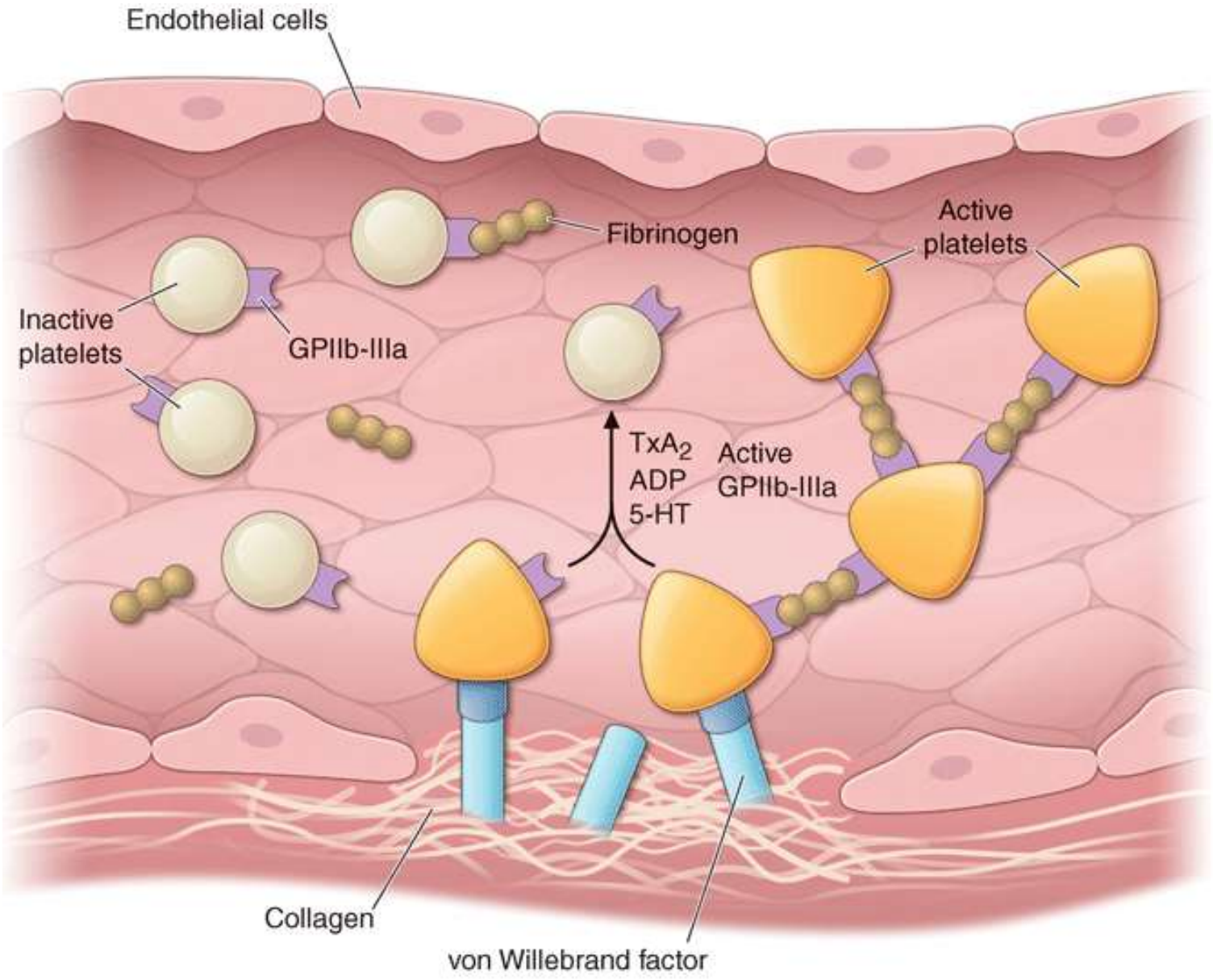
Direct Thrombin inhibitors: Overview and Meta-analyses/EHRA guidelines discussion

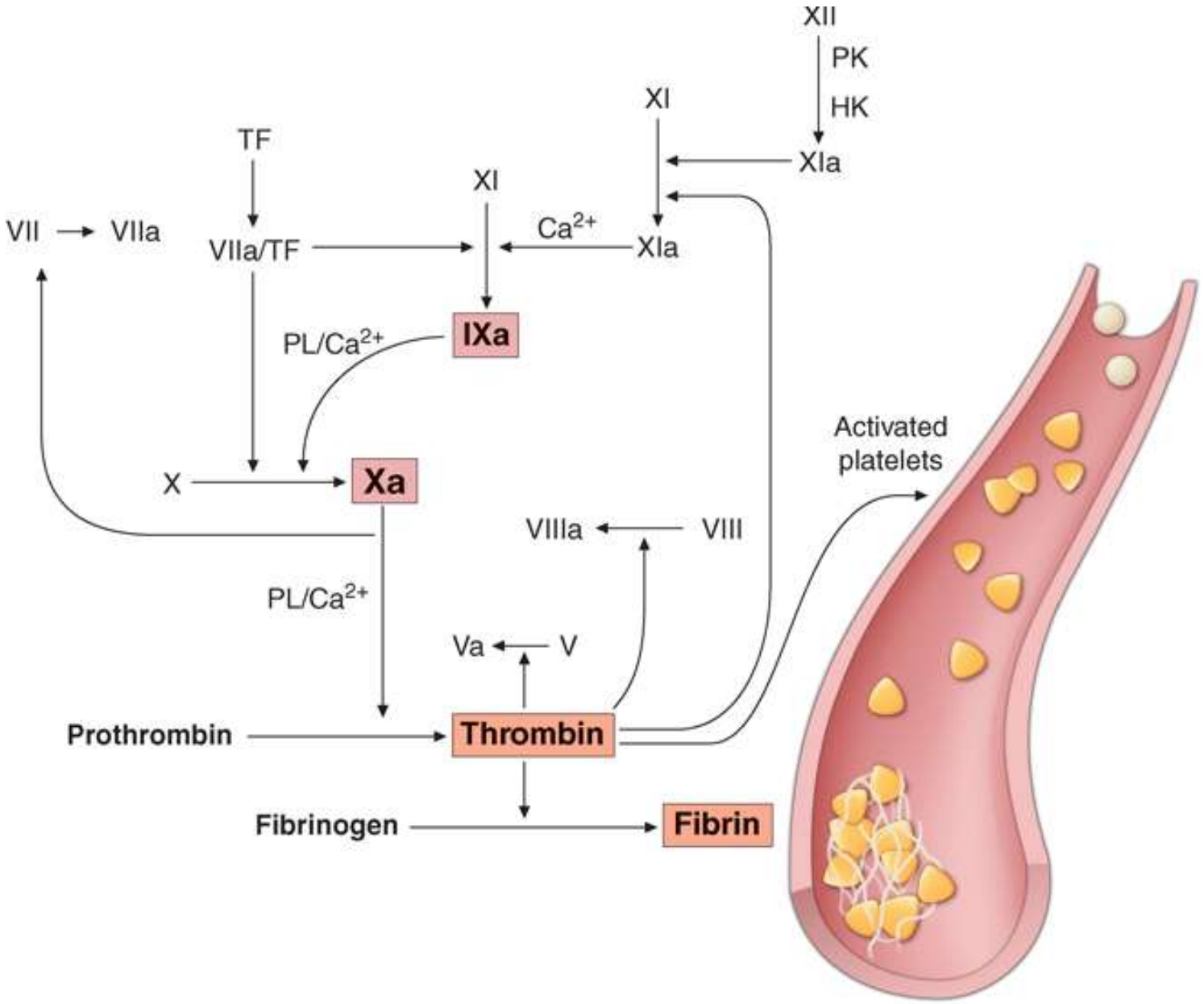
Arun Chaudhury

Sep 12th 2013

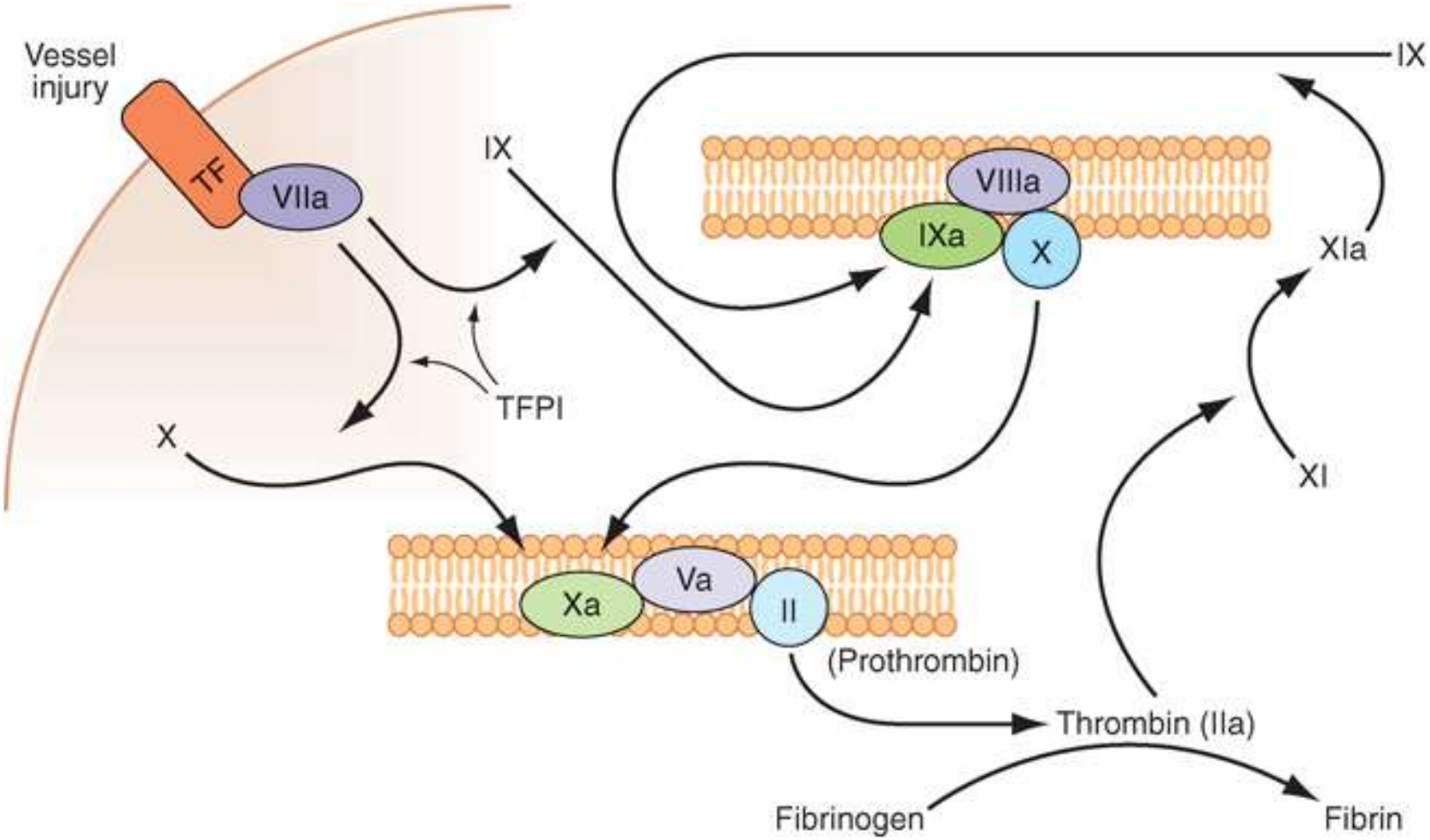
Initial events when integrity of vessel wall is breached



