The Peri-operative Management of Patients on Anticoagulant Therapy

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No conflict of interest to declare
Learning Objectives


2. Vitamin K antagonists (e.g. Warfarin) & Direct Oral Anticoagulants (DOACs): elective and emergency peri-operative management

3. How DOACs affect global assays of coagulation and pitfalls in assay interpretation

4. A brief summary of the available reversal strategies for DOACs
Can you advise......?

• Frequently encountered clinical query

• Not straightforward –
  • Many issues to consider
    • Stratification of patients according to thrombotic and bleeding risk
    • Is interruption of antithrombotic therapy necessary
    • When to discontinue and when to resume therapies
    • If an anticoagulant “bridge” is necessary
  • Lack of high quality evidence until 2015
  • Empiric use of many different strategies and protocols
  • No consensus regarding optimal peri-operative strategy
  • 4 new non vit K oral anticoagulants

Ortel T. Blood 2012; 120: 4699-4705
Van Veen JJ, Makris M. Anaesthesia 2015 70 (Suppl 1) 58-67
Balancing Risks

Pre-operative assessment must consider each patient’s risk for thromboembolic events BALANCED against the risk for peri-operative bleeding.
Definition of “Bridging”

“the administration of a short-acting anticoagulant such as LMWH or UFH (at treatment dose) during the time when a long-acting anticoagulant such as warfarin is withheld before surgery, and subsequently after the surgery or procedure until the long-acting anticoagulant is again within the target therapeutic range”

Ortel T. Blood 2012 120: 4699-4705
Procedures associated with very low bleeding risk

PERI-OPERATIVE INTERRUPTION OF WARFARIN IS NOT NECESSARY

• MINOR DENTAL PROCEDURES
  – SDCEP advisory document

• DERMATOLOGICAL

• CATARACT SURGERY

• JOINT INJECTIONS

• ENDOSCOPY: BSG and ESGE guidelines, 2016

• PPM and defibrillator surgery:


Alcalay J. Dermatol Surg 2001; 27(8): 756-8

Billingsley EM, Maloney ME. Dermatol Surg 1997; 23 (5): 381-3


Ahmed I, Gertner E. J Hosp Med. 2011, 2: 51

Assessment of Bleeding Risk

**Patient specific**

- History of bleeding
- Mechanical mitral valve
- Active cancer
- Thrombocytopenia  
  *(BLEEDMAP risk score)*

**HAS-BLED score**

- Hypertension, abnormal renal and liver function, stroke, bleeding predisposition, labile INR, elderly (>65yrs), drugs/alcohol

**Procedure specific**

- Highly vascular organs
- Bleeding into confined critical locations
- Bowel resection with risk of bleeding at anastomotic sites

- Also urological procedures, colonic polyp resection broad base, major surgery associated with extensive tissue injury  
  *(joint arthroplasty, cancer surgery)*

Douketis JD, Spyropoulos AC, Spencer FA et al. Chest 2012; 141 (2 suppl): 326-350
### Assessment of thromboembolic risk

**Previously used system**

**Patient related risk factors**

<table>
<thead>
<tr>
<th>Risk stratum</th>
<th>Mechanical heart valve</th>
<th>Atrial fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>· any mitral valve prosthesis &lt;br&gt; · caged-ball / tilting disc aortic valve prosthesis &lt;br&gt; · recent (within 6 mo) stroke or TIA</td>
<td>· CHADS₂ score of 5 or 6 &lt;br&gt; · recent (within 3 mo) stroke or TIA &lt;br&gt; · rheumatic valvular heart disease</td>
<td>· recent (within 3 months) VTE &lt;br&gt; · severe thrombophilia (e.g. deficiency of protein C, S, AT, APLAbs, multiple abnormalities)</td>
</tr>
<tr>
<td>Moderate</td>
<td>· bileaflet aortic valve prosthesis and one or more of: Afib, prior stroke or TIA, hypertension, diabetes, congestive cardiac failure, age &gt;75y</td>
<td>· CHADS₂ score of 3 or 4</td>
<td>· VTE within the past 3-12 mo &lt;br&gt; · Non-severe thrombophilia (e.g. heterozygous factor V Leiden or prothrombin gene mutation &lt;br&gt; · recurrent VTE &lt;br&gt; · active cancer (treated within 6 mo or palliative)</td>
</tr>
<tr>
<td>Low</td>
<td>· bileaflet aortic valve prosthesis without Afib and no other risk factors for stroke</td>
<td>· CHADS₂ score of 0 to 2 (assuming no prior stroke or TIA)</td>
<td>· VTE &gt;12 mo previous and no other risk factors</td>
</tr>
</tbody>
</table>

