The New Oral Anticoagulants: what emergency physicians need to know

HK College of Emergency Medicine
Joint Clinical and Didactic Lectures
7 Aug 2013
Outline of talk

1. What are new oral anticoagulants
2. Bleed x Vitamin K Antagonist (VKA) vs. NOAC
3. Any lab test useful?
4. How to reverse of NOAC
Bleeding with VKA

- Reduce factor II VII IX X and PC PS
- Most feared: intra-cerebral hemorrhage (ICH)
- 0.5-1.2% per year, 40% die
- Among 125195 Canadian Af age >66
- 3.8% per year (5yr)
- 18% major bleed die in 7 days.
- No prove that reversal saves lives.
Limitations of VKA therapy

Narrow therapeutic window (INR range 2-3)
Unpredictable response
Numerous drug-drug interactions
Numerous food-drug interactions
Warfarin resistance
Slow onset/offset of action
Routine coagulation monitoring
Frequent dose adjustments

VKA therapy has several limitations leading to underuse and leaving patients at risk of bleeding

Novel Oral Anti-Coagulants (NOAC)

- **Direct Thrombin Inhibitors**
  - Dabigatran

- **Direct Xa Inhibitors**
  - Rivaroxaban
  - Apixaban
  - Edoxaban

Reversible mild hemophilias
<table>
<thead>
<tr>
<th>Feature</th>
<th>Warfarin</th>
<th>New OAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Dosing</td>
<td>Variable</td>
<td>Fixed</td>
</tr>
<tr>
<td>Food effect</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Interactions</td>
<td>Many</td>
<td>Few</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Offset</td>
<td>Long</td>
<td>Shorter</td>
</tr>
</tbody>
</table>

Eikelboom and Weitz. Circulation 2010
# Dose Considerations

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Factor Xa</td>
<td></td>
<td>Thrombin</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>80%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>q.d. (b.i.d.)</td>
<td>b.i.d. (o.d.)</td>
<td></td>
</tr>
<tr>
<td>Half life</td>
<td>7-11 h</td>
<td></td>
<td>12-17 h</td>
</tr>
<tr>
<td>Renal</td>
<td>33% (66%)</td>
<td></td>
<td>80%</td>
</tr>
<tr>
<td>Monitoring</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Interactions</td>
<td>3A4/P-gp</td>
<td></td>
<td>P-gp</td>
</tr>
</tbody>
</table>
Efficacy in 12000 patients

RE-LY Primary end-point:
Dabigatran 150 mg twice daily was significant in reducing the risk of stroke and systemic embolism vs warfarin

Dabigatran 150 vs warfarin:
HR 0.65 (95% CI: 0.52, 0.81)
\( p \)-value for superiority = 0.0001

35% RRR
<table>
<thead>
<tr>
<th>INDICATION</th>
<th>Rivaroxaban (FXa)</th>
<th>Dabigatran (DTI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTEp THR</td>
<td>RECORD1 RECORD2 Superior Superior</td>
<td>RE-NOVATE RE-NOVATEII Non-inferior Non-inferior</td>
</tr>
<tr>
<td>VTEp TKR</td>
<td>RECORD3 RECORD4 Superior Superior</td>
<td>RE-MODEL RE-MOBILIZE Non-inferior Failed</td>
</tr>
<tr>
<td>SPAF</td>
<td>ROCKET-AF Superior</td>
<td>RE-LY Non-inferior (110mg) Superior (150mg)</td>
</tr>
<tr>
<td>DVT treatment</td>
<td>EINSTEIN DVT Non-inferior</td>
<td>RECOVER Non-inferior</td>
</tr>
<tr>
<td>PE treatment</td>
<td>EINSTEIN PE Non-inferior</td>
<td>RECOVERII Results not yet available</td>
</tr>
<tr>
<td>Secondary prevention of VTE</td>
<td>EINSTEIN EXT Superior to placebo</td>
<td>RE-MEDY Non-inferior to warfarin Superior to placebo</td>
</tr>
<tr>
<td>ACS add to anti Plt</td>
<td>ATLAS ACS 2 Significant reduction in primary endpoint</td>
<td>RE-DEEM (Phase 2) Phase 3 trial not conducted</td>
</tr>
<tr>
<td>Medically ill</td>
<td>MAGELLAN Non-inferior to enoxaparin Superior to placebo but more bleeding</td>
<td>Not conducted N/A</td>
</tr>
</tbody>
</table>
## Country for Regulatory Approval

