NOVEL ANTICOAGULANTS

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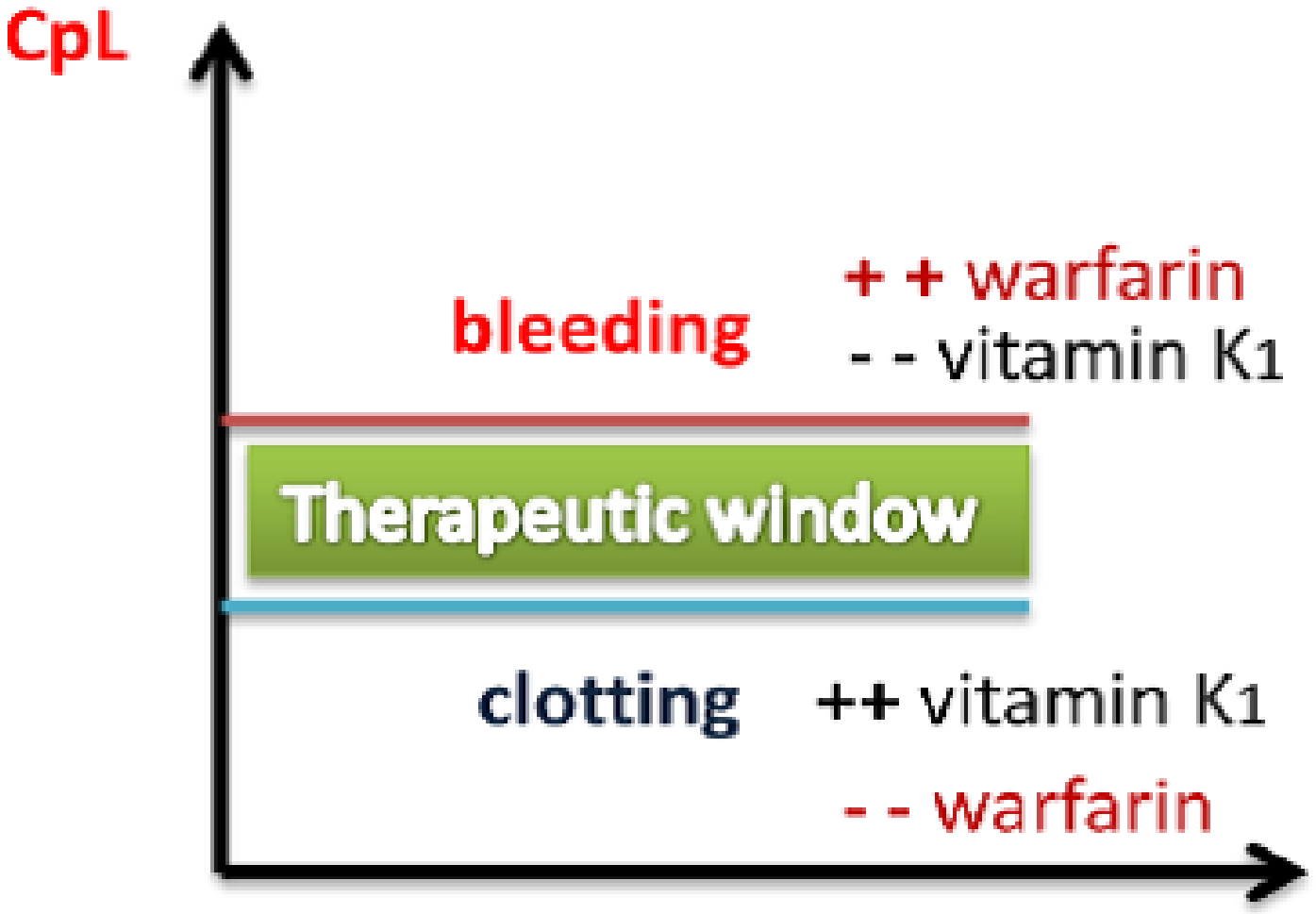
- Thirty years ago, unfractionated heparin was preferably administered as an intravenous infusion, and vitamin K antagonists (VKAs) were the only available agents.
- Of VKAs, warfarin had and still has the most widespread use.

