Nuovi Anticoagulanti Orali: gestione delle emergenze emorragiche

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EHRA Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary†

Hein Heidbuchel1*, Peter Verhamme1, Marco Alings2, Matthias Antz3, Werner Hacke4, Jonas Oldgren5, Peter Sinnaeve1, A. John Camm6, and Paulus Kirchhof7,8

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Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel1*, Peter Verhamme2, Marco Alings3, Matthias Antz4, Hans-Christoph Diener5, Werner Hacke6, Jonas Oldgren7, Peter Sinnaeve2, A. John Camm8, and Paulus Kirchhof9,10
1.2 How to organize follow-up?

Initiator of anticoagulant treatment:
- Sets indication for anticoagulation;
- Makes choice of anticoagulant;
- Decides on need of proton pump inhibitor;
- Baseline hemoglobin, renal and liver function;
- Provides education;
- Hands out anticoagulation card;
- Organises follow-up (when, by whom, what?);
- Remains responsible coordinator for follow-up.

First FU: 1 month

Follow-up: GP; anticoagulant clinic; initiator of therapy; ...
- Checks:
  1. Compliance (patient should bring remaining oils);
  2. Thrombo-embolic events;
  3. Bleeding events;
  4. Other side effects;
  5. Co-medications and over-the-counter drugs;
  6. Need for blood sampling?

1 m?
3 m
6 m

In case of problems: contacts initiator of treatment.

Else: Fills out anticoagulation card and sets date/place for next follow-up.

Figure 2 Structured follow-up of patients on NOACs. It is mandatory to ensure safe and effective drug intake. The anticoagulation card, as proposed in Figure 1, is intended to document each planned visit, each relevant observation or examination, and any medication change, so that every person following up the patient is well-informed. Moreover, written communication between the different (para)medical players is required to inform them about the follow-up plan and execution.
Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; G. Caleb Alexander, MD, MS; William Crown, PhD; Victor M. Montori, MD, MSc; Lindsey R. Sangaralingham, MPH; Bernard J. Gersh, MB, ChB, DPhil, FRCP; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

Table 3. Adherence to OACs (PDC ≥80%), Stratified by Index Medication (N=64 661)

<table>
<thead>
<tr>
<th></th>
<th>Apixaban (n=3900)</th>
<th>Dabigatran (n=10 235)</th>
<th>Rivaroxaban (n=12 336)</th>
<th>All NOACs (n=26 471)</th>
<th>Warfarin (n=38 190)</th>
<th>P Value (All NOACs Pooled vs Warfarin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted adherence*</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>All</td>
<td>61.9%</td>
<td>38.5%</td>
<td>50.5%</td>
<td>47.5%</td>
<td>40.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score 0 or 1</td>
<td>50.1%</td>
<td>24.6%</td>
<td>36.5%</td>
<td>32.6%</td>
<td>27.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score 2 or 3</td>
<td>62.0%</td>
<td>40.3%</td>
<td>52.8%</td>
<td>49.1%</td>
<td>38.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score ≥4</td>
<td>64.0%</td>
<td>42.4%</td>
<td>53.2%</td>
<td>51.1%</td>
<td>42.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted adherence, 95% CI</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>52.1% (50.3–53.9)</td>
<td>45.9% (44.8–47.1)</td>
<td>47.6% (46.6–48.7)</td>
<td>47.5% (46.7–48.2)</td>
<td>38.7% (38.1–39.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score 0 or 1</td>
<td>40.6% (35.8–45.4)</td>
<td>28.6% (26.3–30.9)</td>
<td>30.8% (28.7–32.9)</td>
<td>30.8% (29.3–32.3)</td>
<td>25.2% (23.4–27.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score 2 or 3</td>
<td>51.9% (48.9–55.0)</td>
<td>46.9% (45.1–48.6)</td>
<td>48.8% (47.2–50.5)</td>
<td>48.3% (47.2–49.5)</td>
<td>37.3% (36.3–38.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHA₂DS₂-VASc score ≥4</td>
<td>54.1% (51.8–56.5)</td>
<td>48.7% (47.1–50.3)</td>
<td>50.1% (48.7–51.5)</td>
<td>50.1% (49.0–51.1)</td>
<td>42.0% (41.3–42.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conclusions—Adherence to anticoagulation is poor in practice and may be modestly improved with NOACs. Adherence to therapy appears to be most important in patients with CHA₂DS₂-VASc score ≥2, whereas the benefits of anticoagulation may not outweigh the harms in patients with CHA₂DS₂-VASc score 0 or 1. (J Am Heart Assoc. 2016;5:e003074 doi: 10.1161/JAHA.115.003074)

