I FARMACI ANTICOAGULANTI

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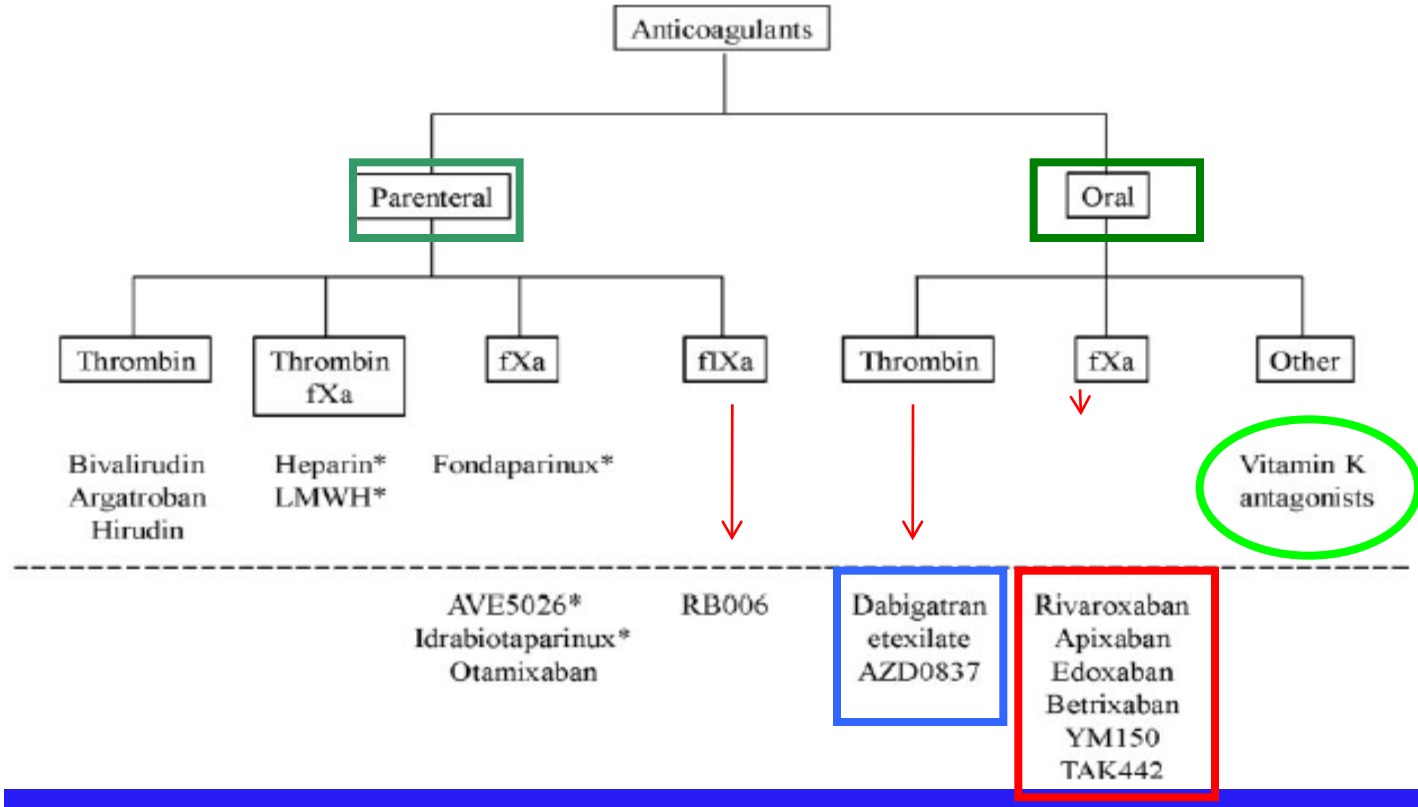
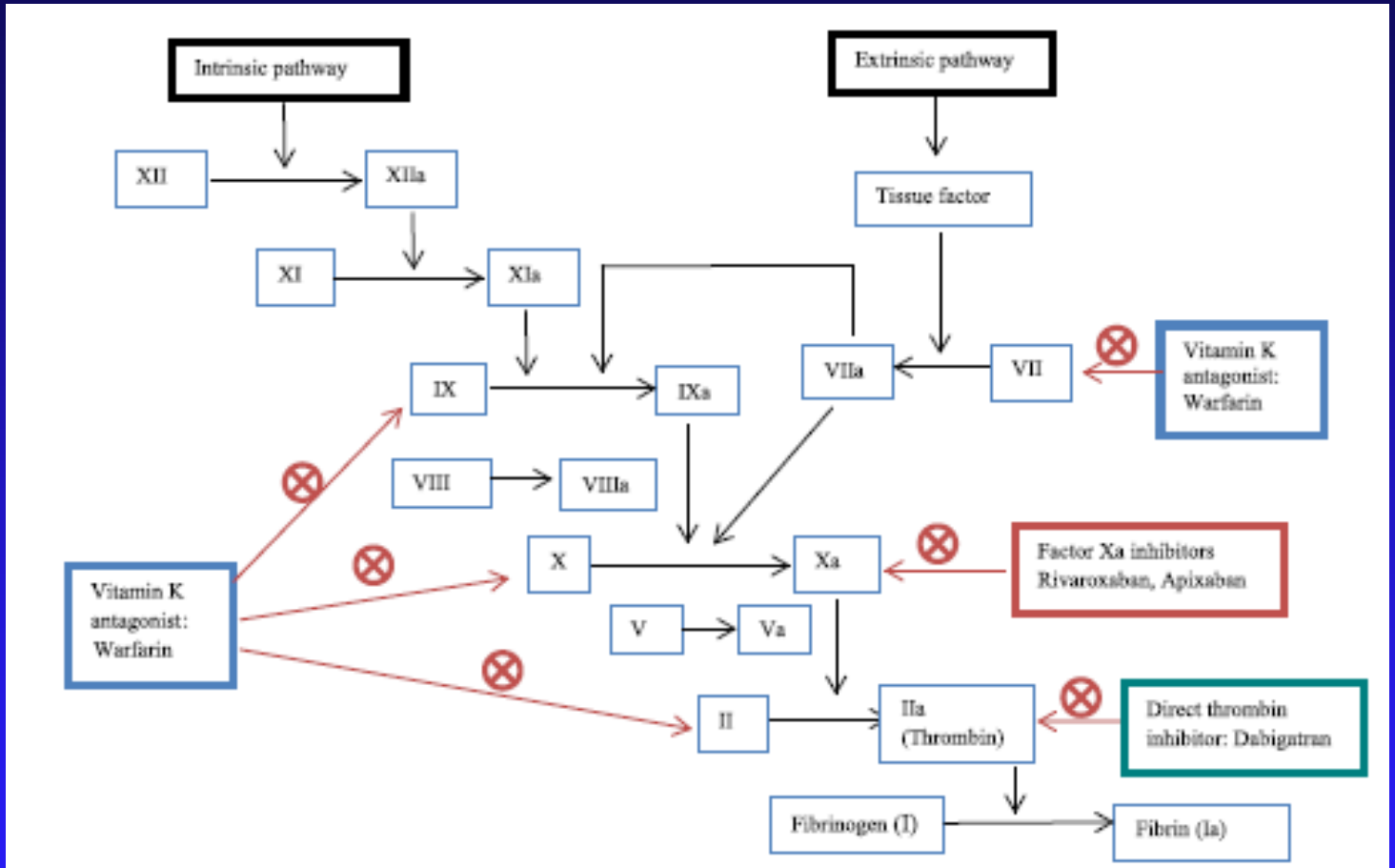
FARMACI ANTICOAGULANTI