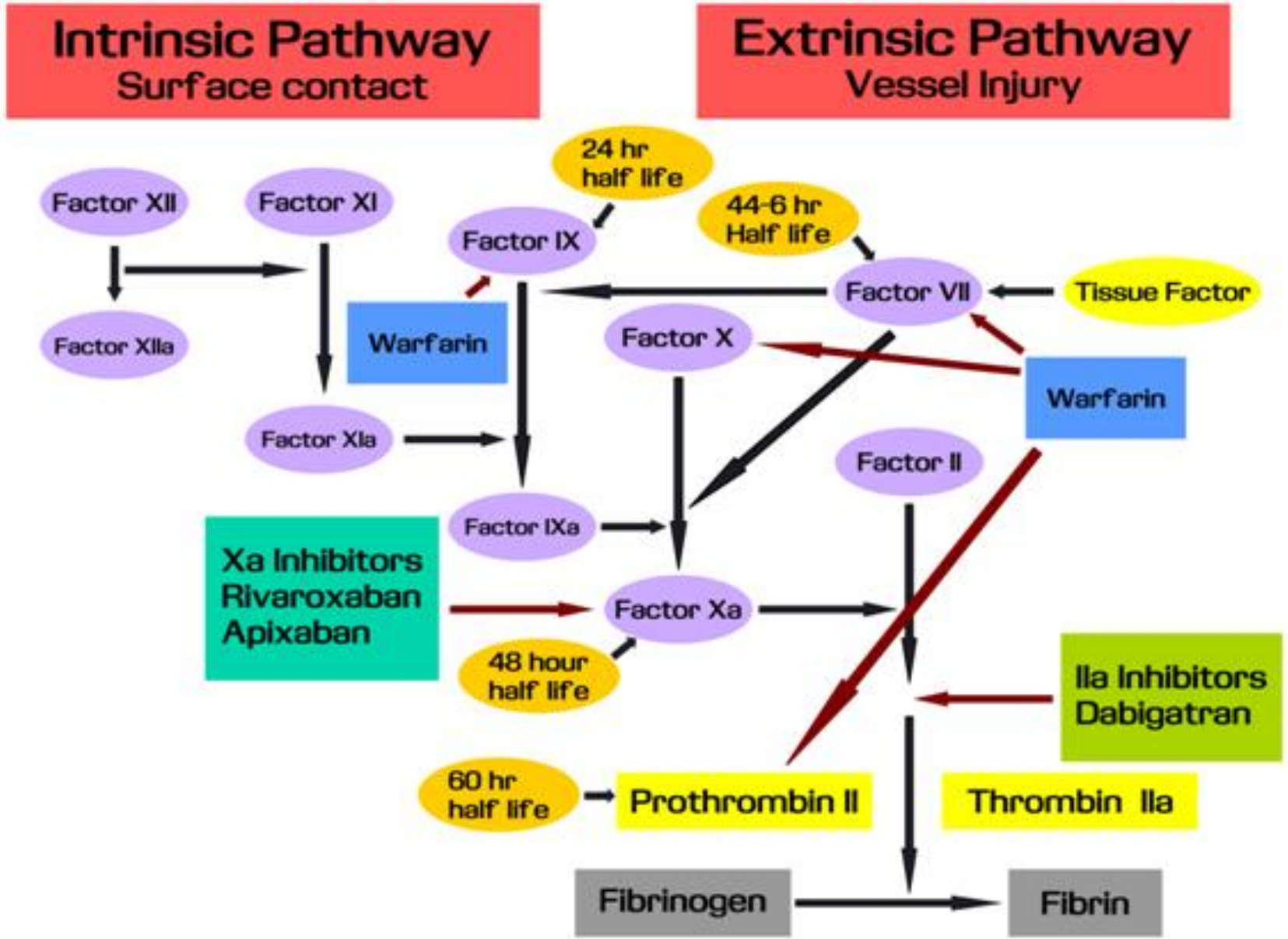
- The development of low-molecular weight heparin (LMWH) enabled unmonitored once-daily subcutaneous injections and outpatient management of many patients, particularly those with venous thromboembolism (VTE).
- Although LMWH replaced VKAs for the long term treatment for VTE in patients with cancer, LMWH is still considered inconvenient due to the need for daily injections

- Warfarin provides a risk reduction for stroke prevention in atrial fibrillation (SPAF) of 62%, which is far better than the reduction of approximately 22% experienced with aspirin .

