Anticoagulation 2014

Bruce Ritchie MD, FRCPC
Director VTE Clinic, UofA Hospital
Director Comprehensive Bleeding Disorder Clinic
Director Comprehensive Rare Blood Disorder Clinic
Director Canadian BioSample Repository (CBSR)

Mar-2014
Conflicts of Interest

- Principle Investigator in Pharmaceutical Trials including: Fragmin, Lovenox, XiMelagatan, Rivaroxaban, Dabigatran, Apixaban, Edoxaban

- **Unpaid** consulting advice to: Baxter, Bayer, Boehringer-Ingelheim, Canadian Blood Service, Canadian Hemophilia Society, Covidien, CSL Behring, Dyax, Leo Pharmaceuticals, Novartis, Novo Nordisk, Pharming, Pfizer, Sanofi, Talecris, Wyeth

- In lieu of Honoraria, I request that donations be made to the University of Alberta to fund summer students ($1300/month X 4 = $5200)

- I have received funding for Investigator Initiated studies (biobanking) from: Baxter, CSL Behring, Novartis, Novo Nordisk, Pfizer, Wyeth. Pending: Bayer, Boehringer-Ingelheim, Leo, Sanofi.
Venous ThromboEmbolism: New Anticoagulant Drugs 2014

1. How do they work
2. How do we measure them
3. How do we reverse them
4. How do we manage elective Surgery

Bruce Ritchie MD, FRCPC³
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Adapted from Wikipedia –
http://en.wikipedia.org/wiki/Coagulation
Microparticles & Tissue Factor,
green=TF, red=platelets, fibrin=blue, platelets/TF=yellow, platelets/fibrin=turquoise,
platelets/TF/fibrin=white.  
http://80-
www.nature.com/login.ezproxy.library.ualberta.ca/nm/journal/v8/n10/suppinfo/nm782_S1.html
Thromboembolic Disease in Alberta

• Incidence 108 in 100,000\(^1\)
  – 3,584,304 people in Alberta in 2011; 4 million (Mar, 2013)
  – 3,871 new cases per year in Alberta; 4,320 (Mar 2013)

• Recurrence in 30% - 40% \(^2,6\)
  – 1161 - 1548 recurrent cases per year in Alberta
  – 1296-1728 (Mar-2013)

• Severe Post thrombotic Syndrome \(^2,3,4\)
  – Severe PTS in 3% at 2 years\(^2\)(116-130), 6% at 10 years\(^3\); (232-260)
  – Disability costs $5,500-7,600\(^3\)

• 10% of symptomatic PE’s are fatal within 1 hour\(^4,5\), 40% at 30 days\(^6\)


Fihn SD; Callahan CM; Martin DC; McDonell MB; Henikoff JG; White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. *Annals of Internal Medicine.* 124(11):970-9, 1996


Risk of VTE Recurrence


Pulmonary Embolism:
A Life-threatening Disease

Cumulative mortality following acute PE

15.3% Mortality
At 3 months

International Cooperative Pulmonary Embolism Registry

N=2454

Mortality rate (%; excluding PE first recognised at necropsy)

Time from diagnosis (days)

PE=pulmonary embolism


Post Thrombotic Syndrome in Canada
Warfarin & Intracranial Hemorrhage in Finland 1993 to 2008
Warfarin & Intracranial Hemorrhage in Finland 1993 to 2008

2004, introduction of PCC
### Table 5. Studies Comparing FFP and PCC to Correct Warfarin Anticoagulation in Nontraumatic ICH

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design (PCC product)</th>
<th>Pts.</th>
<th>Bleeding</th>
<th>Results</th>
<th>Evidence Grade*</th>
</tr>
</thead>
</table>
| Fredriksson (1992) | Retrospective (3-factor PCC) | PCC, n = 10; FFP, n = 7 | ICH        | All pts. received vitamin K 10-20 mg iv  
PCC decreased INR from 2.83 to 1.22 within 4.8 hours  
FFP decreased INR from 2.97 to 1.74 within 7.3 hours; p < 0.001  
Signs and symptoms of ICH progressed less, with nonsignificant trend toward less severe outcomes in pts. treated with 3-factor PCC | Low             |
| Makris (1997)      | Prospective (4-factor PCC) | PCC, n = 29; FFP, n = 12 | WAICH, other | 4-factor PCC corrected INR in 28 pts. (mean, 1.3; range, 0.9-3.8)  
FFP partially corrected INR (mean, 2.3; range, 1.6-3.8)  
Posttreatment factor II, VII, IX, and X levels higher with PCC vs FFP | Moderat          |
| Boullis (1999)     | Prospective (3-factor PCC) | PCC, n = 5; FFP, n = 8 | WAICH      | All pts. received vitamin K  
All PCC pts. also received FFP  
3-factor PCC plus FFP corrected INR significantly faster (2.95 ± 0.46 hours) vs FFP alone (8.9 ± 1.51 hours); p < 0.01  
No significant difference in neurologic outcomes | Moderat          |
| Cartmill (2000)    | Prospective (3-factor PCC) | PCC, n = 6; FFP, n = 6 | WAICH      | All pts. received vitamin K  
At 15 minutes posttreatment, 3-factor PCC decreased mean INR from 4.86 before treatment to 1.32 vs FFP, which decreased mean INR from 5.32 before treatment to 2.30  
PCC reversal significantly faster (41 vs 115 minutes); p < 0.001 | Low              |
| Siddiq (2008)      | Retrospective (factor IX complex concentrate) | PCC, n = 10; FFP, n = 9 | WAICH      | All pts. received concurrent vitamin K  
All PCC pts. also received FFP  
3-factor PCC (4.3 ± 2.1 hours) vs FFP group (8.5 ± 5.6); p < 0.005 | Low              |
| Demeyere (2010)    | Prospective, randomized (4-factor PCC) | PCC, n = 18; FFP, n = 20 | Cardiac surgery; no pt. received vitamin K | No pt. received concurrent vitamin K  
4-factor PCC achieved target INR faster than FFP at 15 minutes after CPB; no significant difference in mean INR values 60 minutes after CPB (PCC, 1.6 vs FFP, 1.7) | Good             |

CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; ICH = intracranial hemorrhage; INR = international normalized ratio; PCC = prothrombin complex concentrate; WAICH = warfarin-associated ICH.
Poor Prognosis in Warfarin-Associated Intracranial Hemorrhage Despite Anticoagulation Reversal.

# New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>target</th>
<th>Peak</th>
<th>T ½</th>
<th>Clearance</th>
<th>Drug Interactions</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>A Fib</td>
<td>II</td>
<td>1-4 h</td>
<td>12-17 h</td>
<td>85% renal</td>
<td>Rifampin, quinidine, amiodarone, Potent P-gp inhibitor</td>
<td>aPCC</td>
</tr>
<tr>
<td></td>
<td>DVT/PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hip/Knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>A Fib</td>
<td>Xa</td>
<td>0.5-2 h</td>
<td>7-11 h</td>
<td>66% renal really 33%</td>
<td>Potent CYP3A4, P-gp inhibitor</td>
<td>PCC</td>
</tr>
<tr>
<td></td>
<td>DVT/PE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hip/Knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>A Fib</td>
<td>Xa</td>
<td>3-4 h</td>
<td>12 h</td>
<td>27% renal</td>
<td>Potent CYP3A4 inhibitor</td>
<td>PCC</td>
</tr>
<tr>
<td></td>
<td>Hip/Knee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edoxaban</td>
<td>No</td>
<td>Xa</td>
<td>1-2 h</td>
<td>6-11 h</td>
<td>35% renal</td>
<td>Potent CYP3A4, P-gp inhibitor</td>
<td>PCC</td>
</tr>
<tr>
<td>Betrixaban</td>
<td>No</td>
<td>Xa</td>
<td>3-4 h</td>
<td>20 h</td>
<td>&lt;8% renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fonda</td>
<td>Hip/Knee</td>
<td>Xa</td>
<td>2 h</td>
<td>17 h</td>
<td>100% renal</td>
<td></td>
<td>protamine</td>
</tr>
</tbody>
</table>

# Dabigatran and Postmarketing Reports of Bleeding

Mary Ross Southworth, Pharm.D., Marsha E. Reichman, Ph.D., and Ellis F. Unger, M.D.
March 13, 2013 | DOI: 10.1056/NEJMp1302834

## Intracranial and Gastrointestinal Bleeding Events in New Users of Dabigatran and Warfarin from the Mini-Sentinel Distributed Database, October 2010 through December 2011.*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Events</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,599</td>
<td>16</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,195</td>
<td>19</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis with required diagnosis of atrial fibrillation</td>
<td>10,587</td>
<td>8</td>
</tr>
<tr>
<td>Sensitivity analysis without required diagnosis of atrial fibrillation</td>
<td>12,182</td>
<td>10</td>
</tr>
</tbody>
</table>

Southworth MR, Reichman ME, Unger EF. Dabigatran and Postmarketing Reports of Bleeding. NEJM Online 13-Mar-2013 DOI: 10.1056/NEJMp1302834
Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

Figure 1. Cumulative Risk of Recurrent Venous Thromboembolism or Related Death during 6 Months of Treatment among Patients Randomly Assigned to Dabigatran or Warfarin.
Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

Oral Rivaroxaban for the Treatment of Symptomatic Pulmonary Embolism

Apixaban in Patients with Atrial Fibrillation

Thrombin Time Ratio Best

Approximates Dabigatran Plasma Levels

Standardized Hemoclot Thrombin Time

Effect of Rivaroxaban On Coagulation Parameters: apTT Ratio

Effect of Apixaban on anti Xa assays


Fig. 1  a Anti-Xa LMWH activity correlated strongly and in a linear fashion with apixaban plasma concentrations. b Anti-Xa apixaban activity correlated strongly and in a linear fashion with apixaban plasma concentrations.
INGELHEIM, GERMANY - The US Food and Drug Administration (FDA) has granted "breakthrough-therapy designation" to idarucizumab, an investigational fully humanized antibody fragment (FAB) intended to be used as an antidote for dabigatran etexilate mesylate (Pradaxa, Boehringer Ingelheim) [1]. The manufacturer announced the news of the agency's decision earlier today, noting that the designation is expected to "expedite its development."

