Novel Anticoagulants: Optimizing Selection for Your Patient

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Venous thromboembolism (DVT, PE)

The third most common vascular death

Venous thromboembolism

DVT & PE

The third most common vascular death

Antithrombotic Therapy for VTE


1. VTE and no Cancer
   - Rivaroxaban
   - Apixaban
     Initial overlap with Parenteral anticoagulation required with
   - Dabigatran
   - Endoxaban

Grade 2B
(Grade 1: strong, Grade 2: Weak; A: High, B: moderate, C: low)
2. VTE and Cancer
   • If not on DOACs LMWH over VKA

3. VTE and no Cancer
   • If not on DOACs VKA over LMWH
## DOACs Comparative Pharmacology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dosing</td>
<td>BID</td>
<td>QD</td>
<td>BID</td>
<td>QD</td>
</tr>
<tr>
<td>Time to C&lt;sub&gt;max&lt;/sub&gt;, h</td>
<td>1-3</td>
<td>2-4</td>
<td>3-4</td>
<td>1-2</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-17</td>
<td>7-11</td>
<td>12</td>
<td>9-11</td>
</tr>
<tr>
<td>Renal clearance,%</td>
<td>80</td>
<td>33</td>
<td>27</td>
<td>50</td>
</tr>
<tr>
<td>Interactions</td>
<td>P-gp</td>
<td>3A4/P-gp</td>
<td>3A4/P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td>CYP metabolism, %</td>
<td>None</td>
<td>32</td>
<td>&lt;32</td>
<td>&lt;4</td>
</tr>
</tbody>
</table>
The coagulation cascade.

Extrinsic pathway

Tissue factor

Factor VII → Factor VIIa → Factor X → Factor IXa → Prothrombin

Intrinsic pathway

Thrombin

Factor XI → Factor Xla → Factor X → Factor IX → Factor IXa → Prothrombin


©2003 by European Respiratory Society
Isolated Platelets

Fibrin Strands in a Blood Clot
Figure. Classification of established anticoagulants and new anticoagulants that were recently licensed for use or are in advanced stages of clinical development. fXa indicates factor IXa. *Indirectly inhibit coagulation by interacting with antithrombin. †AVE5026 is an ultralow-molecular-weight heparin that primarily inhibits fXa and has minimal activity against thrombin.

John W. Eikelboom, and Jeffrey I. Weitz Circulation. 2010;121:1523-1532
The coagulation cascade. Solid arrow (→) indicates conversion; broken arrow (−−−−) indicates catalytic action.
<table>
<thead>
<tr>
<th>INR Range</th>
<th>Percent patient months in range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0</td>
<td>20.8</td>
</tr>
<tr>
<td>2.0-3.0</td>
<td>63.9</td>
</tr>
<tr>
<td>&gt;3.0</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Disadvantage of VKA

- Narrow therapeutic window;
- They exhibit considerable variability in dose response among subjects;
- They are subject to interactions with drugs and diet;
- They have laboratory control that can be difficult to standardize;
- They have problems in dosing as a result of patient nonadherence and miscommunication between the patient and physician..

- Chest. 2004; 126(3_suppl):204S-233S. doi:10.1378/chest.126.3_suppl.204S
DOAC (NOAC) doses for VTE treatment:

- **Dabigatran**: LMWH for 7 days then 150mg twice daily

- **Endoxaban**: 5-10 days of paranteral agent, then 60mg po daily
  1. 30mg daily if CrCl is 15-50ml/min, or body weight less than 60kg,
  2. do not use if CrCl is greater than 95ml/min.
• Rivaroxaban: 15mg po twice daily for 3 weeks then 20mg daily

• Apixaban: 10mg po twice daily for 7 days then 5mg twice daily
Indications

- Reduction of stroke and systemic embolism in non valvular Afib
- Treatment of DVT
- Treatment of PE
- DVT prophylaxis Knee or hip replacement.
Rivaroxaban

- Selective Inhibitor of Factor Xa and the prothrombinase activity.