Adapted from Douketis JD, Spyropoulos A, Spencer FA, Mayr M et al. Chest 2012; 141 (2) (Suppl): e326S-350S

**CHADS₂:** estimates the postoperative risk for stroke  
Gage BF, Waterman AD, Shannon W et al. JAMA 2001; 285 (22):2864-70

Cumulative score: CCF, hypertension, age>75yrs, diabetes mellitus (each 1 point) and stroke or TIAs (each 2 points)

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

- BRIDGE AF Trial; funded by NIH, ClinicalTrials.gov: NCT00786474
- Background: Uncertainty regarding the need for bridging anticoagulation in the elective surgery setting in patients on warfarin for atrial fibrillation

• Hypothesis: withholding bridging would be non-inferior to bridging with LMWH for the prevention of perioperative arterial thromboembolism and would be superior with respect to major bleeding

• Randomised double blind placebo-controlled trial

• Random assignment to
  – either bridging anticoagulation therapy with LMWH (100 units dalteparin /Kg sc BD),
  – or matching placebo sc BD,
  – from day-3 prior to procedure until 24 hrs before procedure ,
  – then for 5-10 days post-procedure
• Warfarin stopped 5 days pre-procedure and resumed 24 hrs after procedure
• F/U for 30 days post-operatively
• Primary outcomes: arterial thromboembolism (stroke, systemic embolism, TIA) and major bleeding
• RESULTS: 1884 patients enrolled: 950 assigned to receive no bridging; 934 assigned to receive bridging

• The incidence of arterial embolism was 0.4% in no bridging group vs 0.3% in the bridging group: CI 0.6-0.8, P=0.01 for non-inferiority

• The incidence of major bleeding was 1.3% in the non-bridging group vs 3.2% in the bridging group (RR, 0.41; CI 0.20-0.78, P=0.005 for superiority)

• CONCLUSION: in patients with AF foregoing bridging anticoagulation was non-inferior to bridging anticoagulation for the prevention of arterial thromboembolism and decreased the risk of major bleeding.
When to consider bridging

<table>
<thead>
<tr>
<th>Consider bridging with treatment dose heparin/LMWH in:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VTE</strong></td>
</tr>
<tr>
<td>Patients with a VTE within previous 3 months</td>
</tr>
<tr>
<td>Previous VTE when on therapeutic anticoagulation with target INR 3.5</td>
</tr>
<tr>
<td><strong>AF</strong></td>
</tr>
<tr>
<td>Patients with a previous stroke/TIA in last 3 months</td>
</tr>
<tr>
<td>Patients with a previous stroke/TIA and 3 or more of: CCF, hypertension (&gt;140/90mmHg or on medication); age ≥75 yrs; diabetes mellitus</td>
</tr>
<tr>
<td><strong>MHV</strong></td>
</tr>
<tr>
<td>MHV patients other than those with a bileaflet aortic valve and no other risk factors</td>
</tr>
</tbody>
</table>

Individual assessments for triple positive antiphospholipid antibody syndrome and cancer associated VTE

Adapted from: Keeling et al. BJ Haematol 2016, 175: 602-613
Practical Issues when Bridging

• Detailed written plan in case notes for multidisciplinary team
• Take account of patient’s weight, age and renal function, past history, baseline INR and FBC
• Clear communication with patient and provision of a written plan with contact numbers
• Memory and cognitive function very important
• Provision of LMWH in pre-filled syringes
• Patient education and written plan for patient
• Takes time and effort
Warfarin instructions

• Outpatient strategy: simple instructions and easy to follow
• Stop warfarin 5 days in advance of elective surgery
  • Limited data in relation to other VKAs
  • Elimination half-life of warfarin is 36-48 hours
  • So cessation 5 days prior to operation corresponds to 5 elimination half-lives
  • Allows sufficient time for the regeneration of functional vit K-dependent coagulation factors to achieve normal haemostasis

Elderly patients may have slower warfarin elimination
Patients with a higher baseline INR may require a longer period of warfarin interruption

• The INR should be determined the day prior to surgery, if possible
  • So that vit K can be given if INR ≥1.5 to reduce the risk of cancellation

• The INR should be checked on the day of surgery

RCT compared a 5-day vs 1-day warfarin +vit K interruption before surgery; the 5-day group had a significantly lower mean INR on the day of surgery compared with the 1-day interruption group despite vit K (1.24 vs 1.61, p<0.01)


Post-operative instructions: WARFARIN

• Early resumption of warfarin after surgery possible due to expected delay of 5-7 days before therapeutic anticoagulant effect
  • Can start on evening of day of operation, or day 1 post-op, or when oral intake resumes
  • Only re-start if post-operative haemostasis is controlled

