
  - **PTT: 60 sec. (26-37)**
  - **PT: 26 % (70-130)**
  - **TZ: 22 sec. (15-21)**
  - **Fibrinogen: 189 mg/dl (210-400)**
  - **Edoxaban: >425 ng/ml**

Which parameters should be performed to clarify the aPTT(60sec) and PT (26 %) in this case

1. Intrinsic coagulation factors
2. Extrinsic coagulation factors
3. Plasminogen and antiplasmin
4. Protein C and protein S activity
5. Lupus anticoagulans (not for clarifing a bleeding situation)
6. Activated Protein C resistance (Faktor V-Leiden)

Coagulation factors after in vitro removal of edoxaban via charcoal

- DOAC-STOP™ (Haematex), DOAC-REMOVE™ (5-Diagnostics, Coachrom)
- Charcoal binds small molecules such as DOACs → centrifugation → the DOAC-free plasma can be used to test for all coagulation parameters

FII-VITK	1	50 # .	nach Doak-Stop
FV	1	29 # .	nach Doak-Stop
FVII-VITK	1	50 # .	nach Doak-Stop
FX-VITK	1	37 # .	nach Doak-Stop
FVIII	1	68 # .	nach Doak-Stop
FIX-VITK	1	55 # .	nach Doak-Stop
FXI	1	31 # .	nach Doak-Stop
FXII	1	31 # .	nach Doak-Stop

The most likely explanation for this general reduction of the coagulation factors

1. Warfarin was given additionally to Edoxaban
2. Acute liver failure
3. Acute phase
4. Loss of all coagulation factors due to bleeding event
5. Inherited deficiency of all coagulation factors
6. It is all about an analytical artefact

FII-VITK	1	50 # .	nach Doak-Stop
FV	1	29 # .	nach Doak-Stop
FVII-VITK	1	50 # .	nach Doak-Stop
FX-VITK	1	37 # .	nach Doak-Stop
FVIII	1	68 # .	nach Doak-Stop
FIX-VITK	1	55 # .	nach Doak-Stop
FXI	1	31 # .	nach Doak-Stop
FXII	1	31 # .	nach Doak-Stop

Thank you for your Attention

Anticoagulant medications become more diverse and coagulation testing becomes more and more complex. A good collaboration between physician and laboratory doctor is of great importance.

