ESISTONO I PAZIENTI RESISTENTI AI DOACs? ESISTE UN RANGE TERAPEUTICO DA MISURARE?

SOPHIE TESTA

Laboratorio Analisi Chimico-Cliniche e Microbiologiche

CENTRO EMOSTASI E TROMBOSI

Istituti Ospitalieri di Cremona

RESISTENZA AI FARMACI

- Pharmacologic management of disease is a proven approach to improved human health.
- However, due to dramatic individual variation in response for a number of therapeutic agents, their application to the treatment of certain patient groups is compromised.
- The magnitude of this problem is evident in the fact that the National Institute of Health is supporting studies focused on understanding the mechanisms underlying individual variation in drug response

Linder MW 2001

FARMACO-RESISTENZA

La resistenza ai farmaci è la riduzione dell'efficacia di un farmaco nel trattamento della malattia o nella cura dei sintomi

Il meccanismo d'azione della resistenza farmacologica varia in relazione alla categoria di farmaco :

1. le cellule non si mostrano sensibili all'azione del farmaco (es. antineoplastici , antibiotici, antimicotici etc, etc)
2. Diversa concentrazione del farmaco rispetto all'atteso in relazione alle caratteristiche del paziente (assorbimento, distribuzione, metabolismo, eliminazione, interazioni farmacologiche)

PUNTI DI DISCUSSIONE

- I DOAC hanno un profilo farmacologico prevedibile?
- Se si, in quali condizioni il profilo farmacologico puo' variare?
- Le osservazioni relative alle caratteristiche farmacologiche hanno una rilevanza clinica?

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	70% renal 30% liver	<5% renal >95% liver	35% renal 65% liver
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)

IL PROFILO FARMACOLOGICO

DABIGATRAN 150 MG

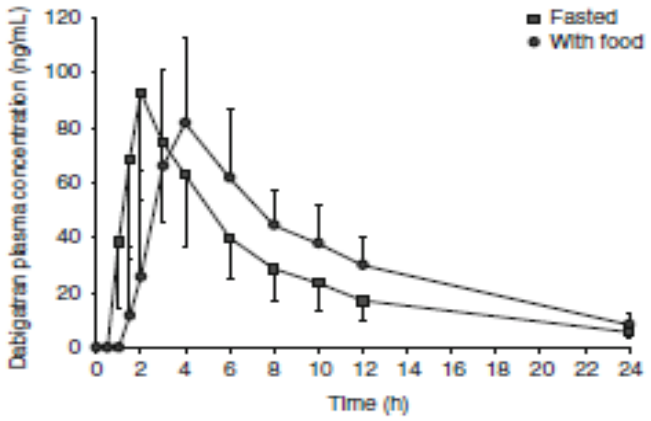
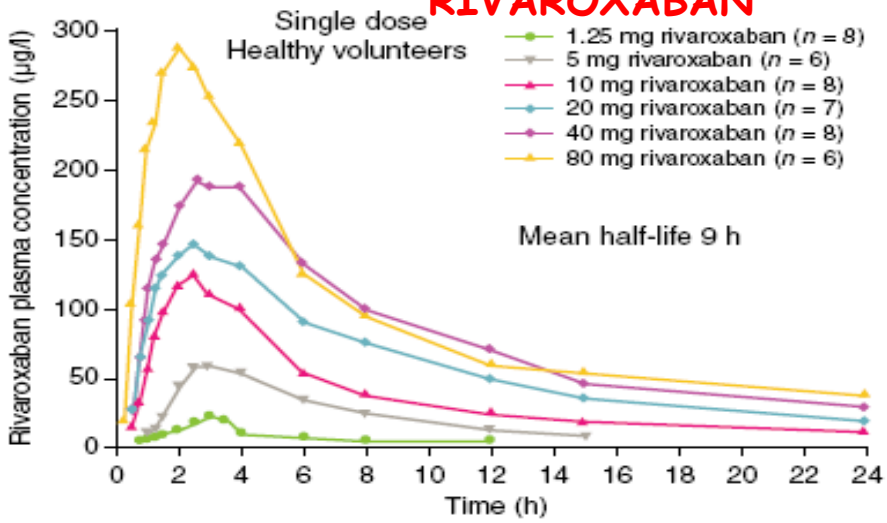
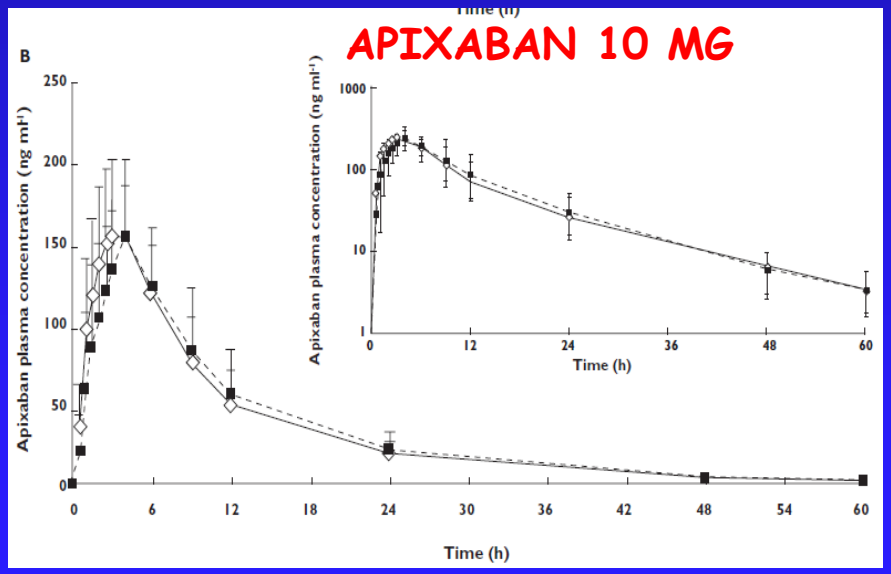


Fig. 5. Mean (±SD) plasma concentration-time profiles of dabigatran after single-dose administration of dabigatran etexilate 150 mg capsules to healthy male volunteers in the fasted and fed states.[34]

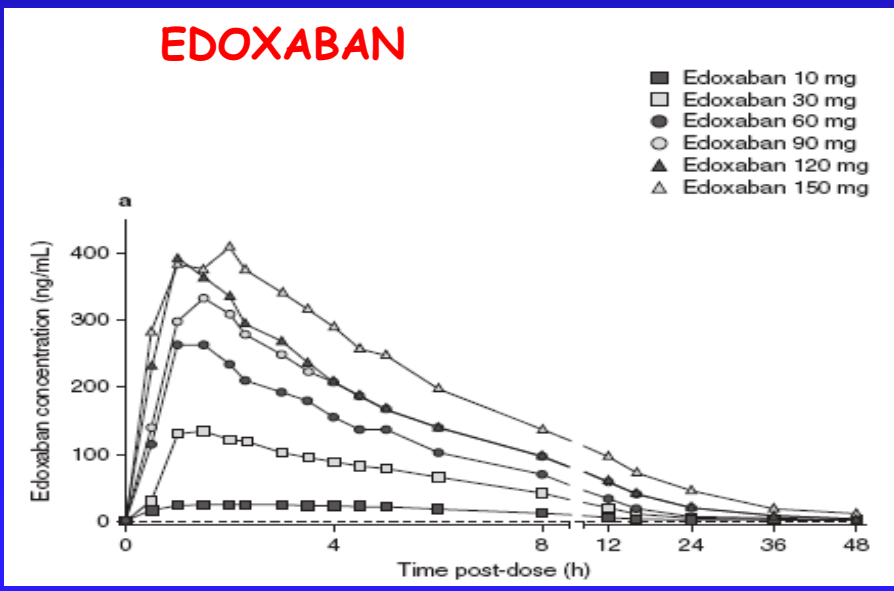
RIVAROXABAN



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

CARATTERISTICHE FARMACOCINETICHE

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

Gong IY et al 2013 (Mod), Krekels EH et al 2016

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.

