LEIDS UNIVERSITAIR MEDISCH CENTRUM

Challenging patients on DOACs and need for monitoring

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Conflicts of interest

- Research grants from Boehringer Ingelheim, GSK and Actelion

- Consulting fees from BI, Pfizer-BMS, Bayer Healthcare, Daiichi-Sankyo

Bleedings in RE-LY trial

Table 1| **Major bleeds in RE-LY trial defined by different criteria***

	No (%) taking dabigatran		
	110 mg twice daily	150 mg twice daily	No (%) taking warfarin (dose adjusted)
Major bleeds	377	460	451
Hospital admission required	275 (73)	358 (78)	345 (77)
Transfusion ≥2 units	229 (61)	304 (66)	238 (53)
Gastrointestinal bleed	150 (40)	209 (45)	132 (29)
Symptomatic intracranial bleed	31 (8)	36 (8)	85 (19)
Surgical intervention required	35 (9)	56 (12)	62 (14)
Died	26 (7)	28 (6)	39 (9)

*Excerpted from EMA Rapporteur Day 80 critical assessment report[13]

Moore T BMJ 2014; 349:g4517

Efficacy endpoints in RE-LY trial

	D 110mg	D 150mg	warfarin	D 110mg vs. Warfarin		D 150mg vs. Warfarin	
	Annual rate	Annual rate	Annual rate	RR 95% CI	P*	RR 95% CI	P
Stroke or systemic Embolism	1.5 %	1.1 %	1.7 %	0.91 0.74-1.11	0.34	0.66 0.53-0.82	<0.001
Stroke	1.4 %	1.0 %	1.6 %	0.92 0.74-1.13	0.41	0.64 0.51-0.81	<0.001

Connolly S et al New Eng J Med 2009; 361:1139- 1151

Guide to indication and dosing

- Local protocol
- EHRA practical guide – **Heidbuchel et al Europace 2015;17: 1467-507**
- eMA website

Dose adjustments found in eMC

- Dabigatran: 150 mg BID; lower doses for patients at higher bleeding risk, e.g. age above 80 years, decreased renal clearance

- Rivaroxaban: 20 mg OD; lower doses for patients with decreased renal clearance

Dose adjustments found in eMC

- Edoxaban: 60 mg OD; reduced dose in patients with one or more of the following clinical factors:
- Renal impairment - clearance 15 - 50 mL/min
- Low body weight ≤ 60 kg

- Apixaban: 5 mg BID; reduced doses for patients with two or more of the following characteristics:
- age ≥ 80 years
- body weight ≤ 60 kg
- creatinine ≥ 133 µmol/L

Clinical situation where lab testing could be useful

- Bleeding patient or emergency surgery including trauma +
- Extreme bodyweight (very low or very high)
- Renal failure – acute situations with recent deterioration +
- Thrombembolic or bleeding complications +
- Prior to thrombolysis in patients with ischemic stroke +
- Lupus anticoagulant testing
- Antidotes – need for applying idarucizumab or andexanet and effect +

