RE-VERSE AD Study

Background and Overview

**Article**

**Background**
- Dabigatran is an orally administered direct thrombin inhibitor approved by the FDA for use in patients with non-valvular atrial fibrillation, DVT/PE, and for VTE prophylaxis after hip surgery based upon data from the RE-LY and RE-COVER studies.
- Idarucizumab is a monoclonal antibody fragment that binds dabigatran with high affinity and inactivates it; has been in the development as a reversal agent for dabigatran.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population/Intervention</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glund S, et al. Lancet. 2015 Randomized, placebo-controlled, double-blind Phase I study</td>
<td>Healthy volunteers aged 18-45 years given dabigatran 220mg BID for 3 days</td>
<td>Primary endpoint (ADE): 66% reported at least one mild ADE such as infusion site reactions, hot flushes, and epistaxis. Secondaries (dT, ECT, apt, TT, AUEC): all returned to baseline at all doses tested → immediate reversal of dabigatran to undetectable levels (sustained for 72 h).</td>
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</tbody>
</table>
| Pollack CV, et al. NEJM. 2015 RE-VERSE-AD interim analysis Prospective multi-center, cohort study | 18 years or older taking dabigatran | Primary endpoint (max % reversal, dTT, ECT): Median max percentage reversal 100%
Secondary endpoints:
- Median time to bleeding cessation 11.4 h
- Normal hemostasis in Group B, n=33(92%)
- 18 deaths overall (20%)
- Thrombotic events in 5 patients |

**Objective**
This report aimed to provide data to validate the results of the previous interim analysis that included 90 patients in the RE-VERSE AD study.

**Methods**

**Study design**
Multicenter, prospective, single-cohort study at 173 sites in 39 countries from June 2014 through July 2016.

**Inclusion Criteria**
Group A (uncontrolled bleeding) and Group B (emergency surgery or procedure)
- Currently taking dabigatran
- Age ≥ 18 years old

**Exclusion Criteria**
- Patients with minor/no bleeding, surgery procedures that is elective or with low bleeding risk, and study drug contraindications/hypersensitivities

**Interventions/Endpoints**
- Dabigatran etexilate treated patients:
  - **Group A:** Uncontrolled bleeding
    - N = 503
    - 5 g idarucizumab (four doses) vs. placebo n=47
  - **Group B:** Emergency surgery or procedure
    - 0–15 min
    - Hospital arrival
    - Baseline
    - Between vials
    - Determined locally
    - Max hemostasis within 4 hours (non-ICH)
    - Hemostasis during procedure/surgery
    - 24 h
    - 24 h
    - 30 d
    - 90 day follow-up

**Statistical Analysis**
- The primary efficacy end point of maximum percentage reversal of dabigatran was calculated for patients in whom pretreatment diluted thrombin times or ecarin clotting times were above the upper limit of normal range.
- The sample size was based on regulatory feedback and practical considerations.
Results

Baseline Characteristics
N=461

Patients had a mean age of 78, were mostly male (54.5%) and white (82.3%). Most were receiving dabigatran for the atrial fibrillation indication (95%). Time to last intake of dabigatran: median 15.6 hrs, range 1.5-105 hrs.

Type of bleed in group A: gastrointestinal (45.5%), intracranial (32.6%), trauma (25.9%).

Primary/Secondary Endpoints

<table>
<thead>
<tr>
<th>End point</th>
<th>Group A (n = 276)</th>
<th>Group B (n = 185)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum reversal within 4 hrs with either prolonged dTT or ecarin clotting time</td>
<td>100%</td>
<td>100%</td>
<td>100-100</td>
</tr>
<tr>
<td>Hemostasis within 24 hours (non-ICH)</td>
<td>134/203 (67.7%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median time to hemostasis</td>
<td>2.5 hours</td>
<td>-</td>
<td>2.2-3.9</td>
</tr>
<tr>
<td>Hemostasis during procedure- normal</td>
<td>-</td>
<td>184/185 (93.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Restart of anticoagulation after 72h</td>
<td>69/301 (22.9%)</td>
<td>135/202 (66.8%)</td>
<td>-</td>
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<tr>
<td>Mortality within 30 days treatment</td>
<td>13.5%</td>
<td>12.6%</td>
<td>-</td>
</tr>
</tbody>
</table>

Safety Endpoints

<table>
<thead>
<tr>
<th>Event</th>
<th>Group A (n = 276)</th>
<th>Group B (n = 185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombotic events within 30 days</td>
<td>14 (2.8%)</td>
<td>10 (2%)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>66 (21.9%)</td>
<td>51 (25.2%)</td>
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Strengths

- Multicenter, prospective, open-label study
- Appropriate inclusion criteria
- Appropriate sample size
- First agent for reversal of a newer oral anticoagulant
- Few contraindications, drug-adverse events and drug interactions

Weaknesses

- This study did not evaluate health outcomes
- No control or comparator group
- Almost 10% of patients were excluded because dTT and ECT were within normal range
- Used adjunct blood products and volume expanders
- Most patients had indication for atrial fibrillation
- Dabigatran use not as prevalent as other new oral anticoagulants

Discussion and Conclusion

Author’s Conclusions

- The administration of 5 g of idarucizumab resulted in immediate, complete and sustained reversal of dabigatran anticoagulation
- In emergency situations, idarucizumab can rapidly, durably, and safely reverse the anticoagulant effect of dabigatran

Personal Conclusions

- Idarucizumab is the first agent approved for the specific reversal of a DOAC and has been shown to immediately and completely reverse the anticoagulant effects of dabigatran as measured by laboratory coagulation parameters and unbound dabigatran concentrations
- Impact on clinical outcomes is unclear

Application

- Use of idarucizumab should be considered for patients on dabigatran with (1) life-threatening or uncontrolled bleeding or (2) for truly emergent procedures where homeostasis is required and where standard treatment is failing
- Labs: dTT and ECT measurements are not provided by our laboratory
- Location: In Glorias office in second to last refrigerator
- Administration: Administer 5 g (2.5 g per 50 mL vial) administered intravenously as two consecutive 2.5 g infusions (no rate defined) or bolus IV push injections (use 60 mL syringe)
- Pricing (lexicomp): 2.5 gm/50 mL vial = $2,100
- Providers should balance the need for complete anticoagulant reversal and the resulting increased possible risks of dabigatran