DOAC

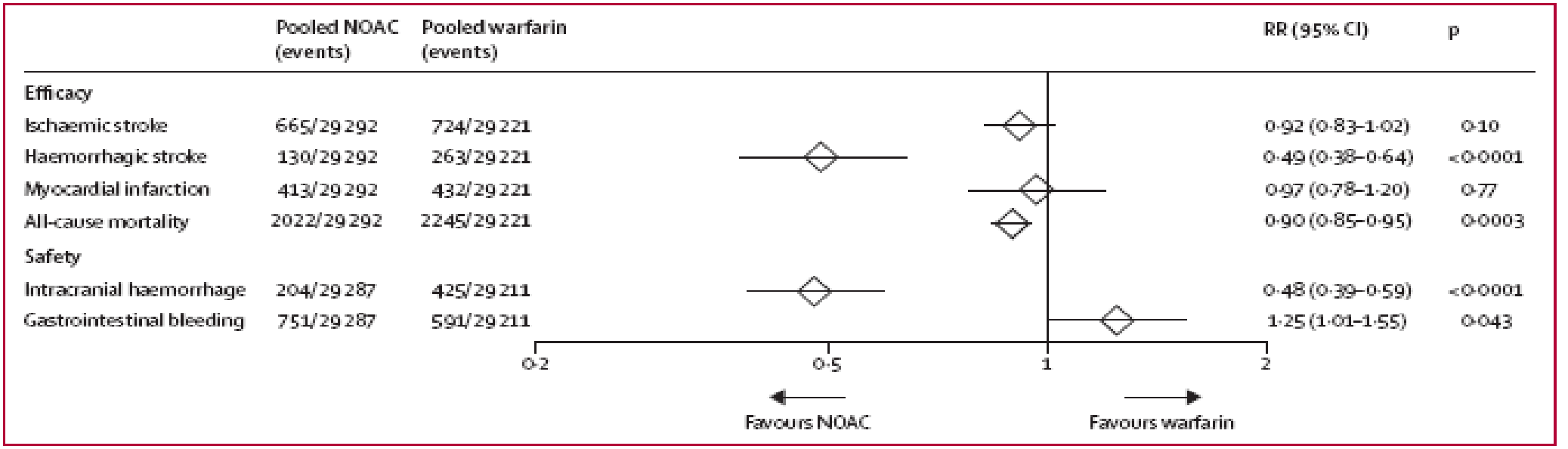
Negli studi farmacologici i DOAC hanno mostrato una risposta anticoagulante prevedibile in condizioni cliniche "standard"

Da ciò è derivato:

1) Scelta posologica in base alle caratteristiche del paziente (patologia, età, peso, etnia, ClCr, farmaci int)
2) Somministrazione a dosaggio fisso giornaliero, costante nel tempo
3) La non indicazione al monitoraggio di laboratorio routinario

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



Gli studi di Fase III hanno mostrato un rischio di complicanza emorragica e tromboembolica pari a circa 1-3% a-p

www.thelancet.com Vol 383 March 15, 2014

MA…

- E' stata identificata un'ampia variabilita' intra/inter individuale

Inter-individual variability : results from phase III trials

Drug (pt n°) (ng/ml)	Referenced*Mean (5°-95° %)
Dabigatran 110mgx2	
Cthrough	37 (10-96)
Cmax	183 (62-447)
Dabigatran 150mgx2	
Cthrough	90 (31-225)
Cmax	184 (64-443)
Rivaroxaban 15mg	
Cthrough	NA
Cmax	NA
Rivaroxaban 20mg	
Cthrough	32 (6-239)
Cmax	215 (22-535)
Apixaban 2.5mgx2	
Cthrough	23 (69-221)
Cmax	79 (34-162)
Apixaban 5mgx2	
Cthrough	103 (41-230)
Cmax	171 (91-321)

Mani et al, 2013

Kubitze et al, 2013

Frost C, 2013

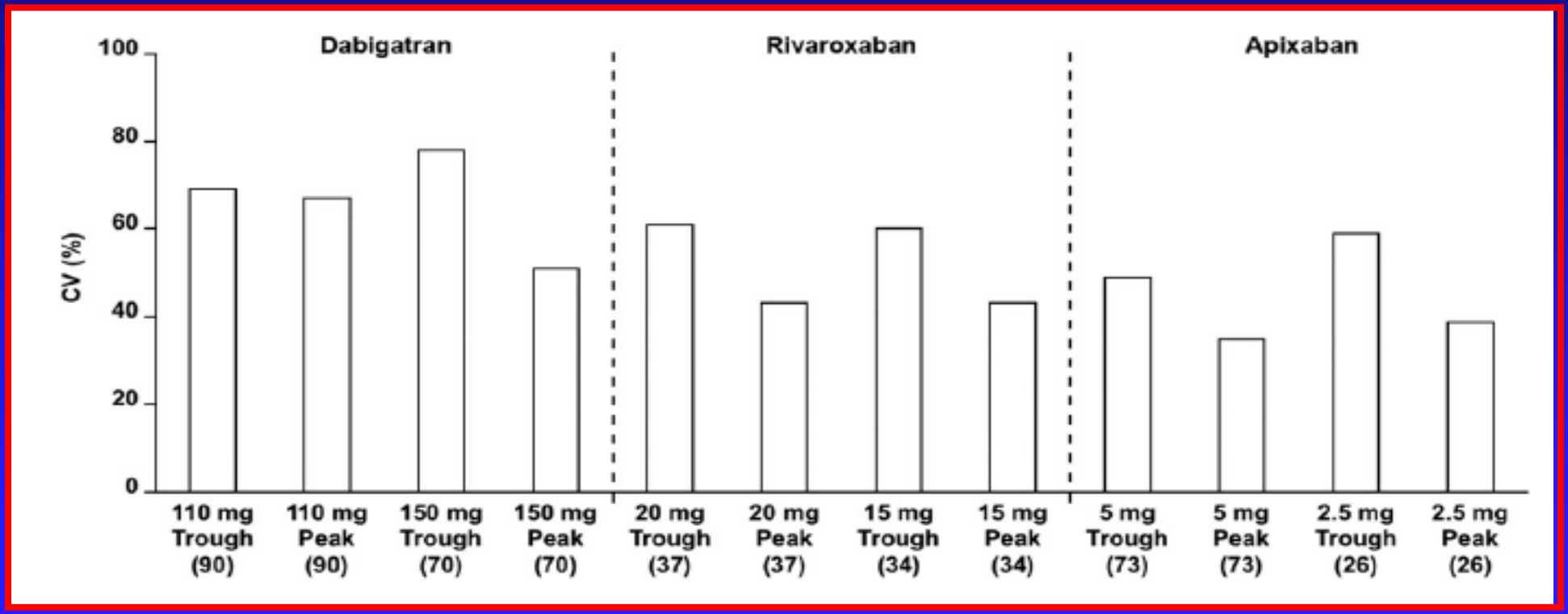
Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics

