ANTICOAGULANTI ORALI DIRETTI: INDICAZIONI, CONTROINDICAZIONI ELEMENTI DI FARMACOCINETICA, INTERAZIONI FARMACOLOGICHE

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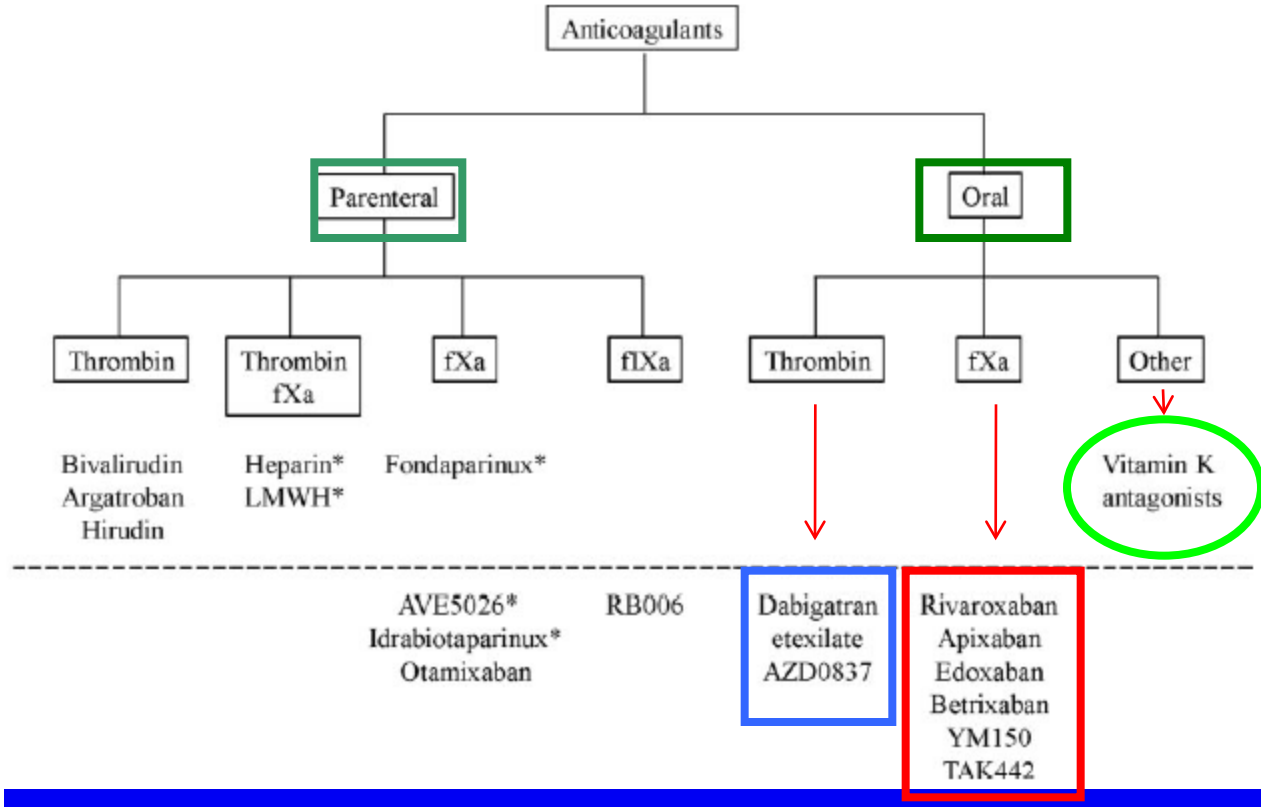
TERAPIA ANTICOAGULANTE ORALE

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

TERAPIA ANTICOAGULANTE ORALE

VAO
Vecchi Anticoagulanti Orali

AVK
Farmaci Anti Vitamina K

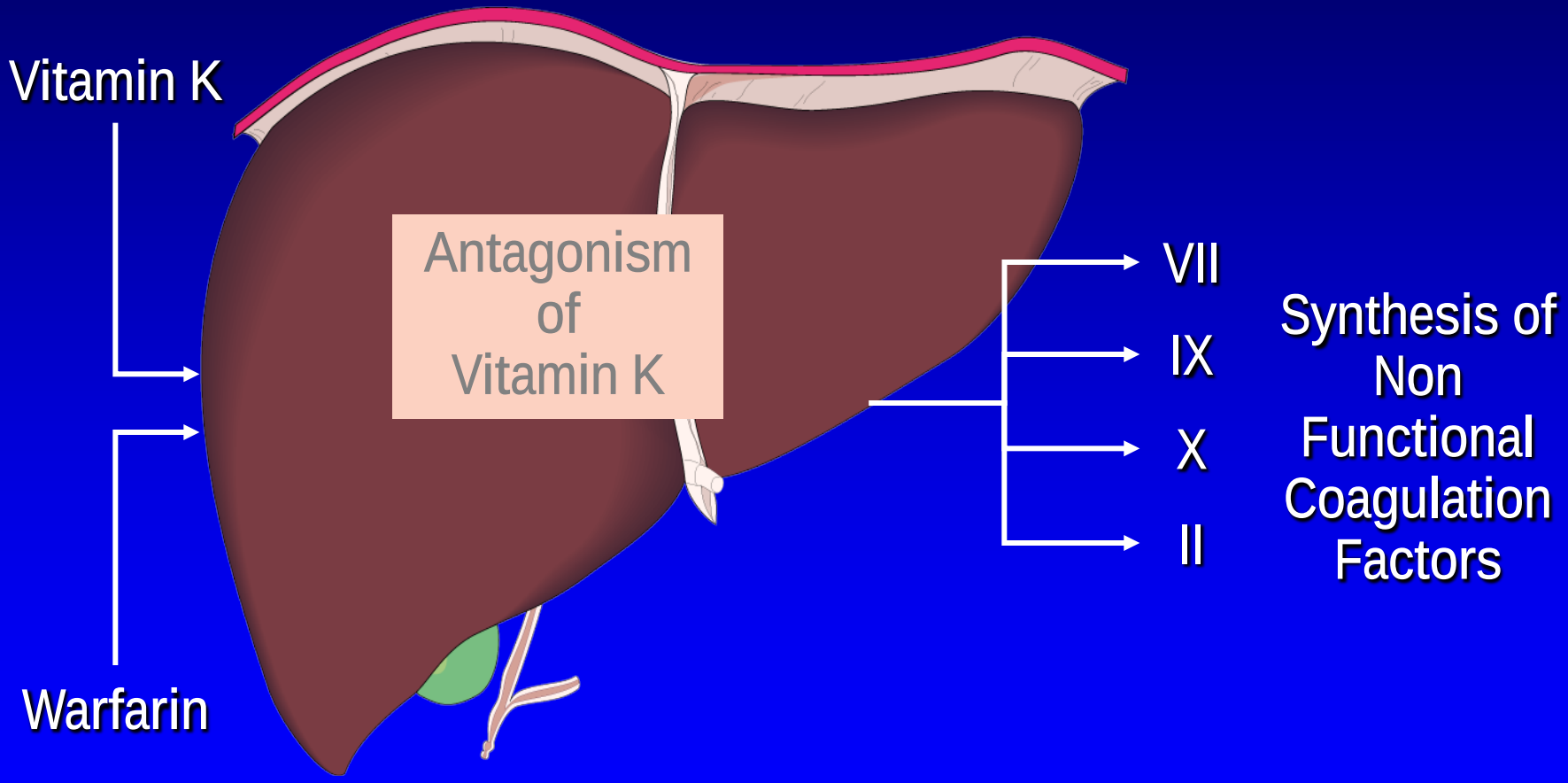
Warfarin = Coumadin®
Acenocumarolo = Sintrom®