<table>
<thead>
<tr>
<th>Indications</th>
<th>Europe (EU)</th>
<th>USA (FDA)</th>
<th>Hong Kong (DOH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rivaroxaban</td>
<td>Dabigatran</td>
<td>Rivaroxaban</td>
</tr>
<tr>
<td>VTEp THR/TKR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>SPAF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DVT treatment</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PE treatment</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevention of recurrent VTE</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>ACS</td>
<td>CHMP positive opinion in Mar, 2013</td>
<td>No</td>
<td>Submitted for approval in Dec, 2011</td>
</tr>
</tbody>
</table>

European, Canadian, American guidelines: first line and PREFERRED over warfarin
1. What are NOAC?

- Specific inhibitors of single coagulation factor
- Oral fix-dose rapid action
- Will replace warfarin in long run
- $35 versus $3 per day
- No need x INR
- Pro warfarin: long safety data, patient interaction, miss dose, monitor and reversal.
Safety in 12000 patients

RE-LY Safety / Bleeding Subgroups comparing Dabigatran 150 mg twice daily with warfarin

- Higher rate of major GI bleeds (1.6% vs 1.1% for warfarin)
- Similar rates of major bleeds (3.3% vs 3.6% for warfarin)
- Higher rate of total GI bleeds [681 (6.1%) vs 452 (4.0%) for warfarin]
- Lower rate of intracranial bleeds [38 (0.3%) vs 90 (0.8%) for warfarin]
Lessons from Clinical Trials in Atrial Fibrillation

All of the new oral anticoagulants are at least as effective as warfarin and can be given without routine monitoring.

All agents reduce the risk of intracranial bleeding.

New agents produce about a 10% reduction in mortality.
Mortality of bleeding
NOAC no different from VKA

<table>
<thead>
<tr>
<th>Type</th>
<th>Warfarin 36% (n/n)</th>
<th>Dabigatran 150 mg 35% (n/n)</th>
<th>Dabigatran 110 mg 41% (n/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All intracranial hemorrhages</td>
<td>36% (32/90)</td>
<td>35% (13/37)</td>
<td>41% (11/27)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>41% (19/46)</td>
<td>64% (7/11)</td>
<td>64% (9/14)</td>
</tr>
<tr>
<td>Subdural hemorrhage</td>
<td>28% (10/36)</td>
<td>21% (5/24)</td>
<td>20% (2/10)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>38% (3/8)</td>
<td>50% (1/2)</td>
<td>0% (0/3)</td>
</tr>
</tbody>
</table>
How to prevent bleed?

• RELY trial 4591 surgeries (12000 pat)
• 7.8% were urgent OT
• no difference DB vs. VKA (but no refined data)
• For normal Cr Cl, 48hrs or 4 half lives (4 x13-18hr) hence <30ng/ml
• ROCKET-AF no data on rivaroxaban E-OT
Interaction with other anticoagulants

No need to bridge with LMWH, can give 12 hours after last dose

Change from warfarin: wait INR 2 or give Vitamin K10mg and start next day

Low Platelets: 50 is probably good enough
Aspirin compatible if indicated
To avoid bleeding

- Patient education to avoid overdose
- Adjust x Cr, age, indication and bleeding risks
- 4 $T_{1/2}$ before elective OT
- No need x absolute absence of drug for OT
- No need x absolute normal TT / FXa
- No need x prophylactic reversal for OT
- Nature of OT: neurosurgery, endoscopy
- Chinese bleed more and clot less
## Table I. Population studies of VTE across different ethnic groups in the USA.