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: INTER-INDIVIDUAL VARIABILITY



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

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

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

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

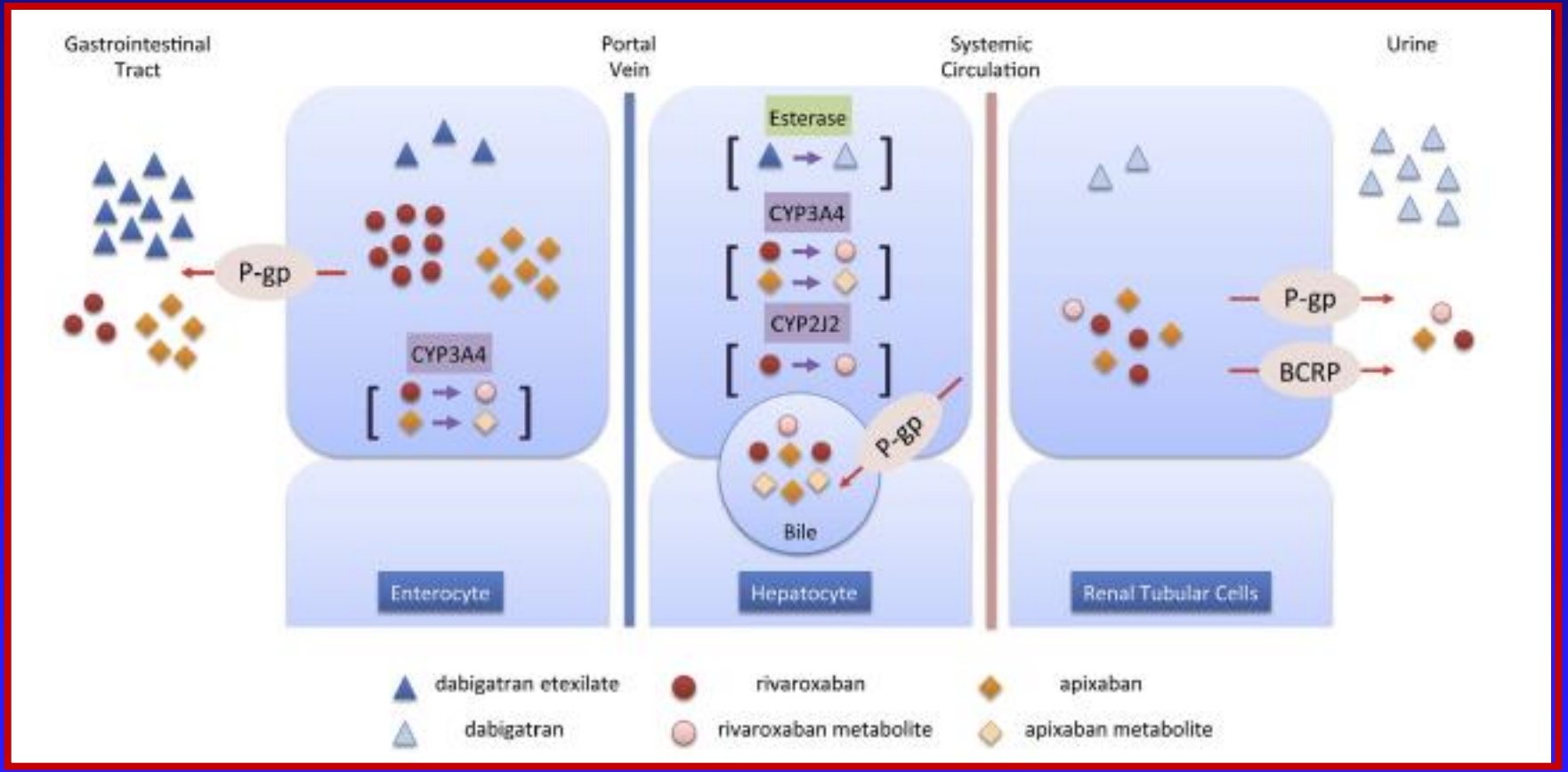
Results: Inter-patient variability in dabigatran levels (geometric coefficient of variation [gCV] 51-64%) was greater than intra-patient variability (gCV 32-40%). Similar medians and distributions of levels were observed in DE110 and DE150. Patients receiving DE110 were older, had lower renal function, 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.

Conclusions: Our data support the practice of selecting 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

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]



Gong, 2013

Pharmacogenetics of dabigatran etexilate interindividual variability

Claudia Dimatteo [a,1], Giovanna D'Andrea [a,1], Gennaro Vecchione [b], Oriana Paoletti [d], Filomena Cappucci [b], Giovanni Luca Tiscia [a], Matteo Buono [c], Elvira Grandone [b], Sophie Testa [d], Maurizio Margaglione [a,*]

In a real world cohort of anticoagulated patients attending two Italian Outpatient Clinics, we confirm that the CES1 SNP rs8192935 may play a significant role in modulating dabigatran trough concentrations. Whether screening for this polymorphism, or other SNPs, would identify patients at risk for adverse events and needing different intensity regimens of anticoagulation is beyond the aims of this study but deserves to be addressed.

Di Matteo C, Thromb Res 2016

ABCB1 SNP rs4148738 modulation of apixaban interindividual variability

In conclusion, for the first time we show that the ABCB1 SNP rs4148738 may play a significant role in modulating apixaban peak concentrations. Whether screening for this polymorphism, or other SNPs, would identify patients at risk for adverse events and needing different intensity regimens of anticoagulation is beyond the aims of this study but deserves to be addressed.

