New Options for Anticoagulation Reversal:
A Practical Approach

Hyung Wook Park
Chonnam National University Hospital, Gwangju, Korea
4 NOACs – Prevention of TE

<table>
<thead>
<tr>
<th>Drug</th>
<th>NOAC No. of events (%/yr.)</th>
<th>Warfarin No. of events (%/yr.)</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID</td>
<td>171 (1.44)</td>
<td>186 (1.58)</td>
<td>0.91</td>
<td>0.74–1.12</td>
</tr>
<tr>
<td>(ITT)1,2</td>
<td></td>
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</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td>122 (1.01)</td>
<td>186 (1.58)</td>
<td>0.65</td>
<td>0.51–0.81</td>
</tr>
<tr>
<td>(ITT)1,2</td>
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</tr>
<tr>
<td>Rivaroxaban</td>
<td>184 (1.65)</td>
<td>221 (1.96)</td>
<td>0.85</td>
<td>0.70–1.03</td>
</tr>
<tr>
<td>(Safety AT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>199 (1.19)</td>
<td>250 (1.51)</td>
<td>0.79</td>
<td>0.65–0.95</td>
</tr>
<tr>
<td>(ITT)4</td>
<td></td>
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</tr>
<tr>
<td>Edoxaban 60 mg OD*</td>
<td>281 (1.49)</td>
<td>317 (1.69)</td>
<td>0.88</td>
<td>0.75–1.03</td>
</tr>
<tr>
<td>(ITT)5</td>
<td></td>
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</tr>
<tr>
<td>Edoxaban 30 mg OD*</td>
<td>360 (1.91)</td>
<td>317 (1.69)</td>
<td>1.13</td>
<td>0.97–1.31</td>
</tr>
<tr>
<td>(ITT)5</td>
<td></td>
<td></td>
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- Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5

- *Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weight <60kg, or concomitant verapamil, quinidine or dronedarone

- AT = as treated; BID = twice daily; CI = confidence interval; HR = hazard ratio; ITT = intention-to-treat

4 NOACs – Prevention of hemorrhagic stroke

<table>
<thead>
<tr>
<th>NO. of events (%/yr.)</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg BID (ITT) &lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>14 (0.12)</td>
<td>45 (0.38)</td>
<td>0.31</td>
<td>0.17–0.56</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID (ITT) &lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>12 (0.10)</td>
<td>45 (0.38)</td>
<td>0.26</td>
<td>0.14–0.49</td>
</tr>
<tr>
<td>Rivaroxaban (Safety AT) &lt;sup&gt;3&lt;/sup&gt;</td>
<td>29 (0.26)</td>
<td>50 (0.44)</td>
<td>0.59</td>
<td>0.37–0.93</td>
</tr>
<tr>
<td>Apixaban (ITT) &lt;sup&gt;4&lt;/sup&gt;</td>
<td>40 (0.24)</td>
<td>78 (0.47)</td>
<td>0.51</td>
<td>0.35–0.75</td>
</tr>
<tr>
<td>Edoxaban 60 mg OD* (ITT) &lt;sup&gt;5&lt;/sup&gt;</td>
<td>49 (0.26)</td>
<td>90 (0.47)</td>
<td>0.54</td>
<td>0.38–0.77</td>
</tr>
<tr>
<td>Edoxaban 30 mg OD* (ITT) &lt;sup&gt;5&lt;/sup&gt;</td>
<td>30 (0.16)</td>
<td>90 (0.47)</td>
<td>0.33</td>
<td>0.22–0.50</td>
</tr>
</tbody>
</table>

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* Edoxaban dose halved (from 60 mg to 30 mg OD in high dose group; from 30 mg to 15 mg OD in low dose group) if CrCl 30–50 mL/min, weight < 60kg, or concomitant verapamil, quinidine or dronedarone

AT = as treated; BID = twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant

