TERAPIE ANTICOAGULANTI E INDICAZIONI CLINICHE

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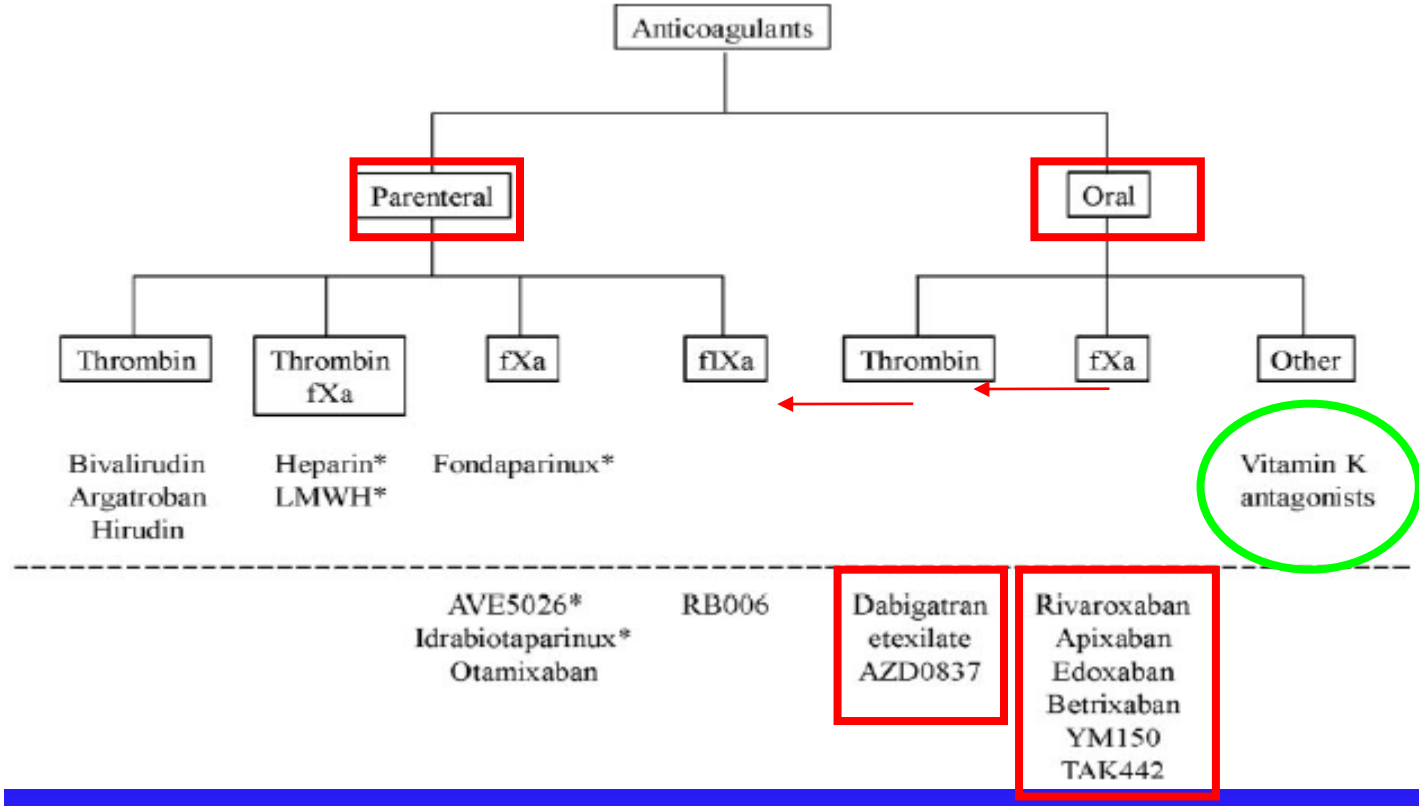
FARMACI ANTICOAGULANTI

- **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



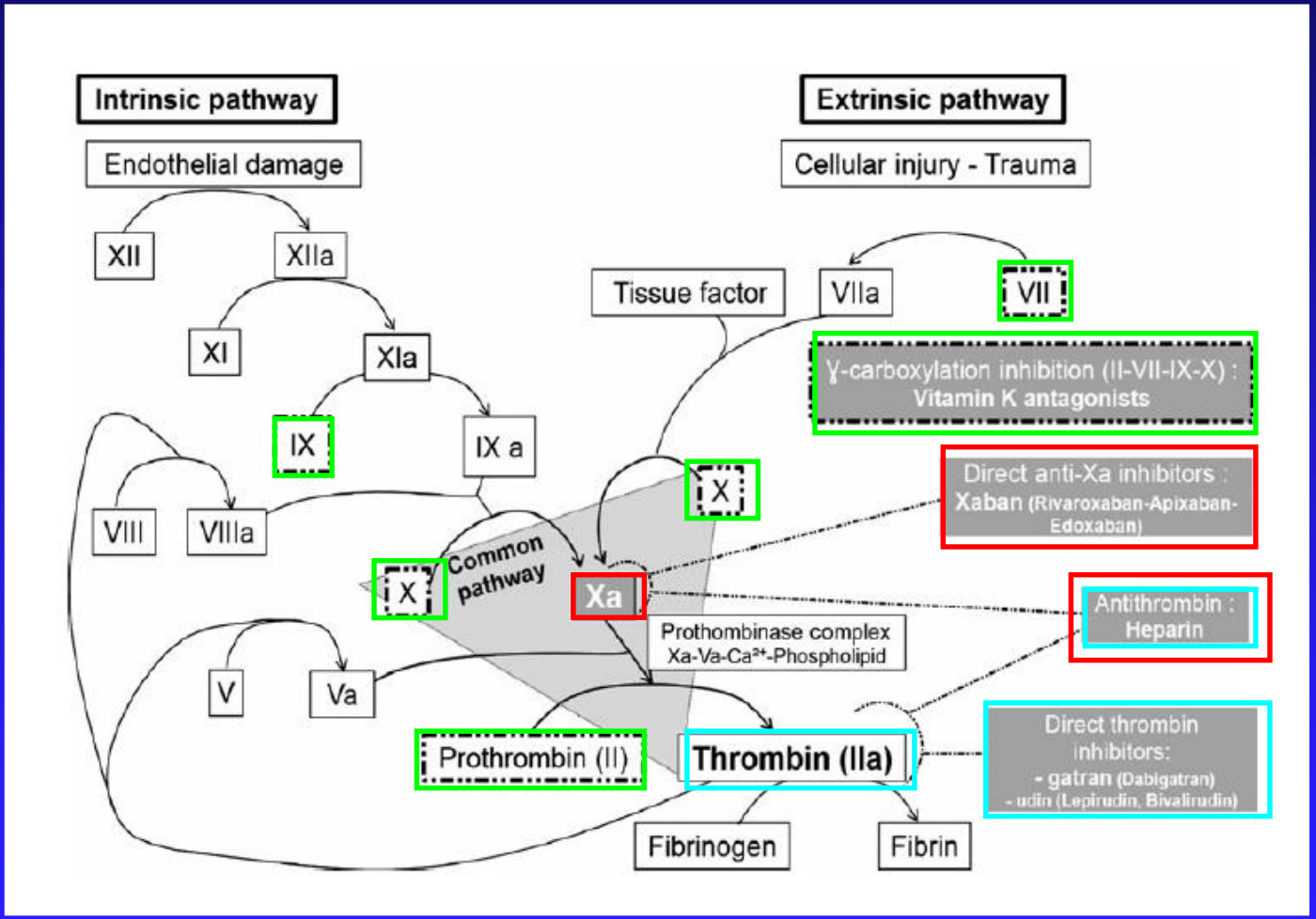
J.W. Eikelboom, Circulation 2010

Advancement in anticoagulant research
Parenteral anticoagulant development
Oral anticoagulant development