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Figure 5  Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn et al. 39
Emorragia. Domande

● Valutazione accurata dello stato emostatico del Paziente? Il Farmaco è presente in quantità significativa? Quali test di Laboratorio Utilizzare?

● E’ necessario Bloccare l’attività anticoagulante?

● Qual è la miglior strategia terapeutica 2013 - 2015?
Valutazione accurata dello stato emostatico del Paziente?

- **Dabigatran**: I test coagulativi globali (aPTT e TT), **NON** correlano con le concentrazioni plasmatiche del farmaco. Il TT può essere utilizzato solamente come criterio di esclusione (TT Normale **NO** Dabigatran).

- **Apixaban/Rivaroxaban**: Il PT **NON** può essere utilizzato in quanto non correla con le concentrazioni plasmatiche dei Farmaci, non possiede la sufficiente sensibilità e i risultati sono dipendenti dalla Tromboplastina utilizzata.
Il Farmaco è presente in quantità significativa?

- **Dabigatran**: È possibile determinare in maniera accurata e clinicamente utile la Concentrazione Plasmatica del Farmaco tramite il Tempo di Trombina diluito, calibrato contro Dabigatran.

- **Apixaban/Rivaroxaban**: È possibile determinare in maniera accurata e clinicamente utile le Concentrazioni Plasmatiche utilizzando il test basato sulla misurazione dell’Inibizione del Fattore Xa, calibrato contro Apixaban e Rivaroxaban.
Coagulazione: D.ssa Tanca Dr. Figari

<table>
<thead>
<tr>
<th>Esame</th>
<th>Risultato</th>
<th>U.d.M.</th>
<th>Valori Riferimento</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentrazione plasmatica di Dabigatran</td>
<td>120</td>
<td>ng/mL</td>
<td>Per concentrazioni, misurate al tempo di Valle, &gt; 200 ng/mL (Pradaxa 150 mg X 2/die) e &gt; 67 ng/mL (Pradaxa 110 mg X 2/die) e’ aumentato il rischio di manifestazioni emorragiche.</td>
</tr>
</tbody>
</table>
Id. Paziente: 93306  
Sesso: F  
Routine  

Sig.ra MONTEVERDE SILVIA  
Data Nascita: 31/12/1937  
Richiedente: TAO Amb. TAO  
Richiesta: 053982 del 11/06/2015 07:30

<table>
<thead>
<tr>
<th>Esame</th>
<th>Risultato</th>
<th>U.d.M.</th>
<th>Valori Riferimento - Note</th>
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</thead>
<tbody>
<tr>
<td>TEMPO DI PROTROMBINA</td>
<td>104%</td>
<td></td>
<td>70 - 130</td>
</tr>
<tr>
<td>INR</td>
<td>1.05</td>
<td></td>
<td>Unità^</td>
</tr>
<tr>
<td>Concentrazione plasmatica di Rivaroxaban</td>
<td>54.6 ng/mL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Coagulazione: D.ssa Tanca Dr. Figari
<table>
<thead>
<tr>
<th>Esame</th>
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<th>U.d.M.</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Coagulazione: D.ssa Tanca Dr. Figari</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>1.08</td>
<td>Unità</td>
<td></td>
</tr>
<tr>
<td>TEMPO DI TROMBOPLASTINA PARZIALE A</td>
<td>29</td>
<td>secondi</td>
<td>26 - 40</td>
</tr>
<tr>
<td>TEMPO DI TROMBINA</td>
<td>17</td>
<td>secondi</td>
<td>14 - 20</td>
</tr>
<tr>
<td>Concentrazione plasmatica di Apixaban</td>
<td>101.0</td>
<td>ng/mL</td>
<td></td>
</tr>
</tbody>
</table>
Come Interpretare le concentrazioni Plasmatiche dei NOAC

- Dati della Letteratura: non presenti per tutti i NOAC; ampia variabilità delle concentrazioni plasmatiche dei NOAC. (Mancano range terapeutici).

