Emergency Management of Patients on Direct Oral Anticoagulants (DOACs)

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NE RTC Annual Education Symposium
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The extent of the problem

≈1-2% of the UK population are anticoagulated
8% of individuals >80 years of age are anticoagulated.
The diagram illustrates the transition from 2010 to 2016 in the treatment of blood clots. In 2010, Warfarin was the primary medication used, while in 2016, Edoxaban, Rivaroxaban, Apixaban, and Dabigatran became more prevalent. Edoxaban is highlighted as a significant addition in 2016.
Targets of Direct Oral Anticoagulants

**ORAL**
- TTP889
- **Xa Inhibitors**
  - Rivaroxaban
  - Apixaban
  - Edoxaban
  - LYS17717
  - YM150
  - PRT-054021

**IIa Inhibitors**
- Dabigatran

**PARENTERAL**
- TFPI (tifacogin)
- APC (drotrecogin alfa) sTM (ART-123)
- **Indirect Xa inhibitors**
  - Fondaparinux
  - Idraparinux
  - SSR-126517

- **Direct Xa Inhibitors**
  - DX-9065a
  - Otamixaban

TF=tissue factor
The ideal anticoagulants?

- Oral administration
- Rapid onset of action
- Relatively short half-life
- Predictable pharmacokinetics
  - No need for monitoring
- Few drug or dietary interactions
- Modest risk of bleeding
- Rapidly reversible
**Table 1: NOACs: Overview and Pharmacology**

<table>
<thead>
<tr>
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Apixaban, dabigatran and rivaroxaban have a rapid onset and short half-life.
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Apixaban, dabigatran and rivaroxaban have a rapid onset and short half-life.
Predictable dose-response relationship

- No monitoring required

Few drug interactions

No dietary interactions
Current agents and licensed indications

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<th></th>
<th>Dabigatran (IIa inhibitor)</th>
<th>Rivaroxaban (Xa inhibitor)</th>
<th>Apixaban (Xa inhibitor)</th>
<th>Edoxaban (Xa inhibitor)</th>
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<tr>
<td><strong>Stroke prevention in AF</strong></td>
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<td><strong>DVT</strong></td>
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<td><strong>PE</strong></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td><strong>Orthopaedic prophylaxis</strong></td>
<td>☐</td>
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Clinical trial data

• Non-inferior to warfarin in terms of efficacy
  – Prevention of VTE in orthopaedic surgery
  – Prevention of stroke in AF
  – Treatment of VTE

• Equivalent safety in terms of bleeding
  – Less intracranial haemorrhage
  – More GI tract bleeding (dabigatran)

• No head-to-head DOAC comparisons
Rates, management and outcome of bleeding complications during rivaroxaban therapy in daily care: results from the Dresden NOAC registry

Jan Beyer-Westendorf, Kati Förster, Sven Pannach, Franziska Ebertz, Vera Gelbracht, Christoph Thieme, Franziska Michalski, Christina Köhler, Sebastian Werth, Kurtulus Sahin, Luise Tittl, Ulrike Hänsel and Norbert Weiss

Efficacy and Safety of Dabigatran Etxilate and Warfarin in “Real-World” Patients With Atrial Fibrillation

A Prospective Nationwide Cohort Study

Torben Bjerregaard Larsen, MD, PhD,† Lars Hvilsted Rasmussen, MD, PhD,† Flemming Skjøth, MSc, PhD,* Karen Margrete Due, MSc,* Torbjörn Callréus, MD, PhD,‡ Mary Rosenzweig, MSc,‡ Gregory Y. H. Lip, MD†§

Aalborg and Copenhagen, Denmark; and Birmingham, United Kingdom
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Apixaban, dabigatran and rivaroxaban have a rapid onset and short half-life.
Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication - Safety Review of Post-Market Reports of Serious Bleeding Events

Posted 12/07/2011

FDA:
July 2011

MHRA:
December 2011

Dabigatran (Pradaxa▼): risk of serious haemorrhage—need for renal function testing

Article date: December 2011

Summary

A number of cases of serious and fatal haemorrhage have been reported in elderly patients with renal impairment who were receiving dabigatran. Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min)
Limitations