- For the prevention of recurrent VTE, the results are even more impressive, with approximately 90% risk reduction .

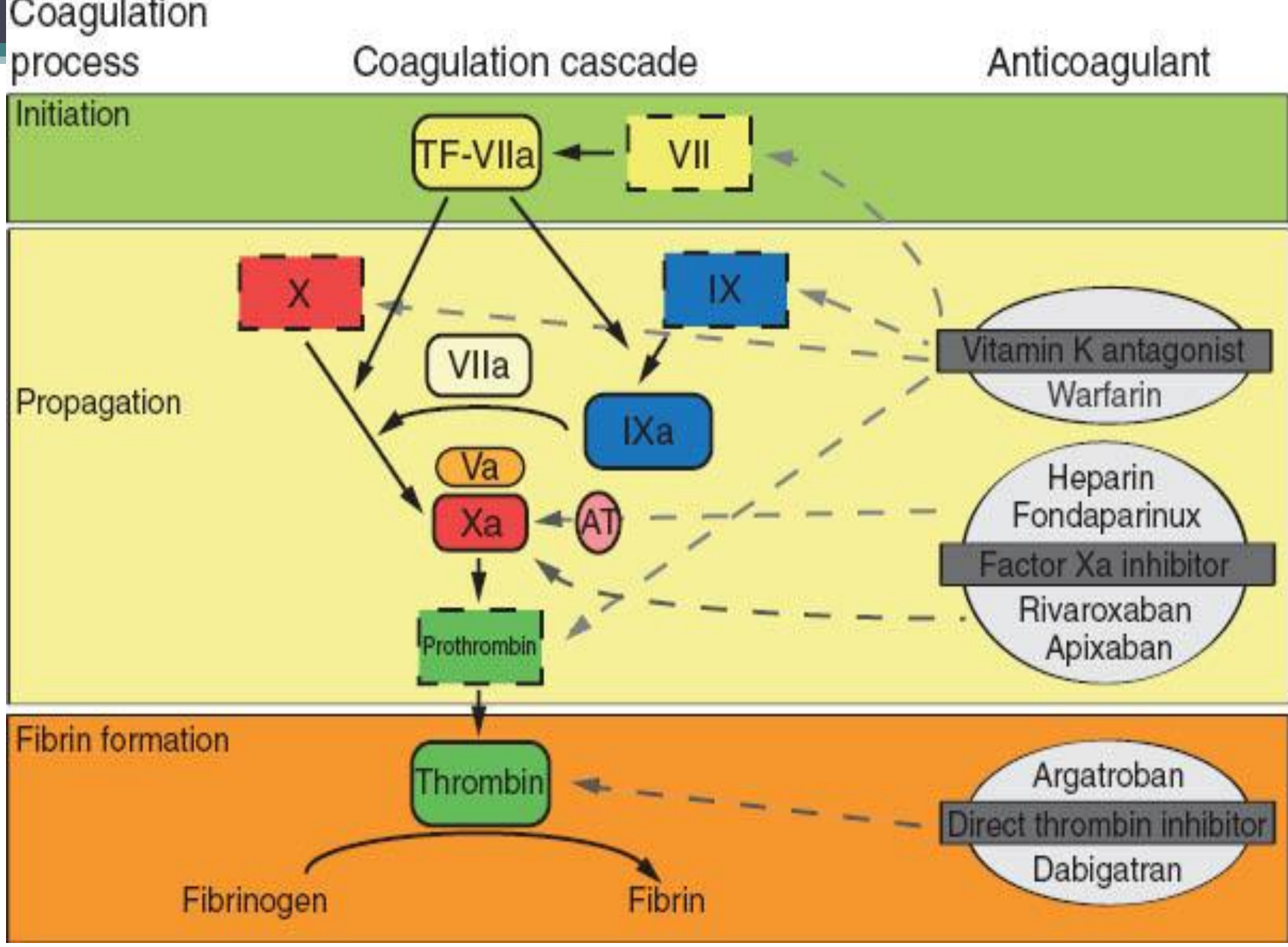

CpL
+ + warfarin
bleeding
- - vitamin K1
Therapeutic window
clotting
++ vitamin K1
- - warfarin

- The most feared bleeding on warfarin is intracranial haemorrhage, which occurs in approximately 4 per 1000 treated per year , and has a mortality of approximately 50%.
- Due to such concerns, nearly 50% of patients with an indication for anticoagulation for stroke prophylaxis in atrial fibrillation are not treated .


Intrinsic Pathway
Surface contact
Extrinsic Pathway
Vessel Injury
24 hr
half life
44-6 hr
Half life
Factor XII
Factor XI
Factor IX
Factor VII
Tissue Factor
Factor XIIa
Warfarin
Factor X
Warfarin
Factor XIa
Factor II
Factor IXa
Xa Inhibitors
Rivaroxaban
Apixaban
Factor Xa
48 hour
half life
IIa Inhibitors
Dabigatran
60 hr
half life
Prothrombin II
Thrombin IIa
Fibrinogen
Fibrin

- The first anticoagulant with high specificity came from nature.
- Hirudin, produced in the salivary gland of the leech, is an inhibitor of thrombin at the last enzymatic step of the coagulation cascade .The irreversible binding of hirudin to thrombin probably contributes to the increased risk of bleeding

- Thereafter, tailormade molecules with a high association rate constant to warrant rapid inhibition of thrombin could be produced, starting with melagatran .