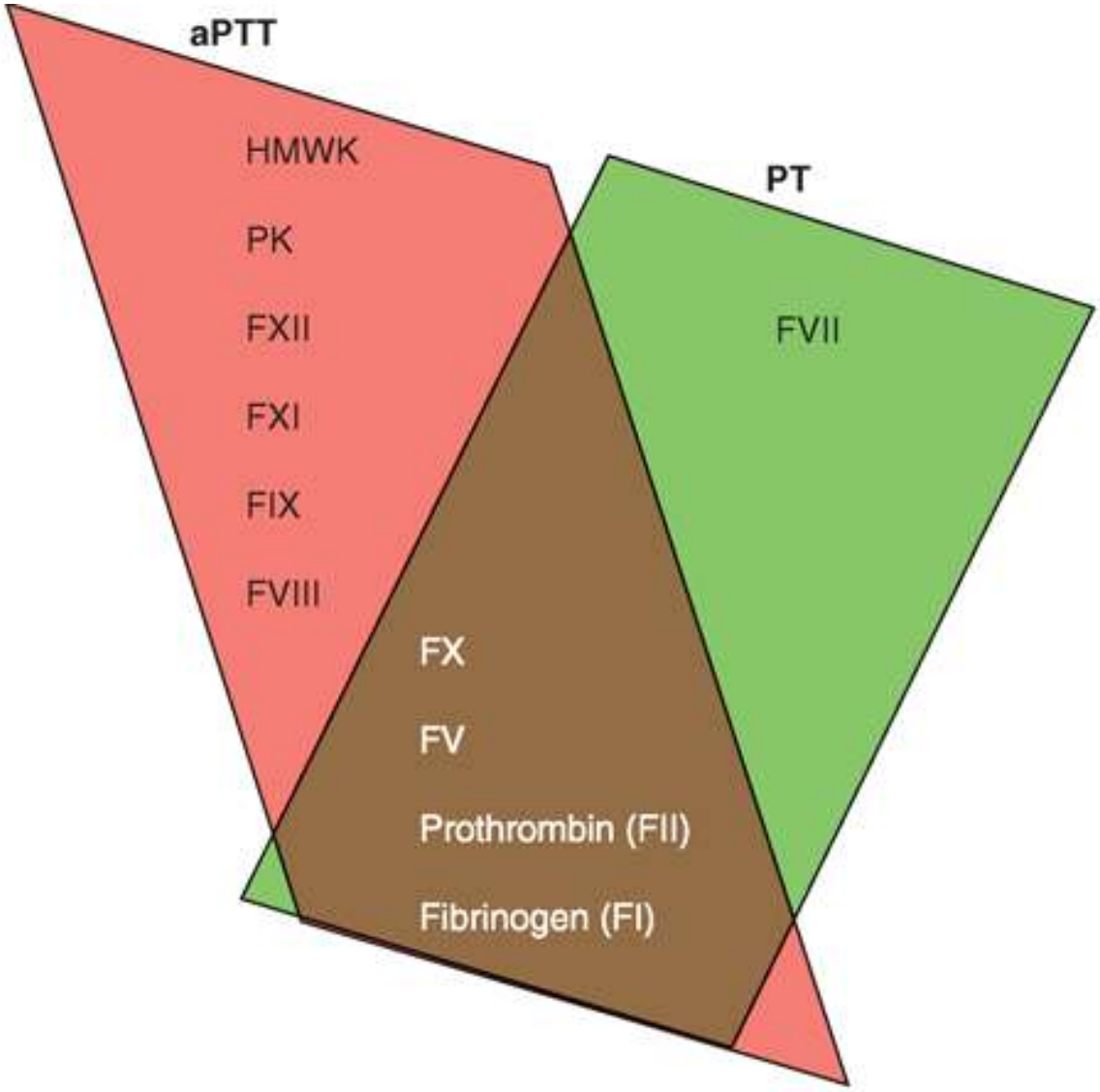
Platelet plug reinforced by set of insoluble proteins produced by cascade of protease activation: a positive feedback system