NOA
Nuovi Anticoagulanti Orali

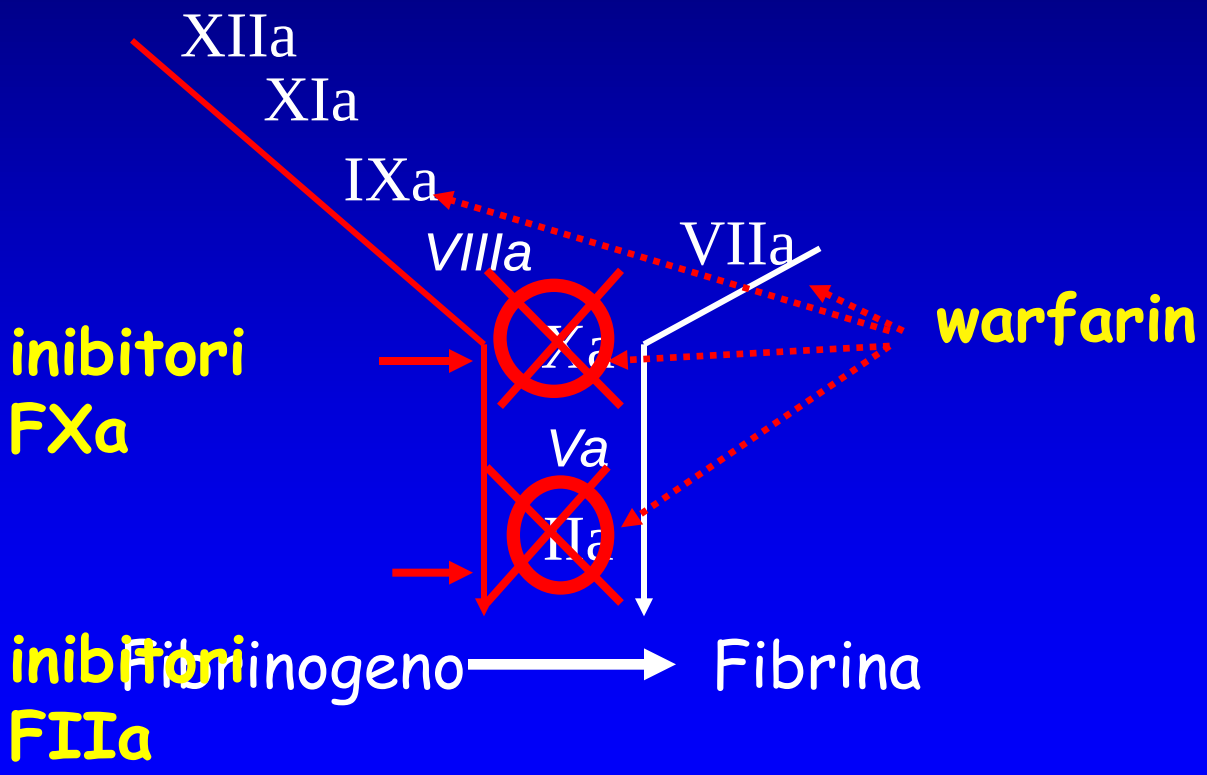
DOA
Anticoagulanti Orali ad azione Diretta

Dabigatran = Pradaxa®
Rivaroxaban = Xarelto®
Apixaban = Eliquis®
Edoxaban = Lixiana®

AVK: MECCANISMO D'AZIONE



DOAC: MECCANISMO D'AZIONE



FARMACOLOGIA

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
$t_{1/2}$ (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)