Results from a phase 1/2 study of idarucizumab, released at last year's American Heart Association Scientific Sessions, showed that the agent can produce immediate, complete, and sustained reversal of dabigatran-induced anticoagulation in healthy human volunteers, with no off-target toxicity. A phase 3 study, RE-VERSE AD, is already under way in people taking dabigatran who develop uncontrolled bleeding or who require emergency surgery or other procedures, the company notes. European sites are actively enrolling in the trial, although no US sites have started enrollment.
Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban

Dabigatran

Reversing NOACs:
FEIBA (Activated PCC)

Contains Factors II, IX, and X mainly non-activated and Factor VII mainly in the activated form.

Dose: 50-100 IU/kg

FEIBA monograph:
Alternative: PCC and rFVIIa

Octaplex/Beriplex
40 IU/kg

+  

NovoSeven (rFVIIa)
1 mg

1. Octaplex monograph:
   http://www.octapharma.com/index.php?eID=tx_nawsecuredl&u=0&file=uploads/media/20120613_PM_Octaplex_approved.pdf&t=1384711575&hash=0ab78e2e273f669f418af3633c86b3bf07ab3da4


Strategies for treating bleeding on NOACs

• Minor or Moderate bleeding: hold NOAC; measure creatinine, PTT/PT; local measures

• Severe/Life-threatening bleeding: hold NOAC; measure creatinine, PTT/PT; local measures, PLUS
  • Dabigatran
    • Activated charcoal suspension if less then 2 hrs
    • Consider dialysis
    • Reverse with FEIBA 50-100 U/kg or PCC+rFVIIa
  • Rivaroxaban
    • Reverse with PCC 20-40 U/kg

Availability of PCCs (Octaplex, Beriplex) in Alberta
http://www.albertahealthservices.ca/3318.asp

North Zone: 37 hospitals,
    not LaCrete (RH Ig), Vilna
Edmonton Zone: 12 hospitals,
    not CCI (IV Ig), East Edmonton Health, Gibbons
Central Zone: 29 hospitals (all)
Calgary: 13 hospitals (all)
South: 12 hospitals,
    not Coaldale, Oyen (rbc's & Rh Ig)
Total: 103 hospitals in Alberta – almost all the hospitals that can
Availability of aPCCs (FEIBA) in Alberta
http://www.albertahealthservices.ca/3318.asp

PCC availability, includes most stroke sites (?Canmore, Medicine Hat), & FVIII Inhibitor patients
Peace River Community Health Centre
Queen Elizabeth II Hospital (Grande Prairie)
Sturgeon Hospital (St. Albert)
University of Alberta Hospital
Royal Alexandra Hospital
Misericordia Hospital
Grey Nuns Hospital
Hinton Healthcare Centre
Westlock Healthcare Centre
Red Deer Hospital
Foothills Hospital
Alberta Children’s Hospital
Chinook Regional Hospital (Lethbridge)
<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Hemorrhages</td>
<td>50-75 U/kg of body weight</td>
<td>• 12 hour intervals&lt;br&gt;• dose can be increased to 100 U/kg of body weight at 12 hour intervals&lt;br&gt;• Treatment should be continued until clear signs of clinical improvement appear, such as relief of pain, reduction of swelling or mobilization of the joint.</td>
</tr>
<tr>
<td>Mucous Membrane Bleeding</td>
<td>50 U/kg of body weight</td>
<td>• 6-hour intervals under careful monitoring (visible bleeding site, repeated measurements of the patient's hematocrit)&lt;br&gt;• If higher dosages are given, take care to prolong dosage intervals so as to make certain that a maximum daily dosage of 200 units per kg of body weight is not exceeded.</td>
</tr>
<tr>
<td>Soft Tissue Hemorrhage (i.e. retroperitoneal bleeding)</td>
<td>100 U/kg of body weight</td>
<td>• 12-hour intervals are recommended&lt;br&gt;• A daily dosage of 200 units per kg of body weight should not be exceeded.</td>
</tr>
<tr>
<td>Other Severe Hemorrhages (i.e. CNS bleedings)</td>
<td>100 U/kg of body weight</td>
<td>• 12-hour intervals&lt;br&gt;• When, in order to achieve a clear clinical improvement, the dosage intervals must be shortened, it is to be ensured that a daily dosage of 200 units per kg of body weight is not exceeded.</td>
</tr>
<tr>
<td>Surgery</td>
<td>50-100 U/kg of body weight</td>
<td>• 6 hours intervals are recommended&lt;br&gt;• A maximum daily dose of 200 U/kg bw should not be exceeded.</td>
</tr>
</tbody>
</table>
Post-marketing surveillance:
1. the risk of thrombosis ranged from 0/4500 infusions⁴, 3.18/100,000 infusion in 18 years⁵, 8.24/100,000 infusions³, and 4.05/100,000 infusions². Risk factors were overdose/frequent dosing in 30-80%.
2. Combining aPCC with tranexamic acid showed no excess thrombosis¹.
Rivaroxaban and enoxaparin have similar effects on Anti-Factor Xa activity beyond 24 hours.

Enoxaparin has a half-life of 4-7 hours and can be dosed either OD or BID.

Adapted from Kubitza et al., ISTH 2005; Lovenox Product Monograph, 2010
Questions

Where the magic happens

Your comfort zone
Questions

FOTOS DE LAURENT SCHWEBEL: http://www.slideshare.net/halffast/fotos-de-laurentschwebel1-16369767?from_search=1
The future for DOAC reversal - Idarucizumab

ClinicalTrials.gov

Safety, Tolerability, PK and PD of BI 655075 and Establishment of BI 655075 Dose(s) Effective to Reverse Prolongation of Blood Coagulation Time by Dabigatran

This study has been completed.

Sponsor:
Boehringer Ingelheim

Information provided by (Responsible Party):
Boehringer Ingelheim

ClinicalTrials.gov Identifier:
NCT01955720

First received: September 30, 2013
Last updated: August 13, 2014
Last verified: August 2014

Purpose

To investigate safety, tolerability, PK and PD of BI 655075 and to establish the BI 655075 dose(s) effective to reverse prolongation of blood coagulation time by dabigatran

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage</td>
<td>Drug: BI 655075</td>
<td>Phase 1</td>
</tr>
<tr>
<td></td>
<td>Drug: Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Randomized

Official Title: Randomized, Double-blind, Placebo-controlled, Two-way Cross-over Phase Ib Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BI 655075 and to Establish the Efficacy of BI 655075 in Reversal of Dabigatran Anticoagulant Activity in Volunteers
The future for DOAC reversal - Andexanet Alfa

Neal Shah. Reversal Agents for Anticoagulants: Focus on Andexanet Alfa. **AMSRJ** Spring 2014; 1, No. 1

*Original artwork by: Mohammad A. Rattu, PharmD*
Discontinuation Before Elective Invasive or Surgical Procedures
Time to discontinue medication prior to procedure

Rivaroxaban
- Determine patients risk of bleeding
  - Standard risk: At least 1 day
  - High risk of bleeding or major surgery: 2-4 days

Dabigatran
- Determine patients risk of bleeding
  - Standard risk
    - Estimate CrCl
      - 30-49 mL/min: 2-3 days
      - 50-79 mL/min: 1-2 days
      - ≥ 80 mL/min: 1 day
  - High risk of bleeding or major surgery
    - Estimate CrCl
      - 30-49 mL/min: 4 days
      - 50-79 mL/min: 2-3 days
      - ≥ 80 mL/min: 2 days

Apixaban
- Determine patients risk of bleeding
  - Standard risk: At least 1 day
  - High risk of bleeding or major surgery: At least 2 days

Xarelto® PM, July 18, 2012;
Eliquis® PM November 27, 2012;
Pradaxa® PM November 12, 2012
Aspirin for the Prevention of Recurrent Venous Thromboembolism: The INSPIRE Collaboration. John Simes, Cecilia Becattini, Giancarlo Agnelli, John W. Eikelboom, Adrienne C. Kirby, Rebecca Mister, Paolo Prandoni, Timothy A. Brighton, for the INSPIRE Study Investigators*. Published online before print August 2014. Circulation DOI: 10.1161/CIRCULATIONAHA.114.008828
Aspirin for the Prevention of Recurrent Venous Thromboembolism: The INSPIRE Collaboration. John Simes, Cecilia Becattini, Giancarlo Agnelli, John W. Eikelboom, Adrienne C. Kirby, Rebecca Mister, Paolo Prandoni, Timothy A. Brighton, for the INSPIRE Study Investigators*. Published online before print August 2014. Circulation DOI: 10.1161/CIRCULATIONAHA.114.008828
ASA for VTE prophylaxis after unprovoked VTE

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ASA for VTE prophylaxis after unprovoked VTE

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Event rate/year (%)</th>
<th>Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=608)</td>
<td>Aspirin (n=616)</td>
<td></td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>112 (7.5)</td>
<td>81 (5.1)</td>
<td>0.65 0.49–0.86 0.003</td>
</tr>
<tr>
<td>Major vascular events</td>
<td>129 (8.7)</td>
<td>91 (5.7)</td>
<td>0.63 0.48–0.83 &lt;0.001</td>
</tr>
<tr>
<td>Net clinical benefit</td>
<td>144 (9.8)</td>
<td>103 (6.5)</td>
<td>0.64 0.50–0.83 &lt;0.001</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>42 (2.6)</td>
<td>27 (1.7)</td>
<td>0.63 0.39–1.02 0.06</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>85 (5.5)</td>
<td>59 (3.6)</td>
<td>0.63 0.45–0.88 0.006</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>23 (1.4)</td>
<td>20 (1.2)</td>
<td>0.82 0.45–1.52 0.53</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (0.4)</td>
<td>9 (0.5)</td>
<td>1.31 0.48–3.53 0.60</td>
</tr>
</tbody>
</table>

Aspirin for the Prevention of Recurrent Venous Thromboembolism: The INSPIRE Collaboration. John Simes, Cecilia Becattini, Giancarlo Agnelli, John W. Eikelboom, Adrienne C. Kirby, Rebecca Mister, Paolo Prandoni, Timothy A. Brighton, for the INSPIRE Study Investigators*. Published online before print August 2014. Circulation DOI: 10.1161/CIRCULATIONAHA.114.008828
ASA for VTE prophylaxis after unprovoked VTE