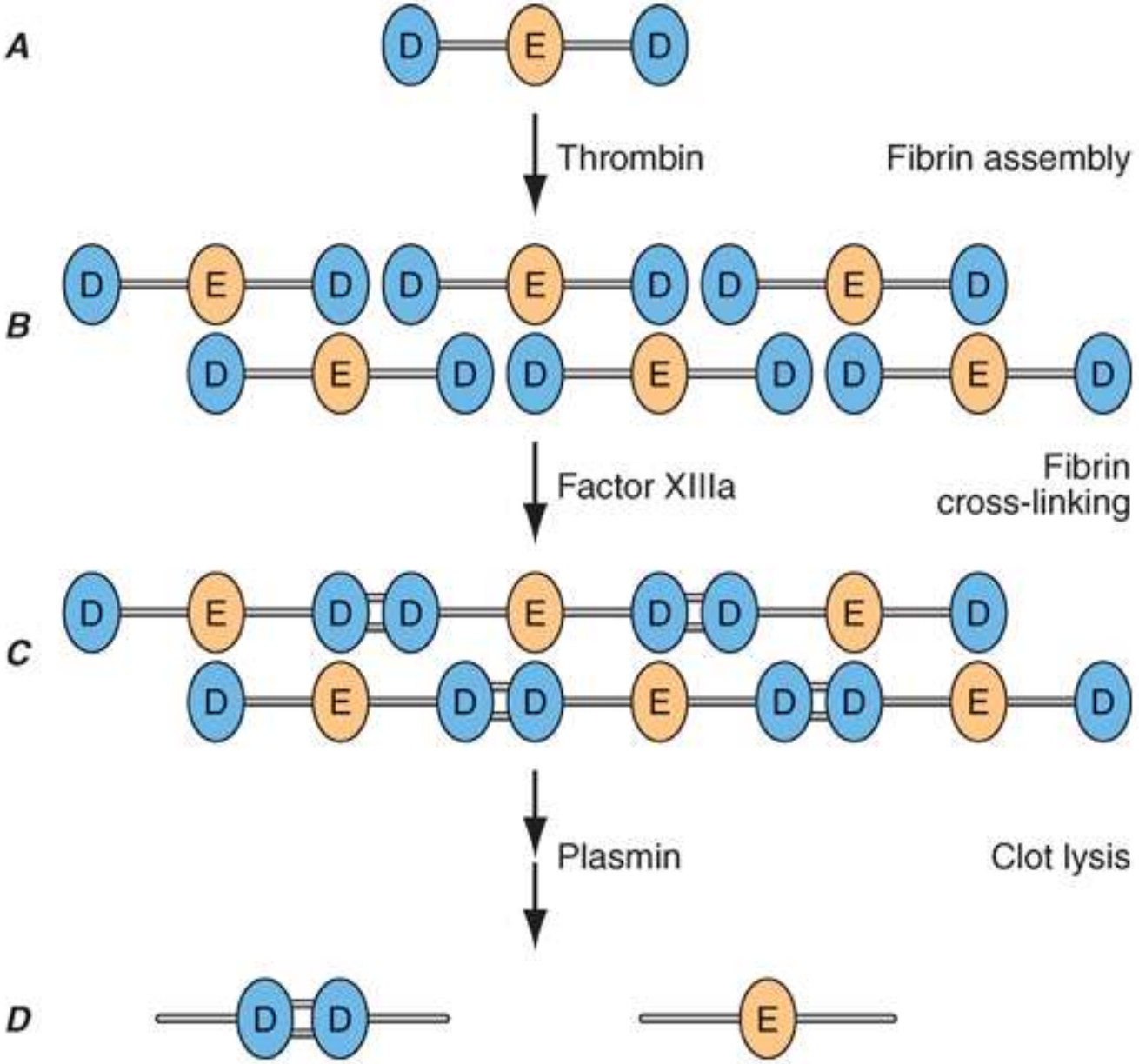
Extrinsic and Intrinsic Pathways



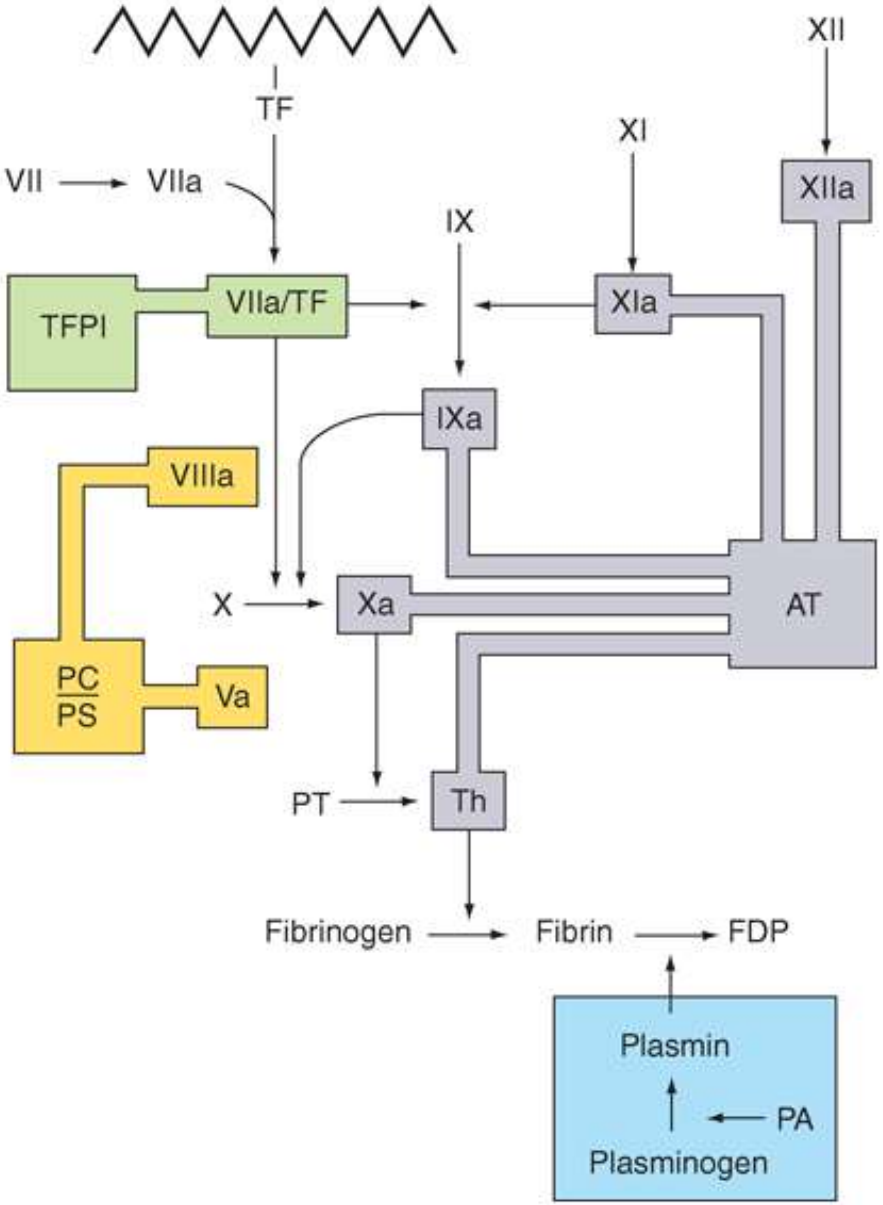
Laboratory examination of clotting pathways

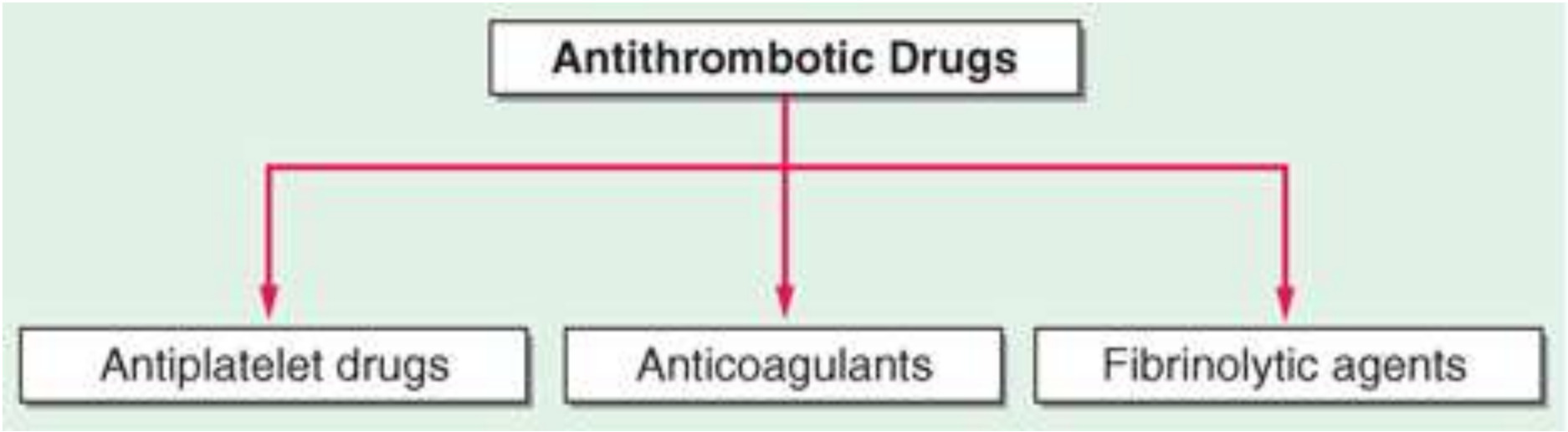


Fate of Fibrin



Counterbalance by 4 major anti-clotting mechanisms





- Aspirin
- Clopidogrel
- GpIIB/IIIa inhibitor (abciximab, tirofiban, eptifibatide)