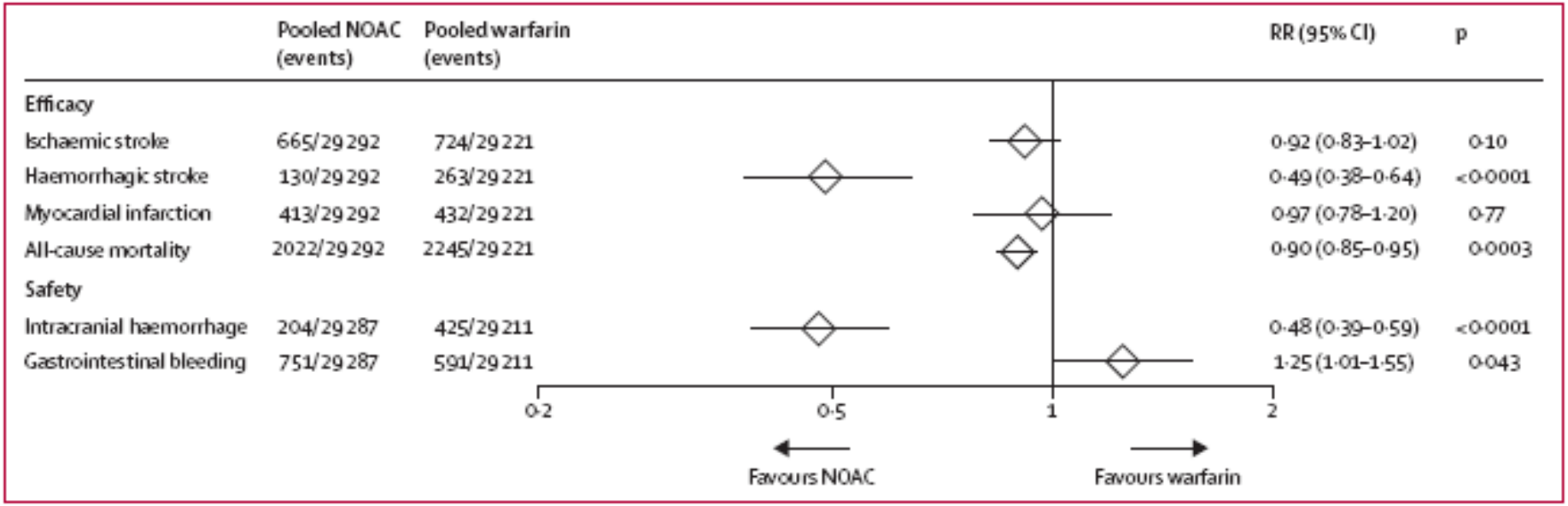
INDICAZIONI ALLA TAO

PROFILASSI DEL TROMBOEMBOLISMO
TRATTAMENTO TROMBOSI VENOSA PROFONDA
TRATTAMENTO EMBOLIA POLMONARE
FIBRILLAZIONE ATRIALE NON VALVOLARE
MIOCARDIOPATIA DILATATIVA
VALVULOPATIE
PROTESI VALVOLARI CARDIACHE (BIOL E MECC)
PREV. SECONDARIA IMA

PROFILASSI DEL TROMBOEMBOLISMO	- AVK - DOAC in chir. ortopedica elettiva
TRATTAMENTO TROMBOSI VENOSA PROFONDA	- AVK - DOAC sec. Piano terapeutico
TRATTAMENTO EMBOLIA POLMONARE	- AVK - DOAC sec. Piano terapeutico
FIBRILLAZIONE ATRIALE NON VALVOLARE	- AVK - DOAC sec P.T. specifico
MIOCARDIOPATIA DILATATIVA	AVK
VALVULOPATIE FIBRILLAZIONE ATRIALE VALVOLARE	AVK
PROTESI VALVOLARI CARDIACHE (BIOL E MECC)	AVK
PREV. SECONDARIA IMA	AVK

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

SICUREZZA ED EFFICACIA



www.thelancet.com Vol 383 March 15, 2014

THROMBOSIS AND HEMOSTASIS

Rates, management, and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

BLEEDING RATES PER 100 PATIENT-YEARS

	All patients	SPAF	VTE	*P* value: SPAF vs VTE
n (%)	1775 (100)	1200 (67.6)	575 (32.4)	
Any bleeding, % (95% CI)	59.4 (55.2-63.9)	59.3 (54.4-64.6)	59.6 (51.7-68.4)	.4989
Minor bleeding, % (95% CI)	36.3 (33.2-39.7)	35.8 (32.2-39.7)	37.8 (31.8-44.6)	.4199
NMCR bleeding, % (95% CI)	19.7 (17.6-22.1)	20.7 (18.1-23.5)	17.2 (13.5-21.6)	.1585
Major bleeding, % (95% CI)	3.4 (2.6-4.4)	3.1 (2.2-4.3)	4.1 (2.5-6.4)	.2849

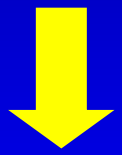
Beyer-Westendorf J, Blood 2014

DOAC

Studi di farmacologia hanno mostrato che la risposta anticoagulante e' prevedibile in condizioni cliniche "standard"

Da ciò è derivato:

1) Somministrazione a dosaggio fisso giornaliero
2) La non indicazione al monitoraggio di laboratorio routinario



1. Diversa percezione delle necessità sanitarie dei pazienti in trattamento cronico con DOAC
2. Le indicazioni date dal Piano Terapeutico (procedura amministrativo) vengono considerate come modello sanitario gestionale

MA

- Esiste ampia variabilita' intra/inter individuale
- Modificazioni farmacocinetiche e farmacodinamiche in relazione a: interazioni farmacologiche, insuff. renale, insuff. epatica, eta', peso.
- Non noti i range terapeutici e il livelli di anticoagulazione (cut-off) sicuri per procedere a chirurgia/manovre invasive

Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics

Sophie Testa [a,*], Armando Tripodi [b], Cristina Legnani [c], Vittorio Pengo [d], Rosanna Abbate [e], Claudia Dellanoce [a], Paolo Carraro [f], Luisa Salomone [c], Rita Paniccia [e], Oriana Paoletti [a], Daniela Poli [f], Gualtiero Palareti [g], for the START-Laboratory Register