PUNTI DI DISCUSSIONE

- Meccanismo d'azione dei farmaci anticoagulanti orali
- Profilo farmacodinamico e farmacocinetico dei DOAC
- Condizioni in cui il profilo farmacologico può variare
- Indicazioni cliniche

MECCANISMO D'AZIONE



Salem J-E et al. Fundamental & Clinical Pharmacology, 2015

PROFILO FARMACOLOGICO

- **FARMACOCINETICA**: assorbimento, distribuzione, metabolismo, escrezione

- **FARMACODINAMICA**: effetti biochimici e funzionali del farmaco e il meccanismo d'azione

  1) identifica i siti d'azione del farmaco

  2) relazione tra dose del farmaco e risposta funzionale

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	33% 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)

CARATTERISTICHE FARMACOCINETICHE

Parameter	Warfarin	Dabigatran	Rivaroxaban	Apixaban
Age	Yes, lower CL as age increase	Yes, lower CL as age increase	None	Yes, lower CL as age increase
Body weight	Yes, higher dose for increased weight	None	None	Yes, higher exposure with low body weight (<60kg)
Sex	Yes, higher dose for increased weight	Yes, lower CL in women	None	Yes higher exposure in women
Ethnicity	Lower in Asian pts; Higher in African-American pts	None	Yes, Lower dose in japanese pts	None

Gong IY et al 2013

IL PROFILO FARMACOLOGICO

DABIGATRAN 150 MG

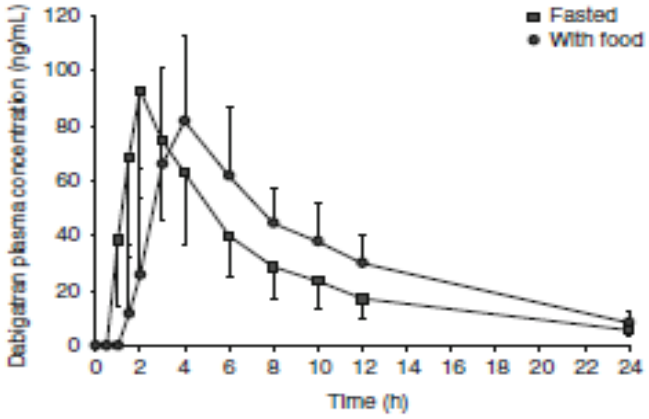
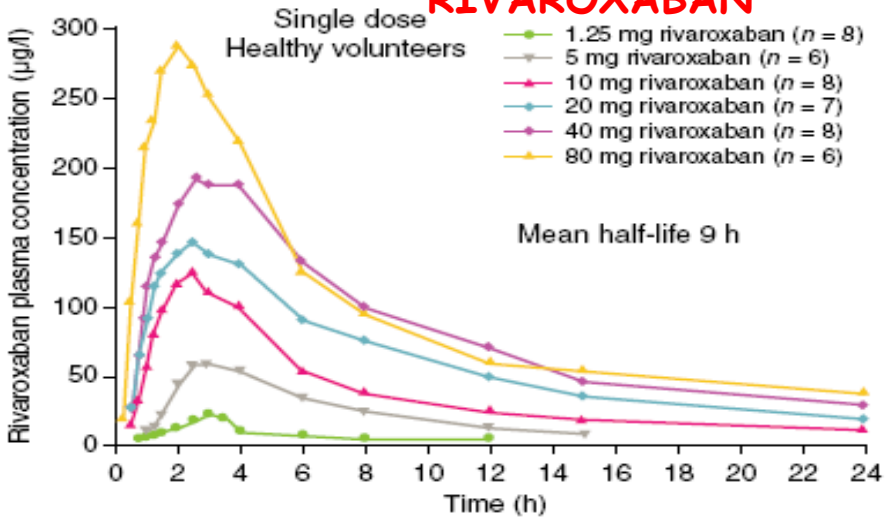
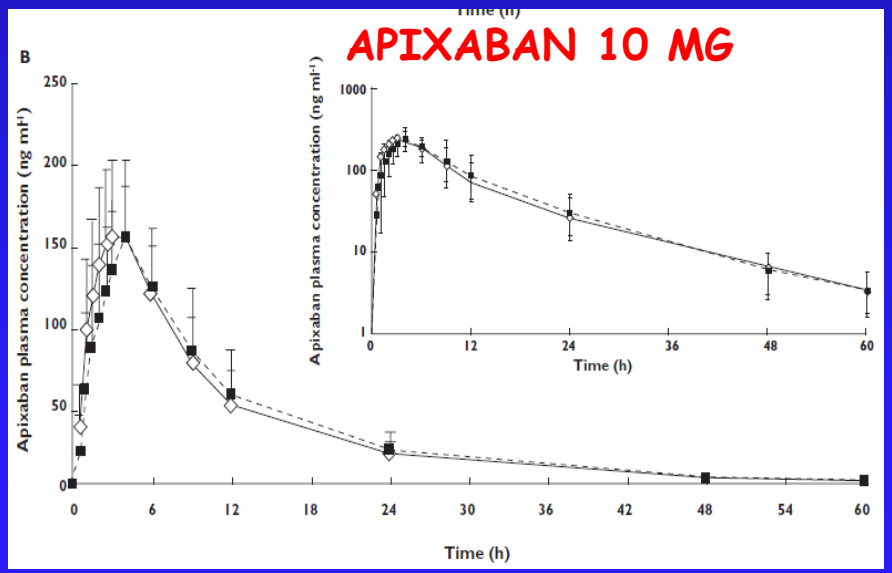


Fig. 5. Mean (±SD) plasma concentration-time profiles of dabigatran after single-dose administration of dabigatran etexilate 150 mg capsules to healthy male volunteers in the fasted and fed states.[34]

