Science For A Better Life

Workshop: The role of pharmacokinetic and pharmacodynamic measurements in the use of direct oral anticoagulants

Industry Perspective: Bayer/Janssen

23 Nov 2015, Scott D. Berkowitz, MD

Rivaroxaban Clinical Development Concept

- Aim: to provide reliable anticoagulation without the routine need to monitor for dose adjustment because of a highly predictable PK PD response
- Doses and dosing regimens were carefully investigated by indication in large phase II dose finding studies with once and twice daily administration reflecting different clinical requirements and populations
  - based on the preventive or therapeutic character of the anticoagulation, as well as
  - concomitant therapy with co-medication affecting the coagulation system
  - for the SPAF indication VTE treatment was used as the model in agreement with HAs
- Dose was selected based on the above available information for each individual indication, and confirmed by the large pivotal Phase III studies
  - 10 mg od rivaroxaban in VTE prevention MOS
  - 15 mg bid/20 mg od in VTE treatment
  - 20 mg od in SPAF (15 mg for renally impaired patients)
  - 2.5 mg bid in ACS

SPC Summarizes The Most Relevant Information To Clinicians

- Section 4.2 Posology/Administration, e.g.
  - Dosing by indication including for special populations
- Section 5.1 Pharmacodynamic properties, e.g.
  - In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) for15 mg rivaroxaban twice daily ranged from 17 to 32 s and for 20 mg rivaroxaban once daily from 15 to 30 s. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18 - 30 h after tablet intake) from 13 to 20 s.
- Section 5.2 Pharmacokinetic properties, e.g.
  - In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.
  - Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Plasma Levels Sensitive To Both Time Of Sampling And Time Of Last Dose Taken As Recalled By Patient

Indication and rivaroxaban dose	VTE prevention: 10 mg od	DVT treatment: 15 mg bid for 3 weeks followed by 20 mg od	Prevention of stroke in patients with AF and CrCl ≥50 ml/min: 20 mg od	Prevention of stroke in patients with AF and CrCl <50 ml/min: 15 mg od	Prevention of CV events in patients with ACS: 2.5 mg bid
Time after dosing (hours)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)	Concentration, µg/l (5/95 percentile)
1	111 (75.1–177)	235 (164–361)	216 (152–316)	189 (134–281)	41.3 (23.5–65.9)
2	122 (90.6–195)	270 (189–419)	250 (177–361)	219 (157–317)	44.1 (26.7–69.5)
3	114 (82.3–186)	259 (180–405)	246 (172–361)	216 (153–317)	42.0 (25.9–66.4)
4	102 (75.8–164)	237 (161–369)	232 (157–349)	205 (141–309)	38.7 (23.3–63.3)
5	90.7 (62.2–143)	213 (145–339)	215 (140–333)	191 (127–297)	35.2 (20.2–59.1)
6	80.2 (51.8–125)	191 (123–311)	198 (123–318)	177 (111–286)	31.7 (17.4–55.5)
9	55.2 (30.5–96.0)	137 (71.3–240)	155 (81.9–276)	141 (74.9–254)	22.8 (10.4–45.2)
12	37.8 (15.2–76.1)	97.8 (42.9–190)	121 (53.4–242)	112 (50.0–225)	16.2 (6.11–36.6)
18	17.9 (4.85–49.9)	50.0 (16.0–124)	73.5 (22.0–187)	70.4 (21.9–180)	–
24	8.54 (1.36–37.2)	25.6 (5.93–86.9)	44.7 (9.02–147)	44.4 (9.42–143)	–

Plasma concentrations given as geometric mean values with 90% prediction intervals (5/95 percentiles). Values given to 3 significant figures.

ACS acute coronary syndrome, *AF* atrial fibrillation, *bid* twice daily, *CrCl* creatinine clearance, *CV* cardiovascular, *DVT* deep vein thrombosis, *od* once daily, *VTE* venous thromboembolism.

Ref: Mueck W, Schwers S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. Thromb J. 2013 Jun 28;11:10. doi: 10.1186/1477-9560-11-10.

