MINISTERIO DE SANIDAD, POLÍTICA SOCIAL E IGUALDAD

agencia española de medicamentos y productos sanitarios

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Session 2: What can we do now and what are the gaps in our knowledge?:

The direct factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)

Workshop on the role of PK and PD measurements in the use of direct oral anticoagulants (DOAC)
23 November 2015, European Medicines Agency, 30 Churchill Place, Canary Wharf, London E14 5EU

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This presentation might not be the view of the EMA-CHMP-CVSWP or AEMPS.

The ideas expressed here represent my personal view and do not bind the organisations mentioned above or any other party.

Public declaration of interests

- **Organisation/Company: Spanish Agency of Medicines and Medical Devices, Spain**
- Do hereby declare on my honour that, to the best of my knowledge, the only direct or indirect interests I have in the pharmaceutical industry are those listed below:

– Employment:	No interest declared
– Consultancy:	No interest declared
– Strategic advisory role:	No interest declared
– Financial interests:	No interest declared
– Principal investigator:	No interest declared
– Investigator:	No Interest declared
– Grant/Funding to organisation/institution:	No interest declared
– Close family member interest:	No interest declared
– Any other interests or facts:	No any other interests or facts.

DIRECT ORAL FACTOR Xa INHIBITORS

PHARMACOLOGY

Agent	Rivaroxaban	Apixaban	Edoxaban
Source	Synthetic	Synthetic	Synthetic
Molecular weight (Da)	436	460	548
Target	FXa	FXa	FXa
Type of inhibition	Direct	Direct	Direct
Prodrug	No	No	No
Bioavailability (%)	80–100	50	62
Tmax	2–4 h	3–4 h	1.5 h
Protein binding (%)	92–95	87	55
Half-life	5–13 h	12 h	6–11 h
Metabolism	CYP3A4 > CYP2J2	CYP3A4/5 > CYP21A2, SC8, 2C9/19, 2J2	Hydrolysis >CYP3A4/5
Renal excretion (% of administered dose)	66 (33 unchanged)	27 (22 unchanged)	35 (24 unchanged)
Renal excretion (% of absorbed dose)	73 (37 unchanged)	54 (44 unchanged)	56 (39 unchanged)
Biliary–fecal excretion (% of administered dose)	34	56	62
Specific antidote	None	None	None
Procoagulant agents used for reversal[1]	PCC, activated PCC, rFVIIa	PCC, activated PCC, rFVIIa	PCC, activated PCC, rFVIIa
Monitoring test	Not required routinely. Anti-Xa assay	Not required routinely. Anti-Xa assay	NA Anti-Xa assay
Year of first marketing authorization (region)	2008 (EU)	2011 (EU)	2011 (Japan)

DOAC, direct oral anticoagulant; EU, European Union; h, hours; FXa, activated factor X; NA, data not available; PCC, prothrombin complex con-:entrate; rVIIa, activated factor VII; Tmax, time to maximum concentration.
[1]Limited evidence, use only in case of life-threatening bleeding

Gómez-Outes, et al. Eur J Haematol. 2015;95:389-404.

INDICATIONS, POSOLOGY

Characteristic	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®, Savaysa®)
Prevention of stroke and systemic embolism in patients with NVAF and at least one additional risk factor	Rivaroxaban 20 mg OD (**15 mg OD in patients with CrCl 15-50 ml/min**)	Apixaban 5 mg BID	Edoxaban 60 mg OD (**30 mg in patients with a CrCl 30-50 ml/min, a body weight ≤ 60 kg, or P-gp inhibitors**)
Treatment of VTE			
Initial therapy	5 mg BID for 21 days (3 weeks)	10 mg BID for 7 days (1 week)	LMWH or fondaparinux for at least 5 days.
Long-term therapy (up to 3-6 months)	Rivaroxaban 20 mg OD (**15 mg OD if CrCl 15-50 ml/min and high risk of bleeding**) from day 22 onwards.	Apixaban 5 mg BID from day 8 onwards.	Edoxaban 60 mg OD [**30 mg if CrCl 30-50 ml/min, body weight ≤ 60 kg, or concomitant potent P-gp inhibitors**)§
Extended therapy†	Same posology as long-term therapy	**Dose reduction to 2.5 mg BID** after 6 months of anticoagulation.	Same as long-term therapy but no clinical experience available > 12 m
Prophylaxis of VTE after TKR or THR	10 mg OD for 2 weeks (TKR) or 5 weeks (THR)	2.5 mg BID for 2 weeks (TKR) or 5 weeks (THR)	Not approved in the EU for this indication*
Secondary prevention after ACS with elevated cardiac biomarkers	Rivaroxaban 2.5 mg BID	Not approved for this indication	Not approved for this indication

ACS = acute coronary syndrome; BID = twice-daily; CrCl = creatinine clearance; EU = European Union; NVAF = non-valvular atrial fibrillation; P-gp = P-glycoprotein; THR = total hip replacement; TKR = total knee replacement; VKA = vitamin K antagonists; VTE = venous thromboembolism,

*Indication approved in Japan only [Edoxaban 30 mg (15 mg if CrCl 30-50 ml/min)].

†In selected patients at high risk of recurrence, according to clinical practice guidelines.

‡ Maximum treatment duration tested in Hokusai-VTE was 12 months. No experience beyond this period is available.

§Potent P-gp inhibitors: cyclosporine, dronedarone, erythromycin, ketoconazol.

Gómez-Outes, et al. Eur J Haematol. 2015;95:389-404.