FARMACO	Basale (ng/ml) media (min-max)	Picco (ng/ml) media (min-max)
Dabigatran 110 mgx2/die	93 (14-386)	190 (31-651)
Dabigatran 150mgx2/die	91 (16-494)	210 (43-538)
Rivaroxaban 15mg/die	27 (0-88)	208 (77-393)
Rivaroxaban 20mg/die	41 (5-119)	235 (61-449)
Apixaban 2,5mgx2/die	79 (26-248)	192 (55-300)
Apixaban 5 mgx2/die	113 (42-283)	200 (102-416)

Thrombosis Research, 2016

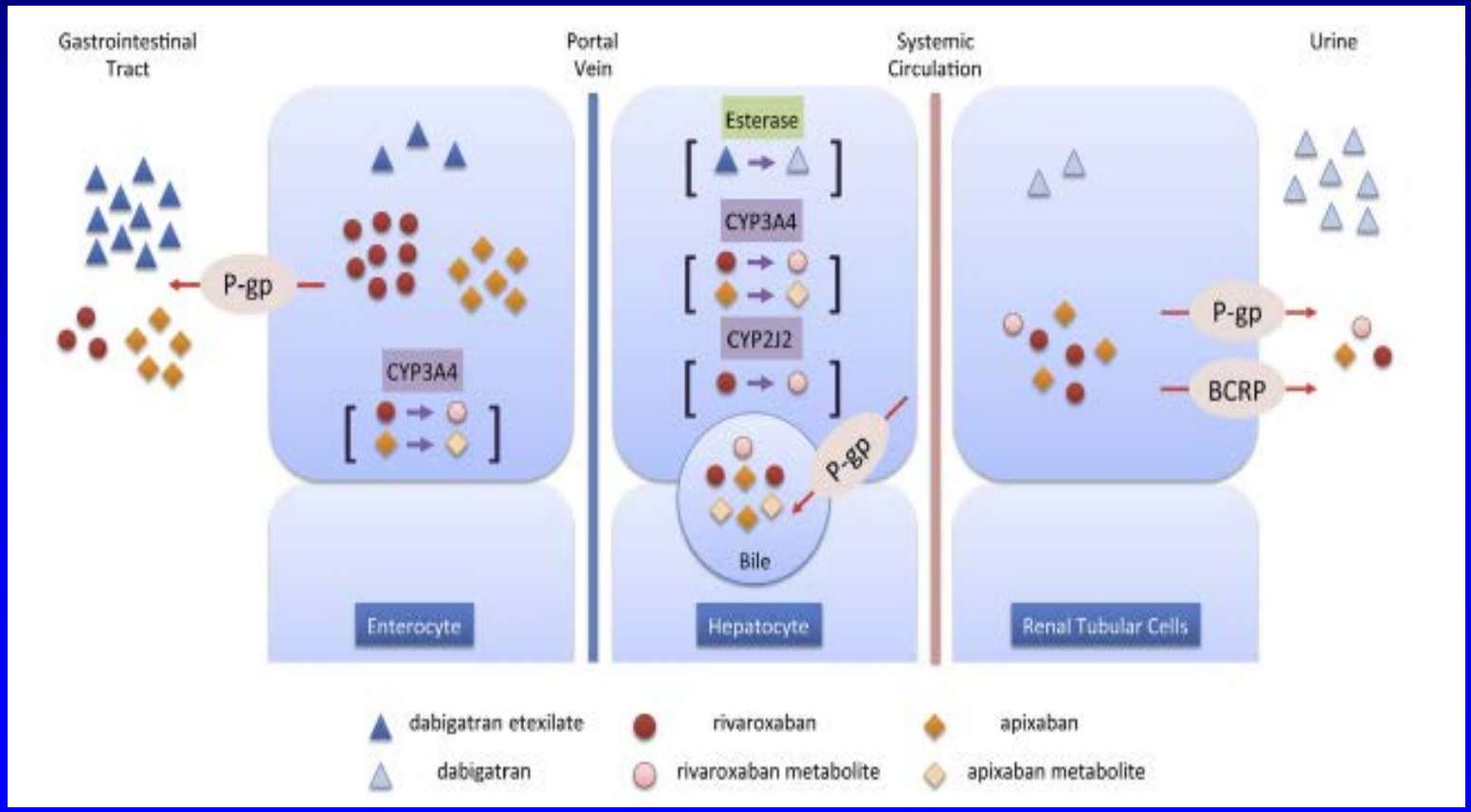
DOAC: INTRA-INDIVIDUAL VARIABILITY

	Intra-individual variability (ng/mL) mean (min-max)	CV% mean (min-max)
DABIGATRAN		
C_{trough}	80.3 (20-341)	36.0 (8.3-64.4)
C_{peak}	205.0 (37.0-465.1)	38.8 (23.8-49.8)
RIVAROXABAN		
C_{trough}	31.0 (20-75.5)	25.2 (1.5-52.6)
C_{peak}	197 (24.6-426.8)	30.7 (5.4-75.7)
APIXABAN		
C_{trough}	122.1 (40.8-249.5)	26 (13.6-54.4)
C_{peak}	224.6 (116-419.2)	25.7 (6.6-40.5)

Thromb Res, 2016

Importance of Pharmacokinetic Profile and Variability as Determinants of Dose and Response to Dabigatran, Rivaroxaban, and Apixaban

Inna Y. Gong, BMSc,[a,b] and Richard B. Kim, MD[a,b]



2013

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).

