I nuovi anticoagulanti orali (DOAC)

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Gli anticoagulanti orali "nuovi" *o* "diretti":

un po' di acronimi, per confondere le idee…

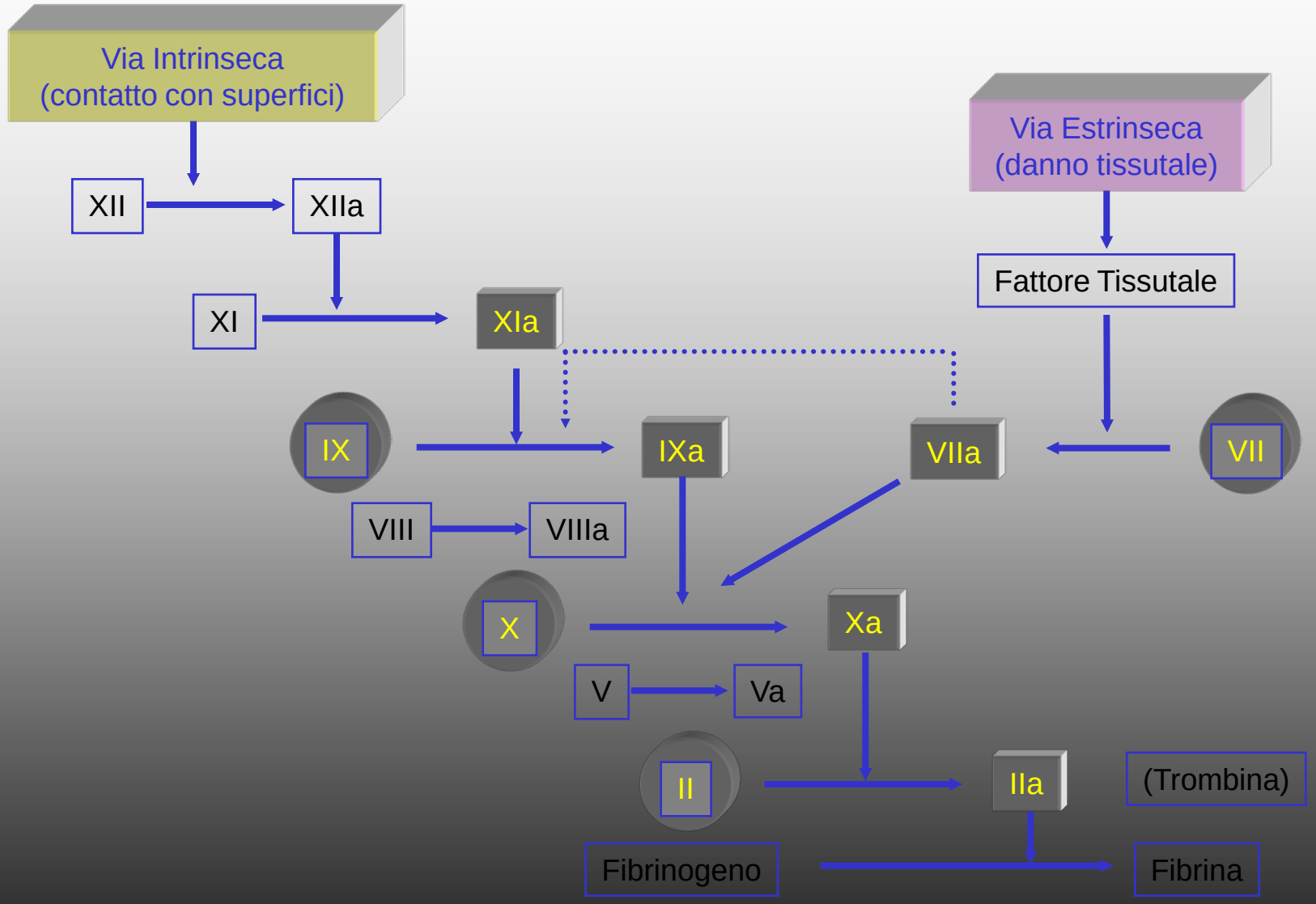
DOAC (Direct Oral AntiCoagulants)

NOAC *o* **NOA** (New Oral AntiCoagulants, Non-VKA Oral AntiCoagulants),

...anche nella variante italiana **NAO**

…e, ultimo arrivato: **TSOACs** (Target-Specific Oral AntiCoagulants)