Di Matteo C, Thromb Res 2016

INTERAZIONI FARMACOLOGICHE

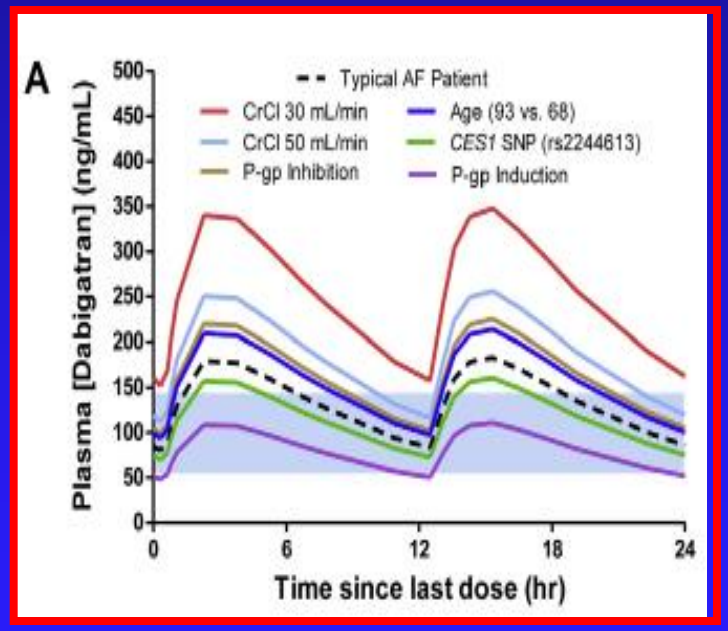
	Dabigatran	Rivaroxaban, edoxaban, apixaban
P-glycoprotein Inhibitors (amiodarone, phenotiazin, carboxylic acid, azole antifungals, verapamil, antimalarial, cyclosporine, thioxanthenes)	Yes	Yes
P-glycoprotein inducers (dexamethasone, rifampicin, St. John's Wort)	Yes	Yes
CYP3A4 Inhibitors (phenotiazin, 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).

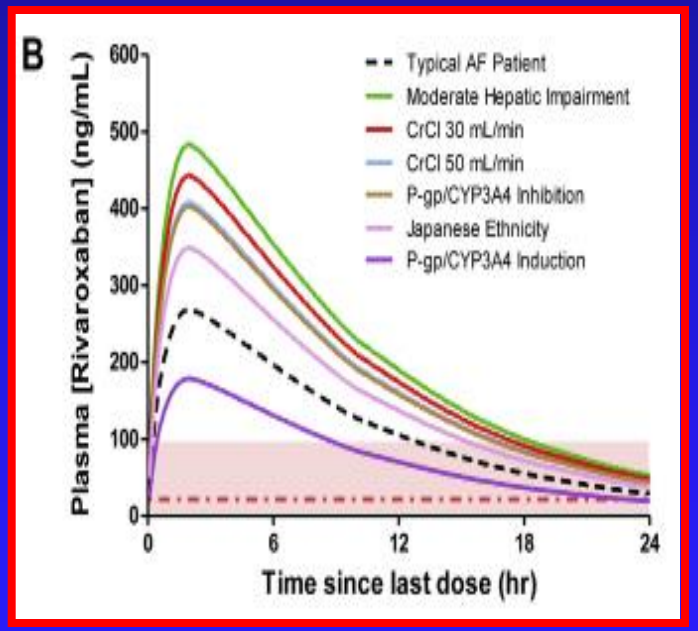
Many of these drugs interact with warfarin, but INR levels allows dose adjustment, which mitigates the risk of concomitant treatment (Schulman S et al, 2012)

VARIABILITA'

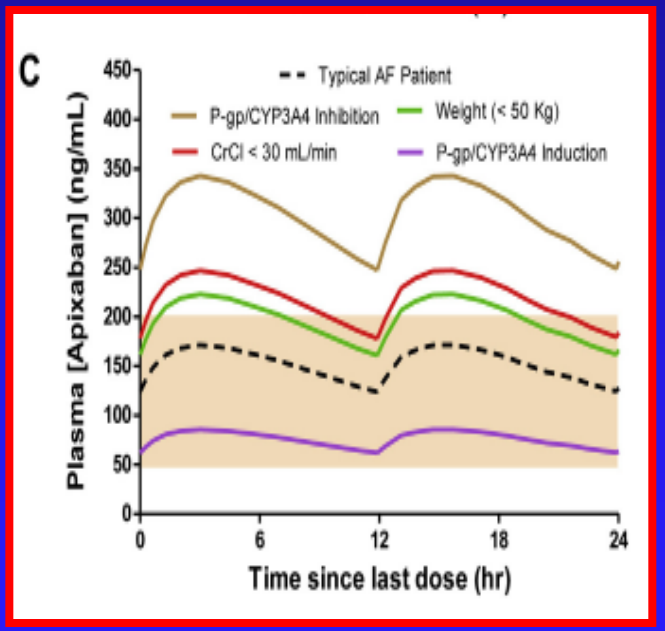
Dipende da: Sesso, Età, Peso, Interazioni farmacologiche, Funzione renale, Funzione epatica, Polimorfismi dei sistemi enzimatici



Dabigatran



Rivaroxaban



Apixaban

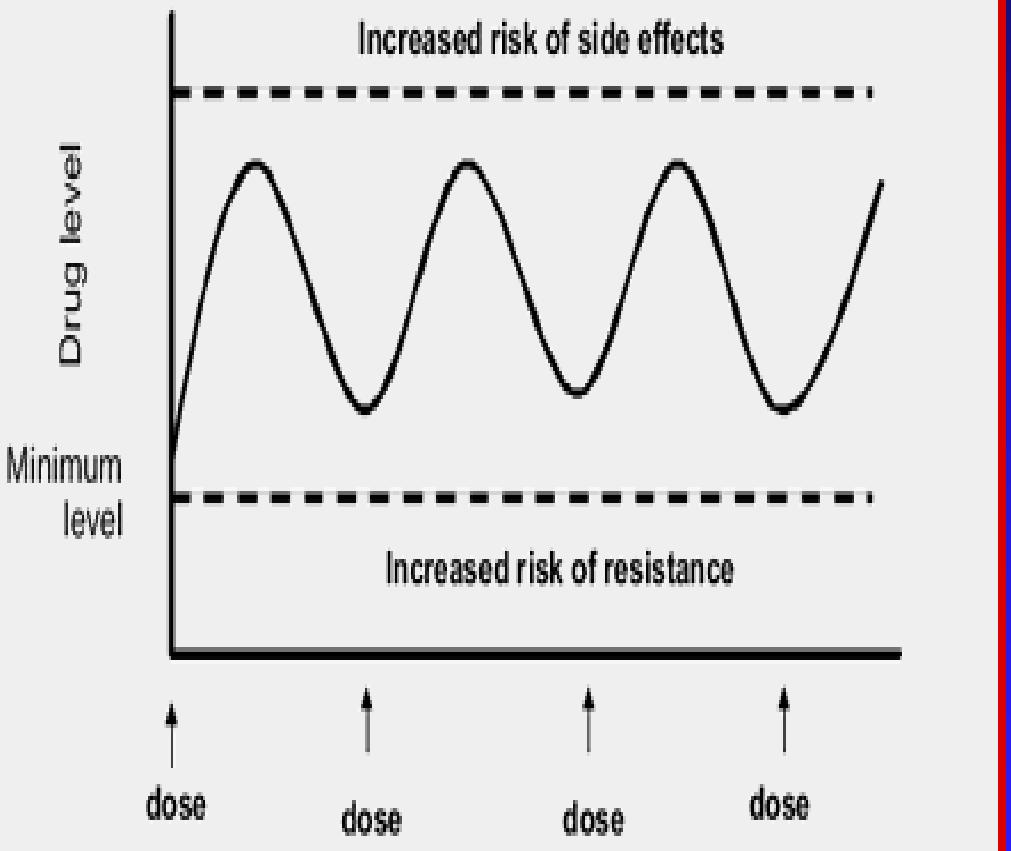
Gong, 2013

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

Gong, 2013

IN BASE AGLI STUDI DI FASE II E III SI ASSUME 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" azione anticoagulante

