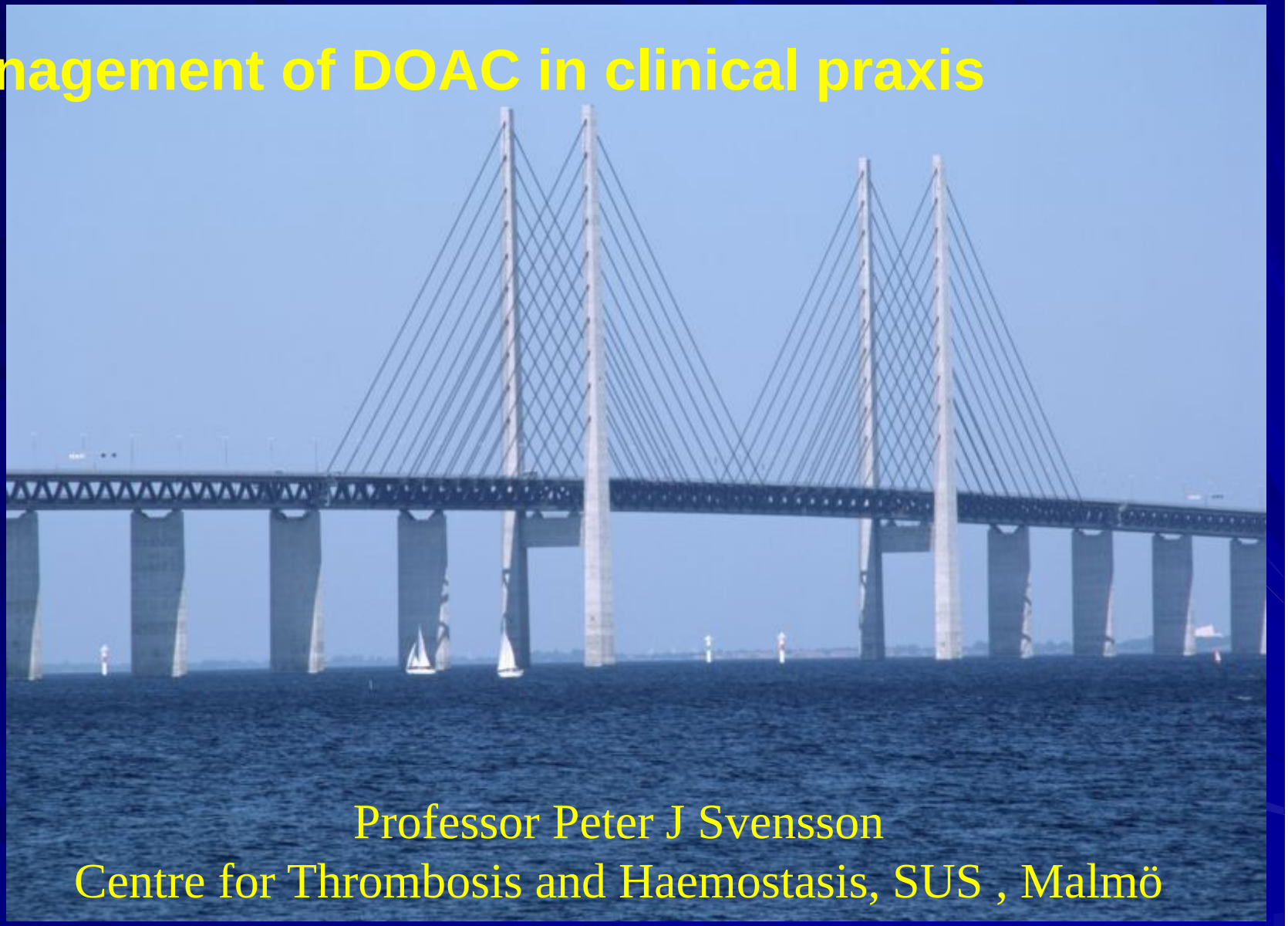
Management of DOAC in clinical praxis

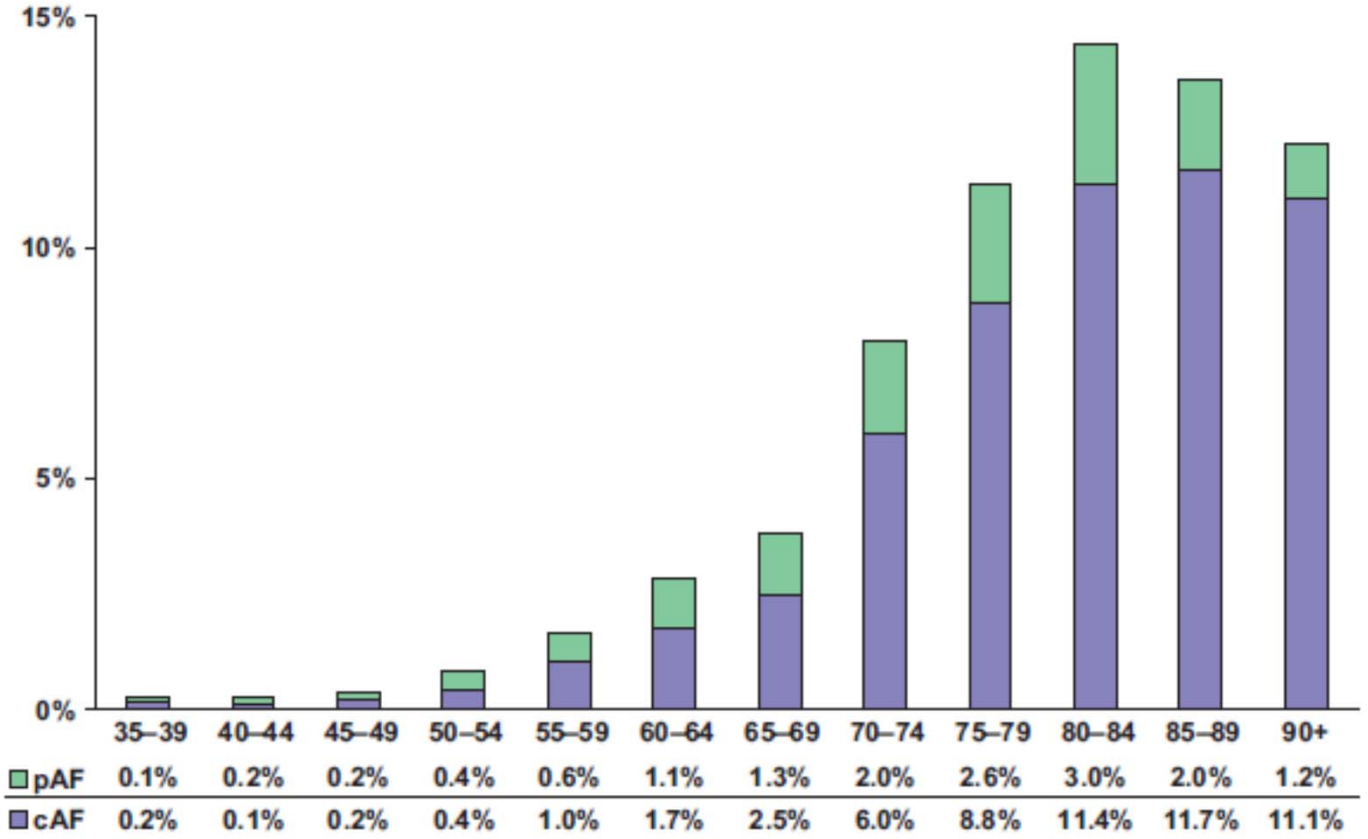


Professor Peter J Svensson
Centre for Thrombosis and Haemostasis, SUS , Malmö

Disclosures for [Peter J Svensson]

- ACCP Guidelines 2012
- Auricula (Chairman)
- Bayer
- Boeringer Ingelheim
- Pfizer / BMS

Prevalence of atrial fibrillation
> 2.5 % in the general population



Andersson et al JIM 2012, SBU 2013 april
Friberg et al JIM 2013

Indications for OAC

- Atrial fibrillation > 80%
- VTE 10%
- Mechanical heart valves 5%
- Other 5%

- Increase of OAC with 5-10% per year
- ***30 % is over the age of 80 years among patients with OAC***

Different laboratory tests

(coagulation-tests)

- 1.Tests that are availbale in most laboratories, easy to perform and semiquantitative for use in ie emergency situations. The test should indicating supra or subtherapeutic anticoagulation

- 2. Test that gives quantitative results to determine the anticoagulant effect (drug level)
- 3 (HPCL-tandem mass spectrometry)

J Throm Haemost 2013; 11: 756-60

Substance group	1. Screening-methods affected	2.Methods for measuring/ monitoring
Direct FIIa-inhibitors	APTT	Thrombin time (TT)
	INR	ECT

Substance group	1. Screening-methods affected	2.Methods for measuring/ monitoring
Direct FXa-inhibitors	APTT	Anti Xa-activity
	INR	

Effect of FII and FX inhibitores on coagulation assays

	FII Effect	FII Measuring	FX Effect	FX Measuring
PT (INR)	+	-	(+)	?
APTT	++	Qualitative	+	Qualitative
Thrombin time	+++	Qualitative	-	-
Diluted TT	++	Quantitative	-	-
ACT	+	?	+	?
Ecarin clotting time	++	Quantitative		
Anti- IIa assay (chromogenic)	++	Quantitative	-	-
Anti- Xa assay (chromogenic)	-	-	++	Quantitative