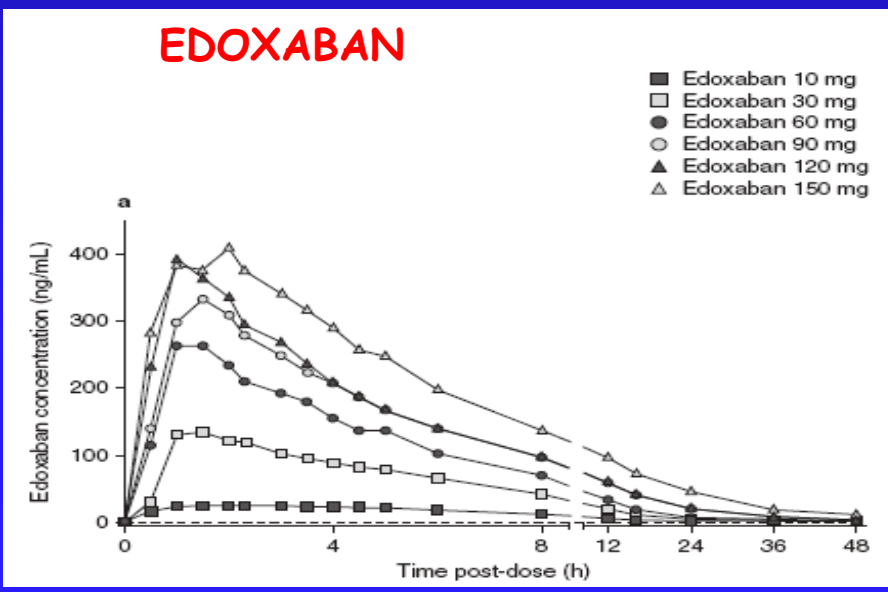
RIVAROXABAN



APIXABAN 10 MG



EDOXABAN



Stangier J et al, 2007; Kreutz R et al, 2011; Frost et al, 2013; Comm AJ et al, 2011

ONCE/TWICE DAILY?

Dabigatran	Studi di dose finding hanno mostrato pari efficacia e sicurezza (Bistro) . Bi-somministrazione: riduce Δ tra Cmax e Cmin
Rivaroxaban	Non sono risultate differenze in termini di sanguinamento ed estensione del trombo (Record). Mono-somministrazione
Apixaban	In base alla relazione dose-risposta sembra essere presente un vantaggio alla bi-somministrazione (Lassen MR 2005, Lopes RD 2010)
Edoxaban	Mono-somministrazione migliora il profilo di sicurezza (Weitz JL 2010)

De Caterina R et al, Vascular Pharmacology 2013

DOAC

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

Da ciò consegue:

- Somministrazione a dosaggio fisso giornaliero:
  - ✓ breve emivita
  - ✓ più ampia finestra terapeutica rispetto ai farmaci AVK
  - ✓ minori interazioni rispetto agli AVK
- La non indicazione al monitoraggio di laboratorio routinario

MA…

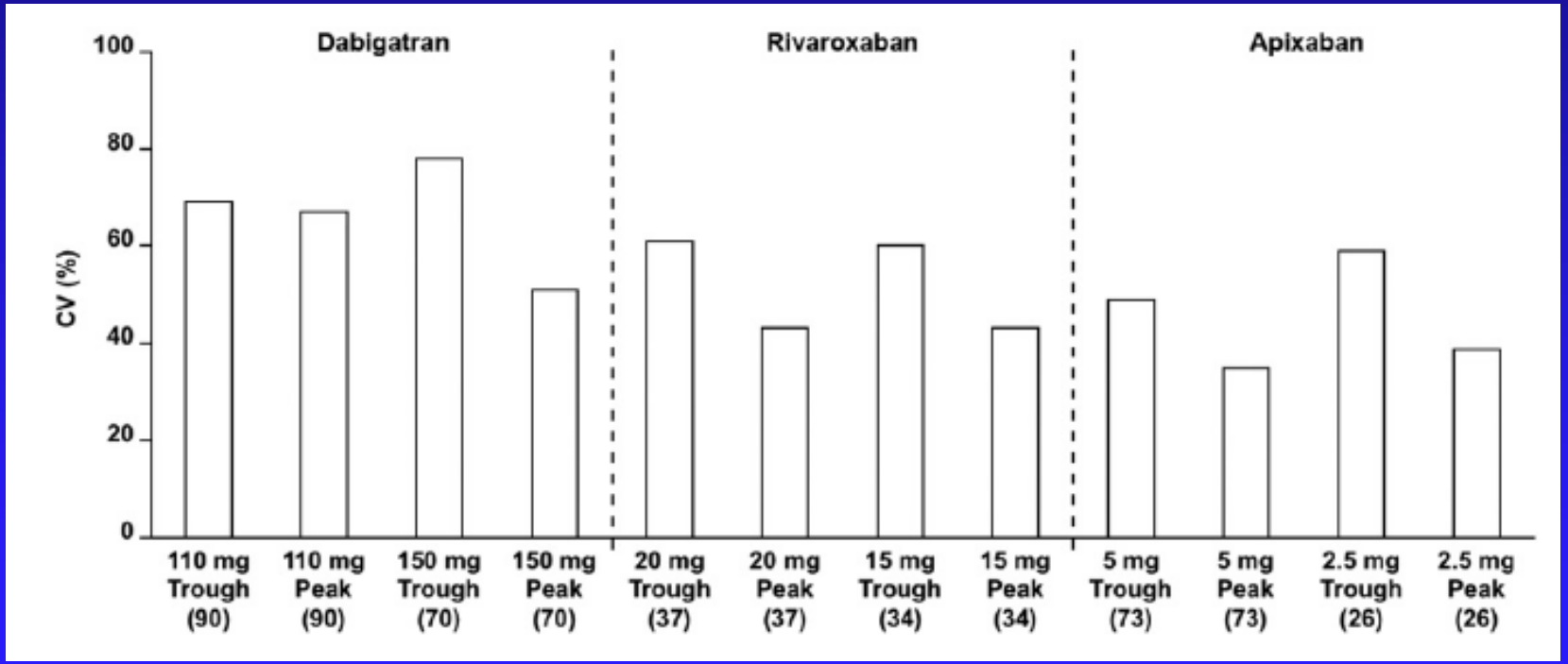
- E' stata identificata un'ampia variabilità inter/intra individuale
- Modificazioni farmacocinetiche e farmacodinamiche in relazione a: interazioni farmacologiche, insuff. renale, insuff. epatica, età, peso.

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

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)

Testa S. et al, Thrombosis Research 2016

DOAC: INTER-INDIVIDUAL VARIABILITY



S. Testa et al. / Thrombosis Research 137 (2016) 178–183

DOAC: INTRA-INDIVIDUAL VARIABILITY

	Intra-individual variability 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)