<table>
<thead>
<tr>
<th>Study population</th>
<th>White/ Caucasian</th>
<th>African American</th>
<th>Hispanic</th>
<th>Asian/Pacific Islander</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stein et al (2004b): number of subjects</td>
<td>2,490,000</td>
<td>2,641,000</td>
<td>440,000</td>
<td>–</td>
</tr>
<tr>
<td>All VTE (age adjusted rate/100,000 per year)</td>
<td>130</td>
<td>138</td>
<td>–</td>
<td>26, $P &lt; 0.0005$</td>
</tr>
<tr>
<td>DVT (age adjusted rate/100,000 per year)</td>
<td>104</td>
<td>107</td>
<td>–</td>
<td>22, $P &lt; 0.0005$</td>
</tr>
<tr>
<td>PE (age adjusted rate/100,000 per year)</td>
<td>36</td>
<td>40</td>
<td>–</td>
<td>7, $P &lt; 0.0005$</td>
</tr>
<tr>
<td>White et al (2005): number of subjects</td>
<td>21,002</td>
<td>16,015</td>
<td>1,794</td>
<td>2,216</td>
</tr>
<tr>
<td>Adjusted standardised incidence of all VTE/100,000</td>
<td>104</td>
<td>141, $P &lt; 0.0001$</td>
<td>55, $P &lt; 0.0001$</td>
<td>21, $P &lt; 0.0001$</td>
</tr>
<tr>
<td>Idiopathic VTE: number of events</td>
<td>5,418</td>
<td>4,209</td>
<td>426</td>
<td>588</td>
</tr>
<tr>
<td>Incidence of idiopathic VTE/100,000 (95% CI)</td>
<td>28 (27–29)</td>
<td>32 (29–35), $P = 0.04$</td>
<td>15 (13–16), $P &lt; 0.0001$</td>
<td>6 (5–7), $P &lt; 0.0001$</td>
</tr>
<tr>
<td>Schneider et al (2006)</td>
<td>10,542</td>
<td>36.47</td>
<td>53.64, $P &lt; 0.001$</td>
<td>–</td>
</tr>
<tr>
<td>PE Male (age adjusted rate/100,000)</td>
<td>37.97</td>
<td>61.53, $P &lt; 0.001$</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PE Female (age adjusted rate/100,000)</td>
<td>36.47</td>
<td>53.64, $P &lt; 0.001$</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; 95% CI: 95% confidence interval; –, group not examined in study.
Less clotting genes?

Table VI. Prevalence of hereditary thrombophilia in the healthy population by ethnicity. Please refer to text for references.

<table>
<thead>
<tr>
<th></th>
<th>F5 R506Q</th>
<th>F2 G20210A</th>
<th>AT deficiency</th>
<th>PS deficiency</th>
<th>PC deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europeans</td>
<td>8.8–15%</td>
<td>1.7–3%</td>
<td>0.02–0.15%</td>
<td>0.03–0.13%</td>
<td>0.2–0.4%</td>
</tr>
<tr>
<td>SE Asian</td>
<td>0</td>
<td>0</td>
<td>0.15%</td>
<td>1.12%</td>
<td>0.13%</td>
</tr>
<tr>
<td>UK blacks</td>
<td>—</td>
<td>0</td>
<td>0</td>
<td>2%*</td>
<td>4%*</td>
</tr>
<tr>
<td>African Americans</td>
<td>1.1–1.23%</td>
<td>&lt;0.001%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Table VII. Prevalence of hereditary thrombophilia in patients with unprovoked deep vein thrombosis. Please refer to text for references.

<table>
<thead>
<tr>
<th></th>
<th>F5 R506Q</th>
<th>G20210A</th>
<th>AT deficiency</th>
<th>PS deficiency</th>
<th>PC deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europeans</td>
<td>20%</td>
<td>6.2%</td>
<td>1–3%</td>
<td>1–5%</td>
<td>3–5%</td>
</tr>
<tr>
<td>SE Asian</td>
<td>0</td>
<td>0</td>
<td>5.6%</td>
<td>18%*</td>
<td>8%</td>
</tr>
<tr>
<td>UK blacks</td>
<td>1.4%</td>
<td>0</td>
<td>0.7%†</td>
<td>2.8%†</td>
<td>4.2%†</td>
</tr>
<tr>
<td>African Americans</td>
<td>2.9%</td>
<td>1.1%</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

—, Data not available.
*Patients with unprovoked DVT.
2. Risk of bleed vs Warfarin

- There will be risk of bleeding (no free lunch)
- Risks vary with age and indication, but either equivalent (MB) or less than warfarin (ICH)
- Bleeding outcome equivalent to warfarin
- Despite we seem to known VKA dosing, monitoring and reversal and seem not to know NOAC dosing, monitoring and reversal
When and What from lab?