- In-Vitro selectively inhibits both free and clot bound Fxa and prothrombinase activity.
Rivaroxaban

• Elimination half life:
  5-9 hours in healthy 20-45 year old
  11-13 hours in the elderly

• 15 & 20 mg dose should be taken food

• 10 mg dose can be taken with or without food.
• Einstein DVT
• Einstein-PE
• Einstein- Extension
EINSTEIN-PE Study Design

Population: objectively confirmed symptomatic PE with or without symptomatic DVT (N=4852)

Randomization

- XARELTO® 15 mg twice daily
- XARELTO® 20 mg once daily
- enoxaparin 1 mg/kg twice daily for ≥5 days
  + warfarin INR 2.5 (range 2.0-3.0)

TREATMENT PERIOD:
3, 6, or 12 months at physicians’ discretion

End of Treatment
Proven Noninferior for Treatment of PE

Time to first occurrence of the composite of recurrent DVT or nonfatal or fatal PE

HR (95% CI): 1.12 (0.75-1.68)

XARELTO®

enoxaparin/warfarin

<table>
<thead>
<tr>
<th>Days From Randomization</th>
<th>XARELTO® (N=2419)</th>
<th>enoxaparin/warfarin (N=2413)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2350</td>
<td>2316</td>
</tr>
<tr>
<td></td>
<td>2321</td>
<td>2295</td>
</tr>
<tr>
<td></td>
<td>2311</td>
<td>2280</td>
</tr>
<tr>
<td></td>
<td>2180</td>
<td>2155</td>
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<tr>
<td></td>
<td>2167</td>
<td>2146</td>
</tr>
<tr>
<td></td>
<td>2133</td>
<td>2113</td>
</tr>
<tr>
<td></td>
<td>837</td>
<td>835</td>
</tr>
<tr>
<td></td>
<td>794</td>
<td>787</td>
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<tr>
<td></td>
<td>785</td>
<td>773</td>
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<tr>
<td></td>
<td>757</td>
<td>746</td>
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<tr>
<td></td>
<td>725</td>
<td>722</td>
</tr>
<tr>
<td></td>
<td>672</td>
<td>675</td>
</tr>
</tbody>
</table>
Cumulative Rates of the Primary Efficacy and Safety Outcomes and Rates of Major Bleeding.

Einstein - DVT

EINSTEIN–DVT Study Design

**Population:** objectively confirmed symptomatic proximal DVT without symptomatic PE (N=3449)

**Randomisation**
- XARELTO® 15 mg twice daily
- Enoxaparin 1 mg/kg twice daily for ≥5 days + warfarin INR 2.5 (range 2.0-3.0)

**Day 21**
- XARELTO® 20 mg once daily

**Follow-up**
- **TREATMENT PERIOD:** 3, 6, or 12 months at physicians’ discretion

**End of Treatment**
Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome in the Two Studies.

Einstein DVT

Proven Noninferior for Treatment of DVT
Time to first occurrence of the composite of recurrent DVT or nonfatal or fatal PE

HR (95% CI): 0.68 (0.44-1.04)

Cumulative Event Rate (%)

Days From Randomization

XARELTO® (N=1731)
1668 1648 1635 1424 1412 1369 400 369 364 345 309 266

enoxaparin/warfarin (N=1718)
1616 1581 1565 1368 1358 1301 380 362 342 325 297 264

Number of Patients at Risk
Proven Risk Reduction for Longer-Term Treatment

Time to first occurrence of the composite of recurrent DVT or nonfatal or fatal PE

