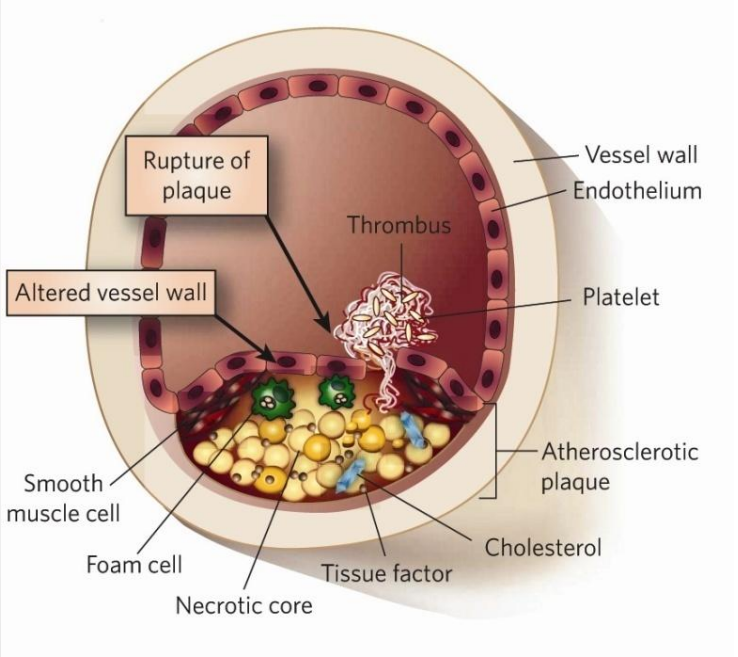
Cardiology update 2013
Satellite Symposium Bayer Healthcare
Selective FXa Inhibition with Rivaroxaban: Current Indications and Future Perspectives



Dosing across indications

Kantonsspital St.Gallen

Prof. H. Rickli

Established/possible rivaroxaban dosing regimens according to indications: What is the evidence behind different dosing?

Indication	Rivaroxaban dose	Duration
VTE prevention after orthopaedic surgery	*10 mg od*	2 weeks (total knee replacement) 5 weeks (total hip replacement)
Stroke prevention in AF	*20 mg od* (15 mg od in patients with moderate renal impairment*)	As long as risk factors persist
VTE treatment	*15 mg bid*†	First 3 weeks
	20 mg od	As long as risk factors persist
ACS	*2.5 mg bid*	

*Creatinine clearance (CrCl) 30–49 ml/min; †to be administered with food
ACS, acute coronary syndromes; AF, atrial fibrillation; bid, twice daily; od, once daily

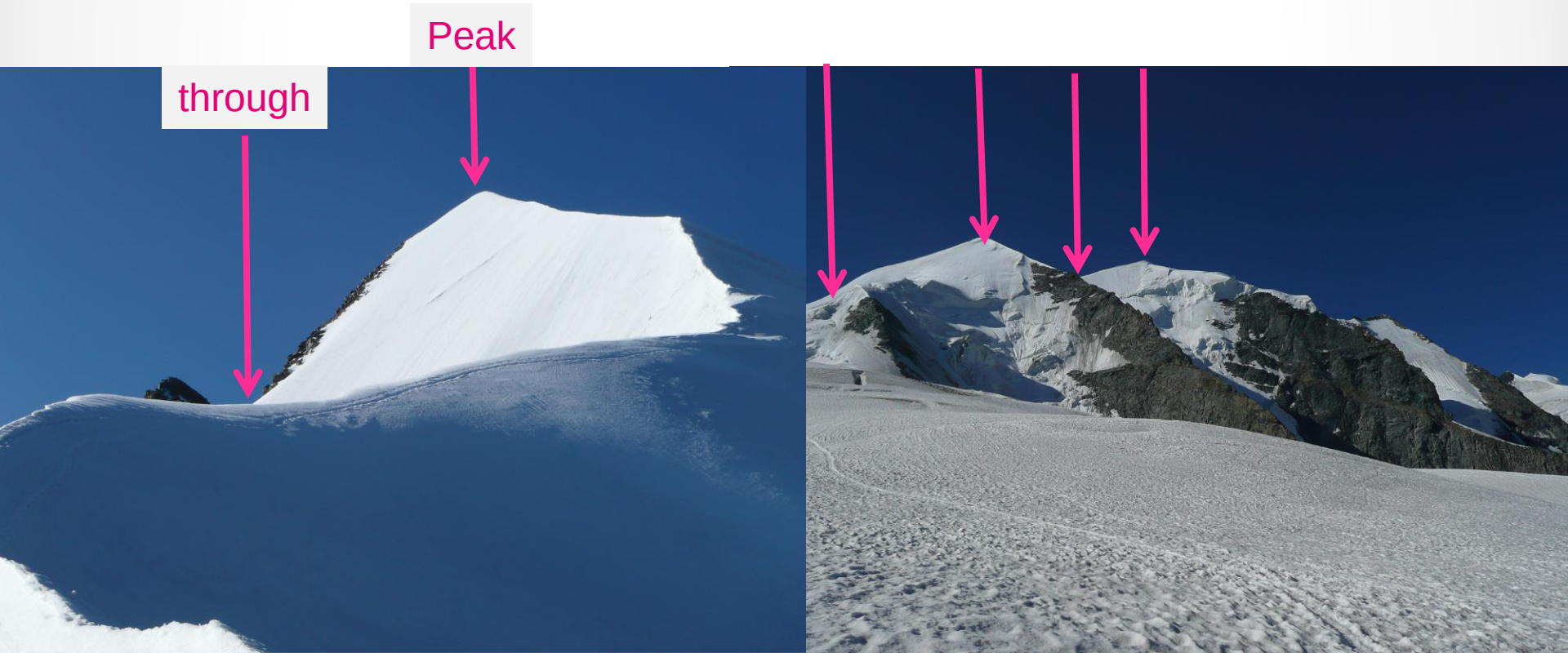
Pharmacological characteristics of the new oral anticoagulants are similar

Parameter	Rivaroxaban	Apixaban	Edoxaban	Dabigatran
Target	Factor Xa	Factor Xa	Factor Xa	Thrombin
Oral bioavailability	~80%	~66%	~50%	~6.5%
Prodrug	No	No	No	Yes
Half-life (h)	5–13	8–15	9–11	12–14
t_{max} (h)	2–4	1.5–3.5	1.5	1.5
Renal clearance	33%	25%	35%	80%
Potential drug interactions	CYP3A4, P-gp inhibitors	CYP3A4 inhibitors	CYP3A4, P--gp inhibitors	Rifampicin, quinidine, amiodarone, P-gp inhibitors

