MANAGING DOACs

IN REAL LIFE

SOPHIE TESTA

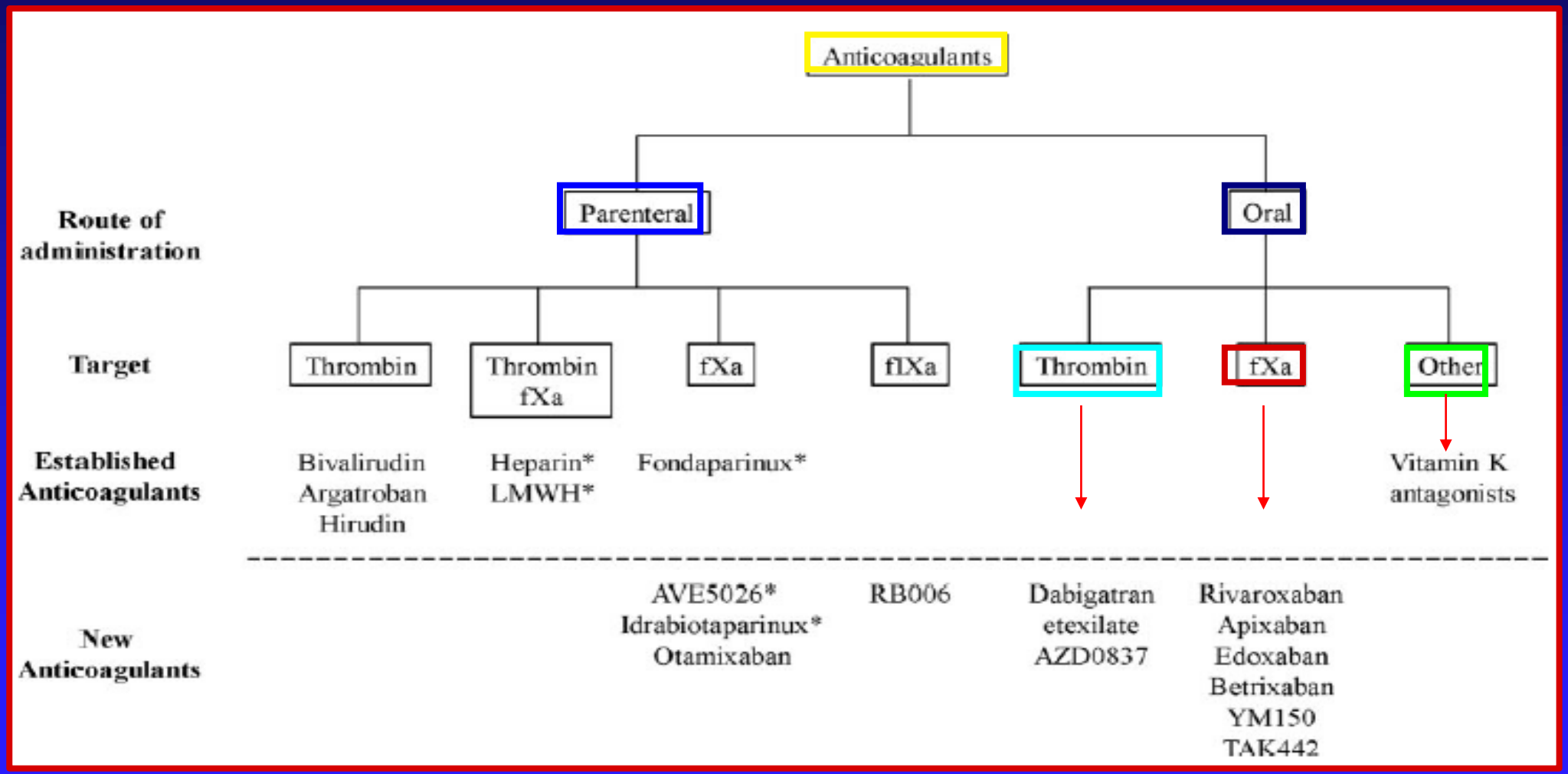
Haemostasis and Thrombosis Center

Istituti Ospitalieri Cremona, Italy

ITEMS

- The " State of the Art" in summary
- Guidelines recommendations
- Which useful evidence from pharmacological and clinical studies ?
- The role of the lab beyond liver and renal function testing
- What are we doing in the "real world"?

ANTICOAGULANT DRUGS



J.W. Eikelboom, Circulation 2010

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)

DOACs POSOLOGY

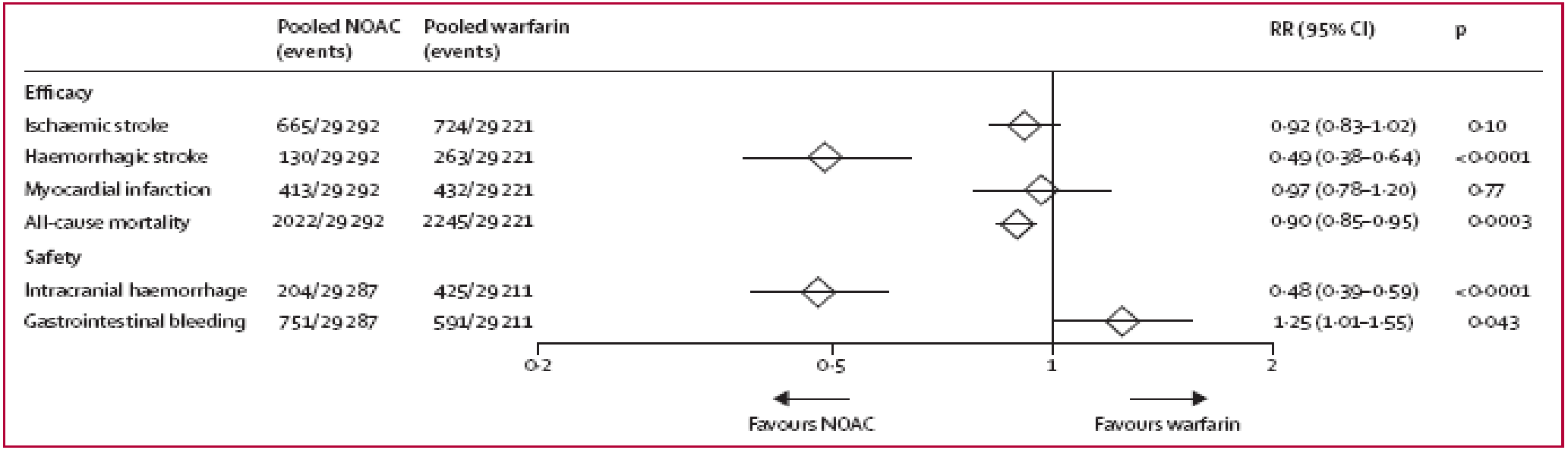
DOSING ADJUSTEMENT IS BASED ON PHARMACOKINETIC S CONSIDERATIONS

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.