• What warfarin dosage?
  • 2 cohort studies
    – 650-patient prospective cohort study, warfarin resumed at maintenance dose within 24 hrs of operation, mean time to achieve therapeutic INR ≥2.0 was 5.1 days (Kovacs MJ, Kearon C et al. Circulation 2004;110(12):1658-63)
    – Resume warfarin with a doubling of maintenance dose for initial 2 postoperative days mean time to achieve therapeutic INR ≥2.0 is 4.6 days (Douketis JD, Johnson JA, Turpie AG. Arch Intern Med 2004; 164 (12):1319-26)

Dunn A. J Thromb Thrombolysis 2006; 21 (1):85-89
Darvish-Kazem S, Douketis JD Semin Thromb Haemost 2012; 38 (7) 652-660
Keeling et al. BJ Haematol 2016, 175: 602-613
Emergency surgery in patients on warfarin/VKAs

• If surgery can be delayed for 6-8 hours, give iv vit K 5mg to restore coagulation factors

• if delay not possible then give 25-50 iu/Kg four-factor prothrombin complex concentrate (PCC), and check INR post-administration

• Post-operatively, either no LMWH or prophylactic dose for 48 hours

• Then can use therapeutic LMWH if haemostasis is adequate; can split LMWH into BD dosing regimen

Keeling et al. BJ Haematol 2016, 175: 602-613
Peri-operative management of patients on direct oral anticoagulants “DOACs”
Direct Oral Anticoagulants

- Rivaroxaban
- Apixaban
- Edoxaban

Thrombin

TF/VIIa

Fibrinogen → Fibrin

Dabigatran
### CHARACTERISTICS OF THE DIRECT ORAL ANTICOAGULANTS

Adapted from Schulman J Int Med 2014; 275 1-11

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to maximum effect</td>
<td>1.5-2h</td>
<td>2h</td>
<td>3-4h</td>
<td>1-2h</td>
<td>5 days</td>
</tr>
<tr>
<td>Half-life</td>
<td>12-17h</td>
<td>5-9h</td>
<td>8-15h</td>
<td>10-14h</td>
<td>36-48h</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>35%</td>
<td>92-95%</td>
<td>87%</td>
<td>40-59%</td>
<td>99%</td>
</tr>
<tr>
<td>Renal elimination</td>
<td>80%</td>
<td>33%</td>
<td>25%</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>Interactions</td>
<td>P-gp</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
<td>P-gp, CYP3A4</td>
<td>CYP2C9 (S) CYP1A2 (R)</td>
</tr>
<tr>
<td>Food effect</td>
<td>Absorption delayed</td>
<td>Required for absorption</td>
<td>Not reported</td>
<td>no</td>
<td>Dark green vegetables etc</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral Twice daily</td>
<td>Oral Once daily</td>
<td>Oral Twice daily</td>
<td>Oral Once daily</td>
<td>Oral Once daily</td>
</tr>
</tbody>
</table>

The new oral anticoagulants exert effect almost immediately, so caution required in re-starting post-operatively.

No need for bridging anticoagulation with heparin pre-operatively in view of half-life:
- Stop 1-2 days before elective surgery if renal function is normal
## Peri-operative Management: a pragmatic approach

**Timing for last dose of anticoagulant**

<table>
<thead>
<tr>
<th></th>
<th>96hrs</th>
<th>72hrs</th>
<th>48hrs</th>
<th>24hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Xa inhibitors</strong></td>
<td><strong>High risk and renal</strong></td>
<td><strong>High risk and renal</strong></td>
<td><strong>High risk /or renal</strong></td>
<td><strong>Low risk</strong></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>High risk <strong>and renal</strong></td>
<td>High risk <strong>and renal</strong></td>
<td>High risk <strong>or low risk +renal</strong></td>
<td>Low risk and no renal</td>
</tr>
<tr>
<td></td>
<td>Creat cl 30-49ml/min</td>
<td>Creat cl 50-80ml/min</td>
<td>Creat cl 50-80ml/min</td>
<td></td>
</tr>
</tbody>
</table>

Current strategies for elective surgery do not routinely include measurement of either non-specific or specific coagulation parameters to assist in quantification of DOAC levels.

*Adapted from Schulman J Int Med 2014; 275: 1-11; Keeling et al. BJ Haematol 2016; 602-613*
Re-introduction of DOACs post-surgery

• Rapidly absorbed with maximum concentrations within hours post-ingestion – leaving the patient fully anticoagulated
  • Given the experience from LMWH bridging avoid new oral anticoagulants for 48-72 hours post high bleeding risk procedures, and for 6-12 or 24 hours post low bleeding risk procedures – depends on the procedure.