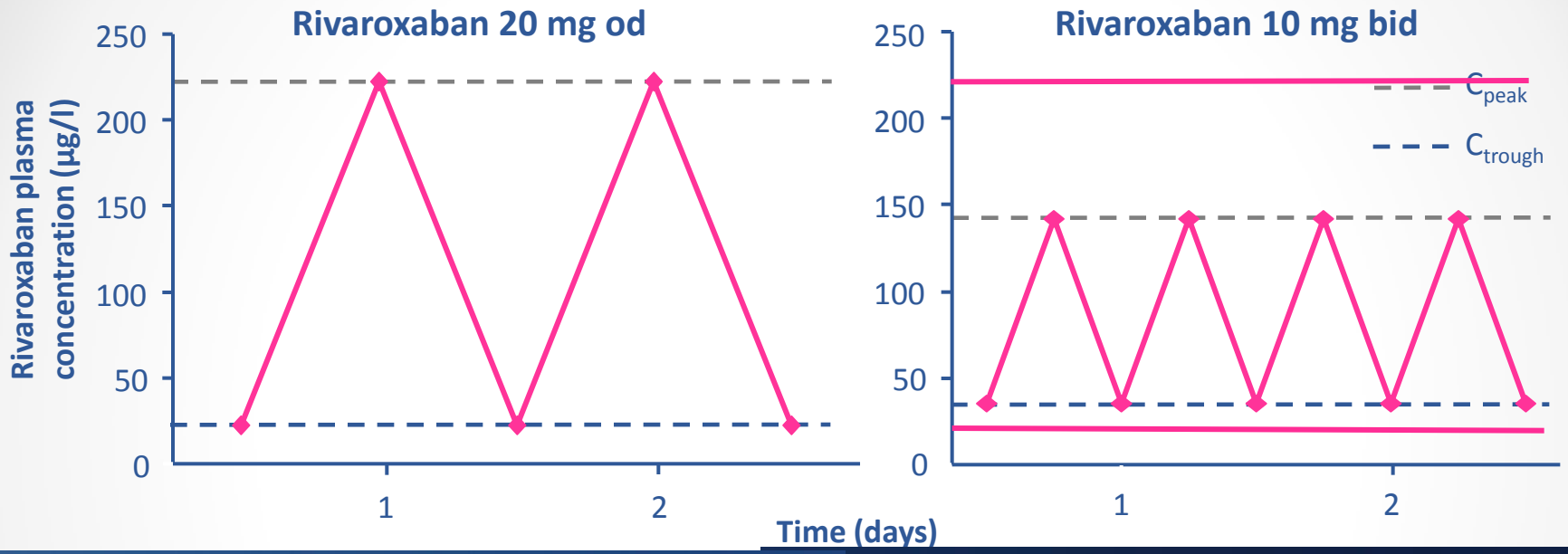
CYP3A4, cytochrome P450 3A4; P-gp, P-glycoprotein; t_{max}, time to reach maximum plasma concentration

Eriksson *et al*, 2011; Mavrakanas *et al*, 2011; Kreutz, 2011

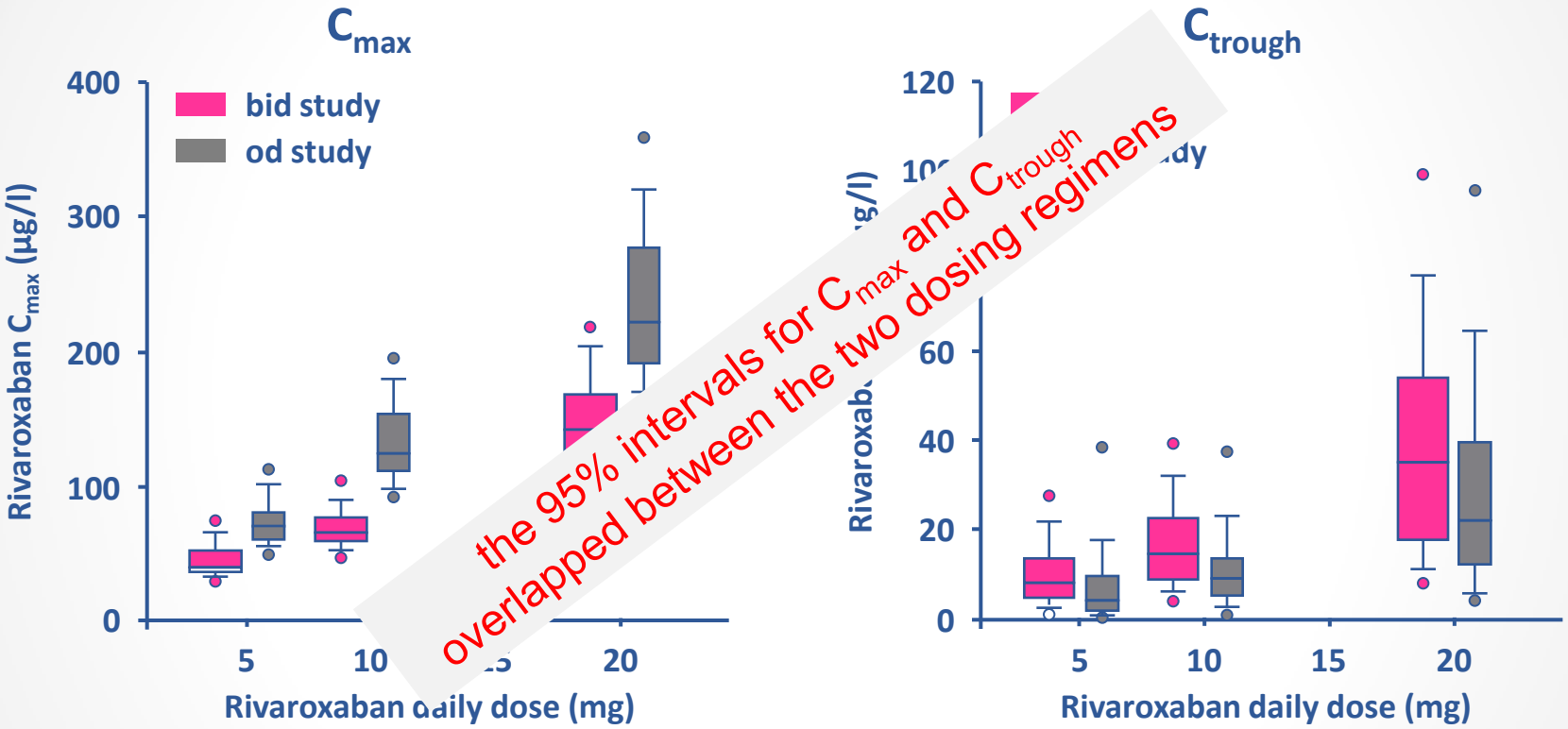
Pharmakokinetics of OD versus BID ?



Rivaroxaban od versus bid dosing: Population pharmacokinetics and pharmacodynamics of once and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement



Rivaroxaban dosing: overlap between od and bid regimens



Maximum (C_{max}) and minimum (C_{trough}) rivaroxaban plasma concentrations in the bid and od studies, with 25th and 75th percentiles (horizontal lines) and 5th and 95th percentiles (circles)

Mueck *et al*, Population pharmacokinetics and pharmacodynamics of once and twice-daily rivaroxaban for the prevention of venous thromboembolism in patients undergoing total hip replacement. Thromb Haemost 2008;100:453–461

Influence of PK and PD parameters on dosing regimens

- The pharmacokinetic characteristics of the new oral anticoagulants provide the *opportunity for either od or bid dosing*
- Determination of the *optimal dosing regimen* must be based on *assessment of benefit (reduction in thrombotic events)* versus *risk (increase in bleeding events) in clinical studies*