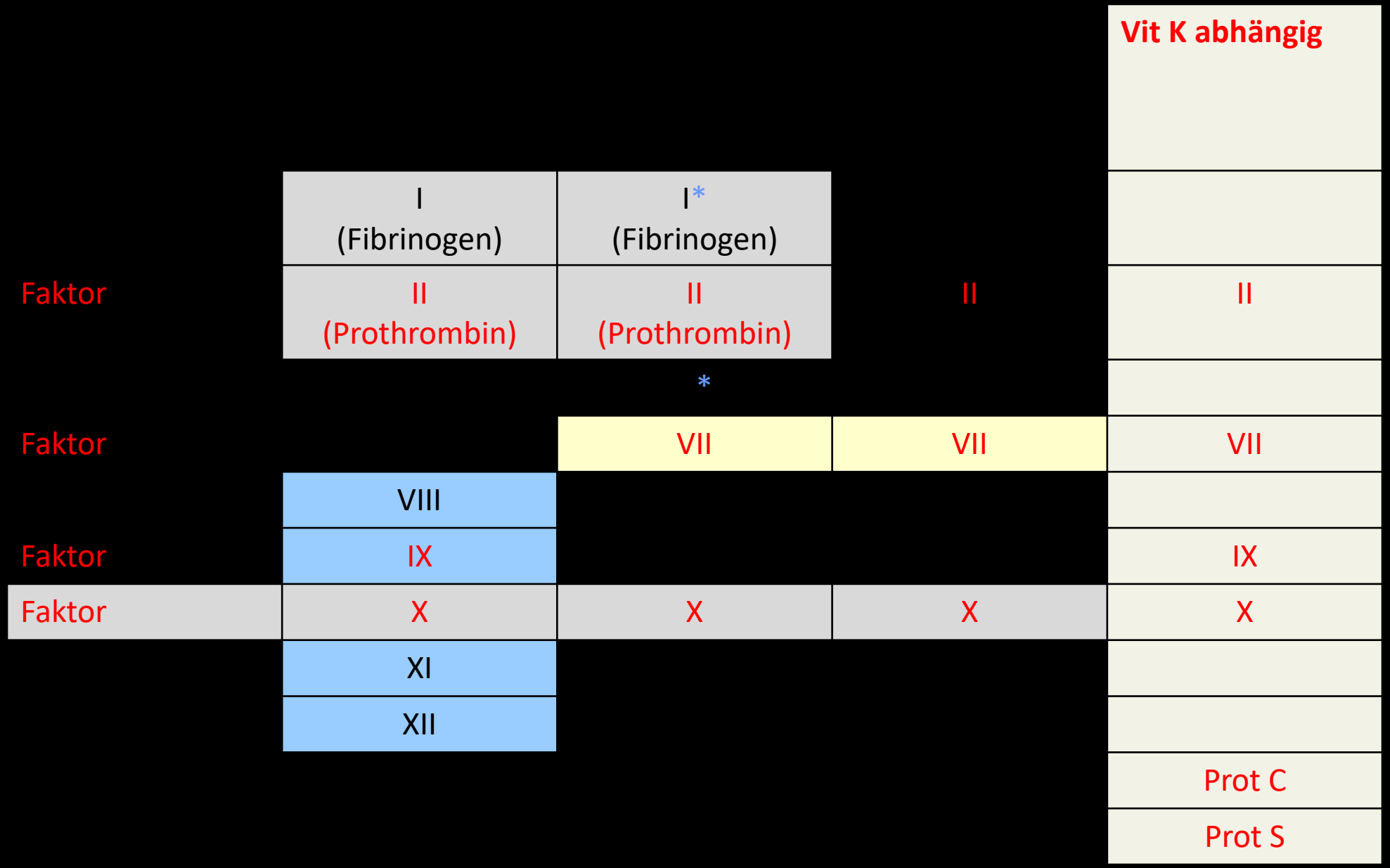
For the correct testing and interpretation it is necessary to know:

a) the used anticoagulant
b) the exact dosage
c) the last time of intake
d) other important clinical information
e) Introduction of Screening Assays for DOACs (TT, antiFXa, antiFXa-direct)

For decades, a very limited number of anticoagulants were available in the clinical setting. Until recently, vitamin K-antagonists (VKA) were the only orally available anticoagulants, whereas parenterally mainly heparins were used. Through the years, many other "blood thinner" have been approved, culminating in the rise of the direct oral anticoagulants (DOAC), the direct oral thrombin inhibitor (DTI), Dabigatran, and four direct oral factor Xa inhibitors (DiXI), Rivaroxaban, Apixaban, Edoxaban, and Betrixaban. While monitoring of VKA and heparins is easily performed by prothrombin time (PT) and activated partial thromboplastin time (aPTT), respectively, testing for new anticoagulants is much more sophisticated. Only large central laboratories have an own specialized haemostasis department, capable of performing a broad range of coagulation testing. Some anticoagulants require *routine* monitoring of their effect, e.g. unfractionated heparins (UFH) and VKA, while others do not, e.g. all DOAC, Fondaparinux and low molecular weight heparins (LMWH). Testing of the latter is required only in special conditions, among them bleeding emergencies, perioperative settings and renal impairment. Measurement of UFH is done by aPTT-ratio, anti-factor Xa-activity (aFXa) or activated clotting time, while LMWH, the direct parenteral DiXI Fondaparinux and the orally available DiXI are monitored only by aFXa (calibrated against the respective anticoagulant). Parenteral (e.g. Argatroban) and oral (Dabigatran) DTI monitoring is preferably performed with diluted thrombin time calibrated against the substance in question, or with ecarin clotting time. DOAC are more and more prescribed and all clinical central laboratories nowadays must be able to perform DOAC screening (e.g. thrombin time, which is overly sensitive for DTI; aFXa for DiXI) for cases of emergency. Another topic is the fact, that certain coagulation tests, such as single coagulation factors and lupus anticoagulant, are non-determinable when different anticoagulants are present in the sample. However, there are several approaches to eliminate the specific anticoagulant in vitro, so that broad coagulation testing is feasible: heparinase enzymes cleave UFH and special charcoal formulations remove low molecular weight anticoagulants such as DOAC or Argatroban. As anticoagulant medications become progressively diverse and coagulation testing increasingly complex, a good collaboration and communication between the referring physician and the laboratory is of mounting importance. Data such as a) the used anticoagulant, b) the exact dosage, c) the last time of intake and d) other important clinical information are indispensable for the coagulation laboratory and should imperatively be provided by the assigning clinicians to ensure correct testing, interpretation of results and last but not least the patients outcome and safety.