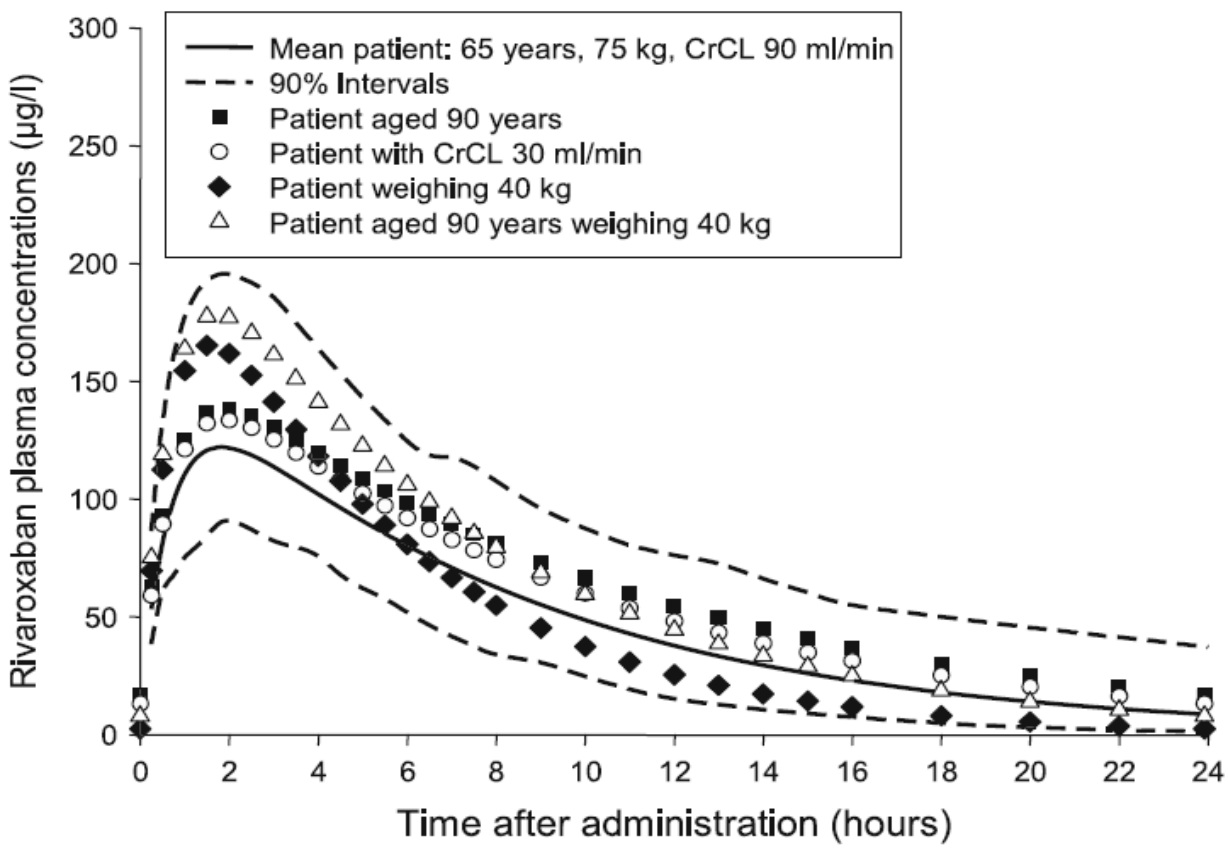
Similarities and differences

- Small synthetic compounds.
- Specific inhibitors of Fxa.
- Relatively short half-life (<15 hours).
- Renal excretion >50% (but less than that of dabigatran).
- Drug-drug interactions with potent inhibitors/inducers of P-gp and CYP3A4.
- Different clinical developments using different posologies (twice-daily vs. Once-daily) and adjustments (body-weight; CrCl; PgP inh/ind, etc.).

Exposure: patients undergoing surgery

Simulations of rivaroxaban plasma concentrations after a 10-mg once-daily dose in patients who have undergone hip replacement surgery.

Patients who are elderly, have renal impairment, have low body weight, or are elderly with low body weight, have predicted average plasma concentrations that fall within the boundaries for the overall population (90%CI).

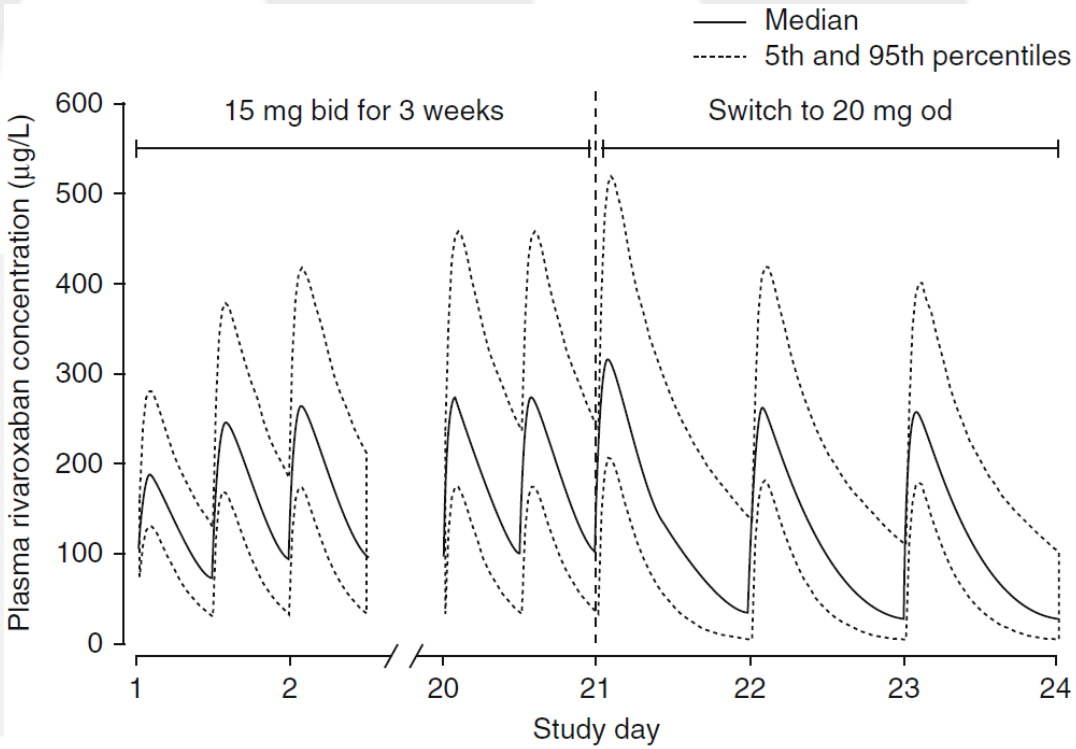


Mueck et al. Thromb Haemost. 2008;100:453–61.