Pathophysiological /evidence based approach: Dosing considerations

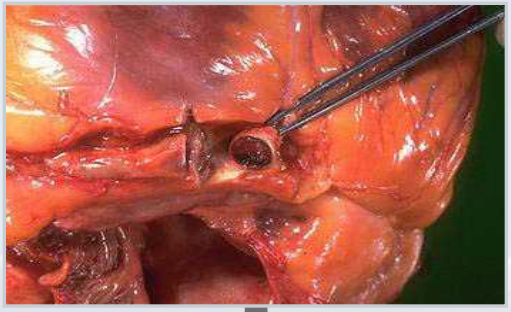
- Clot type
  - Venous/venous-like versus arterial
- Indication
  - Prophylaxis versus treatment/secondary prevention
- Co-medications use e.g. antiplatelet therapy for ACS
- Timing/intensity
  - High pressure for treatment versus lower pressure for prophylaxis
- Compliance
  - od versus bid dosing
- Renal function
  - Dose adjustment for renally impaired patients

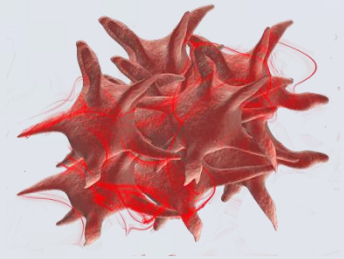
Clot type

Pathophysiology of the clot

Thrombosis

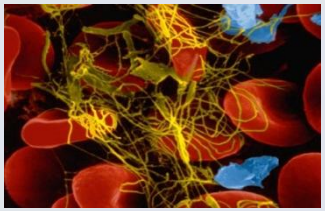
Arterial





Platelet-rich clot
(platelets *and* coagulation)

Venous



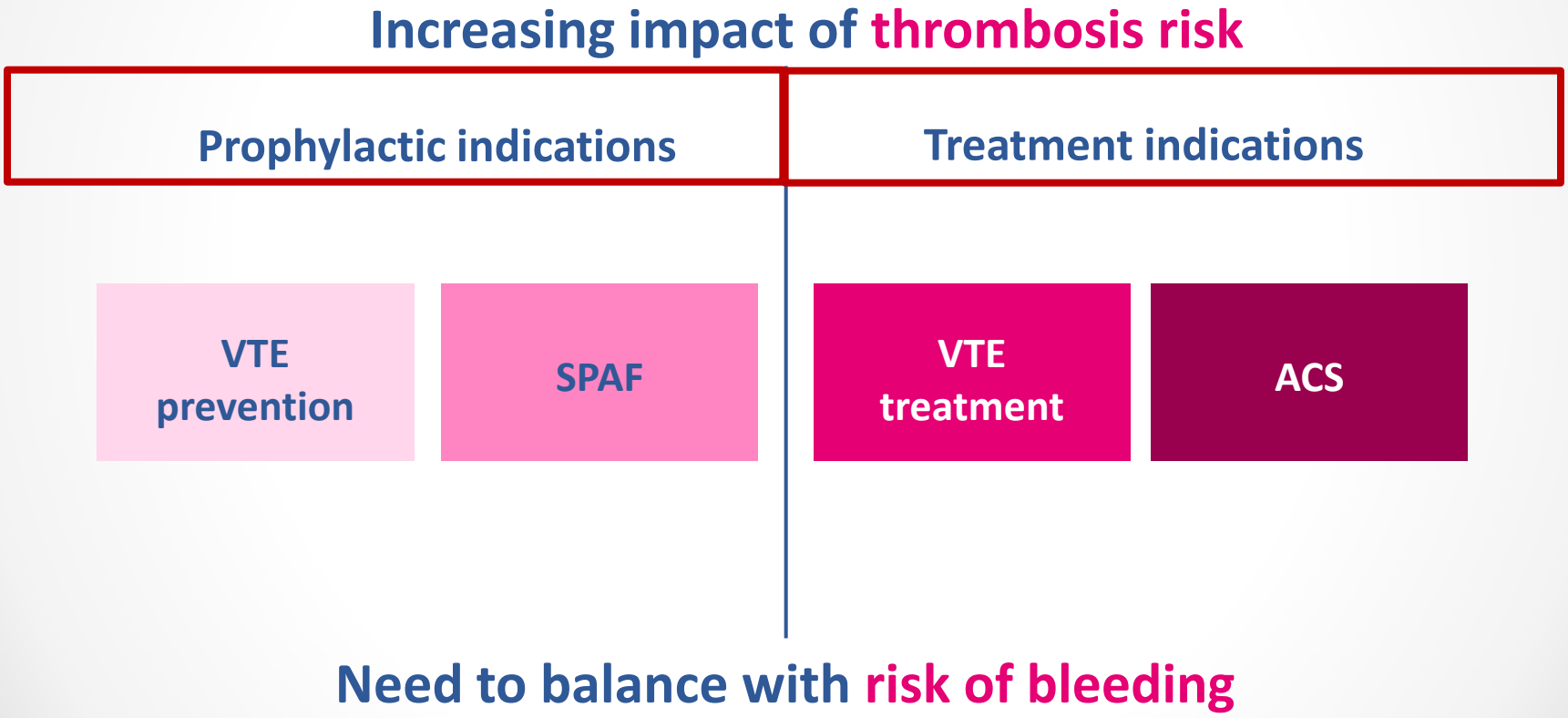
Fibrin-rich clot
(coagulation)

Arterial and venous clots: different pathogenesis and clot characteristics

	Venous clots (DVT, PE)	AF clots	Arterial clots (ACS)
Clot type	Venous	Venous-like	Arterial
Composition	Fibrin rich	Fibrin rich	Platelet rich
Size	Large	Large	Small
Growth	Slow	Slow	Rapid*
Location	Large venous vessels	Atria (usually left appendage)	Small arterial vessels (coronary artery)
Potential outcome	PE	Ischaemic stroke	MI
Antiplatelet therapy required	No	Not recommended	Yes, evidence based drug therapy