- Caution in renal impairment
- Applicability to non-trial population
  - Extremes of weight
  - Elderly
  - Pregnancy
  - Children
- Thromboembolism in patients with artificial heart valves
- Cost
- Availability of antidote
Anticoagulant-associated ICH: Is reversibility important?
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Lobar</th>
<th>Cerebellar</th>
<th>Mortality, %</th>
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</thead>
<tbody>
<tr>
<td>Kase et al, 1985^21</td>
<td>24</td>
<td>6</td>
<td>9 (37%)</td>
<td>63</td>
</tr>
<tr>
<td>Franke et al, 1990^15</td>
<td>79</td>
<td>...</td>
<td>1 (1%)</td>
<td>67</td>
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<tr>
<td>Radberg et al, 1991^22</td>
<td>28</td>
<td>12</td>
<td>4 (14%)</td>
<td>57</td>
</tr>
<tr>
<td>Forsting et al, 1991^16</td>
<td>40</td>
<td>...</td>
<td>1 (3%)</td>
<td>50</td>
</tr>
<tr>
<td>Fredriksson et al, 1992^23</td>
<td>29</td>
<td>6</td>
<td>1 (3%)</td>
<td>55</td>
</tr>
<tr>
<td>SPAF II Study, 1994^7</td>
<td>9</td>
<td>3</td>
<td>2 (22%)</td>
<td>67</td>
</tr>
<tr>
<td>Staaf et al, 1987^24</td>
<td>33</td>
<td>...</td>
<td>...</td>
<td>64</td>
</tr>
<tr>
<td>Fogelholm et al, 1992^20</td>
<td>41</td>
<td>...</td>
<td>...</td>
<td>54</td>
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<tr>
<td>Hylek and Singer, 1994^13</td>
<td>77</td>
<td>...</td>
<td>...</td>
<td>46</td>
</tr>
<tr>
<td>ASPECT Study, 1994^6</td>
<td>17</td>
<td>...</td>
<td>...</td>
<td>47</td>
</tr>
<tr>
<td>Sixty-Plus Study, 1982^19</td>
<td>4</td>
<td>...</td>
<td>...</td>
<td>75</td>
</tr>
<tr>
<td>Smith et al, 1990^5</td>
<td>6</td>
<td>...</td>
<td>...</td>
<td>67</td>
</tr>
<tr>
<td>Wintzen et al, 1984^17</td>
<td>38</td>
<td>...</td>
<td>...</td>
<td>68</td>
</tr>
<tr>
<td>Dawson et al, 1993^14</td>
<td>18</td>
<td>...</td>
<td>...</td>
<td>56*</td>
</tr>
<tr>
<td>Landefeld and Goldman, 1989^2</td>
<td>11</td>
<td>...</td>
<td>...</td>
<td>63*</td>
</tr>
<tr>
<td>Aggregate</td>
<td>454</td>
<td>30%</td>
<td>9%†</td>
<td>60%‡</td>
</tr>
</tbody>
</table>

SPAF indicates Stroke Prevention in Atrial Fibrillation; ASPECT, Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis.

*All sites of intracranial bleeds, including subarachnoid and subdural bleeding.

†Cerebellar hemorrhages constitute 5% to 10% of intracerebral hemorrhages in nonanticoagulated patients.

‡In nonanticoagulated patients, approximately 40% (range, 20% to 50%) of intracerebral hemorrhages and 15% of infarcts are fatal by 30 days.
Features of anticoagulant-associated ICH

- Rapid deterioration with first 24-48 hours, increasing ICH volume
- Poor outcome associated with:
  - ICH volume
  - Intraventricular extension of bleeding
- Majority of warfarin-related ICH occurs with INR 2-3.5
- Rapid reversal of anticoagulant effect essential:
  - To prevent haematoma expansion
  - To facilitate appropriate surgical intervention

Sjoblom et al. Stroke (2001), 32, 2567-2574
Management and prognostic features of ICH during anticoagulant therapy: A Swedish Multicenter Study
• Surgery should occur within 48 hours of presentation with hip fracture
• Examined time to surgery in 2258 patients:
  • 233 on warfarin
  • 27 on a DOAC
The ideal anticoagulant in a patient who bleeds or requires urgent surgery?

- Oral administration
- Rapid onset (2 hours) of action
- Relatively short half-life
- Predictable pharmacokinetics
  - No need for monitoring
- Few drug or dietary interactions
- Rapidly reversible (antidote)
- If not reversible...
  - Short half-life
  - Ability to measure anticoagulant effect – rapidly and accurately
Effect of the direct oral anticoagulants on basic coagulation screening

<table>
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<tr>
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<tr>
<td>PT</td>
<td>↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>APTT</td>
<td>↑↑</td>
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<tr>
<td>Fibrinogen</td>
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<td>D dimers</td>
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<td>↓</td>
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<tr>
<td>Platelet count</td>
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- Assays for dabigatran and factor Xa antagonists are available;
  - **Therapeutic** level: 200 – 400 ng/ml
  - **Prophylactic** level: 50 – 150 ng/ml
  - **Minimal** effect: < 50 ng/ml
Warfarin

Prothrombin complex concentrate

Vitamin K
Warfarin vs DOAC

Prothrombin complex concentrate

Vitamin K
Dabigatran antidote (Idarucizumab: Praxbind)
Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

N Engl J Med. 2015;373:511-20

• 91 patients taking dabigatran
  • Group A: 51, serious bleeding
  • Group B: 39, requiring urgent surgery
• 5g idarucizumab – two 2.5g IV boluses, no more than 15 minutes apart
- Test results normalised in 88-98% of subjects within minutes
- Good clinical response
- Effect was sustained for up to 24 hours
- No safety concerns
Indications for Idarucizumab