<table>
<thead>
<tr>
<th>Year</th>
<th>Events (n/N)</th>
<th>Event rate (%)</th>
<th>HR (95% CI)</th>
<th>P for trend</th>
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<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Aspirin</td>
<td>Placebo</td>
<td>Aspirin</td>
</tr>
<tr>
<td>1</td>
<td>60/608</td>
<td>31/616</td>
<td>11.0</td>
<td>5.4</td>
</tr>
<tr>
<td>2</td>
<td>25/489</td>
<td>26/531</td>
<td>2.7</td>
<td>2.6</td>
</tr>
<tr>
<td>3</td>
<td>18/378</td>
<td>15/412</td>
<td>1.7</td>
<td>1.3</td>
</tr>
<tr>
<td>4</td>
<td>9/240</td>
<td>9/259</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>All</td>
<td>112/608</td>
<td>81/616</td>
<td>7.5</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Aspirin for the Prevention of Recurrent Venous Thromboembolism: The INSPIRE Collaboration. John Simes, Cecilia Becattini, Giancarlo Agnelli, John W. Eikelboom, Adrienne C. Kirby, Rebecca Mister, Paolo Prandoni, Timothy A. Brighton, for the INSPIRE Study Investigators*. Published online before print August 2014. Circulation DOI: 10.1161/CIRCULATIONAHA.114.008828
Rivaroxaban Clinical Programme Overview: > 60,000 Patients Enrolled

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase III</th>
<th>Customized Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE prevention after major orthopaedic surgery</td>
<td>RECORD&lt;sup&gt;1&lt;/sup&gt; RECORD&lt;sup&gt;2&lt;/sup&gt; RECORD&lt;sup&gt;3&lt;/sup&gt; RECORD&lt;sup&gt;4&lt;/sup&gt;</td>
<td>10 mg od (2 weeks, knee; 5 weeks, hip)</td>
</tr>
<tr>
<td>VTE prevention in hospitalized medically ill patients</td>
<td>MAGELLAN&lt;sup&gt;5&lt;/sup&gt;</td>
<td>10 mg od (5 weeks)</td>
</tr>
<tr>
<td>VTE treatment</td>
<td>EINSTEIN&lt;sup&gt;5&lt;/sup&gt; EINSTEIN-DVT EINSTEIN-PE EINSTEIN-EXT</td>
<td>15 mg bid for first 3 weeks 20 mg od 3, 6, or 12 months</td>
</tr>
<tr>
<td>Stroke prevention in atrial fibrillation</td>
<td>ROCKET AF&lt;sup&gt;5&lt;/sup&gt;</td>
<td>20 mg od 15 mg od for CrCl 30-49 mL/min</td>
</tr>
<tr>
<td>Secondary prevention of acute coronary syndromes</td>
<td>ATLAS ACS 2 TIMI&lt;sup&gt;5&lt;/sup&gt;</td>
<td>2.5 mg bid 5 mg bid</td>
</tr>
</tbody>
</table>
Dear Health Care Provider,

**The new oral anticoagulants Eliquis®▼, Pradaxa®, Xarelto®▼**

Beware of the risk factors for bleeding, pay attention to posology, contraindications, and warnings and precautions for use to reduce the risk of bleeding.

**Eliquis®** (apixaban), **Pradaxa®** (dabigatran etexilate) and **Xarelto®** (rivaroxaban) are oral anticoagulants which in recent years have been authorised for indications where vitamin K antagonists (warfarin, phenprocoumon and acenocoumarol) or low molecular weight heparins (LMWH) have been used for decades. Unlike vitamin K antagonists, there is no need for routine monitoring of anticoagulant activity when administering these new medicines.

However, clinical trials and post-marketing experience have shown that major bleeding events, including events leading to death, are not confined to vitamin K antagonists/LMWH but are also significant risks for the new oral anticoagulants. Furthermore, post-marketing reports indicate that not all prescribers are sufficiently aware of the product information in terms of managing bleeding risks.

The information provided in this letter has been reviewed and endorsed by the European Medicines Agency (EMA) and the Medicines and Healthcare Products Regulatory Agency (MHRA).
Bleeding with NOACs

Recommendations

In light of the above, prescribers should consider the individual patient risk of bleeding and observe posology, contraindications, and warnings and precautions for use. While differences in contraindications exist between the new oral anticoagulants, they share the following contraindications:

- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, other) except under the circumstances of switching therapy to or from the medicine, or when UFH is given at doses necessary to maintain an open central venous or arterial catheter

Please refer to the respective product information for Eliquis®, Pradaxa® and Xarelto® for information about additional contraindications specific to each medicine. Copies of the Summary of Product Characteristics can be obtained by electronic download from the EMA website: http://www.ema.europa.eu (under ‘Find medicine’ then ‘Human medicines’. Select the correct drug from the alphabetical list and click on the header at the bottom of the page “More detail is available in the summary of product characteristics”. This site also contains the European Public Assessment Reports). The full links are as follows:
Bleeding with NOACs

Call for reporting

Healthcare professionals should report any adverse events suspected to be associated with the use of Eliquis®, Pradaxa® or Xarelto® to the MHRA through the Yellow Card Scheme online at www.mhra.gov.uk/yellowcard. Alternatively, prepaid Yellow Cards for reporting are available:

- upon request by mail ("FREEPOST YELLOW CARD")
- at the back of the British National Formulary (BNF)
- by telephoning the Commission on Human Medicines (CHM) free phone line (0800 731 6789)
- or by electronic download through the Yellow Card section of the MHRA website (www.mhra.gov.uk/yellowcard)

When reporting, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates. Any suspected adverse reactions may also be reported to Bristol-Myers Squibb for Eliquis® (telephone: 0800 731 1736, e-mail: medical.information@bms.com); Boehringer Ingelheim for Pradaxa® (telephone: 0800 3281627, fax: 0800 3281628, e-mail: PV_local_UK_Ireland@boehringer-ingelheim.com); or Bayer plc for Xarelto® (telephone: 01635 563500, fax: 01635 563703, e-mail: phdsguk@bayer.co.uk).

Should you require any further information, please contact Bristol-Myers Squibb Medical Information for Eliquis® (telephone: 0800 731 1736, e-mail: medical.information@bms.com); Boehringer Ingelheim Medical Information for Pradaxa® (telephone: 0845 6017880, e-mail: medinfo.bra@boehringer-ingelheim.com); or Bayer plc Medical Information for Xarelto® (telephone: 01635 563116, e-mail: medical.information@bayer.co.uk).
Bleeding with NOACs

Should you require any further information, please contact Bristol-Myers Squibb Medical Information for Eliquis® (telephone: 0800 731 1736, e-mail: medical.information@bms.com); Boehringer Ingelheim Medical Information for Pradaxa® (telephone: 0845 6017880, e-mail: medinfo.bra@boehringer-ingelheim.com); or Bayer plc Medical Information for Xarelto® (telephone: 01635 563116, e-mail: medical.information@bayer.co.uk).

Sincerely yours,

Dr Rick Lones
Executive Medical Director, UK & Ireland
Bristol-Myers Squibb Pharmaceuticals Limited

Dr C.S. de Wet
Medical Director UK & Ireland
Boehringer Ingelheim
432UK13NP06982-01; SPAF106; v001_0

Dr Berkeley Phillips
UK Medical Director
Pfizer Limited

Dr Luis-Felipe Graterol
Medical Director
Bayer plc
Long-term Prophylaxis

**Einstein Choice- Study Design**

**Objective of the study:**
Demonstrate that both rivaroxaban 20 mg or 10 mg are superior in the long term secondary prevention of recurrent VTE to ASA 100 mg with comparable rates of major bleeding.

**Patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment***

**Day 1**
- Rivaroxaban 20 mg od  n~ 950
- Rivaroxaban 10 mg od  n~ 950
- ASA 100mg od  n~ 950

**12-month treatment duration**

**1 month observation period**

**Primary endpoint:**
Fatal or non-fatal symptomatic recurrent VTE

**Study Start Date:** February 2014

**Estimated Study Completion Date:** December 2016

*Completed 6 to 12 months (± 1 month) with interruption of anticoagulation ≤ 1 week at randomisation*
Non-interventional study: Xarelto® (XALIA) – study design

Prospective, non-interventional cohort field study

Objective: To collect real-life data on adverse events (AEs), bleeding, thromboembolic events and mortality in patients diagnosed with acute DVT treated with rivaroxaban or standard of care (SOC)

Study population: Patients (N~4800) with diagnosis of acute DVT (not PE) and with an indication for anticoagulant therapy for ≥3 months

Type, dose and duration of drug used at discretion of attending physician

Rivaroxaban for ≥3 months

N~2400

Investigators to collect data at initial visit, at 1 month and then quarterly*

SOC: e.g. initial treatment with LMWH or fondaparinux, followed by VKA for ≥3 months

N~2400

(1 month after end of treatment)

Final assessment

Primary outcomes: Major bleeding events, symptomatic recurrent venous thromboembolic events, all-cause mortality

Study Start Date: June 2012
Estimated Study Completion Date: March 2015

www.clinicaltrials.gov/ct2/show/NCT01619007

DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; SOC, standard of care; VKA, vitamin K antagonist
Fihn SD; Callahan CM; Martin DC; McDonell MB; Henikoff JG; White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Annals of Internal Medicine. 124(11):970-9, 1996 Jun 1
Factor VII, Tissue Factor & Factor X


Factor X activation of Thrombin

Low Molecular Weight Heparins

- Rapid onset of action - Peak 4-6 hr
- Half life 3-4 h
- 100% renal excretion & 100% bioavailability
- Predictable and consistent anticoagulant effects
- No requirement for routine coagulation monitoring – can do anti-Xa
- Reversible w protamine 1mg/100u, but only 60% reversible and protamine is a potent anticoagulant when you overdose.
- Average size (60%) less then 8,000 daltons (vs UFH 3 - 4 kdaltons)
# Low Molecular Weight Heparins

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mol Wt</th>
<th>target</th>
<th>Peak</th>
<th>T ½</th>
<th>Clearance</th>
<th>Antidote</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF Heparin</td>
<td>15 kDa</td>
<td>II, Xa</td>
<td>1-4 hr</td>
<td>3-4 hr</td>
<td>Endothelial / renal</td>
<td>Protamine</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>4.5 kDa</td>
<td>Xa</td>
<td>4-6 hr</td>
<td>3-4 hr</td>
<td>renal</td>
<td>Protamine 60%</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>4.5 kDa</td>
<td>Xa</td>
<td>4-6 hr</td>
<td>3-4 hr</td>
<td>renal</td>
<td>Protamine 60%</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>4.5 kDa</td>
<td>Xa</td>
<td>4-6 hr</td>
<td>3-4 hr</td>
<td>renal</td>
<td>Protamine 60%</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>1.7 kDa</td>
<td>Xa</td>
<td>2 hr</td>
<td>17-21 hr</td>
<td>renal</td>
<td>aPCC, Txa</td>
</tr>
</tbody>
</table>
Enoxaparin significantly reduces major ischaemic events when compared with UFH in the treatment of thromboembolic diseases


Thromboembolic complications of a subtherapeutic INR

• 501 patients with INR 0.5–1 INR units below lower limit of target INR included (280 with MHV, 221 with AF and CHADS2 score 3).
• LMWH was prescribed for 64 patients (12.8%).
• Seven patients had a TE (1.40%; 95% confidence interval 0.68, 2.86%; 5.58 events for 100 patients year). All occurred within 14 days.
• If only patients not bridged, incidence of TE was 1.14% (5 of 437 patients; 95% confidence interval 0.49, 2.64%; 4.58 events for 100 patients year).
• There were no major bleeding events.