1. To identify mechanism of bleeding
2. To detect overdose
   - Renal / Liver impairment / Elderly
3. To determine the offset of activity
   - Pre-operative / thrombolysis for ischemic stroke
4. To monitor adherence
   - To distinguish treatment failure from non-adherence
In vitro: test tube
Intrinsic / extrinsic PT/APTT/TT

Coagulation Cascade

Intrinsic Pathway

"Contact Activation"

XI

XIIa

Prekallikrein HMW Kininogen

XIIa

Activated Protein C, Protein S

IX

IXa

TF:VIIa

TFPI

"TF Pathway"

TF

PI

PL

Ca^{2+}

(Tenase)

VIIIa

(Promotribinase)

Xa

Activated Protein C, Protein S

Antithrombin

Common Pathway

Prothrombin

PL, Ca^{2+}

V_{a}

Thrombin

Fibrinogen

Fibrin Monomer

XIII

XIIIa

XL-Fibrin Polymer

Jennifer L. Klawitter
Technical & Regulatory Affairs Manager
DiaPharma Group, Inc. 2004
In vivo: blood vessels
no pathways no clotting times
Coagulation vs. Anti-coagulation
Fibrinolysis vs. Anti-fibrinolysis
Real time Thrombin Generation Assay

PT & APTT are responsive only to procoagulant factors...
Shows that same INR variable thrombin generation
What can we monitor?

Laboratory Detection of DTI and FXa Inhibitors

- **Global assays (APTT, PT, TT):**
  - Responsiveness of different reagents varies significantly
  - Tend to be too sensitive, too insensitive, or fail to show the appropriate dose response

- **Measuring Direct FXa inhibitors using the PT**
  - Too much variability in results in seconds depending on anticoagulant agent and reagent used

- **Measuring Dabigatran with the APTT**
  - Responsiveness of different reagents varies
  - There is a non-linear dose response
  - There are no published data correlating APTT to clinical outcome
  - APTT value can be normal despite therapeutic dabigatran levels*
  - A normal TT indicates that minimal or no dabigatran is present

*Hawes E, Adcock D, et al. Submitted for publication

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>How to monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumadin</td>
<td>INR</td>
</tr>
<tr>
<td>Heparin</td>
<td>PTT, anti-factor Xa</td>
</tr>
<tr>
<td>LMW heparin</td>
<td>Anti-factor Xa if needed</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Anti-factor Xa if needed</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Anti-factor Xa if needed</td>
</tr>
</tbody>
</table>
| Dabigatran        | Thrombin time to test for residual drug. Dilute thrombin time to assess extent of anticoagulation or test for residual drug.
Indirect monitor calibrated tests

• Dabigatran
  – Hemoclot thrombin inhibitor assay
    • TAT 2 – 4 hours (non-batch)
    • HKS&H test charge HK$ 1,570
• Rivaroxaban
  – Anti-FXa assay using rivaroxaban calibrators
    • TAT 2 – 4 hours (non-batch)
    • HKS&H test charge: HK$ 1,195

• BUT no absolute safety e.g. neurosurgery
• Other causes of prolongation (heparin contamination / DIC / afibrinogenemia)
• may change with rescue use of PCC / PCC / FVIIa.
Drug level guide to OT (30/200/400)

**Urgent surgery and RIVAROXABAN (XARELTO®)**

- **[Rivaroxaban] ≤ 30 ng/ml**
  - Operate

- **30 ng/ml < [Rivaroxaban] ≤ 200 ng/ml**
  - Wait up to 12 h* and obtain new dosage**
  - Operate, if abnormal bleeding: antagonise the anticoagulant effect***

- **200 ng/ml < [Rivaroxaban] ≤ 400 ng/ml**
  - Wait up to 12-24 h and obtain new dosage**
  - Operate, if abnormal bleeding: antagonise ***

- **[Rivaroxaban] > 400 ng/ml**
  - Overdose – Major haemorrhagic risk

*It is not possible to accurately determine the time to reach a threshold of 30 ng/ml, so the sentence “until 12h”