What are the likeliest reasons for the high rivaroxaban level

1. The patient took more than the prescribed 20 mg daily
2. Analytical error in the lab
3. Drug interaction (e.g. Azole antimycotics, HIV protease inhibitors)
4. Renal impairment
5. Heart failure
6. Hypothyreosis



*Manche Ragentien (z.B. NormoTest/ThromboTest, PT owren) erfassen Fibrinogen und FV nicht, da dem Reagens zugesetzt. cave unterschiedliche Heparinempfindlichkeit

Parameter (Nachweisart/Hersteller)	**Veränderung** (dosisabhängig)	Einheit
PTZ	↓↓	%
INR	↑↑	Ratio
aPTT	↑↑	s
Thrombinzeit	↑↑↑ bis Unmessbarkeit	s
Fibrinogen (Clauss, mit <50 U Thrombin im Reagenz)	↓↓	mg/dl oder g/l
Faktoren VIII, IX, XI, XII	↓↓	%
Faktoren II, V, VII, X	↓	%
Faktor XIII (Fa. Siemens)	↓↓↓	%
APC-Resistenz (klassisch über aPTT)	↑↑↑ Gerinnungszeit / Ratio ↑	s / Ratio
APC-Resistenz (Prothrombinaktivierung)	↑↑↑ Gerinnungszeit / Ratio ↑	s / Ratio
Protein C Aktivität (chromogen)	↔	%
Protein S Aktivität (clotting)	↑↑	%
Antithrombin-III (chromogen über IIa)	↑	%
Antithrombin-III (chromogen über Xa)	↔	%
Plasminogen Aktivität (chromogen)	↔	%
Von Wilebrand Faktor Aktivität/ VWF:RCo	↔	%
Von Wilebrand Faktor Antigen	↔	%
Lupusantikoagulanz (dRVVT)	↑↑↑ Gerinnungszeit / Ratio ↑	s / Ratio

Xa-/IIa-Hemmer Monitoring

Substanz	Wirkung	PTZ	APTT	a-Xa/IIa Assay
Fondaparinux s.c.	Indir. Xa Hemmer	(↓ 10%)	(↑ 20%)	Ja
	Dir. Xa Hemmer			
	Dir. Xa Hemmer			
Argatroban i.v.	Dir. IIa Hemmer	(↓)	1,5-3-fache ↑ lt. Codex	Ja und ev. PICT (ECT)
Dabigatran oral Prodrug	Dir. IIa Hemmer	Ja aber ?		Ja und ev. PICT? ECT? TZ?

PiCT®: Prothombinase-Induced Clotting Test,

ECT: Ecarin Clotting Time

DOACs – „true“ plasma concentrations

- HPLC-MS

- **DTI (Dabigatran):**
  - Dabigatran 150 mg 1-0-1 → peak level: 64-443 ng/ml (P5-P95), trough level: 31-225 ng/ml (P5 – P95)

- **DXI (Rivaroxaban, Apixaban, Edoxaban):**
  - Rivaroxaban 20 mg 1-0-0 → peak level: 274 ng/ml (mean), trough level: 129 ng/ml (mean)
  - Apixaban 5 mg 1-0-1 → Peak: 30 ng/ml (Mittelwert), Tal: 50 ng/ml (Mittelwert)

DOAC-STOP / REMOVE

Thromb Res.