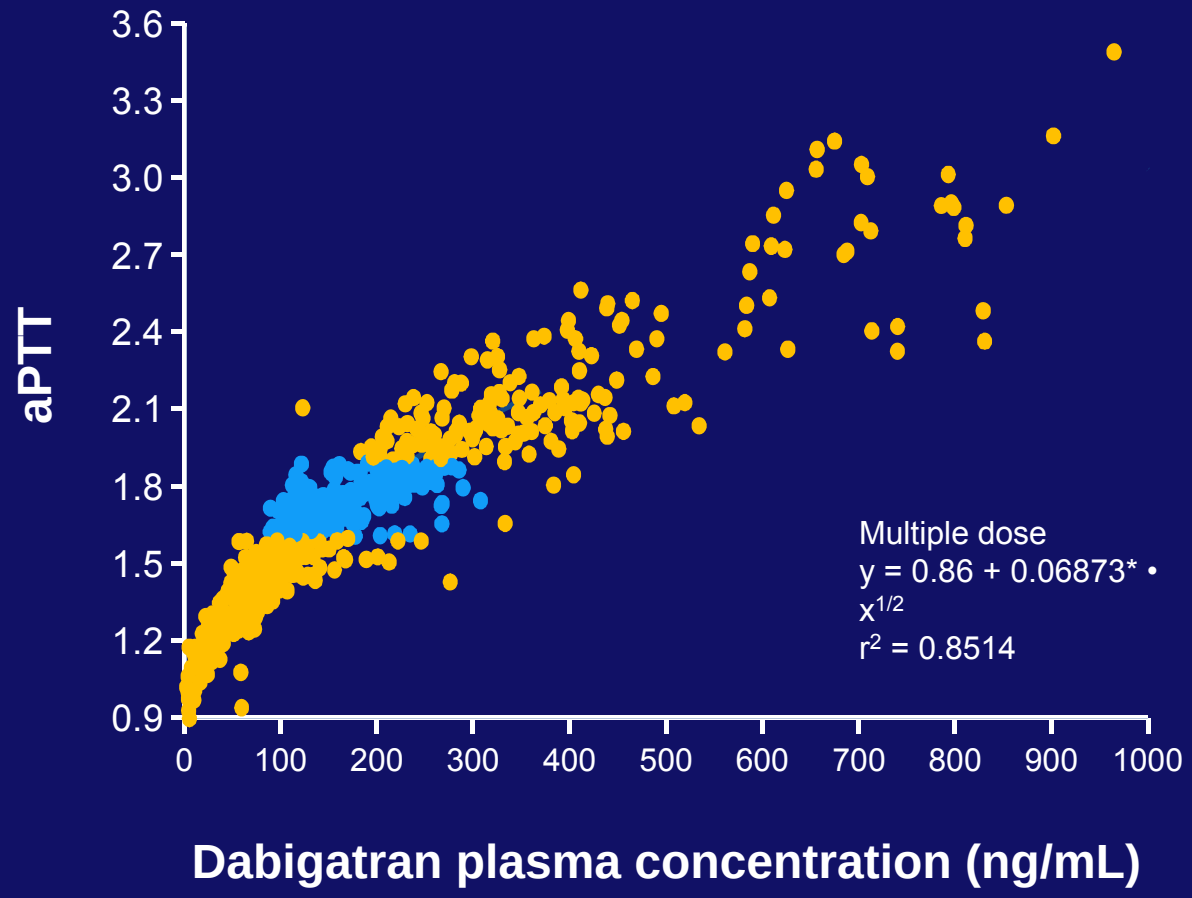
Laboratory tests

- No routine lab testing needed
- In acute patients screen tests (APTT, PT) mostly sufficient
- Blood for peak level 3 hours after last intake of DOAC

Screen tests

- Dabigatran:
  - APTT (completely normal - no relevant dabigatran anticoagulant activity)
  - If prolonged APTT, no quantitative idea
- Rivaroxaban, apixaban, edoxaban:
  - PT (completely normal – no relevant anti-Xa activity)
  - If prolonged PT, no quantitative idea