Dove agiscono i farmaci anticoagulanti



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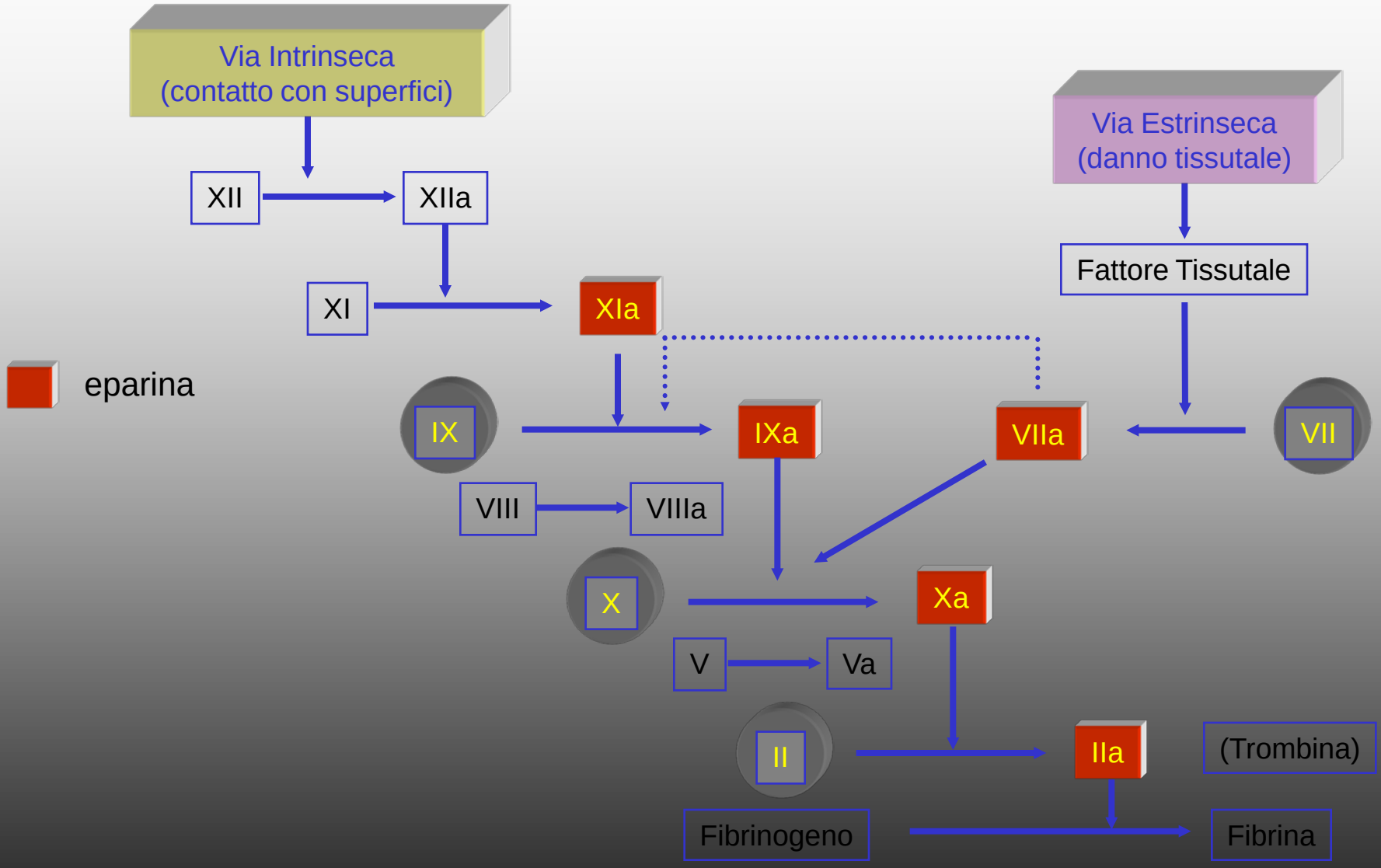