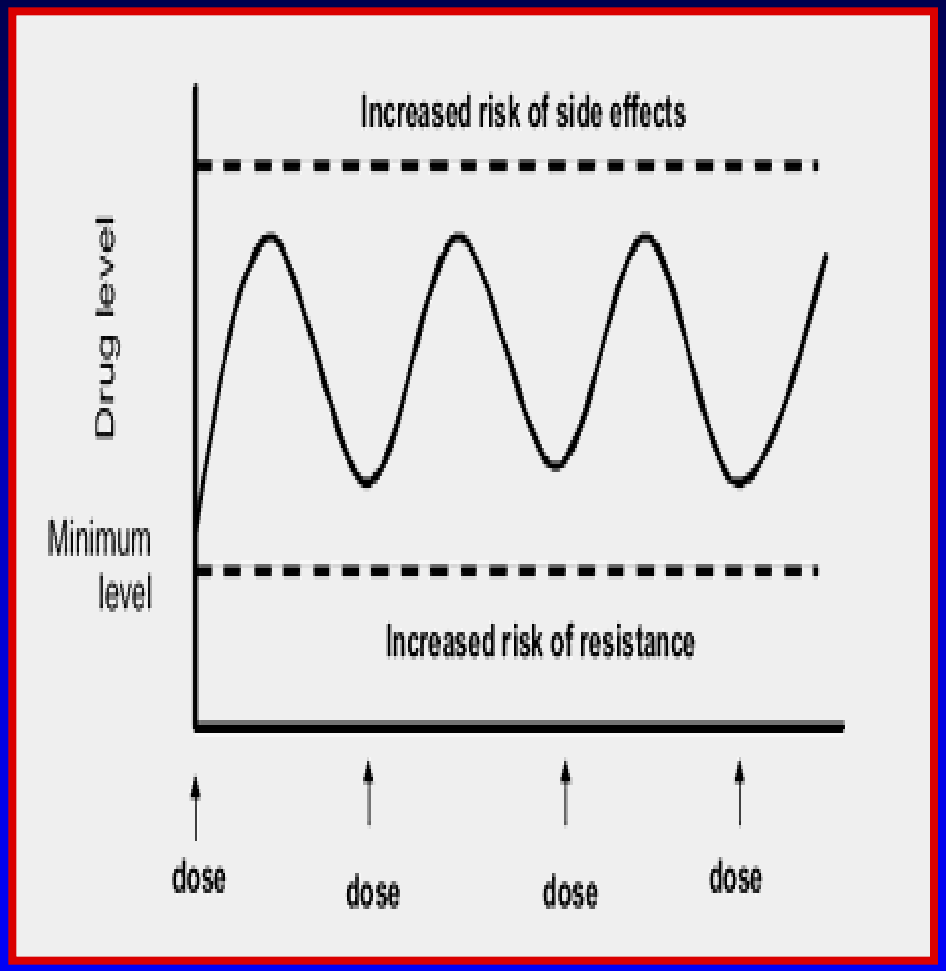
Many of these drugs interact with warfarin, but INR levels allows dose adjustment, which mitigates the risk of concomitant treatment (Schulman S et al, 2012)

Table 5 Effect on NOAC plasma levels ('area under the curve, AUC') from drug–drug interactions and clinical factors, and recommendations towards NOAC dosing

	Via	Dabigatran	Apixaban	Edoxaban[a]	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition	+18%[29]	No data yet	No effect[30]	No effect[27,31]
Digoxin	P-gp competition	No effect[32]	No data yet	No effect[30]	No effect[27,33]
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12–180%[24] (reduce dose and take simultaneously)	No data yet	+53% (SR)[30] (reduce dose by 50%)[a]	Minor effect (use with caution if CrCl 15–50 ml/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[24]	+40%[5mPC]	No data yet	Minor effect (use with caution if CrCl 15–50 ml/min)
Quinidine	P-gp competition	+50%	No data yet	+80%[30] (reduce dose by 50%)[b]	+50%
Amiodarone	P-gp competition	+12–60%[24]	No data yet	No effect[30]	Minor effect (use with caution if CrCl 15–50 ml/min)
Dronedarone	P-gp and CYP3A4 inhibitor	+70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%)[b]	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition	+140–150% (US: 2 × 75 mg)	+100%[5mPC]	No data yet	Up to +160%[27]
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[27]
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%[24,27]
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[5mPC]	No data yet	Up to +153%[27]
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers	−66%[34]	−54%[5mPC]	−35%	Up to −50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption	−12–30%[22–24]	No data yet	No effect	No effect[21,25]
Other factors					
Age ≥80 years	Increased plasma level			No data yet	
Age ≥75 years	Increased plasma level			No data yet	
Weight ≤60 kg	Increased plasma level				
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			

EUROPEAN SOCIETY OF CARDIOLOGY®
Europace (2013) **15**, 625–651
doi:10.1093/europace/eut083

INOLTRE



In base agli studi di fase II e III si è assunto che:

- nel tempo (mesi/anni) si mantengano sempre livelli "accettabili"

- non si verifichino "accumuli" persistenti di farmaco

-non si verifichino condizioni persistenti di "assenza o insufficiente" attività anticoagulante

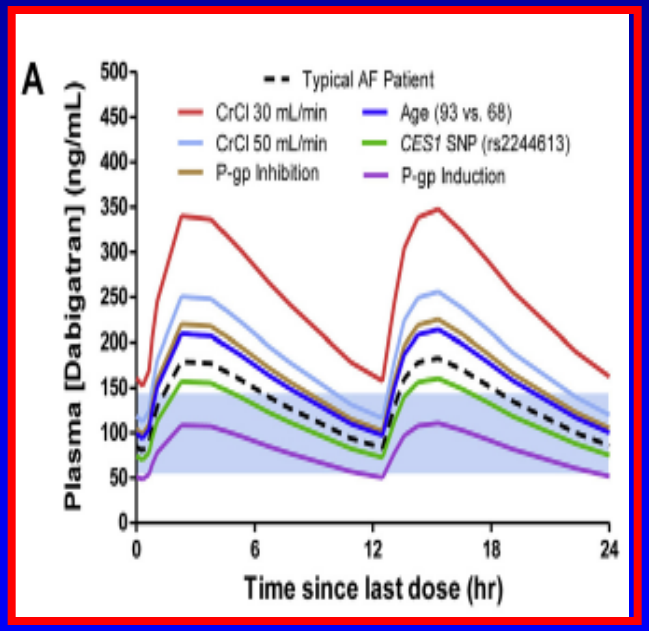
Sappiamo, però, che le complicanze con altri farmaci (es AVK) correlano con il tempo trascorso a livelli non adeguati di anticoagulazione (TTR)