- **1916** • Discovery of **heparin**
- **1940** • Discovery of **dicoumarol**
- **1941** •First reported use of **dicoumarol**, a vitamin K antagonist, as an anticoagulant in humans.
- **1950** •**Hirudin**, a specific thrombin inhibitor, extracted from leeches
- **1953** •Initial report of use of **warfarin**, a dicoumarol derivative, as an anticoagulant in humans.
- **1980s** • Discovery of **LMWH**, which targets fXa more than thrombin
- **1989** •Crystal structure of thrombin reported
- **1990** •**TAP** and **antistasin** provide proof-of-principle for fXa as a target
- **1992** •Crystal structure of fXa reported
- **1993** •Development of **DX-9065a**, the first small molecule fXa inhibitor
- **1995** •Crystal structure of the fXa-**DX9065a** complex reported
- **1998** •Drug discovery programs begin for oral fXa inhibitors
- **2000** •**Fondaparinux** validates fXa as a target for new anticoagulants
- **2001** •Development of **dabigatran**
- **2004** •**Ximelagatran** briefly licensed
- **2005** •Development of **rivaroxaban**
- **2007** •Development of **apixaban**
- **2008** •**Rivaroxaban** and **dabigatran** licensed for VTE prophylaxis in Europe and Canada
- **2009** •Development of **edoxaban**
- **2010** •**Dabigatran** licensed for stroke prevention in AF in the US, Europe, and Canada
- **2011** •**Rivaroxaban** licensed for VTE by the US
- **2012** •**Rivaroxaban** licensed for stroke prevention in AF in the US. **Apixaban** under consideration
- **2012** •**Apixaban** licensed in Europe and Canada for VTE prevention



J.W. Eikelboom, Circulation 2010

Advancement in anticoagulant research
Parenteral anticoagulant development
Oral anticoagulant development



1 Description of coagulation cascade and the sites targeted by old and new oral anticoagulants

Wang Y, Bajorek B. Am Journal Cardiovasc Drugs 2014

PHARMACOKINETIC PARAMETERS

Table II. Pharmacokinetics of warfarin and the new oral anticoagulants

Characteristics	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Betrixaban	Edoxaban
Molecular weight (Da)	308	628	460	436	452	548
Bioavailability (%)	98	6–7	66	63–79	40–80[a]	50[a]
t_{max} (h)	72–120	2–3	1–3	2–4	NR	2–3
$t_{½}$ (h)	20–60	7–17	8–15	7–13	5[a]	9–11
Protein binding (%)	99	35	87	95	NR	54
Food effect	Yes	Delayed absorption	No	Delayed absorption	No	No
Dosing regimen	od	bid	bid	od	od	od
Metabolism/elimination	100% liver	80% renal 20% liver	27% renal	35% renal	5% renal	35% renal
Substrate CYp	2C9, 3A4	No	3A4	3A4, 2J2	No	3A4
Substrate P-gp	No	Yes	Yes	Yes	No	Yes
Food interaction	Yes	No	No	No	No	NR
Monitoring required	INR	No	No	No	No	No
Target	II, VII, IX, X, P-S, P-C	II	Xa	Xa	Xa	Xa

a 33% unchanged and 33% inactive metabolite.

b In animals.