Initial 6 to 14 months of anticoagulation therapy

<table>
<thead>
<tr>
<th>Days From Randomization</th>
<th>XARELTO® (N=602)</th>
<th>Placebo (N=594)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>590</td>
<td>582</td>
</tr>
<tr>
<td></td>
<td>583</td>
<td>570</td>
</tr>
<tr>
<td></td>
<td>577</td>
<td>559</td>
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<td></td>
<td>552</td>
<td>522</td>
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<tr>
<td></td>
<td>503</td>
<td>468</td>
</tr>
<tr>
<td></td>
<td>491</td>
<td>453</td>
</tr>
<tr>
<td></td>
<td>171</td>
<td>164</td>
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<tr>
<td></td>
<td>138</td>
<td>138</td>
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<td></td>
<td>133</td>
<td>134</td>
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<tr>
<td></td>
<td>114</td>
<td>110</td>
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<td></td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>81</td>
<td>85</td>
</tr>
</tbody>
</table>
APIXABAN

• AMPLIFY

• AMPLIFY EXTENSION
Oral Apixaban for the Treatment of Acute Venous Thromboembolism

Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M.,
Alexander S. Gallus, M.D., Margot Johnson, M.D., Urszula Masiukiewicz, M.D., Raphael Pak, Ph.D., John
Thompson, Ph.D., Gary E. Raskob, Ph.D., Jeffrey I. Weitz, M.D., for the AMPLIFY Investigators

N Engl J Med
Volume 369(9):799-808
August 29, 2013
Kaplan–Meier Cumulative Event Rates.

Conclusions

• A fixed-dose regimen of apixaban alone was noninferior to conventional therapy for the treatment of acute venous thromboembolism and was associated with significantly less bleeding.
ENDOXABAN
Original Article

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

The Hokusai-VTE Investigators

N Engl J Med
Volume 369(15):1406-1415
October 10, 2013
Randomization and Follow-up.

8292 Patients underwent randomization

4143 Were assigned to receive heparin–edoxaban

25 Did not receive heparin–edoxaban

4118 Were included in modified intention-to-treat and safety analyses

181 Did not complete the overall study period

132 Died

36 Withdrew consent

7 Were lost to follow-up

6 Had other reasons

4149 Were assigned to receive heparin–warfarin

27 Did not receive heparin–warfarin

4122 Were included in modified intention-to-treat and safety analyses

167 Did not complete the overall study period

126 Died

34 Withdrew consent

4 Were lost to follow-up

3 Had other reasons

Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome.

Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome.

Conclusions

• Edoxaban administered once daily after initial treatment with heparin was noninferior to high-quality standard therapy and caused significantly less bleeding in a broad spectrum of patients with venous thromboembolism, including those with severe pulmonary embolism.
Original Article

Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism

Sam Schulman, M.D., Clive Kearon, M.D., Ajay K. Kakkar, M.D., Patrick Mismetti, M.D., Sebastian Schellong, M.D., Henry Eriksson, M.D., David Baanstra, M.Sc., Janet Schnee, M.D., Samuel Z. Goldhaber, M.D., for the RE-COVER Study Group

N Engl J Med
Volume 361(24):2342-2352
December 10, 2009
Cumulative Risks of a First Event of Major Bleeding and of Any Bleeding among Patients Randomly Assigned to Dabigatran or Warfarin

Cumulative Risk of Recurrent Venous Thromboembolism or Related Death during 6 Months of Treatment among Patients Randomly Assigned to Dabigatran or Warfarin

Table 3. Adverse Events during the Double-Dummy Phase and during the Total Period of Treatment.\textsuperscript{a, b}