Real-world variability in dabigatran levels in patients with atrial fibrillation

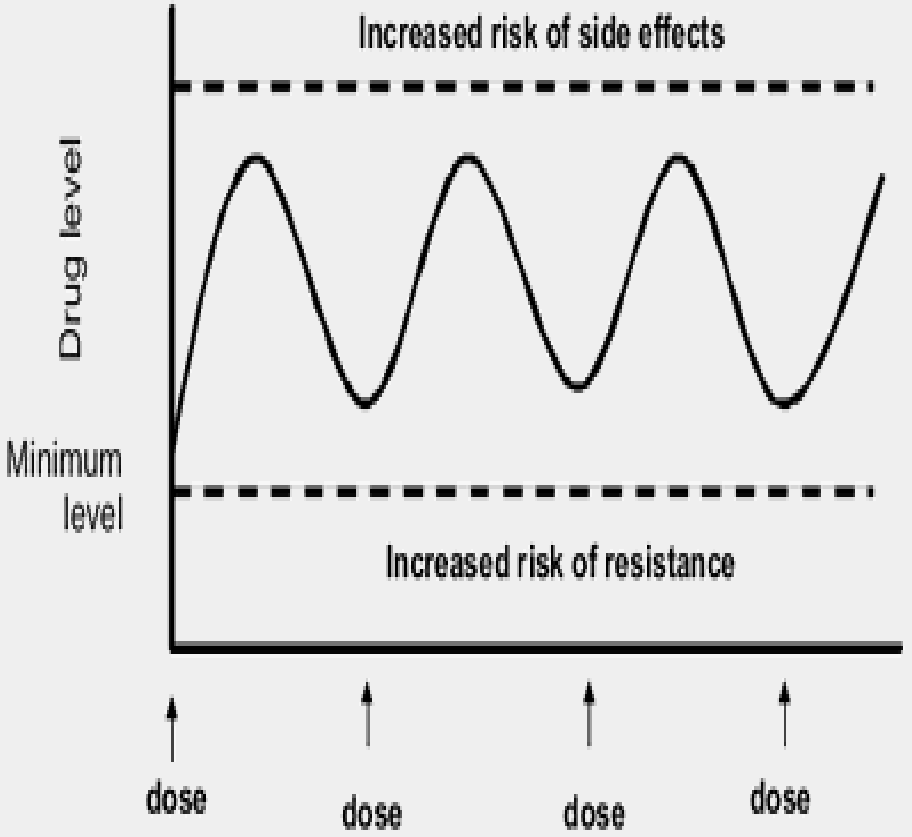
- Inter-patient variability in dabigatran level was greater than intra-patient variability
- Similar medians and distributions of levels were observed in DE110 and DE150 subgroups: patients receiving DE110 were older, had lower renal function and weighed less than those receiving DE150.
- Up to 40% of patients whose trough levels were in the upper extremes, and up to 80% of patients whose trough levels were in the lower extremes at baseline, showed subsequent levels that fell in the middle quartiles.

⇓

- Our data support the practice of selecting the dabigatran dose based upon clinical characteristics because it results in similar levels of drug exposure in patients given DE110 or DE150.
- They do not support the concept that a single Hemoclot® measurement reliably identifies patients with consistently high or low values.

Chan NC et al, J Thromb Haemost 2014

HOW MUCH IS ENOUGH?



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)

Abbiamo a disposizione sufficienti evidenze per raccomandare controlli periodici di routine dei DOAC, non conoscendo i range terapeutici ?

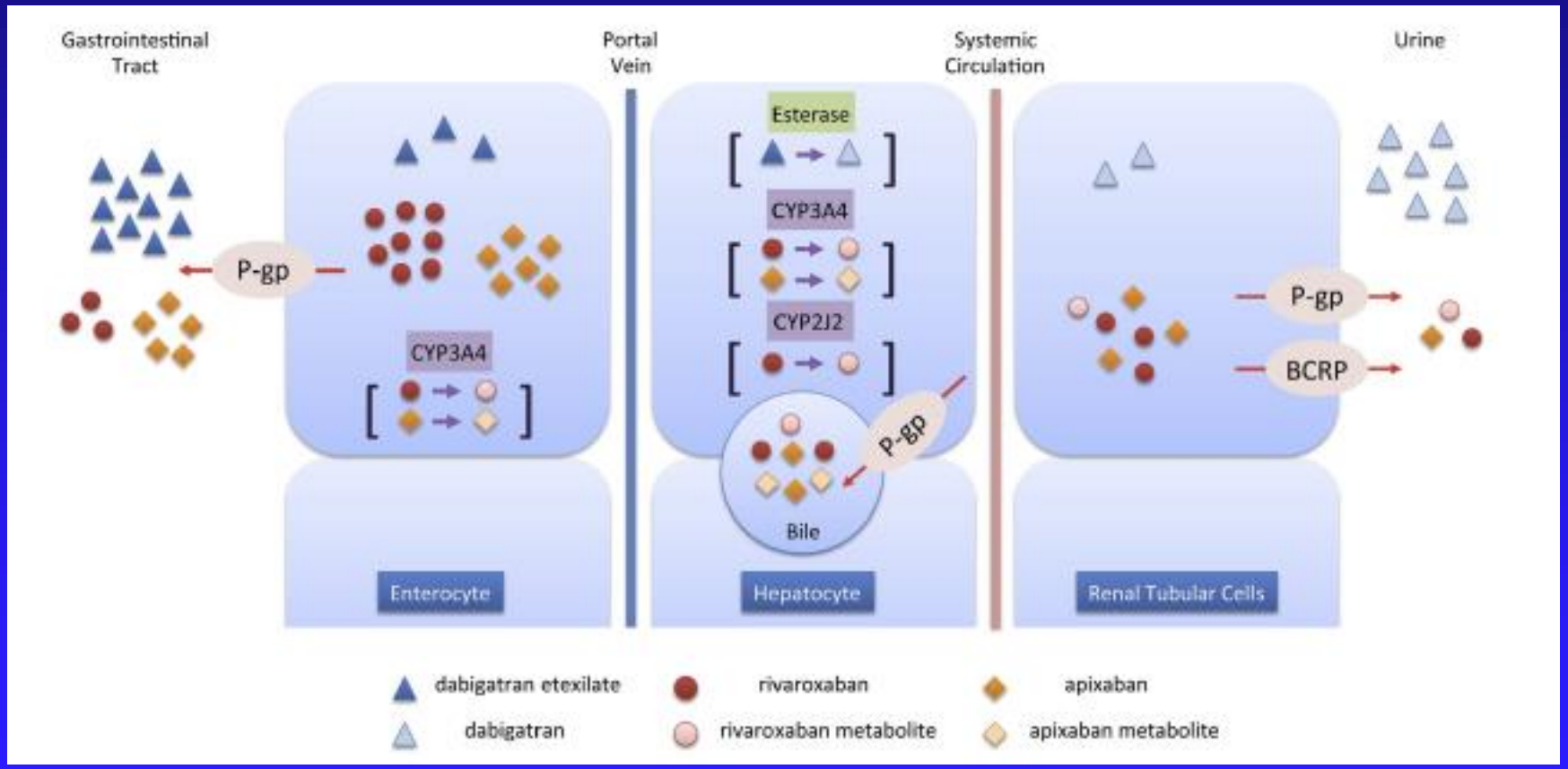
CORRELAZIONE TRA CONCENTRAZIONI PLASMATICHE E CLEARANCE DELLA CREATININA

Drug and dose (mg)	C trough (r/r^2)	p	C peak (r/r^2)	p
Dabigatran 110	−0.25/0.0625	0.04	−0.12/0.014	ns
Dabigatran 150	−0.32/0.1024	0.03	−0.18/0.0324	ns
Rivaroxaban 20	−0.18/0.0324	ns	−0.15/0.0225	ns
Rivaroxaban 15	−0.09/0.0081	ns	0.07/0.0049	ns
Apixaban 5	−0.03/0.0009	ns	−0.17/0.0289	ns
Apixaban 2.5	−0.02/0.0004	ns	−0.01/0.0001	ns