Penserete: " …ma le LMWH si utilizzano senza controlli"

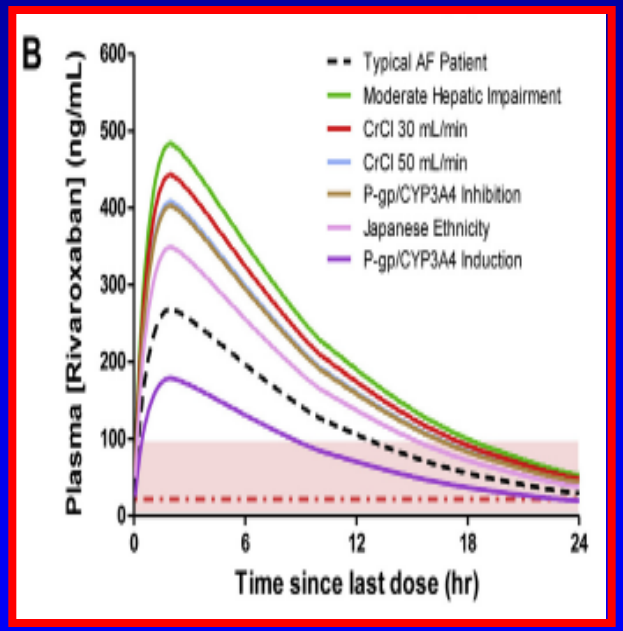
Risposta: "Si, non sempre, e generalmente vengono somministrate per brevi periodi di tempo non per anni…"

VARIABILITA'

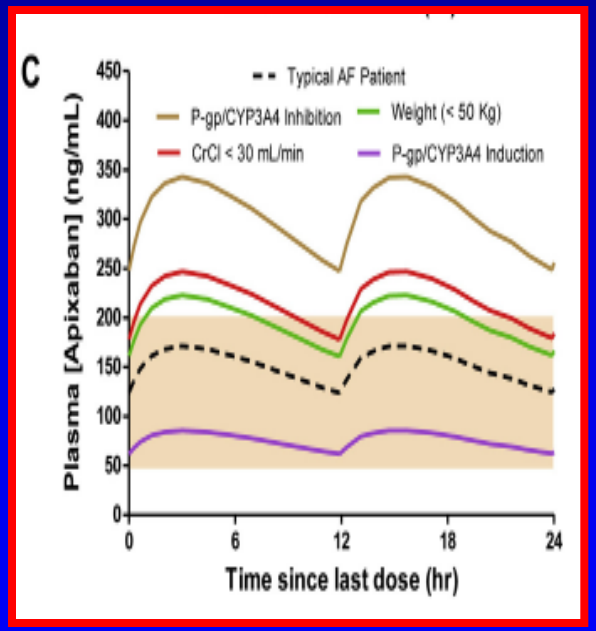
Dipende da: Sesso, Età, Peso, Interazioni farmacologiche, Funzione renale, Funzione epatica, Polimorfismi dei sistemi enzimatici