Exposure: Patients with acute VTE

Simulated VTE treatment dosing regimen of rivaroxaban 15 mg bid for 3 weeks, followed by 20 mg od.

Rivaroxaban exposure remains consistent during the transition, indicating that antithrombotic activity should be maintained. bid twice daily, od once daily

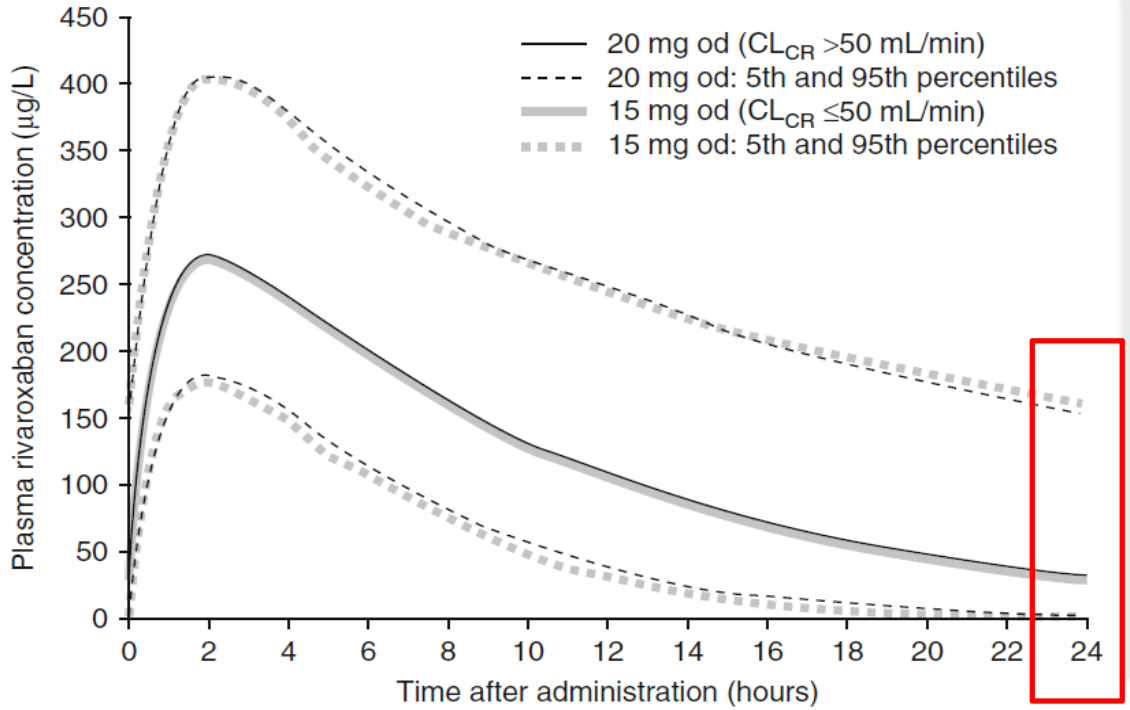


Mueck et al. Clin Pharmacokinet. 2011;50:675–86.

Exposure: Patients with Atrial Fibrillation

Simulated rivaroxaban plasma concentration–time profiles for a virtual population of patients with atrial fibrillation.

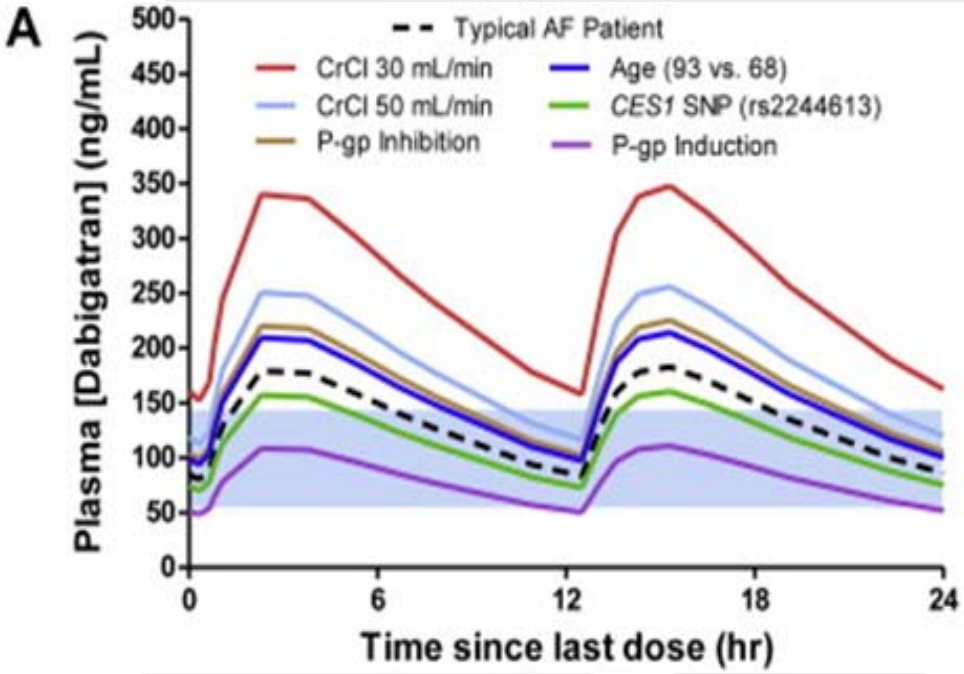
For patients with mildly impaired or normal CrCl (>50 mL/min), exposure is the same with a 20 mg od dose as for patients with moderate renal impairment (≤50 mL/min) with a 15 mg od dose.
CrCl creatinine clearance, od once daily