Exner T Michalopoulos N Pearce J Xavier R Ahuja M

- Charcoal
- Binds small molecular weight substances, among them all DOACs:
  - Rivaroxaban: 436 Dalton, g/mol
  - Apixaban: 460 Dalton, g/mol
  - Edoxaban: 548 Dalton, g/mol
  - Betrixaban: 452 Dalton, g/mol
  - Dabigatran: 628 Dalton, g/mol

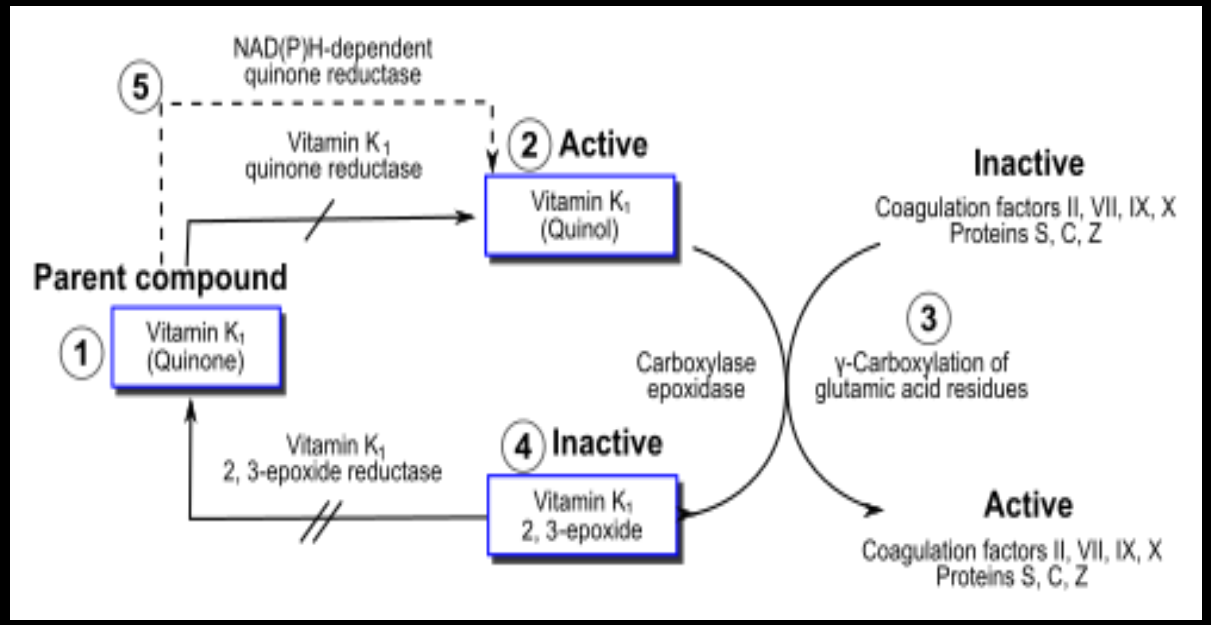
DOAC		APTT (sec)		dRVT-DCT (sec)	
	ng/ml	Before DS	After DS	Before DS	After DS
None (PNP)	0	33.3	32.9	36.1	35.8
Dabigatran	44	46.1	35.4	48.6	35.7
Dabigatran	286	78.8	34.9	99.5	36.8
Dabigatran	550	98.2	35.9	166	36.2
Apixaban	0	35.2	35.1	40.8	40.5
Apixaban	274	50.1	36.1	149	39.1
Apixaban	615	56.2	38.1	> 200	39.6
Rivaroxaban	0	30.4	33.5	35.8	35.8
Rivaroxaban	300	46.9	30.6	155	36.1
Rivaroxaban	525	59.1	31.2	> 200	34.1
Edoxaban	500	61.1	32.5	> 200	36.1

Rivaroxaban overdose?