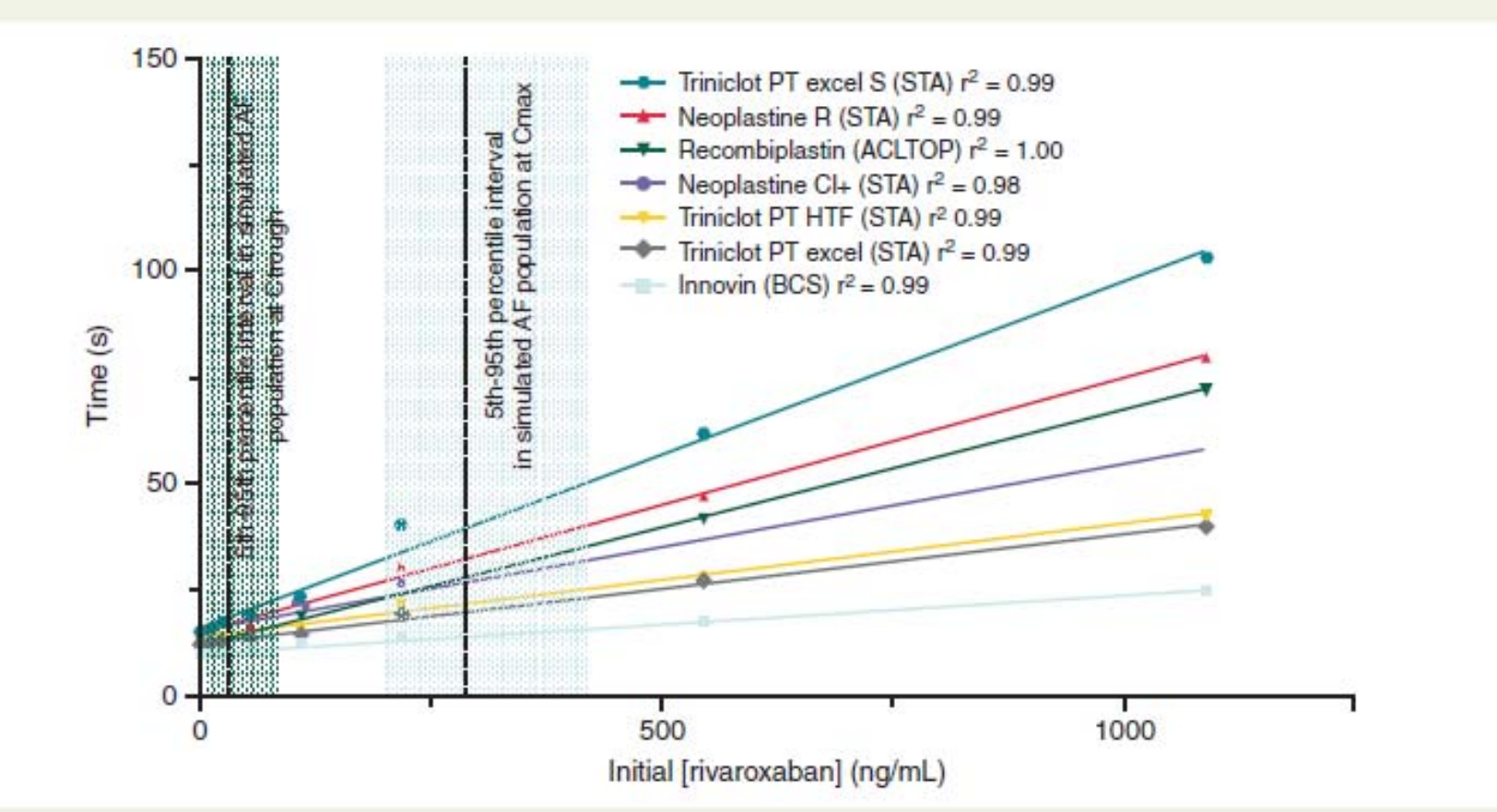
APTT and dabigatran



- A 2.5-fold prolongation in aPTT correlates with an excessive anticoagulant effect[1,2]
- Correlation is not linear, especially at higher concentrations[1,2]

1. Stangier J et al. Br J Clin Pharmacol 2007;64:292–303; **2**. Stangier J. Clin Pharmacokinet 2008;47:285–95

Sensitivity PT for rivaroxaban



Specific tests

- Dabigatran
  - direct thrombin inhibitor test
- Rivaroxaban, apixaban, edoxaban
  - direct Xa inhibitor test
- Good quantitative information
  - No relevant reference values
  - availability 24/7 is a problem

Bleeding patient

- Patient 68 years old, non valvular AF
- Treatment with apixaban 5 mg BID
- Presents with hematemesis (‘vomiting blood)

Bleeding management in DOACs

Laboratory
-PT (aPTT for dabigatran) – dTT/anti Xa tests
-Hb, platelets, renal function