4 NOACs – Major bleedings

<table>
<thead>
<tr>
<th>Drug</th>
<th>NOAC</th>
<th>Warfarin</th>
<th>HR</th>
<th>95% CI</th>
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<tr>
<td>Dabigatran 110 mg BID</td>
<td></td>
<td>342 (2.71)</td>
<td>421 (3.36)</td>
<td>0.80</td>
</tr>
<tr>
<td>(ITT)¹,²</td>
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</tr>
<tr>
<td>Dabigatran 150 mg BID</td>
<td></td>
<td>399 (3.11)</td>
<td>421 (3.36)</td>
<td>0.93</td>
</tr>
<tr>
<td>(ITT)¹,²</td>
<td></td>
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</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
<td>395 (3.6)</td>
<td>386 (3.4)</td>
<td>1.04</td>
</tr>
<tr>
<td>(Safety AT)³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td></td>
<td>327 (2.13)</td>
<td>462 (3.09)</td>
<td>0.69</td>
</tr>
<tr>
<td>(ITT)⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban 60 mg OD*</td>
<td></td>
<td>418 (2.75)</td>
<td>524 (3.43)</td>
<td>0.80</td>
</tr>
<tr>
<td>(ITT)⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban 30 mg OD*</td>
<td></td>
<td>254 (1.61)</td>
<td>524 (3.43)</td>
<td>0.47</td>
</tr>
<tr>
<td>(ITT)⁵</td>
<td></td>
<td></td>
<td></td>
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Not head-to-head comparison – no clinical conclusions can be drawn – adapted from references 1–5

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AT = as treated; BID = twice daily; HR = hazard ratio; ITT = intention-to-treat; NOAC = novel oral anticoagulant

Limitations of NOACs

- **Less clinical experience with NOACs**
  - vs. 60 years of warfarin experience

- **Measurement issues**
  - Not widely available in clinical settings
    - ECT, DTT - Dabigatran
      - Anti-Factor Xa – Rivaroxaban or Apixaban

- **No established reversal agents**
  - Lack of guidance in emergency surgery or major bleeding due to NOAC use
Candidates for reversal agents

• Patients presenting with bleeding
  - Life-threatening bleeding (eg, intracranial)
  - Critical organ or closed-space bleeding (eg, pericardial, retroperitoneal)
  - Ongoing bleeding despite measures to control bleeding

• Patients at high risk bleeding
  - Requiring emergent/urgent procedure
  - Expected long delay in spontaneous restoration of normal hemostasis
    (eg, over-anticoagulation, renal failure)
Key milestones

**INITIAL IDEA**
- 2008 onwards

**PRECLINICAL AND PHASE I TESTING**
- 2009 onwards

**REGULATORY APPROVAL and WIDE AVAILABILITY**
- 2015 onwards
Reversal agents for NOACs may encourage appropriate stroke prevention in patients with AF

Up to half of patients with AF are still not receiving anticoagulants

‘The availability of specific reversal agents for the NOACs would improve the confidence of clinicians and patients in these new agents and encourage an increase in appropriate stroke preventive therapy for patients with NVAF’

Rapid reversal of the anticoagulant effects of NOACs may be required in certain emergency situations.

A specific reversal agent could take the NOAC out of the equation in these situations.

While a specific reversal agent could remove the anticoagulant effect, other measures (e.g. surgery, fluid replacement) would still be required to correct the underlying cause of the bleed and its consequences.
What are the characteristics of an ideal reversal agent?

- Widely available
- Specifically targets only the NOAC
- Acts immediately
- Complete reversal
- Easy to use
- No pro-coagulant effects
- Effect is sustained
- Predictable effects
Idarucizumab is the only approved and widely available NOAC reversal agent

Idarucizumab was designed as a specific reversal agent for the anticoagulant activity of dabigatran

- **Humanized antibody fragment (Fab)**
- **Binding affinity for dabigatran ~350× higher than dabigatran to thrombin, resulting in essentially irreversible binding**
- **Immediate onset of action**
- **No intrinsic procoagulant or anticoagulant activity**
- **Idarucizumab–dabigatran complex is eliminated in a few hours**

Idarucizumab provided immediate, complete, and sustained reversal of dabigatran anticoagulation in volunteers

Idarucizumab also showed immediate, complete, and sustained reversal in volunteers with renal impairment.

