The laboratory and new anticoagulant drugs

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Disclosures for Andreas Hillarp:

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Alternatives to warfarin: NOAC/DOAC/TSOAC etc.

- Pradaxa® = dabigatran etexilate
- Xarelto® = rivaroxaban
- Eliquis® = apixaban
- Lixiana® = edoxaban

NOAC = non-vitamin K-dependent oral anticoagulants (ESC)
DOAC = direct oral anticoagulant (SSC-ISTH)
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Apixaban (Eliquis)</th>
<th>Edoxaban (Lixiana)</th>
<th>Warfarin (Waran)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Factor Xa-inhibitor</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Trombin inhibitor</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>6</td>
<td>&gt;80</td>
<td>&gt;50</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>Monitoring</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>Yes</td>
</tr>
<tr>
<td>Time to peak (h)</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1,5</td>
<td>120</td>
</tr>
<tr>
<td>T½ (h)</td>
<td>12-17</td>
<td>9</td>
<td>9-14</td>
<td>9-11</td>
<td>50</td>
</tr>
<tr>
<td>Interactions</td>
<td>Proton pump inhibitors P-glyco-protein</td>
<td>CYP3A4 P-glyco-protein</td>
<td>CYP3A4 P-glyco-protein</td>
<td>CYP3A4 P-glyco-protein</td>
<td>Long list</td>
</tr>
<tr>
<td>Renal excretion(%)</td>
<td>80</td>
<td>33</td>
<td>25</td>
<td>35</td>
<td>1</td>
</tr>
<tr>
<td>Antidot (specific)</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Measurements are dependent on when the last drug dose was taken!

Expected plasma concentration after
- 200 mg dabigatran etexilate
- 10 mg rivaroxaban

Mod. from: Heindl B & Spannagl M 2009
What does the drug level (plasma concentration) mean?
Correlation PT(INR) and outcomes
Narrow therapeutic interval: INR 2-3

MONITORING IMPROVES THE INDIVIDUAL BENEFIT-RISK OF THE TREATMENT!

ACC/AHA/ESC 2006 guidelines, Europace 2006;8:651-745
The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients

The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Paul A. Reilly, PhD,* Thorsten Lehr, PhD,†‡ Sebastian Haertter, PhD,†
Stuart J. Connolly, MD,§ Salim Yusuf, MD, DPHIL,§ John W. Eikelboom, MB BS,§
Michael D. Ezekowitz, MD, PhD,|| Gerhard Nehmiz, PhD,† Susan Wang, PhD,*
Lars Wallentin, MD, PhD,¶ on behalf of the RE-LY Investigators

Ridgefield, Connecticut; Biberach and Saarbrücken, Germany; Hamilton, Ontario, Canada;
Wynnewood, Pennsylvania; and Uppsala, Sweden

"Individual benefit-risk might be improved by tailoring dabigatran dose"
Figure 2

**Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran**

Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. **Lines and boxes at the top of the panel** indicate median dabigatran concentrations in the RELY trial with 10th and 90th percentiles.

Conc. = concentration; DE = dabigatran etexilate; SEE = systemic embolic event(s).
Measuring NOAC – when?

**Necessary** in various acute situations:
- Surgery, bleeding, intoxications…

Could be useful in specific situations:
- Adverse events/failure of therapy, compliance
- Extreme body weight (high/low)
- Patients with deteriorating renal function
- Before initiation/baseline values
- At regular check-ups…
Measuring NOACs - how?

1. Qualitative tests (screening assays)
   Readily available in emergency situations.
   Indicating supra- or subtherapeutic effects.

2. Quantitative tests (specific)
   Determination of anticoagulant effects and plasma concentrations.

3. Reference methods
   LC-MS/MS
NOAC will interfere, more or less, with most coagulation-based assays!

- Screening assays: APTT, PT(INR)
- Factor assays, antithrombin, fibrinogen, protein S/C activity, lupus, etc. (thrombophilia invest.)
- Effect correlated to type of drug and concentration.
- Large differences between methods/reagents.
- Effect dependent on time since last dose due to short half-life with ("peak" and "trough").
Dabigatran (spiked samples) and APTT
Dabigatran and APTT "in real life"
Differences (in vitro) between rivaroxaban and apixaban!
Differences in PT(INR) responsiveness:
edoxaban > rivaroxaban >> apixaban

Specific assays for measuring the effect of NOACs

- **Thrombin inhibitor (dabigatran)**
  - *Dilute thrombin time (dTT) or ecarin-based assays*
    - Calibrated with dabigatran standard
    - Results given in mass concentration (µg/L)

- **Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban)**
  - *Anti-Xa assay*
    - Calibrated with drug-specific standards
    - Results given in mass concentration (µg/L)
APIXABAN RESULTS: ANTI-XA ASSAYS

Hillarp A  JTH 2014
Low <on-therapy range  |  On-therapy range  |  High >on-therapy range
Plasma concentration of NOAC

Apixaban: anti-Xa
Rivaroxaban: anti-Xa
Rivaroxaban: PT
Rivaroxaban: APTT
Dabigatran: Dilute TT, ECA
Dabigatran: APTT
Dabigatran: PT

Quantitative

Modified from Cuker et al. J Am Coll Cardiol 2014;64:1128
Conclusions

• Correlation between NOAC plasma concentration, effect on assays and outcome (tailoring possible?)

• Measuring is valuable at certain clinical situations.

• Dabigatran (thrombin-inhibitor) is best measured with dTT or ECA

• Xa-inhibitors (rivaroxaban, apixaban and edoxaban) are measured with anti-Xa assays

• Variable effect *in vitro* with anti-Xa NOACs
Thank you for your attention

with greeting from the county of Halland