**This second assay can be used to estimate the time required to obtain the threshold of 30 ng/ml

***This proposal applies primarily to emergency situations where you cannot wait:

- PCC 25-50 U/kg or FEIBA=30-50 U/Kg depending on the availability
- No data are available on the thrombotic risk of high doses of PCC or FEIBA in these patients
- Reversal by CCP or FEIBA does not fully correct the abnormalities of haemostasis tests
- rFVIIa is not considered first-line
**Drug level guide to OT (30/200/400)**

### Urgent surgery and DABIGATRAN (PRADAXA®)

<table>
<thead>
<tr>
<th>Drug Level Range</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Dabigatran] ≤ 30 ng/ml</td>
<td>Operate</td>
</tr>
<tr>
<td>30 ng/ml &lt; [Dabigatran] ≤ 200 ng/ml</td>
<td>Wait up to 12 h* and obtain new dosage** or (if time is not compatible with emergency) Operate, if abnormal bleeding: antagonise the anticoagulant effect***</td>
</tr>
<tr>
<td>200 ng/ml &lt; [Dabigatran] ≤ 400 ng/ml</td>
<td>Wait up to 12 h* and obtain new dosage** or (if time is not compatible with emergency) Maximum delay surgery Discuss haemodialysis, especially if CkrCl &lt; 50 ml/mn Operate, if abnormal bleeding: antagonise ***</td>
</tr>
<tr>
<td>[Dabigatran] &gt; 400 ng/ml</td>
<td>Overdose – Major haemorrhagic risk Discuss haemodialysis before surgery</td>
</tr>
</tbody>
</table>

* In case of renal insufficiency, half-life of dabigatran is clearly increased
** It is not possible to accurately determine the time to reach a threshold of 30 ng/ml, so the sentence "until 12 h" ** This second assay can be used to estimate the time required to obtain the threshold of 30 ng/ml
*** This proposal applies primarily to emergency situations where you cannot wait:
- PCC 25-50 UI/kg or FEIBA=30-50 UI/Kg depending on the availability
- No data are available on the thrombotic risk of high doses of PCC or FEIBA in these patients
- Reversal by CCP or FEIBA does not fully correct the abnormalities of haemostasis tests
- rFVIIa is not considered first-line
Jungle version: use at own risk (1.2/1.5)

Urgent surgery and RIVAROXABAN (XARELTO®)
There is a worse proposal in case of unavailability of immediate dosage. It does not guarantee the absence of formal haemorrhagic complications

- **Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2**
  - Operate

- **Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2**
  - Wait up to 12 h and obtain specific dosage / new aPTT - PT or (if time is not compatible with emergency)
  - Operate, if abnormal bleeding: antagonise the anticoagulant effect**

- **Ratio aPTT > 1.5**
  - Wait up to 12–24 h and obtain specific dosage or (if time is not compatible with emergency)
  - Maximum delay surgery
  - Operate, if abnormal bleeding: antagonise **

Urgent surgery and DABIGATRAN (PRADAXA®)
There is a worse proposal in case of unavailability of immediate dosage. It does not guarantee the absence of formal haemorrhagic complications

- **Ratio aPTT ≤ 1.2 and ratio PT ≤ 1.2**
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- **Ratio 1.2 < aPTT ≤ 1.5 or ratio PT > 1.2**
  - Wait up to 12 h and obtain specific dosage / new aPTT - PT or (if time is not compatible with emergency)
  - Operate, if abnormal bleeding: antagonise the anticoagulant effect**

- **Ratio aPTT > 1.5**
  - Wait up to 12–24 h and obtain specific dosage / new aPTT - PT or (if time is not compatible with emergency)
  - If CrCl Cockcroft < 50 ml/min, obtained specific dosage to detect overdose and discuss haemodialysis
  - Maximum delay surgery
  - Operate, if abnormal bleeding: antagonise **
3. How to guide ourselves

- From the phase III mega-trials, treatment level between 30-200 and <30ng/ml probably safe
- Timing of last dose, and coagulation tests are rough guides only.
- Sought hematopathologist advice x test interpretations
- Clot based assays are indirect estimates and repeat testing to<30ng/ml is best
- Save blood first (2 vials of citrate to lab or in fridge)
**Table 2** Definition of serious or potentially serious bleeding with vitamin K antagonists, according to the French Health Authority [27].