AVK | aIIa | aXa

Poulsen BK et al, Drugs 2011 (mod)

DOAC: CARATTERISTICHE GENERALI

Anticoagulant	Hours to [C] max	Half-life hours	Renal elimination	Sustrate CYp/P-gp
Dabigatran	2	12-14	80 %	P-gp
Rivaroxaban	2-4	9-13	33 (66) %	CYp/P-gp
Apixaban	1-3	8-15	25 %	CYp/P-gp
Edoxaban	1-2	9-10	33 %	CYp/P-gp
Warfarin	72-120	20-60	0%	CYp

Ericksson BI, Clin Phatmacokinet 2009
Ruff CR, Am Heart J 2010
Ahrens I, Bode C, Hämostaseologie 2012

DOAC

Studi farmacodinamici e farmacocinetici hanno mostrato che la risposta anticoagulante è prevedibile in condizioni cliniche "standard".

Da ciò è derivato:

1) Somministrazione a dosaggio fisso giornaliero
2) La non indicazione al monitoraggio di laboratorio routinario
3) Non "necessità" di antidoti (breve emivita)

MA…

- E' stata identificata un'ampia variabilità intra/inter individuale
- Modificazioni farmacocinetiche e farmacodinamiche in relazione a: interazioni farmacologiche, insufficienza renale, insufficienza epatica, età, peso.

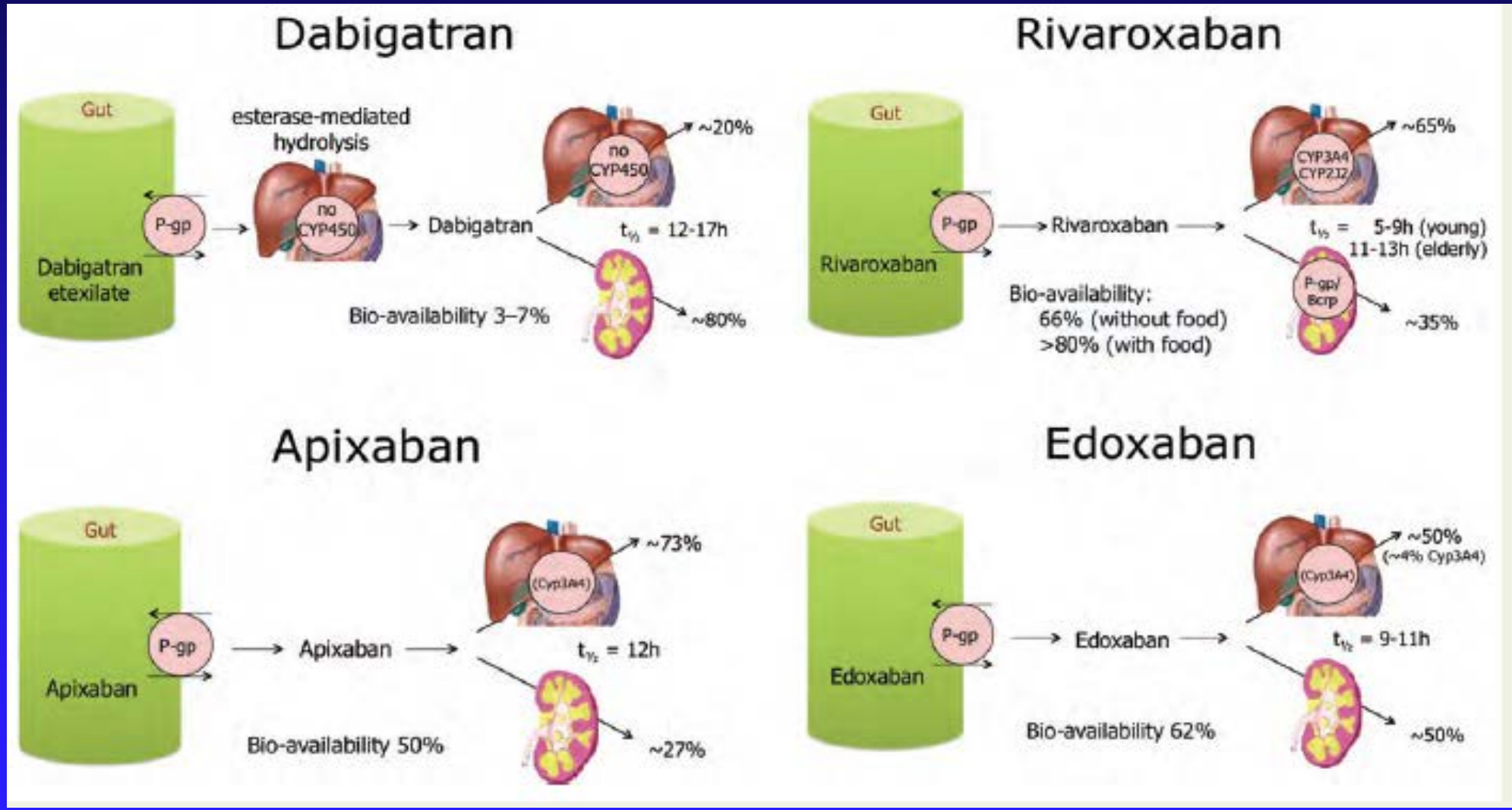
SIAMO TUTTI UGUALI ?