- Utile avere lo storico del Paziente, per poter gestire in maniera ottimale le urgenze emorragiche e non solo. Le concentrazioni plasmatiche individuali sono molto stabili nel tempo salvo: IRC, IRA, Epatopatie, Interferenze Farmacologiche....
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
Ischemic events was inversely related to trough dabigatran concentrations \((p < 0.045)\), with age and previous stroke (both \(p < 0.0001\)).

Major bleeding risk increased with dabigatran exposure \((p < 0.0001)\), age \((p < 0.0001)\) and ASA use \((p < 0.0003)\).

Concentrations of dabigatran increased with age, with a 68% increase in trough concentrations in patients age \(\geq 75\) years compared with those < 65 years.

Reilly PA et al. JACC 2014; 63: 32
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 RE-LY trial with 10th and 90th percentiles. Conc. = concentration; DE = dabigatran etexilale; SEE = systemic embolic event(s).
Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial

Christian T Ruff, Robert P Giugliano, Eugene Braunwald, David A Morrow, Sabina A Murphy, Julia F Kuder, Naveen Deenadayalu, Petr Jarolim, Joshua Betcher, Minggao Shi, Karen Brown, Indravadan Patel, Michele Mercuri, Elliott M Antman

Lancet 2015; 385: 2288–95
Figure 2: Probability of clinical outcomes versus edoxaban concentration
Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2.8 years). ICH = intracranial haemorrhage. SEE = systemic embolic event.
E’ necessario bloccare l’attività anticoagulante?

- I Farmaci anticoagulanti NON causano emorragie di per se (se in Range Terapeutico), ma spesso slatentizzano una patologia sottostante che deve sempre essere ricercata e corretta anche e soprattutto in Emergenza (Epistassi, Ematuria, Ematemesi, Melena..).
- Sospensione del Farmaco ?
- Aspettare ?? Basandosi sulla breve emivita dei NOAC e su una cinetica di eliminazione certa?
- Dobbiamo sempre misurare le concentrazioni plasmatiche dei NOAC. (INR similari).
Quale migliore strategia Terapeutica

- Intervento multidisciplinare sul singolo caso.
- Agenti Pro Emostatici: DDAVP, Acido Tranexamico, rFVII.
- Fattori della Coagulazione: PCC/ aPCC.
- Emodialisi.
- Carbone attivo (Timing di assunzione).
- Plasmaferesi.
Reversing anticoagulant effects of novel oral anticoagulants: role of ciraparantag, andexanet alfa, and idarucizumab
Figure 1  Management of bleeding associated with NOACs.

- Minor bleeding
  - Local measures
  - Discontinue 1 or 2 doses if necessary

- Major or life-threatening bleeding
  - FIIa inhibitor (Dabigatran)
    - Discontinue drug
    - Mechanical compression, surgical hemostasis, transfusion of RBC or PT (if concomitant antiplatelet use)
    - Activated charcoal (if last dose <2 h)
    - PCC/aPCC/rFVIIa
    - Consider hemodialysis
    - Idarucizumab, Ciraparantag
  
  - FXa inhibitor (Rivaroxaban, Apixaban, Edoxaban)
    - Discontinue drug
    - Mechanical compression, surgical hemostasis, transfusion of RBC or PT (if concomitant antiplatelet use)
    - Activated charcoal (if last dose <2 h)
    - PCC/aPCC/rFVIIa
    - Andexanet alfa, Ciraparantag
Figure 1 Coagulation cascade depicting site of action of anticoagulants and reversal agents.