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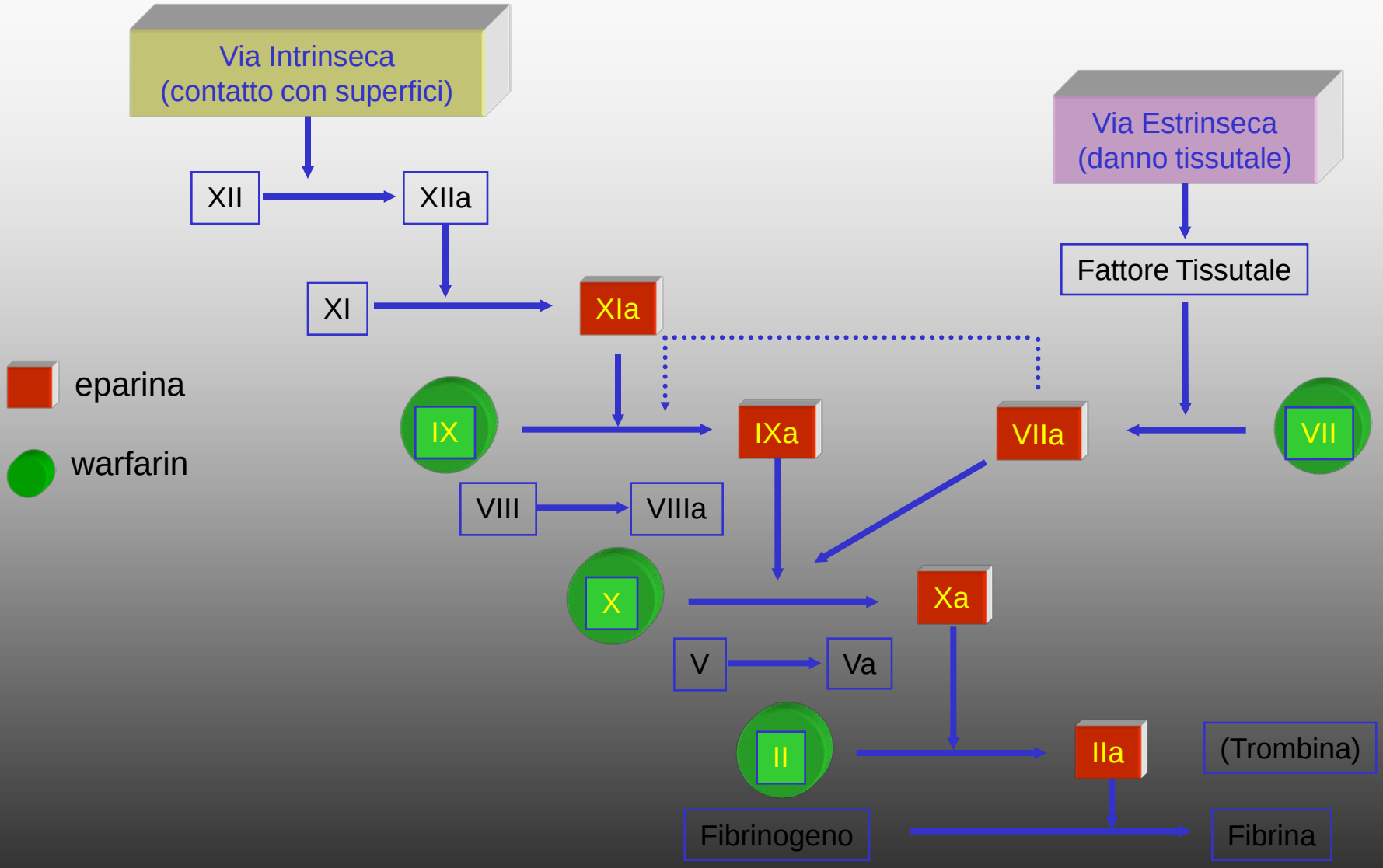