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

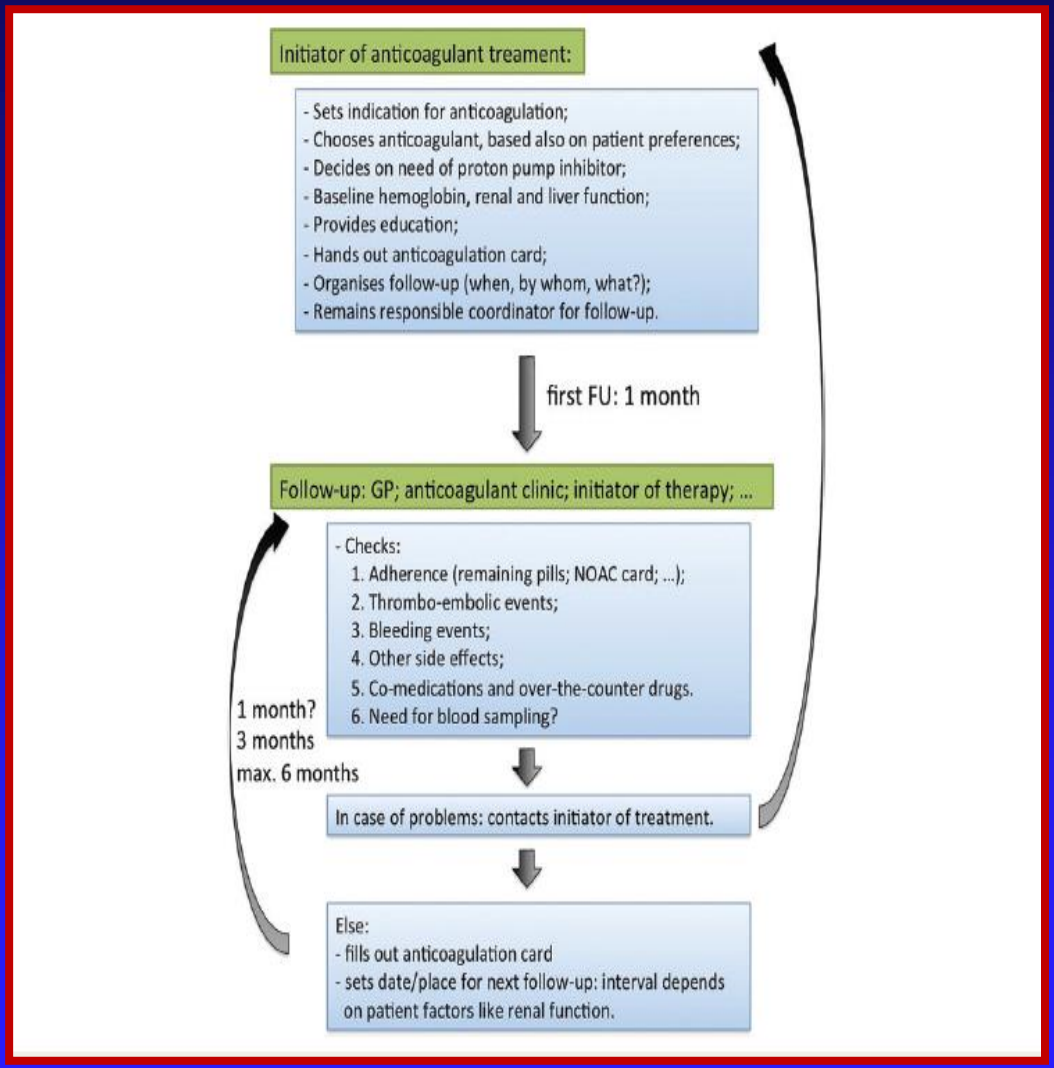
EFFICACY AND SAFETY



Bleeding and Thromboembolic complications: ~ 1-3% pt/y

www.thelancet.com Vol 383 March 15, 2014

MANAGEMENT: THE GUIDELINES



EHRA, ESC 2015

DIRECT ORAL ANTICOAGULANT (DOAC) FOLLOW-UP CHECKLIST

Patient name: | *Date* _____
Age: | *DOAC* _____
Dose _____
Dosing Time(s) _____
Weight _____
$CHADS_2$ _____

	HEALTH STATUS SINCE LAST ASSESSMENT			
	Any new relevant medical problems, ED visits/hospitalizations?		❒ Y	❒ N
	Any embolic events (stroke / TIA / systemic embolism)?		❒ Y	❒ N
A	**ADHERENCE WITH DOAC THERAPY**	Issues?	❒ Y	❒ N
	1 or more missed doses in an average week? If yes, number of missed doses: _____			
	Any issues with taking the DOAC properly? (i.e. rivaroxaban with food/don't open or chew dabigatran/etc.)			
B	**BLEEDING RISK ASSESSMENT** *NB: a YES to any of the following requires individualized assessment and does not imply that DOAC should be discontinued*	Issues?	❒ Y	❒ N
	Any signs / symptoms of GI bleeding? Any other bleeding?			
	Any drop in hemoglobin or new anemia? Latest hemoglobin: _____			
	EtOH overuse?			
	Uncontrolled hypertension (SBP >160 mmHg)? Hypotension with syncope/falls?			
C	**CREATININE CLEARANCE**	Issues?	❒ Y	❒ N
	Latest creatinine: _____ Latest eGFR (or calculated creatinine clearance if eGFR <50ml/min): _____ http://thrombosiscanada.ca/?page_id=502&calc=cockcroft			
	Any recent dehydrating illness or medications added/changed? (i.e. diuretics)			
D	**DRUG INTERACTIONS**	Issues?	❒ Y	❒ N
	ASA / other antiplatelets? **NSAID**?			
	Other drug interactions? (Review med list / OTCs; see Table)			
E	**EXAMINATION**	Issues?	❒ Y	❒ N
	Blood Pressure: ❒ Within Target ❒ High ❒ Low	Actual BP (Opt.): ___/___		
	Does patient need referral for gait assessment/walking aids for falls prevention?			
F	**FINAL ASSESSMENT & RECOMMENDATIONS**			
	Overall patient appears stable from the anticoagulant standpoint; benefits of continued anticoagulant therapy outweigh risks; Recommend continue current anticoagulant therapy.		❒ Y	❒ N
	Dose verified and is appropriate for patient's age/weight/renal function/health status http://thrombosiscanada.ca/?page_id=502&calc=antithromboticAlgorithm		❒ Y	❒ N
	Any changes to current therapy needed?		❒ Y	❒ N
	Provide details:			
	PATIENT EDUCATION & COUNSELING *I have counselled about the following:*		❒ Y	❒ N
	The rationale for continued DOAC therapy			
	The potential for minor, major or life-threatening bleeding			
	Dosing instructions, adherence, risks of non-adherence, handling missed doses			
	Avoiding OTC **ASA** & **NSAIDs** & minimizing EtOH to reduce bleeding risks			

Next F/U Date _____
Next Bloodwork _____
Initials _____

Gladstone et at, Ann Intern Med 2015

OTHER INFORMATIONS FROM PHARMACOLOGICAL AND CLINICAL STUDIES?

(I)

1. Pharmacologycal studies have shown that DOAC have predictable anticoagulant response in “standard” clinical condition

2. Clinical trials have been successfully conducted at fixed-dose regimen, without laboratory controls

(II)

As a consequence, DOAC have been introduced in clinical practice :

1) at fixed daily dose
2) *without lab controls (no coagulation testing recommended)*
3) *Without specific antidotes*

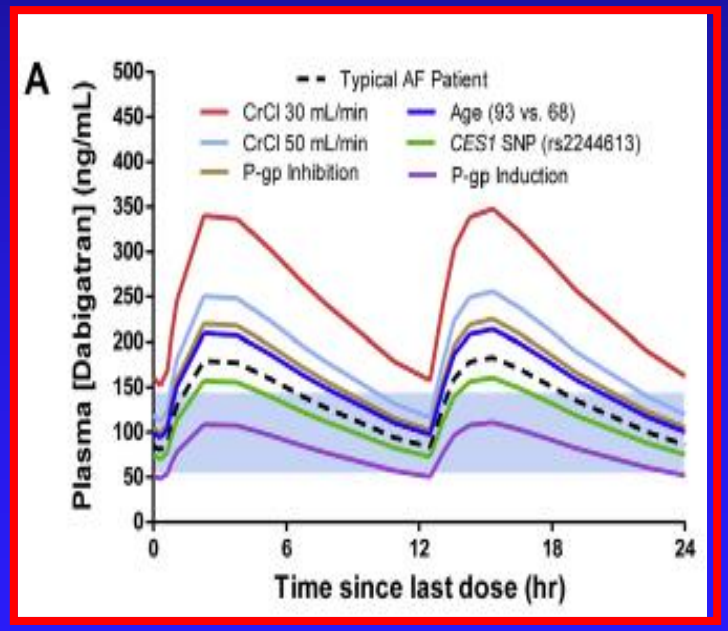
1. Different perception about DOAC patient's health care necessities
2. In Italy: regulatory health authorities defined rules for DOAC reimbursement, often interpreted as a "sort of clinical guideline"

BUT…

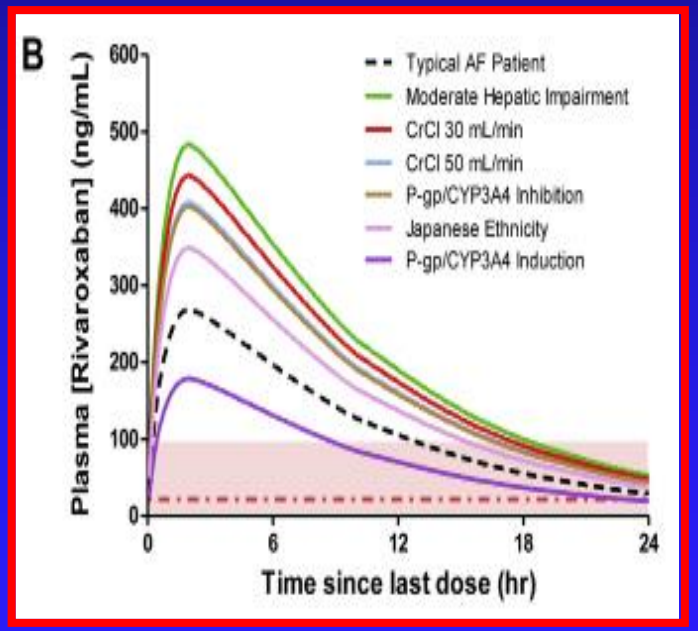
- High inter/intra individual variability has been demonstrated
- Pharmacological modifications have been showed in relation to: drug interaction, liver and renal function, age , weight.