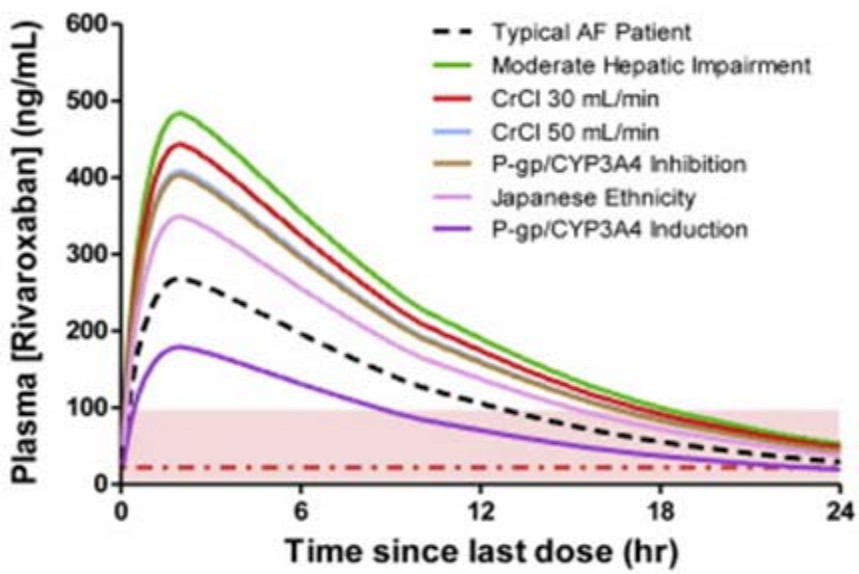
Mueck et al. Clin Pharmacokinet. 2011;50:675–86.