Abbreviation: LMWH, low molecular weight heparin.
| Mechanism of action | Universal reversal agent  
|                     | Synthetic molecule binds:  
|                     | Direct Xa inhibitors (apixaban, rivaroxaban, and edoxaban)  
|                     | Direct thrombin inhibitors (dabigatran)  
|                     | Unfractionated and low molecular weight heparin  
| Proposed dose       | Single 100 mg IV dose*  
| Time to effect      | 30 minutes: restoration of WBCT and mean fibrin–fibrin diameter**  
| Adverse effects     | Mild perioral and facial flushing, dysgeusia**  
|                     | PT remains elevated  
|                     | Does not appear to be sensitive marker for PER977-mediated anticoagulation reversal*  
| Possible indications| Life threatening hemorrhage  
|                     | Emergent surgery  
|                     | Elective procedures to minimize time off anticoagulation  

**Notes:** *Dose being investigated in Phase II trial; **data from Laulicht et al;*\(^5\)\(^0\) *data from Ansell et al.*\(^3\)\(^8\)

**Abbreviations:** FDA, Food and Drug Administration; PT, prothrombin time; WBCT, whole-blood clotting time; IV, intravenous.
Ciraparantag/PER977: NOACs and heparin antidote

In a preliminary study involving 80 healthy patients, PER977 (100–300 mg IV) was administered to subjects 3 hours after receiving edoxaban (60 mg oral). Anticoagulation reversal was monitored with whole-blood clotting time, which correlated with edoxaban plasma concentration. PER977 restored baseline hemostasis within 10–30 minutes and effects were sustained for 24 hours.\(^{38}\) Phase II trials investigating reversal of edoxaban with escalating doses of PER977 are underway. Plans for Phase III trials with edoxaban have also been announced.\(^{39}\)

Possible procoagulant effects of PER977 have been questioned. PER977 was not found to reverse oral factor Xa inhibitors in human plasma, but instead exhibited possible human platelet activation potentiation. This however was in the absence of signs of platelet aggregation.\(^{40}\)
<table>
<thead>
<tr>
<th>Antidote</th>
<th>Study</th>
<th>Study description</th>
<th>Enrollment</th>
<th>Results/anticipated completion date</th>
<th>Clinical trial identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perosphere</td>
<td>Phase I, non-randomized</td>
<td>Pharmacokinetic study of single-dose administration of PER977 in healthy subjects</td>
<td>6</td>
<td>August 2014</td>
<td>NCT02205905</td>
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<tr>
<td></td>
<td>Phase I, RCT</td>
<td>Safety/efficacy of escalating doses of PER977 alone and following one dose of edoxaban</td>
<td>80 Randomized 8:2 to PER977 or placebo</td>
<td>Achieved baseline hemostasis within 10–30 minutes following administration (whole-blood clotting time); effects sustained for 24 hours</td>
<td>NCT01826266</td>
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<tr>
<td></td>
<td>Phase II, RCT</td>
<td>Safety/efficacy of escalating reversal doses of PER977 following edoxaban. Additionally investigating effects of PER977 on re-anticoagulation with edoxaban and second PER977 reversal</td>
<td>69 Randomized 4:1 to PER977 or placebo</td>
<td>September 2015</td>
<td>NCT02207257</td>
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<tr>
<td>Andexanet at a glance</td>
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<tr>
<td>Mechanism of action</td>
<td>Recombinant and inactivated form of factor Xa</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Binds factor Xa inhibitors: apixaban, rivaroxaban, and edoxaban</td>
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<td></td>
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<tr>
<td>Proposed dose</td>
<td>400 mg IV bolus ±2 hours infusion at 4 mg/min*</td>
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<tr>
<td>Time to effect</td>
<td>2 minutes: 94% decrease in anti fXa activity§</td>
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<tr>
<td></td>
<td>Effects of bolus last 1–2 hours</td>
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<tr>
<td>Adverse effects</td>
<td>No known prothrombotic effect – tissue factor pathway inhibitor interaction deserves further investigation</td>
<td></td>
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<tr>
<td>Possible indications</td>
<td>Life-threatening hemorrhage</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Emergent surgery</td>
<td></td>
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</tbody>
</table>

**Notes:** *Dose currently being investigated in Phase III, part 2 trial; §data from Crowther et al.44**

**Abbreviation:** FDA, Food and Drug Administration; IV, intravenous.
Figure 2. Schematic structure and mechanism of action of andexanet alfa.\textsuperscript{9,43,56,58}