S. Testa et al. / Thrombosis Research 137 (2016) 178–183

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

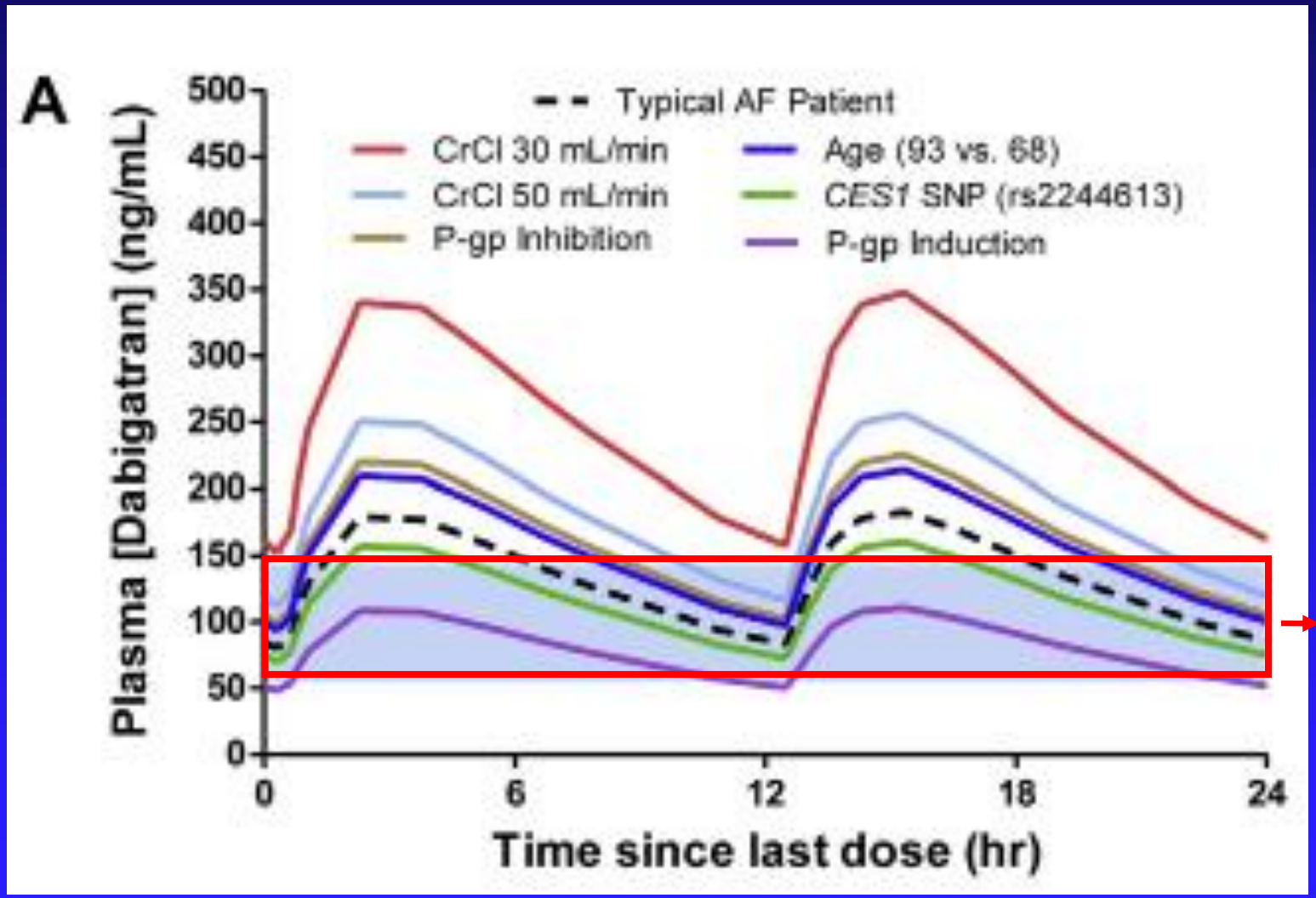
INTERAZIONI FARMACOLOGICHE

	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, wich mitigates the risk of concomitant treatment (Schulman S et al, 2012)

PLASMA CONCENTRATION PROFILE: DABIGATRAN 150mgx2/die



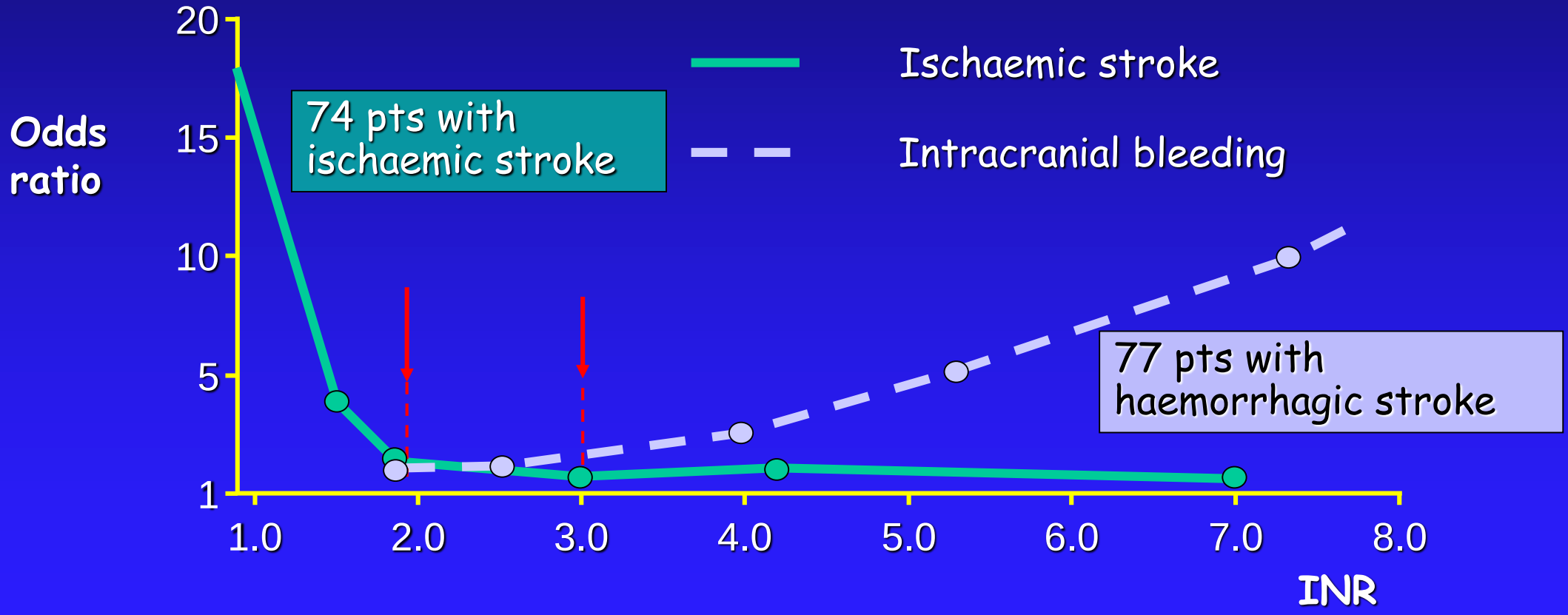
Cmin associata all'aumento dell'efficacia antitrombotica e al ridotto rischio emorragico