- Adult patients treated with dabigatran, when rapid reversal of anticoagulant effect is required:
  - For emergency surgery/urgent procedures
  - In life-threatening or uncontrolled bleeding
Idarucizumab: Newcastle experience

Case 1

- 71 y o female
- Dabigatran for AF and previous DVTs
- Presented with acute cholecystitis and AKI
- Dabigatran stopped
- 2 days later required emergency cholecystectomy
  - PT 29s, APTT 84s, TT >300s, dabigatran level 400 ng/mL
  - Given 2x 2.5g idarucizumab
  - Complete correction of coagulopathy, dabigatran level <1 ng/mL
- Discharged from hospital one month later on rivaroxaban
Idarucizumab: Newcastle experience

Case 2

• 54 y o man
• Dabigatran for paroxysmal AF (4 months post successful ablation)
• Presented with increasing SOB, ECHO showed large pericardial effusion
• Required emergency pericardiocentesis for cardiac tamponade
  – PT 18s, APTT 45s, dabigatran level 83 ng/mL
  – Given 2x 2.5g idarucizumab
  – Pericardiocentesis performed, drained 1 litre of blood-stained fluid
  – PT and APTT normalised
• Discharged from hospital, off anticoagulant therapy
Idarucizumab: Newcastle experience

Case 3

• 72 y o man
• Dabigatran for AF
• Background of lung cancer
• Found lying on floor. Sepsis/Malaena/AKI
  – PT 51s, APTT 86s, TT >300s, dabigatran 923 ng/mL
  – Creatinine 320 (baseline 75)
  – Given 2x 2.5g idarucizumab
• Died
Idarucizumab: Newcastle experience

Case 4
• 82 y o female
• Dabigatran for AF
• Presented with 2 week history of malaena, hypotensive and tachycardic
  – PT 12s, APTT 43s, TT 220s, dabigatran level 86 ng/mL
  – Given 2x 2.5g idarucizumab
  – PT 12s, APTT 28s, TT 19s, dabigatran level 0.59 ng/mL
• No further GI tract bleeding
• Remains an inpatient, not currently anticoagulated
PRT064445: recombinant FXa variant

- Two modifications introduced to human fXa
  - Removal of the Gla-domain
  - Mutation at the active site (S419A)
- PRT064445 (r-Antidote)
  - No pro- or anti-coagulant activity
  - Retains binding ability for FXa inhibitors
Mechanism for reversal of oral FXa inhibitor by PRT064445

\[ \text{Prothrombin} \xrightarrow{\text{Ki}} \text{Inhibited Ilase} \]

\[ \text{Inhibited Ilase} \xrightarrow{\text{Thrombin}} \text{Prothrombin} \]

\[ \text{FXa inhibitor} \xrightarrow{+} \text{Ilase} \]

\[ \text{PRT064445} \xrightarrow{+} \text{FXa inhibitor-PRT064445 complex} \]

\[ \text{Ki} \quad \text{Kd} \]
• 67 patients with acute major bleeding on a factor Xa inhibitor
• Bolus of andexanet, followed by 2-hour infusion
• Dose dependent on timing of last dose of Xa inhibitor, <7 hours
- Anti-factor Xa activity decreased by 89%-93% initially
- 79% had good clinical response at 12 hours
- 18% had a thrombotic event
DOACs: Management of bleeding or urgent surgery

- **General measures:**
  - Stop the drug
  - Document timing of last dose
  - Check FBC, coagulation screen, creatinine/eGFR, (drug assay)
  - Correct haemodynamic compromise
  - Defer surgery if able
  - Control haemorrhage:
    - Mechanical compression
    - Surgical/radiological intervention
DOACs: Management of bleeding or urgent surgery

- **Specific measures:**
  - Dabigatran
    - Oral activated charcoal if last dose < 2 hours
    - Consider haemodialysis/haemofiltration
      - ≈60% removed within 2 hours
        - guided by normalisation of APTT
        - caution re rebound increases in Dabigatran concentration
    - Idarucizumab (Praxbind) 5g
  - Rivaroxaban/Apicaban/Edoxaban
    - Oral activated charcoal if last dose < 2 hours
    - Antidote???
DOACs: Management of bleeding or urgent surgery

• Non-specific pharmacological measures:
  ➢ Antifibrinolytics- Tranexamic acid, oral/IV/topical
  ➢ Other haemostatic agents-
    ➢ PCC (Beriplex)
    ➢ rFVIIa (NovoSeven)
    ➢ aPCC (FEIBA)
Summary

• DOACs are being increasingly used in the UK
• No rapidly available test to assess anticoagulant effect, but drug assays may be requested in the lab
  – estimate anticoagulant intensity by timing of last dose, renal function
• Antidote for dabigatran (Idarucizumab: Praxbind) is now available for use - may ‘wear off’ after 12-24 hours
• Supportive measures continue to be mainstay of therapy for bleeding due to factor Xa antagonists