Peri-operative bridging of anticoagulant therapy

Peri-operative evaluation of the patient with bleeding diathesis

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How to Bridge Antiplatelet and Antithrombotic Therapy?
How to Bridge Antiplatelet and Antithrombotic Therapy?

- Risk of bleeding
  - Anesthetic bleeding risk
    - Spinal hematoma
  - Surgical bleeding risk
    - Per/postoperative bleeding

- Risk of thromboembolism
  - Venous TE
  - Cardiovascular
How to bridge anticoagulants?

- **Vitamin K-antagonists (VKAs)**
  - Fenprocoumon (Marcoumar®)
  - Warfarine (Marevan®)
  - Acenocoumarol (Sintrom®)
Coumarins. How do they work?

Antagonism of Vitamin K

Synthesis of Non-Functional Coagulation Factors

- VII: 6h T1/2
- IX: 18-24h
- X: 40-50h
- II: 48-60h
- PS: 48h
- PC: 6-8h

Vitamin K

Warfarine
coumarins

- Delayed onset
  - Delayed working
- Unpredictable therapeutic response
- Narrow therapeutic margin
Bridging of OAC in surgery

- Risk of thromboembolism: dependent on indication for oral anticoagulation

- Bleeding risk: site and type of surgery
  - Minor dental surgery, dermatological surgery: no interruption needed

- Chest 2004,126: the Seventh ACCP Conference on antithrombotic and thrombolytic therapy
What is the incidence of thromboembolism in absence of anticoagulant therapy?

- **High (>10%/year)**
  - multiple MHV, MitralMHV, AFib with history of stroke or multiple risk factors, Recent VTE

- **Moderate (5-10%/year)**
  - Afib with additional risk factors, history of idiopathic VTE, AorticMHV

- **Low (<5%/year)**
  - Afib without or with few risk factors, history of ‘triggered’VTE, biological heart valves
How to bridge anticoagulant therapy in the surgical patient?

1) Stop VKAs, perform surgery upon normal INR (INR <1,5). Restart as soon as safe.

2) Reduced INR. Perform surgical procedure in ‘subtherapeutic’ range (INR 1,5 – 2).

3) Hold intake of VKAs. Bridge with LMWH if INR ≤ 2. Hold LMWH 12-24h before surgery. Restart as soon as safe with safe dose.
How to bridge anticoagulant therapy in the surgical patient?

1) Stop VKAs, perform surgery upon normal INR (INR <1.5). Restart as soon as safe.

- Interruption of anticoagulation for diagnostic or therapeutic procedures in patients with AF: anticoagulation may be interrupted for a period of up to 1 wk for surgical or diagnostic procedures without substituting heparin.

- In high-risk patients (particularly those with prior stroke, TIA, or systemic embolism), or when interruption of oral anticoagulant therapy for longer periods is required, ...UFH or low-molecular-weight heparin may be administered.

ACC/AHA/ESC 2006 guidelines
How to bridge anticoagulant therapy in the surgical patient?

1) Stop VKAs, perform surgery upon normal INR (INR <1.5). Restart as soon as safe.

2) Reduced INR. Perform surgical procedure in ‘subtherapeutic’ range (INR 1.5 – 2).

3) Stop AVK, bridge with LMWH if INR ≤ 2. Hold LMWH 12-24h before surgery. Restart as soon as safe.

What Dose LMWH?
LMWH to bridge oral anticoagulant therapy

- **High risk of Thrombo-embolism:**
  (recente VTE, mitral MHV, multiple MHV, …)
  therapeutic dose LMWH
  100 anti-Xa Units/kg BD

- **Moderate risk of Thrombo-embolism:**
  (non-recent VTE, Afib, Bi-leaflet AoMHV)
  intermediate (or half-therapeutic) dose LMWH
  100 anti-Xa Units / kg OD

- **Low risk of Thrombo-embolism / High risk of Bleeding**
  (non-recent VTE, lone Afib, …)
  High-prophylactic dose LMWH
  50 anti-Xa Units / kg OD
LMWH to bridge oral anticoagulant therapy

- **High risk of Thrombo-embolism:**
  (recent VTE, mitral MHV, multiple MHV, ...)
  therapeutic dose LMWH
  100 anti-Xa Units/kg BD
  (150-200 anti-Xa Units/kg OD)

- **Low / Moderate risk of Thrombo-embolism:**
  (non-recent VTE, Afib, Bi-leaflet AoMHV)
  intermediate (or half-therapeutic) dose LMWH
  100 anti-Xa Units / kg OD

- Assess bleeding risk, Assess renal function
- Window of >12h pre-op, Restart post-op 6-8h if no bleeding complications (restart with lower dose !)
- Start with LMWH if INR <2
How to bridge anticoagulant therapy in the surgical patient?