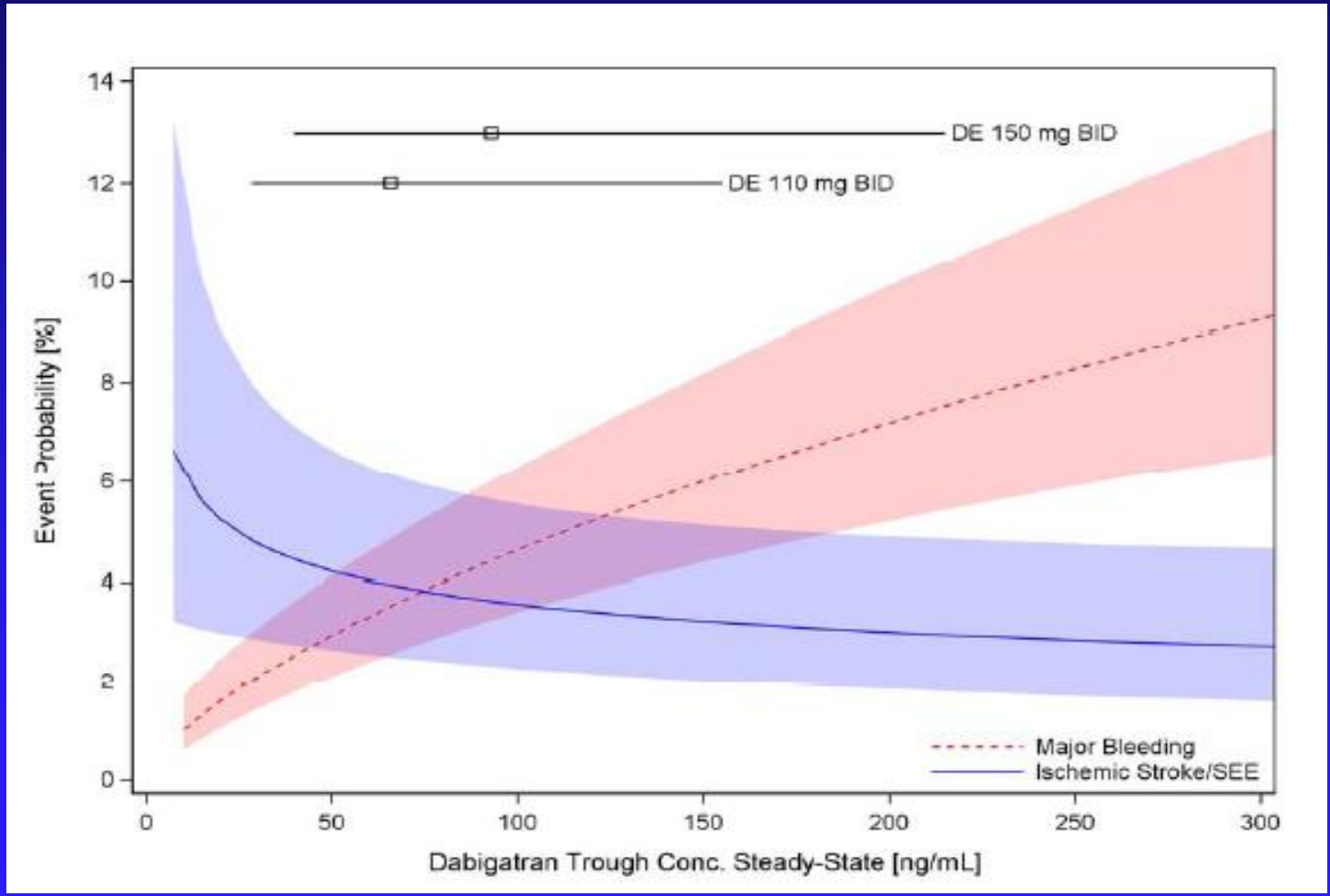
E' noto, però, che le complicanze con altri farmaci (es AVK) siano correlate con il tempo trascorso a livelli non adeguati di anticoagulazione (TTR)

VARIABILITA' BIOLOGICA

FARMACO	10-90% (ng/ml) Basale	Median (ng/ml) Basale
Dabigatran ng/ml	50-170	80
Rivaroxaban ng/ml	0-100	40
Apixaban ng/ml	60-200	110

E' CLINICAMENTE UTILE CONOSCERE I LIVELLI DI ANTICOAGULAZIONE (EFFETTO FARMACODINAMICO)?