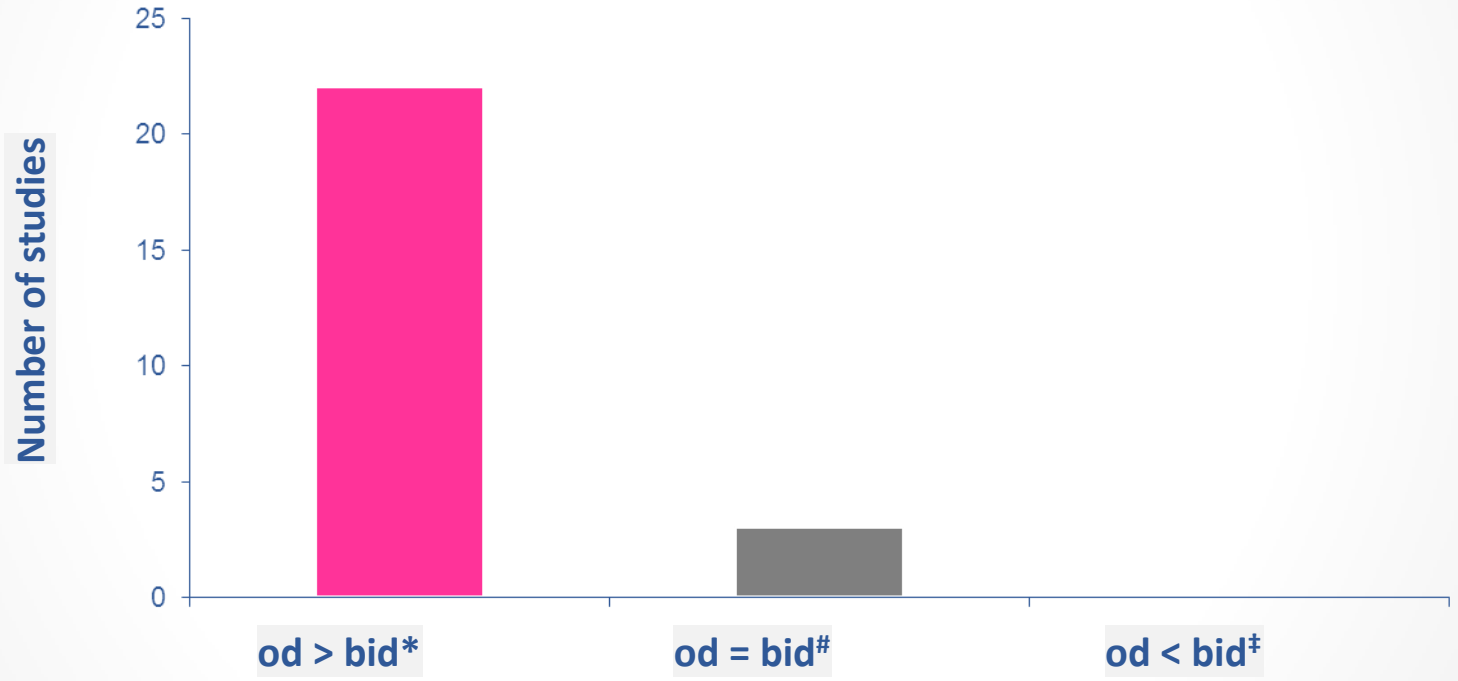
*Usually rapid response to plaque rupture

Prophylactic versus treatment indications



Compliance with od versus bid regimens is generally better for chronic conditions

Number of studies that directly assessed compliance



*Patient compliance (assessed in study) with od regimen is significantly better than with bid regimen
#No significant difference in patient compliance (assessed in study) between od and bid regimens
‡Patient compliance (assessed in study) with bid regimen is significantly better than with od regimen

Pubmed search; March 2001–2011

Dosing considerations: *VTE prevention*

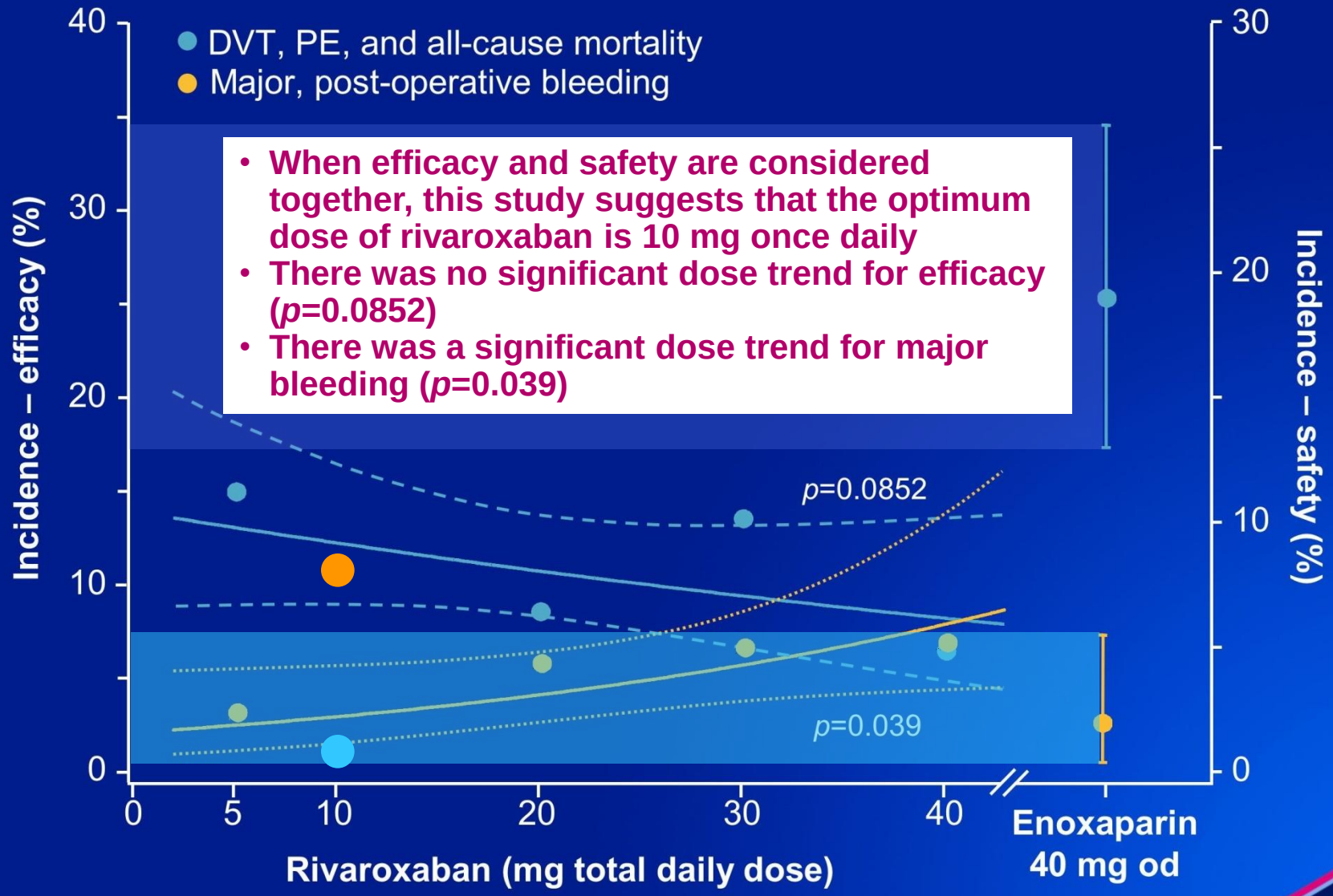
- Clot type
  - Venous/venous-like versus arterial
- Indication
  - Prophylaxis versus treatment/secondary prevention
- Co-medications use e.g. antiplatelet therapy for ACS
- Timing/intensity
  - High pressure for treatment versus lower pressure for prophylaxis
- Compliance
  - od versus bid dosing
- Renal function
  - Dose adjustment for renally impaired patients

Extensive rivaroxaban phase II clinical development in VTE prevention

- A 12-fold dose range of rivaroxaban (total daily doses 5–60 mg) given bid was investigated in the ODIXa-HIP1, -HIP2 and -KNEE studies[1–3]
- An 8-fold dose range of rivaroxaban (total daily doses 5–40 mg) given od was investigated in the OD.HIP study[4]
- No arm was discontinued in any study
- All four studies had the same efficacy and safety endpoints

1. Turpie *et al*, 2005; 2. Eriksson *et al*, 2006; 3. Eriksson et al, 2007, 4. Eriksson et al, 2006

Dose–response relationships between rivaroxaban and the primary efficacy and safety endpoints



- When efficacy and safety are considered together, this study suggests that the optimum dose of rivaroxaban is 10 mg once daily
- There was no significant dose trend for efficacy (p=0.0852)
- There was a significant dose trend for major bleeding (p=0.039)