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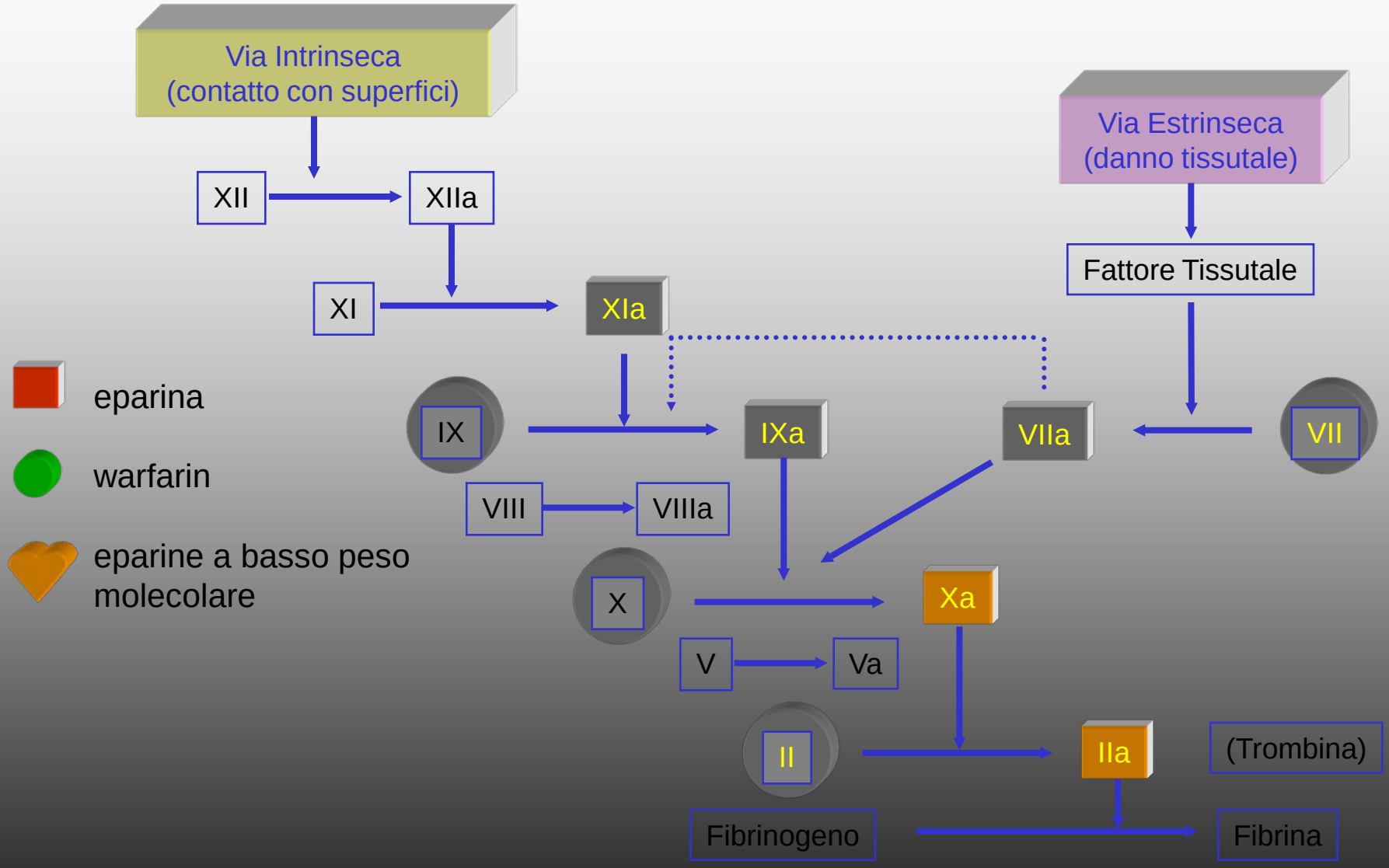

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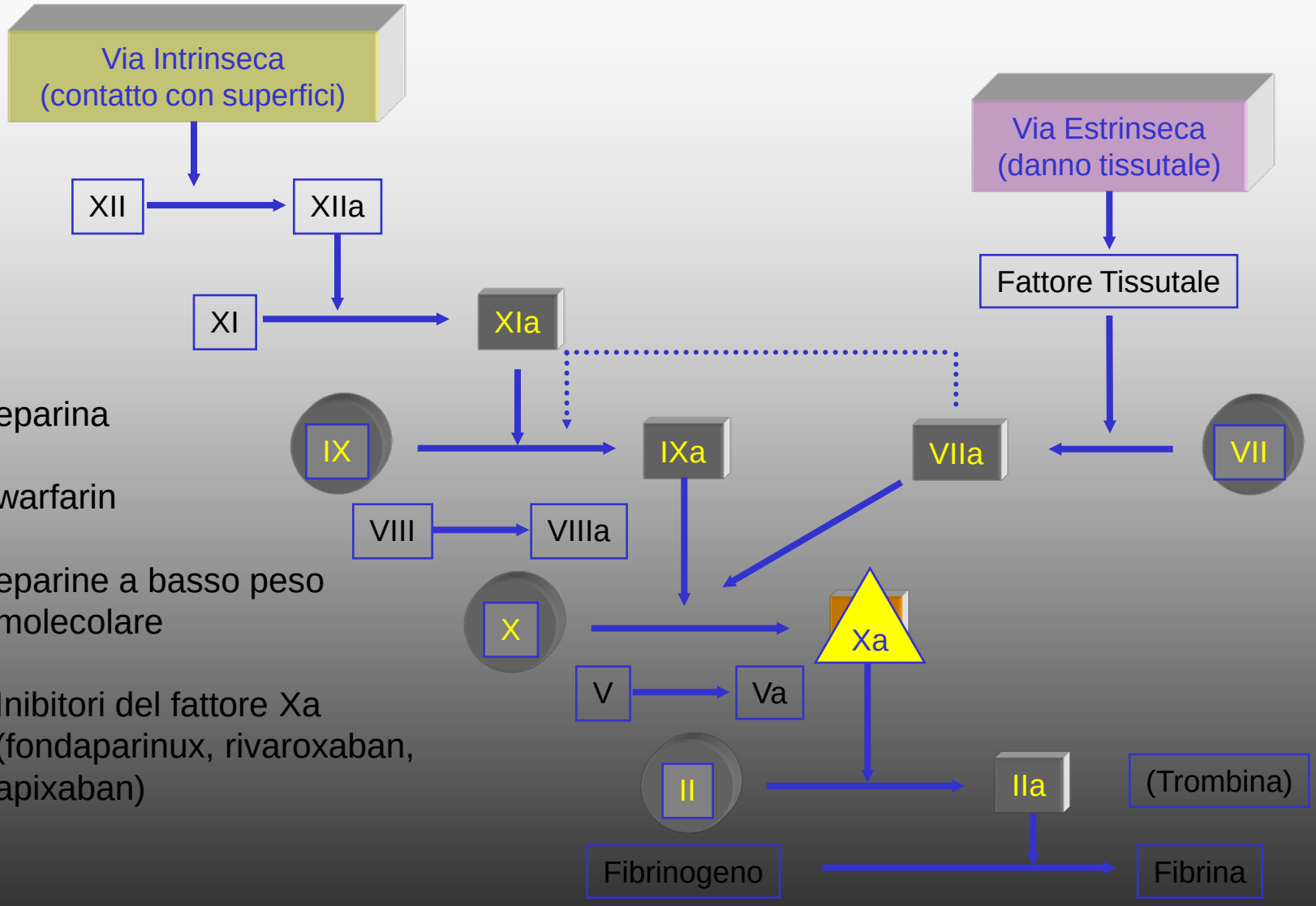