VARIABILITY IN CONCENTRATIONS DEPENDING ON CLINICAL FACTORS AND DOSING INTERVALS

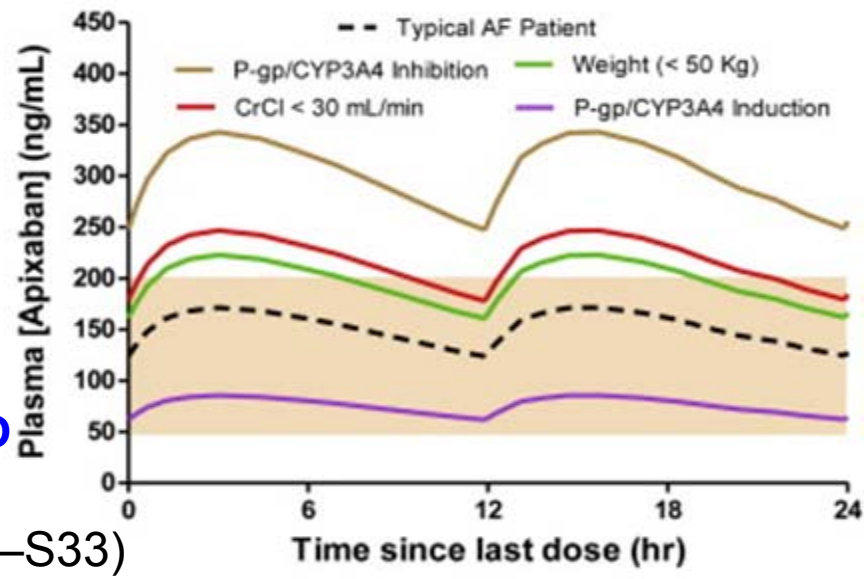
DABIGATRAN BID



RIVAROXABAN OD



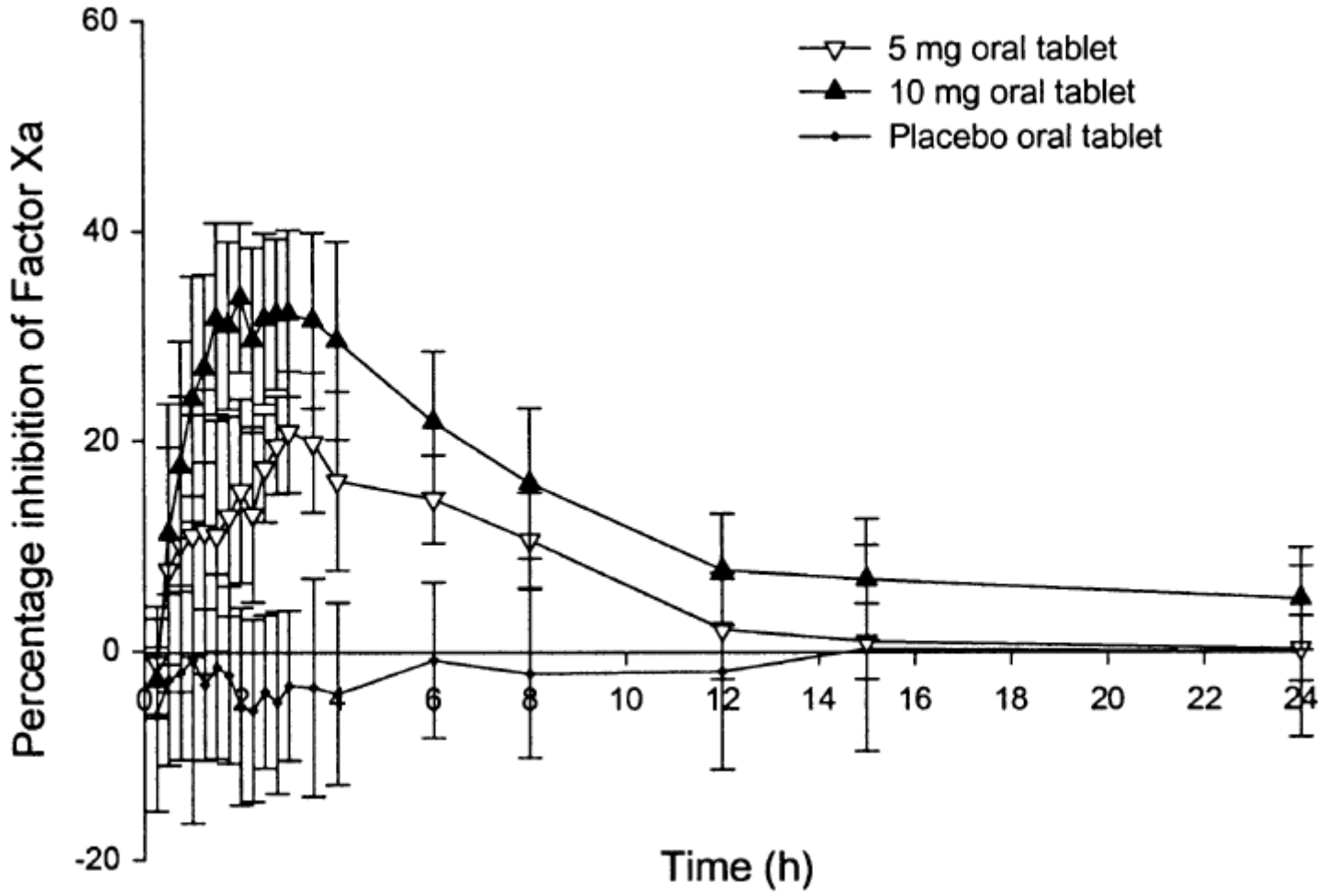
APIXABAN BID



Gong & Kim. Can J Cardiol. 2013;29(Suppl:S24–S33)

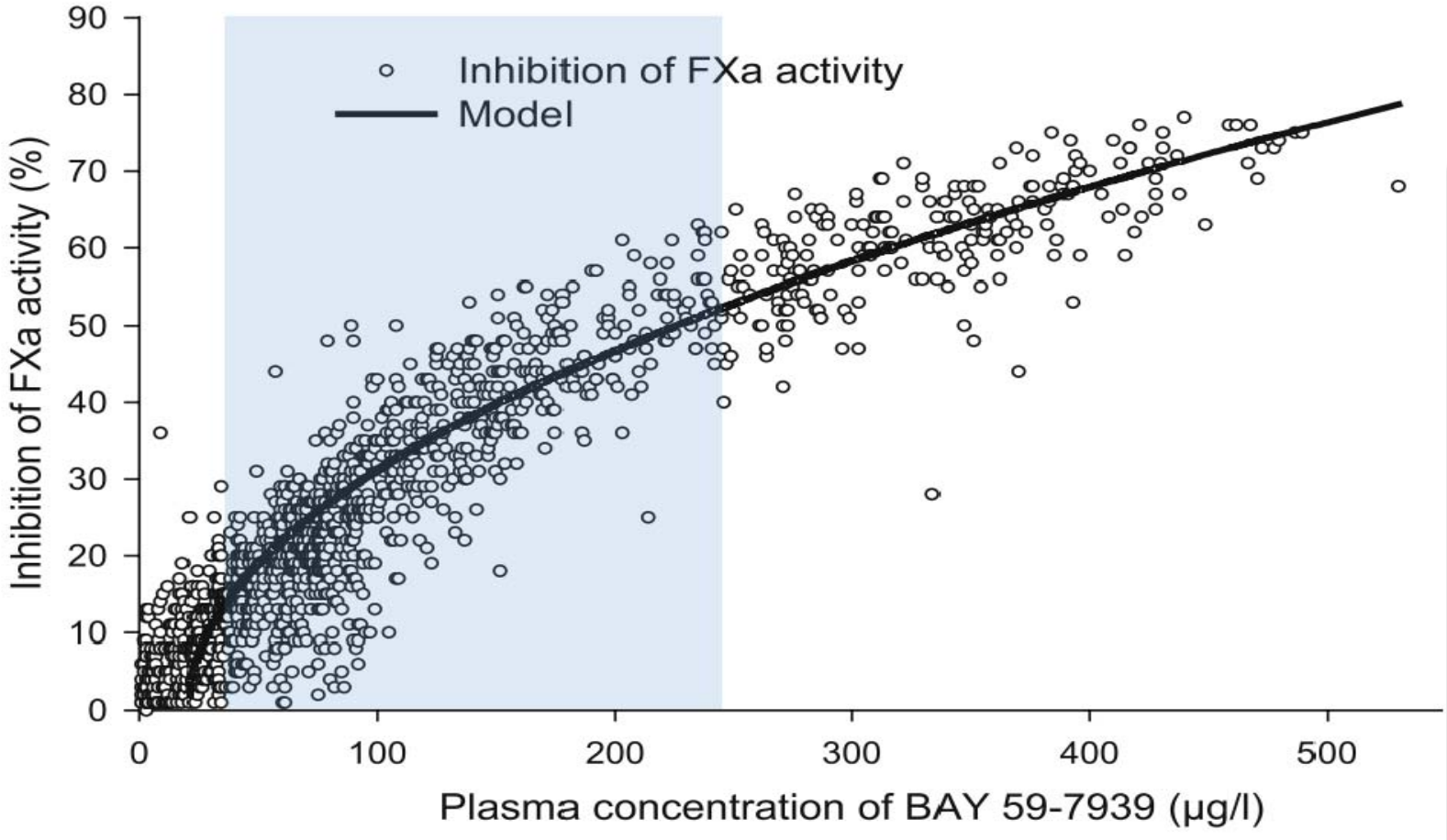
Biomarkers

Median percentage change from baseline in Factor Xa inhibition after administration of rivaroxaban.



Mueck et al. Thromb Haemost. 2008;100:453–61.