8235377606

Action of Vit K Antagonists

These drugs deplete the active form of the vitamin by inhibiting the VitK epoxid reductase and thus the recycling of the inactive Vit K epoxide back to the active reduced form of VitK. The drugs are structurally similar to VitK and act as competitive inhibitors of the enzyme. The term "vitamin K antagonist" is a misnomer, as the drugs do not directly antagonize the action of vitamin K in the pharmacological sense, but rather the recycling of VitK.



VKAs interfere with the recycling of Vitamin K epoxide into Vitamin K (step 4 to 1).
Source: Wikipedia 2019-04

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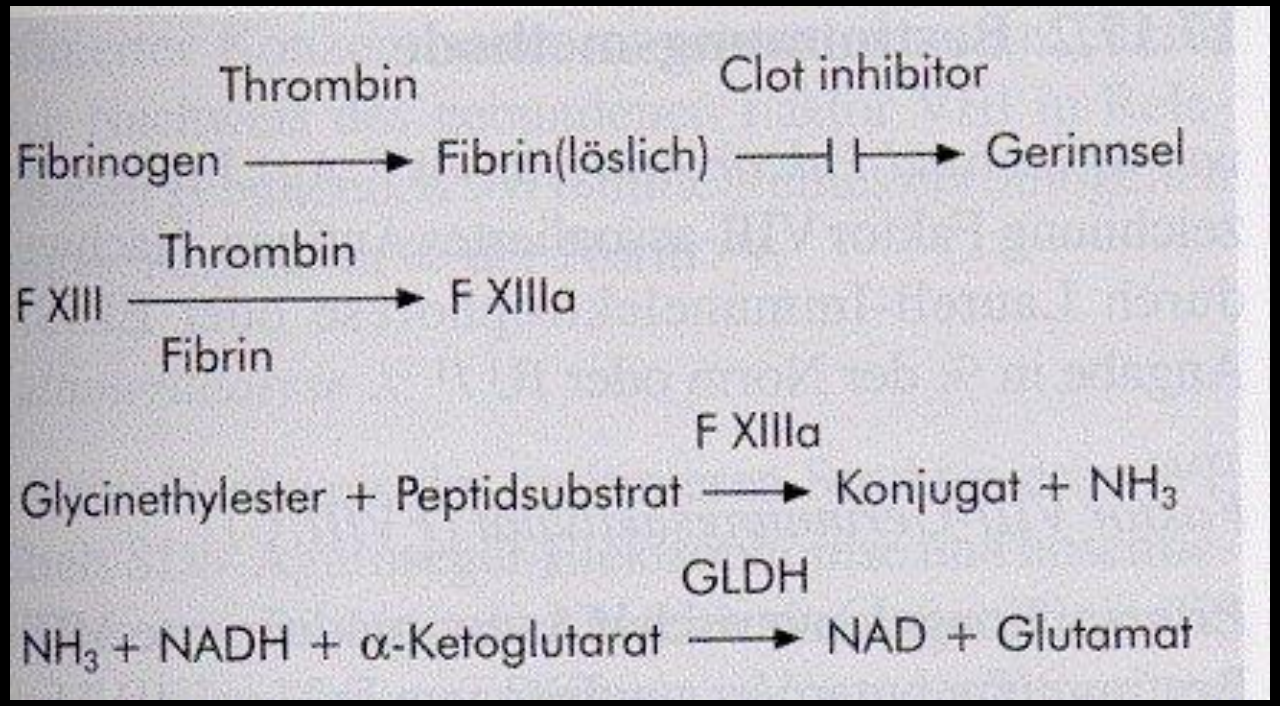
FXIII-Bestmmungsmethode



F.R Rosendaal (2000): Thromb. Haemost. 83: 1 - 2

Which statements regarding edoxaban are correct?