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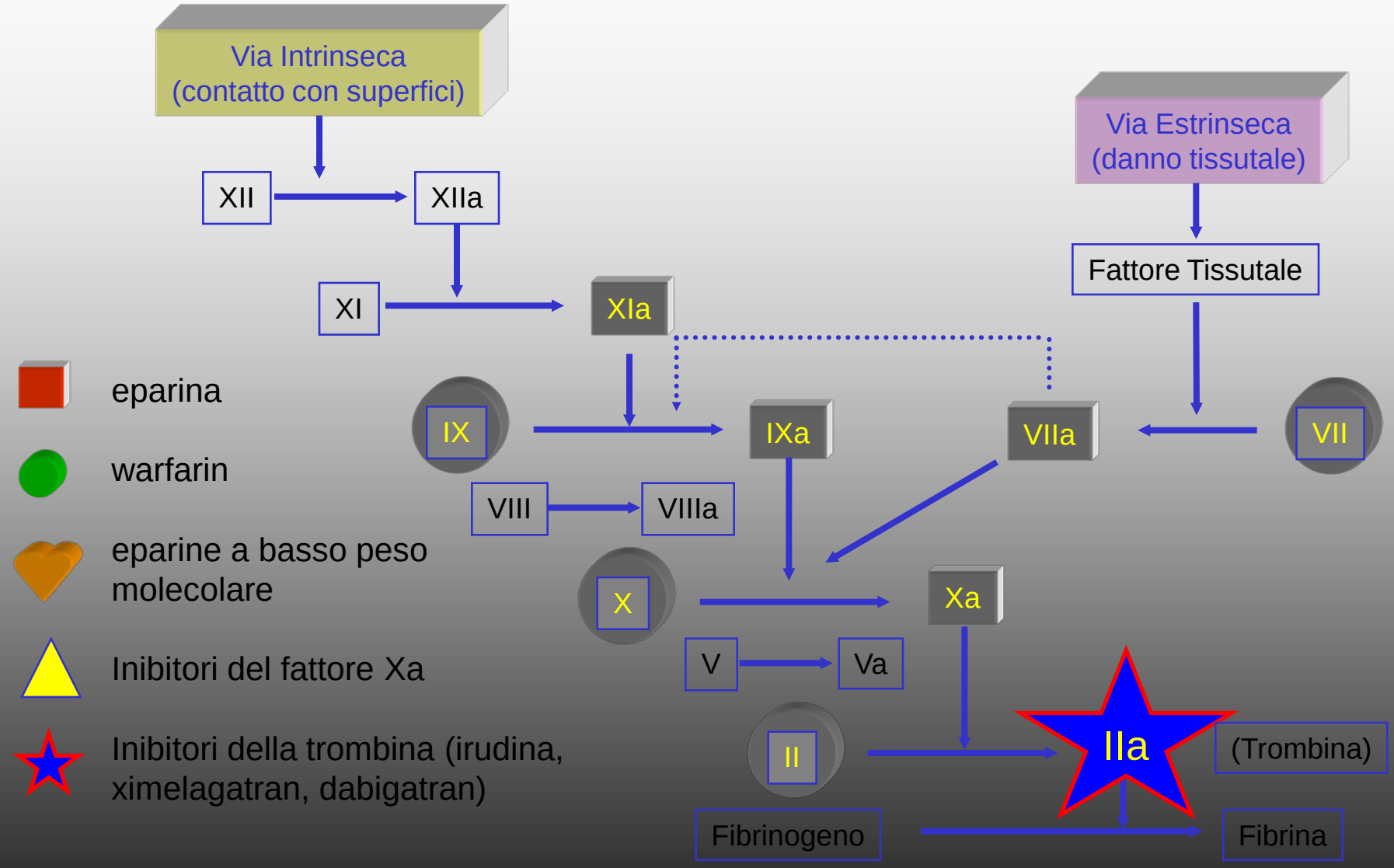
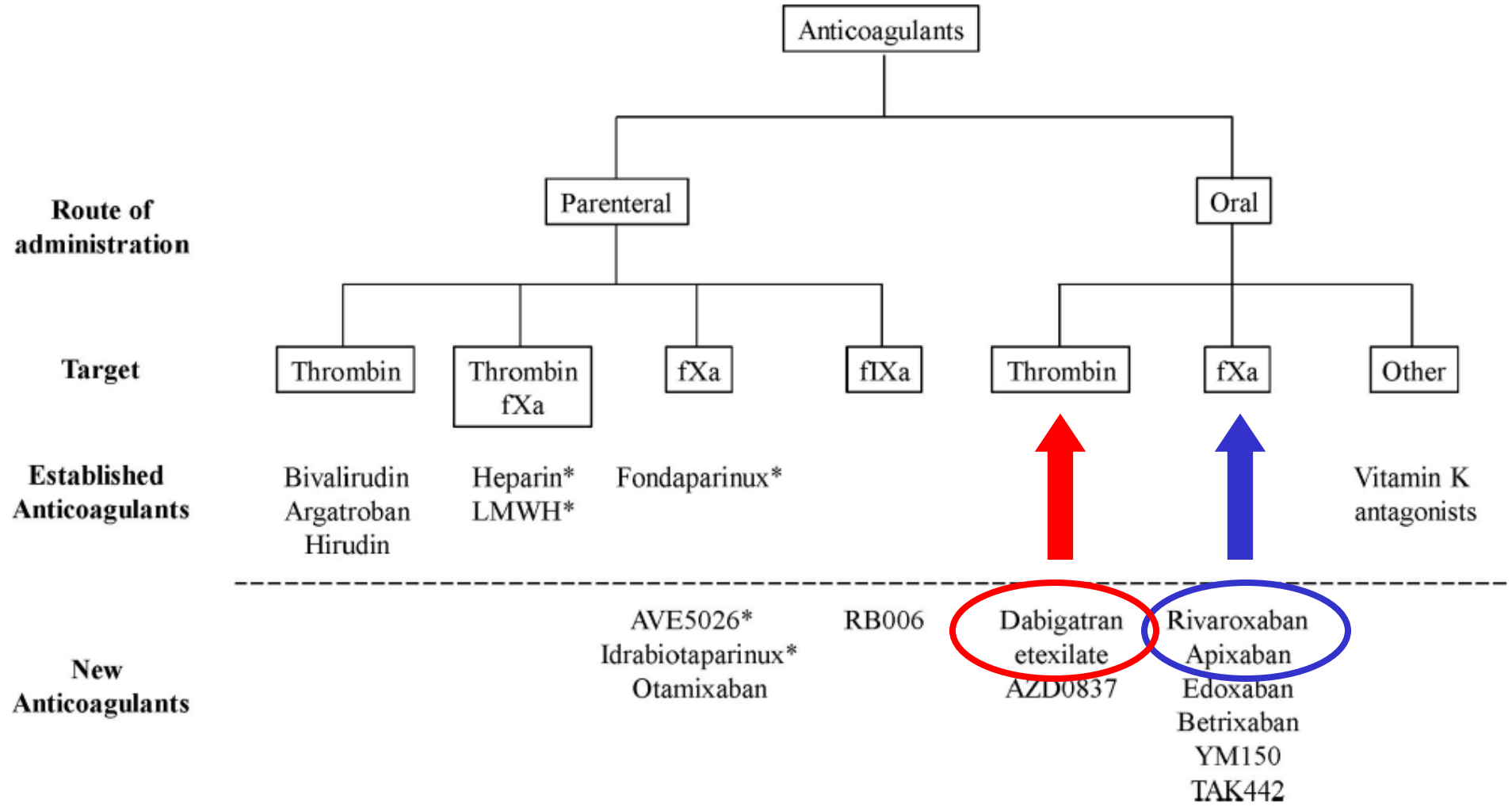