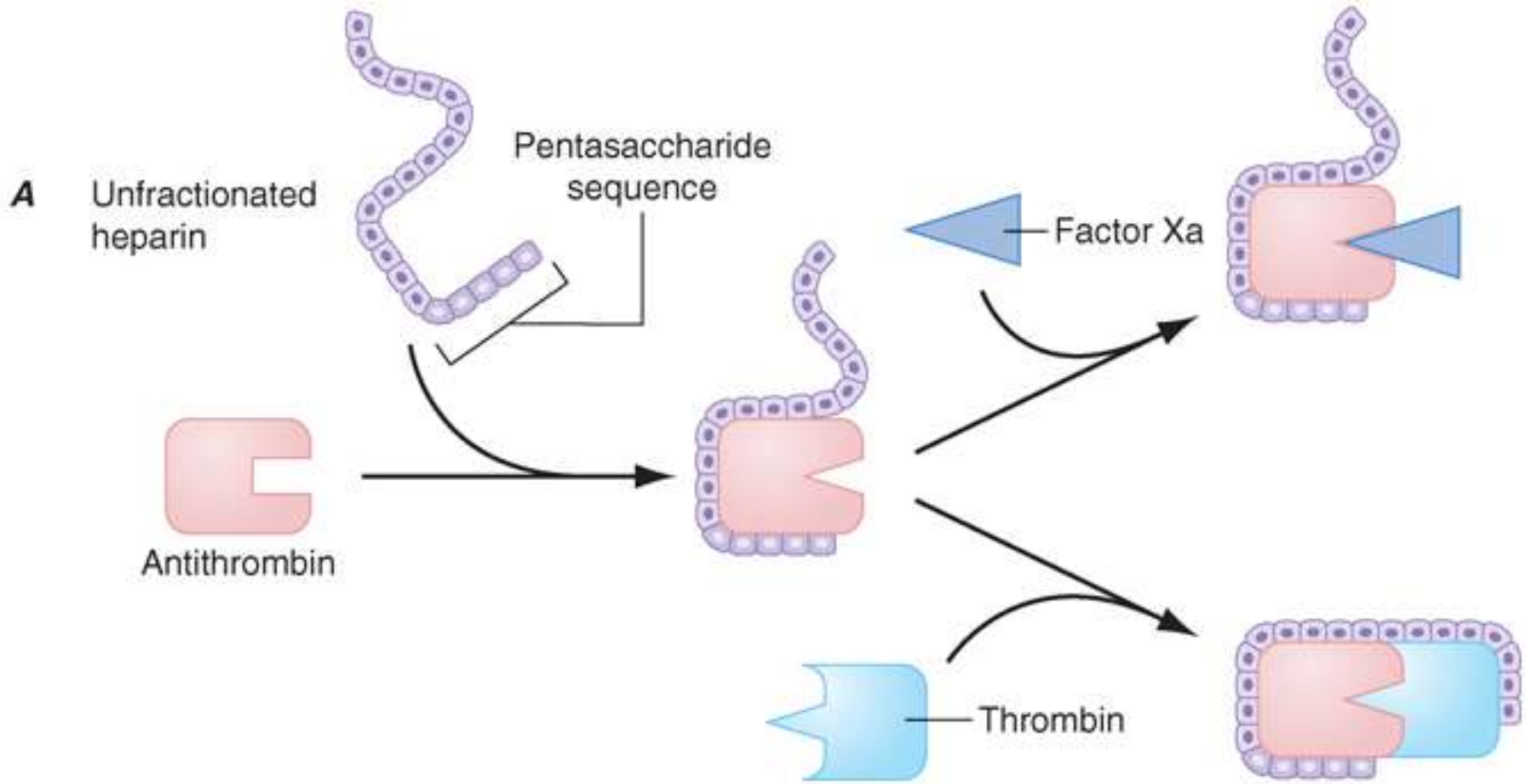
- To discuss today

- rt PA

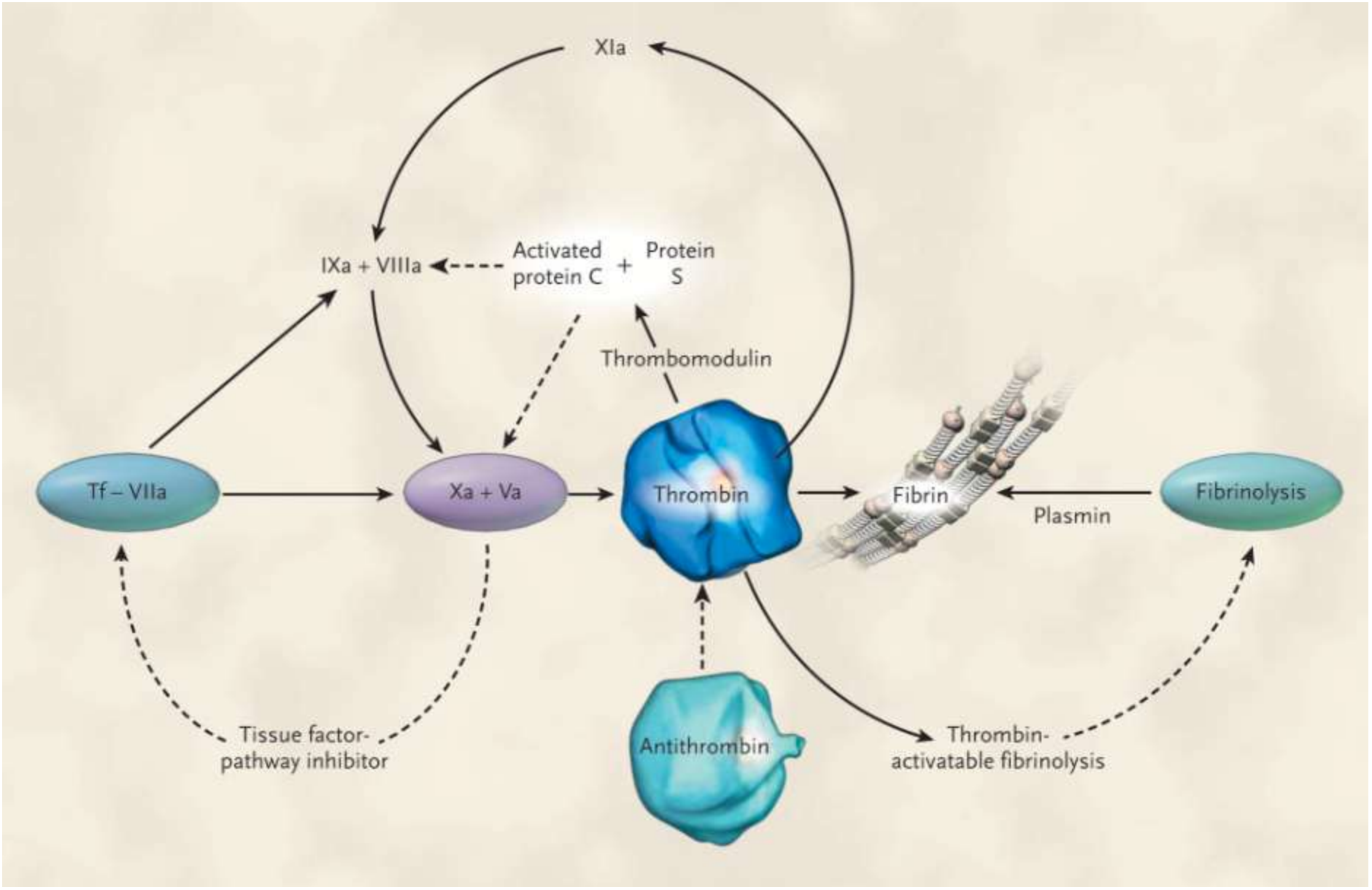
Anticoagulants

- Targeting downstream effectors mainly

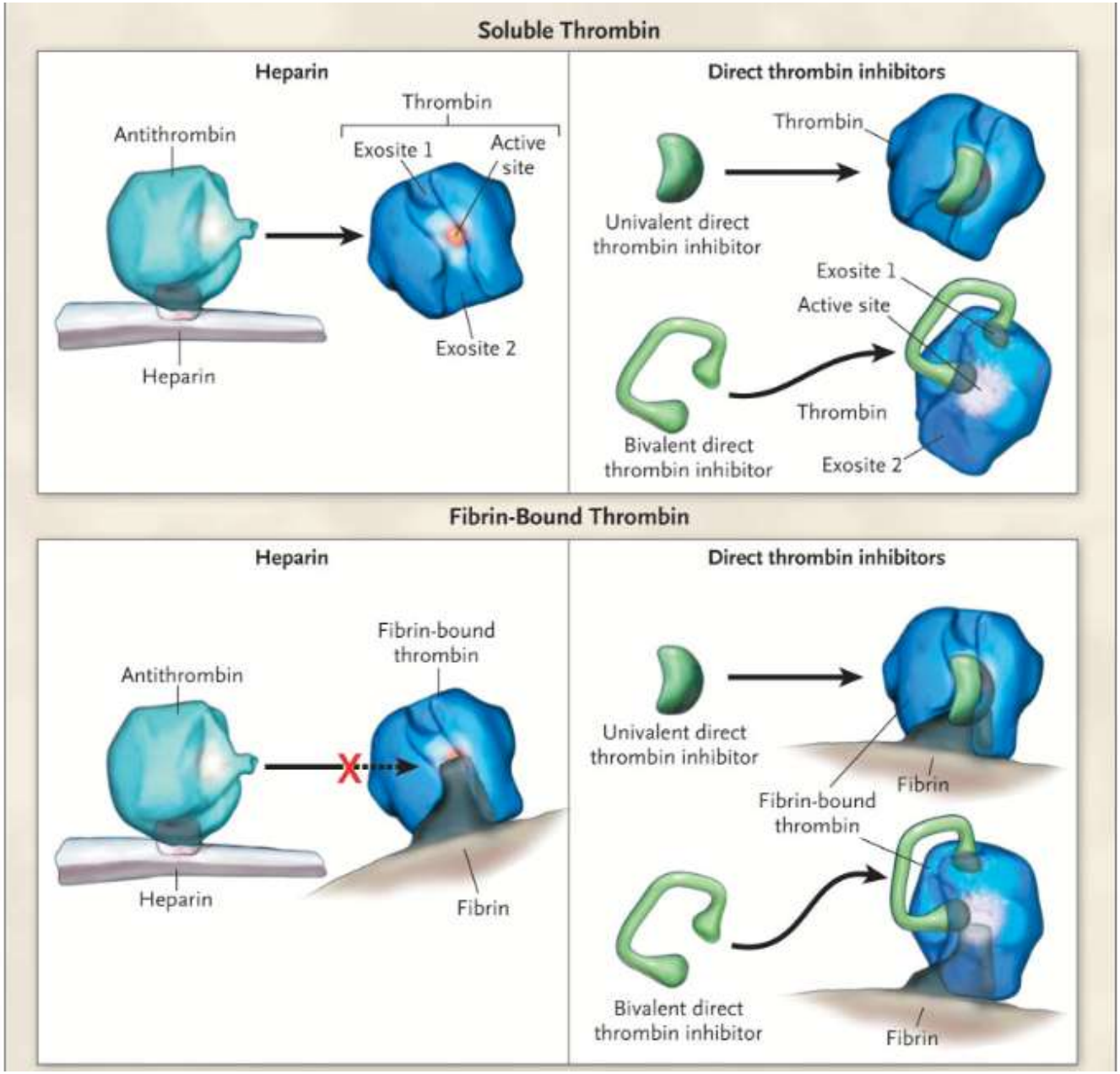
Heparin


A
Unfractionated heparin
Pentasaccharide sequence
Antithrombin
Factor Xa
Thrombin

Recapitulation



Thrombin active site



Direct Thrombin Inhibitors (DTIs)

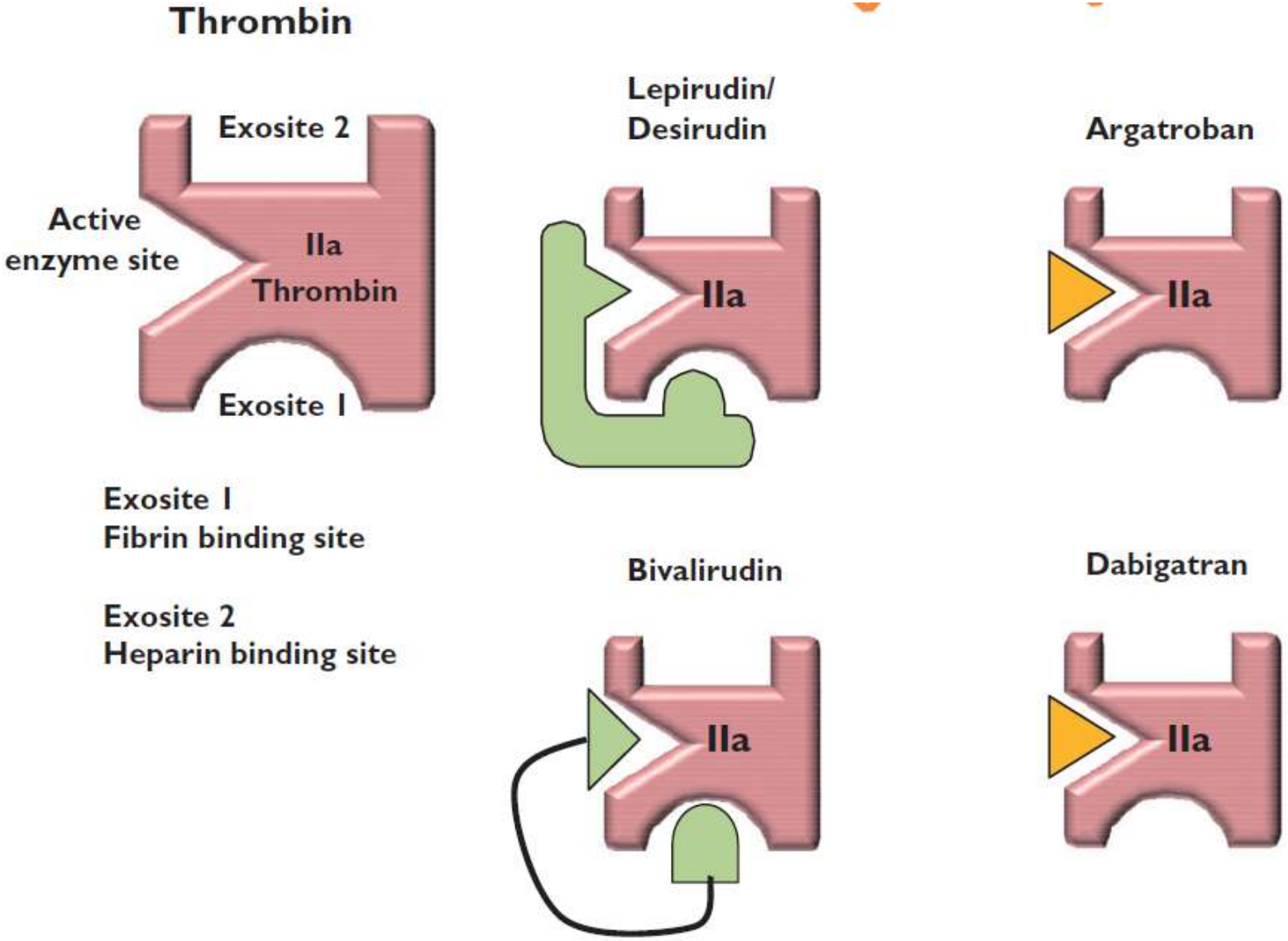


Table 1. Main Properties and Pharmacokinetic Characteristics of Direct Thrombin Inhibitors.

