Peri-operative management of anti-thrombotics: Fast-track warfarin reversal

Kate Burbury MBBS(Hons) FRACP FRCPA DPhil
Haematologist
Anti-thrombotics in our patients

• Increased use:
  – community (AF/cardiac)
  – cancer-associated thrombosis
  – Warfarin remains common agent

• Expanded repertoire of agents

• Balance: TE risk (hiatus) vs surgical bleeding risk
Emergence of anticoagulants

- Unfractionated heparin (1884)
- Warfarin (1930)
- LMWH (1980s)
- Pentasaccharides (C21st)
- DOACS
  - Rivaroxaban
  - Dabigatran
  - Apixaban
  - Edoxaban
  - Betrixaban

- Isolated Hirudin (1974)
- Recombinant Lepirudin

“Leeches”: hirudin (1916)
Key principles

• No “one-size” fits all – tailored approach
  – Type of drug
  – Patient profile
  – Type surgery
  – Type anaesthetic

• Consult and communicate!
  – Ensure patient knows exactly the plan and rationale
  – Understand the indication for the antithrombotic
  – Understand the onset and offset of the drug – and the factors that will influence

• Questions that are often forgotten
  – Every medication including over-the-counter and complimentary...have a ready list to prompt patient
  – How important is the surgery ...and how risky is the surgery (bleeding and TE)
  – is the medical centre equipped to cope with both TE and bleeding complications
  – Be prepared: What additional measures can be put in place in peri-operative period
Peri-procedural risks

- **TE risk:** inherent and procedural....”unknown”
  - TE risk during anticoagulation hiatus (and rate recurrence) is extrapolated from non-surgical population according to indication
  - Additional risk of surgery....up to 100-fold venous and 10-fold arterial
  - TE complication: 70% major morbidity or death

- **Bleeding risk** lacks prediction guide – non-surgical population
  - Surgical procedure
  - Bridging heparin
  - Morbidity and mortality attributable (major bleed): 2-4%

- **Risk – patient and procedure:** multifactorial, heterogeneous and dynamic

- **Haemostatic measure:** factor levels, fibrinogen, platelet

Douketis et al. Chest 2012
Spyropoulos and Douketis Blood 2013
Garcia et al. JTH 2008
Spyropoulos et al. Curr Opin Hematol 2010
Halbritter et al. JTH 2005
Birnie et al. NEJM 2013
# Thrombotic risk: hiatus

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>ATE:</th>
<th>VTE:</th>
<th>Antithrombotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>&lt;4%/year</td>
<td>&lt;2%/month</td>
<td>Mechanical valve (AVR bileaflet) (no other RF CVA)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>4-10%/year</td>
<td>4-10%/month</td>
<td>Intermediate therapy (AVR Bileaflet + RF CVA)</td>
</tr>
<tr>
<td>High</td>
<td>&gt;10%/year</td>
<td>&gt;10%/month</td>
<td>High therapy (MVR (20-25% pa) AVR (10-15% pa) Caged-ball, tilting disc (A/M) Recent CVA/TIA: &lt;6mth)</td>
</tr>
</tbody>
</table>

### Active Indication Antithrombotic - Cessation VKA:

- 40% in first month
- 10% in subsequent 2 months
- Beyond 3 months: 15% for first year
- Beyond 12 months: 3-5%/year

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Douketis et al. Chest 2012
Spyropoulos and Douketis Blood 2013
## Bleeding risk: procedural

<table>
<thead>
<tr>
<th>Bleeding risk: 2d</th>
<th>Low: 0-2%</th>
<th>High: 2-4+%</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>LN biopsy</td>
<td>Major surgery: &gt;45mins</td>
</tr>
<tr>
<td></td>
<td>Hernia repair</td>
<td></td>
</tr>
<tr>
<td>Cardiac/vascular</td>
<td>I/O PPM/defibrillator</td>
<td>Heart valve replacement</td>
</tr>
<tr>
<td></td>
<td>Electrophysiologic testing</td>
<td>CABG</td>
</tr>
<tr>
<td></td>
<td>Non-coronary angiography</td>
<td>AAA repair</td>
</tr>
<tr>
<td></td>
<td>CVAD</td>
<td>Vascular surgery</td>
</tr>
<tr>
<td>Cancer</td>
<td>Skin</td>
<td>“all”</td>
</tr>
<tr>
<td>Neuro</td>
<td></td>
<td>Laminectomy; Cranial</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>TK/HR</td>
<td>Bilat TKR</td>
</tr>
<tr>
<td></td>
<td>Arthroscopy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shoulder, foot, hand</td>
<td></td>
</tr>
<tr>
<td>Dental</td>
<td>Tooth extraction</td>
<td>Multiple tooth extractions</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Cataract</td>
<td></td>
</tr>
</tbody>
</table>