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

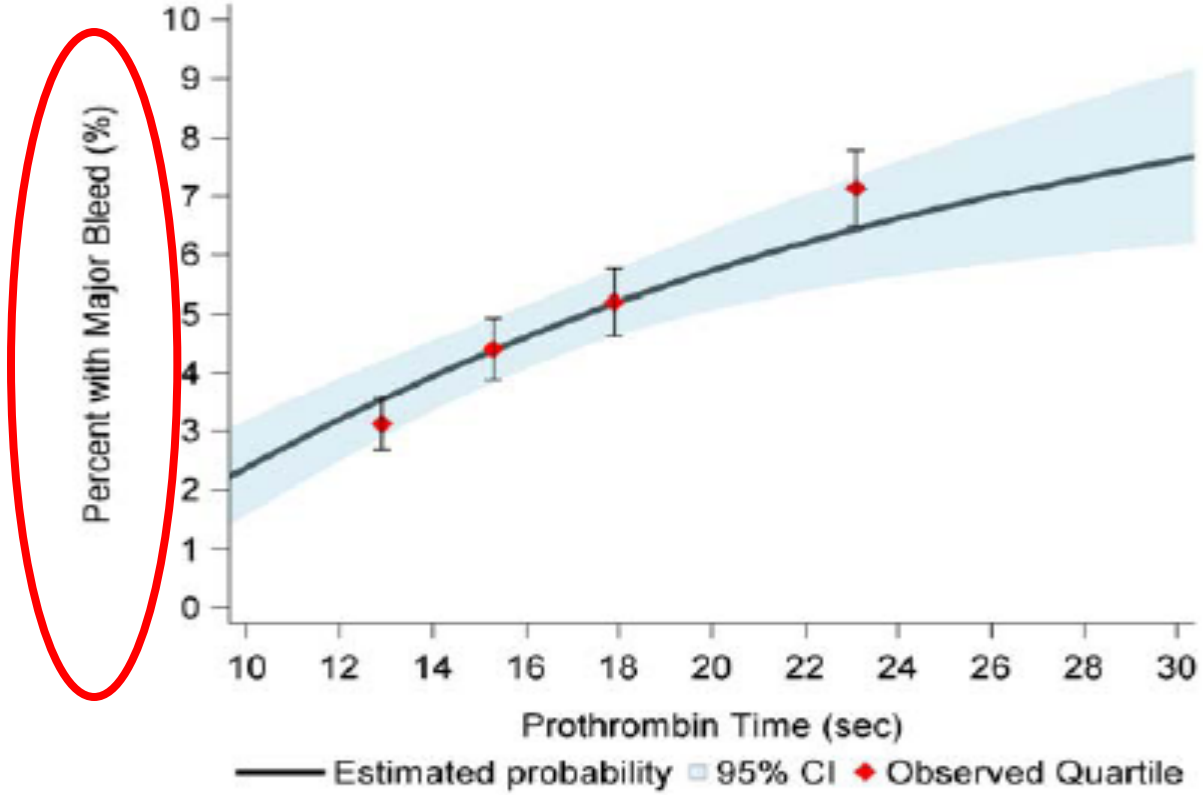
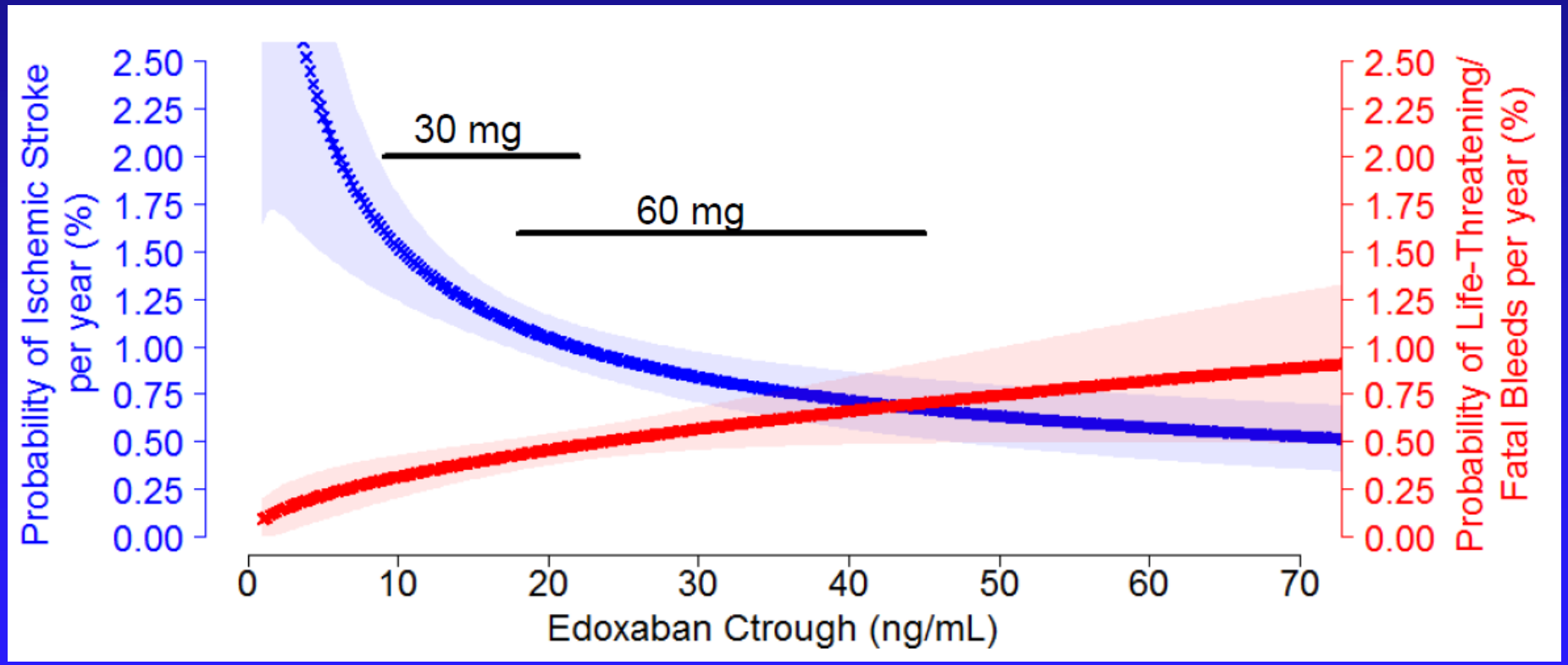


Figure 9 Probability of major bleeding as a function of pre-dose PT for rivaroxaban. The solid line represents the predicted probability from an E_{max} logistic regression and the shaded region represents the 95% confidence interval. The point represents the observed probability at the median value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