Characteristic	Recombinant Hirudins*	Bivalirudin (Hirulog)	Argatroban (Novastan)	Ximelagatran and Melagatran (Exanta)	Dabigatran
Route of administration	Intravenous, subcutaneous	Intravenous	Intravenous	Intravenous, subcutaneous (melagatran), oral (ximelagatran)	Oral
Plasma half-life	Intravenous, 60 min; subcutaneous, 120 min	25 min	45 min	Intravenous and subcutaneous, 2–3 hr; oral, 3–5 hr	12 hr
Main site of clearance	Kidney	Kidney, liver, other sites	Liver	Kidney	Kidney

* Recombinant hirudins include lepirudin (Refludan) and desirudin (Iprivask).

NEJM

1st manuscript

Direct thrombin inhibitors in cardiovascular disease

Kyle A. Arsenault, Jack Hirsh, Richard P. Whitlock and John W. Eikelboom

Indications for anticoagulation

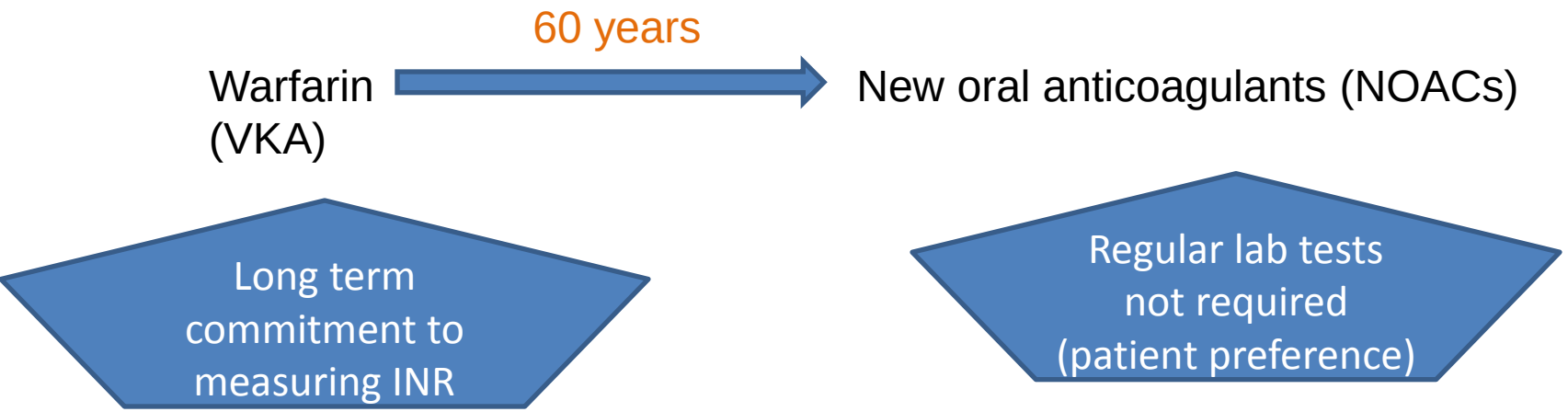
- PCI
- ACS
- CABG
- Orthopedic Surgery
- Initial and long term t/t of venous thromboembolism
- Prevention of thromboembolism in AF or mechanical valves

Ideal anticoagulants

- Rapid onset
- Predictable effect
- Short duration of action
- Readily reversible

Warfarin: Vit K antagonist

- delayed onset of action
- interaction with food and drugs
- inter-individual variability
- frequent monitoring



Key points

- Bivalirudin is an effective and safer alternative to heparin with or without the addition of a glycoprotein IIb/IIIa inhibitor in patients with acute coronary syndromes or those undergoing percutaneous coronary intervention
- Argatroban seems to be a viable treatment for patients with heparin-induced thrombocytopenia, but its role in treating other conditions remains uncertain
- Dabigatran is an attractive alternative to low-molecular-weight heparin for the prevention of venous thromboembolism in patients undergoing major orthopedic surgery, and to warfarin for the long-term treatment of venous thromboembolism
- The most-compelling indication for dabigatran is as an alternative to warfarin for stroke prevention in patients with atrial fibrillation, where it has been shown to reduce morbidity and mortality

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Table 1 | Properties of parenteral direct thrombin inhibitors and heparin

Property	Bivalirudin	Argatroban	Unfractionated heparin
Onset of action	Immediate	Immediate	Immediate
Time to peak plasma concentration	2–15 min	1–3 h	20–60 min
Half-life	25 min (1 h in patients with renal impairment)	45 min (2.5 h in patients with hepatic impairment)	40–60 min (dose-dependent)
Main site(s) of clearance	Intravascular proteolysis (80%), kidneys (20%)	Liver	Depolymerization by endothelial cells and macrophages
Antidote	No	No	Yes (protamine sulfate)

No
HIT

No
HIT

HIT

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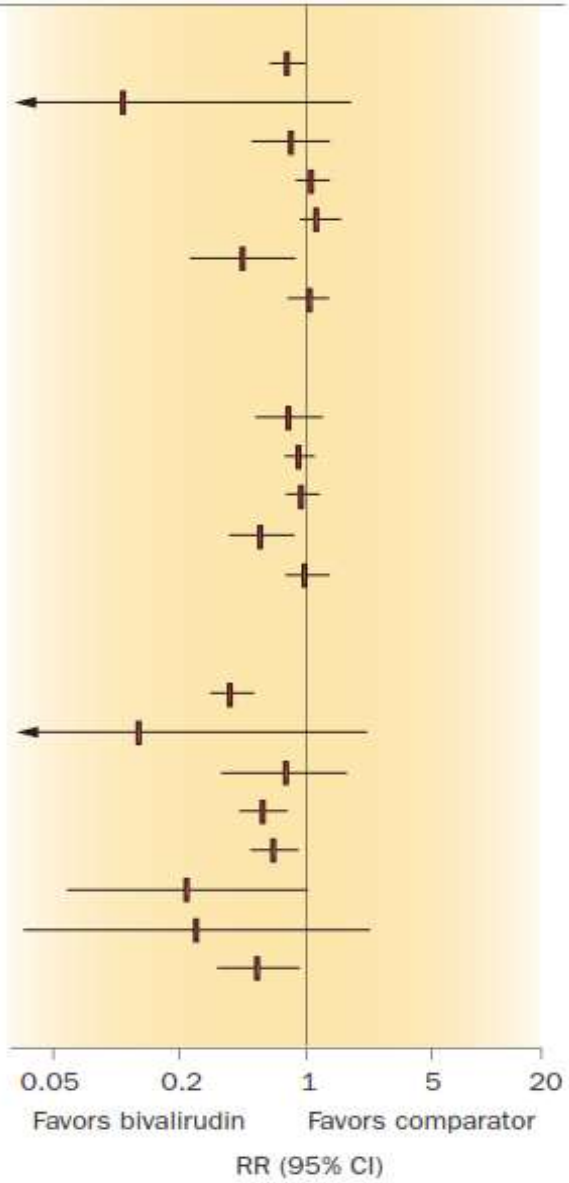
Forest Plot: bivalirudin vs heparin+GpIIB/IIIa inhibitor (PCI)

Study or subgroup	Bivalirudin Events	Bivalirudin Total	Comparator Events	Comparator Total	RR (95% CI)
Composite ischemia					
HAS[17,18]	135	2,161	169	2,151	0.80 (0.64–0.99)
CACHET[19]*	0	59	5	64	0.10 (0.01–1.74)
REPLACE-1[20]	30	532	36	524	0.82 (0.51–1.31)
REPLACE-2[21]‡	227	2,975	211	2,990	1.08 (0.90–1.30)
ISAR-REACT 3[24]	134	2,289	115	2,281	1.16 (0.91–1.48)
ARNO[25]	12	425	27	425	0.44 (0.23–0.87)
ISAR-REACT 4[27]§	115	860	110	861	1.05 (0.82–1.34)
Composite ischemia or major bleeding					
REPLACE-1[20]	38	532	46	524	0.81 (0.54–1.23)
REPLACE-2[21]‡	275	2,975	299	2,991	0.92 (0.79–1.08)
ISAR-REACT 3[24]	190	2,289	199	2,281	0.95 (0.79–1.15)
NAPLES[26]	30	167	53	168	0.57 (0.38–0.84)
ISAR-REACT4[27]§	95	860	94	861	1.01 (0.77–1.32)
Major bleeding					
HAS[17,18]	76	2,161	199	2,151	0.38 (0.29–0.49)
CACHET[19]*	0	59	4	64	0.12 (0.01–2.19)
REPLACE-1[20]	11	532	14	524	0.77 (0.35–1.69)
REPLACE-2[21]‡	71	2,993	123	3,008	0.58 (0.44–0.77)
ISAR-REACT 3[24]	70	2,289	104	2,281	0.67 (0.50–0.90)
ARNO[25]	2	425	9	425	0.22 (0.05–1.02)
NAPLES[26]	1	167	4	168	0.25 (0.03–2.23)
ISAR-REACT 4[27]§	22	860	40	861	0.55 (0.33–0.92)



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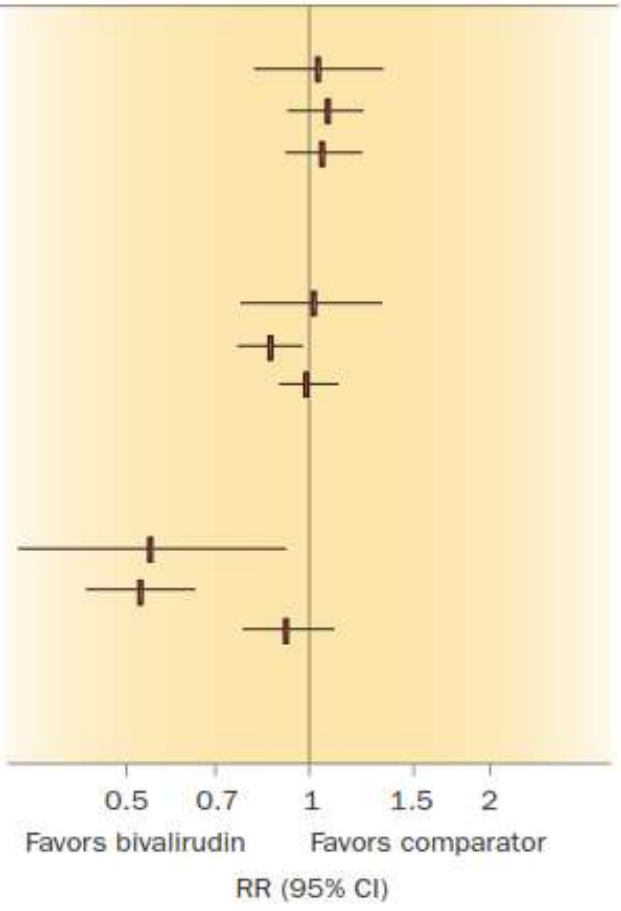
Forest Plot: bivalirudin vs heparin+GpIIB/IIIa inhibitor (NSTEMI ACS)