Douketis et al. Thr Res 2002
Eisen et al. Gastr Endosc 2002
Which procedures: “risk” bleeding

“Risk” TE and bleeding - and repercussions from clinically significant bleeding

• Operative intent
  – Major: >30mins lap/thorac
  – Malignant vs benign

• Surgical field
  – Vascular territories
  – Fibrinolysis

• Surgical technique and ability to manage (occult) bleeding

• Patient factors:
  – Personal History
  – *Concomitant antithrombotic agents – what impact they have on haemostasis*

• **Clinical implications: TE and bleeding**
Peri-procedural warfarin management

Warfarin

• Widely used antithrombotic for majority of indications for long-term TP
## Warfarin reversal: options

<table>
<thead>
<tr>
<th>Type of reversal</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid (&quot;complete&quot;; &lt;10–15 mins)</td>
<td>PTx +/- FFP: immediate replacement of vitK-dependent coagulation factors</td>
</tr>
<tr>
<td></td>
<td>+ IV vitK (activation, hepatic synthesis within 4 hrs)</td>
</tr>
<tr>
<td>Prompt (within 4–6 hours)</td>
<td>IV vitamin K</td>
</tr>
<tr>
<td>Slow (within 24 hours)</td>
<td>Oral vitamin K</td>
</tr>
<tr>
<td>Ultraslow (over days)</td>
<td>Omit warfarin dose (no vitamin K)</td>
</tr>
</tbody>
</table>

PTx: Prothombinex-HT™ FFP: fresh frozen plasma;
**Consensus guidelines**

- **Pre-assessment clinic**
- **Bridging anticoagulation**
- **INR**
- **Vitamin K**
- **Further reversal: vit K, PCC, FFP**
- **Proceed**
- **Defer surgery**

**Complex process**

**Douketis - ACCP. CHEST 2013**

Warfarin reversal: Consensus guidelines, on behalf of ASTH. MJA 2013
4. Complexity of process compounded by

a. Delegation of responsibility

b. Surgical risk stratification

c. Coordination and planning of all the management steps - elective surgical setting which is often unsettled.

5. Aim: primary outcome of “reversing” warfarin

a. Repletion of “active factors”; to what level
   i. Warfarin depletes factor activity - ?absolute amounts in SS
   ii. Replacement of vitK – replete “equally”: rate and amount

b. INR level: correlate with individual factor activity
Rapid warfarin reversal

**Conventional method**

- Bridging “heparin”
- INR monitoring
- Vit K
- Warfarin ceased
- Warfarin recommenced

**Alternative method**

- Pre-assessment clinic
- Vit K
- INR monitoring (Bridging “heparin”)

- D-5
- D-1
- D0
Outcomes

• Safety and efficacy of intravenous vitK
  – Adverse reactions
  – “Normalisation” of INR
  – Bleeding and thrombotic complications
  – Warfarin “resistance”

• Vit K-dependent factor activity – effect of
  – Warfarin therapy
  – Vit K administration (“reversal”)
  – Correlation between INR and Factor activity
Results

Included: all indication for VKA and all surgical procedures

No patient suffered adverse reaction to vit K

Efficacy

- INR DOS: median 1.2 (1.0-1.7)
- 99% achieved INR ≤1.5
- ALL achieved INR≤1.7
- ALL proceeded to surgery, no delays

DOS: Day of surgery/procedure
Results

• **TE post procedure: n=1 (＞400 patients)**
  - D+9 post major abdominopelvic surgery colorectal cancer
  - LMWH 40mg sc daily from +6 hours post surgery
  - Recent proximal DVT and pulmonary embolus (＜3 months)

• **＜20% receive bridging heparin post-procedure**

• **＜3% clinically significant bleeding:** ALL INR ≤1.5 and factor activity ＞30%

• **Time to re-stabilisation warfarin:**
  - Median 4 days (Range: 2-11 days)
  - Commenced within 24 hours: median 3 days (Range: 2-6 days)
  - 6-week INR: 2.1 (1.6-4.3)  [mechanical valves: 2.8 (1.7-3.7)]
VitK-dependent coagulation factors

Impact:
Therapeutic anticoagulation (warfarin)
Administration intravenous vit K
Vitamin K-dependent coagulation factor activity (median and range) pre and post vitamin K IVI.
Correlation INR with vitamin K dependent coagulation factor activity - pre and post vitK IVI.

Factor II: 
- $r = -0.841; p < 0.0001$

Factor VII: 
- $r = -0.854; p < 0.0001$

Factor IX: 
- $r = -0.784; p < 0.0001$

Factor X: 
- $r = -0.904; p < 0.0001$
Correlation INR with vit K dependent coagulation factor activity: pre and post vit K IVI.
Fast-track warfarin reversal: summary

- Simple process
- Relevant for all patients on warfarin who require “reversal” for invasive procedures
- Not affected by changeable surgical dates
- Does not require complex coordination or delegation
- **Reliable, safe and convenient** for patients and health institutions, including geographically remote patients.
- **Avoids pre-procedure heparin:** contributor to procedural-related bleeding.