Coumarins: When to stop the intake?

- **Fenprocoumon (Marcoumar®)**
  - 10 d (t1/2: 4-7 d)

- **Warfarin (Marevan®)**
  - 7d (t1/2: 20-60 u)

- **Acenocoumarol (Sintrom®)**
  - 4d (t1/2: 8-11 u)
What is an intermediate dose?

- 100 anti-Xa units/kg / day
  
  (enoxaparin 1 mg/kg – Clexane°)
  
  (nadroparin 0.1 ml/10kg – Fraxiparine°)
  
  (tinzaparin 100 anti-Xa units/kg – Innohep°)
  
  (dalteparin 100 anti-Xa units/kg – Fragmin°)

- OD vs BD?
**Orale anticoagulation : Emergencies...**

Bleeding while on VKA:

- **mild**: hold intake, consider administration of Vitamin K
- **major**: Vitamin K + prothrombin complex concentrate

No bleeding and supratherapeutic INR

- INR 4 - 8(6): hold intake
  - sintrom (T ½ 8h): 1-2 days
  - marevan (T ½ 20 – 60h): 2-3 days
  - marcoumar (T ½ 43 – 130h): 3-5 days
- INR > 8 (6): hold intake + 2 (4-5) mg vit K p.o.
Bridging in the future?

- **Specific Factor Xa inhibitors**
  - **Indirect (ATIII mediated) FXa inhibitors**
    - Fondaparinux/Arixtra® (GSK) - parenteral
    - Idraparinux (Sanofi-Aventis) - parenteral
  - **Direct (non-ATIII mediated) FXa inhibitors**
    - BAY 59-7939 (Bayer) – oral – XARELTO® phase III
    - DPC-423 (Bristol-Myers Squib) – oral phase III
    - DX-9065a (Daiichi) - parenteral/oral phase II
    - LY 517717 (Lilly) – oral phase II
    - Razaxaban (DPC-906) (Bristol-Myers Squib) – oral phase II
    - PD029843 (Pfizer) – oral phase II

- **Direct Thrombin inhibitors**
  - Dabigatran/Pradaxa® (Boehringer)
  - Lepirudin (Refludan®); Bivalirudin (Angiox®)
Belgian guidelines concerning central neural blockade in patients with drug-induced alteration of coagulation: an update

Vandermeulen, Acta Anaesth. Belg., 2005, 56, 139-146
BELGIAN GUIDELINES

- Prophylactic use
  - 12 h interval between last prophylactic dose and puncture
  - 12 h interval between last prophylactic dose and catheter removal
  - 4 h interval between puncture or catheter removal and next prophylactic dose

- Therapeutic use
  - Wait for 24 hours after last therapeutic dose
How to bridge Antiplatelet agents?

- Acetylsalicylic acid (ASA)
- Thienopyridines (TNP)
  - Ticlopidin
  - Clopidogrel
- Dipyridamole
- Glycoprotein IIb-IIIa receptor antagonists
  - Abciximab
  - Eptifibatide
  - Tirofiban
Risk of Atherothrombosis

- Acute coronary syndromes:
  - 5.4% recent withdrawal of antiplatelet agents (73/1358) elective surgical procedure most frequent reason

Interrupt LD ASA in patients with CAD?