GLA: gamma(γ)-carboxyglutamic acid; EGF1,2: epidermal growth factor-like domains 1 and 2; ATIII: antithrombin III; LMWH: low-molecular-weight heparins.
Currently Phase III ANNEXA trials (Andexanet Alfa a Novel Antidote to the Anticoagulant Effects of fXA Inhibitors) are testing the safety and efficacy of andexanet alfa in healthy subjects anticoagulated with apixaban (ANNEXA-A) and rivaroxaban (ANNEXA-R). Preliminary data in n=33 (treatment n=24) showed that an andexanet alfa bolus reduced apixaban-mediated anticoagulation immediately. Anti-factor Xa activity decreased by 94% ($P<0.0001$), and near normalization of coagulation (activated clotting time [ACT]) lasted 1–2 hours.\textsuperscript{43} In part two of this phase, a 400 mg IV bolus followed by a 2-hour infusion was evaluated for efficacy in reduction of the plasma-free fraction of apixaban and normalization of thrombin generation and sustained effect. Complete results from these Phase III studies are anticipated.\textsuperscript{44}

### Table 2 Antidotes for NOACs, ongoing and completed clinical trials

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Phase, Study Design</th>
<th>Study Details</th>
<th>Planned Publication Date</th>
<th>NCT Number</th>
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<tr>
<td>Andexanet alfa</td>
<td>Phase II, RCT</td>
<td>Pharmacokinetics/safety of andexanet alfa in reversing rivaroxaban, apixaban, edoxaban, enoxaparin, and betrixaban</td>
<td>November 2013</td>
<td>NCT01758432</td>
</tr>
<tr>
<td></td>
<td>Phase III, RCT ANNEXA</td>
<td>ANNEX – A Safety/efficacy of andexanet alfa in reversal of apixaban in healthy 50–75 yo subjects</td>
<td>Preliminary data: Immediate reversal of anticoagulation lasting 1–2 hours. Anti-factor Xa activity decreased by 94% and near normalization of ACT</td>
<td>NCT02207725</td>
</tr>
<tr>
<td></td>
<td>Phase III, cohort study</td>
<td>Safety and efficacy of andexanet alfa in achieving hemostasis in patients with major bleeding on direct or indirect factor Xa inhibitors (except lovenox)</td>
<td>November 2022</td>
<td>NCT02329327</td>
</tr>
<tr>
<td><strong>Idarucizumab at a glance</strong></td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td><strong>Mechanism of action</strong></td>
<td>Binds free and thrombin-bound dabigatran</td>
<td></td>
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<tr>
<td></td>
<td>Renal elimination of complex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Two 2.5 g 50 mL bolus IV infusions within 15 minutes: total 5 g*</td>
<td></td>
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</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>45 minutes, may require repeat dosing*</td>
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<tr>
<td><strong>Time to effect</strong></td>
<td>Normalization of dTT and ECT minutes after infusion*</td>
<td></td>
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<tr>
<td></td>
<td>Median time to cessation of bleeding: 11.4 hours*</td>
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<tr>
<td><strong>Adverse effects</strong></td>
<td>Headache, nasopharyngitis, back pain, skin irritation – similar to placebo§</td>
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<tr>
<td></td>
<td>No prothrombotic effect§</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Possible indications</strong></td>
<td>Life-threatening hemorrhage</td>
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<td></td>
<td>Emergent surgery</td>
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<tr>
<td></td>
<td>Dabigatran overdose</td>
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</tbody>
</table>

**Notes:** *Data from Pollack et al.\textsuperscript{49} interim analysis of Phase III study; §data from Glund et al.\textsuperscript{47,48} Phase I studies.*

**Abbreviations:** dTT, dilute thrombin time; FDA, Food and Drug Administration; ECT, ecarin-clotting time; IV, intravenous.
Idarucizumab was designed as a specific reversal agent for anticoagulant activity of dabigatran

- **Humanized Fab fragment**
- **Binding affinity ~350× higher** than dabigatran to thrombin
- **No intrinsic procoagulant or anticoagulant activity**
- **IV dosing by bolus or rapid infusion, immediate onset of action**
- **Short half-life**