VARIABILITY

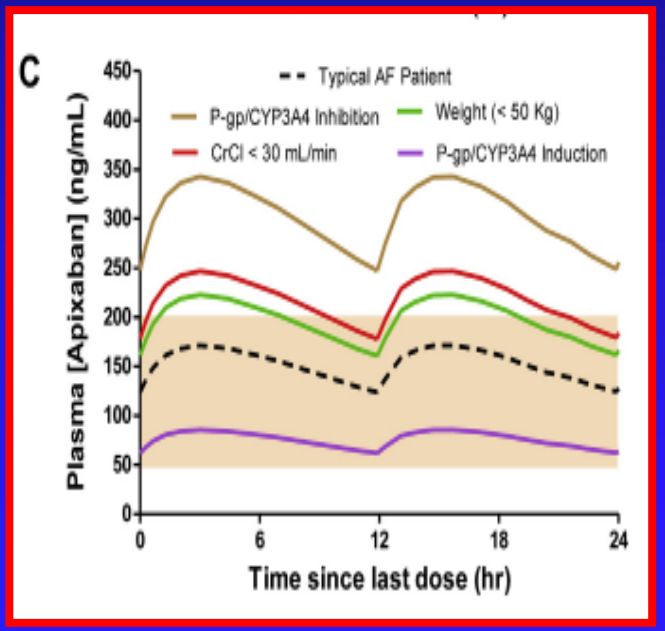
Drug interactions, renal and liver function, age, weight, genetic polymorphisms…



Dabigatran



Rivaroxaban



Apixaban

Gong IY et al, 2013

SOME CONSIDERATIONS

- 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

DOACs INTER-INDIVIDUAL VARIABILITY

Population	CV%
Healthy and young volunteers	~ 20
Phase III randomized clinical studied	~ 40
“Real world” patients	~ up to 75

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

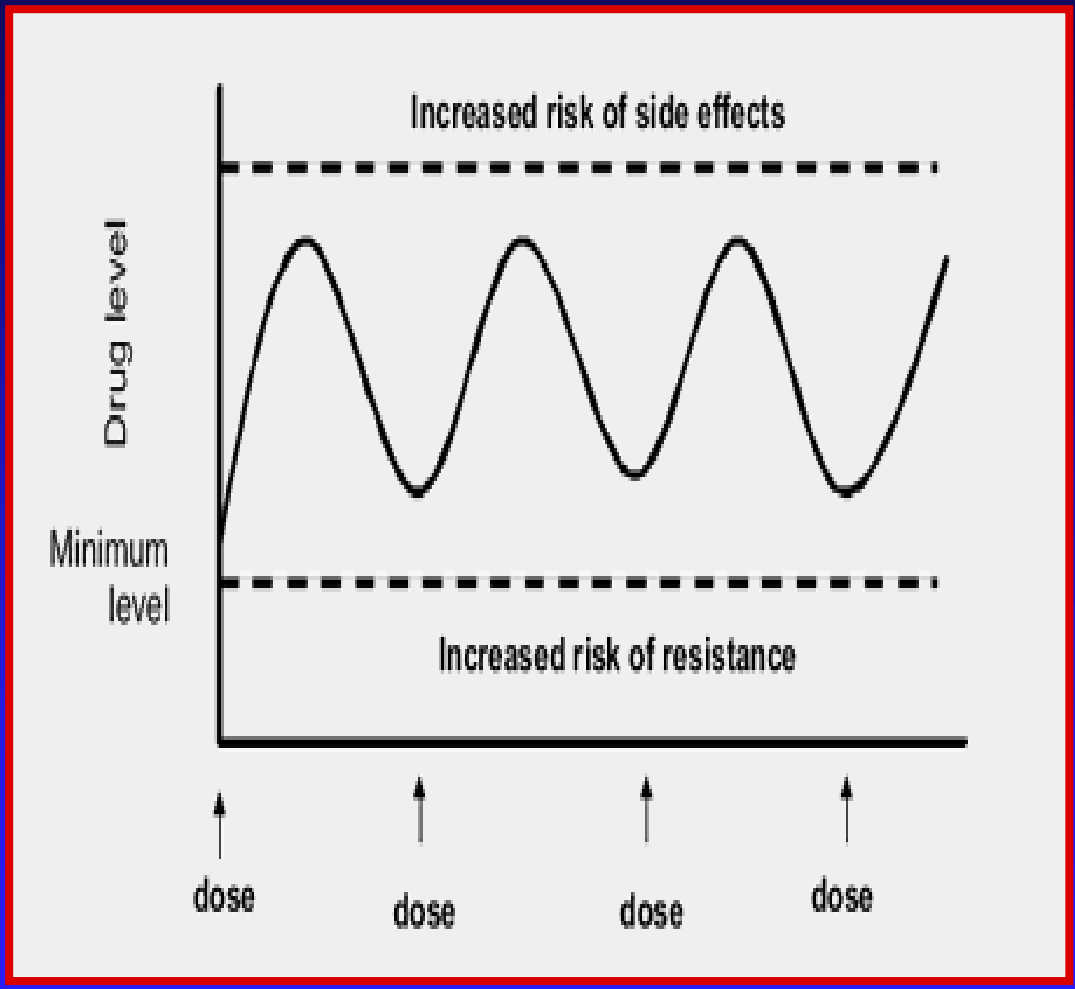
Drug	Trough (ng/ml) mean (min-max)	Peak (ng/ml) media (min-max)
Dabigatran 110 mgx2/die	93 (14-386)	190 (31-651)
Dabigatran 150mgx2/die	91 (16-494)	210 (43-538)
Rivaroxaban 15mg/die	27 (0-88)	208 (77-393)
Rivaroxaban 20mg/die	41 (5-119)	235 (61-449)
Apixaban 2,5mgx2/die	79 (26-248)	192 (55-300)
Apixaban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

Thrombosis Research, 2016

EUROPEAN MEDICINE AGENCY AND "REAL WORLD"

Drug	Trough (ng/ml) mean (min-max)	Peak (ng/ml) mean (min-max)
Dabigatran 110 mgx2/die	93 (14-386) NA	190 (31-651) NA
Dabigatran 150mgx2/die	91 (16-494) 91 (61-143)	210 (43-538) 175 (117-275)
Rivaroxaban 15mg/die	27 (0-88) NA	208 (77-393) NA
Rivaroxaban 20mg/die	41 (5-119) 32 (6-239)	235 (61-449) 215 (22-535)
Apixaban 2,5mgx2/die	79 (26-248) 32 (11-90)	192 (55-300) 67 (30-153)
Apixaban 5 mgx2/die	113 (42-283) 63 (22-177)	200 (102-416) 132 (59-302)

FURTHERMORE…



Based on phase II and III clinical trials, it has been assumed that during time:

- anticoagulant levels are always "acceptable"
- do not occur: 1. persistent drug accumulation and 2. persistent absence or insufficient drug activity

If we compare:

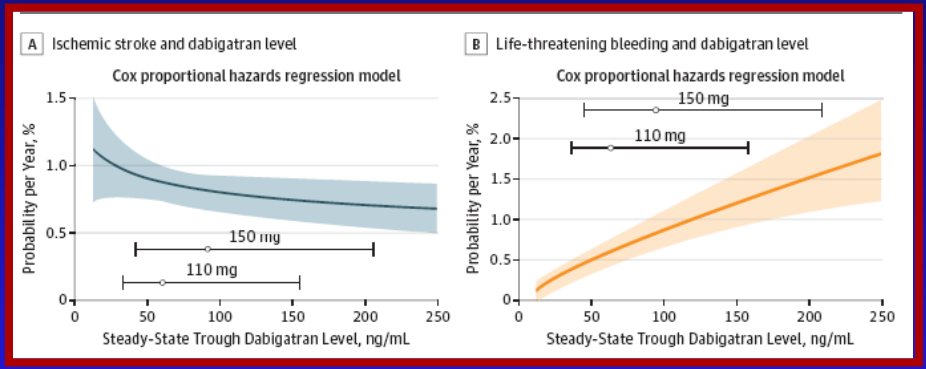
a) AVK complications are correlated with TTR

b) LMWH, not generally monitored, are administered for short period

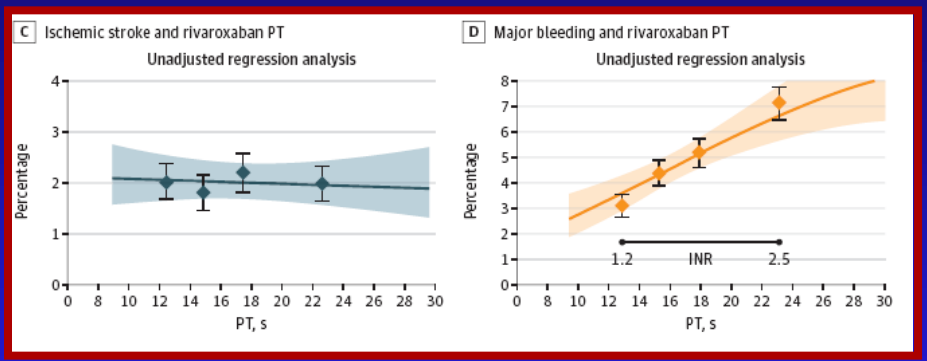
ARE THESE INFORMATIONS USEFUL FROM A CLINICAL POINT OF VIEW?

FDA REPORTS: DOACs EXPOSURE-RESPONSE ASSOCIATION FOR EFFICACY AND SAFETY

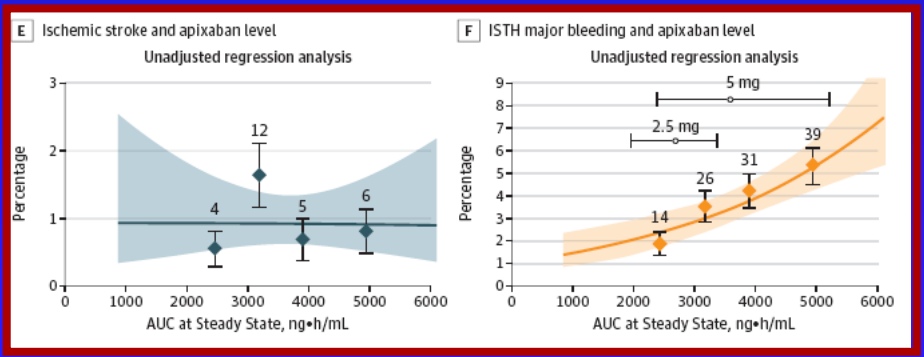
dabigatran



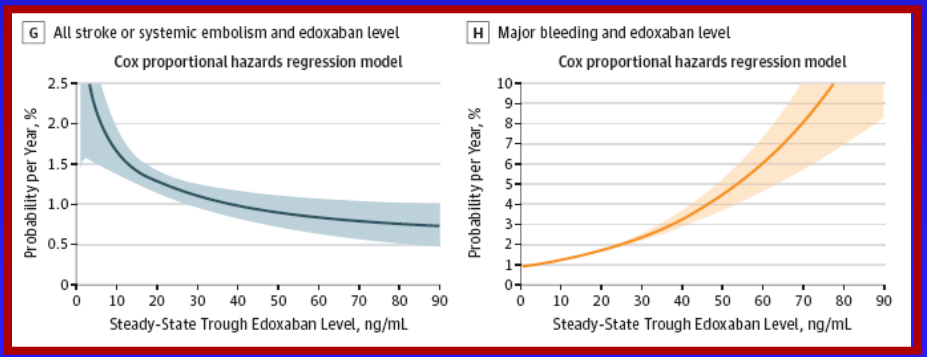
rivaroxaban



apixaban



edoxaban



Eikelboom JW et al, JAMA Cardiol 2017

DOACs AND THE LAB

Test	Recommendation	Comments
ClCr	1.Before starting DOACs and in the follow up to continue treatments (or adapt posology). 2. CrCl is also considered as surrogate of good anticoagulant action	- ClCr not validated in older population - CrCl>30ml/min not correlate with aXa drugs
AST/ALT	1. Before starting DOACs and in the follow up to continue treatments	No clear timing of controls
Blood Cell Count	Should be recommended	Before starting and during the follow up
PT/aPTT	Not recommended to assess levels of anticoagulation	Should be recommended before starting DOAC to assess haemostatic status
DOAC specific test	Only In specific clinical situation	To guide clinical approach
DOAC specific test	Monitoring and assess safety anticoagulation	We need further evidences

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

Table 6. Correlation (r value), coefficient of determination (r^2) and statistical significance (p) of DOAC plasma concentrations (at peak or trough) vs. creatinine clearance.

Drug and Dose (mg)	C Trough (r/r^2)	p	Cpeak (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

Tromb Res, 2016

Stroke and Bleeding in Atrial Fibrillation with Chronic Kidney Disease

Table 2. Event Rates, According to Status with Respect to Renal Disease.*

Event	No. of Person-yr	No. of Events	Event Rate per 100 Person-yr (95% CI)
Stroke or thromboembolism			
No renal disease	461,734	16,648	3.61 (3.55–3.66)
Non–end-stage CKD	13,078	842	6.44 (6.02–6.89)
Disease requiring renal-replacement therapy	2,922	164	5.61 (4.82–6.54)
Bleeding			
No renal disease	457,605	16,195	3.54 (3.48–3.59)
Non–end-stage CKD	12,515	1,097	8.77 (8.26–9.30)
Disease requiring renal-replacement therapy	2,734	243	8.89 (7.84–10.08)

Olesen J et al, N Engl J Med 2012

DOACs MEASUREMENT

1. PERIODICAL MEASUREMENT (MONITORING) TO DOSE-ADJUSTEMENT

2. PERIODICAL MEASUREMENT (CONTROL) TO HIGHLIGHT UNDER/OVER ANTICOAGULATION

3. MEASUREMENT IN SPECIAL CLINICAL CONDITIONS

Eikelboom JW et al, 2017; Tripodi A et al, submitted 2017

1.

PERIODICAL MEASUREMENTS (MONITORING) TO DRUG DOSE-ADJUSTMENT

VIEWPOINT

Are New Oral Anticoagulant Dosing Recommendations Optimal for All Patients?

Even though the one-size-fits-all DOAC dosing may perform as well as or better than warfarin on average... patient safety can be further improved through individualized patient dosing.