VARIABILITA' INTER-INDIVIDUALE

Farmaco	Basale (ng/ml)	Picco (ng/ml)
Dabigatran 110 mgx2/die	10-96	62-447
Dabigatran 150 mgx2/die	31-225	64-443
Rivaroxaban 10 mg/die	3-25	90-190
Rivaroxaban 20 mg/die	12-137	184-343
Apixaban 2,5 mgx2/die	14-28	16-108
Apixaban 5 mgx2/die	30-70	103-155

Mueck W et al, T&H 2008; Frost et al, Brit J Clin Pharmacol 2013; Summary of product characteristics. Dabigatran. http://wwwmedicinesorguk/emc/medicine/24839. 2012.; Baglin 2013

ABSORPTION AND METABOLISM



EHRA PRACTICAL GUIDE

Europace (2013) **15**, 625–651

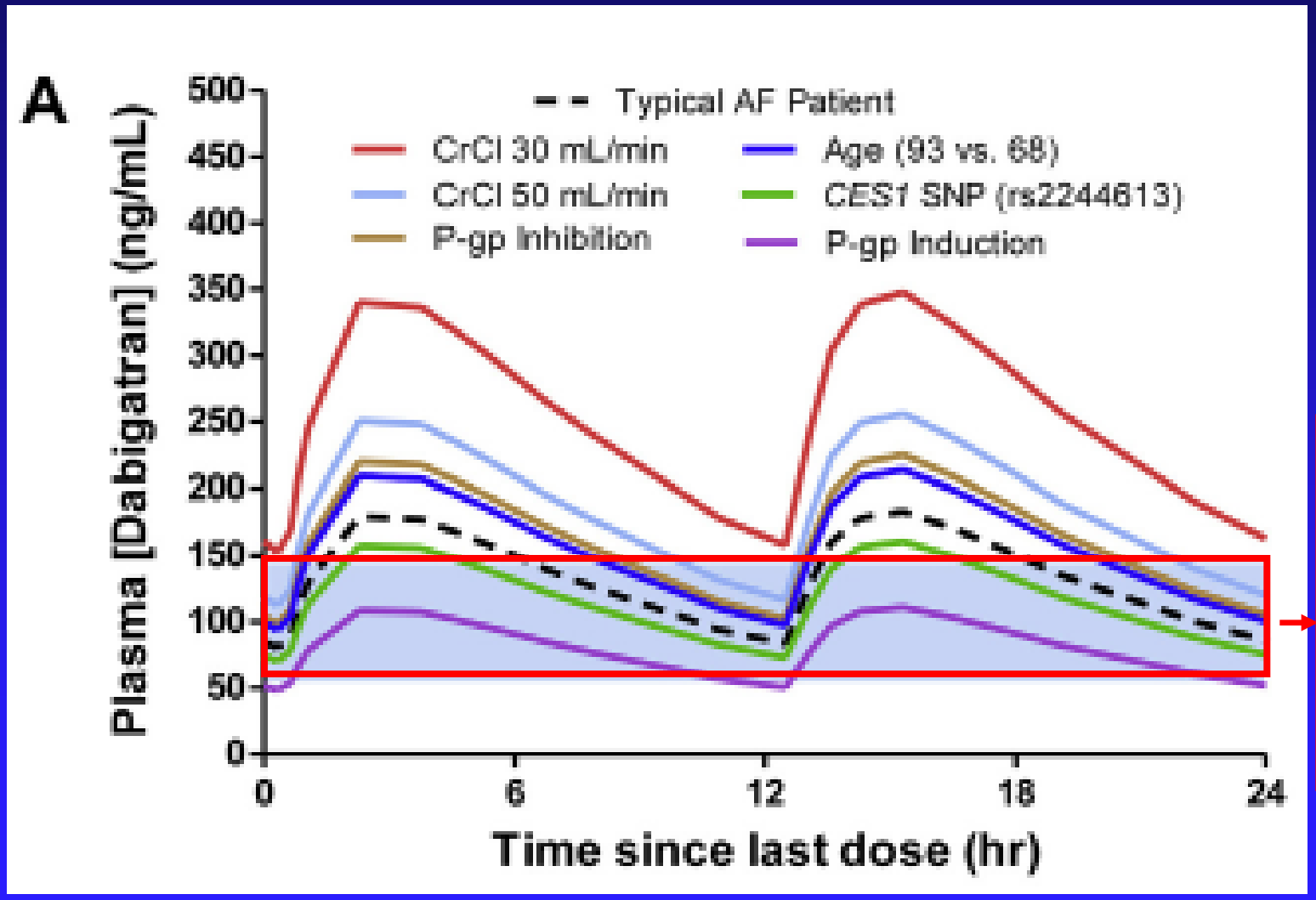
INTERAZIONI FARMACOLOGICHE

	Dabigatran	Rivaroxaban, edoxaban, apixaban
P-glycoprotein Inhibitors (amiodarone, phenotiazin, carboxylic acid, azole antifungals, verapamil, antimalarial, cyclosporine, thioxanthenes)	Yes	Yes
P-glycoprotein inducers (dexamethasone, rifampicin, St. John's Wort)	Yes	Yes