Eriksson *et al*, *Circulation* 2006;114:2374–2381

Dosing considerations: VTE treatment

- Clot type
  - Venous/venous-like versus arterial
- Indication
  - Prophylaxis versus treatment/secondary prevention
- Co-medications use e.g. antiplatelet therapy for ACS
- Timing/intensity
  - High pressure for treatment versus lower pressure for prophylaxis
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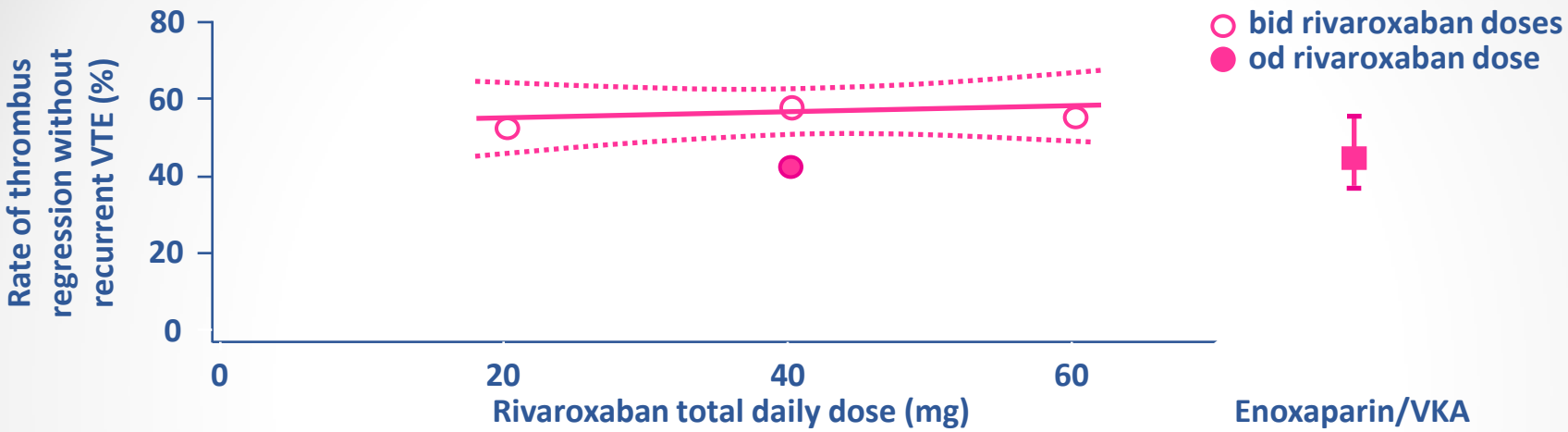
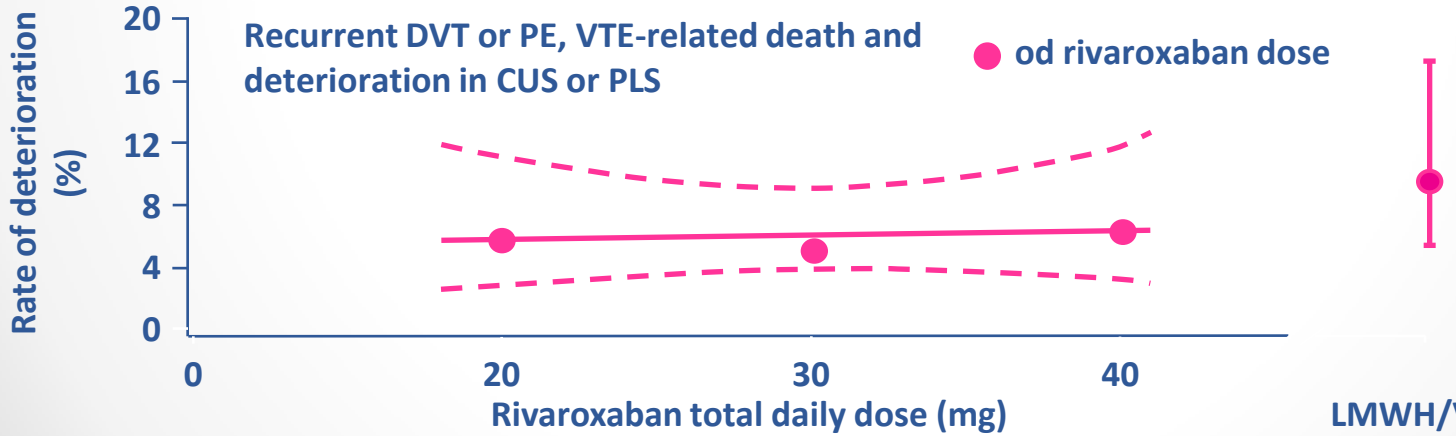
Phase II study results: primary efficacy outcomes

ODIXa-DVT[1]: rivaroxaban showed similar efficacy to standard therapy



EINSTEIN DVT (phase II)[2]: rivaroxaban showed similar efficacy to standard therapy



CUS, compression ultrasound; LMWH, low molecular weight heparin; PLS, perfusion lung scan; VKA, vitamin K antagonist

1. Agnelli *et al,* 2007; 2. Büller *et al,* 2008

Phase II study results: efficacy and safety outcomes

Results after 12 weeks' treatment

ODIXa-DVT[1]

	Enoxaparin/VKA	Rivaroxaban dose			
		10 mg bid	20 mg bid	30 mg bid	40 mg od
Any event, %*	0.9	1.9	2.0	1.8	2.6
Major bleeding, %#	0	1.7	1.7	3.3	1.7

*Incidence of recurrent DVT, PE (non-fatal) and VTE-related death up to day 84 (+14): ITT population (n=543); #Incidence of bleeding events occurring <2 days after last dose of study drug: safety population (n=604)

EINSTEIN DVT[2]

	LMWH/VKA	Rivaroxaban dose		
		20 mg od	30 mg od	40 mg od
Symptomatic events, %‡	6.9	2.6	3.6	1.7
Major bleeding, %¶	1.5	0.7	1.5	0

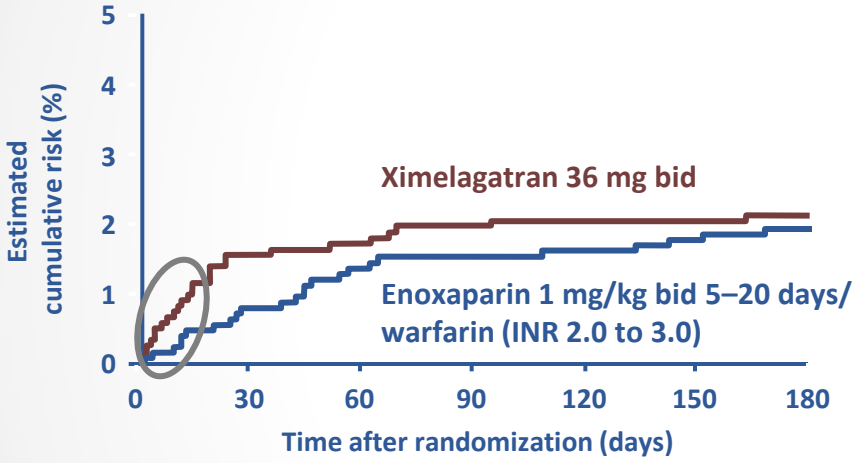
‡Incidence of composite of symptomatic recurrent DVT, symptomatic fatal or non-fatal PE and asymptomatic deterioration in thrombotic burden (n=449);
¶Safety population (n=542)