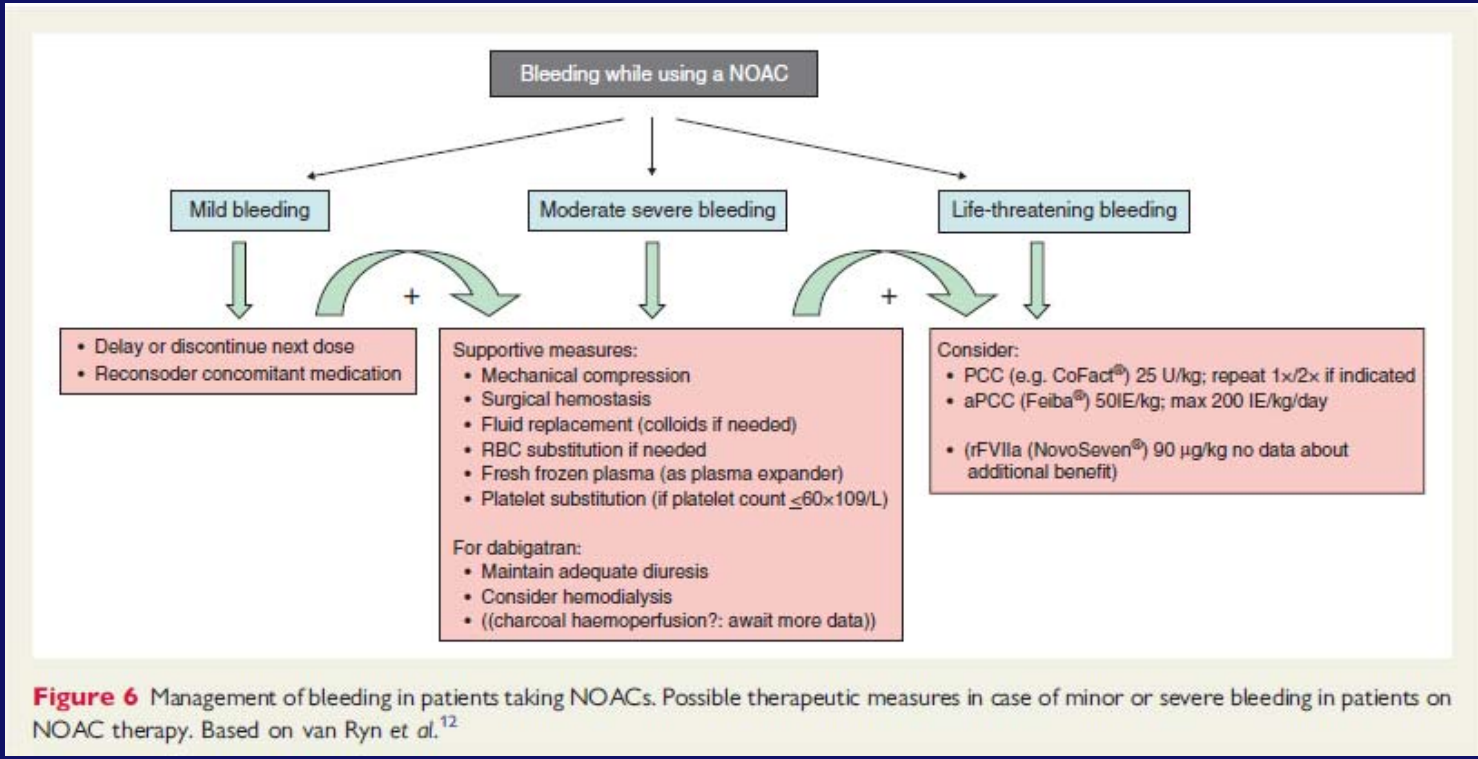


Figure 6 Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn *et al.*[12]

Heidbuchel Europace 2015;17:1467-507

Renal insufficiency

- A 66-year-old woman developed acute diarrhea and vomiting and was admitted 4 days later in shock (70/40 mm Hg)
- Rx: rivaroxaban (20 mg OD), erythromycin for urinary tract infection
- Oral mucosal bleeding noted on intubation
- Laboratory tests: PT 34 sec, creat. clearance 20 ml/min and signs of liver impairment, anti-Xa level: 420 ng/ml
- Patient recovered upon i.v. fluid support, PCC and antibiotic treatment

Quote from other speaker (H ten Cate)

- "Here, the lessons from VKA therapy should warn us that any form of comorbidity may have serious consequences for drug intake, absorption and metabolism, in general, certainly in the elderly."

