How do NOACs hold up in day to day practice?
Looking at real life evidence

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HELIOS Park-Klinikum Leipzig
LINC January 26th 2016
Disclosures

Speaker Name: Arne Kieback

Potential Conflicts of Interest:
Consulting: Bayer, Bristol-Myers Squibb
Rivaroxaban demonstrated to be non-inferior to warfarin in phase III trials

- Prevention of recurrent VTE in DVT patients (EINSTEIN DVT\textsuperscript{1})
- Prevention of stroke/systemic embolism in AF patients (ROCKET AF\textsuperscript{2})

XALIA – New Real World Evidence in VTE

Rivaroxaban vs Standard Anticoagulation as Therapy in Deep Vein Thrombosis
Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study

Walter Ageno, Lorenzo G Mantovani, Sylvia Haas, Reinhold Kreutz, Danja Monje, Jonas Schneider, Martin van Eickels, Martin Gebel, Elizabeth Zell, Alexander G G Turpie

Summary

Background The efficacy and safety of the anticoagulant rivaroxaban for the treatment and secondary prevention of deep-vein thrombosis and pulmonary embolism has been shown in phase 3 trials. However, data about rivaroxaban use in routine clinical practice are needed.
XALIA: A Prospective, Non-interventional Study

Objective: collect real-life data in patients with acute DVT treated with rivaroxaban or standard anticoagulation

Patients with diagnosis of acute DVT* and with an indication for anticoagulant therapy for ≥3 months

Type, dose and duration of drug used at discretion of attending physician

Rivaroxaban for ≥3 months

Investigators to collect data at initial visit, at 1 month and then quarterly#

Standard anticoagulation, e.g. initial treatment with LMWH/fondaparinux, followed by VKA or parenteral anticoagulation for ≥3 months

(1 month after end of treatment)

Final assessment

Primary outcomes
Major bleeding events, symptomatic recurrent VTE and all-cause mortality

ClinicalTrials.gov NCT01619007; *After PE EU licence, DVT with concomitant PE permitted; isolated PE excluded
#Data were collected at the initial visit and during routine follow-up visits or via mail, telephone, or email

Treatment-Emergent Clinical Outcomes (Propensity-Score Adjusted)

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=2505)</th>
<th>Standard anticoagulation (n=2010)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>19 (0.8)</td>
<td>43 (2.1)</td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>36 (1.4)</td>
<td>47 (2.3)</td>
<td></td>
<td>0.72</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>11 (0.4)</td>
<td>69 (3.4)</td>
<td></td>
<td>0.07</td>
</tr>
</tbody>
</table>

Propensity score-adjusted population

**EINSTEIN DVT and XALIA: Rivaroxaban Outcomes**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Incidence (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding* (14/1718)</td>
<td>0.8</td>
</tr>
<tr>
<td>Recurrent VTE* (36/1731)</td>
<td>2.1</td>
</tr>
</tbody>
</table>

| Major bleeding* (19/2505)       | 0.8                       |
| Recurrent VTE* (36/2505)        | 1.4                       |

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Previous VTE</th>
<th>Baseline active cancer</th>
<th>Known thrombophilia</th>
</tr>
</thead>
<tbody>
<tr>
<td>55.8</td>
<td>57.4%</td>
<td>19.4%</td>
<td>6.8%</td>
<td>6.2%</td>
</tr>
<tr>
<td>57.3</td>
<td>54.5%</td>
<td>24.1%</td>
<td>5.6%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

*ITT analysis; *Safety population (patients taking ≥1 dose of study drug); Propensity-score: Carried out to balance covariates across treatment groups and minimize potential bias in the estimate of treatment effects.