ITT, intention to treat

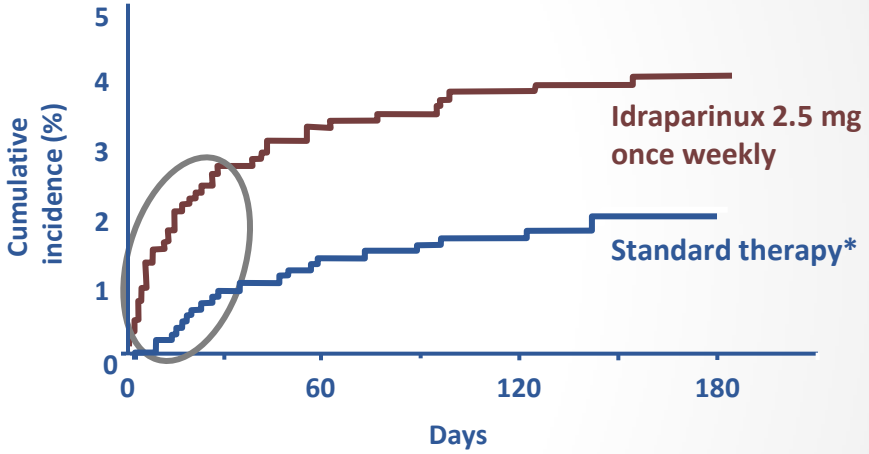
1. Agnelli *et al,* 2007; 2. Büller *et al,* 2008

Rationale for intensified initial treatment in phase III EINSTEIN DVT/PE studies

Evidence of early recurrent VTE in THRIVE study with Ximelagatran[1]



Evidence of early recurrent VTE in the van Gogh PE study with Idraparinux[2]



- Early separation of the curves indicates the need for intensified anticoagulant treatment in the acute phase

*Heparin followed by an adjusted-dose VKA for either 3 or 6 months

1. Fiessinger et *al,* 2005; 2. The van Gogh Investigators. 2007

Rationale for dose selection in the EINSTEIN phase III study programme

- Efficacy in rivaroxaban bid and od study arms in both dose-ranging studies was similar to LMWH/VKA comparator arms
- Greater thrombus regression at day 21 without recurrent symptomatic VTE or VTE-related death was observed for bid dose arms at 3 weeks in ODIXa-DVT dose-ranging study
- Higher C_{trough} levels with bid regimens (intensified anticoagulant effect) could be beneficial in the acute treatment phase
- Relative safety, in terms of bleeding versus standard care control treatment, was better for od versus bid regimens

The lowest od dose studied (20 mg) was selected for the EINSTEIN phase III programme, with an initial 3 weeks of rivaroxaban 15 mg bid

1. Agnelli *et al,* 2007;2. Büller *et al,* 2008

Do we need a rivaroxaban dose adjustment in patients with moderate renal impairment?

- EU - DVT indication 2010
  - Moderate renal impairment: adjust rivaroxaban to 15 mg od
  - Severe renal impairment: rivaroxaban contraindicated

- EU – PE indication 2012
  - Moderate renal impairment: no need for dose adjustment in PE
    <u>no need anymore to dose adjust in DVT!</u>
  - Severe renal impairment: rivaroxaban contraindicated

Recurrent VTE and baseline CRcl in placebo recipients in Einstein Extension

	Placebo in Einstein Extension	
Recurrent VTE CRcl (ml/min)		
≥ 80	5.9%	(22/373)
50 – < 80	7.4%	(9/122)
< 50	12.2%	(6/49)

- A moderate renal impairment is an independent risk factor for recurrent VTE

Major bleeding, recurrent VTE and baseline creatinine clearance (CrCl)

Pooled Einstein DVT and PE

	Rivaroxaban (n=4150)	Enox/VKA (n=4131)
Major bleeding CRcl (ml/min)		
≥ 80	0.8%	1.0%
50 – < 80	1.4%	3.0%
< 50	0.9%	4.1%
Recurrent VTE CRcl (ml/min)		
≥ 80	1.8%	1.9%
50 – 80	2.3%	3.0%
< 50	3.3%	3.4%

Conclusions
Impaired renal function and rivaroxaban dosing

Patients with renal impairment treated with 20 mg rivaroxaban have

- A 50% increased exposure
- No increased risk for major bleeding
- An inherent increased risk for recurrent VTE

A rivaroxaban dose reduction in renally impaired patients does not have the potential to lower the bleeding risk but carries the risk to further increase the recurrent VTE rate

Dosing considerations: stroke prevention in AF

- Clot type
  - Venous/venous-like versus arterial
- Indication
  - Prophylaxis versus treatment/secondary prevention
- Co-medications use e.g. antiplatelet therapy for ACS
- Timing/intensity
  - High pressure for treatment versus lower pressure for prophylaxis
- Compliance
  - od versus bid dosing
- Renal function
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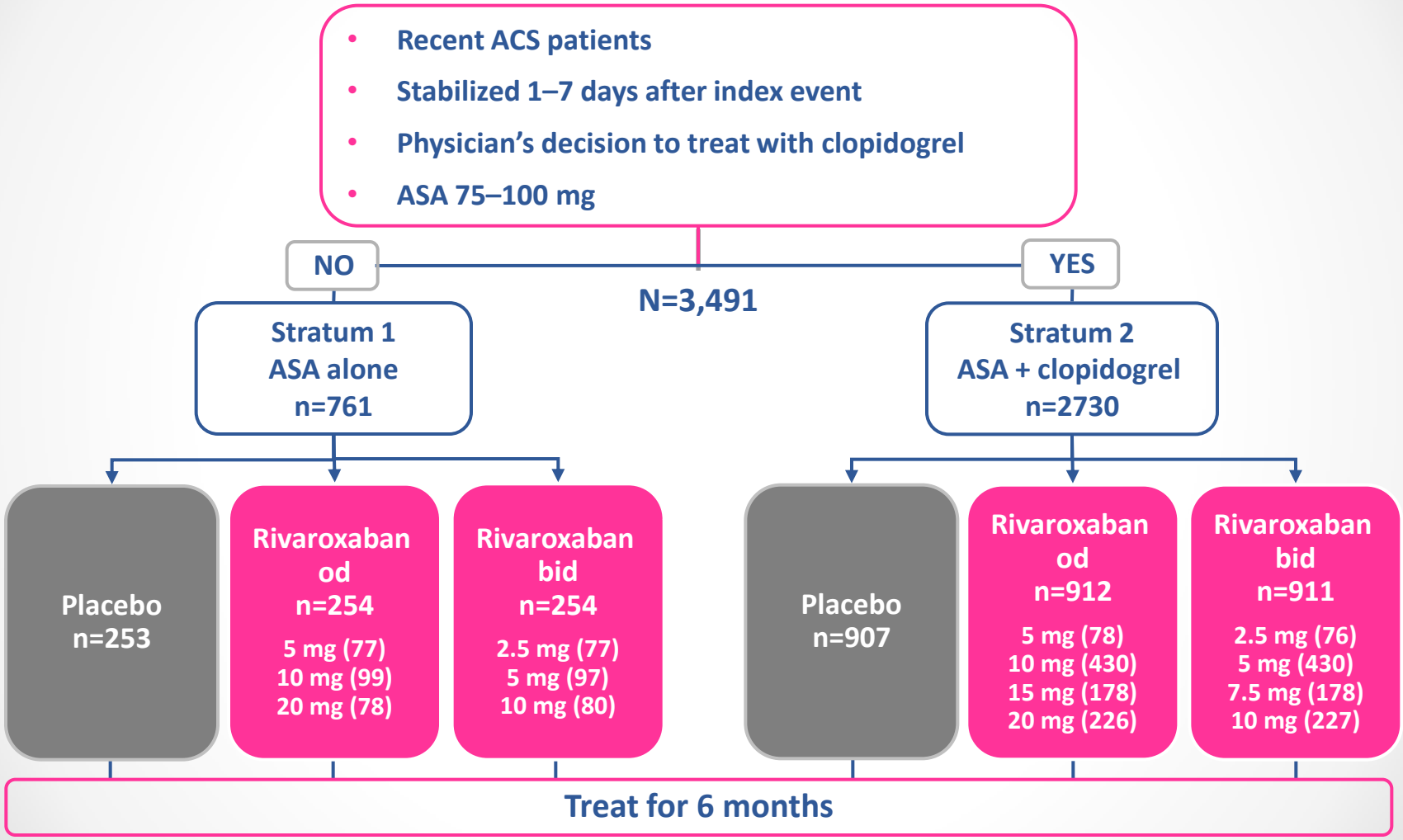
Rationale for the rivaroxaban dose in ROCKET AF