<table>
<thead>
<tr>
<th>Anticoagulation activity (dTT, s)</th>
<th>Time after end of infusion (hrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean baseline</td>
<td>24</td>
</tr>
<tr>
<td>Upper limit of normal</td>
<td>24</td>
</tr>
</tbody>
</table>

dTT, diluted thrombin time
Idarucizumab was well tolerated across subject groups

- No drug-related AEs reported in total >200 volunteers
- No AEs indicative of immunogenic reactions
- AEs and local tolerability reactions similar for placebo and active treatment
- No relevant changes in any of the investigated safety parameters
- No procoagulant effects

What clinical data are available for idarucizumab, and what are the implications for patients and physicians?
RE-VERSE AD™ is a multicentre, open-label, single-arm Phase III trial

**Group A:** Uncontrolled bleeding + dabigatran treated

**Group B:** Emergency surgery or procedure* + dabigatran treated

Patients were treated based on presenting condition, not coagulation tests

Primary endpoint: dabigatran reversal within 4 hours (dTT or ECT)

*Other than for bleeding.
dTT, diluted thrombin time; ECT, ecarin clotting time
Group B results: reasons for surgery

Acute renal failure
Aortic aneurysm repair

Acute abdomen

Bone fracture
Pericardiocentesis
Lumbar puncture
Heart transplant
Pacemaker implant

Infection

ICH (surgical intervention)

Incarcerated hernia

Other
Reperfusion for MI

Pneumothorax for tube thoracostomy

Pollack C et al. AHA 2016
RE-VERSE AD™: reversal of dabigatran anticoagulation in Group A and B, based on dTT

Group A: uncontrolled bleeding (N=298)

- Baseline and 10-30 min
- 1 hr, 2 hrs, 4 hrs, 12 hrs, 24 hrs

Group B: emergency surgery or procedure (N=196)

- Baseline and 10-30 min
- 1 hr, 2 hrs, 4 hrs, 12 hrs, 24 hrs

Anticoagulation activity (d'TT, s)

Idarucizumab 5 g

d'TT, diluted thrombin time
Adapted from Pollack C et al. AHA 2016
RE-VERSE AD™: primary endpoint showed immediate reversal of dabigatran-mediated anticoagulation in the majority of patients

Median maximum reversal within 4 hours was 100% for both dTT and ECT (95% CI: 100–100)

dTT normalized within 4 hours in 235/238 patients (98.7%) in group A and 141/143 patients (98.6%) in group B*

Similar results with ECT and central laboratory aPTT

*Calculated for patients with elevated levels at baseline (efficacy population)
aPTT, activated partial thromboplastin time; dTT, diluted thrombin time; ECT, ecarin clotting time
Pollack C et al. AHA 2016
Clinical results indicate rapid cessation of extracranial bleeding in Group A

Group A

298 patients with bleeding type classed as:

- 53% ICH
- 33% Non-assessable non-ICH
- 14% Non-GI
- 33% GI

The 158 assessable non-ICH bleeds were:

- With a median time to bleeding cessation of:
  - 3.5 hrs
  - 4.5 hrs

Pollack C et al. AHA 2016
Clinical results indicate mostly normal haemostasis during surgery in Group B

191 of 196 (97.4%) patients underwent surgery/procedure with periprocedural haemostasis classed as:

- Normal: 93%
- Mildly abnormal: 5%
- Moderately abnormal: 1%
- Severely abnormal: 0%

Overall median time from first vial to procedure: 1.6 hrs

Pollack C et al. AHA 2016
Idarucizumab is indicated when rapid reversal of the anticoagulant effects of dabigatran is required for emergency surgery/urgent procedures or in life-threatening bleeding.

- No contraindications to use
- No dose adjustment for age or renal impairment etc.
- The dose of idarucizumab is 5 g
- Vials contain solution (2.5 g/50 mL) ready for infusion or injection
Idarucizumab can be used alongside other supportive therapy, and allows for anticoagulation to be resumed soon after administration

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

Can be used alongside other supportive therapy (e.g. PCC, FFP)

Dabigatran can be re-started 24 hours after administration*

FP, fresh frozen plasma; PCC, prothrombin complex concentrate
*If the patient is clinically stable and adequate haemostasis has been achieved
Praxbind®: EU SPC, 2015
South Korea case – CNUH experience