<table>
<thead>
<tr>
<th></th>
<th>II U/mL</th>
<th>VII U/mL</th>
<th>IX U/mL</th>
<th>X U/mL</th>
<th>C U/mL</th>
<th>S U/mL</th>
<th>Z</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Octaplex, OctaPharma</strong></td>
<td>31</td>
<td>16</td>
<td>22</td>
<td>24</td>
<td>12</td>
<td>24</td>
<td>Yes</td>
<td>Heparin added, low amnt FVIIa</td>
</tr>
<tr>
<td><strong>500 U/20 mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Beriplex, CSL Behring</strong></td>
<td>20-48</td>
<td>10-25</td>
<td>20-31</td>
<td>22-60</td>
<td>22-31</td>
<td>17-19</td>
<td>Yes</td>
<td>Heparin, ATII added</td>
</tr>
<tr>
<td><strong>500 U/20mL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FEIBA, Baxter</strong></td>
<td>28-38,</td>
<td>20-40,</td>
<td>17-44,</td>
<td>24-28,</td>
<td>Activated</td>
<td></td>
<td></td>
<td>Activated Protein C, FVIII 0.1U/U</td>
</tr>
<tr>
<td><strong>400-1200 U/20 mL</strong></td>
<td>Trace IIa</td>
<td>Trace IXa</td>
<td>Trace Xa</td>
<td></td>
<td>Protein C (APC)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1750-3250 U/50ml</strong></td>
<td>89-98% FVIIa=</td>
<td>50U=</td>
<td>37 mcg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Units reqd to correct pTT</strong></td>
<td>17-44,</td>
<td>Trace IXa</td>
<td>Trace Xa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FFP 1U/mL, 200-250 mL</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CPD, ABO compatible</td>
</tr>
</tbody>
</table>

2. FEIBA NF monograph
Once-Daily Dosing Associated With Higher Adherence

- 10,697 adult AF patients with full insurance drug coverage, newly initiated on diabetes or antihypertensive medication
  - Those (n=8,256) on once daily regimens had a 26% higher adherence than those (n=2,441) on twice daily regimens
  - Among those aged ≥65 years, once daily medication was associated with a 52% higher probability of being compliant

Diluted Thrombin Time to Measure Dabigatran

Avecilla ST, Ferrell C, Chandler WL, Reyes M. Plasma-Diluted Thrombin Time to Measure Dabigatran Concentrations During Dabigatran Etxilate Therapy. Am J Clin Pathol 2012;137:572-574. DOI: 10.1309/AJCPAU7OQM0SRPZQ
Activated Charcoal for removal of Dabigatran

Dabigatran etixilate is lipophilic, & binds to Activated Charcoal

- Dabigatran etexilate in water (pH 2.4–2.7) + Activated charcoal,
- Dabigatran etexilate could not be detected, > 99.99% adsorbed

- Dabigatran in human plasma pool at 470 and 940 ng/ml + Active charcoal (125 mg/ ml) or a 1:11 dilution.
- Dabigatran levels to <1.01 ng/ml.

Hemodialysis for removal of Dabigatran


ATAN (Alberta Thromboembolism and Anticoagulation Network)

Unanswered Questions
Early death from PE – can we prevent it with TPA on-site
Recurrence of DVT – can we prevent it with anticoagulant strategies, D-dimers
Post-phlebitic syndrome – can we prevent or minimize this

Unquestioned Answers
Start coumadin immediately
Stop treatment at 3, 6, 12 months
Abandon patients to follow-up
VENOUS THROMBOEMBOLISM (VTE) PROPHYLAXIS

The team identifies medical and surgical clients at risk of venous thromboembolism (deep vein thrombosis and pulmonary embolism) and provides appropriate thromboprophylaxis.

GUIDELINES

Venous thromboembolism (VTE) is the collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a serious and common complication for clients in hospital or undergoing surgery. Evidence shows that incidence of VTE can be substantially reduced or prevented by identifying clients at risk and providing appropriate, evidence-based thromboprophylaxis interventions. Currently, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition) are the generally accepted standard of practice for the prevention of VTE.

The widespread human and financial impact of thromboembolism is well documented. Development of VTE is associated with increased patient mortality, and is the most common preventable cause of hospital death. In addition, both hospital costs and median length of stay are greatly increased for patients developing VTE.

NOTE: This ROP is not a requirement for pediatric hospitals. The ROP applies to clients 18 years of age or older.

TESTS FOR COMPLIANCE

- The organization has a written thromboprophylaxis policy or guideline.
- The team identifies clients at risk for venous thromboembolism (VTE), [(deep vein thrombosis (DVT) and pulmonary embolism (PE)] and provides appropriate evidence-based, VTE prophylaxis.
- The team establishes measures for appropriate thromboprophylaxis, audits implementation of appropriate thromboprophylaxis, and uses this information to make improvements to their services.
- *The team identifies major orthopaedic surgery clients (hip and knee replacements, hip fracture surgery) who require post-discharge prophylaxis and has a mechanism in place to provide appropriate post-discharge prophylaxis to such clients.
- The team provides information to health professionals and clients about the risks of VTE and how to prevent it.
# AHS Pocket Card

## PHARMACOLOGICAL OPTIONS FOR THROMBOPROPHYLAXIS

**RIGHT PATIENT** – patients at high risk of bleeding or currently bleeding should be considered for mechanical prophylaxis and those with very high risk of VTE should be considered for both mechanical and pharmacological thromboprophylaxis.

**RISK FACTORS**
- Immobilization, bed rest
- Stroke
- Previous history of VTE
- Central venous catheter
- Pregnancy
- Birth control pill, hormone replacement therapy
- Severe obesity
- Family history of VTE
- Increasing age
- Heart failure

**RIGHT AGENT:** Low molecular weight heparins are equally efficacious, safer, and more cost effective than unfractionated heparin.

**RIGHT MONITORING:** only patients with a 1% or higher risk of HIT require platelet monitoring.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RECOMMENDED DOSAGE</th>
<th>VTE Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin**</td>
<td>5,000 units subcutaneously once daily</td>
<td>Moderate, High and Very High Risk</td>
<td>$$</td>
</tr>
<tr>
<td>(Fragmin®)</td>
<td>Renal failure dosage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2500 – 5000 units subcutaneously DAILY</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;120 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low weight dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 40 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2500 units subcutaneously DAILY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enoxaparin**</td>
<td>40 mg subcutaneously once daily OR 30 mg subcutaneously twice daily</td>
<td>Moderate, High and Very High Risk</td>
<td>$$-$$$$</td>
</tr>
<tr>
<td>(Lovenox®)</td>
<td>Renal failure dosage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-30 mg subcutaneously DAILY</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;120 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low weight dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 40 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20-30 mg subcutaneously DAILY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinzaparin**</td>
<td>4500 units subcutaneously once daily</td>
<td>Moderate, High and Very High Risk</td>
<td>$$</td>
</tr>
<tr>
<td>(Innohep®)</td>
<td>Renal failure dosage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CrCl &lt; 30 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No Adjustment needed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obesity dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;120 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low weight dosage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 40 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>75 units/kg (ABW) subcutaneously DAILY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# AHS Pocket Card

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RECOMMENDED DOSAGE</th>
<th>VTE Risk</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unfractionated Heparin</strong></td>
<td>5,000 units subcutaneously every 12 hours OR every 8 hours</td>
<td>Moderate, High and Very High Risk</td>
<td>$</td>
</tr>
<tr>
<td>Renal failure dosage*</td>
<td>CrCl &lt; 30 ml/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity dosage &gt;120 kg</td>
<td>5000 units subcutaneously TWICE DAILY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low weight dosage &lt; 40 kg</td>
<td>5000 units subcutaneously TWICE DAILY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Hip fracture prophylaxis: 2.5 mg subcutaneously once daily</td>
<td>Very High Risk</td>
<td>$$$$</td>
</tr>
<tr>
<td>(Arixtra®)</td>
<td>Renal failure dosage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt; 30 ml/min</td>
<td>Use is Contraindicated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Hip or knee replacement surgery prophylaxis: 10 mg by mouth once daily</td>
<td>Very High Risk</td>
<td>$</td>
</tr>
<tr>
<td>(Xarelto®)</td>
<td>Renal failure dosage*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CrCl &lt; 30 ml/min</td>
<td>Use is Contraindicated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Renal failure Patients have a greater tendency to bleed as well as propensity for thrombotic events. Clinical judgement must be used in adjusting dose for renal failure patients. **Anti-Xa levels may be useful in selected patients." LMWHs have been found to have a lower incidence of heparin-induced thrombocytopenia (HIT) and thrombosis (HITT) than UFH. The incidence of HIT in postoperative patients ranges from 0.1-1% with LMWHs versus 1-5% with UFH, while the incidence in medically ill patients is 0.6% with LMWHs versus up to 1% with UFH. Note: Effective April 30, 2013 all laboratories in Alberta Health Services are reporting estimated glomerular filtration rates (eGFRs) based on the CKD-EPI equation. The Cockcroft-Gault (CG) formula to calculate creatinine clearance (CrCl) continues to be the used for Drug dose adjustments ([http://nephron.com/cgi-bin/CGSI.cgi](http://nephron.com/cgi-bin/CGSI.cgi)). For more useful information, see the Safer Healthcare Now! VTE Getting Started Kit: [www.saferhealthcarenow.ca](http://www.saferhealthcarenow.ca).*

$<5.00/day, $=$5.00-10.00/day, $$$=$10.00-$15.00/day, $$$$$>$15.00/day
Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial

Tone Enden, Ylva Haig, Nils-Einar Kløw, Carl-Erik Slagsvold, Leiv Sandvik, Waleed Ghanima, Geir Hafshol, Pål Andre Holme, Lars Olaf Holmen, Anne Mette Njaastad, Gunnar Sandbæk, Per Morten Sandset, on behalf of the CaVenT Study Group

Summary

Background Conventional anticoagulant treatment for acute deep vein thrombosis (DVT) effectively prevents thrombus extension and recurrence, but does not dissolve the clot, and many patients develop post-thrombotic syndrome (PTS). We aimed to examine whether additional treatment with catheter-directed thrombolysis (CDT) using alteplase reduced development of PTS.