Serious or potentially serious bleeding in the context of treatment with a VKA is defined by the presence of at least one of the following criteria:

- Externalized bleeding uncontrollable by conventional procedure
- Haemodynamic instability
  - SBP < 90 mmHg or
  - 40 mmHg decrease in SBP compared with usual or
  - Mean arterial pressure < 65 mmHg or
  - Signs of shock
- Need for urgent haemostatic surgery, interventional radiology, endoscopy
- Need for blood transfusion
- Threatening or functional location
  - Intracranial or intraspinal haemorrhage
  - Retro-orbital and intraocular bleeding
  - Haemothorax, haemoperitoneum and retroperitoneum, haemopericardium
  - Deep muscular haematoma and/or compartment syndrome
- Acute gastrointestinal bleeding
- Haemarthrosis

**SBP**: systolic blood pressure; **VKA**: vitamin K antagonist.
Antidotes

• Humanized monoclonal Ab fragment Fab vs dabigatran, (aDabi-Fab) monkey / rat tail bleed

• Plasma derived and recombinant Xa (pd-Xa and r-Xa, r-Antidote PRT064445) lack catalytic and membrane binding domains. Rabbit laceration model, also ok x heparin / LMWH
Extreme measures

- Hemodialysis remove 55-65% DB after 1-4hr
- Successful in urgent Heart Transplant case (Wanek et al Ann Pharmacotherapy 2012 46:e21)
- Oral activated charcoal within 2 hrs adsorb 99% DB. Please consider use within 4hrs
- Successful in 57 yr-old 11.25g DB (970ng/ml) (Woo et al J Med Toxicol 2013 9:192-5.)
Specific factor deficiency = hemophilia
Reversal strategies

Give factor to overcome factor inhibition
Factor derivatives: Fresh frozen plasma FFP, prothrombin complex concentrates (PCC / impure FIX) activated prothrombin complex concentrates (aPCC), recombinant activated factor VII (rFVIIa)

Survey: 221 US surgeons 73% will try to reverse dabigatran in ICH
Choice of agents PCC 61%, FFP 53%, rFVIIa 24%, HD 24%, Plt 7%
PROTHROMBIN COMPLEX CONCENTRATE THERAPY FOR WARFARIN ASSOCIATED INTRACRANIAL HAEOMORRHAGE

PCC FIRST PROTOCOL TREATMENT FORM
A&E, MEDICAL and NS DEPARTMENT QUEEN ELIZABETH HOSPITAL

Please ensure PT/INR/APTT and Type & Screen had been checked and send urgently to the lab
Please contact haematology lab to trace INR result if intracranial haemorrhage is confirmed in CT brain

INDICATIONS
1. Current on Warfarin
2. Intracranial Haemorrhage noticed in CT brain:
   • Intracerebral haemorrhage
   • Subdural haemorrhage
   • Subarachnoid haemorrhage
3. <24 hours after onset of neurological symptoms/signs, OR
   >24 hours after onset of Sx/Sign with progression on presentation

Note: If all of the above are yes, proceed to CONTRAINDICATIONS.
If not, patient is not indicated.

CONTRAINDICATIONS FOR STAT PCC Rx
1. Any known history of DVT or PE
2. Known LA/LV clots
3. Known Antiphospholipid Antibody Syndrome/Protein C/S/Antithrombin III def
4. Suspected to have ischemic stroke with haemorrhagic transformation or minimal subdural haematoma
5. Suspected to have intracranial calcification instead of ICH
6. Suspected to have disseminated intravascular coagulation (DIC)
7. Others: (please specify)

Patient decided INDICATED for STAT Prothrombinex HT Therapy

ADMINISTRATION
1. Start Prothrombinex HT ___ vials
   Slow injection 3ml per min
2. GCS after treatment
3. BP after treatment

Note: After completion of the injection, proceed to WARD ADMISSION
2.1 Implementation Date
1st July 2012