- 84yr-old male patient
  - He has Hypertension, Presence of pacemaker, AF and liver Cirrhosis
  - Pradaxa 110mg BID for AF
  - Gum bleeding (uncontrolled bleeding)
South Korea case – CNUH experience

CBC
- WBC: 6700 /mm³
- Hgb: 5.6 g/dL
- PLT: 212 x10³ /mm³

LFT
- AST: 11 U/L
- ALT: <6 U/L

RFT and Electrolyte
- Cr: 2.5 mg/dL
- Na/K: 136/4.9/104 mEq/L

Coagulation profile
- PT: 57.0/10.3/4.84 sec/%/INR
- aPTT: No coagulation (>180 sec)

Cardiac enzymes
- TnT: 0.045 ng/mL
Major Bleeding in Non-Surgical Patients

1. Fatal bleeding.
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome.
3. Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.
South Korea case – CNUH experience

Graph showing changes in hemoglobin (Hgb) and activated partial thromboplastin time (aPTT) levels. Key points:
- Hgb levels: 14, > 200
- aPTT levels: 5.6, 8, 11.4
- Dates:
  - Jul 23, 2015
  - Nov 23, 2016
  - Nov 28, 2016
- Interventions:
  - 110 mg
  - 5 g
Andexanet Alfa

- Recombinant modified human Factor Xa decoy protein
- Catalytically inactive
- Binds to Factor Xa inhibitors in their active site
- Enhances the activity of endogenous factor Xa and attenuates levels of anticoagulant activity
- Half life; - 1 hr
Andexanet Alfa; ANNEXA-A and ANNEXA-R

- Anticoagulant effects of Fxa inhibitors Apixaban (ANNEXA-A) and Rivaroxaban (ANNEXA-R)
  - 2 parallel trials

- Study objective;
  - To determine the efficacy and safety of andexanet alfa for the reversal of anticoagulation with apixaban or rivaroxaban in older healthy volunteers
Andexanet Alfa; ANNEXA-A and ANNEXA-R

A Apixaban Study, Andexanet Bolus

B Rivaroxaban Study, Andexanet Bolus

C Apixaban Study, Andexanet Bolus plus Infusion

D Rivaroxaban Study, Andexanet Bolus plus Infusion

ANNEXA-4; Inclusion/Exclusion criteria

Prospective, Open-Label Study of Andexanet Alfa in patients receiving a Factor Xa inhibitor who have acute major bleeding

- Acute major bleeding that is
  - Potentially life-threatening or
  - Associated with a fall in Hb of ≥ 2 g/dL or
  - Associated with Hb of ≤ 8 g/dL or
  - In a critical area or organ
- Demonstrated ICH by MRI/CT
- Received factor Xa inhibitor within prior 18 hours

- Surgery expected in < 12 hr, except minimally invasive procedures
- Intracerebral hemorrhage with
  - Glasgow coma score < 7 or
  - Intracerebral hematoma > 60 cc
- Expected history (within 2 days) of thrombotic event
- Severe sepsis or septic shock
- Received VKA, dabigatran, PCC, rFVIIa, whole blood, or plasma fractions
## Ciraparantag/Aripazine

<table>
<thead>
<tr>
<th>Structure</th>
<th>Synthetic small molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Direct Xa inhibitors, DTIs, UFH, LMWH (universal antidote)</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Noncovalent hydrogen bind (exact mechanism unsure)</td>
</tr>
<tr>
<td><strong>Current status</strong></td>
<td>Phase 2 study ongoing</td>
</tr>
</tbody>
</table>
Ciraparantag/Aripazine; reversal of edoxaban activity

Summary I

1. A specific reversal agent for dabigatran is now widely available in Europe, the USA, and other countries.

2. Idarucizumab immediately reverses the anticoagulant activity of dabigatran and is easy to use.

3. The availability of a specific reversal agent for dabigatran adds more control and is an important factor in NOAC choice.
Need for reversal agents expected in increase with
- Aging population (increased risk of AF and VTE)
- Increase in uptake of NOACs

Reversal agents
- Idarucizumab currently available
- Andexanet alfa in late stage development
- Ciranparantag/ariipazine in early stage development

Available of reversal agents
- Reassures clinicians of starting OACs in high-risk patients