- The drug became the first orally available thrombin inhibitor after a small modification to improve absorption


Coagulation process
Coagulation cascade
Anticoagulant
Initiation
TF-VIIa
VII
Propagation
X
IX
VIIa
IXa
Va
Xa
AT
Prothrombin
Vitamin K antagonist
Warfarin
Heparin
Fondaparinux
Factor Xa inhibitor
Rivaroxaban
Apixaban
Fibrin formation
Thrombin
Argatroban
Direct thrombin inhibitor
Dabigatran
Fibrinogen
Fibrin

General principles for the new anticoagulants

RAPID ONSET/SHORT T1/2

Table 1 *Important preclinical characteristics of the new anticoagulants*

Drug	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
Time to maximum effect (t_{max})	1.5–2 h	2 h	3–4 h	1–2 h	5 days
Half-life ($t_{½}$)	12–17 h	5–9 h	8–15 h	9–10 h	36–48 h
Plasma protein binding	35%	92–95%	87%	40–59%	99%
Volume of distribution (V_d)	60–70 L	50 L	"low"	>300 L	8 L
Renal elimination	80%	33%	25%	35–39%	0%
Interactions	P-gp	P-gp, CYP3A4	P-gp, CYP3A4	P-gp, CYP3A4	CYP2C9 (S) CYP1A2 (R)[a]
Food effect	Absorption delayed, not reduced	Required for absorption of doses > 10 mg	Not reported	No	Dark green vegetables etc.

[a]The metabolism for the S- and R-enantiomers of warfarin, as indicated.

Less complicated perioperative management

- The half-life of the new anticoagulants is slightly longer than LMWH, but definitively shorter than warfarin .
- Thus, with rapid offset and onset, there is usually no need for bridging anticoagulation with heparin in case of interruption for surgery, as often carried out with VKAs.