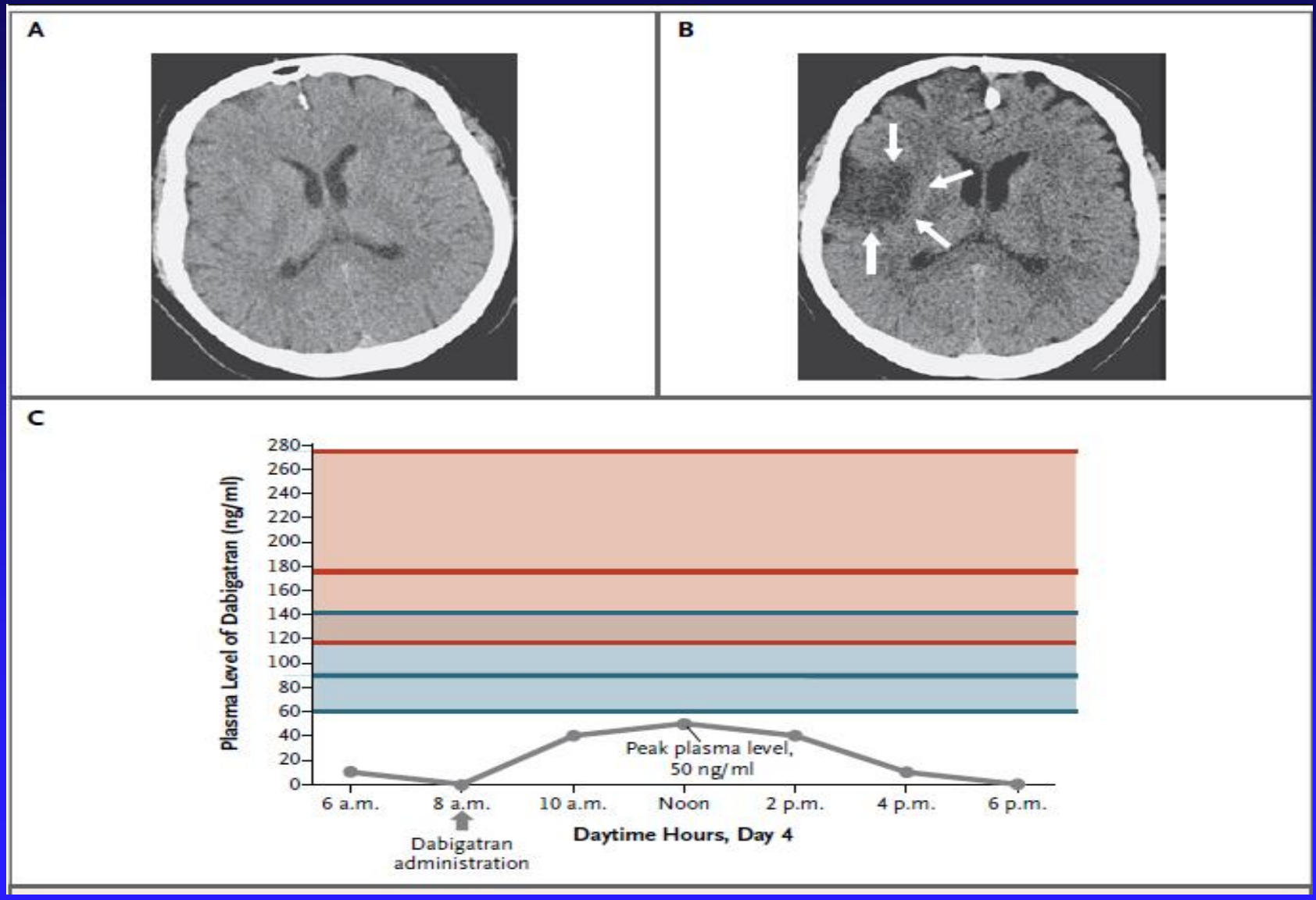
EDOXABAN : CORRELATION OF DRUG LEVELS AND OUTCOMES IN PHASE III TRIALS



FDA, October 26, 2015

The NEW ENGLAND JOURNAL of MEDICINE

Ischemic Stroke in an Obese Patient Receiving Dabigatran



Breuer L, N Engl J Med 2013

ICTUS CEREBRI IN PAZIENTE TRATTATO CON DOAC

- Paziente di sesso femminile, anni 58, in trattamento da circa 4 mesi con dabigatran 150 mg x2/die per FA parossistica (CHA2DS2-VASc Score=4, HAS-BLED Score=0), giunta in PS per improvvisa comparsa di difficoltà al movimento dell'arto superiore sx insorta 1 ora prima
- In anamnesi: HTA, scompenso cardiaco (FE=43%), diabete mellito tipo 2, obesità (peso=108 Kg; BMI>30)
- Il giorno precedente al ricovero la pz si era recata in PS per episodio di FA ad elevata risposta ventricolare, cardiovertita farmacologicamente con flecainide ev, con ripristino del RS

OBIETTIVITA' ALL'INGRESSO

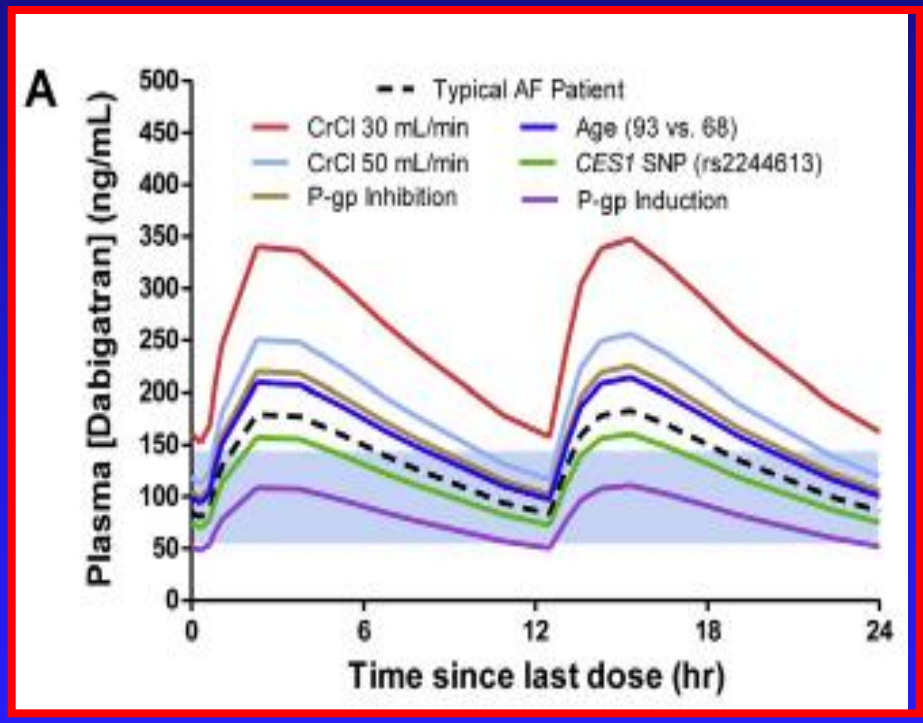
- Deficit VII nervo cranico bilateralmente, disartria, deviazione della rima buccale, lieve disfonia, episodio di vomito
- PA: 175/90 mmHg, Fc 65 bpm ritmico, frequenza respiratoria: 16/min
- NIHSS (National Institutes of Health Stroke Scale)=6, GCS=15

ESAMI STRUMENTALI

- TAC encefalo all'ingresso risultata negativa per lesioni ischemiche ed emorragiche all'ingresso
- Angio-TC : kinking bilaterale del tratto distale delle a. carotidi interne, un'ipoplasia dell'arteria vertebrale sx e la normale opacizzazione dei principali vasi costituenti il poligono di Willis

- Veniva riferita l'assunzione di dabigatran 1 ora prima del ricovero

- Consigliato: dosaggio dabigatran, da ripetere dopo 1 ora per valutare il livello al picco