J Throm Haemost 2013; 11: 756-60

How I handle DOAC in my clinical practice

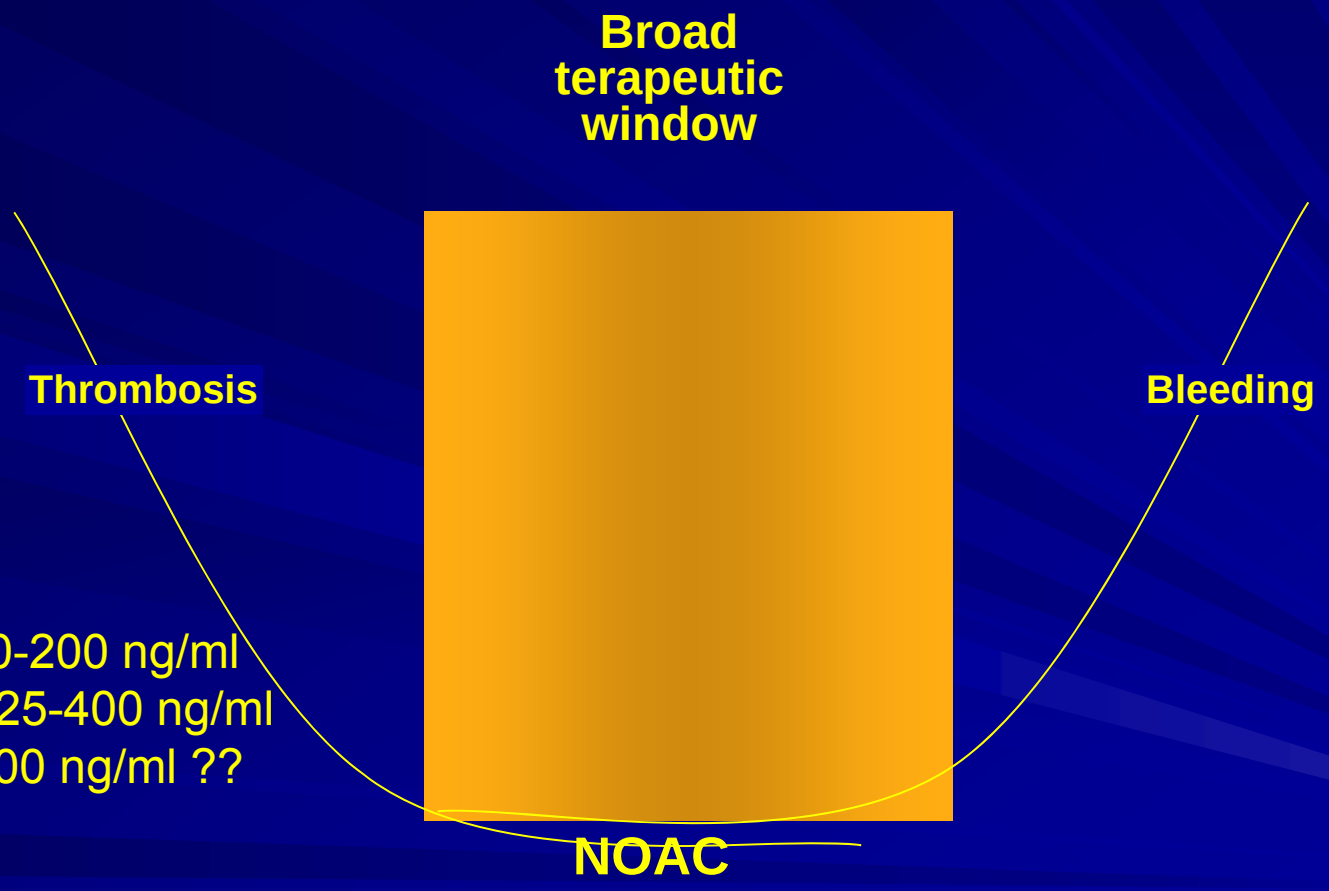
- Anticoagulation clinic; 12.000 patients
- DOAC >3000 patients
- **Start on DOACs**
- Information (nurse 15- 20 minutes)
- Basic laboratory tests (Hemoglobin, platlets and coagulation test APTT INR and kidney function eGFR)
- First year on DOAC eGFR 3, 6 and 12 months after start.

Bergman et al **Thromb Res. 2013**

How I handle DOAC in my clinical practice

- Strategies to minimize the risk of bleeding
- Review the patients risk factors; age, weight, renal function
- Prescribe the dose of DOAC that is recommended
- Have a strategy for discontinue DOAC before surgery and how to resume DOAC after surgery
- Local guidelines / Education!!!!