Burbury et al. Brit J Haem. 2010
Burbury et al. Anaesth Intensive Care. 2015
Lower doses (<3mg) vit K: achieve same results?

Dosing strategy – “individualised” according to:
  - Baseline INR
  - Target INR
  - TE risk: patient and procedure
  - Surgical bleeding risk

Oral vs IV: but less reliability/predictability

Delivery of vit K: HITH, GP

Extrapolation to all procedures, including epidurals
DOACS: 7 years old

- Limited data in cancer or other high risk populations: drug interactions
- What is the ideal therapeutic target(s): II, X, TF
  - Off target effects
- Ability to reverse the anticoagulant effect
  - Specific reversal agents
- Ability to monitor or assess anticoagulant effect

>50 phase II and III studies
>200,000 patients
6 indications
<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target</strong></td>
<td>Ila</td>
<td>Xa</td>
<td>Xa</td>
<td>Xa</td>
</tr>
<tr>
<td><strong>Hrs to Cmax</strong></td>
<td>2</td>
<td>3-4</td>
<td>2-4</td>
<td>1-2</td>
</tr>
<tr>
<td><strong>CYP450</strong></td>
<td>None</td>
<td>15%</td>
<td>32%</td>
<td>30%</td>
</tr>
<tr>
<td><strong>Drug interactions</strong></td>
<td>P-gp</td>
<td></td>
<td>CYP3A4/5; P-gp</td>
<td></td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>80%</td>
<td>25%</td>
<td>33%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Half-Life</strong></td>
<td>12-17h</td>
<td>8-15h</td>
<td>5-9-13h</td>
<td>9-12h</td>
</tr>
<tr>
<td><strong>Time: restore haemostasis</strong></td>
<td>48h (3-5d CrCL&lt;30)</td>
<td>20-30h</td>
<td>20-30h</td>
<td>20-30h</td>
</tr>
<tr>
<td><strong>Recommence post-procedure</strong></td>
<td>+6-12h</td>
<td>+6-12h</td>
<td>+6-12h</td>
<td>+6-12h</td>
</tr>
</tbody>
</table>

These drugs INHIBIT, not DEPLETE factor… so replacement of factors will only be effective if able to “by-pass” or overwhelm the inhibition of Xa or Ila.
## Reversal anticoagulant effect

<table>
<thead>
<tr>
<th>Strategy</th>
<th>FXa inhibitors</th>
<th>FIIa inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated oral charcoal</td>
<td>Unlikely to be helpful</td>
<td>&lt;1-2 oral ingestion</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>Unlikely to be helpful</td>
<td>Can remove drug (30-60%)</td>
</tr>
<tr>
<td></td>
<td>• Highly protein bound</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Partial renal clearance</td>
<td></td>
</tr>
<tr>
<td>Factor replacement “temporary replacement factor”</td>
<td>PCC (in pref to rFVIIa)</td>
<td>PCC or rFVIIa</td>
</tr>
<tr>
<td>Specific antidote</td>
<td>Recombinant protein: FXa decoy with structural modifications</td>
<td>Humanised Fab fragment: idarucizumab</td>
</tr>
</tbody>
</table>

Lu et al. Nat Med 2013  
Pollack et al. NEJM 2016
Bleeding rates and risk factors

Rates:
- **VKA**: 2-13% (2-3% pa)
- **Heparins**: 0-2%
  - Prophylactic dose: 0.1-0.5%
- **DOACS**
  - Rivaroxaban: 0.7-6%
  - Apixaban: 0.6-2.2%
  - Edoxaban: 1.4-2.8%
  - Dabigatran: 0.6-4%

Risk factors
- Intensity anticoagulation
  - Duration anticoagulation
- Age
- Renal function
- Hepatic function
- Concomitant drugs
- Comorbidities

**DOACS:**
- **Quick onset** – early resumption will give more effect than we are used to with warfarin and LMWH
- **Urinary excretion of active anticoagulant** – recurrent haematuria
- **Dabigatran** – prodrug (5-7% BIOAVAILABILITY) – anti-IIa impact – **increase risk GI bleeding, impaired healing**
Smartphone APP

- **STEP:** SURGICAL TE PREVENTION
- **MAD:** MANAGEMENT of ANTITHROMBOTIC DRUGS
- **HO:** HAEMATINIC OPTIMISATION
- **FTWR:** FAST TRACK WARFARIN REVERSAL
The Team

- Bernhard Riedel
- Rani Chahal
- Hilmy Ismail
- Kay Kenchington
- Anaesthetic department
- Surgical and sub-surgical specialties