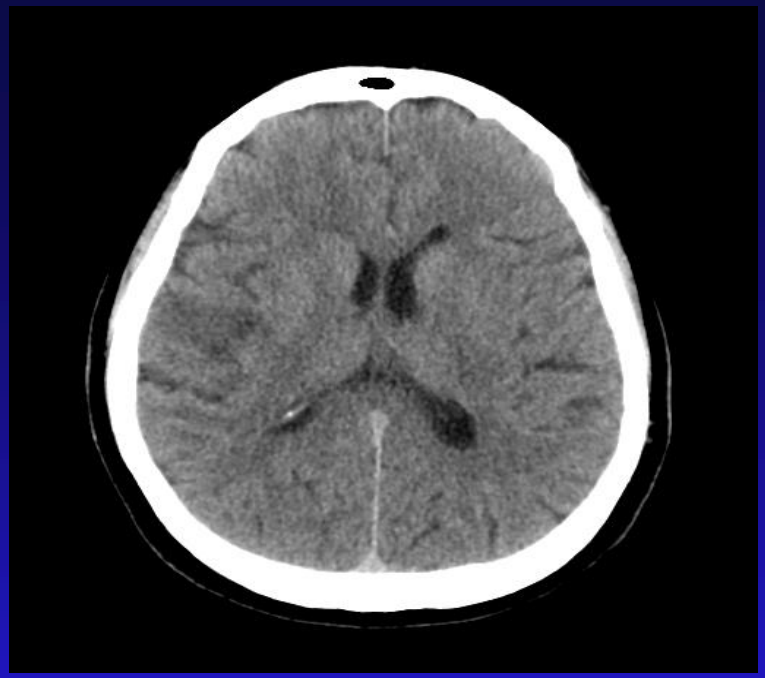


dabigatran

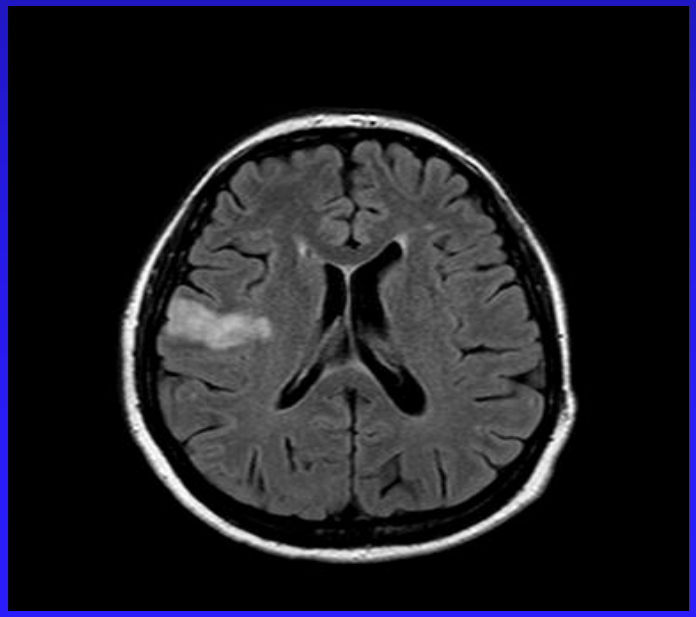
ESAMI EMATOCHIMICI E STRUMENTALI

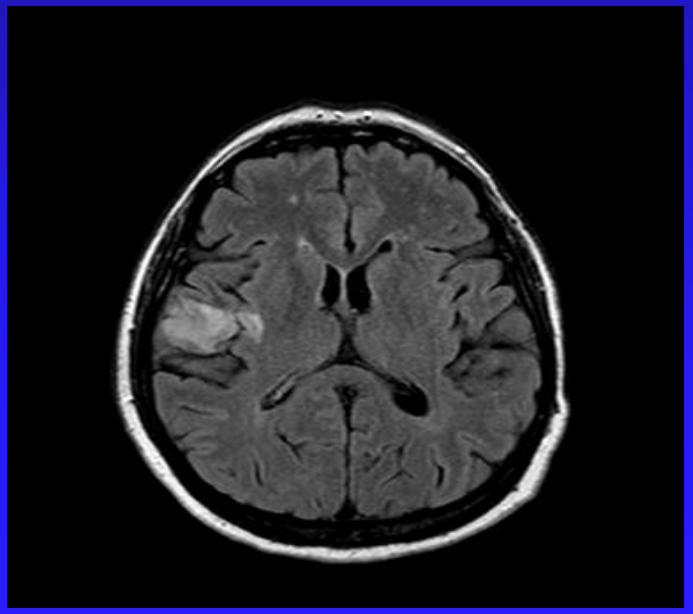
- Parametri ematochimici: Hb=14.9 g/dL, PLT=207.000/mmc, ClCr=82, aPTT R=0.97, PT R=1.01
- Dosaggio dabigatran (dTT) eseguito a distanza di 1 ora dall'assunzione dell'ultima dose, risultato al di sotto della soglia di sensibilità del test nel nostro laboratorio (<15 ng/mL). Lo stesso dosaggio ripetuto dopo un'ora dal primo controllo confermava l'assenza di farmaco.

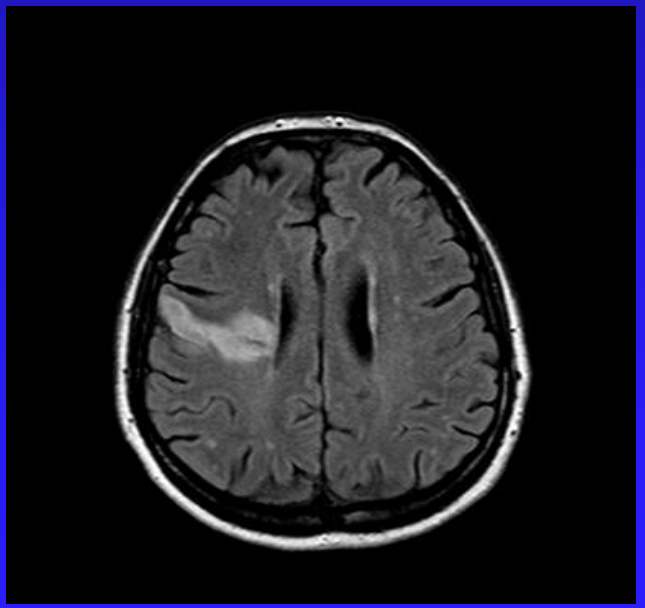
- Si è quindi proceduto a trombolisi con anteplase
- TC encefalo, eseguita a distanza di 5 ore dalla procedura ha mostrato la comparsa di una ipodensità cortico-sottocorticale insulare e fronto-opercolare dx, riferibile a stroke in fase sub-acuta
- Iniziato trattamento eparinico con Clexane 8000 UI 1flx2/die controllando l'anti-Xa e, a 48 ore dall'evento, ripreso trattamento anticoagulante orale con AVK (Coumadin range 2.0-3.0)
- RMN encefalo eseguita in 5° giornata ha confermato il quadro TC ed un quadro di leucoencefalopatia vascolare cronica



TAC ENCEFALO
post-trombolisi







RMN ENCEFALO in V° giornata dopo il trattamento trombolitico

QUANDO L'EFFETTO FARMACODINAMICO PUO' ESSERE DIVERSO DALL'ATTESO E QUANDO E' UTILE IL DOSAGGIO DELL'ATTIVITA' ANTICOAGULANTE

- 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

CONSIDERAZIONI CONCLUSIVE

ESISTONO I PAZIENTI RESISTENTI AI DOACs?

Nel "mondo reale" esistono pazienti che presentano,rispetto alla variabilità biologica attesa, livelli estremamente bassi (o elevati)

ESISTE UN RANGE TERAPEUTICO DA MISURARE?

- E' dimostrata un'ampia variabilità biologica delle concentrazioni dei farmaci
- I report FDA su dabigatran, rivaroxaban e edoxaban mostrano una correlazione tra livello dell'attività anticoagulante e rischio di complicanze
- I range terapeutici, definiti come intervallo delle concentrazioni entro il quale si manifestano gli effetti terapeutici (efficacia) senza effetti tossici (sicurezza), devono ancora essere correttamente definiti.

STUDI IN CORSO: START-Lab 3