Real World Evidence for Rivaroxaban in SPAF
XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation

A. John Camm\textsuperscript{1*}, Pierre Amarenco\textsuperscript{2}, Sylvia Haas\textsuperscript{3}, Susanne Hess\textsuperscript{4}, Paulus Kirchhof\textsuperscript{5,6}, Silvia Kuhls\textsuperscript{7}, Martin van Eickels\textsuperscript{4}, and Alexander G.G. Turpie\textsuperscript{8}, on behalf of the XANTUS Investigators

\textsuperscript{1}Cardiovascular and Cell Sciences Research Institute, St George’s, University of London, Cranmer Terrace, SW170RE London, UK; \textsuperscript{2}Department of Neurology and Stroke Center, Paris-Diderot-Sorbonne University, Paris, France; \textsuperscript{3}Vascular Center, Munich, Germany; \textsuperscript{4}Global Medical Affairs, Bayer HealthCare Pharmaceuticals, Berlin, Germany; \textsuperscript{5}Centre for Cardiovascular Sciences, University of Birmingham and Sandwell & West Birmingham Hospitals NHS Trust, Birmingham, UK; \textsuperscript{6}Department of Cardiovascular Medicine, University of Münster, Münster, Germany; \textsuperscript{7}Global Integrated Analysis, Bayer HealthCare Pharmaceuticals, Wuppertal, Germany; and \textsuperscript{8}Department of Medicine, McMaster University, Hamilton, ON, Canada

Received 27 July 2015; revised 11 August 2015; accepted 20 August 2015
XANTUS: Study Objective and Design

To collect real world data on adverse events in patients with NVAF treated with rivaroxaban to determine the safety profile of rivaroxaban across the broad range of patient risk profiles encountered in routine clinical practice.

Primary outcomes: major bleeding (ISTH definition), all-cause mortality, any other adverse events

Population:
Adult patients with NVAF receiving rivaroxaban for stroke/non-CNS SE prevention

Rivaroxaban; treatment duration and dose at physician’s discretion

N=6,784

Data collection at initial visit, hospital discharge (if applicable) and quarterly*

1 year

Prospective, single-arm, observational, non-interventional phase IV study

Statistical analyses were descriptive and exploratory in nature

Final visit:
1 year#

*Exact referral dates for follow-up visits not defined (every 3 months recommended); #for rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose. Observational design means no interference with clinical practice was allowed

Rivaroxaban Provides Reassuring Safety, Reaffirmed in the Real World

![Graph showing event rates for Major Bleeding, ICH, and GI Bleeding](image)

<table>
<thead>
<tr>
<th>Event Rate, %/year*</th>
<th>ROCKET AF²</th>
<th>Baseline</th>
<th>XANTUS¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>3.6</td>
<td>CHADS₂</td>
<td>2.0</td>
</tr>
<tr>
<td>ICH</td>
<td>0.5</td>
<td>0-1</td>
<td>0.9</td>
</tr>
<tr>
<td>GI Bleeding</td>
<td>2.0</td>
<td>≥3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Event Rate, %/year*</th>
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<td>GI Bleeding</td>
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</tbody>
</table>

Results are not intended for direct comparison

*Includes prior stroke, SE or TIA; *Events per 100 patient-years

Rivaroxaban is Highly Effective in Both Randomized Clinical Trials and the Real World

**ROCKET AF**

<table>
<thead>
<tr>
<th>Event rate, %/year*</th>
<th>Stroke/SE</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>0.8</td>
<td>1.9</td>
</tr>
<tr>
<td>13%</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>87%</td>
<td>0%</td>
<td>0-1</td>
</tr>
<tr>
<td>63%</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>91%</td>
<td>0%</td>
<td>0-1</td>
</tr>
<tr>
<td>44%</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>40%</td>
<td>0%</td>
<td>0-1</td>
</tr>
<tr>
<td>55%</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>17%</td>
<td>0%</td>
<td>0-1</td>
</tr>
</tbody>
</table>

**Results are not intended for direct comparison**

*Includes prior stroke, SE or TIA; *Events per 100 patient-years

Conclusion

Phase IV studies
XALIA and XANTUS

confirm safety and efficacy of Rivaroxaban
which had been demonstrated in

Phase III trials
EINSTEIN DVT and ROCKET AF

Thank you for your attention!
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