<table>
<thead>
<tr>
<th>Event</th>
<th>Dalbigatran Double-Dummy Phase (N=1220)</th>
<th>Total Period of Treatment (N=1,375)</th>
<th>Warfarin Double-Dummy Phase (N=1214)</th>
<th>Total Period of Treatment (N=1,266)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event — no. of subjects (%)</td>
<td>770 (62.8)</td>
<td>844 (66.3)</td>
<td>792 (65.2)</td>
<td>856 (67.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Serious event — no. of subjects (%)</td>
<td>147 (12.0)</td>
<td>165 (12.0)</td>
<td>133 (11.0)</td>
<td>150 (11.8)</td>
<td>0.43</td>
</tr>
<tr>
<td>Event leading to discontinuation of study drug — no. of subjects (%)</td>
<td>97 (7.9)</td>
<td>115 (9.0)</td>
<td>79 (6.5)</td>
<td>86 (6.8)</td>
<td>0.05</td>
</tr>
<tr>
<td>Events with an incidence of at least 3% — no. of subjects (%)\textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>60 (4.9)</td>
<td>79 (6.2)</td>
<td>64 (5.3)</td>
<td>88 (7.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>59 (4.8)</td>
<td>64 (5.0)</td>
<td>69 (5.7)</td>
<td>71 (5.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Nausea</td>
<td>43 (3.5)</td>
<td>49 (3.8)</td>
<td>43 (3.5)</td>
<td>58 (4.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46 (3.8)</td>
<td>57 (4.5)</td>
<td>34 (2.8)</td>
<td>38 (3.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>47 (3.8)</td>
<td>50 (3.9)</td>
<td>53 (4.4)</td>
<td>54 (4.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>33 (2.7)</td>
<td>41 (3.2)</td>
<td>47 (3.9)</td>
<td>53 (4.2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Back pain</td>
<td>42 (3.4)</td>
<td>46 (3.6)</td>
<td>44 (3.6)</td>
<td>50 (3.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>45 (3.7)</td>
<td>48 (3.8)</td>
<td>30 (2.5)</td>
<td>33 (2.6)</td>
<td>0.12</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>41 (3.3)</td>
<td>43 (3.4)</td>
<td>45 (3.7)</td>
<td>48 (3.8)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>36 (2.9)</td>
<td>39 (3.1)</td>
<td>7 (0.6)</td>
<td>9 (0.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Acute coronary syndrome — no. of subjects (%)\textsuperscript{d}</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>4 (0.3)</td>
<td>5 (0.4)</td>
<td>3 (0.2)</td>
<td>3 (0.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (0.2)</td>
<td>4 (0.3)</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>Abnormal liver-function tests — no. of subjects/total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST &gt;3 x ULN</td>
<td>33/1204 (2.7)</td>
<td>38/1320 (2.1)</td>
<td>20/1188 (1.7)</td>
<td>25/1199 (2.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>ALT &gt;3 x ULN</td>
<td>35/1204 (2.9)</td>
<td>42/1220 (3.4)</td>
<td>42/1188 (3.5)</td>
<td>46/1199 (3.8)</td>
<td>0.68</td>
</tr>
<tr>
<td>ALT &gt;3 x ULN plus bilirubin &gt;2 x ULN</td>
<td>2/1195 (0.2)</td>
<td>2/1055 (0.2)</td>
<td>4/1182 (0.3)</td>
<td>4/1106 (0.4)</td>
<td>0.69</td>
</tr>
</tbody>
</table>

\textsuperscript{a} In the double-dummy phase, patients received only the oral treatment (dalbigatran and warfarin-like placebo or warfarin and dalbigatran-like placebo). The total period of treatment included the single-dummy phase (in which patients received a parenteral anticoagulant agent and warfarin or warfarin-like placebo) and the double-dummy phase. A 5-day washout period was included in both cases. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, and ULN upper limit of normal.

\textsuperscript{b} The \( P \) values are for the comparison between the two groups during the total treatment period. The \( P \) value for adverse events leading to discontinuation of treatment was calculated with the use of the Cox model, including treatment; active cancer at baseline; symptomatic pulmonary embolism at baseline; the interaction between active cancer and symptomatic pulmonary embolism at baseline as factors. The \( P \) values for acute coronary syndrome, myocardial infarction, and ALT exceeding three times the upper limit of normal plus bilirubin exceeding two times the upper limit of normal were calculated with the use of Fisher’s exact test. The \( P \) values for the rest of the events were calculated with the use of the chi-square test.

\textsuperscript{c} Bleeding events not presented in this table; epistaxis and hematuria occurred in 3% or more of patients in the warfarin group.

\textsuperscript{d} In the case of acute coronary syndromes that were classified as definite or likely by the independent adjudication committee.