Gong IY et al, 2013

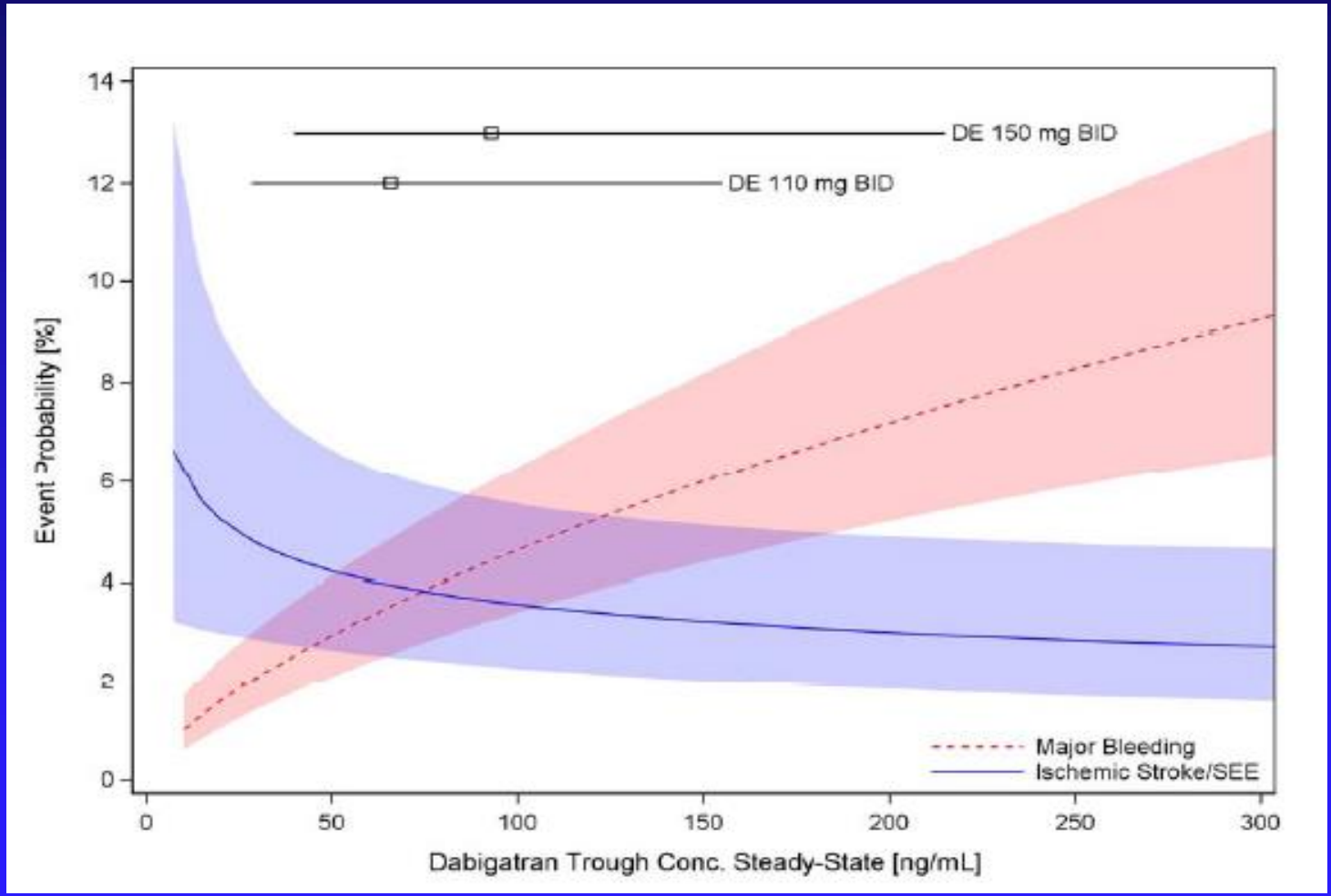
TRA SCILLA E CARIDDI

(Hylek EM et al. N Engl J Med 1996; 335:540-46)

Adjusted odds ratios for ischaemic stroke and intracranial bleeding in relation to INR