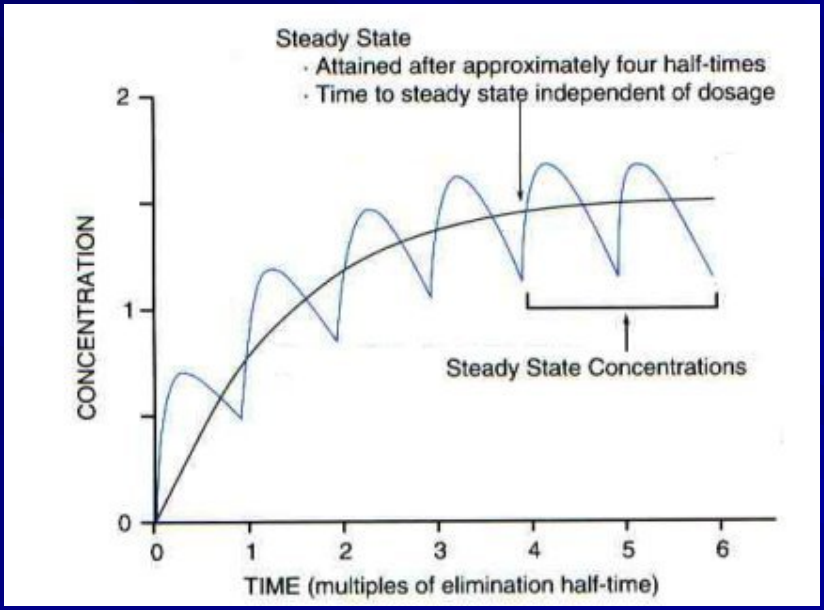
DOAC – broad terapeutic window



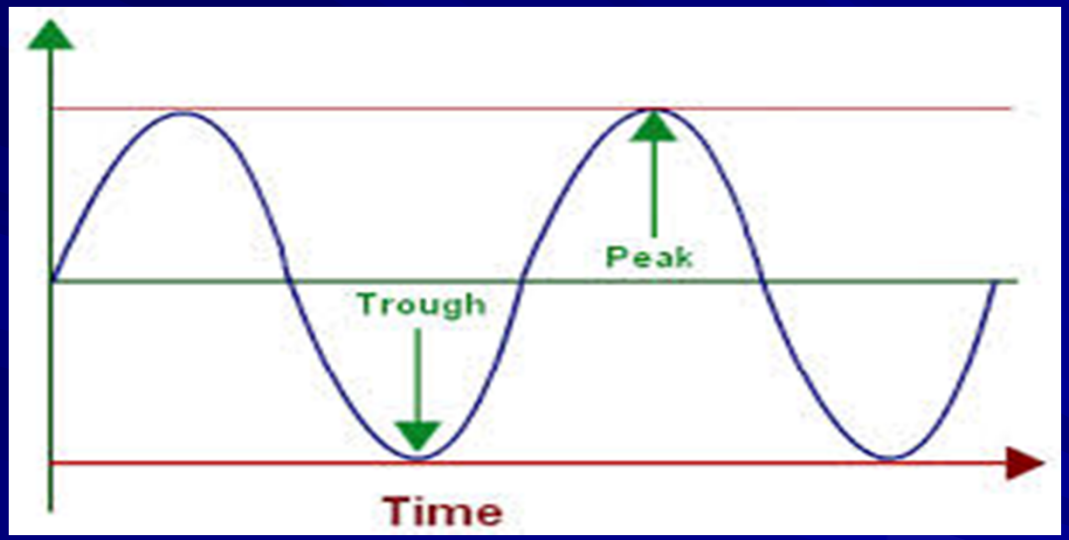
Dabigatran ~ 50-200 ng/ml
Rivaroxaban ~ 25-400 ng/ml
Apixaban ~ < 300 ng/ml ??

FDA

Steady State



Peak and Trough



Peak and Trough

Table 1 Steady-state plasma NOAC concentrations

Drug	Dose	Peak concentration (ng/mL)		Trough concentration (ng/mL)	
		Median	5th to 95th percentile	Median	5th to 95th percentile
Dabigatran [2]	150 mg BID	184	64–443[a]	90	31–225[a]
Rivaroxaban [3]	20 mg daily	270	189–419[b]	26	6–87[b]
Apixaban [4]	5 mg BID	171	91–321[b]	103	41–230[b]
Edoxaban [5]	60 mg daily	170	120–250[b,c]	22	10–40[b,c]

[a] Based on direct measurement of clinical samples

[b] Based on pharmacokinetic modeling

[c] Interquartile range

Cuker. J Thrombosis and Thrombolysis 2015

- Is kidney function important to measure and monitor for DOAC ??