Study or subgroup	Bivalirudin Events	Bivalirudin Total	Comparator Events	Comparator Total	RR (95% CI)
Composite ischemia					
ISAR-REACT 4[27]*	115	860	110	861	1.05 (0.82–1.34)
ACUITY bivalirudin only[30]	360	4,612	334	4,603	1.08 (0.93–1.24)
ACUITY plus GP IIb/IIIa inhibitor[30]	356	4,604	334	4,603	1.07 (0.92–1.23)
Composite ischemia or major bleeding					
ISAR-REACT 4[27]*	95	860	94	861	1.01 (0.77–1.32)
ACUITY bivalirudin only[30]	466	4,612	538	4,603	0.86 (0.77–0.97)
ACUITY plus GP IIb/IIIa inhibitor[30]	541	4,604	538	4,603	1.01 (0.90–1.12)
Major bleeding (not related to CABG surgery)					
ISAR-REACT 4[27]*	22	860	40	861	0.55 (0.33–0.92)
ACUITY bivalirudin only[30]	139	4,612	262	4,603	0.53 (0.43–0.65)
ACUITY plus GP IIb/IIIa inhibitor[30]	243	4,604	262	4,603	0.93 (0.78–1.10)



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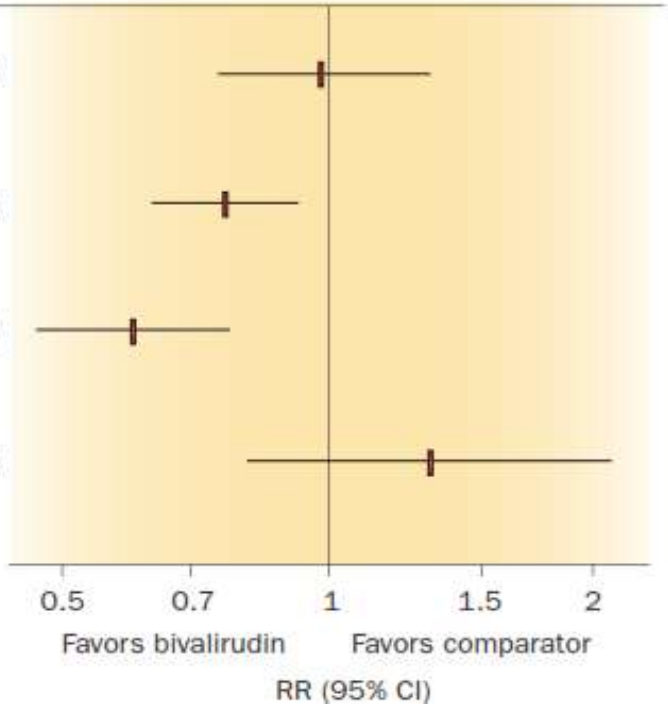
Forest Plot: bivalirudin vs heparin ± GpIIB/IIIa inhibitor (STEMI ACS)

Study or subgroup	Bivalirudin Events	Bivalirudin Total	Comparator Events	Comparator Total	RR (95% CI)
Major adverse cardiac events					
HORIZONS-AMI[33]	98	1,800	99	1,802	0.99 (0.76–1.30)
Composite ischemia or major bleeding					
HORIZONS-AMI[33]	166	1,800	218	1,802	0.76 (0.63–0.92)
Major bleeding (not related to CABG surgery)					
HORIZONS-AMI[33]	89	1,800	149	1,802	0.60 (0.46–0.77)
Stent thrombosis					
HORIZONS-AMI[33]	39	1,800	30	1,802	1.30 (0.81–2.09)



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Forest Plot: Argatroban in HIT (heparin induced thrombocytopenia)

Study or subgroup	Argatroban Events	Argatroban Total	Control Events	Control Total	RR (95% CI)
Composite ischemia					
ARG-911[44] and ARG-915[45] – HIT	94	349	54	139	0.69 (0.53–0.91)
ARG-911[44] and ARG-915[45] – HIT with thrombosis	158	373	26	46	0.75 (0.57–0.99)
Major bleeding					
ARG-911[44] and ARG-915[45] – HIT	15	349	12	139	0.50 (0.24–1.04)
ARG-911[44] and ARG-915[45] – HIT with thrombosis	30	373	1	46	3.70 (0.52–26.49)

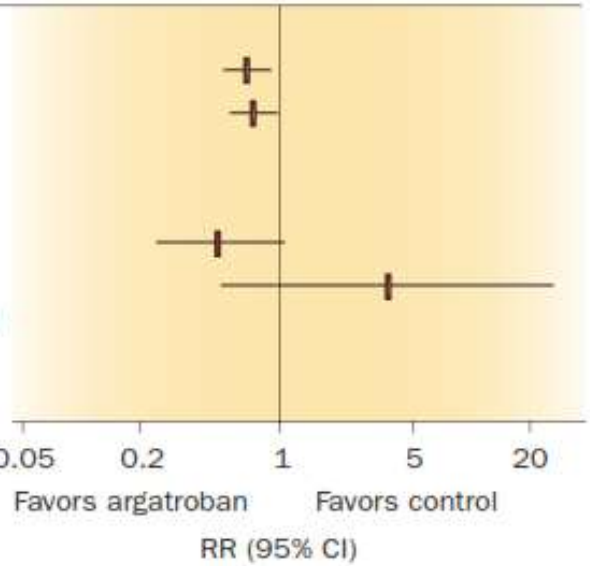

Figure 4 | Trials of argatroban in patients with HIT. Argatroban was associated with a significant decrease in the primary composite outcome of all-cause mortality, all-cause amputation, or new thrombosis, and a similar rate of bleeding in both the HIT and HIT with thrombosis groups. Argatroban seems to be a viable treatment for patients with HIT, but its role in the context of other effective therapies, such as danaparoid and fondaparinux, remains uncertain. Abbreviations: HIT, heparin-induced thrombocytopenia; RR, risk ratio.

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Forest Plot: Argatroban vs Enoxaparin in venous TE post-Orthopedic surgery

Study or subgroup	Dabigatran Events	Dabigatran Total	Enoxaparin Events	Enoxaparin Total	RR (95% CI)
Venous thromboembolism or all-cause mortality					
RE·NOVATE 220 mg[56]	53	880	60	897	0.90 (0.63–1.29)
RE·NOVATE 150 mg[56]	75	874	60	897	1.28 (0.93–1.78)
RE·NOVATE II[57]	61	792	69	785	0.88 (0.63–1.22)
RE·MODEL 220 mg[58]	183	503	193	512	0.97 (0.82–1.13)
RE·MODEL 150 mg[58]	213	526	193	512	1.07 (0.92–1.25)
RE·MOBILIZE 220 mg[59]	188	604	163	643	1.23 (1.03–1.47)
RE·MOBILIZE 150 mg[59]	219	649	163	643	1.33 (1.12–1.58)
Major bleeding					
RE·NOVATE 220 mg[56]	23	1,146	18	1,154	1.29 (0.70–2.37)
RE·NOVATE 150 mg[56]	15	1,163	18	1,154	0.83 (0.42–1.63)
RE·NOVATE II[57]	14	1,010	9	1,003	1.54 (0.67–3.55)
RE·MODEL 220 mg[58]	10	679	9	694	1.14 (0.46–2.78)
RE·MODEL 150 mg[58]	9	703	9	694	0.99 (0.39–2.47)
RE·MOBILIZE 220 mg[59]	5	857	12	868	0.42 (0.15–1.19)
RE·MOBILIZE 150 mg[59]	5	871	12	868	0.42 (0.15–1.17)

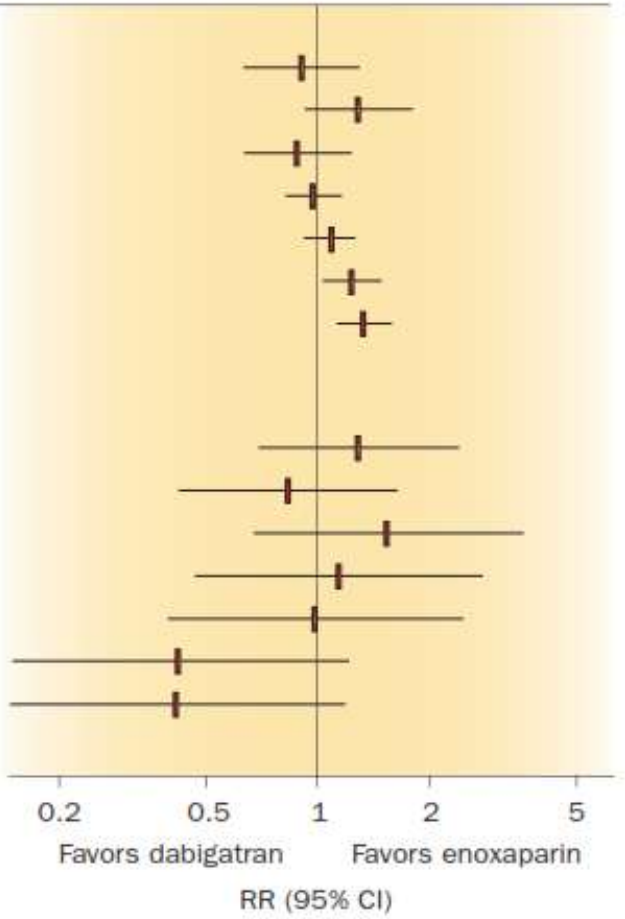

Figure 5 | Trials of dabigatran in the prevention of venous thromboembolism. Dabigatran has shown similar efficacy and safety as enoxaparin 40 mg once daily, but is less effective than enoxaparin 30 mg twice daily for the prevention of venous thromboembolism after orthopedic surgery. Abbreviation: RR, risk ratio.