Retrospective analysis of 141 patients treated with FEIBA (72) vs PCC (69)

- FEIBA significantly better than PCC for reversing INR
- No difference in clinical outcomes
- AE with FEIBA include: 1 fatal v fib, chest pain, troponin bump, MI, DVT

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>rFVIIa Dose</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ilyas (2008)</td>
<td>Standard care (n = 30) rFVIIa (n = 24)</td>
<td>10-100 μg/kg</td>
<td>Most pts. received concurrent FFP and vitamin K; all pts. receiving rFVIIa achieved INR &lt;1.4 (average time INR measured after rFVII dose was 2.4 ± 1.5 hours); standard care pts. required 13.7 ± 15.6 hours to correct INR; 14 rFVII pts. had rebound INR; more FFP used in non-rFVIIa group</td>
</tr>
<tr>
<td>Dager (2006)</td>
<td>rFVIIa plus FFP and/or vitamin K (n = 16; 8 with ICH)</td>
<td>1200 μg (11-25 μg/kg)</td>
<td>Initial INR (mean 2.8; range 1.44-6.34) reduced to &lt;1.4 10-30 minutes after rFVIIa dose in 15 pts., p &lt; 0.001</td>
</tr>
<tr>
<td>Roitberg (2005)</td>
<td>FFP plus standard care vitamin K (n = 24; 9 on warfarin) rFVIIa after FFP and/or vitamin K (n = 29; 14 on warfarin)</td>
<td>1200-2400 μg</td>
<td>rFVIIa corrected INR faster (6.8 ± 2.7 hours) vs standard care (47.4 ± 9.9 hours); 9 rFVIIa pts. had good functional outcome vs 2 standard care pts.</td>
</tr>
<tr>
<td>Brody (2005)</td>
<td>FFP plus standard care vitamin K (n = 15) FFP, vitamin K, and rFVIIa (n = 12)</td>
<td>2400-9600 μg</td>
<td>Faster correction of INR with rFVIIa (8.8 vs 32.2 hours with standard care); twice as much FFP was used in standard care group; 5 rFVII pts. died vs 2 standard care pts.</td>
</tr>
<tr>
<td>Freeman (2004)</td>
<td>rFVIIa plus FFP and/or vitamin K (n = 7)</td>
<td>15-90 μg/kg</td>
<td>INR rapidly corrected to &lt;1.5 within 7 hours in 6 pts.; some INR rebound</td>
</tr>
<tr>
<td>Lin (2003)</td>
<td>rFVIIa plus FFP (n = 4; 2 pts. with ICH)</td>
<td>1200 μg</td>
<td>Initial INR 1.9-5.6; all INRs corrected to ≤1.1 (variable sampling times)</td>
</tr>
<tr>
<td>Sorensen (2003)</td>
<td>rFVIIa plus FFP and/or vitamin K (n = 7)</td>
<td>10-40 μg/kg</td>
<td>Pretreatment INRs 1.7-6.6; all reversed to ≤1.5 at 10 minutes</td>
</tr>
<tr>
<td>Veshchev (2002)</td>
<td>rFVIIa (n = 1)</td>
<td>120 μg/kg</td>
<td>INR 6.4 corrected to 1.3 within 1 hour after rFVIIa dose; remained corrected for 14 additional hours</td>
</tr>
</tbody>
</table>

FFP = fresh frozen plasma; ICH = intracranial hemorrhage; INR = international normalized ratio; rFVII = recombinant activated factor VII.

*Adapted with permission.*

**Table 6. Studies of rFVIIa to Correct Warfarin-Associated Intracranial Hemorrhage**

Discontinuation Before Elective Invasive or Surgical Procedures

Time to discontinue medication prior to procedure

Rivaroxaban
- Determine patients risk of bleeding
  - Standard risk
    - At least 1 day
  - High risk of bleeding or major surgery
    - 2-4 days

- Estimate CrCl
  - 30-49 mL/min
    - 2-3 days
  - 50-79 mL/min
    - 1 day
  - ≥ 80 mL/min
    - 4 days

Dabigatran
- Determine patients risk of bleeding
  - Standard risk
    - 2-3 days
  - High risk of bleeding or major surgery
    - 2-4 days

- Estimate CrCl
  - 30-49 mL/min
    - 2 days
  - 50-79 mL/min
    - 4 days
  - ≥ 80 mL/min
    - 2-3 days

Apixaban
- Determine patients risk of bleeding
  - Standard risk
    - At least 1 day
  - High risk of bleeding or major surgery
    - At least 2 days

- Recommended
  - May be considered
EINSTEIN Extension Outcomes

**Symptomatic recurrent VTE**

- Placebo: 7.1%
- Rivaroxaban 20 mg OD: 1.3%
- Relative Risk Reduction (RRR): 82%
- p < 0.0001

**Major Bleeding**

- Placebo: 0%
- Rivaroxaban 20 mg OD: 0.7%

Rivaroxaban Currently Has Three Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPAF (Stroke Prevention in Atrial Fibrillation)</td>
<td>Prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.</td>
</tr>
<tr>
<td>VTE (Venous thromboembolic events)</td>
<td>Treatment of venous thromboembolic events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE.</td>
</tr>
<tr>
<td>VTE-OS</td>
<td>Prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery.</td>
</tr>
</tbody>
</table>
Danish Registry of Medicinal Product Statistics: Dabigatran vs warfarin-treated group, 4,978 vs 8,936. Comparisons on efficacy & safety based on Cox-proportional hazards models.

- Stroke & systemic embolism NOT significantly different between warfarin and dabigatran.
- Adjusted mortality significantly lower with both dabigatran doses (110 mg bid [aHR]: 0.79, 95% confidence interval [CI]: 0.65 to 0.95; 150 mg bid, aHR: 0.57, 95% CI: 0.40 to 0.80), vs warfarin.
- Pulmonary embolism lower with both doses of dabigatran.
- MI lower with both dabigatran doses (110 mg b.i.d., aHR: 0.309; 150 mg b.i.d., aHR: 0.40.
- Less intracranial bleeding seen with dabigatran (110 mg bid, aHR: 0.24; 150 mg bid, aHR: 0.08.
- Less gastrointestinal bleeding with dabigatran (110 mg bid aHR: 0.60 vs warfarin but not dabigatran 150 mg bid.
The MAH concluded and the CHMP agreed that the post-marketing bleeding rates for dabigatran etexilate are substantially less than the respective rates seen in the RE-LY groups for both doses of dabigatran etexilate. If the reporting rate in the post-marketing phase had been higher than in the RE-LY study, there would clearly have been a safety concern. The fact that reporting rate in the post-marketing phase is lower gives some reassurance as to the safety profile of the product.

“Following further explanation the CHMP agreed with the MAH that the results from the RE-LY study on the frequency of MI in warfarin-treated patients with or without VHD lacked biological/clinical plausibility and were not readily explainable other than as a spurious finding.”
Who am I

Born Edmonton 1954
Father from Nelson, BC; Mother born in Edmonton
1954 Census Edmonton 209,353; Calgary 168,840; Alberta 1,061,859
2012 Census Edmonton 817,498; Calgary 1,120,225; Alberta 3,699,939
BMedSc 1974, MD 1978,
Post-graduate training NZ 1978-83; Calgary 1983-86; Vancouver 1986-91;
Post-doctoral Fellowship 1987-91
FRCPC: Internal Medicine 1985, Oncology 1987, Hematology 1988

Clinical work:
Bleeding Disorder Clinic, Rare Blood Disorder Clinic, Thromboembolism Clinic

Research Work:
Clinical Trials in VTE, Hemophilia, Hereditary Angioedema, Primary Immunodeficiency,

Basic Research Work:
Blood Borne Pathogens
Iron Metabolism
BioBanking
## Prothrombin Complex Concentrates vs aPCC

<table>
<thead>
<tr>
<th></th>
<th>II  U/mL</th>
<th>VII U/mL</th>
<th>IX  U/mL</th>
<th>X  U/mL</th>
<th>C  U/mL</th>
<th>S  U/mL</th>
<th>Z</th>
<th>other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octaplex, OctaPharma 500 U/20 mL</td>
<td>31</td>
<td>16</td>
<td>22</td>
<td>24</td>
<td>12</td>
<td>24</td>
<td>Yes</td>
<td>Heparin added, low amnt FVIIa</td>
</tr>
<tr>
<td>Beriplex, CSL Behring 500 U/20mL</td>
<td>20-48</td>
<td>10-25</td>
<td>20-31</td>
<td>22-60</td>
<td>22-31</td>
<td>17-19</td>
<td>Yes</td>
<td>Heparin, ATII added</td>
</tr>
<tr>
<td>FEIBA, Baxter 400-1200 U/20 mL 1750-3250 U/50ml Units reqd to correct pTT</td>
<td>28-38, Trace IIa</td>
<td>20-40, 89-98% FVIIa= 50U= 37 mcg</td>
<td>17-44, Trace IXa</td>
<td>24-28, Trace Xa</td>
<td>Activated Protein C (APC)</td>
<td></td>
<td></td>
<td>Activated Protein C, FVIII 0.1U/U</td>
</tr>
<tr>
<td>FFP 1U/mL, 200-250 mL</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>CPD, ABO compatible</td>
</tr>
</tbody>
</table>