DOAC: come agiscono



Comparative PK/PD of DOAC

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to C_{max}	1-3	2-4	3-4	1-2
Half-life, hours	12-17	5-13	12	10-14
Renal Clearance, %	80	33*	27	50
Transporters	P-gp	P-gp	P-gp	P-gp
CYP Metabolism, %	None	32	<32	<4

CYP = cytochrome P450; P-gp = P-glycoprotein

*33% renally cleared; 33% excreted unchanged in urine

Vantaggi dei DOAC

- Rapido effetto terapeutico
- Target su specifico enzima coagulazione
- Bassa interferenza con i cibi
- Basse interazioni con farmaci
- **Effetto anticoagulante prevedibile**

Non necessario “bridging”

Basso rischio di eventi avversi

No restrizioni dietetiche

Meno restrizioni farmacologiche

NON necessario monitoraggio di laboratorio

DOAC: quali problemi pongono

- Appropriata prescrizione
- Compliance, aderenza e persistenza
- Identificazione del farmaco assunto in urgenza/emergenza
- Procedure di “bridging” (diverse a seconda dei casi)
- Antidoto (neutralizzazione in urgenza/emergenza)
- Costi

DOAC: quando ?

DOAC: indicazioni registrate in Italia

- Profilassi primaria del TEV in protesi elettiva di anca o ginocchio: apixaban, dabigatran, rivaroxaban
- Terapia del TEV: rivaroxaban, dabigatran (solo dopo iniziale eparina)
- Profilassi degli eventi ischemici nella FANV: apixaban, dabigatran, rivaroxaban

I risultati dei clinical trials forniscono dati convincenti su efficacia e sicurezza dei DOAC nella FA e nel TEV?

Sì !

DOAC: come ?


ONE-SIZE FITS ALL
STORE
SALE

One size ?

Regimi nella FA

- Dabigatran, 150 mg (*o* 110 mg) ogni 12 ore
  - » (75 mg ogni 12 ore, USA)
- Rivaroxaban, 20 mg (*o* 15 mg) ogni 24 ore
- Apixaban, 5 mg (*o* 2.5 mg) ogni 12 ore

- Edoxaban, 60 mg (*o* 30 mg) ogni 24 ore


ONE SIZE FITS ALL.

Scelta in base a….

- Età
- Funzione renale
- Interazione con altri farmaci
- “Fragilità” del paziente (pregresse emorragie..) ?
- Altro ? (ad es. laboratorio …)

Come ottenere una buona aderenza e persistenza in assenza di monitoraggio di laboratorio?

- Follow-up: chi fa che cosa
- Educazione del paziente !
- Rivalutazione nel tempo
- Avvisi telefonici (o telematici) ?
- Controllo del consumo del farmaco (in collaborazione con il farmacista) ?

Interazione con altri farmaci

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY (2014)
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3648

ORIGINAL REPORT

An international comparison of spontaneous adverse event reports and potentially inappropriate medicine use associated with dabigatran

Cameron J. McDonald, Lisa M. Kalisch Ellett, John D. Barratt and Gillian E. Caughey*

Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia

- Spontaneous adverse event (SAE) reports associated with the oral anticoagulant dabigatran from Australia, Canada and USA
- A large proportion of adverse events were associated with concomitant therapies, which may have placed the patient at increased risk of harm

Key points

- Gastrointestinal disorders, namely gastrointestinal haemorrhage were the most common adverse event associated with dabigatran SAE reports
- Over a third of patients had at least one concomitant medicine reported that potentially may have placed the patient at increased risk of harm (namely haemorrhage)

Prevalence of potentially inappropriate concomitant therapy in dabigatran spontaneous adverse event reports