J. Robert Powell,
JAMA March 10, 2015 Volume 313, Number 10

JAMA Cardiology | Review

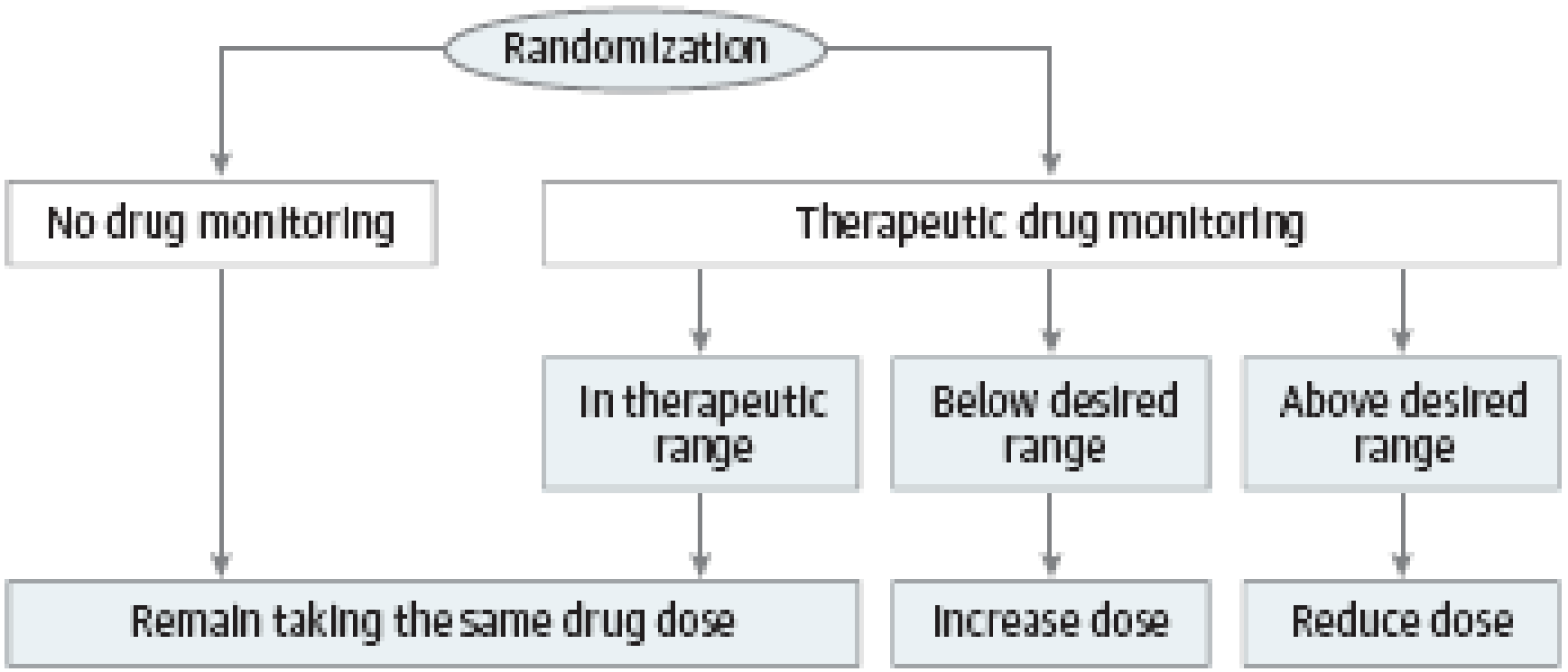
Laboratory Monitoring of Non-Vitamin K Antagonist Oral Anticoagulant Use in Patients With Atrial Fibrillation
A Review

John W. Eikelboom, MBBS; Daniel J. Quinlan, MBBS; Jack Hirsh, MD; Stuart J. Connolly, MD; Jeffrey I. Weitz, MD

OBSERVATIONS The predictable anticoagulant response of NOACs has provided the pharmacological basis for their administration in fixed doses without routine coagulation monitoring. Although it is possible to accurately measure NOAC drug levels, within-patient variability complicates interpretation of these results. Furthermore, patient characteristics, such as age and renal function, confound the association between NOAC drug levels and clinical outcomes. Information is lacking on the optimal drug level in particular patient groups (eg, elderly, the renally impaired, and those with high bleeding risk), the appropriate dose adjustment to achieve expected levels, and whether routine laboratory monitoring and dose adjustment will improve clinical outcomes. A benefit of a management strategy that incorporates routine therapeutic drug monitoring and dose adjustment over current standard-of-care metrics without such monitoring remains unproven.

Ejkelboom JW, 2017

Figure 4. Proposed Randomized Clinical Trial Design to Evaluate the Clinical Utility of Dose Adaptation



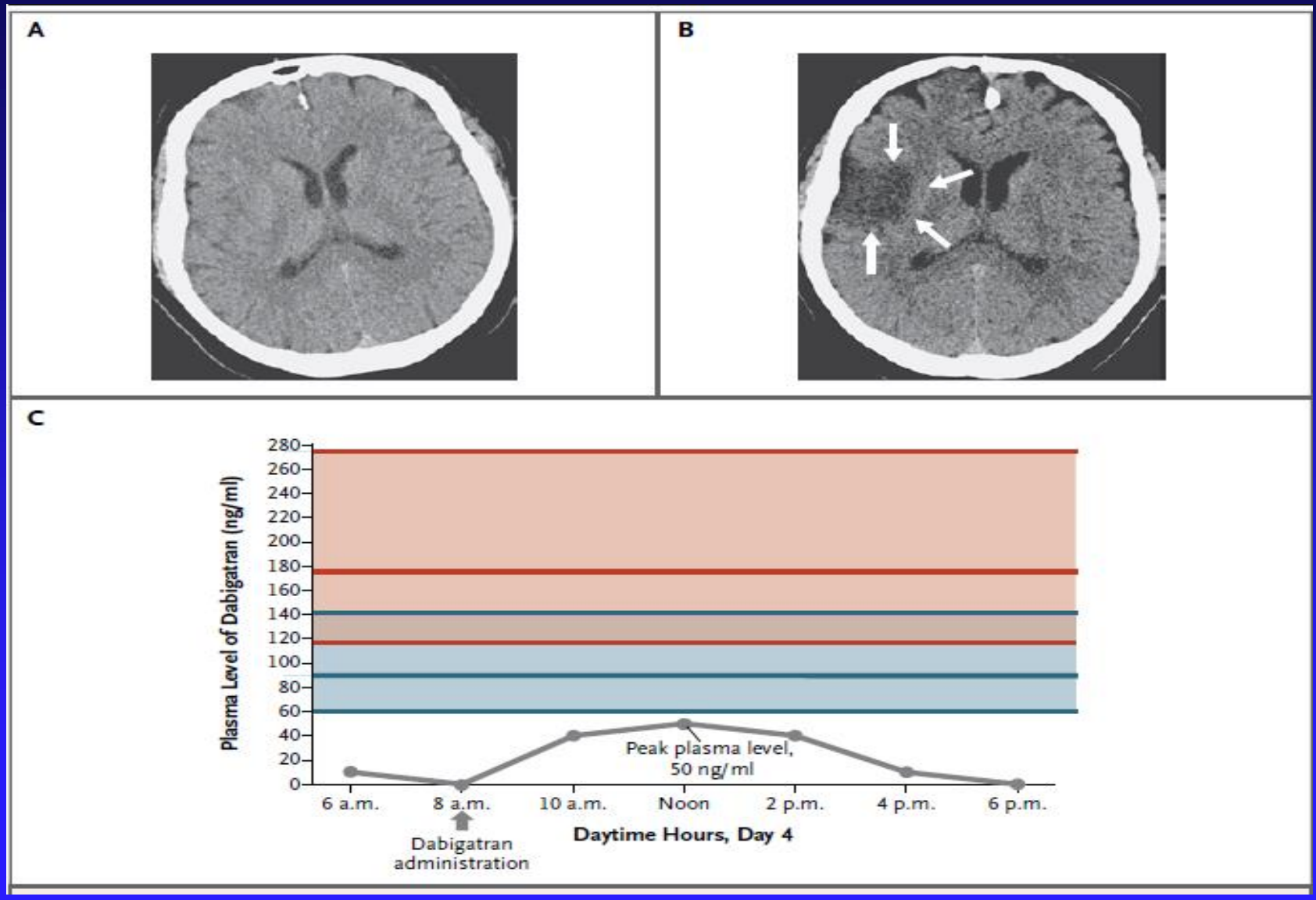
Ejkelboom JW, 2017

2.