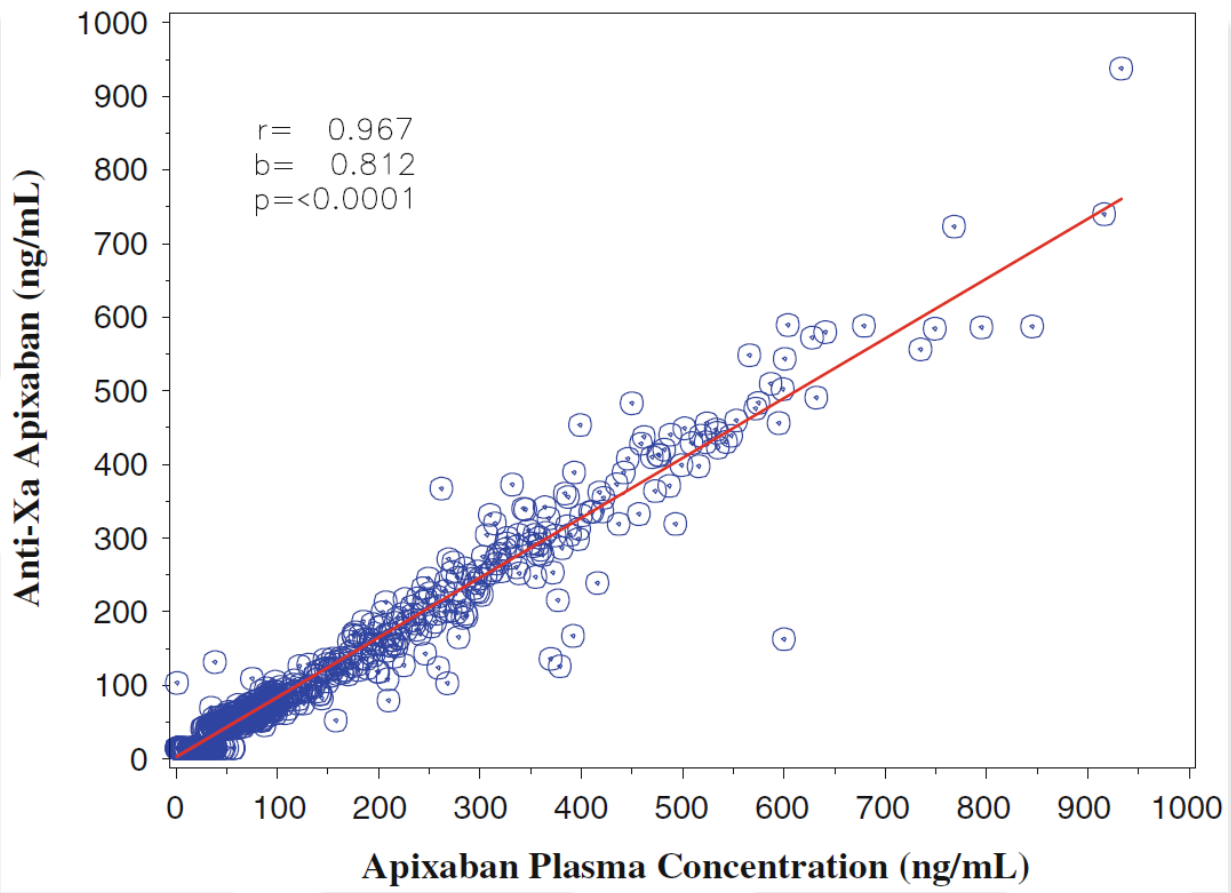
CORRELATION BETWEEN RIVAROXABAN CONCENTRATION AND ANTI-Xa ACTIVITY



"The relationship between rivaroxaban concentration and factor Xa activity was best described by an Emax model" (Xarelto SmPC).

Kubitza, et al. Eur J Clin Pharmacol. 2005;61:873-80

CORRELATION BETWEEN APIXABAN CONCENTRATION AND ANTI-Xa ACTIVITY



"Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations" (Eliquis SmPC).

Becker et al. J Thromb Thrombolysis. 2011;32:183-7.