Anti-factor Xa Chromogenic Assays Are Available To Measure Rivaroxaban Plasma Concentrations

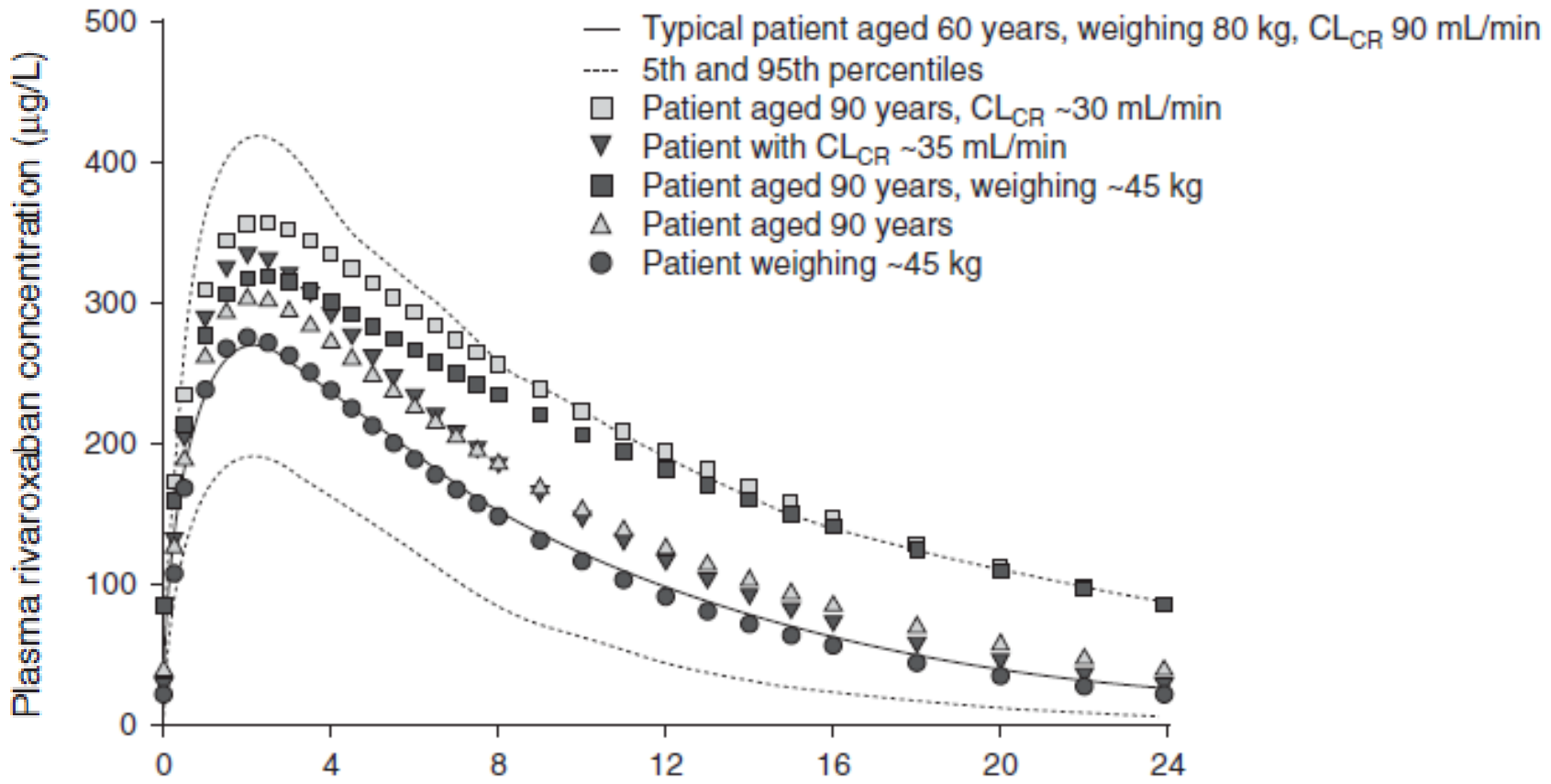
Diagnostic company	Assay name	CE mark for rivaroxaban calibrator/control
Diagnostica Stago www.stago.com	STA® - Liquid anti-Xa	☑
Hyphen Biomed www.hyphen-biomed.com	Biophen DiXaI®	☑
Instrumentation Laboratories www.instrumentationlaboratory.com	HemosIL® Liquid anti-Xa	☑
Technoclone www.technoclone.com	Technochrom® anti-Xa	☑

Dedicated Phase I Studies Identified PK Covariates

	AUC	C_{max}
Body weight [a]	AUC (LS means ratio)	C_{max} (LS means ratio)
< 50 kg / 70 to 80 kg	1.14	1.24
>120 kg / 70 to 80 kg	1.12	1.04
Age [b]		
>75 years / 18 to 45 years	1.41	1.08
Renal function [c]	AUC ratio (Anova)	C_{max} ratio (Anova)
50-79 mL/min	1.44	1.28
30-59 mL/min	1.52	1.12
15-29 mL/min	1.64	1.26