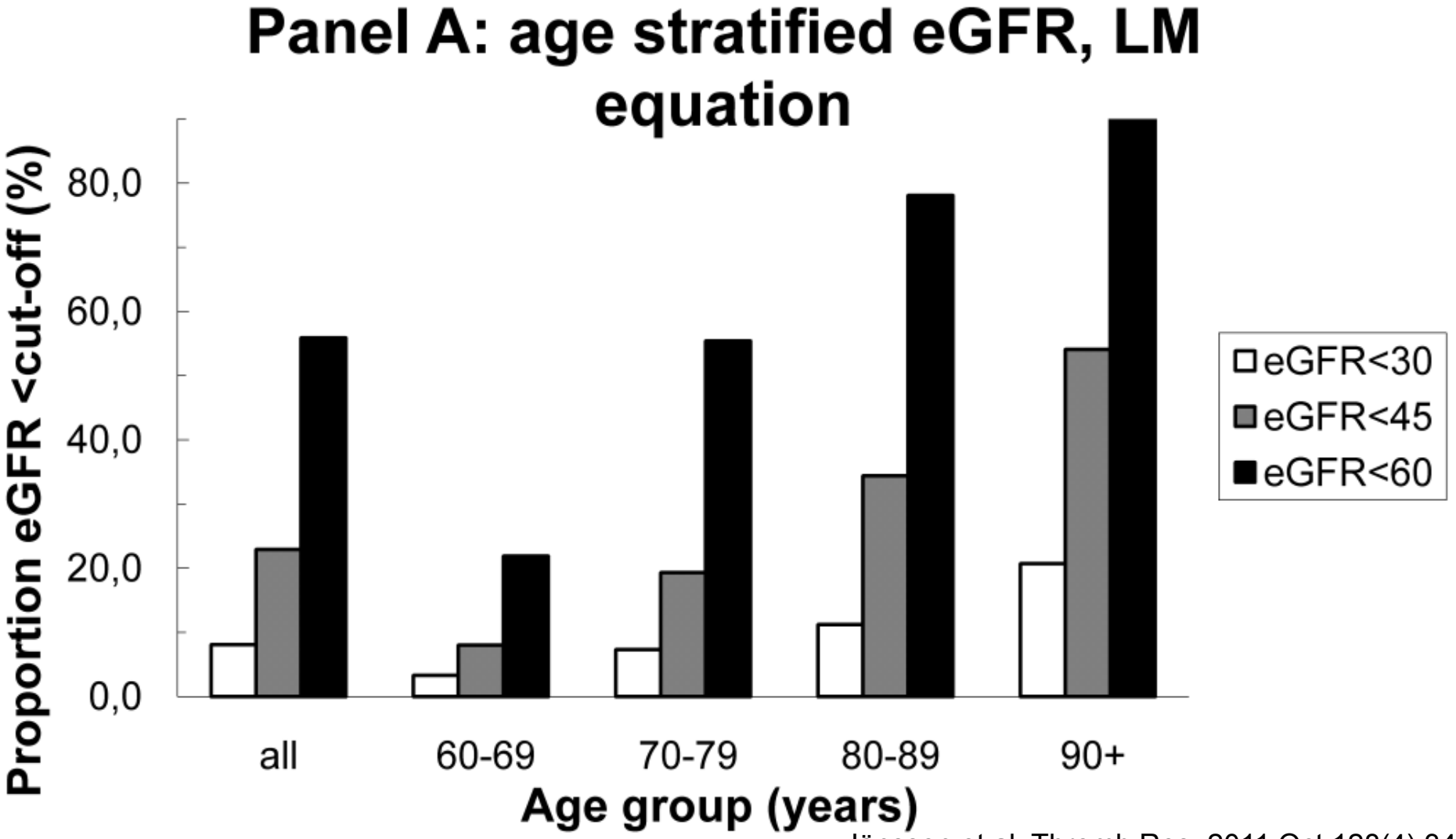
CKD
Chronic Kidney Disese

CKD*-stadium	Description	GFR* (mL/min/1,73 m²)
No CKD	Normal	≥90
1	Normal with i.e. proteinuria	≥90
2	Mild	60–89
3	Moderate	30–59
4	Severe	15–29
5	Kidney failure	<15 or dialysis
	ESRD*	

*GFR = glomerulär filtrationshastighet; Njurskada definieras som t ex mikroalbuminuri; CKD = chronic kidney disease; ESRD = end-stage renal disease (terminal njursvikt)

1. Koro CE, et al. Clin Ther 2009; 31: 2608–17. 2. National Kidney Foundation. Am J Kidney Dis 2002;39(suppl1):S1–S266.

Prevalence of kidney dysfunction in patients with AF



Jönsson et al. Thromb Res. 2011 Oct;128(4):34

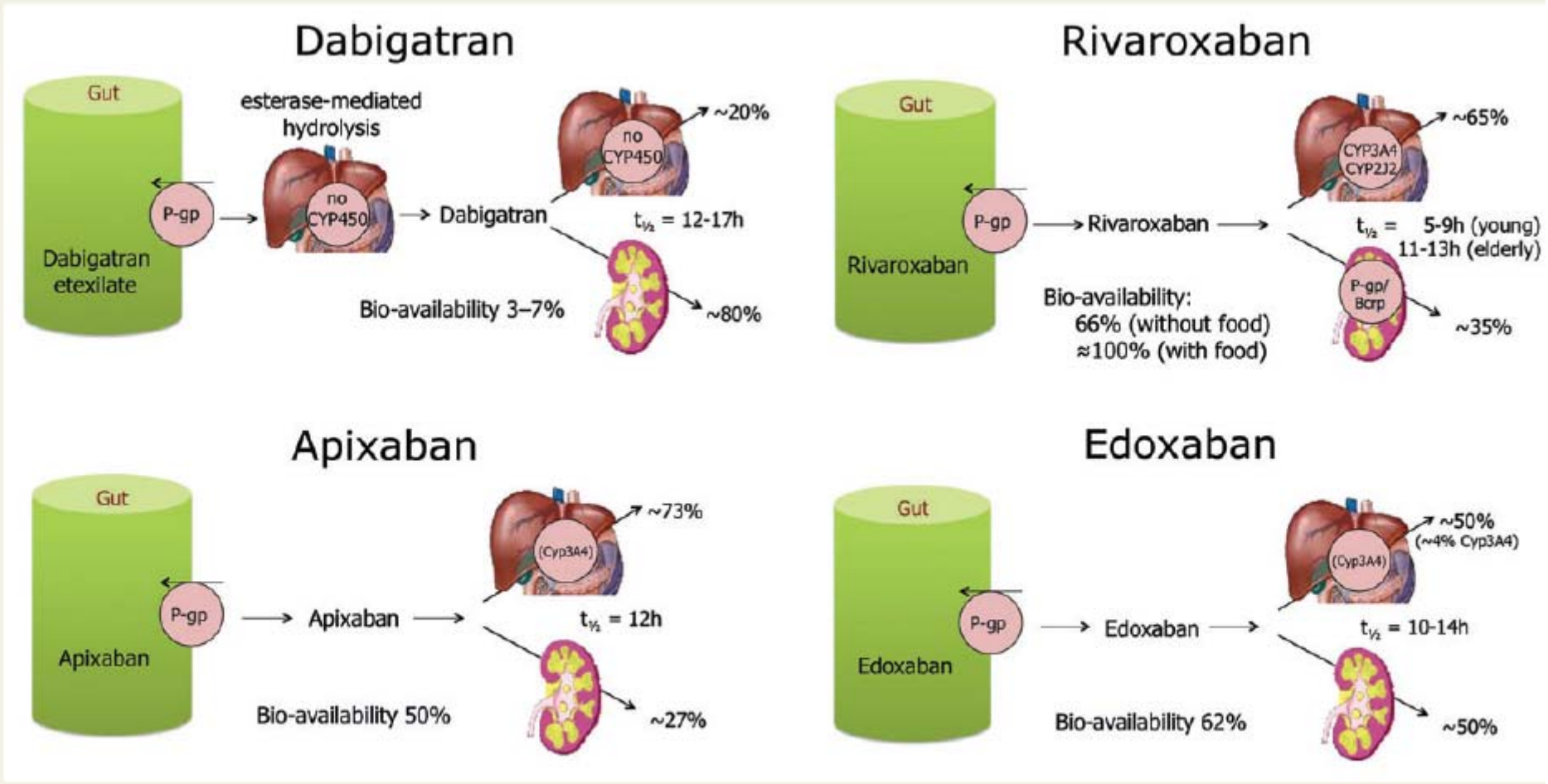


Figure 3 Absorption and metabolism of the different new anticoagulant drugs. There are interaction possibilities at the level of absorption c first transformation, and at the level of metabilization and excretion. See also *Table 5* for the size of the interactions based on these schemes.