2. FEIBA NF monograph
## Table 5: Studies Comparing FFP and PCC to Correct Warfarin Anticoagulation in Nontraumatic ICH

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design (PCC product)</th>
<th>Pts.</th>
<th>Bleeding</th>
<th>Results</th>
<th>Evidence Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fredriksson (1992) &lt;sup&gt;50&lt;/sup&gt;</td>
<td>Retrospective (3-factor PCC)</td>
<td>PCC, n = 10</td>
<td>ICH</td>
<td>All pts. received vitamin K 10-20 mg iv&lt;br&gt;PCC decreased INR from 2.83 to 1.22 within 4.8 hours&lt;br&gt;FFP decreased INR from 2.97 to 1.74 within 7.3 hours; p &lt; 0.001&lt;br&gt;Signs and symptoms of ICH progressed less, with nonsignificant trend toward less severe outcomes in pts. treated with 3-factor PCC</td>
<td>Low</td>
</tr>
<tr>
<td>Makris (1997) &lt;sup&gt;51&lt;/sup&gt;</td>
<td>Prospective (4-factor PCC)</td>
<td>PCC, n = 29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>WAICH, other</td>
<td>4-factor PCC corrected INR in 28 pts. (mean, 1.3; range, 0.9-3.8)&lt;br&gt;FFP partially corrected INR (mean, 2.3; range, 1.6-3.8)&lt;br&gt;Posttreatment factor II, VII, IX, and X levels higher with PCC vs FFP</td>
<td>Moderate</td>
</tr>
<tr>
<td>Boulis (1999) &lt;sup&gt;52&lt;/sup&gt;</td>
<td>Prospective (3-factor PCC)</td>
<td>PCC, n = 5</td>
<td>WAICH</td>
<td>All pts. received vitamin K&lt;br&gt;All PCC pts. also received FFP&lt;br&gt;3-factor PCC plus FFP corrected INR significantly faster (2.95 ± 0.46 hours) vs FFP alone (8.9 ± 1.51 hours); p &lt; 0.01&lt;br&gt;No significant difference in neurologic outcomes</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cartmill (2000) &lt;sup&gt;53&lt;/sup&gt;</td>
<td>Prospective (3-factor PCC)</td>
<td>PCC, n = 6</td>
<td>WAICH</td>
<td>All pts. received vitamin K&lt;br&gt;At 15 minutes posttreatment, 3-factor PCC decreased mean INR from 4.86 before treatment to 1.32 vs FFP, which decreased mean INR from 5.32 before treatment to 2.30&lt;br&gt;PCC reversal significantly faster (41 vs 115 minutes); p &lt; 0.001</td>
<td>Low</td>
</tr>
<tr>
<td>Siddiq (2008) &lt;sup&gt;54&lt;/sup&gt;</td>
<td>Retrospective (factor IX complex concentrate)</td>
<td>PCC, n = 10</td>
<td>WAICH</td>
<td>All pts. received concurrent vitamin K&lt;br&gt;All PCC pts. also received FFP&lt;br&gt;3-factor PCC (4.3 ± 2.1 hours) vs FFP group (8.5 ± 5.6); p &lt; 0.005</td>
<td>Low</td>
</tr>
<tr>
<td>Demeyere (2010) &lt;sup&gt;55&lt;/sup&gt;</td>
<td>Prospective, randomized (4-factor PCC)</td>
<td>PCC, n = 18</td>
<td>Cardiac surgery; no pt. received vitamin K</td>
<td>No pt. received concurrent vitamin K&lt;br&gt;4-factor PCC achieved target INR faster than FFP at 15 minutes after CPB; no significant difference in mean INR values 60 minutes after CPB (PCC, 1.6 vs FFP, 1.7)</td>
<td>Good</td>
</tr>
</tbody>
</table>

CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; ICH = intracranial hemorrhage; INR = international normalized ratio; PCC = prothrombin complex concentrate; WAICH = warfarin-associated ICH.

### EINSTEIN DVT: Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=1,718)</th>
<th>Enox/VKA (n=1,711)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>p value</td>
</tr>
<tr>
<td>First major or clinically relevant non-major bleeding</td>
<td>139 (8.1)</td>
<td>138 (8.1)</td>
<td>0.97 (0.76–1.22)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.77</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14 (0.8)</td>
<td>20 (1.2)</td>
<td>0.65 (0.33–1.30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p=0.21</td>
</tr>
<tr>
<td>Contributing to death</td>
<td>1 (&lt;0.1)</td>
<td>5 (0.3)</td>
<td></td>
</tr>
<tr>
<td>In a critical site</td>
<td>3 (0.2)</td>
<td>3 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Associated with fall in Hb ≥2 g/dL and/or transfusion of ≥2 units</td>
<td>10 (0.6)</td>
<td>12 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding</td>
<td>126 (7.3)</td>
<td>119 (7.0)</td>
<td></td>
</tr>
</tbody>
</table>

Safety population
## EINSTEIN PE: Safety Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Rivaroxaban (N=2412)</th>
<th>Enoxaparin/VKA (N=2405)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First major or non-major clinically relevant bleeding event</td>
<td>249 (10.3)</td>
<td>274 (11.4)</td>
<td>0.90 (0.76–1.07)</td>
<td>0.23</td>
</tr>
<tr>
<td>Major bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contributing to death</td>
<td>26 (1.1)</td>
<td>52 (2.2)</td>
<td>0.49 (0.31–0.80)</td>
<td>0.0032</td>
</tr>
<tr>
<td>In a critical site</td>
<td>6 (0.2)</td>
<td>27 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>1 (&lt;0.1)</td>
<td>10 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated with fall in haemoglobin ≥2 g/dl and/or transfusion of ≥2 units</td>
<td>18 (0.7)</td>
<td>26 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-major clinically relevant bleeding</td>
<td>228 (9.5)</td>
<td>235 (9.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Safety population
Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban

Catheter Directed Thrombolysis

<table>
<thead>
<tr>
<th></th>
<th>Additional catheter-directed thrombolysis (n=90)</th>
<th>Standard treatment only (n=99)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>% (95% CI)</td>
<td>n</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 24 months†</td>
<td>41·1% (31·5–51·4)</td>
<td>55</td>
<td>55·6% (45·7–65·0)</td>
</tr>
<tr>
<td>Iliofemoral patency at 6 months‡‡</td>
<td>65·9% (55·5–75·0)</td>
<td>45</td>
<td>47·4% (37·6–57·3)</td>
</tr>
<tr>
<td>Post-thrombotic syndrome at 6 months§</td>
<td>30·3% (21·8–40·5)</td>
<td>32</td>
<td>32·2% (23·9–42·1)</td>
</tr>
</tbody>
</table>

Post-thrombotic syndrome defined as Villalta score of 5 points or higher. *χ² test. †Co-primary outcomes. ‡Five patients had inconclusive patency assessments and one was lost to follow-up at 6 months. §Secondary outcome.

Table 2: Short-term and long-term outcomes

Hemodialysis for removal of Dabigatran


<table>
<thead>
<tr>
<th>Test</th>
<th>Testa</th>
<th>Preoperative Timeb</th>
<th>Intraoperative Time</th>
<th>Postoperative Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0900</td>
<td>1500</td>
<td>1845</td>
<td>2040</td>
</tr>
<tr>
<td>TT, seconds (15.1-19.9)</td>
<td>90.6</td>
<td>65.5</td>
<td>60.2</td>
<td></td>
</tr>
<tr>
<td>ACT, seconds (100-140)</td>
<td></td>
<td></td>
<td></td>
<td>133</td>
</tr>
<tr>
<td>aPTT, seconds (22-34)</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PT, seconds (11.4-14)</td>
<td>14.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR (0.9-1.1)</td>
<td>1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL (14-17.4)</td>
<td>9.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum creatinine, mg/dL (0.7-1.5)</td>
<td>1.23</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ACT = activated clotting time; aPTT = activated partial thromboplastin time; INR = international normalized ratio; PT = prothrombin time; TT = thrombin time.

*Reference range shown in parentheses.

Hemodialysis was begun at 1745 and stopped at 2015.
Apixaban in Medically Ill Patients

**Figure 2.** Kaplan–Meier Curves for Adjudicated Symptomatic Venous Thromboembolism or Death Related to Venous Thromboembolism during the Treatment Period.
The inset shows the same data on an enlarged y axis.

**Figure 3.** Kaplan–Meier Curves for the Composite of Major and Clinically Relevant Nonmajor Bleeding Events during the Treatment Period.
The inset shows the same data on an enlarged y axis.
Poor Prognosis in Warfarin-Associated Intracranial Hemorrhage Despite Anticoagulation Reversal


Table 5. Outcome by aICH Classification

<table>
<thead>
<tr>
<th>Intracranial Hemorrhage Type</th>
<th>No.</th>
<th>In-Hospital Mortality*</th>
<th>Discharge mRS (Median [IQR])†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraparenchymal</td>
<td>71</td>
<td>30 (42.3%)</td>
<td>5 [3]‡</td>
</tr>
<tr>
<td>Subdural</td>
<td>61</td>
<td>21 (34.4%)</td>
<td>3 [4]§</td>
</tr>
<tr>
<td>Epidural</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Subarachnoid</td>
<td>8</td>
<td>1 (12.5%)</td>
<td>3 [3]</td>
</tr>
</tbody>
</table>
**Poor Prognosis in Warfarin-Associated Intracranial Hemorrhage Despite Anticoagulation Reversal**


<table>
<thead>
<tr>
<th>Table 2. PCC Therapy in the Study Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to PCC treatment time (median [IQR])</td>
</tr>
<tr>
<td>Presentation to PCC treatment time (median [IQR])</td>
</tr>
<tr>
<td>CT to PCC treatment time (median [IQR])</td>
</tr>
<tr>
<td>Total PCC (Octaplex) dose (median [IQR])</td>
</tr>
<tr>
<td>Post-PCC INR (median [IQR])</td>
</tr>
<tr>
<td>Time from infusion to post-PCC INR (median [IQR])</td>
</tr>
<tr>
<td>INR &lt;1.5 within 1 h of PCC infusion (%)</td>
</tr>
<tr>
<td>INR &lt;1.5 within 6 h of PCC infusion (%)</td>
</tr>
<tr>
<td>Vitamin K administered (%)</td>
</tr>
<tr>
<td>FFP administered (%)</td>
</tr>
</tbody>
</table>
Dabigatran etexilate: a direct thrombin inhibitor (Wikipedia)