Which DOAC?

**Specific Patient Characteristics**
- High Risk of Bleeding (eg, HAS-BLED ≥3)
  - Consider agent/dose with lowest incident of bleeding
    - Apixaban
    - Edoxaban
- Previous GI bleeding or high risk
  - Consider agent with lowest reported incident of GI bleed
    - Apixaban
- High risk of ischemia stroke, low bleeding risk
  - Consider agent/dose with best reduction of ischemia stroke
    - Dabigatran
- Previous stroke (secondary prevention)
  - Consider best investigated agent
    - Rivaroxaban
- CAD, previous MI or high risk for ACS/MI
  - Consider agent with a positive effect in ACS
    - Rivaroxaban
- Renal impairment
  - Consider agent least dependent on renal function/best data
    - Apixaban
    - Edoxaban
- GI/upset disorders
  - Consider agent/dose with no reported GI/effects
    - Apixaban
    - Edoxaban
    - Rivaroxaban
- Patient preference
  - Consider once-daily formulation
    - Edoxaban
    - Rivaroxaban
Discuss important treatment consideration with patient

• Do not discontinue therapy without consulting healthcare provider

• Be alert for signs and symptoms of bleeding

• Inform clinician before undergoing any invasive procedure, including dental work, Neuraxial procedures
### Management of Interruption of DOAC Therapy

<table>
<thead>
<tr>
<th>Drug half-life</th>
<th>Patient</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>Renal function</td>
<td>Bleeding risk</td>
</tr>
<tr>
<td>Route of clearance</td>
<td>Concomitant drugs (eg, Aspirin)</td>
<td>Thrombotic risk</td>
</tr>
</tbody>
</table>

Epidural or spinal hematoma, which may result in long term or permanent paralysis, have occurred in patients treated with Dabigatran or Rivaroxaban who are receiving neuroaxial anesthesia or undergoing spinal puncture.
### Cessation of NOAC Before Planned Surgery

<table>
<thead>
<tr>
<th>CrCl, mL/min</th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>High Risk</td>
<td>Low Risk</td>
<td>High Risk</td>
<td>Low Risk</td>
</tr>
<tr>
<td>≥80</td>
<td>≥24h</td>
<td>≥48h</td>
<td>≥24h</td>
<td>≥48h</td>
</tr>
<tr>
<td>50-80</td>
<td>≥36h</td>
<td>≥72h</td>
<td>≥24h</td>
<td>≥48h</td>
</tr>
<tr>
<td>30-50</td>
<td>≥48h</td>
<td>≥96h</td>
<td>≥24h</td>
<td>≥48h</td>
</tr>
<tr>
<td>15-30</td>
<td>Not indicated</td>
<td>≥36h</td>
<td>≥48h</td>
<td>≥36h</td>
</tr>
<tr>
<td>&lt;15</td>
<td>No official indication for use</td>
<td>No official indication for use</td>
<td>No official indication for use</td>
<td>No official indication for use</td>
</tr>
</tbody>
</table>

No important bleeding risk/ or adequate local hemostasis possible: perform at trough level (ie, ≥12h or 24h after last intake)
FDA News Release

FDA approves Praxbind, the first reversal agent for the anticoagulant Pradaxa

Praxbind approved for specific emergency situations

For Immediate Release
October 16, 2015
Idarucizumab

Humanized monoclonal antibody fragment that binds to dabigatran

3 clinical trial, 283 healthy volunteers subjected to Dabigatran, the reversal agent dropped the Dabigatran plasma level;

REVERSE-AD
Thank You
Novel Anticoagulants: Optimizing Selection for Your Patient

Getu Assefa, MD, FACC; FSCAI

Assistant Clinical Professor
Regional Affiliate of Medicine
University of Louisville
Madisonville, KY, USA

Interventional Cardiology
Baptist Health
Madisonville, KY, USA

Insert academic affiliation, practice or hospital logo(s) of preference here. Product and/or sponsor logos not permitted, per CME guidelines.