2.2 Criteria to start Prothrombinex-HT at A&E level:
- Prothrombinex-HT slow injection (over 3 mins) can be given if intracerebral haemorrhage, subdural haemorrhage or subarachnoid haemorrhage are noticed in the urgent CT brain.
- In the following rare situation in which the prothrombotic risk of prothrombinex-HT may be significant and potentially outweigh its expected benefit, it should not be given and the patient should be immediately transferred to ward for further management and the case should be handed over to the medical officer directly:
  - History pointed to ICH onset more than 24 hrs (e.g. patient with sudden onset of focal weakness > 24 hrs ago, static in severity, attended A&E afterward with CT brain performed > 24 hrs from onset of focal weakness)
  - Difficulties in differentiating between ICH vs calcification
  - Patient with acute DVT/ pulmonary embolism
  - Patient with known LA/LV clots
  - Patient with known antiphospholipid antibody syndrome or Protein C/Protein S/Antithrombin III deficiency

2.3 Key Logistics in A&E Department
- Book urgent CT by informing CT scan room via pre-admission CT brain protocol for acute stroke patient (effective 1 Jan 2006) OR urgent CT brain protocol for selected patients on warfarin (effective 1 Feb 2011)
- Perform blood tests including PT/APTT/INR and Type & screen immediately, contact haematology laboratory for immediate analysis of the specimen.
- Escort patients to CT room by A&E physician and A&E nurse.
- Review the CT films +/- with radiologist (if performed during office hour) to look for intracranial haemorrhage.
- If ICH/SAH/SDH is identified, transfer the patient back to A&E, check whether INR result is available or not, follow the Prothrombinex-HT dosage guide to start the treatment accordingly to the INR result or empirically accordingly to the protocol if INR result is not yet available. (see Protocol for Urgent Reversal of Warfarin Effect in Intracranial Haemorrhage for details)
- After Prothrombinex-HT is given, the patient is immediately transferred to ward. **Medical officer**
Prothrombin complex concentrates PCC

Licensed x hemophilia B prophylaxis and treatment & Factor II VII IX X deficiency Warfarin reversal (plus Vit K)

Prefer over FFP (ACCP 2012, FDA approved)
1. 80% correction in one hr.,
2. Improved survival for early use vs FFP
3. Less volume TRALI infection hypersensitivity
4. 500 unit in 20ml vs. (FFP 220ml has 220 units) No thawing or cross match
Plasma products: limited supply

1990 Plasma fractionation for Hong Kong, Singapore, and Malaysia
Cohn Fractionation Process

Plasma

Cryoprecipitate
- Factor VIII (fibrinogen vWF)

Cryosupernatant
- 8% Ethanol
  - Fraction I Paste
  - Waste

Supernatant I
- 20% Ethanol
  - Fraction II+III Paste

Factor IX (2,7,10) Antithrombin III

Supernatant II+III
- 20% Ethanol
  - Fraction II+III W
  - Supernatant II+III W

Fraction II+III W
- 16% Ethanol
  - Fraction III Paste
  - Supernatant III

Fraction III Paste
- Waste

Supernatant III
- Immunoglobulins

Albumin
Plasma products: viral safety

- Population
- Donor screening
- Donor testing
- NAT Testing
- Plasma pooling
- Viral removal/inactivation
- Patient

Relative risk

Donors - Pooling - Fractionation - Packaging - Distribution - Patient
Thalassaemia Hemophilia Care Summit 2010 2012
Dear Medical and Nursing colleagues,

This is a patient with HAEMOPHILIA. Bleeding complication in such patient can be serious, excruciatingly painful or even life-threatening. It can be controlled with Factor Replacement Therapy. Appropriate IV factor infusion as early as possible is recommended in case of pain or symptoms suggestive of bleeding. Please refer to the table below for the suggested dose of factor required, and consider paging the Adult or Pediatric hematologist named below for further advice. The factors are available in the emergency fridge of the Dept. of A&E. We thank you for your swift action to save this patient from unnecessary suffering and possible life-threatening events.

Yours truly,

Dr SY Lin
Medicine, UCH

Dr Desmond Chan
Pediatrics, UCH

The dosage below is expected to bring the factor level up to about 50% in severe haemophilia.