- Half life of 12-17 h
- ~ 80% renally excreted & 6.5% bioavailability
- Predictable and consistent anticoagulant effects
- Low potential for drug-drug interactions (p Glycoprotein Inhibitor Effect), no drug-food interactions
- No requirement for routine coagulation monitoring
- Rapid onset of action (1-4 hrs)
- Twice daily treatment

van Ryn J; Stangier J; Haertter S; Liesenfeld K-H; WienenW; Feuring M; Clemens A. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. Thrombosis and Haemostasis 103.6/2010 1116-1127
Rivaroxaban Is Structurally Similar To Linezolid

(Wikipedia)

- No Antimicrobial Activity, No Observed Mitochondrial Toxicity
- Primarily renal elimination (66% - **only half** of this is active drug), remainder feces – potent inhibitor of p glycoprotein
- T1/2 7-11 hr (5-9 hr in young, 11-13 hr in elderly)
- No laboratory monitoring required
- No dosage adjustment for gender, age, extreme body weight
- Once daily dosing – 80% bioavailability

Apixaban: a direct Factor Xa inhibitor (Wikipedia)

- **Apixaban**, tradename **Eliquis**, is a **direct factor Xa inhibitor**
- Available today for hip/knee prophylaxis 2.5 mg bid at 24 hr post-op.
- Mostly liver clearance, 27% renal T1/2 12 hours
- Assay Rotachrom anti-FXa
- Joint venture by Pfizer and Bristol-Myers Squibb.[2][3]


**Edoxaban**: a direct Factor Xa inhibitor (Wikipedia)

- **Edoxaban**, is a **direct factor Xa inhibitor** undergoing phase III trials
- Mostly liver clearance,
- Daichi (Japan)

---


Betrixaban: a direct Factor Xa inhibitor (Wikipedia)

- **Betrixaban**, is a **direct factor Xa inhibitor** undergoing phase
- Mostly liver clearance,
- Portola


Andexanet Alfa (PRT4445*): a Factor Xa analogue (Portola Pharmaceuticals)

- **Andexanet**, is a factor Xa analogue, similar to native Factor Xa, but modified to restrict ability to cleave thrombin.
- Acts as a Factor Xa decoy to bind & sequester direct Factor Xa inhibitors in the blood.

https://ash.confex.com/ash/2013/webprogram/Paper56863.html
Andexanet Alfa (PRT4445*):
a Factor Xa analogue (Portola Pharmaceuticals)

**Methods:** Randomized, placebo-controlled, double-blind, cohort dose-escalation, Phase 2
- Healthy volunteers loaded with oral XARELTO, 20 mg qd for 6 days
- Randomized in a 6:3 ratio to andexanet alfa in different dosing cohorts.
- First two cohorts received single IV bolus of andexanet alfa, 210 mg or 420 mg.

**Results:** Within two minutes following completion of the 210 mg and 420 mg bolus of andexanet alfa, anti-Factor Xa activity decreased dose-dependently by 20% & 53%.
- AND plasma concentrations of *unbound* riva were decreased by 32% & 51%,
- AND molar ratio of AnXa to total plasma riva was 0.8 for the 210 mg dose (1.2 µM/1.6 µM,) and 1.2 for the 420 mg dose (2.6 µM/2.1 µM, respectively)
- AND showed dose-dependent reversal of XARELTO®-induced:
  - inhibition of thrombin generation and
  - prolongation of protxhrombin time and activated clotting time

**Serious Adverse Events:** No thrombotic events, SAEs reported.
**Adverse events:** infusion-related reaction (n = 3, all mild) & post-procedural hematoma, headache, or postural dizziness (n = 2 each).

https://ash.confex.com/ash/2013/webprogram/Paper56863.html
Andexanet Alfa (PRT4445*)

andexanet, is a factor Xa analogue undergoing phase III trials
Andexanet is similar to native Factor Xa, but has been modified to restrict its biological activity, such as its ability to cleave thrombin, an enzyme involved in the clotting cascade.
Andexanet alfa acts as a Factor Xa decoy that binds and sequesters direct Factor Xa inhibitors in the blood.
Portola Pharmaceuticals

# Caribbean Drug Registration/Licensing

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Sources:
- Lise Jantzon, Canadian National Sales Mgr. BioPharm, Baxter Corporation Biopharmaceutical, [Lise_Jantzon@baxter.com](mailto:Lise_Jantzon@baxter.com)
- Sri Adapa, President, Octapharma Canada Inc., [Sri.Adapa@octapharma.ca](mailto:Sri.Adapa@octapharma.ca)
- Joseph Andolfatto, Canadian National Manager Coagulation and Critical Care, CSL Behring Biotherapies for Life, [Joseph.Andolfatto@cslbehring.com](mailto:Joseph.Andolfatto@cslbehring.com)
PCC Registration in the Caribbean

Octaplex – Netherland Antilles, Dominican Republic
Beriplex – Netherlands
FEIBA – Netherlands

Sources:
• Lise Jantzon, Canadian National Sales Mgr. BioPharm, Baxter Corporation Biopharmaceutical, Lise_Jantzon@baxter.com
• Sri Adapa, President, Octapharma Canada Inc., Sri.Adapa@octapharma.ca
• Joseph Andolfatto, Canadian National Manager Coagulation and Critical Care, CSL Behring Biotherapies for Life, Joseph.Andolfatto@cslbehring.com
VTE Clinical Features

Fihn SD; Callahan CM; Martin DC; McDonell MB; Henikoff JG; White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. The National Consortium of Anticoagulation Clinics. Annals of Internal Medicine. 124(11):970-9, 1996

Anticoagulation control in Sweden

• 18,391 patients in 67 different centres in Sweden analysed. (Mean age 70 years)
• main indications: A fib (64%), VTE (19%), valve (13%).
• Time in therapeutic range 76.2%.
• Warfarin dose decreased, TTR increased with age.
• In 4273 patients from two centres in AuriculA,
  – 2.6% major bleedings
  – 1.7% venous/arterial thrombo-embolism were and per treatment year.
• Correlation of age and the risk of major bleeding (P < 0.001), but not thrombo-embolic complications (P > 0.147), was seen.

Wieloch M et al. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA.
European Heart Journal (2011) 32, 2282–2289
Warfarin & Intracranial Hemorrhage in Finland 1993 to 2008

- Subjects with first 1º ICH during 1993 (pop 356 026) to 2008 (389 671) in N Ostrobothnia, Finland.
- Warfarin users increased 3.6-fold, 0.68% in 1993 to 2.28% in 2008.
- 982 patients with ICH, 182 (18.5%) warfarin.
- One-year survival rate after onset of stroke 35.2% in warfarin users & 67.9% in nonusers.
- Incidence (P<0.062) and 28-day fatality of warfarin-related ICHs (P<0.002) decreased.
Warfarin & Intracranial Hemorrhage in Finland 1993 to 2008
Warfarin in the Real World
# Warfarin in the Real World

## Table 3.
**Results of Post Hoc Subgroup and Metaregression Analyses of U.S. and Canadian Warfarin Studies**

<table>
<thead>
<tr>
<th>Study-Level Factor</th>
<th>No. Groups (%)</th>
<th>Subgroup Analysis: Percentage of Time INR Values in Range (95% CI)</th>
<th>Metaregression Analysis$^b$: Adjusted Difference in Percentage of Time INR Values in Range (95% CI)</th>
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</thead>
<tbody>
<tr>
<td><strong>Study setting</strong></td>
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<tr>
<td>Anticoagulation clinic</td>
<td>23 (43.4)</td>
<td>65.0 (61.0–69.0)</td>
<td>Referent$^d$</td>
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<tr>
<td>RCT</td>
<td>6 (11.3)</td>
<td>63.0 (59.0–69.0)</td>
<td>−5.9 (−13.7 to −2.0)</td>
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<tr>
<td>Community</td>
<td>24 (45.3)</td>
<td>53.0 (50.0–56.0)</td>
<td>−11.3 (−16.2 to −6.3)</td>
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<tr>
<td><strong>Study year</strong></td>
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<tr>
<td>2003–08</td>
<td>43 (79.6)</td>
<td>61.0 (58.0–63.0)</td>
<td>Referent$^e$</td>
</tr>
<tr>
<td>1998–2002</td>
<td>11 (20.4)</td>
<td>49.0 (41.0–59.0)</td>
<td>−8.0 (−14.1 to −2.0)</td>
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<tr>
<td><strong>Interpolation method</strong></td>
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<tr>
<td>Other</td>
<td>10 (18.5)</td>
<td>54.0 (47.0–62.0)</td>
<td>Referent$^f$</td>
</tr>
<tr>
<td>Linear</td>
<td>44 (81.5)</td>
<td>60.0 (58.0–63.0)</td>
<td>7.2 (1.2 to 13.2)</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
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<tr>
<td>Retrospective</td>
<td>28 (51.9)</td>
<td>56.0 (53.0–58.0)</td>
<td>Referent$^g$</td>
</tr>
<tr>
<td>Prospective</td>
<td>26 (48.1)</td>
<td>63.0 (59.0–67.0)</td>
<td>9.8 (4.5 to 15.1)</td>
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<td><strong>Self-management</strong></td>
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<tr>
<td>No</td>
<td>51 (94.4)</td>
<td>59.0 (56.0–61.0)</td>
<td>Referent</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (5.6)</td>
<td>65.0 (55.0–76.0)</td>
<td>−2.0 (−15.3 to 11.2)</td>
</tr>
</tbody>
</table>
Effectiveness of Warfarin in Patients with Cancer

- 95 patients undergoing treatment for cancer matched to 283 patients without cancer.
- Cancer group spent less time in the target INR range (54 vs 66%, P<.001) and had more variable INR values (standard deviation around the mean INR value 1.30 vs 0.71, P<.001).
- More thrombotic events in the cancer group than control group (5 vs 0 events, P<.001).

**OBJECTIVES**

To outline the recommended approach to venous thromboembolism (VTE) prophylaxis for all patients admitted to an Alberta Health Services acute care facility.

**APPLICABILITY**

This guideline applies to all Alberta Health Services employees, members of the medical and midwifery staffs, students, volunteers, and other persons acting on behalf of Alberta Health Services (including contracted services providers as necessary). This guideline does not limit any legal rights to which you may otherwise be entitled.