PERIODICAL MEASUREMENT (CONTROL) TO HIGHLIGHT UNDER/OVER ANTICOAGULATION

The NEW ENGLAND JOURNAL of MEDICINE

Ischemic Stroke in an Obese Patient Receiving Dabigatran



Breuer L, N Engl J Med 2013

A CASE REPORT

- An 58 year old woman (weight=108 Kg; BMI>30) was admitted to the emergency department for sudden hemiparesis.
- She had been treated for 4 months with dabigatran etexilate, 150mgx2/die, for NVAF (CHA2DS2-VASc Score=4 : HAS –BLED=0) and confirmed last dose intake one hour before hospital admission
- In anamnesis: HTA, diabetes , obesity, left ventricular dysfunction

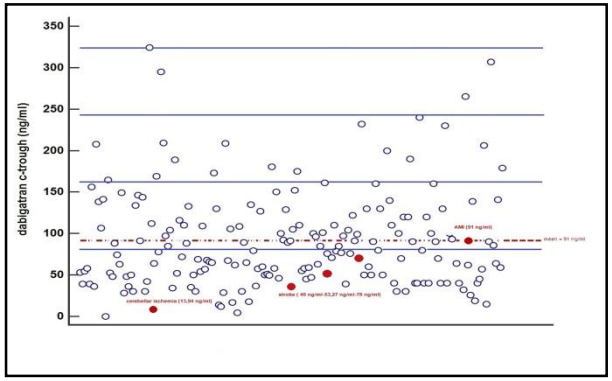
Cremona 2016 (unpublished)

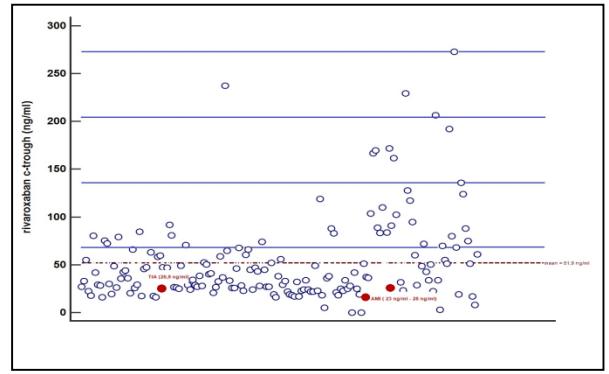
On admission:

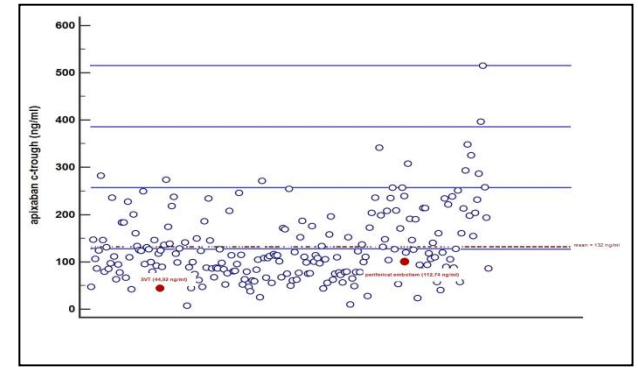
- Cerebral CT scan was negative for bleeding lesions
- Hb=14.9 g/dL, PLT=207.000/mmc, CrCl=82mL/min/1.73m^2, aPTT R=0.97, PT R=1.01
- Dabigatran (dTT) : <15ng/ml (=0)
- Dabigatran measurement repeated after neraly one hour confirmed the total absence of specific anticoagulant activity
- After multidisciplinary discussion she was treated with thrombolytic agent
- She was discharged two weeks later, without sequalae, on warfarin

Cremona 2016 (unpublished)

LOW DRUG LEVELS AND THROMBOTIC COMPLICATIONS IN HIGH RISK ATRIAL FIBRILLATION PATIENTS TREATED WITH DOACs







CHA_2DS_2-VASc >3.0 **(291/595pts; 51.5%)**	25° Percentile **(Lower drug levels)**	> 25 th percentile **(Highest drug levels)**	Total **(n)**
Thrombosis	**9**	**1**	**10**
No Thrombosis	**118**	**163**	**281**
	9/127 (7.09%)	**1/164 (0.61%)**	

Testa S, et al *for the START-Lab Registry. ISTH Berlin 2017, Submitted Am J Cardiol*

LOW DRUG LEVELS AND THROMBOTIC COMPLICATIONS IN HIGH RISK ATRIAL FIBRILLATION PATIENTS TREATED WITH DOACs

1. **Our data show a relationship between low DOACs trough plasma levels and subsequent thrombotic events**

2. **Higher cardiovascular risk patients with low DOACs levels show significantly higher risk of thrombosis compared to patients with higher DOACs levels** P=0.03; OR 12.4 (CI=1.5-99.4)

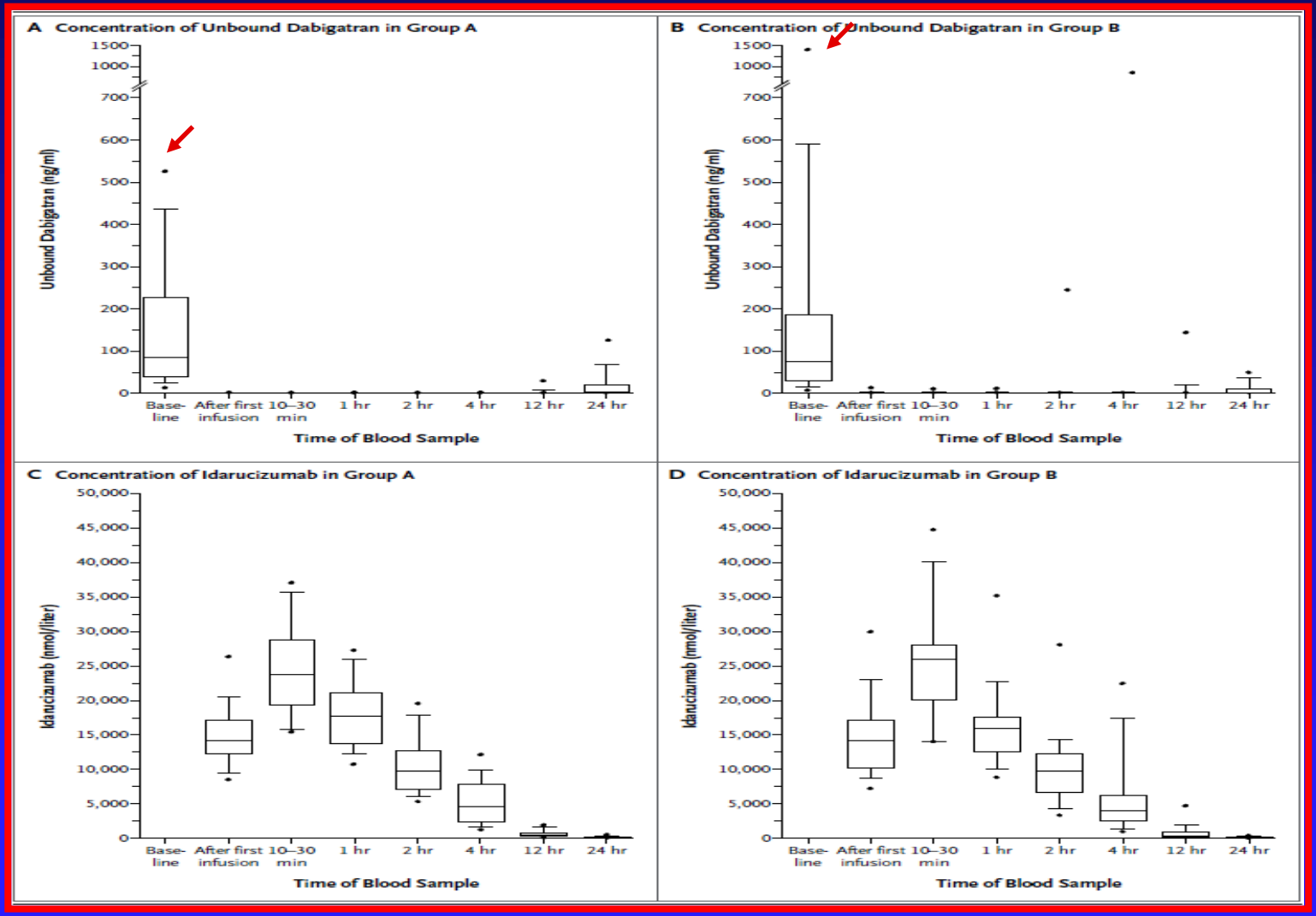
3. **DOACs measurement seems particularly indicated in higher cardiovascular risk patients**

Testa S, et al *for the START-Lab Registry. ISTH Berlin 2017, Submitted Am J Cardiol*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