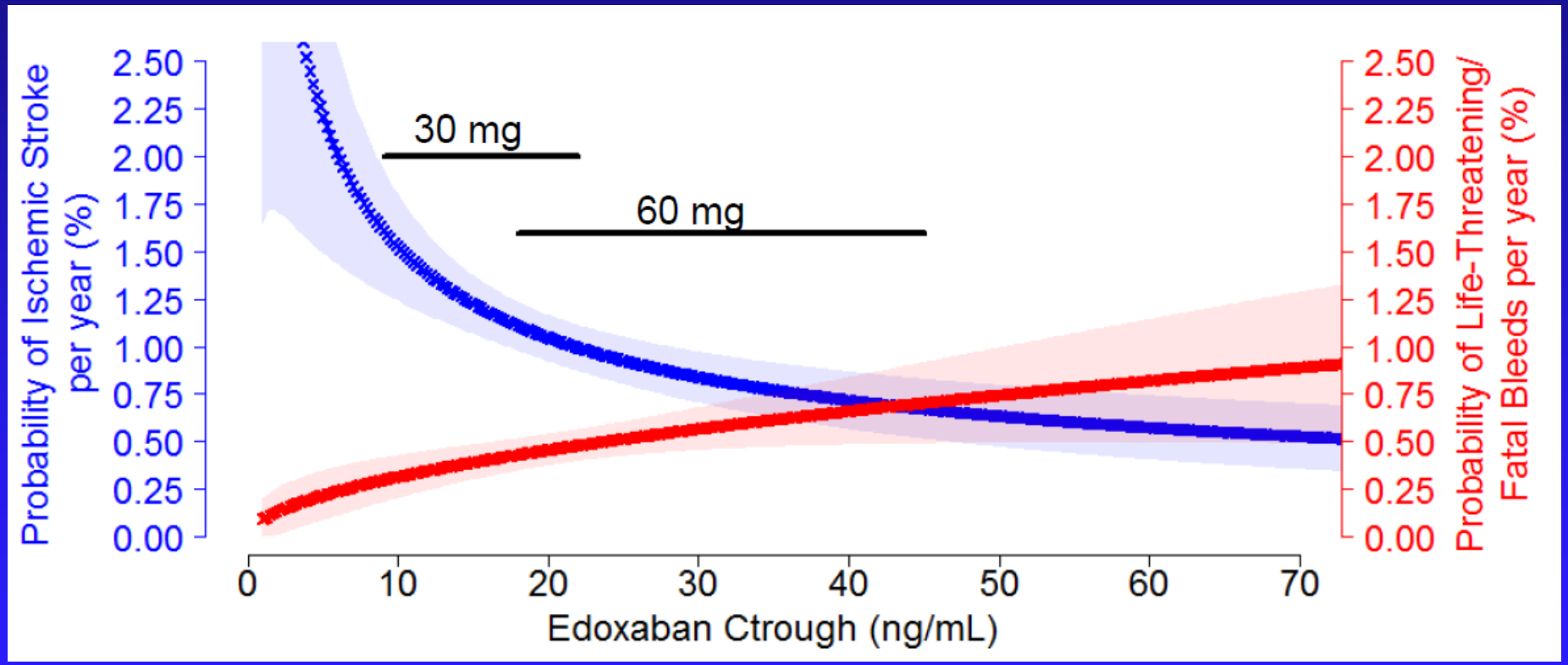


The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients in the RE-LY Trial



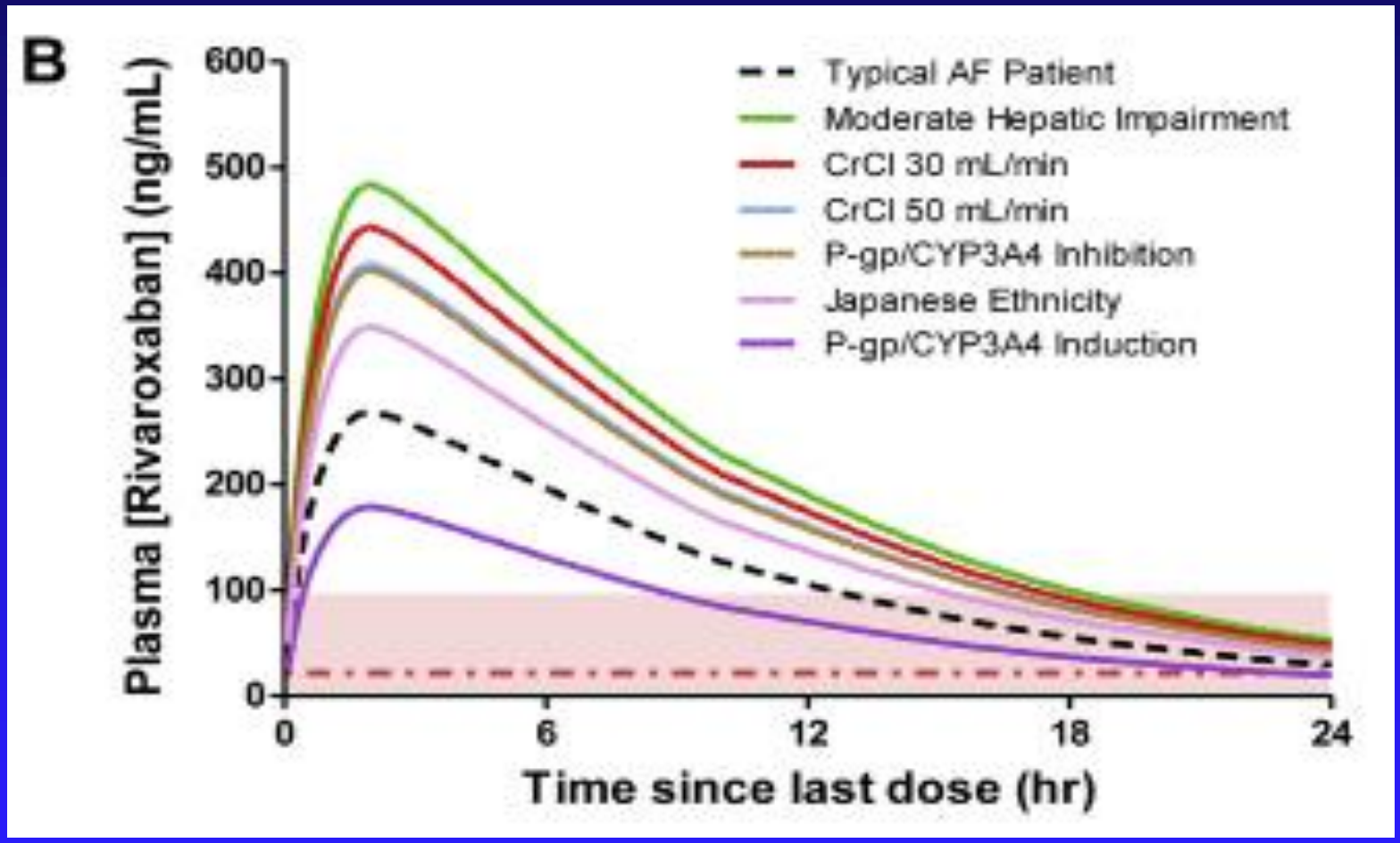
Reilly PA, JACC 2013

CORRELATION OF DRUGS LEVELS AND OUTCOMES IN PHASE III NOAC TRIALS



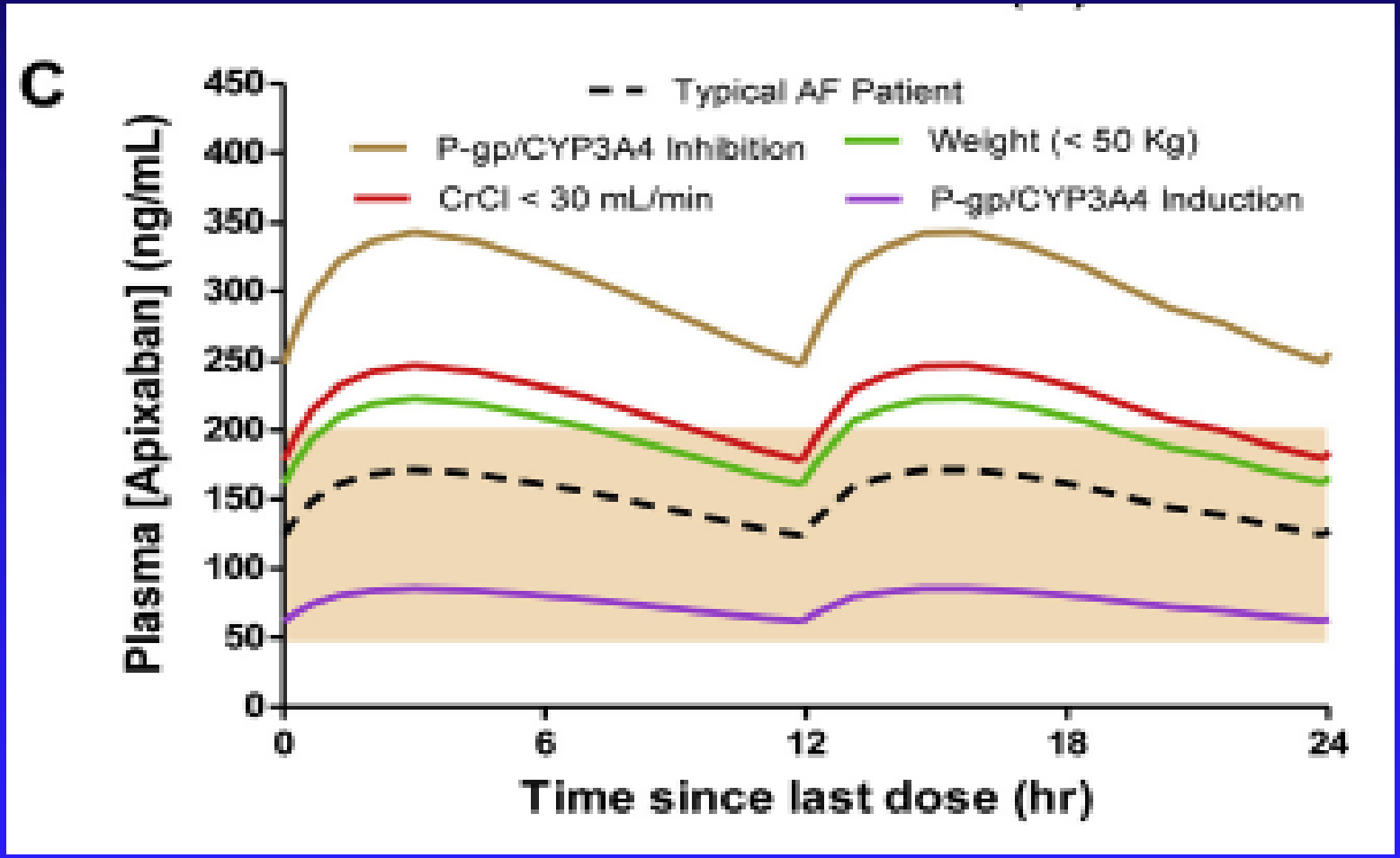
FDA, October 26, 2015

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*

DOSING ADJUSTEMENTS BASED ON PHARMACOKINETICS CONSIDERATIONS

Table 4. Dosing adjustments based on pharmacokinetic considerations

	Dabigatran (mg BID)	Rivaroxaban (mg OD)	Apixaban (mg BID)
Renal impairment			
Mild (CrCl 51-80 mL/min)	150	20	5
Moderate (CrCl 30-50 mL/min)	110	15	5
Severe (CrCl < 30 mL/min)	n.r.	15	2.5
Hepatic impairment			
Mild (Child-Pugh A)	150	20	5
Moderate (Child-Pugh B)	150	n.r.	5
Severe (Child-Pugh C)	n.r.	n.r.	n.r.
Hepatic dysfunction	n.r.	n.r.	n.r.
Demographic variables			
Ethnicity, Asian	150	15	5
Age, older than 75-80 y	110	20	2.5
Weight, < 50 kg	150	20	2.5
Drug-drug interactions			
P-gp inhibitor	110	15	2.5
CYP3A4 inhibitor	150	15	2.5
P-gp/CYP3A4 inducer	n.r.*	n.r.	n.r.

CLINICALS TRIALS VS REAL WORLD

Clinical trials: contesto clinico sicuro e ben controllato

Pazienti selezionati

↓

Monitoraggio non necessario

… ma nel mondo reale !!!

Suryanarayan D,. Mc Master University, 2015

CONSIDERAZIONI

- Clinical significance of concomitant use of multiple moderate interference drugs in the same patient-particularly in the elderly in whom polypharmacy is common-remains to be established
- The full spectrum of these interactions remains to be addressed in the real-world population
- Until then, dose lowering adjustements in conjunction with anticoagulation monitoring should be used to ensure efficacy and safety

QUANDO L'EFFETTO FARMACODINAMICO PUO' ESSERE DIVERSO DALL'ATTESO E QUANDO PUO' ESSERE UTILE IL DOSAGGIO FARMACOLOGICO

- Patients presenting in emergency with adverse events (Thrombosis, Bleeding)
- Recurrent thrombosis on DOAC
- Immediate reverse of anticoagulation
- Perioperative management
- Renal Disease / Liver Disease
- Suspicion or known interaction with other drugs
- Fragile elderly patients
- Under/over weight
- Check for patient compliance

Pengo V et al, 2011
FDA report, 2015

TAO: LE INDICAZIONI CLINICHE

INDICAZIONI CLINICHE	AVK	DOAC (in terapia solo con PIANO TERAPEUTICO)
Profilassi del tromboembolismo	SI	Solo Chirurgia Ortopedica Maggiore in elezione (anca-ginocchio)
Terapia del TEV (TVP prossimale e EP) e prevenzione delle recidive	SI	SI
Fibrillazione Atriale Non Valvolare	SI	SI
Miocardiopatia Dilatativa	SI	NO
Trombosi endocavitaria	SI	NO
Valvulopatie	SI	NO
Protesi Valvolari	SI	NO (studi interrotti per aumento di complicanze in DOAC)

SCELTA DELL'ANTICOAGULANTE IN BASE ALLE CARATTERISTICHE CLINICHE DEL PAZIENTE

Patient Characteristic	Drug Choice	Rationale
Mechanical Heart Valve	warfarin	Dabigatran inferior to warfarin and contraindicated in this group; other TSOACs not studied in this patient population