RE-LY trial: comparison of oral anticoagulants in prevention of stroke/TE in Afib patients

Study or subgroup	Dabigatran Events	Dabigatran Total	Warfarin Events	Warfarin Total	RR (95% CI)
Stroke or systemic embolism					
RE-LY 150 mg[66,67]	134	6,076	202	6,022	0.66 (0.53–0.82)
RE-LY 110 mg[66,67]	183	6,015	202	6,022	0.91 (0.74–1.10)
Myocardial infarction					
RE-LY 150 mg[66,67]	97	6,076	75	6,022	1.28 (0.95–1.73)
RE-LY 110 mg[66,67]	98	6,015	75	6,022	1.31 (0.97–1.76)
Major bleeding					
RE-LY 150 mg[66,67]	399	6,076	421	6,022	0.94 (0.82–1.07)
RE-LY 110 mg[66,67]	342	6,015	421	6,022	0.81 (0.71–0.93)
Intracranial hemorrhage					
RE-LY 150 mg[66,67]	36	6,076	87	6,022	0.41 (0.28–0.60)
RE-LY 110 mg[66,67]	27	6,015	87	6,022	0.31 (0.20–0.48)
Gastrointestinal bleeding					
RE-LY 150 mg[66,67]	182	6,076	120	6,022	1.50 (1.20–1.89)
RE-LY 110 mg[66,67]	133	6,015	120	6,022	1.11 (0.87–1.42)
Dyspepsia					
RE-LY 150 mg[66,67]	688	6,076	348	6,022	1.96 (1.73–2.22)
RE-LY 110 mg[66,67]	707	6,015	348	6,022	2.03 (1.80–2.30)

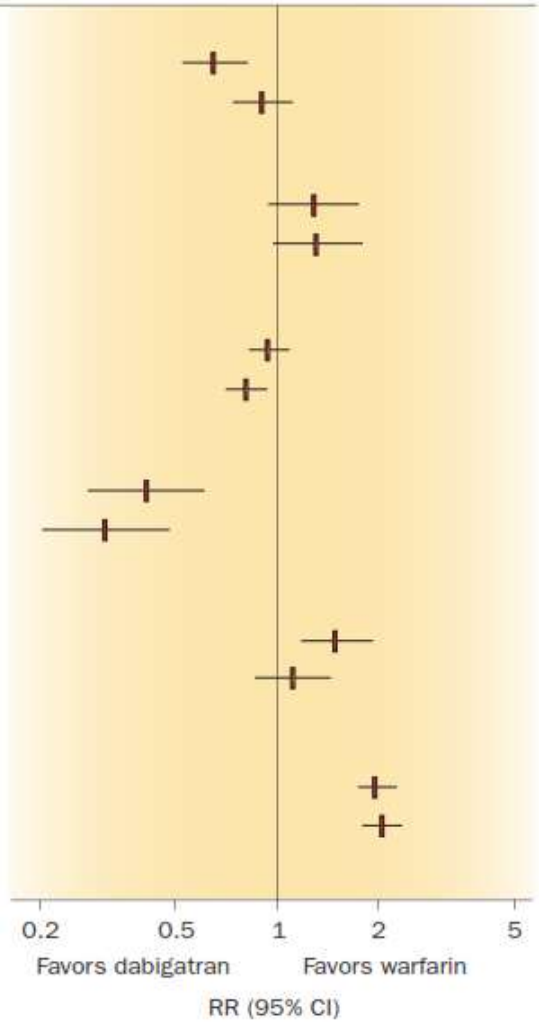

Figure 6 | Trials of dabigatran in the prevention of stroke and thromboembolism in patients with atrial fibrillation. Dabigatran 110 mg twice daily was noninferior to warfarin for the prevention of stroke or systemic embolism, and superior to warfarin for the primary safety outcome of major hemorrhage. Dabigatran 150 mg demonstrated the reverse pattern; at this dose, the drug was superior to warfarin for the primary efficacy outcome, but was similar to warfarin for the risk of major hemorrhage. Both doses of dabigatran tend to increase the risk of myocardial infarction. The results of RE-LY[66,67] provide a strong rationale to consider dabigatran as a first-line therapy for stroke prevention in patients with AF and additional risk factors for stroke who do not have contraindications. Abbreviation: RR, risk ratio.

Table 2 | Properties of dabigatran, enoxaparin, and warfarin

Property	Dabigatran	Enoxaparin	Warfarin
Route of administration	Oral	Parenteral	Oral
Onset of action	0.5–2.0 h	1 h	36–72 h
Time to peak plasma concentration	2–3 h	3–5 h	1.5–3.0 days
Half-life	12–14 h	4.5–7.0 h	20–60 h
Main site of clearance	Kidneys (80%)	Kidneys	Liver
Antidote	No	Partial (60% by protamine sulfate)	Yes (vitamin K, fresh-frozen plasma, or prothrombin-complex concentrates)

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2nd manuscript

European Heart Journal
doi:10.1093/eurheartj/eht134

EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

Hein Heidbuchel[1]*, Peter Verhamme[1], Marco Alings[2], Matthias Antz[3], Werner Hacke[4], Jonas Oldgren[5], Peter Sinnaeve[1], A. John Camm[6], and Paulus Kirchhof[7,8]

1. Practical start-up and follow-up scheme for patients on new oral anticoagulants

Atrial fibrillation
oral anticoagulation card
for non-vitamin-K anticoagulants

Patient name: DOB:

Patient address:

Oral anticoagulant, dosing, timing, with or without food:

Treatment indication:

Treatment started:

Name and address of anticoagulant prescriber:

Telephone number of prescriber or clinic:

More info:
www.NOACforAF.eu
www.noacforaf.eu

Planned or unplanned visits

Date (or date range):	Site (GP, clinic, cardiologist, ...):	To do / findings:

Recommended follow-up

(see EHRA at www.NOACforAF.eu for information & practical advice)

Check each visit: 1. Compliance (pt. should bring remaining meds)?
2. Thrombo-embolic events?
3. Bleeding events?
4. Other side effects?
5. Co-medications and over-the-counter drugs.

Blood sampling: - monitoring of anticoagulation level is not required!
- yearly: Hb, renal and liver function
- if CrCl 30-60 ml/min, >75y, or fragile:
6-monthly renal function
- if CrCl 15-30 ml/min:
3-monthly renal function
- if intercurring condition that may have impact:
renal and/or liver function

Date	Serum creatinine	Creatinine clearance	Hemo-globin	Liver tests

Important patient instructions

Take your drug exactly as prescribed (once or twice daily).
No drug is no protection!

Never stop your medsinc without consulting your physician.

Never add any other medication without consulting your physician, not even short-term painkillers that you can get without prescription.

Alert your dentist, surgeon or other physician before an intervention.

Concomitant medication

Name:	Dose:

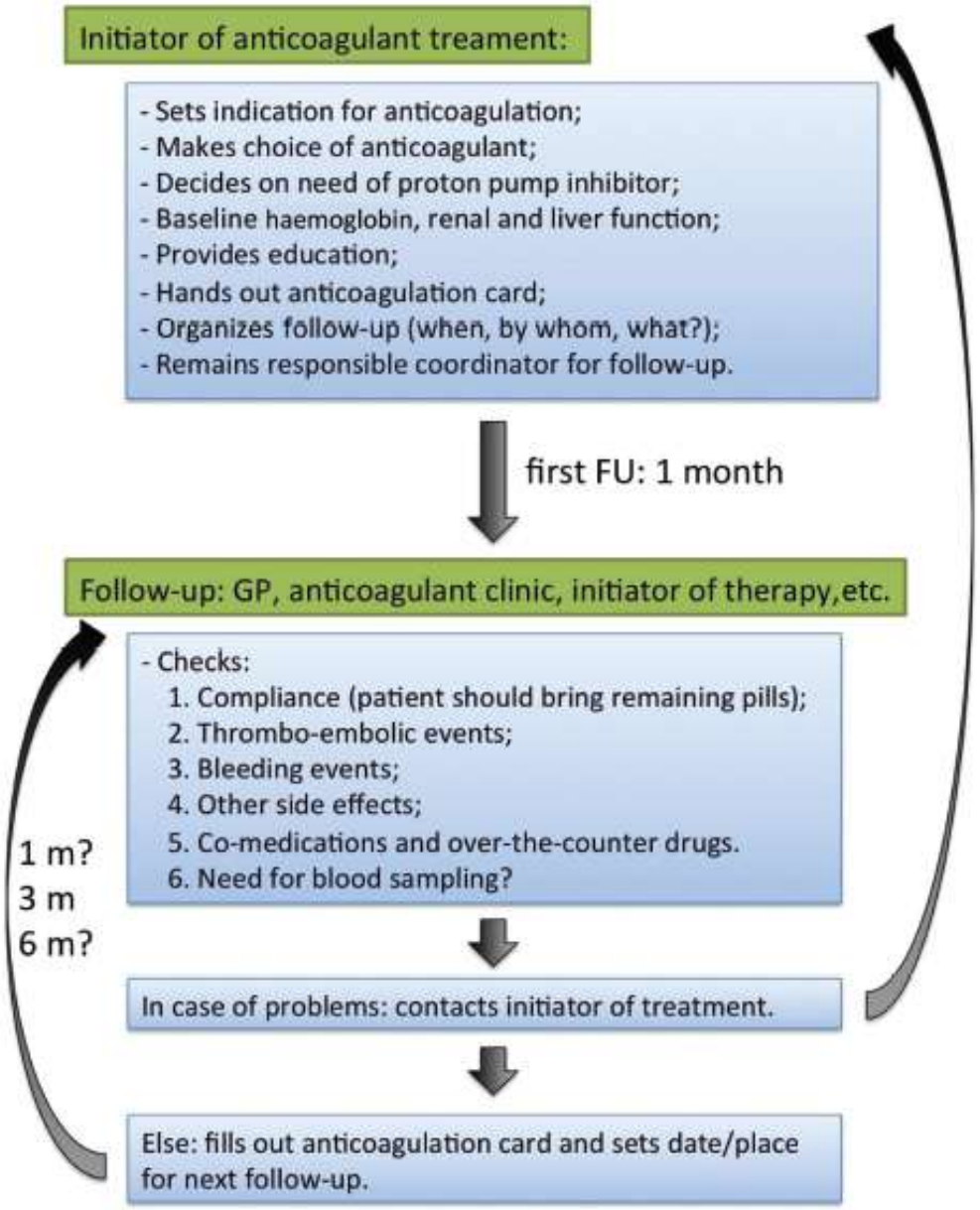
Emergency information

Standard tests do no quantitatively reflect level of anticoagulation!