CYP3A4 Inhibitors (phenotiazin, carboxylic acid, azole antifungals, verapamil, erythromycin, telithromycin, nefazodone, antimalarial, cyclosporine, thioxanthenes)	No	Yes
CYP3A4 Inducers (carbamazepine, efavirenz, nevirapine, phenytoin, phenobarbitone, rifabutin, rifapentine, rifampicin, St. John's Wort, alcohol, eucalyptol)	No	Yes
NSAIDS (aspirin, naproxen, diclofenac)	Yes	Yes
Antiplatelet agents (clopidogrel)	Yes	Yes

Interactions should be properly evaluated. Whenever a concomitant therapy is ongoing with a drug likely to interfere with NAO, a lab control should be performed (Pengo, 2011).

Many of these drugs interact with warfarin, but INR levels allows dose adjustment, which mitigates the risk of concomitant treatment (Schulman S et al, 2012)

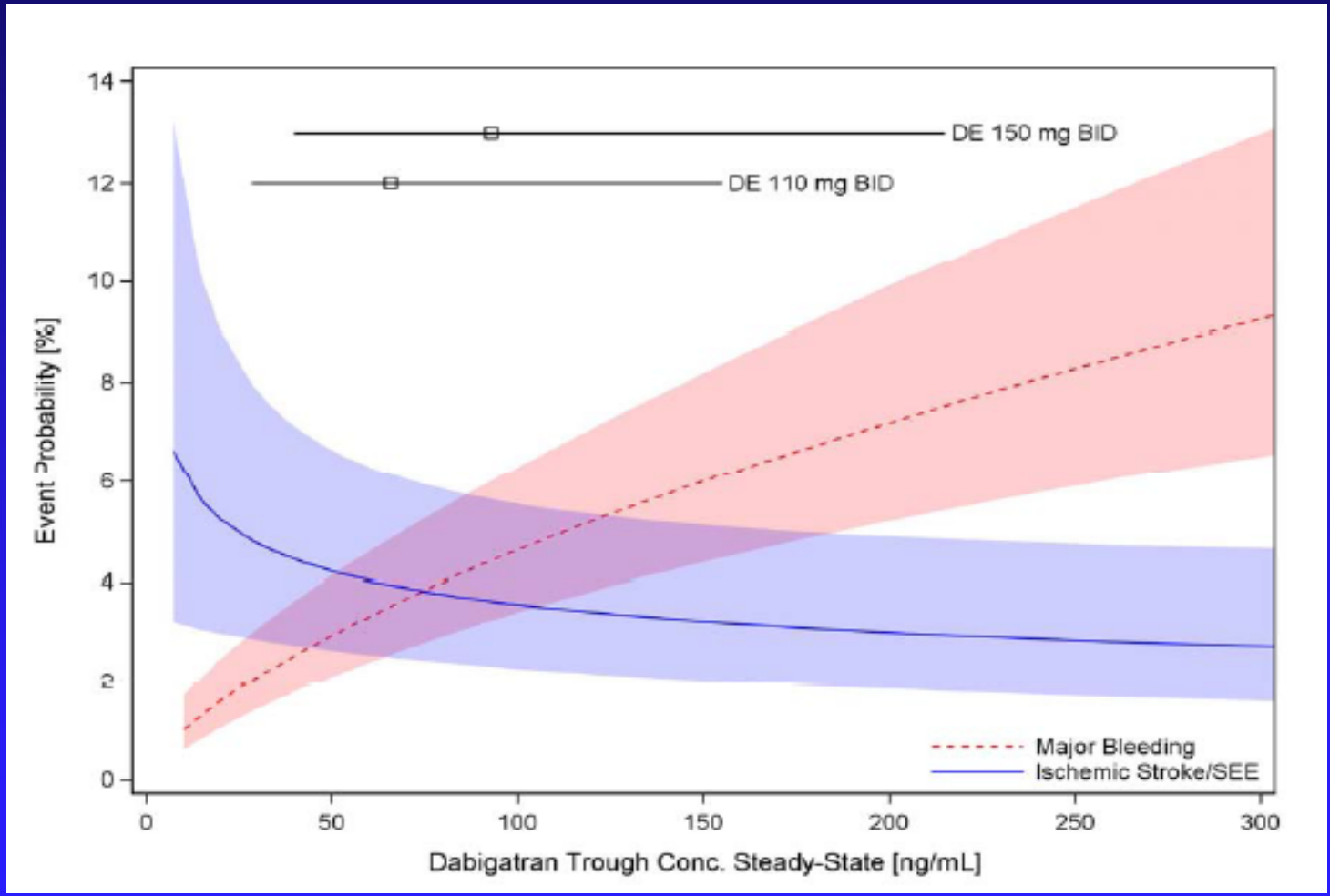
PLASMA CONCENTRATION PROFILE: DABIGATRAN 150mgx2/die