- Rivaroxaban 20 mg od was chosen as the dose for the phase III ROCKET AF trial based on the phase II dose-finding programme for DVT treatment
- EINSTEIN DVT[1] and ODIXa-DVT[2] both demonstrated:
  - Efficacy of rivaroxaban did not increase with increasing total daily dose (20, 40, 60 mg in ODIXa-DVT; 20, 30, 40 mg in EINSTEIN DVT)
  - Major bleeding was similar irrespective of total daily dose and similar to the standard of care
    - Supports 20 mg total daily dose (as lowest effective dose evaluated)
  - Early clinical pharmacology studies showed that rivaroxaban inhibited thrombin generation (and thereby continued to prevent coagulation) beyond 24 hours after administration[3]
    - Supports once daily dosing

1. Büller *et al,* 2008; 2. Agnelli *et al,* 2007; 3. Kubitza *et al*, 2005

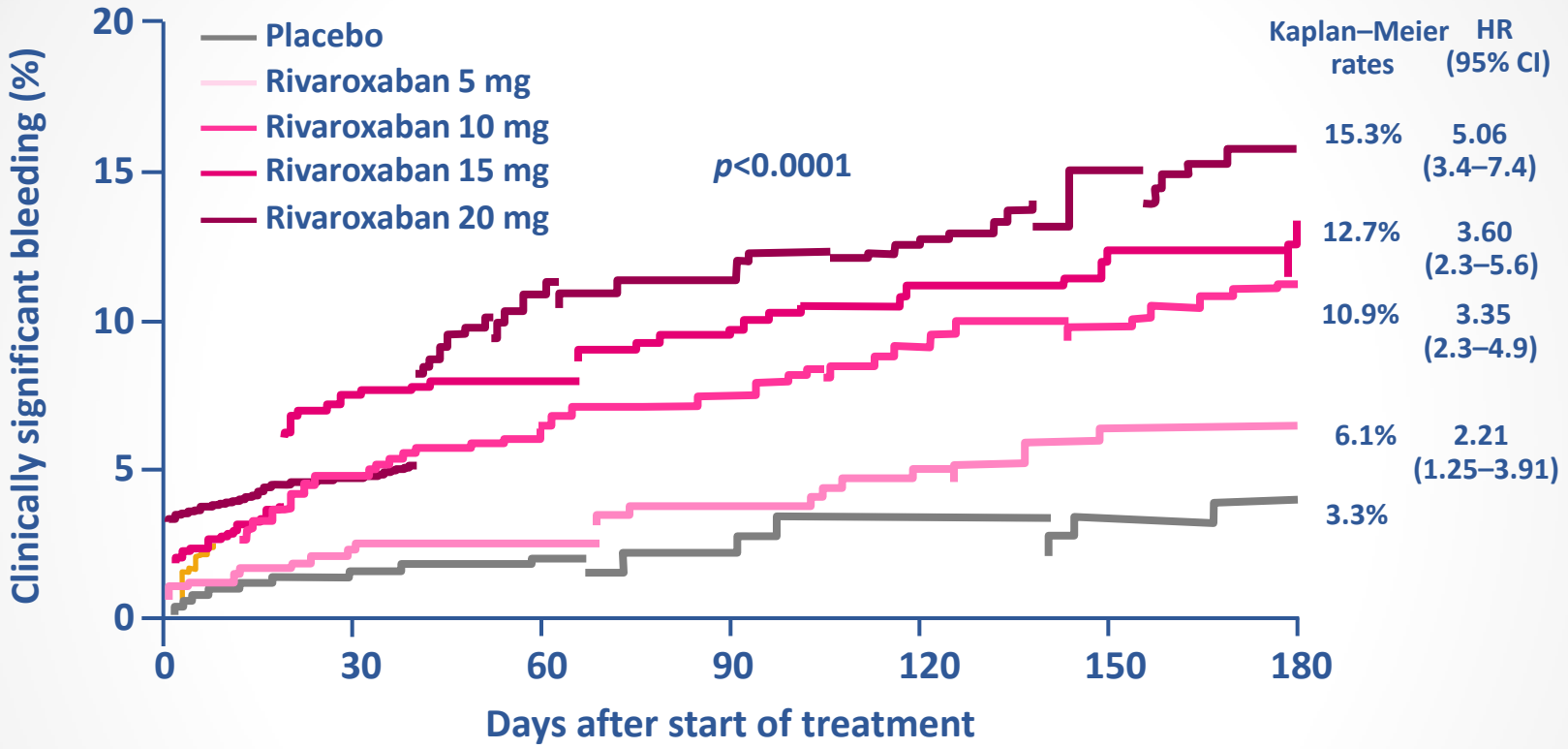
ATLAS ACS TIMI 46: Phase II study



ASA, acetylsalicylic acid

Mega *et al*, 2009

ATLAS ACS TIMI 46: clinically significant bleeding – total daily doses

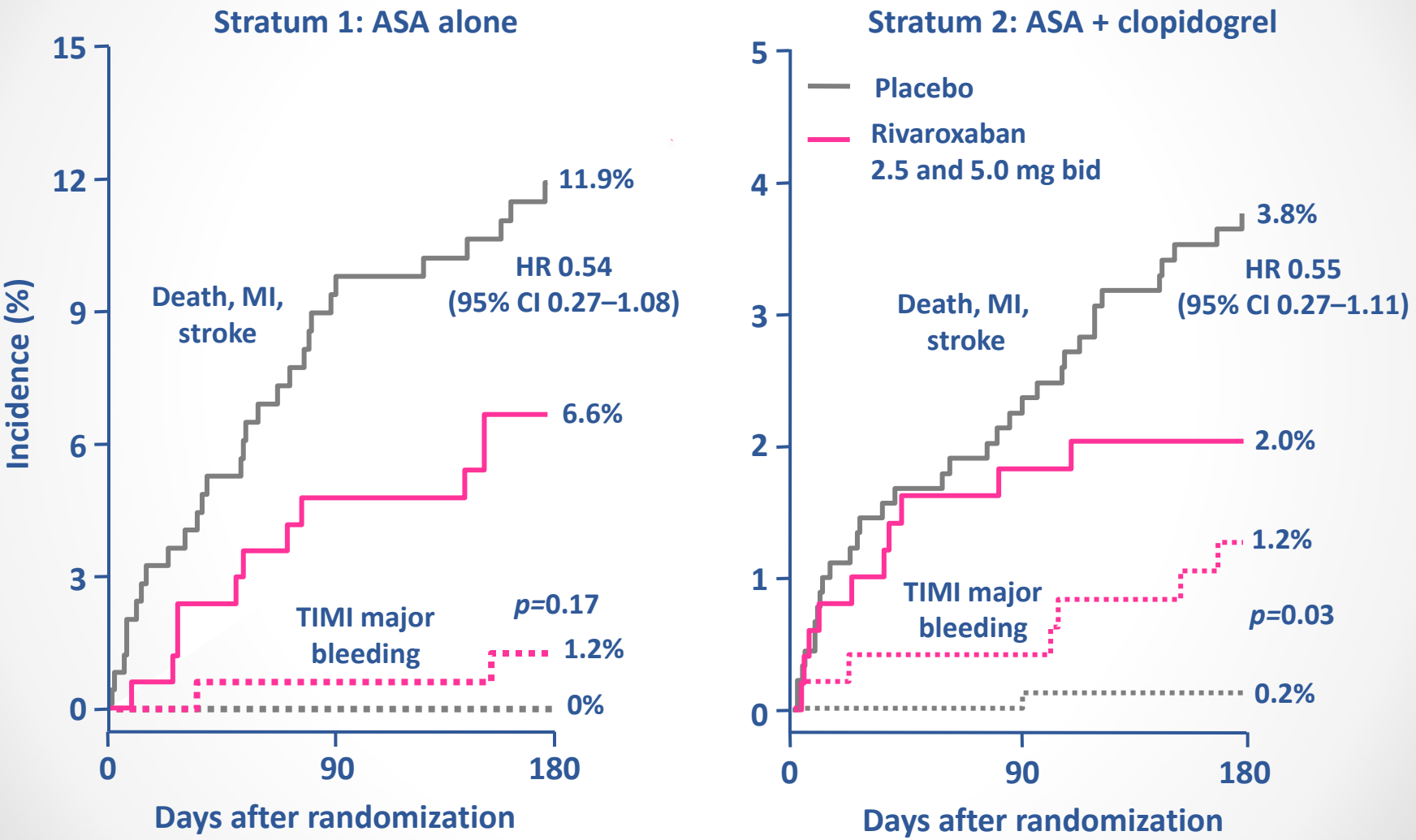


Number at risk

Placebo	1153	1116	1090	1075	1055	1041	1026
Rivaroxaban 5 mg	307	292	292	283	274	269	265
Rivaroxaban 10 mg	1046	980	937	920	888	868	850
Rivaroxaban 15 mg	353	325	318	310	299	292	288
Rivaroxaban 20 mg	603	557	530	521	506	492	476

Mega *et al*, 2009

ATLAS ACS TIMI 46: efficacy versus bleeding