Perioperative management

Timing of last dose before and first dose after surgery

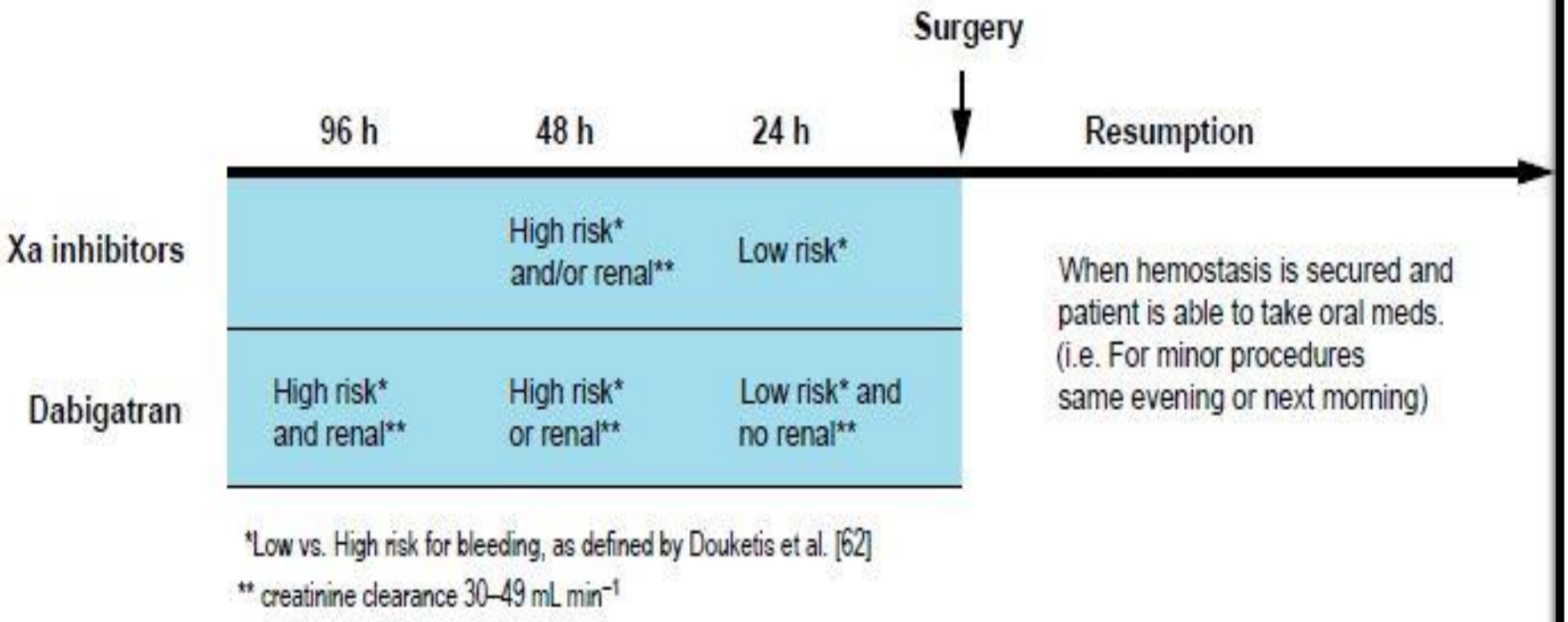


Fig. 1 *Timing for last dose and resumption of new anticoagulants for surgery.*

Table 2 *Drug interactions with the new anticoagulants*

Mechanism	Dabigatran		Rivaroxaban[a], apixaban, edoxaban	
P-gp inhibition	Interacting drug	Δ exposure	Interacting drug	Δ exposure
	Ketoconazole[b]	+150%	Ketoconazole[b]	+160%
	Quinidine	+53%		
	Amiodarone	+60%		
	Verapamil	≈ +50%[c]		
P-gp induction	Rifampicin	−67%	Rifampicin	−50%
	St. John's Wort	n.d.	St. John's Wort	n.d.
CYP3A4 inhibition			Ketoconazole[b]	+160%
			Clarithromycin	+50%
			Ritonavir	+50%
CYP3A4 induction			Rifampicin	−50%
			St. John's Wort	n.d.