CORRELATION BETWEEN EDOXABAN CONCENTRATION AND ANTI-Xa ACTIVITY

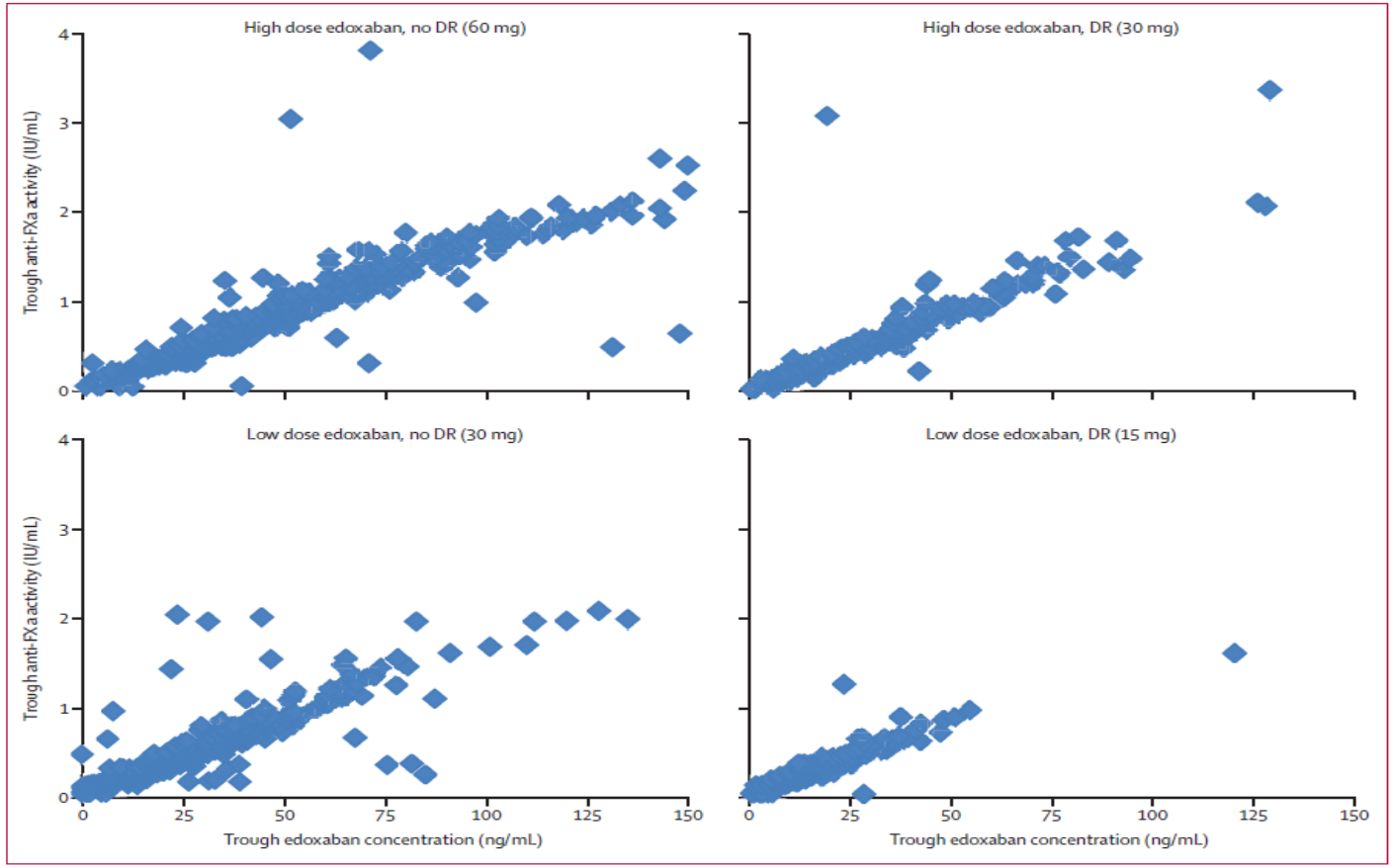


Figure 1: **Correlation between edoxaban concentration and anti-FXa Activity**
Trough edoxaban plasma concentration and anti-FXa activity at 1 month after randomisation. Spearman correlation: overall, *r*=0·96, 95% CI 0·95–0·96; low-dose edoxaban, dose reduced, *r*=0·92, 95% CI 0·89–0·94; low-dose edoxaban, no dose reduction, *r*=0·93, 95% CI 0·92–0·94; higher-dose edoxaban, dose reduced, *r*=0·95, 95% CI 0·93–0·96; higher-dose edoxaban, no dose reduction, *r*=0·97, 95% CI 0·96–0·97; p<0·0001 for all. IU=international units. DR=dose reduction.

"There is a linear correlation between edoxaban plasma concentration and anti-FXa activity regardless of renal function" (Lixiana SmPC).

Ruff et al. Lancet 2015;385:2288-95.

APIXABAN CONCENTRATIONS AND ANTI-Xa ACTIVITY BY INDICATION

Table 3: Predicted Apixaban Steady-state Exposure and Anti-Xa Activity				
	Apix. Cmax (ng/mL)	**Apix. Cmin (ng/mL)**	**Apix. Anti-Xa Activity Max (IU/mL)**	**Apix. Anti-Xa Activity Min (IU/mL)**
	Median [5th, 95th Percentile]			
Prevention of VTE: elective hip or knee replacement surgery				
2.5 mg bid	77 [41, 146]	51 [23, 109]	1.3 [0.67, 2.4]	0.84 [0.37, 1.8]
Prevention of stroke and systemic embolism: NVAF				
2.5 mg bid*	123 [69, 221]	79 [34, 162]	1.8 [1.0, 3.3]	1.2 [0.51, 2.4]
5 mg bid	171 [91, 321]	103 [41, 230]	2.6 [1.4, 4.8]	1.5 [0.61, 3.4]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTEt)				
2.5 mg bid	67 [30, 153]	32 [11, 90]	1.0 [0.46, 2.5]	0.49 [0.17, 1.4]
5 mg bid	132 [59, 302]	63 [22, 177]	2.1 [0.91, 5.2]	1.0 [0.33, 2.9]
10 mg bid	251 [111, 572]	120 [41, 335]	4.2 [1.8, 10.8]	1.9 [0.64, 5.8]

* Dose adjusted population based on 2 of 3 dose reduction criteria in the ARISTOTLE study.

Eliquis (apixaban). Summary of product characteristics (SmPC).

EDOXABAN ANTI-Xa ACTIVITY BY INDICATION AND CrCl

Table 12: Edoxaban Anti-FXa activity by creatinine clearance

Edoxaban Dose	CrCL (mL/min)	Edoxaban Anti-FXa activity post-dose (IU/mL)[1]	Edoxaban Anti-FXa activity pre-dose (IU/mL)[2]
	Median [2.5 – 97.5% range]		
Prevention of stroke and systemic embolism: NVAF			
30 mg QD	≥ 30 to ≤ 50	2.92 [0.33 – 5.88]	0.53 [0.11 – 2.06]
60 mg QD*	> 50 to ≤ 70	4.52 [0.38 – 7.64]	0.83 [0.16 – 2.61]
	> 70 to ≤ 90	4.12 [0.19 – 7.55]	0.68 [0.05 – 2.33]
	> 90 to ≤ 110	3.82 [0.36 – 7.39]	0.60 [0.14 – 3.57]
	> 110 to ≤ 130	3.16 [0.28 – 6.71]	0.41 [0.15 – 1.51]
	> 130	2.76 [0.12 – 6.10]	0.45 [0.00 – 3.10]
Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE)			
30 mg QD	≥ 30 to ≤ 50	2.21 [0.14 – 4.47]	0.22 [0.00 – 1.09]
60 mg QD*	> 50 to ≤ 70	3.42 [0.19 – 6.13]	0.34 [0.00 – 3.10]
	> 70 to ≤ 90	2.97 [0.24 – 5.82]	0.24 [0.00 – 1.77]
	> 90 to ≤ 110	2.82 [0.14 – 5.31]	0.20 [0.00 – 2.52]
	> 110 to ≤ 130	2.64 [0.13 – 5.57]	0.17 [0.00 – 1.86]
	> 130	2.39 [0.10 – 4.92]	0.13 [0.00 – 2.43]

*Dose reduction to 30 mg for low body weight ≤ 60 kg or specific concomitant P-glycoprotein (P-gp) inhibitors

[1] Post-dose is equivalent to C_{max} (post-dose samples were drawn 1 – 3 hours after edoxaban administration)

[2] Pre-dose is equivalent to C_{min}

Lixiana (edoxaban). Summary of product characteristics (SmPC).