Effect on DOAC plasma level.

Table 6 Effect on NOAC plasma levels (AUC) from drug–drug interactions and clinical factors, and recommendations towards NOAC dose adaptation

	via	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Antiarrhythmic drugs:					
Amiodarone	moderate P-gp competition	+12-60%[58]	No PK data[$]	+40%[63, 64, 244]	Minor effect[$] (use with caution if CrCl <50 ml/min)
Digoxin	P-gp competition	No effect[245]	No data yet	No effect	No effect[246, 247]
Diltiazem	P-gp competition and weak CYP3A4 inhibition	No effect[58]	+40%[60]	No data yet	Minor effect[#] (use with caution if CrCl 15-50 ml/min)
Dronedarone	P-gp competition and CYP3A4 inhibition	+70-100% (US: 2 x 75 mg if CrCl 30-50 ml/min)	No PK or PD data: caution	+85% (Reduce NOAC dose by 50%)	Moderate effect[#] but no PK or PD data: caution and try to avoid
Quinidine	P-gp competition	+53%[248 & SMPC]	No data yet	+77%[240, 249, 250] (No dose reduction required by label)	Extent of increase unknown
Verapamil	P-gp competition (and weak CYP3A4 inhibition)	+12-180%[58] (reduce NOAC dose and take simultaneously)	No PK data	+53% (SR)[64, 249] (No dose reduction required by label)	Minor effect[$$] (use with caution if CrCl 15-50 ml/min)

Effect on DOAC plasma level increase or decrease

Antibiotics					
Clarithromycin; Erythromycin	moderate P-gp competition and CYP3A4 inhibition	+15-20%	No data yet	+90%[64] (reduce NOAC dose by 50%)	+30-54%[42, 247]
Rifampicin***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[238]	avoid if possible: minus 35%, but with compensatory increase of active metabolites[243]	Up to minus 50%
Others					
Carbamazepine***; Phenobarbital***; Phenytoin***; St John's wort***	P-gp/ BCRP and CYP3A4/CYP2J 2 inducers	minus 66%[253]	minus 54%[SmPC]	minus 35%	Up to minus 50%
Other factors:					

One possible way to handle a clinical situation

Concomitant use of dronedarone with dabigatran in patients with atrial fibrillation in clinical practice ☆

Natalia Mochalina [a,*], Tord Juhlin [b], Pyotr G. Platonov [c], Peter J. Svensson [d], Mattias Wieloch [a]

[a] Department of Emergency Medicine, Skåne University Hospital, Malmö, S-20502, Sweden
[b] Department of Cardiology, Skåne University Hospital, Malmö, S-20502, Sweden
[c] Department of Cardiology, Lund University and Arrhythmia Clinic, Skåne University Hospital, Lund, S-22185, Sweden
[d] Department of Haematology and Coagulation Disorders, Skåne University Hospital, Malmö, S-20502, Sweden

ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form 7 March 2015
Accepted 10 March 2015
Available online 19 March 2015

Keywords:
Dabigatran
Dronedarone
Atrial fibrillation
Concomitant treatment
Plasma concentration

ABSTRACT

Introduction: Dronedarone is a strong P-glycoprotein inhibitor with a potential to increase bioavailability of dabigatran. We sought to measure and report plasma concentrations of dabigatran in patients with atrial fibrillation (AF) on concomitant dronedarone treatment.

Materials and methods: A cohort of 33 patients (mean age 64 years, 16 men) concomitantly treated with dabigatran at a dose of 110 mg twice a day (bid) and dronedarone at a dose of 400 mg bid at the discretion of the patient's cardiologist were followed prospectively.

Results: Median trough plasma concentration of dabigatran at one week and one month after the concomitant treatment start was 102.0 (range 8-251) ng/ml and 84 (range 27-302) ng/ml respectively. Median treatment length was 13 (range 1-21) months. There was one major bleeding event (2,8% per patient-year) and no thrombotic events during a total of 35.5 patient-years.

Conclusions: Median trough plasma concentration of dabigatran in our study was observed to be similar to median trough plasma concentration of dabigatran at a dose of 150 mg bid without concomitant dronedarone in earlier studies with low reported rate of bleeding and thrombosis. Since concomitant treatment offers potential benefits to patients with AF, larger future trials that might refute the current contraindication are warranted.