1. It is a direct oral thrombin inhibitor
2. It is a direct oral coagulation factor X inhibitor
3. The distinct impact on coagulation screening parameters (PTT 60 sec, PT 26 %) is typical and no further evaluation is needed
4. Edoxaban can be reversed via Idarucizumab (Praxbind®)
5. Direct oral anticoagulants such as Edoxaban influence the thrombelastogramm (ROTEM, TEM) in a very specific manner and thus can be monitored via ROTEM
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Which parameters should be performed to further clarify the aPTT(60sec) and PT (26 %) in this case

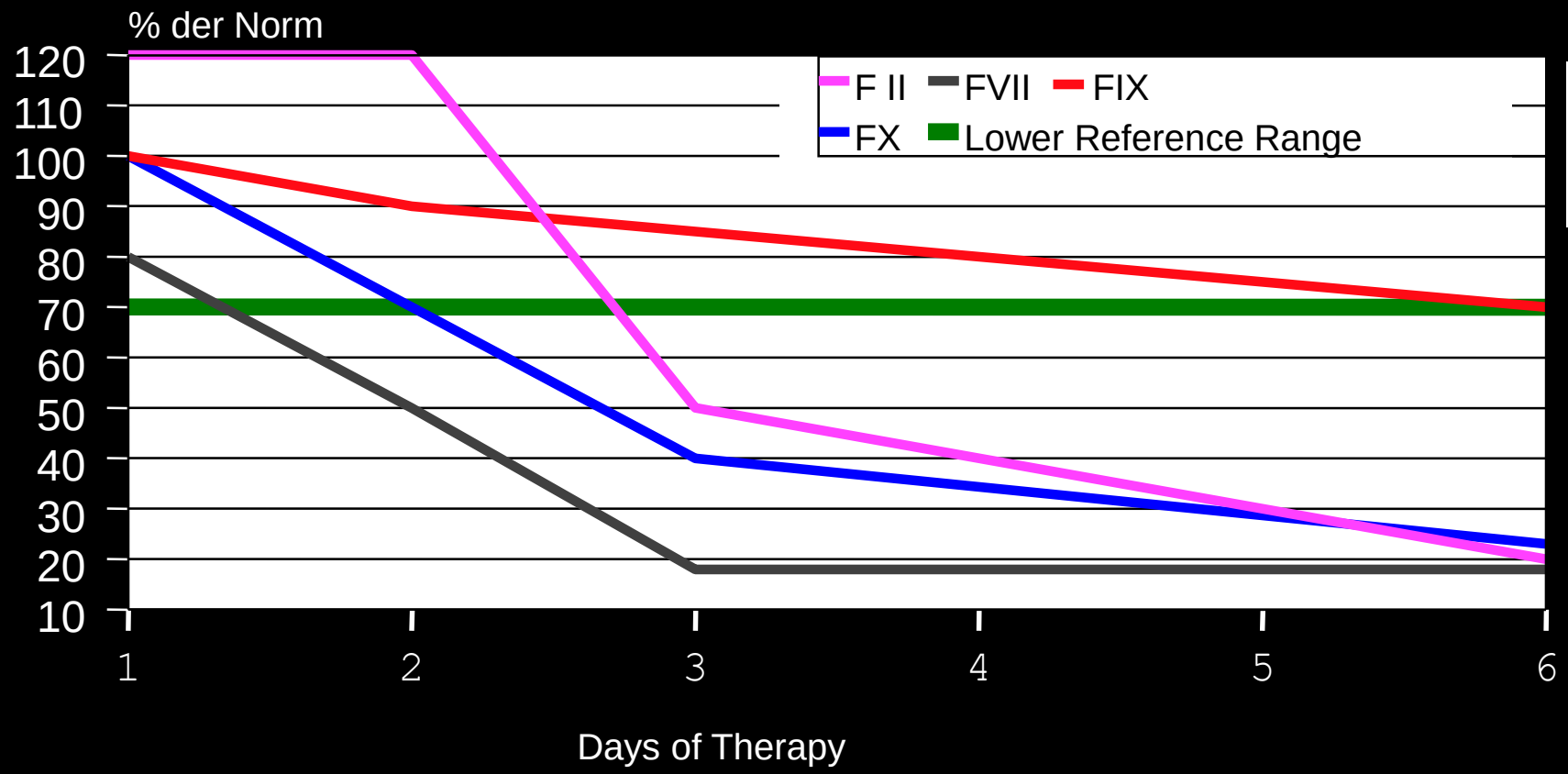
1. Intrinsic coagulation factors
2. Extrinsic coagulation factors
3. Plasminogen and antiplasmin
4. Protein C and protein S activity
5. Lupus anticoagulans
6. Activated Protein C resistance (Faktor V-Leiden)