<table>
<thead>
<tr>
<th>Factor (dosage)</th>
<th>Hemophilia A</th>
<th>Hemophilia B</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 kg</td>
<td>≤1 vial</td>
<td>≤1 vial</td>
</tr>
<tr>
<td>10 – &lt; 20 kg</td>
<td>2 vials</td>
<td>1 vial</td>
</tr>
<tr>
<td>20 – &lt; 30 kg</td>
<td>3 vials</td>
<td>2 vials</td>
</tr>
<tr>
<td>30 – &lt; 40 kg</td>
<td>4 vials</td>
<td>3 vials</td>
</tr>
<tr>
<td>40 – &lt; 50 kg</td>
<td>5 vials</td>
<td>4 vials</td>
</tr>
<tr>
<td>50 – &lt; 60 kg</td>
<td>6 vials</td>
<td>5 vials</td>
</tr>
<tr>
<td>≥ 60 kg</td>
<td>≥ 6 vials (1 vial/10 kg rounding up)</td>
<td>≥ 5 vials</td>
</tr>
</tbody>
</table>

Double dose in case of life threatening bleeding.

*There are 11 patients in Hong Kong with inhibitors (antibody to Factor VIII or Factor IX) may need by-passing agent (Novoseven, FEIBA or Prothrombinex) to stop bleeding. ASK the patient and CALL the Adult or Paediatric hematologist.
No pain, no gain
Many thanks for A and E support
<table>
<thead>
<tr>
<th></th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
<th>2013 to date</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTX</td>
<td>80%</td>
<td>63%</td>
<td>56%</td>
<td>46%</td>
</tr>
<tr>
<td>MonoFIX</td>
<td>20%</td>
<td>37%</td>
<td>44%</td>
<td>54%</td>
</tr>
</tbody>
</table>

This data based on the quantities released to HA hospitals from HKRCBTS.
PCC for NOAC reversal

For NOAC reversal PCC (50U/kg, 7 vials) higher than VKA reversal (20U/kg) but lower than severe hemophilia bleed (100U/kg)

1.8% thrombosis (hi dose and liver ds, never seen in Chinese hemophilia B)

4-factor PCC Beriplex (Europe Canada)

3-factor PCC Prothrombinex (USA HK HA $500)

DO NOT USE MONOFIX OR MONONINE (pd or recombinant Factor IX only)

Need supplement FFP or rFVII 15-30 for 3-F?

Latest studies no difference between the two
Activated aPCC or Factor Eight Inhibitor Bypass Activity

Licensed indication for hemophilia with inhibitors (50-100 U/kg q12) $7980 per vial
Same as PCC but with activated factors (esp FVII) during freeze dry process
For NOAC reversal FEIBA 30-50 U/kg (3.5 vials)
Dosage is half that of hemophilia
Reported success vs. Dabigatran in cardiac ablation with FEIBA q8h
Thrombosis 4-8 per 10^5 doses 80% with thrombotic factors
Usage change the coagulation prolife
May need repeat depend on clinical scenario
(Dager et al Crit Care Med 2013 41:e42-6)
Recombinant activated factor VII Novoseven

Licensed indication for hemophilia with inhibitor and for FVII deficiency
Off labeled Used x ICH, peripartum hemorrhage, liver transplant and trauma
Also in severe thrombocytopenia and Plt function disorders
One vial 1mg (90ug /kg, 6 vials) $9900
rVIIa reported ineffective in Dabigatran epidural
rFVII poorly effective In some animal models

(Trummees et al Spine 201214:E863-5.)
Reversal of the anticoagulation effects of dabigatran by 4F-PCC
4. Use of reversal agents

- Dabigatran: FEIBA 30-80/kg preferred
- Rivaroxaban: 4-PCC 25-50/kg preferred
- 50U/kg use intraoperative postoperative at lower dose.
- If ICH IOH then PCC or FEIBA q8hr
- If <30ng/ml not needed
- Case reports are biased
- In vitro studies / animal models / volunteer in vivo volunteers all non-realistic and end points are arbitrary
- there will never be clinical RCT data
Conclusions

1. Less ICH than VKA. Not more complex in terms of dosing, monitoring and reversal
2. Rational dosing less iatrogenic bleeding
3. Laboratory monitoring available (not everywhere, in doubt call hematopathologist)
4. Reversing agents available (not everywhere, in doubt call hematologist)
Periodic Table of the Elements

Where to find me

Au 196.97

Where to find me