Trough plasma concentrations of dabigatran: concomitant treatment dabigatran 110 mg BID and dronedarone 400 mg BID

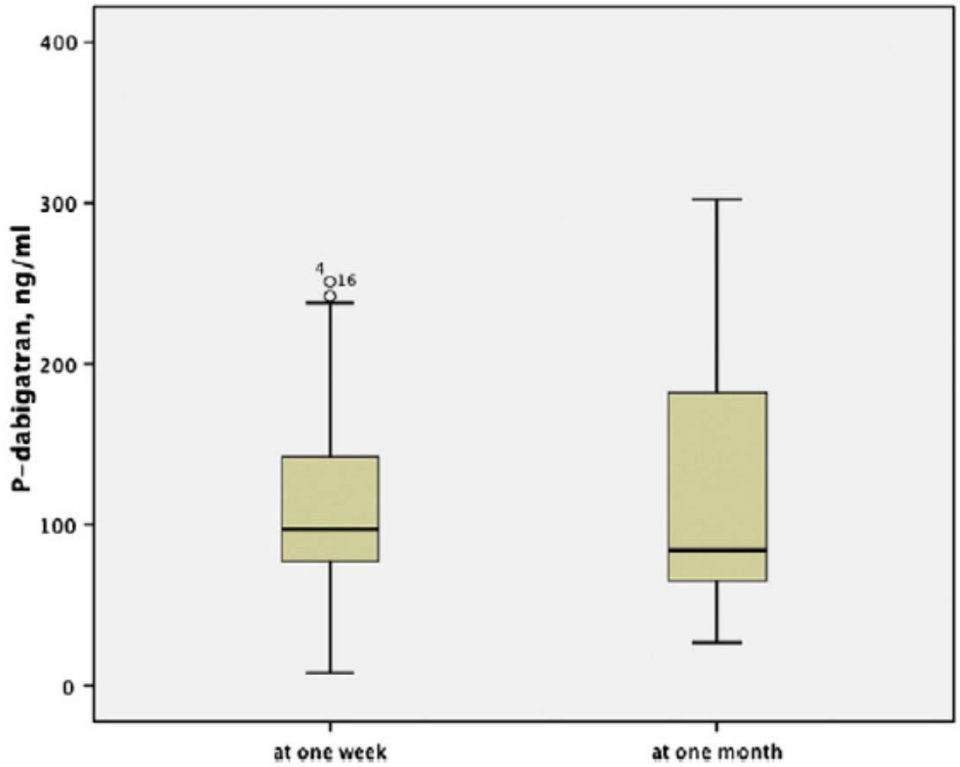


Fig. 1. Plasma dabigatran concentration one week and one month after the start of concomitant treatment.

Median trough concentration of dabigatran 150 mg bid without concomitant dronedarone was 93 ng/ml (10th to 90th percentile 39.8-215), in the RE-LY substudy

What is the size of the ”bridging” issue

- Peri-Procedual Bleeding and Thromboembolic Events with Dabigatran compared to Warfarin: Results from the RE-LY trail
- A total of 4591 (25%) patients underwent at least one invasive procedure during the study.
- Pacemaker/ICD 10%
- Dental procedure 10%
- Different Diagnostic procedures 10%
- Cataract removal 9.5%
- Colonoscopy 9%
- Hip or knee Replacement 6%

Circulation 2012; 126:343-48

Kidney function and half life of DOAC

eGFR (ml/min)	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
>80	12-17h	12h	10-14h	5-9h (yngre) 11-13h (äldre)
60-80	14h	14h	8.6h	8.5h
30-60	18h	17h	9.4h	9h
15-30	28h	17h	17h	9.5h
≤15	No data	No data	No data	N data

Patients undergoing a planned intervention or surgery

- Low risk 1 day
- High risk 2 days
- fX , eGFR 15-30, high risk 3 days
- fII, eGFR 15-30, högrisk 4 days

Douketis et al-J Thromb Haemostas
Online October 2015

Clinical situation were DOAC theoretically could be measured

- Bleeding
- Emergancy surgery
- Body weigt (low or high)
- Renal failure
- Trauma
- Trombolysis
- Antidot

Regular Article

Does the Russell Viper Venom time test provide a rapid estimation of the intensity of oral anticoagulation? A cohort study

Jonathan Douxfils [a,*], Bernard Chatelain [b], Paul Hjemdahl [c], Bérangère Devalet [b], Anne-Laure Sennesael [b], Pierre Wallemacq [d], Yuko Rönquist-Nii [c], Anton Pohanka [c], Jean-Michel Dogné [a], François Mullier [a,b]

[a] Department of Pharmacy, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for LIfe Sciences (NARILIS), University of Namur, Belgium
[b] Haematology Laboratory, Namur Thrombosis and Hemostasis Center (NTHC), Namur Research Institute for LIfe Sciences (NARILIS), CHU Dinant Godinne UcL Namur, Université Catholique de Louvain, Belgium
[c] Department of Clinical Pharmacology, Karolinska University Hospital and Clinical Pharmacology Unit, Department of Medicine Solna, Karolinska Institutet, SE-171 76 Stockholm, Sweden.
[d] Laboratory of Clinical Chemistry, Saint-Luc University Hospital, Université catholique de Louvain, Brussels, Belgium