What is the most likely cause for the coagulation factor results in this case

1. Warfarin was given additionally to Edoxaban
2. Acute liver failure
3. Acute phase
4. Loss of coagulation factors due to haematochezia
5. Inherited deficiency of all coagulation factors
6. It is all about an analytical artefact

FII-VITK	1	50 # .	nach Doak-Stop
FV	1	29 # .	nach Doak-Stop
FVII-VITK	1	50 # .	nach Doak-Stop
FX-VITK	1	37 # .	nach Doak-Stop
FVIII	1	68 # .	nach Doak-Stop
FIX-VITK	1	55 # .	nach Doak-Stop
FXI	1	31 # .	nach Doak-Stop
FXII	1	31 # .	nach Doak-Stop

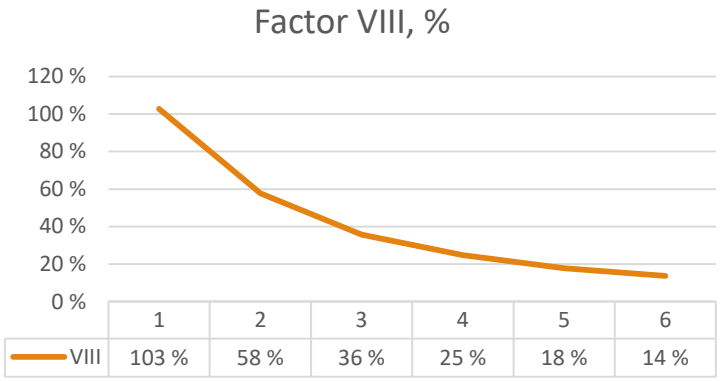
Influence of Vitamin K Antagonists

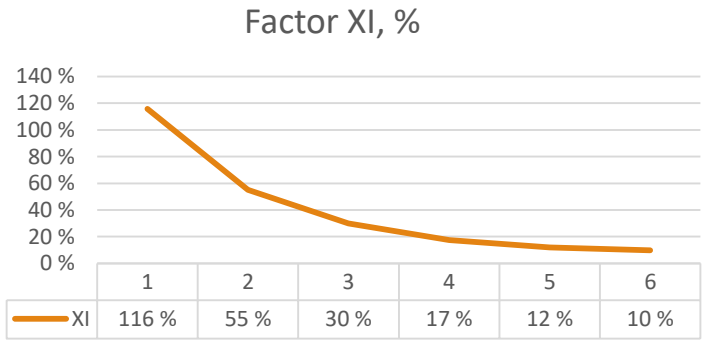


FVII ($T_{1/2}$: 6 h) and Protein C ($T_{1/2}$: 7 h)
FIX ($T_{1/2}$: 1 – 5 d)
FX ($T_{1/2}$: 32h)
FII ($T_{1/2}$: 2 – 5 d)

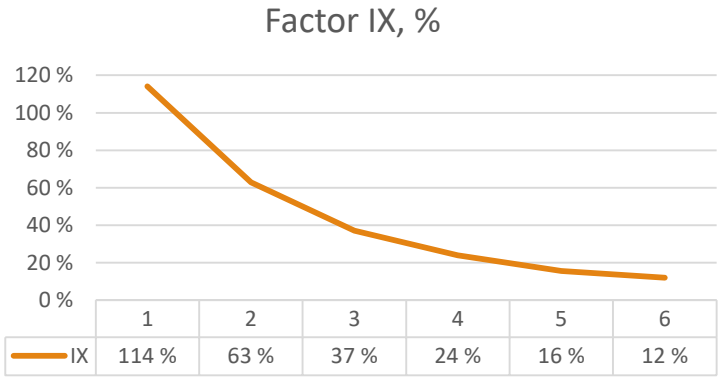
M. Barthels et al. (1998) Gerinnungsanalysen