Dabigatran



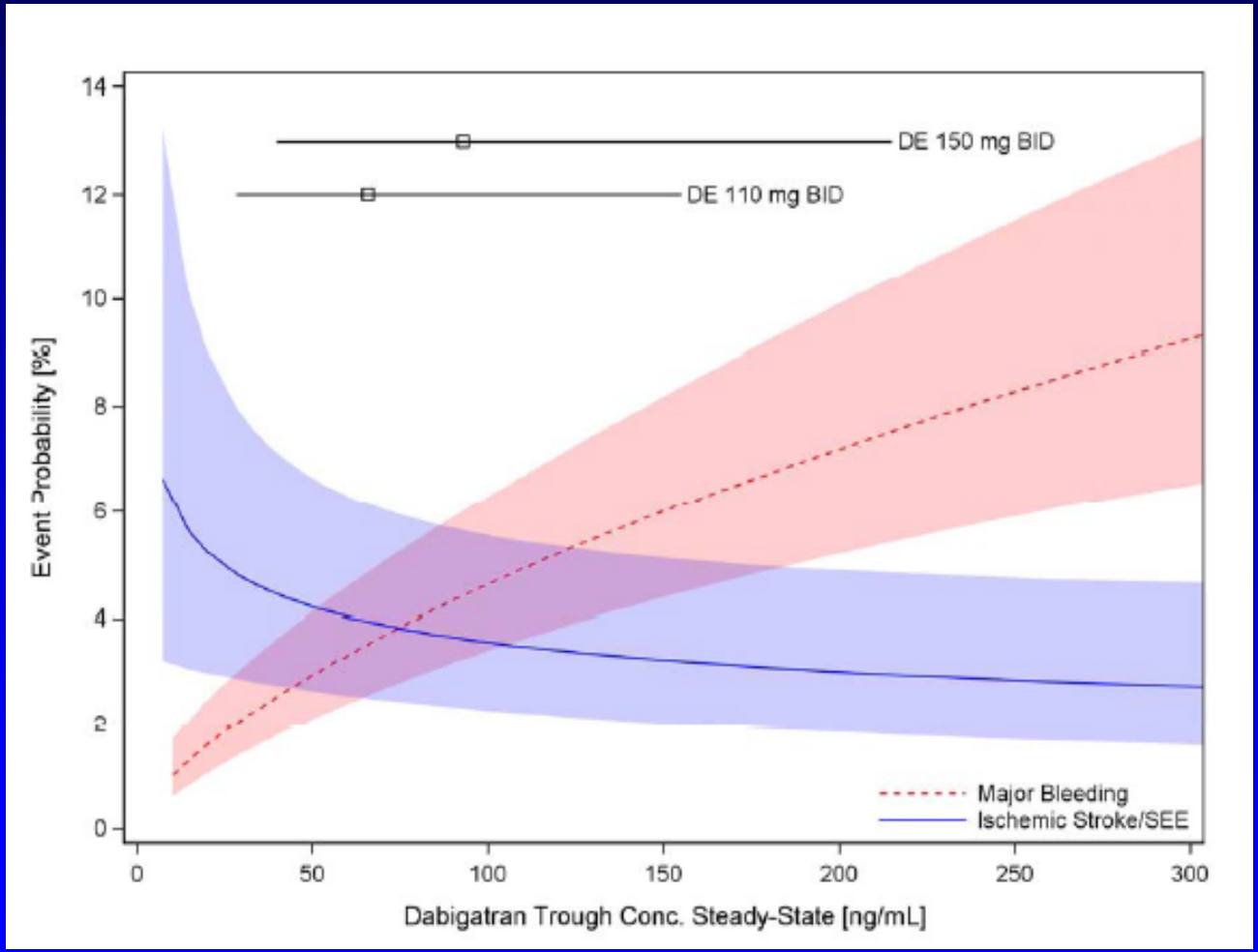
Rivaroxaban



Apixaban

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

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

FDA Draft Briefing Document for the
Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

Meeting Date: 8 September 2011

FDA ANALYSIS OF ROCKET

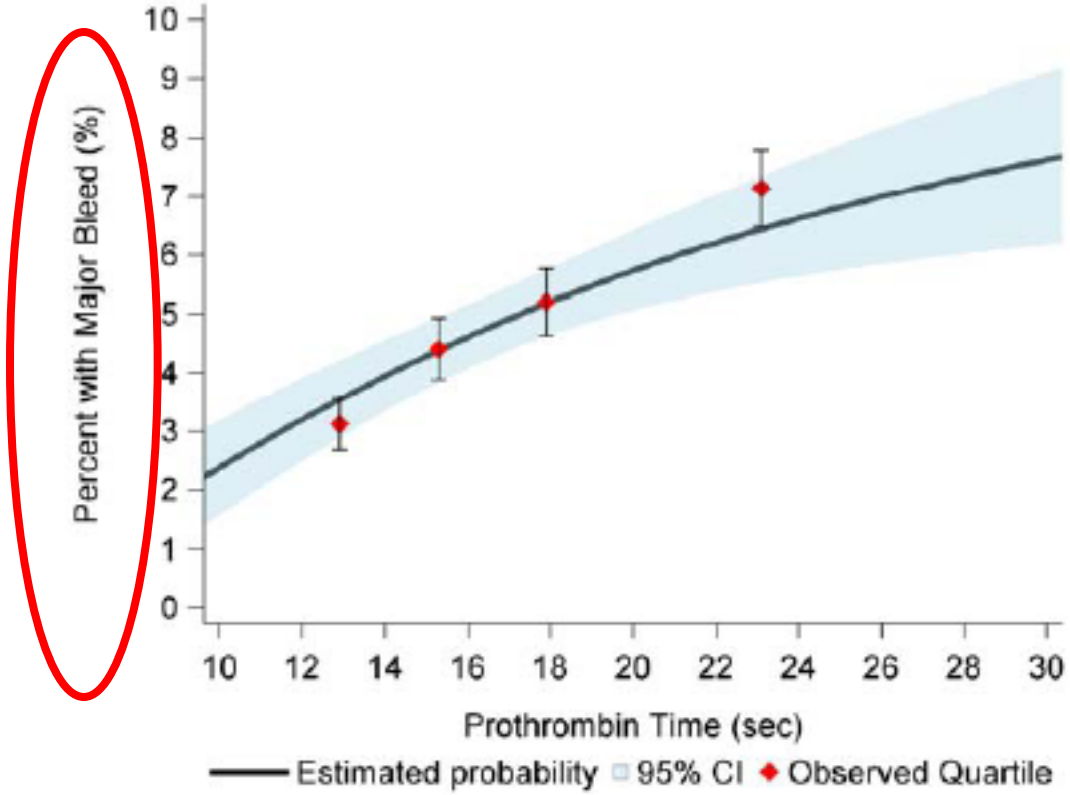
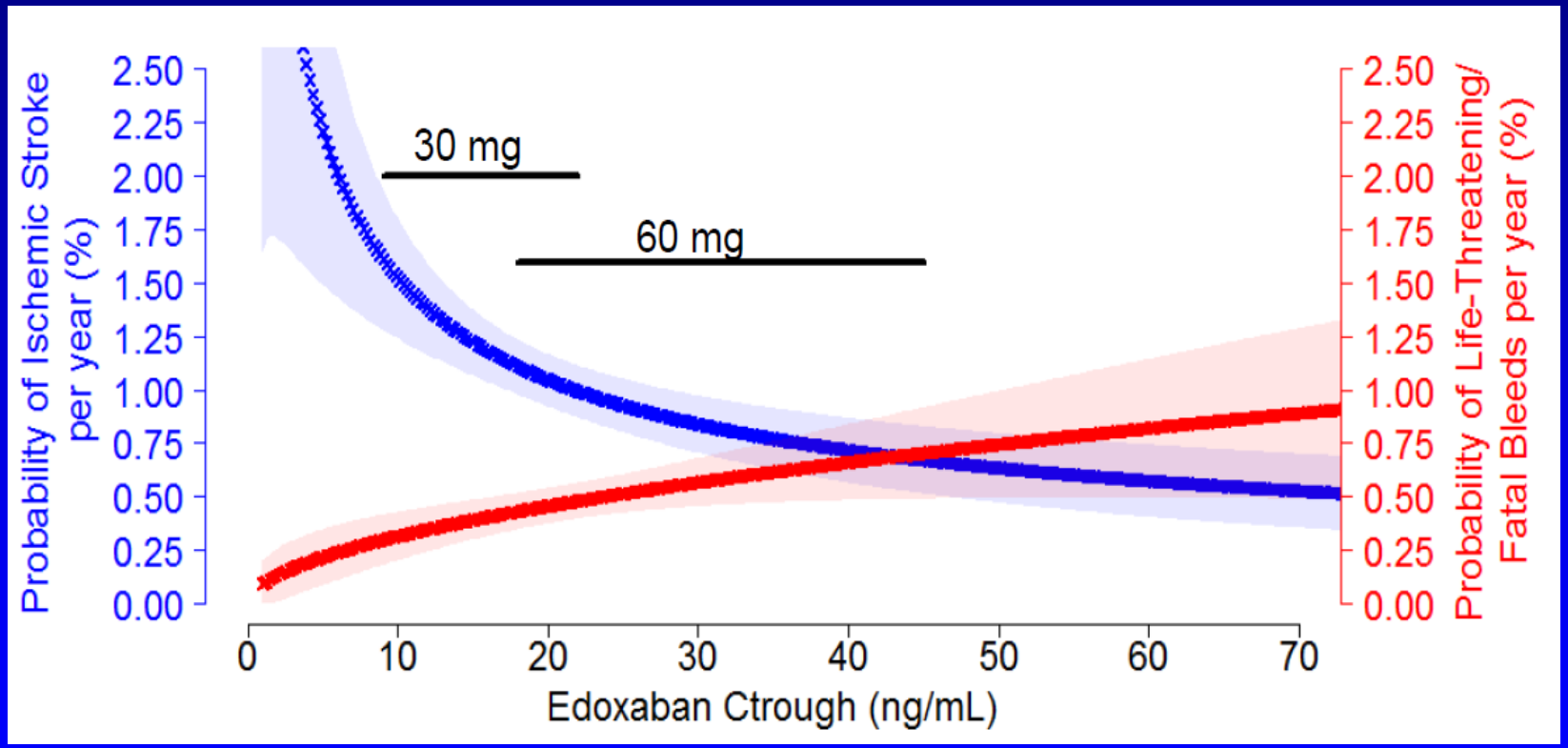