**GUIDELINE**

The underlying principle guiding the use of thromboprophylaxis in Alberta Health Services is that all acute care patients at risk receive venous thromboprophylaxis. An assessment of risk of venous thromboembolism (VTE) and bleeding risk should be made by the most responsible health practitioner at the time of admission to an acute care facility. All health care professionals should identify patients who are at risk that are not receiving thromboprophylaxis or whose bleeding risk has subsided. This information is to be provided to the patient’s health care team immediately.

The approach to thromboprophylaxis in Alberta Health Services involves three steps:

**Step 1: Is Thromboprophylaxis NOT INDICATED?**

1.1 For patients who are fully mobile and expected to have a length of stay less than 48 hours, thromboprophylaxis is generally not needed unless multiple other VTE risk factors are present.
Recommended Thromboprophylaxis Therapy by Patient Group

General Considerations:

1. Although the recommended options apply to most patients in each group, individual Patient factors may suggest an alternate approach.

2. For all Patients in whom it is possible and appropriate, early and frequent mobilization and ambulation are essential.

3. In general, for weight less than 40 kg or creatinine clearance less than 30 mL/min, it is suggested that the prophylactic LMWH dose be reduced to the next lower pre-filled syringe dose for enoxaparin only. In general, for weight greater than 100 kg, consider doubling the LMWH dose. At weights greater than 120 kg, even higher doses should be considered.

4. The duration of TP is not based on mobility status alone.

Given evidence suggesting low to moderate bleeding risk associated with use of prophylactic dosages of LMWH, in absence of clinically significant bleeding or in setting of procedures involving critical areas where achieving hemostasis is limited or potentially catastrophic bleeding is possible, in most instances, TP should not be withheld. [Bump, 2008]

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended Thromboprophylaxis Options1,2,3</th>
<th>Initiation</th>
<th>Duration</th>
</tr>
</thead>
</table>
| High bleeding risk¹               | Properly-fitted, bilateral calf-length GCS or IPC used continuously (except for bathing or ambulating) | ASAP after emergency admission  
Just prior to surgery for elective surgical procedures | Until bleeding risk allows the use of anticoagulants |
| Neuraxial blockade/spinal anaesthesia | UFH bid/tid  
Can use LMWH after epidural removed  
Hold LMWH for 18 to 24 hour prior to insertion or removal of neuraxial catheter | 2-4 hours after insertion of neuraxial catheter  
At least 2 hours after removal of neuraxial catheter | Until discharge                                      |
<table>
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<tr>
<th>Patient group</th>
<th>Recommended Thromboprophylaxis Options</th>
<th>Initiation</th>
<th>Duration</th>
</tr>
</thead>
</table>
| Heparin-induced thrombocytopenia (HIT)      | Suggest haematology/internal medicine consult  
No heparin or LMWH  
fondaparinux 2.5 mg SC once daily or argatroban | As soon as the diagnosis of HIT considered | Discharge and platelet count >120x10^9/L |
| Burn unit Patients                          | LMWH q 24 hours or LDUH bid/tid        | When there is evidence of primary hemostasis    | Until discharge                        |
| Cardiovascular surgery                      | LMWH q 24 hours or LDUH bid/tid        | primary hemostasis                              | Until discharge                        |
| Chronic kidney disease                      | UFH bid/tid                            | On admission                                     | Until discharge                        |
| Critical care                               | Use Critical Care order sets           | 1st dosing time after admission, if possible  
See Critical Care order sets                  | Until discharge                           |
<p>| complications                               |                                        |                                                | Include TP in transfer orders           |
| General surgery (major)                     | Use General Surgery order sets         | 0-1 hour preop (if no epidural) or 2-4 hours after insertion of epidural | Until discharge                        |</p>
<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended Thromboprophylaxis Options¹,²,³</th>
<th>Initiation</th>
<th>Duration⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynaecology</td>
<td>Use Gynaecology order sets</td>
<td>1ˢᵗ dosing time after ER admission or postop or the following morning if there are bleeding concerns</td>
<td>Until discharge</td>
</tr>
<tr>
<td></td>
<td>In most cases, the prophylaxis is LMWH q 24 hours or LDUH bid/tid</td>
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<tr>
<td></td>
<td>For Patients at high risk of bleeding, properly-fitted, bilateral calf-length CGS or IPC until anticoagulants can be started</td>
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<td></td>
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<tr>
<td>Hip &amp; knee arthroplasty</td>
<td>Use Arthroplasty order sets</td>
<td>6 hours post op</td>
<td>15 days</td>
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<tr>
<td></td>
<td>In most cases, the prophylaxis is LMWH q 24 hours</td>
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<tr>
<td></td>
<td>For Patients with moderate renal dysfunction, use dose reduced LMWH SC Q24 hours or LDUH bid</td>
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<td>28 days if higher risk and THR</td>
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<tr>
<td></td>
<td>Or fondiparinux or rivaroxaban or Vitamin K antagonist</td>
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<tr>
<td>Hip fracture</td>
<td>Use Hip Fracture admission and postop order sets</td>
<td>If surgery is delayed, start LMWH on admission</td>
<td>28-35 days</td>
</tr>
<tr>
<td></td>
<td>LMWH q 24 hours or fondiparinux or warfarin Dosage reduction if weight less than 40 kg or CrCl &lt;30 mL/min</td>
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<tr>
<td>Patient group</td>
<td>Recommended Thromboprophylaxis Options&lt;sup&gt;1,2,3&lt;/sup&gt;</td>
<td>Initiation</td>
<td>Duration&lt;sup&gt;4&lt;/sup&gt;</td>
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</table>
| Internal medicine (and medical subspecialties) | Use Medicine admission order sets/DVT prophylaxis order sets  
For most Patients, LMWH q 24 hours  
or LDUH bid/tid or fondiparinux  
Dosage adjustment for high or low weight and renal dysfunction  
For Patients at high risk of bleeding, properly-fitted, bilateral calf-length GCS/IPC until anticoagulant can be started | 1<sup>st</sup> dosing time after admission | Until discharge  
Consider extended for cancer, stroke |
| Neurosurgery                          | Three options:  
For Patients at high risk of bleeding, properly-fitted, bilateral calf-length GCS or IPC  
LMWH q 24 hours  
LDUH bid/tid  
Start with bilateral calf-length GCS/IPC and switch to LMWH when risk of bleeding decreases | For GCS/IPC, start just prior to surgery for elective surgical procedure and ASAP after admission for major neurotrauma or non-traumatic intracranial haemorrhage  
For LMWH, no sooner than day after surgery | Until discharge |
| Obstetrics                            | LMWH q 24 hours                                                                                                         | Initial dose of UFH given immediately post caesarean for high risk individuals  
LMWH started at least 2 hours after epidural removed | Until discharge  
Extended for 6 weeks and/or converted to warfarin for those with prior VTE or with thrombophilia |
| Oncology (medical and radiation)      | LMWH q 24 hours                                                                                                         | 1<sup>st</sup> dosing time after admission | Until discharge  
Consider benefits vs. risk of post-discharge TP |
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<th>Patient group</th>
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<th>Initiation</th>
<th>Duration&lt;sup&gt;4&lt;/sup&gt;</th>
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</table>
| Paediatrics           | Early mobilization except in very high risk population  
No clear evidence supporting TP in paediatric population                                                                                                                                                                     |                                                                           |                     |
| Plastic surgery       | LMWH, q 24 hours, fondaparinux, LDUH bid/tid                                                                                                                                                                                                                      | Preop or post op 6-12 hours                                              | Until discharge     |
| Spinal cord injury    | LMWH q 12 or 24 hours                                                                                                                                                                                                                                             | ASAP after admission (once hemostasis is evident)                         | Until discharge from rehab |
| Spine surgery         | LMWH q 24 hours                                                                                                                                                                                                                                                   | Evening or morning after surgery                                        | Until discharge     |
| Stroke — ischemic     | Use Stroke admission order sets  
For most Patients, LMWH q 24 hours  
Dosage adjustment for low or high weight and renal dysfunction  
For Patients at high risk of bleeding, properly-fitted, bilateral calf-length GCS or IPC until LMWH can be started | 1<sup>st</sup> dosing time after admission                                | Until discharge     |
| Stroke — hemorrhagic  | Use Stroke admission order sets  
Bilateral, properly-fitted, calf-length GCS or IPC  
After approx. 5-7 days, consider switch to LMWH as for ischemic stroke                                                                                                                                  | On admission                                                             | Until discharge     |
| Sub-Acute Care        | LMWH q 24 hours or LDUH bid  
For extended prophylaxis in spinal cord injury, stroke associated with paralysis, hip fracture or total joint and abdominal/pelvic cancer therapy                                                                 | Continuation of prophylaxis at transitions                               | 10-35 days          |
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<tr>
<th>Patient group</th>
<th>Recommended Thromboprophylaxis Options(^{1,2,3})</th>
<th>Initiation</th>
<th>Duration*</th>
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</table>
| Trauma        | For Patients at high risk of bleeding, properly-fitted, bilateral calf-length GCS/IPC until LMWH can be started  
Usual risk Patients: LMWH q 24 hours  
High risk Patients (lower extremity fracture): LMWH q12 | ASAP after admission (once hemostasis is evident) | Until discharge from rehab |
| Urology       | Use Urology order sets  
In most cases, the prophylaxis is LMWH q 24 hours or LDUH bid  
For Patients at high risk of bleeding, properly fitted, bilateral, calf-length GCS/IPC until LMWH can be started | Options:  
1st dosing time after surgery  
Morning after surgery if there are bleeding concerns  
1st dosing time after ER admission or postop | Until discharge |

**Legend:**  
ER = emergency room  
GCS = graduated compression stockings  
TP = thromboprophylaxis  
IPC = intermittent pneumatic compression  
LMWH = low-molecular-weight heparin  
TJR = total joint replacement  
VTE = Venous Thromboembolism  
LDUH = low dose unfractionated heparin
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- Joseph Andolfatto, Canadian National Manager Coagulation and Critical Care, CSL Behring Biotherapies for Life, [Joseph.Andolfatto@cslbehring.com](mailto:Joseph.Andolfatto@cslbehring.com)
Enoxaparin significantly reduces major ischaemic events when compared with UFH in the treatment of thromboembolic diseases


CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013, 382: 516–24