	Australia	Canada	US
	$n=425$	$n=550$	$N=6123$
Medication class	*N* (%)	*N* (%)	*N* (%)
Concomitant antithrombotic	74 (17.4%)	112 (20.4%)	1952 (31.9%)
Aspirin	46 (10.8%)	50 (9.1%)	1474 (24.1%)
Warfarin	17 (4.0%)	31 (5.6%)	341 (5.6%)
Clopidogrel	14 (3.3%)	28 (5.1%)	295 (4.8%)
Concomitant bleeding-risk medicines	51 (12.0%)	63 (11.5%)	841 (13.7%)
NSAIDs	9 (2.1%)	27 (4.9%)	327 (5.3%)
SSRIs	26 (6.1%)	20 (3.6%)	420 (6.9%)
Corticosteroids (systemic)	20 (4.7%)	21 (3.8%)	192 (3.1%)
Concomitant medicines with potential drug-drug interactions	45 (10.6%)	54 (9.8%)	1045 (17.1%)
Amioderone	25 (5.9%)	27 (4.9%)	431 (7.0%)
Verapamil	17 (4.0%)	—	143 (2.3%)
Dronedarone	—	17 (3.1%)	473 (7.7%)
Overall proportion of potentially inappropriate therapy[†]	34.1%	40.2%	51.1%

Possible drug-drug interactions – effect on NOAC plasma levels (I)

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Atorvastatin	P-gp/ CYP3A4	+18%	no data yet	no effect	no effect
Digoxin	P-gp	no effect	no data yet	no effect	no effect
Verapamil	P-gp/ wk CYP3A4	+12–180% (reduce dose)	no data yet	+ 53% (SR) (reduce dose 50%)	minor effect
Diltiazem	P-gp/ wk CYP3A4	no effect	+40%	No data	minor effect
Quinidine	P-gp	+50%	no data yet	+80% (reduce dose 50%)	+50%
Amiodarone	P-gp	+12–60%	no data yet	no effect	minor effect
Dronedarone	P-gp/CYP3A4	+70–100%	no data yet	+85% (reduce dose 50%)	no data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP/ CYP3A4	+140–150%	+100%	no data yet	up to +160%

Red = contraindicated; Orange = adapt dose; Yellow = consider dose reduction if two concomitant yellow interactions present

Heidbuchel H et al. Europace 2013;15:625–51

Possible drug-drug interactions – effect on NOAC plasma levels (II)

	Interaction	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fluconazole	CYP3A4	no data	no data	no data	+42%
Cyclosporin; tacrolimus	P-gp	no data	no data	no data	+50%
Clarithromycin; erythromycin	P-gp/ CYP3A4	+15–20%	no data	no data	+30–54%
HIV protease inhibitors	P-gp and BCRP/ CYP3A4	no data	strong increase	no data	up to +153%
Rifampicin; St John's wort; carbamezepine; phenytoin; phenobarbital	P-gp and BCRP/ CYP3A4/CYP2J2	-66%	-54%	-35%	up to -50%
Antacids	GI absorption	-12–30%	no data	no effect	no effect

Red = contraindicated; Orange = adapt dose; Yellow = consider dose reduction if two concomitant yellow interactions present

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Possible drug-drug interactions – effect on NOAC plasma levels (III)

		Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Aged ≥80 years	Increased plasma level				
Aged ≥75 years	Increased plasma level				
Weight ≤60 kg	Increased plasma level				
Renal function	Increased plasma level				

Other increased bleeding risk

Pharmacodynamic interactions – antiplatelet drugs, NSAIDs

Systemic steroid therapy

Other anticoagulants

Recent surgery on critical organ (brain, eye)

Thrombocytopenia (e.g. chemotherapy)

HAS-BLED ≥3

Red = contraindicated; Orange = adapt dose; Yellow = consider dose reduction if two concomitant yellow interactions present

NSAIDs = non-steroidal anti-inflammatory drugs

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Checklist during follow-up of AF patients on NOACs

	Interval	Comments
Compliance	Each visit	Inspect remaining medication Stress importance of compliance Inform about compliance aids
Thrombo-embolism	Each visit	Cerebral, systemic and pulmonary circulation
Bleeding	Each visit	'Nuisance' bleeding – prevention possible? Bleeding with risk or impact on QoL – prevention possible? Need to revise dose?
Side effects	Each visit	Continuation? Temporary cessation with bridging? Change of anticoagulant drug?
Co-medications	Each visit	Prescription or over-the counter drugs? Even temporary use can be risky
Blood sampling	Yearly 6-monthly 3-monthly On indication	Haemoglobin, renal, liver function Renal function if CrCl 30–60 mL/min or if on dabigatran and aged >75 years or fragile If CrCl 15–30 mL/min If intercurring condition may impact renal or hepatic function

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Take-home messages

- Efficacia e sicurezza dei DOAC non sono in discussione
- L’esperienza (e probabilmente il laboratorio) potranno ulteriormente migliorarle
- Attenzione e buon senso clinico nella prescrizione e nel follow-up
- Supporto e rinforzo della compliance anche in assenza di monitoraggio di laboratorio

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