- For a few drugs with strong inhibition of both P-gp and CYP3A4, treatment with factor Xa inhibitors is contraindicated

Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Quinidine	Azole antimycotics	Azole antimycotics	(Not approved outside of Japan yet)
	Ketoconazole	Ketoconazole	
	Itrakonazole	Itrakonazole	
	Vorikonazole	Vorikonazole	
	Posakonazole	Posakonazole	
	HIV protease inhibitors	HIV protease inhibitors	
	Ritonavir	Ritonavir	

Table 3 *Concomitant medications constituting contraindications to the use of new anticoagulants*

Predictable dose

- The maintenance dose of warfarin varies 40-fold between the extreme patient variants (0.5–20 mg/ day) and even more if patients with warfarin resistance are included.

For the new anticoagulants, the dose is uniform for the majority of patients

- For patients with difficulties achieving a stable effect from VKAs, or with variable international normalized ratio (INR) results, a switch to a new agent can provide great relief.
- Whereas this is advisable for patients with unstable INRs due to frequent treatment courses with drugs that interact with VKAs, for example antibiotics and prednisone, it can be problematic if the cause is poor adherence.

Lower risk of intracranial bleeding

Table 4 *Incidence of intracranial haemorrhage during treatment with new anticoagulants or vitamin K antagonists in phase III trials*

Drug, study	ICH, new anticoagulant, N (% per patient-year)	ICH, VKA N (% per patient-year)	Hazard ratio (95% CI)	*P*-value
Stroke prevention in atrial fibrillation				
Dabigatran 110 mg, RE-LY[a] [57]	27 (0.23)	90 (0.76)	0.30 (0.19–0.45)	<0.001
Dabigatran 150 mg, RE-LY[a] [57]	38 (0.32)	90 (0.76)	0.41 (0.28–0.60)	<0.001
Rivaroxaban, ROCKET-AF [28]	55 (0.5)	84 (0.7)	0.67 (0.47–0.93)	0.02
Apixaban, ARISTOTLE [27]	52 (0.33)	122 (0.80)	0.42 (0.30–0.58)	<0.001
VTE treatment[b]				
Dabigatran, RE-COVER + RE-COVER II + RE-MEDY [30, 59]	4 (0.13)	9 (0.29)	0.44 (0.10–1.59)	0.16
Rivaroxaban, EINSTEIN-DVT + EINSTEIN-PE [29, 60]	5 (0.21)	14 (0.58)	0.36 (0.10–1.04)	0.038
Apixaban, AMPLIFY [61]	3 (0.22)	6 (0.45)	0.50 (0.08–2.35)	0.51

Potential problems with the new anticoagulants

Assessment of drug level

- Over the decades, clinicians have become accustomed to the INR, which provides a good correlation with the risk of bleeding related to VKAs .
- For unfractionated heparin and LMWH, there is a belief that the activated partial thromboplastin time (APTT) and antifactor Xa are useful, but in reality, the correlation with the risk of clinical events is poor.

- Dabigatran levels can be reliably assessed quantitatively with the dilute thrombin time, which is commercially available as Hemoclot, a result >65 s, corresponding to >200 ng /mL, is associated with an increased risk of bleeding
- An APTT > 80 s (at trough) is associated with an increased risk of bleeding; with a normal APTT, the drug level is probably so low that surgery can be safely performed

- Rivaroxaban can be qualitatively assessed with the prothrombin time, but unfortunately the sensitivity varies widely between the thromboplastin reagents; STA Neoplastin Plus (Stago, Asnieres, France) has been recommended as the most accurate assay
- It is important to note that the results should be based on the prothrombin time and not converted to INR, which is specific for VKAs

REVERSAL

- For those on dabigatran, the highest quality data available for reversal are for idarucizumab, although it is not yet clear whether patients derive clinical benefit from this reversal. In the absence or failure of idarucizumab, activated prothrombin complex concentrate (aPCC) is recommended. For those on factor Xa inhibitors, the ideal reversal agent is not clear. Many providers use 4F-PCC or aPCC, but more specific agents are in clinical trials and may soon be available