• Use LMWH prophylaxis while waiting to re-introduce the DOAC

• A suggested alternative strategy is to use lower doses of new oral anticoagulants – off licence approach, except in elective total hip and knee arthroplasty
Emergency Surgery: decision making

• When was the last dose taken?

• Stop drug; try to postpone surgery with a high bleeding risk for at least 1-2 half lives of drug and provide supportive care

• Is the drug still present?
  – Check anti-Xa level for apixaban, rivaroxaban and edoxaban, and diluted thrombin time (Hemoclot assay) for dabigatran
    • but uncertainty over the concentration of each drug that equates to haemostatic safety
    • variation in specific assay results from lab to lab dependent on reagents and instrumentation

• Does the drug need reversed?
  – What is the strategy?

• Neuraxial anaesthesia contra-indicated if an anticoagulant effect cannot be excluded

Van Veen JJ, Makris M. Anaesthesia 2015 70 (Suppl 1) e21-e23
Plots of global assays vs Dabigatran concentration (ng/mL)

(Stangier J, Rathgen H, Stahle H et al. BJ Clin Pharm. 2007 64(3) 292-303)
Pro-haemostatic agents

• Use of PCC and aPCC to reduce risk of peri-surgical bleeding?
  • Data relates to animal expts and in vitro studies
  • Potential for adverse thrombotic outcomes

• Few data to support use in emergency surgery
  • BSH suggest use PCC in the event of diffuse coagulopathic bleeding
  • BSH recommend use of tranexamic acid to reduce bleeding
Specific reversal agents for DOACs

IDARUCIZUMAB:
- Target: dabigatran
- Phase I
- Phase II
- Phase III
  - Patients requiring urgent surgery/with major bleeding; May 2014
  - EMA and FDA Approval 2015/16
  - SMC Approval 2016

Andexanet alfa (PRT064445)
- Target: FXa inhibitors
- Phase I
- Phase II
- Phase III
  - Patients with major bleeding Jan 2015

Ciraparantag (PER977)
- Target: universal
- Phase I
- Phase II
- Ongoing
Idarucizumab

• Humanised Fab fragment
• Binding affinity ~350 times higher than dabigatran to thrombin
• No intrinsic procoagulant or anticoagulant activity
  – intravenous dosing by bolus or rapid infusion
  – immediate onset of action
Prospective trial of 5g Idarucizumab to 36 patients undergoing an invasive procedure

- Normal intra-operative haemostasis reported in 33
- Mildly abnormal haemostasis in 2
- Moderately abnormal haemostasis in 1
- 1 thrombotic event within 72 hrs after Idarucizumab
- Major reversal of coagulation tests in 88-98% of patients
Andexanet alfa

Recombinant human factor Xa decoy protein
Reverses the inhibition of fXa in healthy volunteers (ANNEXA – A and R trials)
Siegal et al. NEJM 2015, 373:2413-2424
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

Stuart J. Connolly, M.D., Truman J. Milling, Jr., M.D., John W. Eikelboom, M.D., C. Michael Gibson, M.D., John T. Curnutte, M.D., Ph.D., Alex Gold, M.D., Michele D. Bronson, Ph.D., Genmin Lu, Ph.D., Pamela B. Conley, Ph.D., Peter Verhamme, M.D., Ph.D., Jeannot Schmidt, M.D., Saskia Middeldorp, M.D., Alexander T. Cohen, M.D., Jan Beyer-Westendorf, M.D., Pierre Albaladejo, M.D., Jose Lopez-Sendon, M.D., Shelly Goodman, Ph.D., Janet Leeds, Ph.D., Brian L. Wiens, Ph.D., Deborah M. Siegal, M.D., Elena Zotova, Ph.D., Brandi Meeks, B.Eng., Juliet Nakamya, Ph.D., W. Ting Lim, M.Sc., and Mark Crowther, M.D., for the ANNEXA-4 Investigators*

Interim report (67 patients) for the ANNEXA-4 trial. Cohort study. Initial bolus + subsequent 2 hour infusion in patients with acute major bleeding associated with fXa inhibitors; effective haemostasis (“excellent” or “good”) described in 79% of patients; thrombotic events in 12 patients (18%) during follow-up
SUMMARY

- New guidance on peri-operative management for patients on anticoagulants published by BSH in October 2016
  - standardises peri-operative advice for the multidisciplinary team
  - outlines the few indications for “bridging” patients on warfarin
  - offers a pragmatic approach to elective and emergency surgery in patients on DOACs
  - Idarucizumab is SMC-approved and licensed for reversal of dabigatran
Any questions?