Ten Cate Thromb J 2013: 11: 8

Patient with ischemic stroke

- Patient 78 years old with non valvular atrial fibrillation presents with ischemic stroke - Rx: Edoxaban 60 mg OD

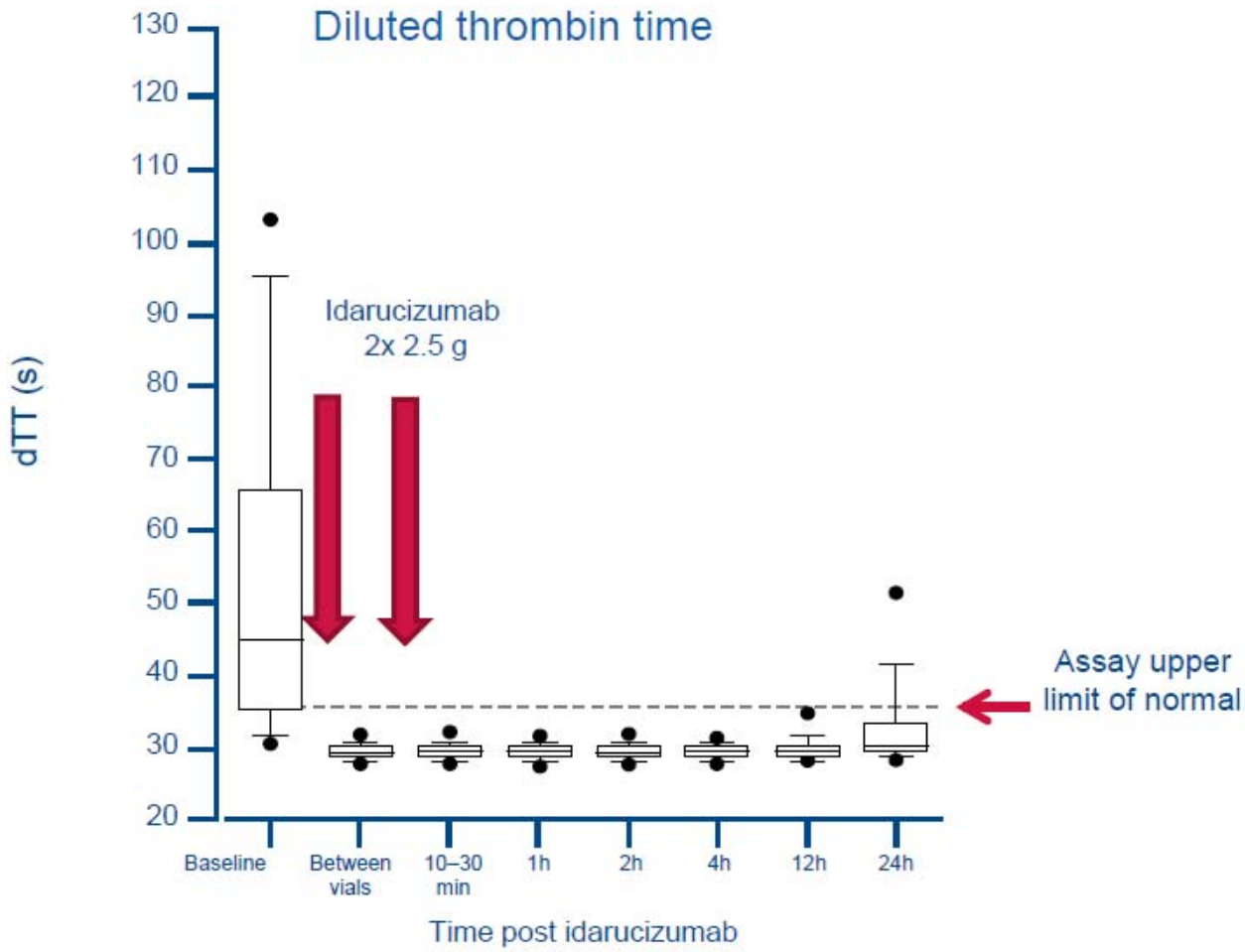
- Can we give thrombolytic treatment and perform thrombectomy?