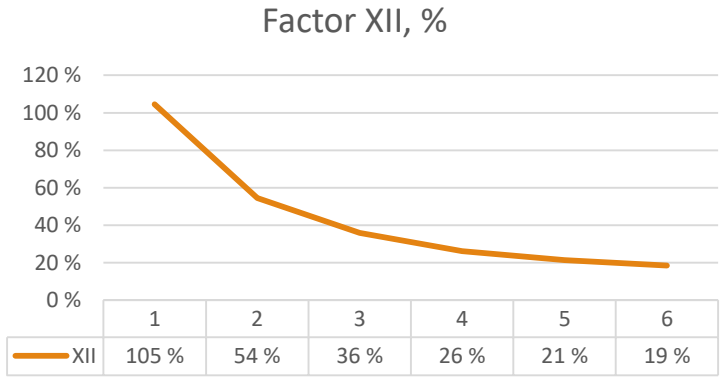
Argatroban-intrinsic factor activity (aPTT-based one stage assay)





Spiking Step	[Arg]
Step 0	**0,01 µg/ml**
Step 1	**0,37 µg/ml**
Step 2	**0,75 µg/ml**
Step 3	**1,09 µg/ml**
Step 4	**1,44 µg/ml**
Step 5	**1,66 µg/ml**





Dabigatran, renal elimination, half life

	Inhibitoren des plasmatisch			
Wirkstoff	**Aragtroban**	**Dabigatranetexilat**	**Rivaroxaban**	**Apixaban**
Handelsname	Argatra®	Pradaxa®	Xarelto®	Eliquis®
Wirkmechanismus	Parenteraler direkter, reversibler Thrombin (IIa)-Inhibitor	Prodrug v. Dabigatran: Oraler direkter Thrombin (IIa)-Inhibitor	Oraler direkter Faktor Xa-Inhibitor	Oraler direkter Faktor Xa-Inhibitor
Indikationen (2018)	Antikoagulation bei Pat. mit HIT-II	Proph. Nach Knie/Hüft-TEP; NV-VHF, TVT + PE (Therapie + Prophylaxe)	NV-VHF, TVT + PE (Therapie + Prophylaxe), nach ACS (2x2.5 mg tgl.)	Proph. Nach Knie/Hüft-TEP; NV-VHF, TVT + PE (Therapie + Prophylaxe)
Standard-Dosierung	Initial 2,0 µg/kg/min	150 mg, 2 x tgl.	20 mg, 1 x tgl.	5 mg, 2 x tgl.
Wirkungseintritt	umgehend	C_{max} innerhalb 0.5 - 2 h	C_{max} innerhalb 2 - 4 h	C_{max} innerhalb 3 - 4 h
Ter.HWZ (Gesunde)	50 min	12 - 14 h	5 - 13 h	13 h
Wirkdauer	aPTT wird ca. 2 h nach absetzen normal	< 48 h*	< 48 h*	< 48 h*
Labor-Monitoring	aPTT (Ziel: 1,5-3x) verdünnte Thrombinzeit (Argatroban-kalibriert)	Thrombinzeit verdünnte Thrombinzeit (Dabigatran-kalibriert)	Anti-Faktor Xa-Aktivität (Rivaroxaban-kalibriert)	Anti-Faktor Xa-Aktivität (Apixaban-kalibriert)
Antidot (AD)	kein spez.AD, (FFP,PPSB)	Praxbind® 5 g i.v.	kein spez.AD, (FFP,PPSB)	kein spez.AD, (FFP,PPSB)
Renale Elimination	20 %	85 %	66 %	27 %
Einfluss der Nierenfunktion	keine Dosisnpassung	<30ml/min → KI	15-30 ml/min: Vorsicht <15ml/min: KI	15-30 ml/min: Vorsicht <15ml/min: KI
Leberfunktions-störung (LFS)	-Dosisanpassung bei mäßiger LFS -KI bei schwerer LFS	KI bei schwerer LFS	KI bei schwerer LFS	KI bei schwerer LFS