Figure 9 Probability of major bleeding as a function of pre-dose PT for rivaroxaban. The solid line represents the predicted probability from an E_{max} logistic regression and the shaded region represents the 95% confidence interval. The point represents the observed probability at the median value of pre-dose PT for a given quartile and error bars represent standard errors.

EDOXABAN : CORRELATION OF DRUG LEVELS AND OUTCOMES IN PHASE III TRIALS



FDA, October 26, 2015

QUINDI: E' UTILE CONOSCERE I LIVELLI DEI DOAC?

1. **DOSAGGIO PERIODICO**

   non è attualmente raccomandato (ma può essere utile per evidenziare un sovra/sottodosaggio persistente)

2. **<u>DOSAGGIO IN CONDIZIONI CLINICHE PARTICOLARI</u>**

IL DOSAGGIO DEI DOAC

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

COME MISURARE I DOAC?

- Tutti i test coagulativi di screening possono essere variamente influenzati dai DOAC a seconda del tipo di reagente
- PT, aPTT e TT, per la scarsa o eccessiva sensibilità, NON SONO TEST UTILI per esprimere l'attività anticoagulante dei DOAC
- PT/PTT nella norma non escludono presenza di concentrazioni significative di DOAC così come PT/PTT allungati si osservano in assenza di farmaco.
- Sono disponibili test specifici per ogni molecola, semplici, di facile esecuzione e a basso costo

Kitchen S et al, BJH 2015; Testa S et al, JTH 2016

DOAC: QUALI TEST?

FARMACO	METODO DI DOSAGGIO DELL'ATTIVITA' ANTICOAGULANTE
dabigatran (ng/ml)	dTT ECT /ECA
rivaroxaban (ng/ml) apixaban (ng/ml) edoxaban (ng/ml)	aXa

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

LE NECESSITA' SANITARIE DEL PAZIENTE IN TERAPIA CON AVK O DOAC

AVK	IL PAZIENTE	DOAC
Si	Visita di prescrizione (anamnesi, condizioni cliniche, assetto emostatico, funzione epatica e renale)	**Si**
Si	Giusta indicazione e dose (o range terapeutico di INR)	**Si**
Si	Informazione/Educazione completa	**Si**
Si (12-15/anno) Monitoraggio	Routinari prelievi ematici per controlli di lab.	**No?** (3-4/anno) Controllo
Si	Aggiustamenti "esperti" delle dosi	**No**
No	Controllo compliance/aderenza	**Si**
Si	Guida per condizioni a rischio/complic.	**Si**
No (routine)	Controlli clinici periodici	**Si**

LE NECESSITA' SANITARIE DEL PAZIENTE IN TERAPIA CON AVK O DOAC

AVK		DOAC
Si	Preparazione interventi chirurgici/manovre invasive (tempi di sospensione e/o eventuale bridging therapy)	Si
Si	Gestione delle complicanze maggiori	Si
Si	Gestione delle complicanze minori	Si
Si	Rivalutazione clinico/terapeutica in caso di cambiamenti dello stato di salute	Si