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

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

*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

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

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 20 mg od

Rivaroxaban 10 mg bid

C<sub>peak</sub>

C<sub>trough</sub>
Rivaroxaban dosing: overlap between od and bid regimens

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

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

Arterial
- Platelet-rich clot
  (platelets and coagulation)

Thrombosis

Venous
- Fibrin-rich clot
  (coagulation)
### Arterial and venous clots: different pathogenesis and clot characteristics

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

*Usually rapid response to plaque rupture
Prophylactic versus treatment indications

Increasing impact of thrombosis risk

Prophylactic indications
- VTE prevention
- SPAF

Treatment indications
- VTE treatment
- ACS

Need to balance with risk of bleeding
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

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 ($p=0.039$)
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

• Compliance
  • od versus bid dosing

• Renal function
  • Dose adjustment for renally impaired patients
Phase II study results: primary efficacy outcomes

ODIXa-DVT\textsuperscript{1}: rivaroxaban showed similar efficacy to standard therapy

![Graph showing rate of thrombus regression without recurrent VTE (%)]

EINSTEIN DVT (phase II)\textsuperscript{2}: rivaroxaban showed similar efficacy to standard therapy

![Graph showing rate of deterioration] (Recurrent DVT or PE, VTE-related death and deterioration in CUS or PLS)

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

# Phase II study results: efficacy and safety outcomes

## Results after 12 weeks’ treatment

### ODIXa-DVT\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin/VKA</th>
<th>Rivaroxaban dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mg bid</td>
</tr>
<tr>
<td>Any event, %(^*)</td>
<td>0.9</td>
<td>1.9</td>
</tr>
<tr>
<td>Major bleeding, %(^#)</td>
<td>0</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*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\(^2\)

<table>
<thead>
<tr>
<th></th>
<th>LMWH/VKA</th>
<th>Rivaroxaban dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 mg od</td>
</tr>
<tr>
<td>Symptomatic events, %(^\d)</td>
<td>6.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Major bleeding, %(^&amp;)</td>
<td>1.5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

\(^\d\)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

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

- 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

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.

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
  ● Severe renal impairment: rivaroxaban contraindicated
  ● no need anymore to dose adjust in DVT!
## Recurrent VTE and baseline CRcl in placebo recipients in Einstein Extension

<table>
<thead>
<tr>
<th>Recurrent VTE CRcl (ml/min)</th>
<th>Placebo in Einstein Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>5.9% (22/373)</td>
</tr>
<tr>
<td>50 – &lt; 80</td>
<td>7.4% (9/122)</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>12.2% (6/49)</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=4150)</th>
<th>Enox/VKA (n=4131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRcl (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>0.8%</td>
<td>1.0%</td>
</tr>
<tr>
<td>50 – &lt; 80</td>
<td>1.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>0.9%</td>
<td>4.1%</td>
</tr>
<tr>
<td><strong>Recurrent VTE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRcl (ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>1.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>50 – 80</td>
<td>2.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>3.3%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>
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**
  - Dose adjustment for renally impaired patients
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**

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ATLAS ACS TIMI 46: Phase II study

- Recent ACS patients
- Stabilized 1–7 days after index event
- Physician’s decision to treat with clopidogrel
- ASA 75–100 mg

N=3,491

Stratum 1
ASA alone
n=761

NO

Placebo n=253
Rivaroxaban od n=254
5 mg (77)
10 mg (99)
20 mg (78)

Rivaroxaban bid n=254
2.5 mg (77)
5 mg (97)
10 mg (80)

Stratum 2
ASA + clopidogrel
n=2730

YES

Rivaroxaban od n=912
5 mg (78)
10 mg (430)
15 mg (178)
20 mg (226)

Rivaroxaban bid n=911
2.5 mg (76)
5 mg (430)
7.5 mg (178)
10 mg (227)

Placebo n=907

Treat for 6 months

ASA, acetylsalicylic acid
Mega et al, 2009
ATLAS ACS TIMI 46: clinically significant bleeding – total daily doses

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rivaroxaban 5 mg</th>
<th>Rivaroxaban 10 mg</th>
<th>Rivaroxaban 15 mg</th>
<th>Rivaroxaban 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 days</td>
<td>1153</td>
<td>307</td>
<td>1046</td>
<td>353</td>
<td>603</td>
</tr>
<tr>
<td>30 days</td>
<td>1116</td>
<td>292</td>
<td>980</td>
<td>325</td>
<td>557</td>
</tr>
<tr>
<td>60 days</td>
<td>1090</td>
<td>292</td>
<td>937</td>
<td>318</td>
<td>530</td>
</tr>
<tr>
<td>90 days</td>
<td>1075</td>
<td>283</td>
<td>920</td>
<td>310</td>
<td>521</td>
</tr>
<tr>
<td>120 days</td>
<td>1055</td>
<td>274</td>
<td>888</td>
<td>299</td>
<td>506</td>
</tr>
<tr>
<td>150 days</td>
<td>1041</td>
<td>269</td>
<td>868</td>
<td>292</td>
<td>492</td>
</tr>
<tr>
<td>180 days</td>
<td>1026</td>
<td>265</td>
<td>850</td>
<td>288</td>
<td>476</td>
</tr>
</tbody>
</table>

Kaplan–Meier rates

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>15.3% (3.4–7.4)</td>
</tr>
<tr>
<td>Rivaroxaban 5 mg</td>
<td>12.7% (2.3–5.6)</td>
</tr>
<tr>
<td>Rivaroxaban 10 mg</td>
<td>10.9% (2.3–4.9)</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg</td>
<td>6.1% (1.25–3.91)</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Mega et al, 2009
ATLAS ACS TIMI 46: efficacy versus bleeding

Stratum 1: ASA alone
- Death, MI, stroke: 11.9%
- TIMI major bleeding: 6.6%
- HR: 0.54 (95% CI 0.27–1.08)
- Days after randomization: 0, 90, 180

Stratum 2: ASA + clopidogrel
- Placebo: 3.8%
- Rivaroxaban: 2.0%
- HR: 0.55 (95% CI 0.27–1.11)
- TIMI major bleeding: 1.2%
- Days after randomization: 0, 90, 180

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.
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!
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.