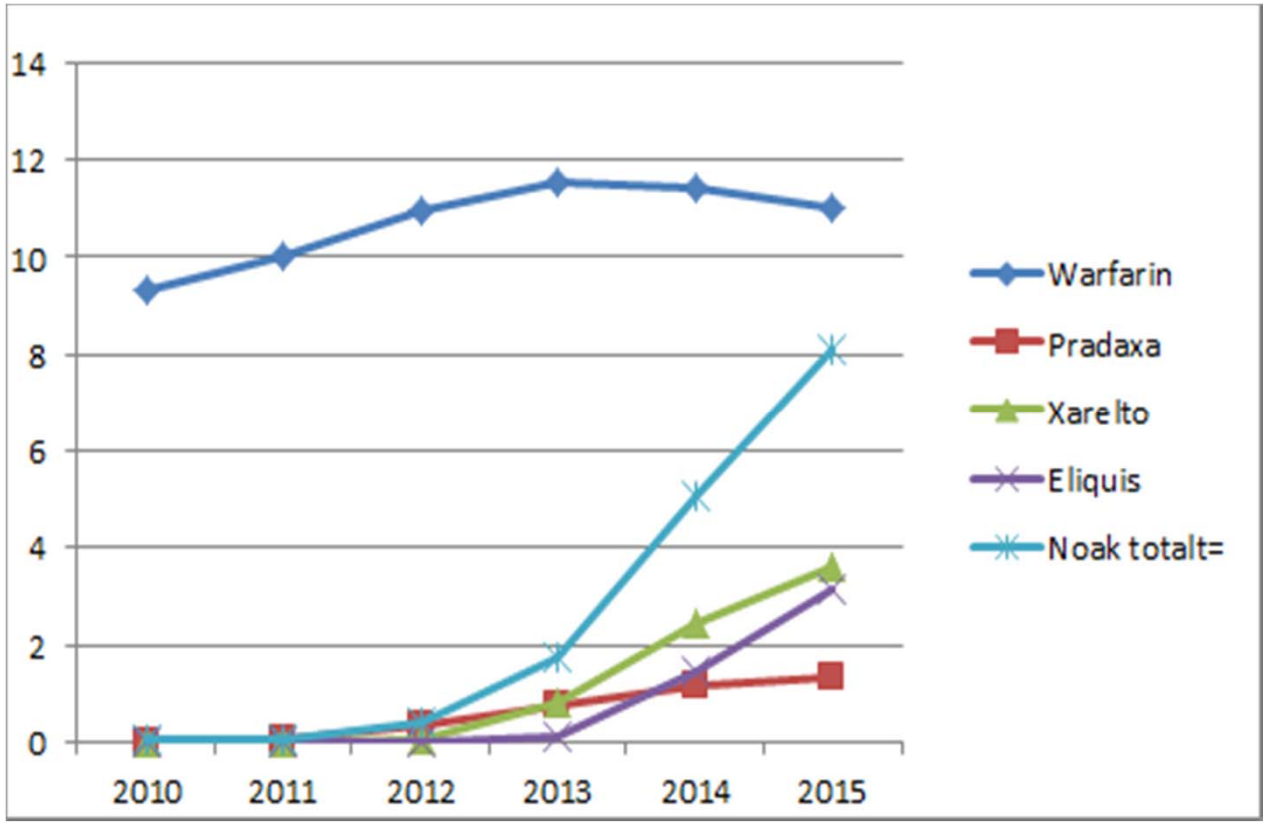
ARTICLE INFO

Article history:
Received 18 November 2014
Received in revised form 4 February 2015
Accepted 18 February 2015
Available online 26 February 2015

ABSTRACT

Background: Dilute Russell Viper Venom Time (DRVV-T) might be useful in urgent settings for screening patients on Non-VKA Oral Anticoagulants (NOACs).
Aim: To compare the accuracy of DRVV-T with gold standard assays for the assessment of pharmacodynamics of dabigatran, rivaroxaban and vitamin K antagonist (VKA) in plasma samples from patients.
Methods: Sixty rivaroxaban, 48 dabigatran and 50 VKA samples from patients were included. DRVV-T was performed in all groups using STA®-Staclot®DRVV-Screen and -Confirm. For NOACs, PT and aPTT were performed using different reagents while plasma drug concentrations were measured by liquid mass-spectrometry (LC-MS/MS). For VKA, INR was performed using RecombiPlasTin 2G®.
Results: For NOACs, correlations between calibrated STA®-Staclot®DRVV-Confirm and LC-MS/MS (rs = 0.88 and 0.97 for rivaroxaban and dabigatran, respectively) were higher than the ones obtained with STA®-Staclot®DRVV-Screen (rs = 0.87 and 0.91), PT (rs = 0.83 to 0.86) or aPTT (rs = 0.84 to 0.89). Bland Altman analyses showed that calibrated DRVV-T methods tend to overestimate plasma concentrations of NOACs. ROC curves revealed that cut-off to exclude supra-therapeutic levels at C_{trough} (i.e. 200 ng/mL) are different for dabigatran and rivaroxaban. Neither STA®-Staclot®DRVV-Screen nor –Confirm correlated sufficiently with the intensity of VKA therapy (rs = 0.35 and 0.52).
Conclusions: STA®-Staclot®DRVV-Confirm provides a rapid estimation of the intensity of anticoagulation with rivaroxaban or dabigatran without specific calibrators. At C_{trough}, thresholds for rivaroxaban and dabigatran can be used to identify supra-therapeutic plasma level. However, this test cannot differentiate the nature of the NOACs. The development of a point-of-care device optimising this method would be of particular interest in emergency situations.

Sweden warfarin vs DOAC



Conclusion and Callenges

- Older and more complex patients with more co-morbidity
- Kidney function
- Follow – up important (register)

- How to interpretate test results (compare to LMWH) i.e. dos adjustment
- Establish reference interval

Malmö Centre for Thrombosis and Haemostasis