- Schiele et al. Blood 2013; Stangier et al. OR 320; presented at ISTH 2015
<table>
<thead>
<tr>
<th>Antidote</th>
<th>Phase</th>
<th>Study Information</th>
<th>Study Details</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idarucizumab</td>
<td>Phase I, RCT</td>
<td>Part 1: Rising dose assessment of idarucizumab in healthy subjects</td>
<td>110 Randomized 3:1 to idarucizumab or placebo</td>
<td>Safe and well tolerated. Rapid peak plasma exposure and elimination achieved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Part 2: Safety and efficacy of idarucizumab in dabigatran reversal in healthy subjects</td>
<td>47 Randomized 3:1 to idarucizumab or placebo</td>
<td>Immediate, complete, and sustained (72 hours) reversal of dabigatran-induced anticoagulation (dTT, ECT, aPTT, TT) in healthy subjects</td>
</tr>
<tr>
<td></td>
<td>Phase III, cohort study REVERSE AD (A Study of the REVERSal Effects of Idarucizumab on Active Dabigatran)</td>
<td>Safety and efficacy of idarucizumab in dabigatran reversal in patients with serious bleeding (group A) or patients requiring urgent procedure (group B)</td>
<td>Estimated enrollment: 300</td>
<td>July 2017</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Interim analysis of 90 patients who received idarucizumab: idarucizumab normalized dTT in ≥93% of patients, ECT in ≥88%, and unbound dabigatran concentration was reduced to minimal levels. Median cessation of bleeding in group A: 11.4 hours. Normal hemostasis achieved in 92% of patients undergoing surgery (92%) in group B</td>
</tr>
</tbody>
</table>
RE-VERSE AD™: interim results from the first 90 patients have been presented and published.

- **Group A:** Uncontrolled bleeding (51 patients)
- **Group B:** Emergency surgery or procedure (39 patients)

Dabigatran levels were reduced immediately after idarucizumab administration

Group A: uncontrolled bleeding (n = 51)

Group B: emergency procedures (n = 39)

Dabigatran levels were <20 ng/mL* in 89/90 patients after infusion of first vial, in 77/83 at 12 hours and 62/78 patients at 24 hours

RE-VERSE AD™: benefit of dabigatran reversal confirmed by favourable secondary clinical endpoints

<table>
<thead>
<tr>
<th>Group A: Uncontrolled bleeding</th>
<th>Group B: Emergency surgery or procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=51</td>
<td>N=39</td>
</tr>
</tbody>
</table>

Bleeding assessable: N=38*

Surgery performed: N=36†

Median local investigator-determined time to bleeding cessation: **11.4 hours**

Intraoperative haemostasis:
- 33 normal (92%)
- 2 mildly abnormal
- 1 moderately abnormal
Anticoagulation can be resumed soon after administration of idarucizumab

Dabigatran can be re-started 24 hours after administration of idarucizumab if patient is clinically stable and adequate haemostasis has been achieved.

Any antithrombotic treatment (e.g. heparin) can be initiated at any time after administration of idarucizumab.

Allows protection against thrombotic risk to be resumed as soon as the need for surgery or the bleeding event has been addressed.
4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

Praxbind è un inattivatore specifico per dabigatran ed è indicato nei pazienti adulti trattati con Pradaxa (dabigatran etexilato) nei casi in cui si rende necessaria l’inattivazione rapida dei suoi effetti anticoagulanti:
  - Negli interventi chirurgici di emergenza/nelle procedure urgenti
  - Nel sanguinamento potenzialmente fatale o non controllato.

4.2 Posologia e modo di somministrazione

Limitato esclusivamente all’uso ospedaliero.

Posologia

La dose raccomandata di Praxbind è di 5 g (2 x 2,5 g/50 mL).
Indicazioni per la Gestione Del Paziente in Terapia con NOAC

In caso di Interventi Chirurgici Programmabili
In caso di Interventi Chirurgici d’Urgenza
In caso di Manifestazioni Emorragiche
Gestione Shift Terapie Anticoagulanti

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