- When last dose of edoxaban taken?
- Perform quick lab tests
- APTT, if sensitive, is useful
- Not formally studied but already practice

Around applying (specific) antidotes

- Idarucizumab and andexanet are specific antidotes for dabigatran and anti-Xa anticoagulant activity
- Both drugs are being evaluated in: life threatening bleeding or urgent surgery with high bleeding risk
- Lab testing may be useful to indicate, evaluate and titrate use of antidote

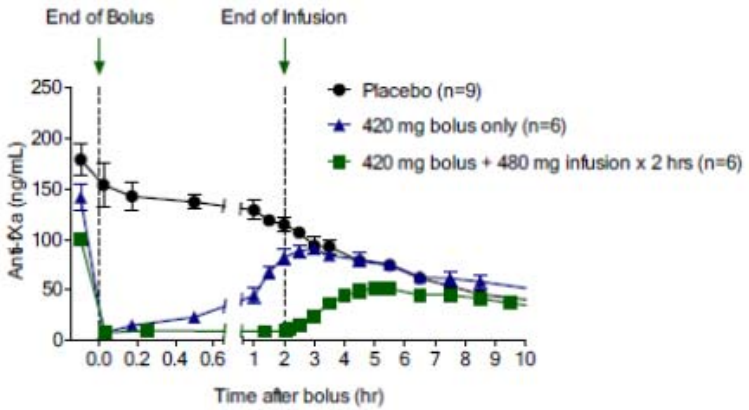
RESULTS: Primary endpoint in Group A by dTT
Reversal of dabigatran-anticoagulation with idarucizumab



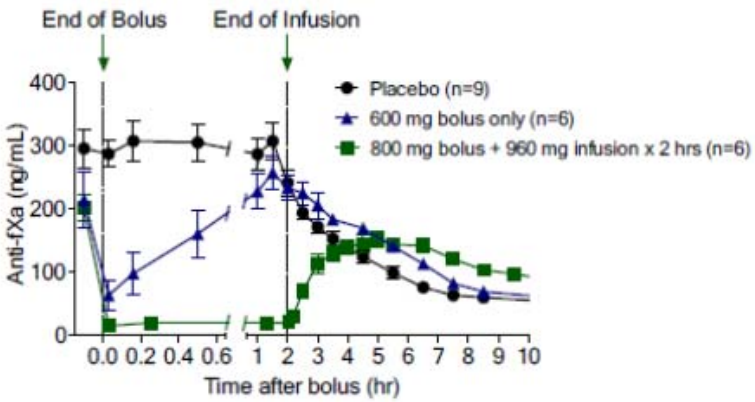
Pollack C et al, New Engl J Med 2015; 373: 511-520

Effects of andexanet alpha on Xa blockers

Apixaban Anti-fXa

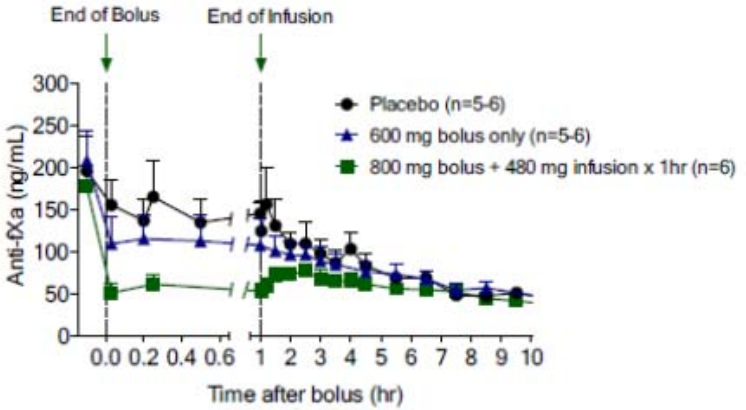


Rivaroxaban Anti-fXa



- Fast reaction
  - 2min post-bolus
- Dose-dependent inhibition
- Staying effect (infusion)

Edoxaban Anti-fXa



Thoughts on routine monitoring

- **Within patient variability in drug levels (with dabigatran) is large: In a study (Chan N et al. JTH 2015) patients had dabigatran levels in the upper or lower quartiles at 1 month, but levels in the middle quartiles on a second determination**
- **If the level is too high or too low, what do we do about dosing if there are limited dose formulations?**
- **We do not know what target levels should be**
- **We have no evidence that dose adjustment based on drug level determination improves clinical outcomes compared with unmonitored fixed dosing**

Conclusions

- Clear guidelines for indications and dosing of DOACs
- No large dose regimens available
- Lab testing is useful in challenging patients on DOACs