Bleeding risk of ASA and clopidogrel after CABG


<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n = 78)</th>
<th>No Aspirin (n = 87)</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Chest tube output (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-h</td>
<td>501 ± 427</td>
<td>530 ± 616</td>
<td>1.000</td>
</tr>
<tr>
<td>24-h</td>
<td>809 ± 545</td>
<td>869 ± 687</td>
<td>1.000</td>
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<tr>
<td>Transfusions (U)</td>
<td></td>
<td></td>
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<tr>
<td>Red blood cells</td>
<td>1.84 ± 2.15</td>
<td>1.64 ± 2.17</td>
<td>1.000</td>
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<tr>
<td>Platelets</td>
<td>0.25 ± 0.54</td>
<td>0.23 ± 0.65</td>
<td>1.000</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>0.22 ± 0.84</td>
<td>0.26 ± 0.86</td>
<td>1.000</td>
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<tr>
<td>Cryoprecipitate</td>
<td>0.14 ± 1.14</td>
<td>0.19 ± 1.25</td>
<td>1.000</td>
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</table>
Anti-platelet therapy and peroperative bleeding

- Aspirin:
  - Low(er) peroperative bleeding risk
  - Interruption not needed / wanted in patients at high(er) risk for atherothrombosis
  - Assess bleeding risk!

- Primary prevention: interrupt for 5 d
- Secondary prevention: Don’t interrupt unless
  - Intracranial surgery: 5 d
  - TURP
  - Vitreoretinal surgery ‘back of the eye’ surgery
  - Amygdalectomy
Clopidogrel – when to stop?

5 (to 7) days

- normalisation of platelet aggregation tests
- normalisation of the excess bleeding

Anti-platelet therapy and peroperative bleeding

- Thienopyridines:
  - increased bleeding and need for transfusion during cardiac surgery
  - interrupt before surgery 5 – 7d
  - Restart as soon as possible
  
- Cave: recent ACS, recent coronary stenting: DO NOT INTERRUPT ANTIPLATELET THERAPY!
stented-patients

- **BMS:** if procedure within 6 weeks of stenting, delay the surgical non urgent procedure or continue 2 antiplatelet drugs. (grade 1C)

- **DES:** if procedure within 12 months of stenting, continue 2 antiplatelet drugs or delay the surgical non urgent procedure. (grade 1C)
Patient with bleeding diathesis and surgical procedures

- Antitrombotic drugs

- Bleeding disorders
  - Congenital
  - Acquired

  - Correction of the bleeding diathesis (if possible) upon surgical procedures

Prevention and treatment of major blood losses, Mannucci, NEJM 200
Acquired bleeding diathesis

- Medication
- ITP
- (Hematological) malignancies
- Hepatic insufficiency
- Uremia
- DIC
- Specific inhibitors for coagulation factors (FVIII, …)
- …
# Inherited disorders of coagulation inheritance and incidence

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Pathophysiology</th>
<th>Inheritance</th>
<th>Incidence Per million</th>
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<tbody>
<tr>
<td>Haemophilia A</td>
<td>Factor VIII</td>
<td>X-linked R</td>
<td>100</td>
</tr>
<tr>
<td>Haemophilia B</td>
<td>Factor IX</td>
<td>X-linked R</td>
<td>20</td>
</tr>
<tr>
<td>Factor XI def</td>
<td>Factor XI</td>
<td>Autos D or R</td>
<td>5%(Ashkenazi jews)</td>
</tr>
<tr>
<td>Von Willebrand’s disease</td>
<td>Von Willebrand factor</td>
<td>Autos D or R</td>
<td>&gt;100</td>
</tr>
<tr>
<td>FV, FVII, FX, FII, afibrinogenemia</td>
<td>Factor V or VII Factor X or II fibrinogen</td>
<td>Autosomal recessive</td>
<td>1</td>
</tr>
</tbody>
</table>
Bleeding disorders: preoperative management

- Inherited bleeding disorders are rare
  - Hemophilia A and B (FVIII, FIX) 100/10^6
  - Autosomal deficiencies (FVII, FV,..) 1/10^6

- Single factor deficiency, specific treatment

- Refer to specialized diagnosis and treatment center
Bleeding disorders: perioperative management

- Dosing and duration of therapy dependent on
  - minimal factor level required for coagulation
  - type of surgery

- Therapy starts usually immediately before invasive procedure, has to be continued days after procedure

- Peri- en postoperative control of clotting factor levels required for major surgery
Hemostatic Agents

- Haemostatic Agents
  - Prothrombin Complex
  - Coagulation Factors
  - Activated Factor VII
  - DDAVP

- Primary Hemostasis
  - Platelet Transfusion
  - Correction of Hematocrit
  - DDAVP

- Anti-fibrinolytic agents
  - Tranexaminic acid
  - (Aprotinin)
Thank you
Initiation of coagulation