MI, myocardial infarction; TIMI, thrombosis in MI

Mega *et al*, 2009

ACS: rationale for rivaroxaban dosing

- **Based on dosing considerations and the results of the phase II ATLAS ACS TIMI 46 study:**

Rivaroxaban 2.5 mg bid and 5 mg bid were selected as optimal doses for phase III studies

Optimal Rivaroxaban dosing: summary

There is clearly a need to have different rivaroxaban dosing regimens for different indications

The optimal rivaroxaban dosing regimens were evaluated in robust phase II clinical trials

Do efficacy and safety data from phase III VTE prevention, VTE treatment and stroke prevention in AF studies support the rivaroxaban doses selected?

Thank you!

ODIXa-Hip: BID vs. Enoxaparin 40mg OD:

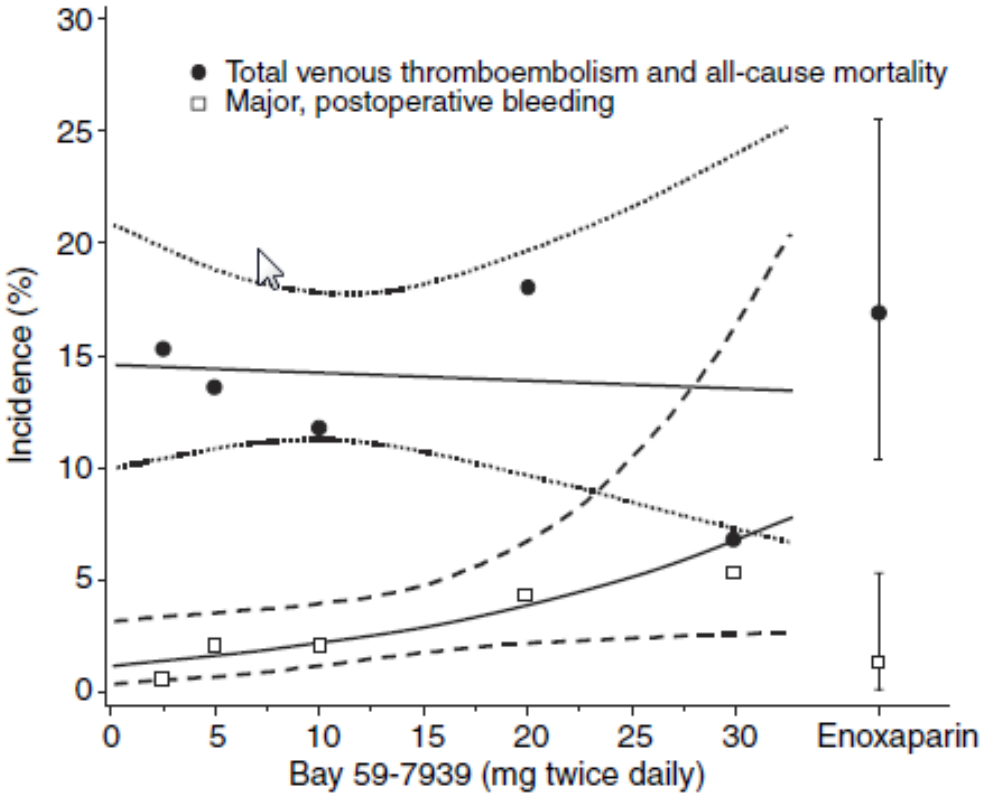


Fig. 3. Dose–response relationship between BAY 59-7939 and the primary efficacy endpoint (DVT, non-fatal PE, all-cause mortality; per-protocol population) and the primary safety endpoint (major, postoperative bleeding events; safety population). The solid lines are the dose–response curves for BAY 59-7939, estimated by logistic regression, including total daily dose as a covariate. The dotted lines represent the 95% confidence intervals for the primary efficacy endpoint, and the dashed lines the 95% confidence intervals for the primary safety endpoint.