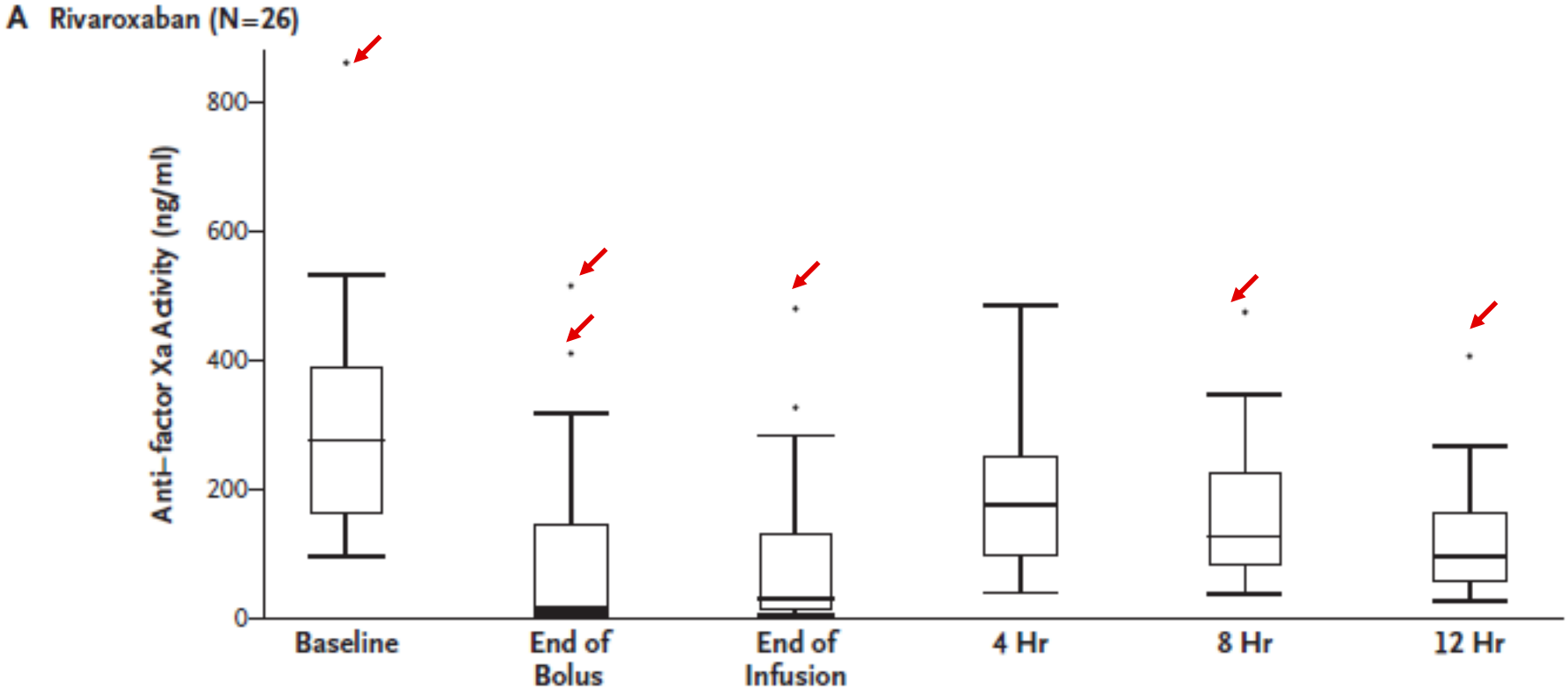
Idarucizumab for Dabigatran Reversal



Pollack et al, N Engl J Med 2015

ORIGINAL ARTICLE

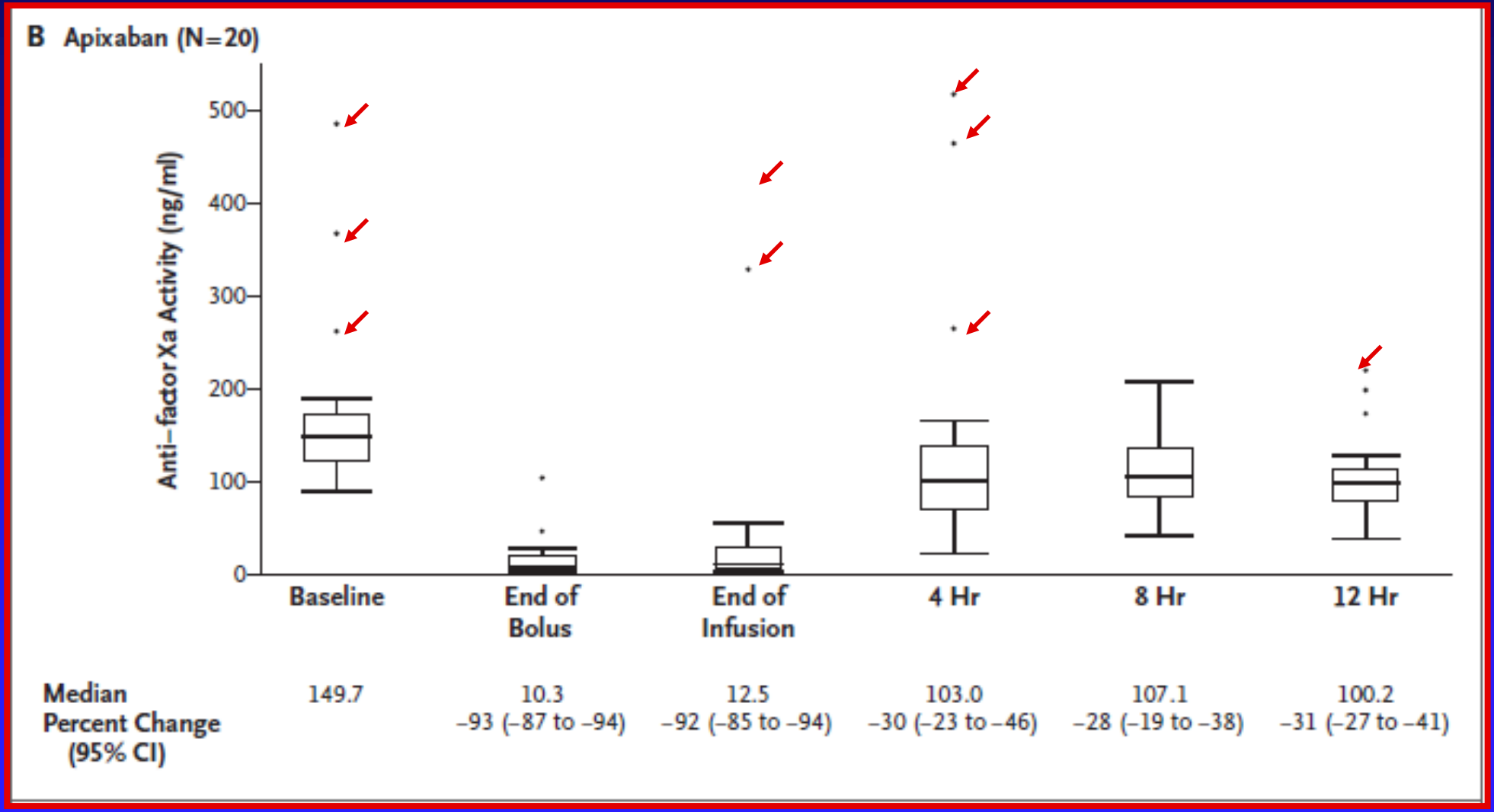
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors



Connolly SJ, N Engl J Med 2016

ORIGINAL ARTICLE

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors



Connolly SJ, N Engl J Med 2016

WHAT CAN WE LEARN ?