Positive feedback
Phospholipids (PL)
Tissue Factor Pathway Inhibitor (TFPI)
Prekallikrein (PK)
High-molecular-weight kininogen (HK)
Antifibrinolytic Agents

- Aprotinine (Trasylol)
  - FDA approved in cardiale heelkunde
  - Onduidelijke balans efficacy / safety

- Lysine analogen (Tranexamine zuur, Exacyl)
  - Cardiale heelkunde
  - Rol bij preventie/behandeling van bloedingen
    - NKO / gyneco : empirisch
    - Gastroentero : geen benefit in trials
    - ICH ?
    - Uro
DDAVP

- Desmopressine (Minirin° 4µg) - 0,3 µg/kg
- Release UL MM vWF

- Preventie van bloeding bij mineure ingrepen
  Behandeling van mineure bloedingen
  bij Milde hemofilie / Milde vWF / BPdysfunctie

- Gebruik van Minirin bij
  - verworven bloedplaatjesdysfunctie ?
  - Uremie

- Safety Issue !
Licensed indications:

- Acquired hemophilia (auto-antibodies to FVIII or IX with titer > 10 BU)
- Hemophilia with inhibitor > 10 BU
- Glanzmann’s thrombasthenia with antibodies to GPIIb/IIIa - FVII deficiency

- Proper dose, timing, number of doses...
- Specialist advises ‘hemostasioloog’
Initiation of coagulation

Positive feedback
Phospholipids (PL)
Tissue Factor Pathway Inhibitor (TFPI)
Prekallikrein (PK)
High-molecular-weight kininogen (HK)

Delayed Onset

• Elimination/synthesis of normal Vit K dep Factors
Anticoagulation in Belgium

België: 60-100 000 patiënten behandeld met orale anti-coagulantia

1 op 2 is NIET in range (INR te hoog, te laag)

Jaarlijks risico op majeure bloedingen (=3-5%)

Point of care in oral anticoagulation BSTH meeting. 20/11/03
Conditions that Alter the Response to Warfarin

Compliance

Drugs
- Affect hepatic metabolism of warfarin
- Affect binding to plasma proteins

Diet
- Availability of vitamin K

Other conditions
- Nephrotic syndrome (low plasma albumin)
- Pregnancy (high levels of coagulation factors)
- Liver disease (low levels of coagulation factors)
- Heart failure

Genetics
Complications of Warfarin Therapy

Bleeding
Incidence varies (~4% major bleeding during 3-month course of treatment for VTE; ~3-4% annual risk thereafter)
Risk increases with INR > 4
Treated with vitamin K (delayed response) or fresh-frozen plasma (immediate response)

Birth defects and abortion
Skeletal and CNS abnormalities

Skin necrosis
Microvascular thrombosis
May occur in patients with heterozygous protein C or S deficiency if a high initial dose is used or heparin overlap is inadequate
Orale antistolling: overdosering

geen bloeding: stop coumarine

INR 4-8 : onderbreken
  sintrom (T½ 8 uur) : 1-2 dagen
  marevan (T½ 20 – 60 uur) : 2-3 dagen
  marcoumar (T½ 43 – 130uur) : 3-5 dagen

INR >8 : onderbreken + 2-4 mg vit K per os

+ bloeding:
  • licht: vit K 2-4 mg per os
  • ernstig: vit K 10 mg IV
  • Levensbedreigend/interventie vereist: PPSB
Chemische Depolymerisation

Enzymatische Depolymerisation

UFH (MW 15000)

LMWH (MW < 8000)
Heparine en LMWH : catalyseren FIIa/FXa inhibitie door antithrombine
Complications of Heparin Therapy

**Bleeding**
- Major bleeding (5-10 day course): ~2% with UFH; ~1% with LMWH
- Usually controlled by discontinuation of heparin

**Osteoporosis**
- Decreased bone density in ~30% of patients after 1 month of full-dose UFH therapy
- Vertebral fractures in ~2%
- Lower incidence with LMWH

**Heparin resistance (>40,000 U/day of UFH with subtherapeutic aPTT)**

**Thrombocytopenia**
- Immune (onset after 5-10 days; HIT antibodies present; thrombosis likely)
- Non-immune (immediate onset; HIT antibodies absent; thrombosis unlikely)