Cmin associata all'aumento dell'efficacia antitrombotica e al ridotto rischio emorragico (FDA)

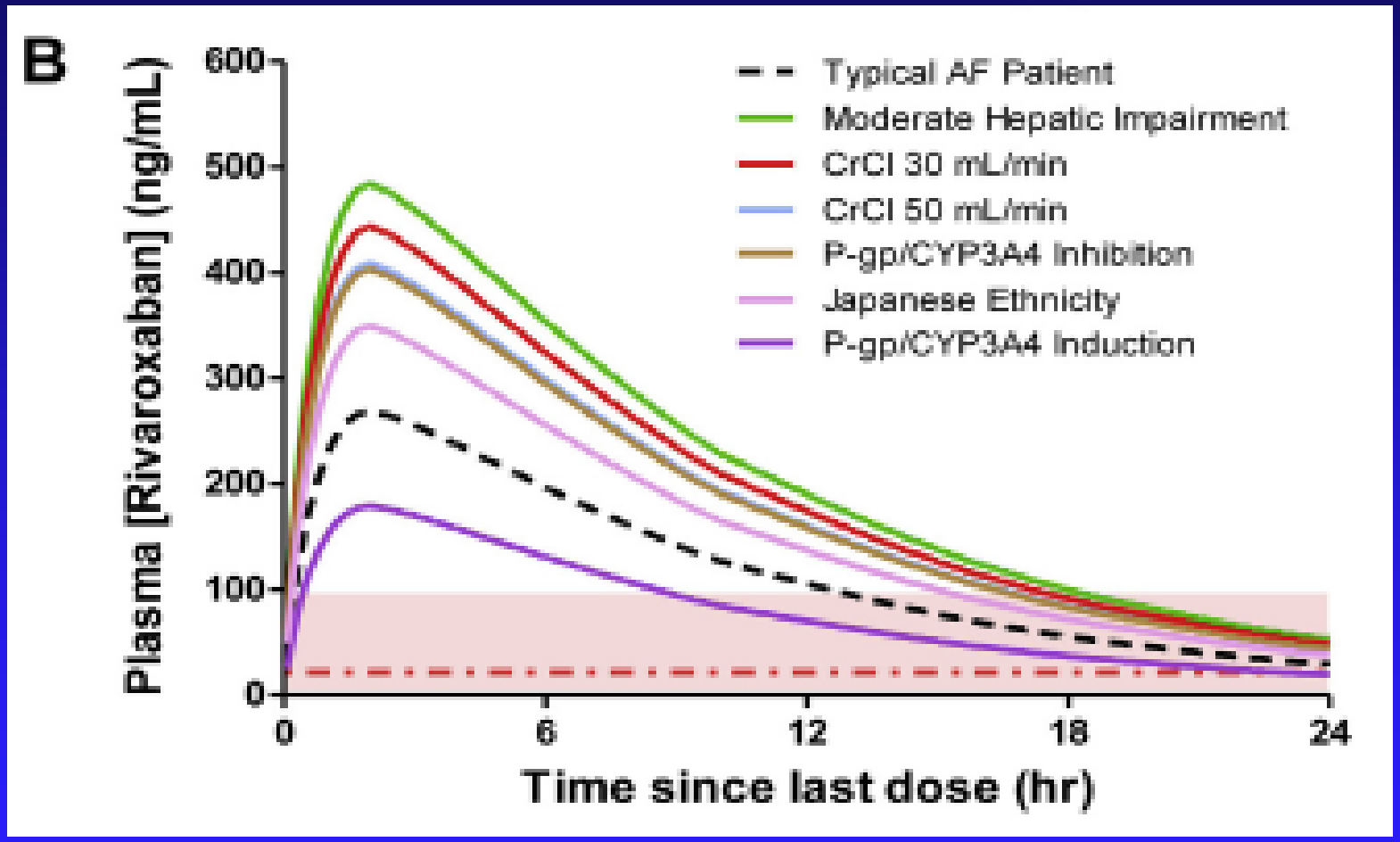
Gong IY et al, 2013

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients in the RE-LY Trial



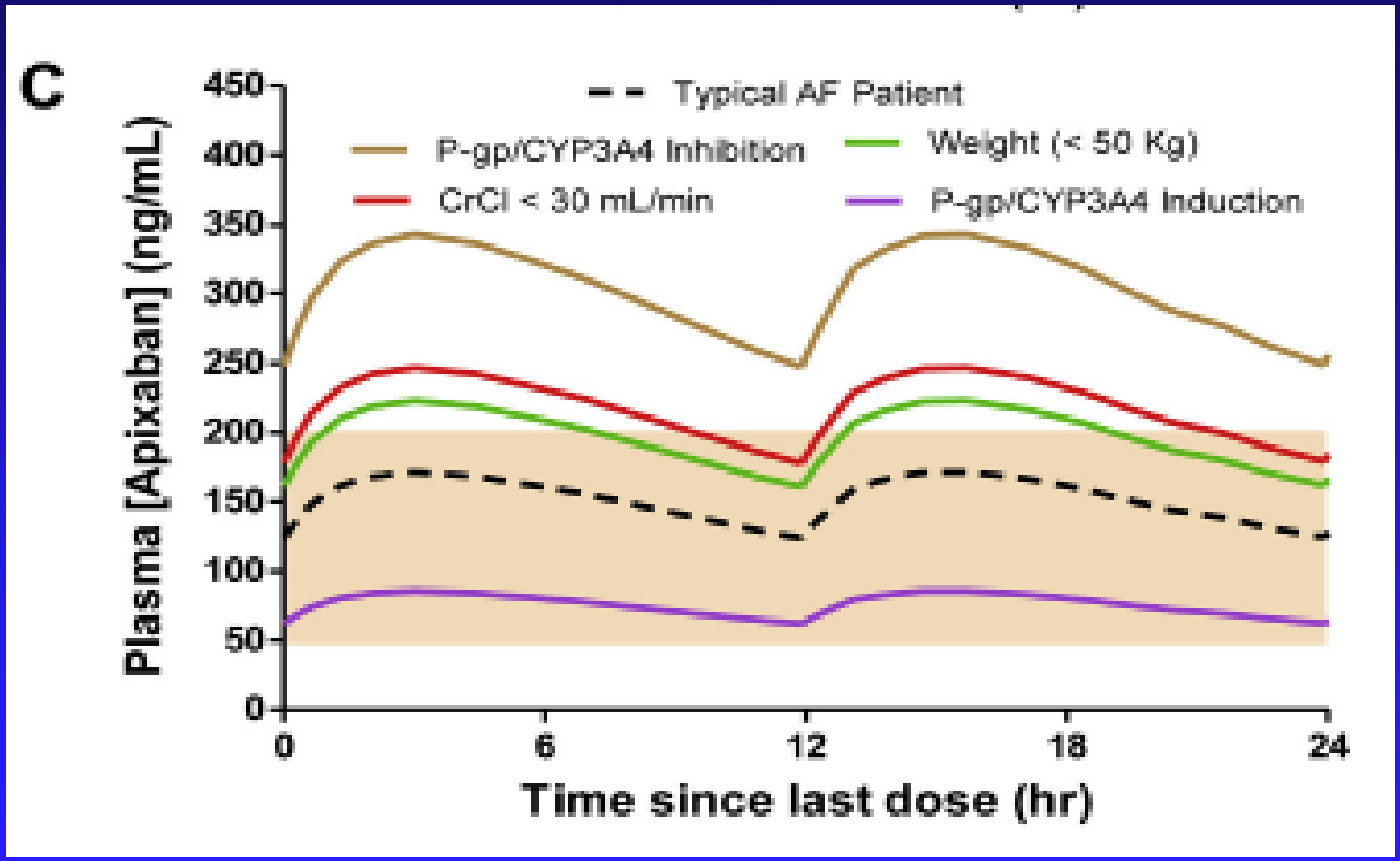
Reilly PA, JACC 2013

PLASMA CONCENTRATION PROFILE: RIVAROXABAN 20mg



•Disclaimer: Although the observed and expected plasma concentrations of rivaroxaban are shown the relationship and interpretation of these concentrations to clinical events/outcomes remains to be seen as more data become available

PLASMA CONCENTRATION PROFILE: APIXABAN 5MGX2/DIE



Disclaimer: Although the observed and expected plasma concentrations of apixaban are shown the relationship and interpretation of these concentrations to clinical events/outcomes remains to be seen as more data become available. *Gong IY et al, 2013*

QUANDO PUO' ESSERE UTILE IL DOSAGGIO FARMACOLOGICO?

Questions and answers on the use of dabigatran and perpectives on the use of other new oral anticoagulants in patients with atrial fibrillation

A consensus document of the Italian Federation of Thrombosis Centers (FCSA)

Vittorio Pengo[1]; Luciano Crippa[2]; Anna Falanga[3]; Guido Finazzi[4]; Francesco Marongiu[5]; Gualtiero Palareti[6]; Daniela Poli[7]; Sophie Testa[8]; Eros Tiraferri[9]; Alberto Tosetto[10]; Armando Tripodi[11]; Cesare Manotti[12]

- Perioperative management
- Patients presenting in emergency with adverse events (Thrombosis, Bleeding)
- Immediate reverse of anticoagulation
- Renal Disease
- Liver Disease
- Suspicion or known interaction with other drugs
- Elderly patients
- Under/over weight

2011

DOAC: QUALI TEST?