1. Some patients show very low (or absence) drug levels
2. Some patients show very high DOAC levels (more than ten times as compared with trough levels and 2-3 times as compared with peak levels)
3. *The fixed dose of antidote infused could be insufficient for high DOAC levels or excessive in case of low drug levels.*

DOAC MEASUREMENT AND BLEEDING OR THROMBOEMBOLIC COMPLICATIONS DURING FOLLOW-UP: A PROSPECTIVE, MULTICENTER, OBSERVATIONAL START-FCSA STUDY

The MAS (Measure And See) Study

Promoted by: Arianna Anticoagulazione Foundation (Bologna, Italy), in collaboration with the Italian Federation of Anticoagulation Clinics (FCSA)

3.
DOAC SPECIFIC MEASUREMENT IN SPECIAL CLINICAL CONDITIONS

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

Pengo V et al, 2011

DOACs MEASUREMENT

=

ESSENTIAL TO GUIDE APPROPRIATE MANAGEMENT

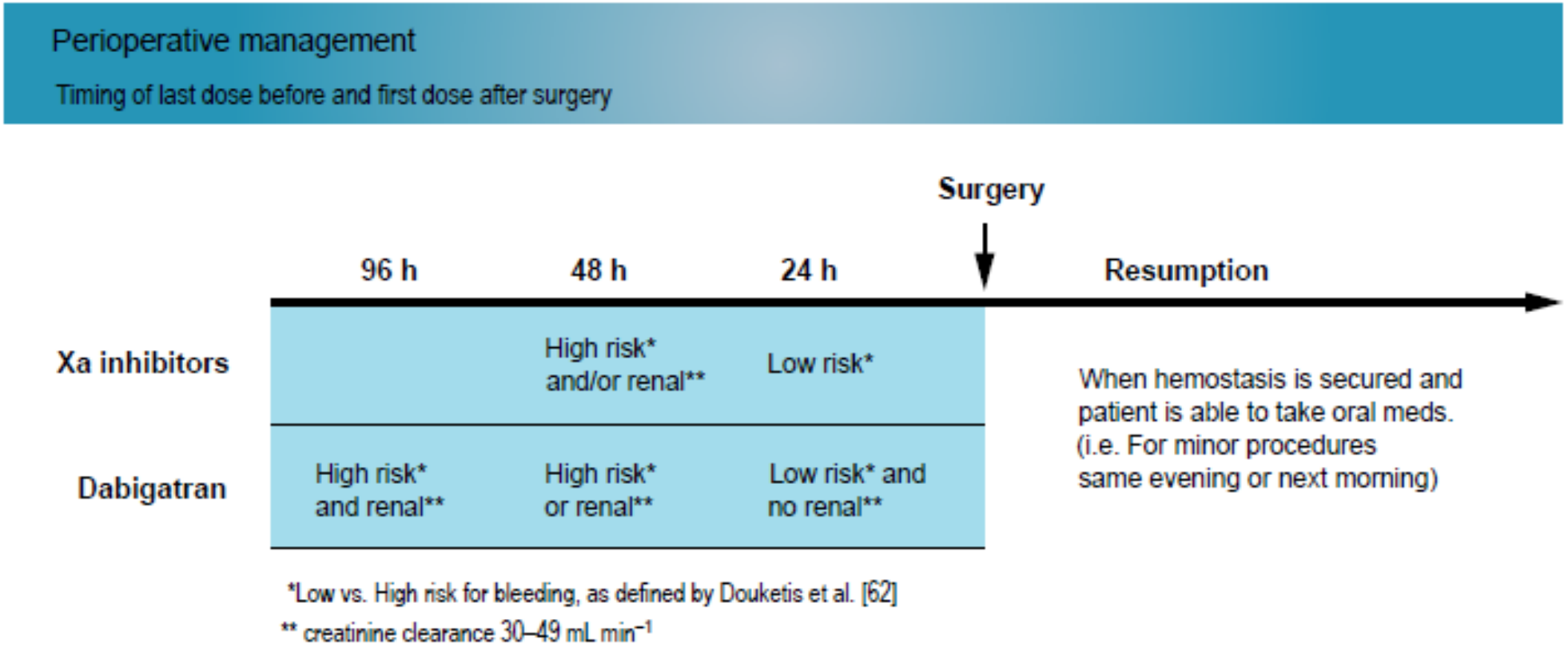
Targeted Anti-Anticoagulants

Kenneth A. Bauer, M.D.

- Laboratory measurements were performed centrally and were not used to guide therapy.
- dTT results were normal in ¼ of the study population. This group of patients would not be expected to benefit from the administration of idarucizumab.
- It will be useful to have activity measurements available for the various direct oral anticoagulants in real time to help guide the treatment of such patients and to prevent overutilization of what will surely be a costly medication

BAUER , N Engl J Med 2015

PERIOPERATIVE MANAGEMENT: THE GUIDELINES



Schulman S, J Intern Med 2013

PERIPROCEDURAL MANAGEMENT OF DOAC SHOULD BE GUIDED BY ACCURATE LABORATORY TESTS

Interruption of DOAC should not be based only on their respective half-life but also on the residual drug concentration

- Poor correlation between renal function and plasma concentration of apixaban and rivaroxaban was found except dabigatran measured at through (Testa S et al, TR 2016)
- Mass spectrometry measured **dabigatran level greater than 20ng/ml in nearly 16% of patients undergoing high bleeding risk procedures** (Douketis JD et al JT&H 2016)

Douxfils J et al, Reg Anesthesia and Pain Medicine, Sept 2016

Position Paper on Laboratory Testing for Patients on Direct Oral Anticoagulants. Consensus Document of SISET, FCSA, SIBIOC and SIPMEL

A. Tripodi, W. Ageno, M.Ciaccio, C.Legnani,G.Lippi, C. Manotti, R.Marcucci, M.Moia,B.Morelli, D.Poli,A.Steffan, S.Testa

1. At the beginning of DOAC treatment to confirm adsorption and to know patient's individual anticoagulant levels
2. Over-under weight
3. In case of potential interferences with co-medications
4. Co-morbidities
5. Bleeding and thromboembolic complications
6. Surgical and invasive procedures

Blood Transfusion, 2017 in press

HOW TO MEASURE?

1. PT and aPTT react differently with DOACs in relation to type of drug and type of reagent
2. Patients having the same DOAC plasma concentration may show different PT or aPTT results
3. Normal PT/aPTT results cannot exclude significantly high concentrations of DOACs, such as abnormal prolongation could be caused by **defects of coagulation other than those stemming from the drug being taken by the patients**
4. Specific test are easily available (dTT, Ecarin Tests, aXa)
5. The use of PT or aPTT in clinical practice to evaluate DOAC anticoagulant activity could cause dangerous misinterpretations.

Kitchen S et al, BJH 2015; Douxfils 2012, Douxfils 2013, Testa S et al, JTH 2016

PATIENT'S HEALTH NEEDS: THE FOLLOW UP

	AVK	DOACs
1° visit (anamnesis, physical examination, liver/renal function, and blood cell count)	YES	YES
Drug Prescribtion (clinical indication, posology)	YES	YES
Information/Education	YES	YES
Lab Coagulation Monitoring to dose adjustment	YES	NO
Clinical periodical controls	Together with lab controls	YES
Lab Control (special situations, highlight over/under treatment)	YES	YES
Measure renal function	Why not?	YES
Adherence/compliance control	NO	YES
Management in special situations (surgery, invasive procedures, complications)	YES	YES

CONCLUSIVE REMARKS

- In the name of simplicity (i.e. no pharmacodynamic monitoring or dose adjustement and rigid dose regimens with “one-size-fits all strategy”) we have taken great drugs, but *(still at present)* truly not good enough for some of our patients (Kaluski E et al, JACC 2012)
- Patients on DOAC need structured follow up to ensure efficacy and safety to their treatments
- We are learning how to perform it
- Using better strategies (i.e.: The Coagulation Laboratory) we could enhance efficacy and safety and probably extend DOAC use to new indications

Thank you for your attention

DOAC: BLEEDING AND THROMBOTIC EVENTS

	AF	VTE
Fup (pt-yrs)	1085	**385**
Major bleeding **rate: % pt ; x100 pt yrs**	28* (2.7;2.5)	3 (0.52;0.77)
Cerebral **Gastrointestinal** **Other**	**6*** **12** **10***	**-** **2** **1**
NMCRB **Rate:%pt; x100 pty rs**	21 (2.0;1.9)	5 (0.87;1.3)
Thromboembolic events **Rate: %pt; x100 pt yrs**	9 (1.0; 0.78)	10 (1.7;2.6)

Fatal bleeding

*1 cerebral; 1 other

HEALTH CARE NEEDS

- Correct clinical indication, DOAC selection and posology
- Information (oral and written instructions) and Education
- Control of Adherence and Compliance
- Evaluate change in comorbidities and comedications
- Assess liver and renal function (Haemostatic assessment and Blood cell count? Other?)
- Management in case of surgery or invasive procedures
- Management of complications and adverse events