CORRELATION BETWEEN DRUG CONCENTRATION AND CLINICAL OUTCOMES

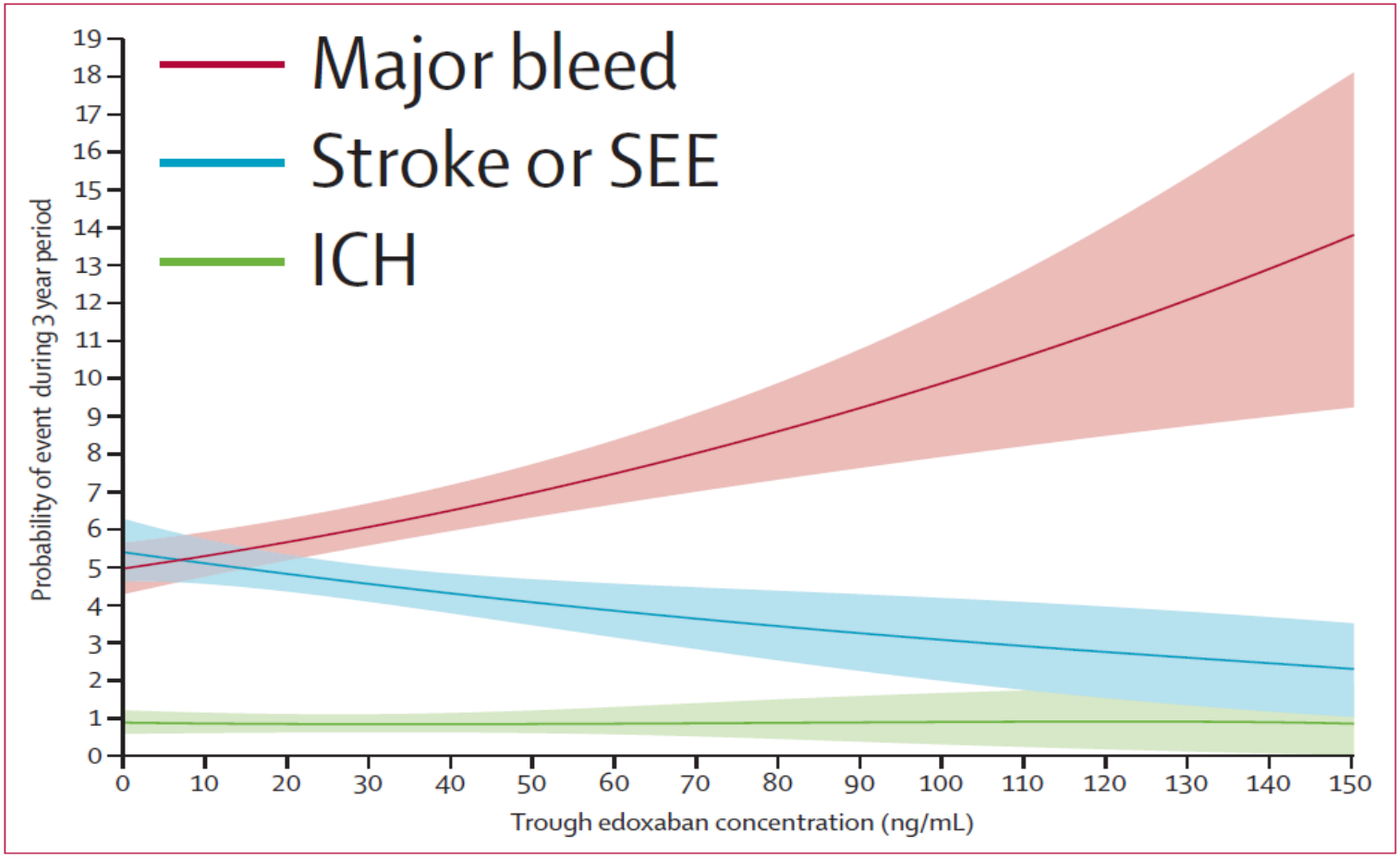


Figure 2: **Probability of clinical outcomes versus edoxaban concentration**
Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2·8 years). ICH=intracranial haemorrhage. SEE=systemic embolic event.

Ruff et al. Lancet 2015;385:2288-95.

Strengths and limitations of PK/PD analyses (1)

- **Good correlation between plasma drug levels and anti-Xa activity.**
- **Probably different PK/PD and efficacy/safety relationship (limited data):**
  - **Flat dose-response for thrombosis/embolism:** significant decrease in plasma levels (and anti-Xa activity) not associated to a significant increase in thromboembolism.
  - **Steeper dose-response for bleeding:** increase in exposure associated to exponential increase in bleeding.
  - **Main concerns:**
    - Increased risk of bleeding at increased exposure.
    - Lack of efficacy is also of concern, particularly in patients with high CrCl.

Strengths and limitations of PK/PD analyses (2)

- **Internal validity:**
  - Population level, not measured in all patients.
  - Measurements at single time-points.
  - Correlated with outcomes that occurred throughout the duration of the trials.
  - Does not incorporate:
    - ✓ Changes in concentration/activity that may occur overtime.
    - ✓ Measurements at the time of the event (thrombosis/bleeding)

Uncertainties

- What PK/PD parameter correlates best with efficacy/safety?:
  - **Drug levels:** average concentration, peak, trough (pre-dose).
  - **Anti-Xa:** peak, trough.
- Validation of the (chromogenic) assay kit to be used:
  - Neoplastin Plus®; STA - Liquid Anti-Xa kits; HemosIL RecombiPlasTin 2G; Rotachrom® Heparin chromogenic assay
- Even if we have the “best” PK/PD marker for monitoring drug activity and a validated assay, can we define a “therapeutic range”?:
  - Variability in anti-Xa activity depending on patients characteristics (e.g.: renal function) as well as by indication.
  - Different clinical situations may require different intensity of anticoagulation (e.g.: baseline risk of thrombosis, concomitant use of antiplatelet drugs, etc.).

Conclusion

- **Predictable anticoagulant effect**: “Fixed” doses (tailored according to clinical factors: renal function, weight, concomitant treatments). No need for routine monitoring, but
- **Measurement of anticoagulant activity or drug concentration** might be necessary:
  - To tailor the dose to help to optimise their relative risk and benefit in individual patients:
    - ✓ To protect vulnerable patients from excess drug concentrations and bleeding risk.
    - ✓ To protect individual patients from lack of efficacy (e.g.: combination of factors decreasing exposure: high CrCl, obesity, PgP/CYP3A4 inducers).
  - In emergency situations: bleeding (e.g.: to confirm “toxic” levels and guide therapy), need for urgent invasive procedures.
- **Challenges:** identification of additional data needed and how to reflect them on current labelling information.

Thanks for your attention

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