[a] Kubitza et al, J Clin Pharm 2007; 47:218 – 227 Erratum in: J Clin Pharmacol. 2008 Nov;48: 1366-7
[b] Kubitza et al, J Clin Pharmacol. 2013; 53: 249-255
[c] Kubitza et al, Br J Clin Pharmacol. 2010 Nov;70: 703-12

Population PK Data Confirmed In Phase II The Identified Co-variates In Patients



Predicted rivaroxaban plasma concentration-time profiles for „extremes“ in age, renal function and body weight in patients

Mueck et al. Clin Pharmacokinet 2011; 50 :675-686

In Phase III Patient Characteristics Determine Safety/Efficacy Profile: Renal Impairment

		Rivaroxaban	LMWH/VKA	HR (95%)
Major Bleeding				
Renal impairment	No	0.8% (23/2763)	1.0% (29/2786)	0.79 (0.46-1.36)
	Mild	1.4% (14/1030)	3.0% (30/1002)	0.44 (0.24-0.84)*
	Moderate	0.9% (3/320)	3.9% (12/310)	0.23 (0.06-0.81)*
	Severe	0% (0/9)	9.1% (1/11)	
		$P_{trend} = 0.92$	$P_{trend} = 0.01$	
Recurrent VTE				
Renal impairment	No	1.8% (50/2772)	1.9% (52/2797)	0.95 (0.65-1.41)
	Mild	2.5% (25/1036)	3.1% (31/1001)	0.77 (0.45-1.30)
	Moderate	3.4% (11/323)	3.2% (10/313)	1.05 (0.44-2.47)
	Severe	0% (0/10)	9.1% (1/11)	
		$P_{trend} = 0.001$	$P_{trend} = 0.001$	

Mild <80-50 ml/min; moderate <50-30 ml/min; severe <30 ml/min

* Statistically significant

Bauersachs R et al, Thromb J 2014, 12:25

In Phase III Patient Characteristics Determine Safety/Efficacy Profile: Fragile

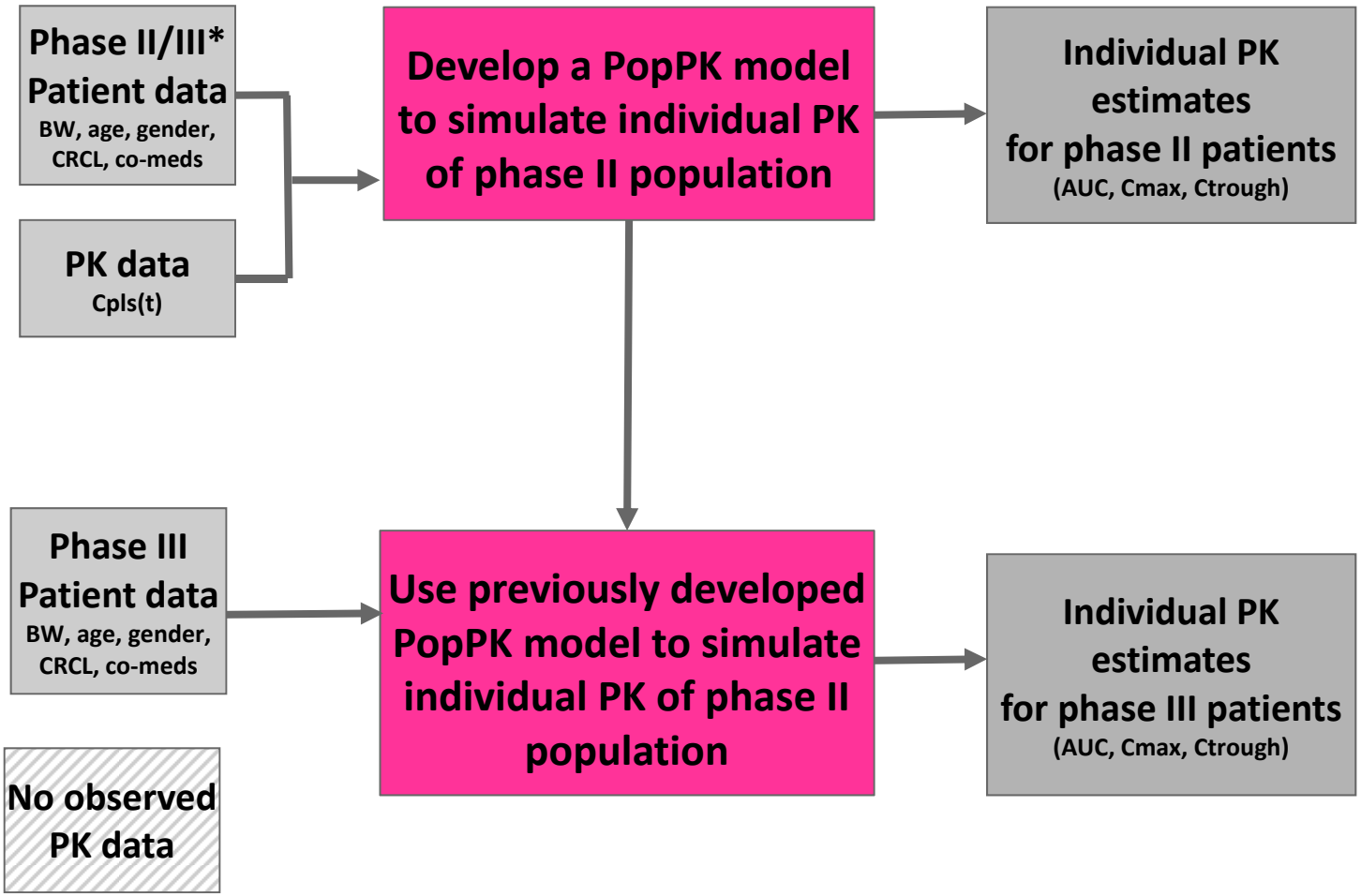
		Rivaroxaban	LMWH/VKA	HR (95%)
Major Bleeding				
Fragile[1]	Yes	1.3% (10/788)	4.5%* (35/799)	0.27 (0.13–0.54)*
	No	0.9% (30/3342)	1.1% (37/3337)	0.80 (0.49–1.29)
Recurrent VTE				
Fragile[1]	Yes	2.7% (21/791)	3.8%* (30/782)	0.68 (0.39–1.18)
	No	1.9% (65/3359)	1.9% (65/3349)	0.98 (0.70–1.38)