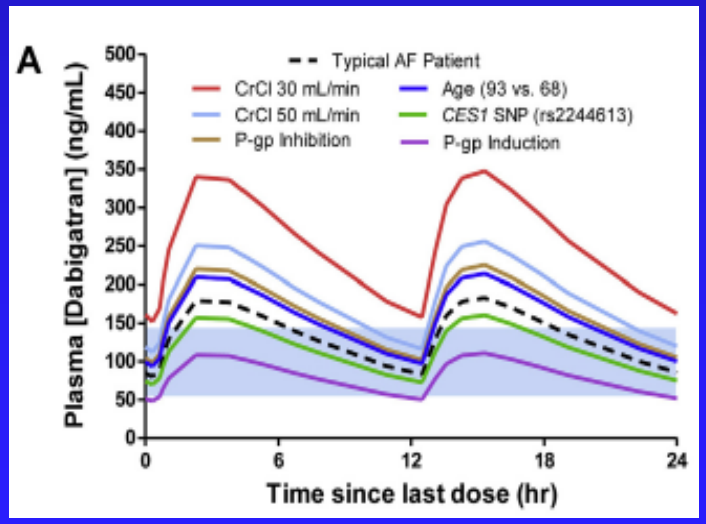
FARMACO	DOSAGGIO DELL'ATTIVITA' ANTICOAGULANTE (metodo)
dabigatran (ng/ml)	dTT (tempo di Trombina diluito) ECT /ECA (test Ecarina)
rivaroxaban (ng/ml)	anti FXa
apixaban (ng/ml) *edoxaban (ng/ml)*	anti FXa

La misura dell'attivita' anticoagulante deve essere espressa in ng/ml. In condizioni stabili le concentrazioni farmacologiche devono essere misurate prima della somministrazione successiva del farmaco.

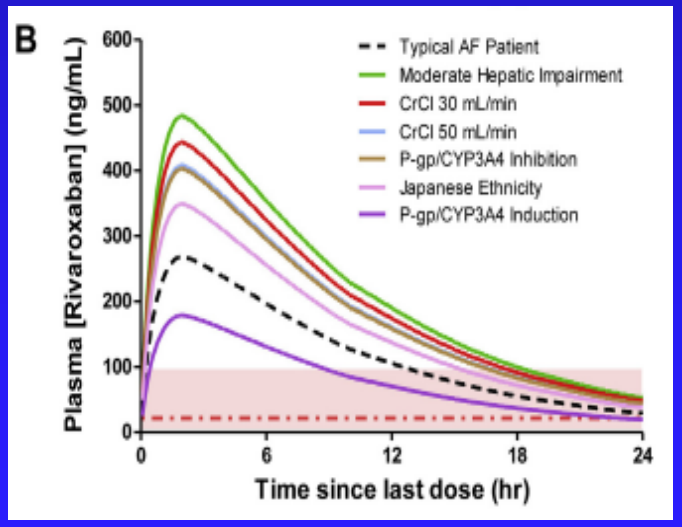
Pengo V et al, T&H 2011; Douxfils J et al, T&H 2012, 2013; Baglin T, JT&H 2013, Tripodi A, 2013

I FATTORI DA CONSIDERARE PER POTERE INTERPRETARE IL RISULTATO DI LABORATORIO

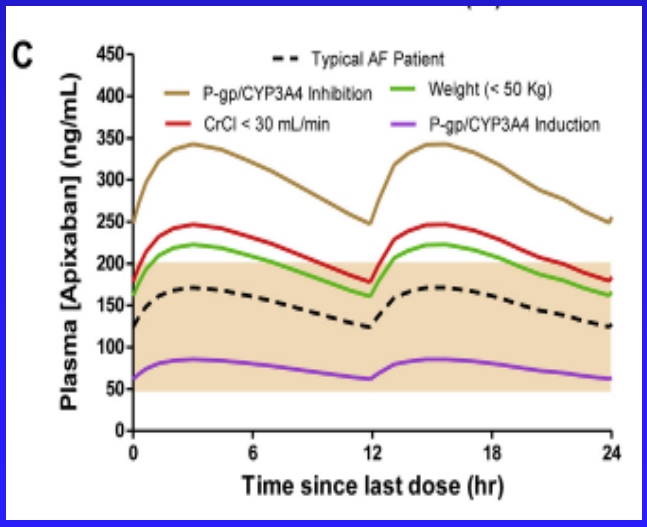
- Quale farmaco?
- A che ora è stato assunta l'ultima dose?
- Quale test richiedere?



Dabigatran



Rivaroxaban



Apixaban

CONSIDERAZIONI

- La somministrazione di farmaco in dosi fisse giornaliere non significa assenza di necessità di controlli sanitari
- Il controllo dell'attività anticoagulante dei DOAC è disponibile attraverso test di laboratorio relativamente semplici e utile in numerose condizioni cliniche
- Dobbiamo aumentare le nostre conoscenze per gestire i pazienti con i sistemi più efficaci e sicuri.