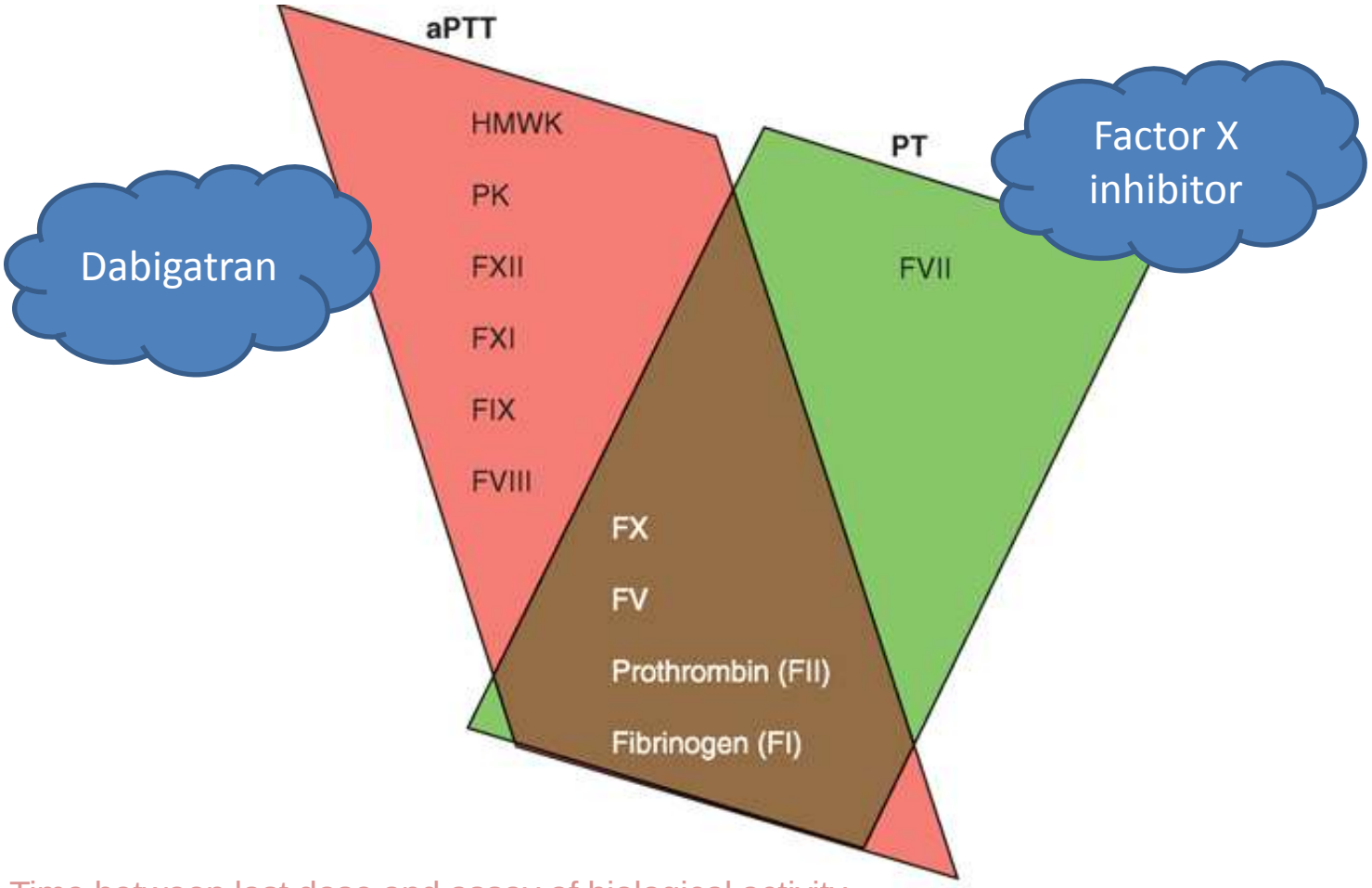
Name & telephone of patient relative to contact if emergency:

Patient blood group (+ physician signature):

First steps


Initiator of anticoagulant treament:
- Sets indication for anticoagulation;
- Makes choice of anticoagulant;
- Decides on need of proton pump inhibitor;
- Baseline haemoglobin, renal and liver function;
- Provides education;
- Hands out anticoagulation card;
- Organizes follow-up (when, by whom, what?);
- Remains responsible coordinator for follow-up.
first FU: 1 month
Follow-up: GP, anticoagulant clinic, initiator of therapy,etc.
- Checks:
1. Compliance (patient should bring remaining pills);
2. Thrombo-embolic events;
3. Bleeding events;
4. Other side effects;
5. Co-medications and over-the-counter drugs.
6. Need for blood sampling?
1 m?
3 m
6 m?
In case of problems: contacts initiator of treatment.
Else: fills out anticoagulation card and sets date/place for next follow-up.

2. How to measure the anticoagulant effect of new oral anticoagulants?



Time between last dose and assay of biological activity

Pharmacokinetic interactions

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[39]	no data yet	no effect[40]	no effect[41, 42]
Digoxin	P-gp competition	no effect [43]	no data yet	no effect[40]	no effect[42, 44]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[45] (reduce dose and take simultaneously)	no data yet	+53% (SR)[40] (Reduce dose by 50%)*	minor effect (use with caution if CrCl 15-50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	no effect[45]	+40%[SmPC]	no data yet	minor effect (use with caution if CrCl 15-50 ml/min)
Quinidine	P-gp competition	+50%	no data yet	+80%[40] (Reduce dose by 50%)§	+50%
Amiodarone	P-gp competition	+12-60%[45]	no data yet	no effect[40]	minor effect (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70-100% (US: 2 x 75 mg)	no data yet	+85% (Reduce dose by 50%)*	no data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140-150% (US: 2 x 75 mg)	+100%[SmPC]	no data yet	up to +160%[42]

Pharmacokinetic interactions

fluconazole	moderate CYP3A4 inhibition	no data yet	no data yet	no data yet	+42% (if systemically administered)[42]
Cyclosporin; tacrolimus	P-gp competition	no data yet	no data yet	no data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition	+15-20%	no data yet	no data yet	+30-54%[42, 46]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	no data yet	Strong increase[5mRC]	no data yet	up to +153%[41]
Rifampicin; St. John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	-66%[47]	-54%[5mRC]	-35%	up to -50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	-12-30%[45, 48, 49]	no data yet	no effect	no effect[50, 51]

Risk Factors

	via	Dabigatran	Apixaban	Edoxaban*	Rivaroxaban
Age ≥ 80 years	Increased plasma level			no data yet	
Age ≥75 years	Increased plasma level			no data yet	
Weight ≤ 60 kg	Increased plasma level			52	
Renal function	Increased plasma level	See Table 7			
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3			

4. Switching between anticoagulant regimens

- NOAC to VKA
- Accurate measurement of INR
- Onset of action of VKA slow and unpredictable

5. Ensuring compliance with new oral anticoagulant intake

6. How to deal with dosing errors?

Effects of NOACs fades in 1 day

Table 2 **Possible measures to take in case of bleeding**

	Direct thrombin inhibitors (dabigatran)	FXa inhibitors (apixaban, edoxaban, rivaroxaban)
Non-life-threatening bleeding	Inquire last intake + dosing regimen Estimate normalization of haemostasis Normal renal function: 12–24 h CrCl 50–80 mL/min: 24–36 h CrCl 30–50 mL/min: 36–48 h CrCl <30 mL/min: ≥48 h Maintain diuresis Local haemostatic measures Fluid replacement(colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9$/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy) Consider dialysis (preliminary evidence: −65% after 4h)[53] Charcoal haemoperfusion not recommended (no data)	Inquire last intake + dosing regimen Normalization of haemostasis: 12–24 h Local haemostatic measures Fluid replacement (colloids if needed) RBC substitution if necessary Platelet substitution (in case of thrombocytopenia $\leq 60 \times 10^9$/L or thrombopathy) Fresh frozen plasma as plasma expander (not as reversal agent) Tranexamic acid can be considered as adjuvans Desmopressin can be considered in special cases (coagulopathy or thrombopathy)
Life-threatening bleeding	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)	All of the above Prothrombin complex concentrate (PCC) 25 U/kg (may be repeated once or twice) (but no clinical evidence) Activated PCC 50 IE/kg; max 200 IE/kg/day): no strong data about additional benefit over PCC. Can be considered before PCC if available. Activated factor VII (rFVIIa; 90 μg/kg) no data about additional benefit + expensive (only animal evidence)

RBC, red blood cells; CrCl, creatinine clearance; PCC, Prothrombin complex concentrate.

7. Patients with chronic kidney disease

New oral anticoagulants in mild to moderate CKD

Surgical intervention, including RF catheter ablation

Table 3 Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban		Edoxaban[a]		Rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)							
	Low risk (h)	**High risk**	**Low risk**	**High risk**	**Low risk**	**High risk**	**Low risk**	**High risk**
CrCl ≥80 mL/min	≥24	≥48	≥24	≥48	no data	no data	≥24	≥48
CrCl 50–80 mL/min	**≥36**	**≥72**	≥24	≥48	no data	no data	≥24	≥48
CrCl 30–50 mL/min[b]	**≥48**	**≥96**	≥24	≥48	no data	no data	≥24	≥48
CrCl 15–30 mL/min[b]	not indicated	not indicated	**≥36**	**≥48**	no data	no data	**≥36**	**≥48**
CrCl <15 mL/min	no official indication for use							

Low risk, surgery with low risk of bleeding; high risk, surgery with high risk of bleeding. CrCl, creatinine clearance.
[a]No EMA approval yet. Needs update after finalization of SmPC.
[b]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (15 mg QD).

Other Complex and high risk case scenarios with less well-defined (evidence based) guidelines

- Afib + CAD
- NOAC +ischemic stroke/intracranial bleed
- Cardioversion
- Afib + malignancy

Thank you!