[1] Age >75 years, CrCl <50 ml/min, or body weight ≤50 kg

* Statistically significant

Prins MH et al, Thromb J 2013,11:21

Rivaroxaban Exposure Prediction Model



*includes small sparse PK substudy Phase III

Exposure-response (E-R) Analyses Based On Simulated PK Data For Each Indication

	VTE-P	VTE-T	SPAF	ACS
Studies	Ph3: RECORD 1 and 2 (THR), RECORD 3 and 4 (TKR)	Ph3: EINSTEIN DVT/PE	Ph3 Global: Rocket AF Ph3 Japan: J-Rocket	Ph3: ATLAS ACS2 TIMI 51 Ph2: ATLAS ACS TIMI 46
Rivaroxaban Dose	10 mg OD	15mg BID 3 weeks followed by 20mg OD	Global: 20 mg OD / 15mg OD if CrCl<50 ml/min Japan: 15 mg OD / 10mg OD if CrCl<50 ml/min	Ph3: 2.5 and 5mg BID Ph2: 5, 10, 15 and 20 mg Total Daily Dose as OD and BID regimen
Rivaroxaban Treatment Duration	2 (TKR) or 5 (THR) weeks	3, 6 or 12 months intended duration	Global: event driven (mean 570 days) Japan: event driven (mean 499 days)	Ph3: event driven (mean 390 days) Ph2: 6 months
Rivaroxaban Subjects	Ph3: N=6097	Ph3: N=4130	Ph3 Global: N=7111 Ph3 Japan: N=639	Ph3: N=10225 Ph2: N=2309

Sampling of Published Rivaroxaban PK/PD Data

- Mueck W, Stampfuss J, Kubitza D, Becka M. Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet. 2014 Jan;53:1-16. doi: 10.1007/s40262-013-0100-7.
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- Xu XS, Moore K, Burton P, Stuyckens K, Mueck W, Rossenu S, Plotnikov A, Gibson M, Vermeulen A. Population pharmacokinetics and pharmacodynamics of rivaroxaban in patients with acute coronary syndromes. Br J Clin Pharmacol; 2012;74:86-97.
- Girgis IG, Patel MR, Peters GR, Moore KT, Mahaffey KW, Nessel CC, Halperin JL, Califf RM, Fox KA, Becker RC. Population pharmacokinetics and pharmacodynamics of rivaroxaban in patients with non-valvular atrial fibrillation: results from ROCKET AF. J Clin Pharmacol. 2014 Aug;54:917-27. doi: 10.1002/jcph.288. Epub 2014 Mar 26.

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Thank you!