Valvular Disease	warfarin	TSOACs not studied in this patient population
Moderate hepatic impairment (Child-Pugh B)	Warfarin	Rivaroxaban and edoxaban are contraindicated in patients with moderate or severe hepatic impairment. Patients with significant liver impairment were excluded from the RE-LY trial for dabigatran. Apixaban should be used with caution in patients with moderate liver dysfunction per package insert.
Severe hepatic impairment (Child-Pugh C)	warfarin	Rivaroxan, apixaban, and edoxaban are contraindicated in patients with severe hepatic impairment. Patients with significant liver impairment were excluded from the RE-LY trial for dabigatran.
Stable on warfarin[1]	warfarin or TSOAC	Warfarin patients should be informed about TSOACs so that they can make an informed decision on preferred anticoagulant
CrCl <30 mL/min	warfarin	Very few patients with CrCl<30 were included in the TSOAC trials. ESC guidelines[2] recommend against the use of TSOACs in this population.
Dyspepsia or upper gastrointestinal symptoms	warfarin, rivaroxaban, apixaban, or edoxaban	Dyspepsia in up to 10% of patients given dabigatran.
Recent gastrointestinal bleed	Warfarin or apixaban	More GI bleeds with dabigatran (150mg), rivaroxaban, or edoxaban (60mg) than with warfarin. Warfarin easier to reverse if there is a further bleed.
Requirement for compliance aid such as medication planner/pill box	warfarin, rivaroxaban, apixaban, or edoxaban	Dabigatran capsules must be kept in their original container.
Stroke prevention in AF patients with CrCl > 95 mL/min	warfarin, dabigatran, rivaroxaban, or apixaban	Edoxaban inferior to warfarin in these patients and is contraindicated.

FDA Approved Oral Anticoagulants, 1/02/15

CONCLUSIONI (I)

- I farmaci aIIa e aXa appartengono a due sottoclassi distinte del gruppo di farmaci anticoagulanti orali ad azione diretta in quanto differiscono per meccanismo d'azione
- Le due sottoclassi presentano un profilo farmacologico simile, ma hanno caratteristiche PK e PD differenti (assorbimento, metabolismo, eliminazione)
- Ampia variabilità inter/intra-intraindividuale
- I range terapeutici dei DOAC non sono ancora stati definiti e non devono essere confusi con la variabilità inter-individuale osservata

CONCLUSIONI (II)

- Una singola determinazione dei livelli non è sufficiente ad identificare i pazienti con livelli persistentemente elevati o bassi di farmaco (fluttuazioni giornaliere dei livelli)
- A differenza dei farmaci AVK i DOAC sono autorizzati solo nella prevenzione delle complicanze cardioemboliche nella FANV e nel trattamento del TEV e prevenzione delle recidive (TVP prossimale ed EP a basso-intermedio rischio)
- Prescrizione regolata da PT

CONCLUSIONI (III)

- I nostri livelli di "conoscenza" devono crescere per poter scegliere e gestire i trattamenti anticoagulanti nel singolo paziente

- Nella scelta del farmaco considerare

✓ Caratteristiche di ogni molecola

✓ Caratteristiche del paziente

farmaco con il miglior profilo efficacia/sicurezza nel singolo paziente