Current Anticoagulation Management in Special Groups and Future Trends

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7 Aug 2010
Special groups

- Surgery
- Pregnancy
- Paediatrics
Warfarin and Surgery
Overview

- Perioperative management of anticoagulation
- Evidence
- Risk stratification
Perioperative management

- Lack of good clinical trials

- Is the risk of thromboembolic (TE) complications with interruption of warfarin overstated?
Balance

Thrombosis- warfarin withheld

Bleeding- surgery
Some increase in the risk of thromboembolism is unavoidable
Surgery increases the risk of venous thromboembolism

Flanc C, Br J Surg 1968
Carter CJ, Prog Cardiovasc Dis 1994
But there is no evidence that surgery increases the risk of arterial embolism in patients with AF or MHV.
Assessment of periop TE risk

- Clinical indications for anticoagulation
- Additional TE risk factors
- Clinical consequences of a TE event
Clinical indications

- Mechanical heart valves
- Chronic atrial fibrillation
- Venous thromboembolism
Mechanical Heart Valves
Mechanical Heart Valves (MHV)

- Estimated incidence of TE not receiving warfarin: 9 - 22% per year
- Mortality rate 15% with valve thrombosis
- Absolute incidence of TE when warfarin interrupted during 6 – 8 days: 0.17 – 0.42%

Martinelli J 1991
Bridging anticoagulant therapy in MHV

- Various studies: 1 - 18% risk of TE events
- Need for large, well designed prospective studies
- Risk stratify- high, moderate or low risk
Not all valves are the same

<table>
<thead>
<tr>
<th>Bi-leaflet tilting disc</th>
<th>Ball in cage</th>
<th>Single tilting disc</th>
</tr>
</thead>
<tbody>
<tr>
<td>St Jude/Carbomedics</td>
<td>Starr Edwards</td>
<td>Bjork-Shiley</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aortic position</th>
<th>Mitral position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large</td>
<td>Small</td>
</tr>
</tbody>
</table>

Increasing thrombogenicity
## Risk stratification in MHV

<table>
<thead>
<tr>
<th>Risk</th>
<th>Patient characteristics</th>
<th>Bridging anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Recent (&lt;1 month) stroke/TIA, Any mitral valve, Aortic valve: caged-ball or single-leaflet tilting disc</td>
<td>Strongly recommended</td>
</tr>
<tr>
<td>Moderate</td>
<td>Aortic valve: bileaflet tilting disc + ≥2 stroke risk factors</td>
<td>Should be considered</td>
</tr>
<tr>
<td>Low</td>
<td>Aortic valve: bileaflet tilting disc + &lt;2 stroke risk factors</td>
<td>Optional</td>
</tr>
</tbody>
</table>

Duoketis JD 2003
Stroke risk factors

- AF
- Previous stroke, TIA or systemic embolism
- LV dysfunction
- Age > 75 years
- HT
- DM
Chronic Atrial Fibrillation
Chronic atrial fibrillation (AF)

Incidence of recurrent stroke

• Low risk: <1% per year
  - Lone AF
  - <65 years
  - No additional stroke risk factors

• Moderate risk: 3-7% per year
  (≥2 risk factors without h/o stroke)

• High risk: 12-15% per year
  (with previous stroke)

EAFT Lancet 1993
Albert GW et al Chest 2001
Chronic AF: warfarin interruption

Estimated risk for stroke during 6-8 days:

- High: 0.28-0.38%
- Moderate: 0.06-0.15%
- Low: 0.02-0.04%

However, no real data
## Risk stratification for chronic AF

<table>
<thead>
<tr>
<th>Risk</th>
<th>Patient characteristics</th>
<th>Bridging anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Recent (&lt;1 month) stroke or TIA, rheumatic valve dis</td>
<td>Strongly recommended</td>
</tr>
<tr>
<td>Moderate</td>
<td>Chronic AF + $\geq 2$ stroke risk factors</td>
<td>Considered</td>
</tr>
<tr>
<td>Low</td>
<td>Chronic AF + &lt;2 stroke risk factors</td>
<td>Optional</td>
</tr>
</tbody>
</table>

*Duoketis JD, Throm Res 2003*
Venous Thromboembolism
Venous thromboembolism (VTE)

- No data on recurrence of VTE when warfarin is interrupted
- Highest recurrence <3 weeks from acute VT
- Idiopathic: 10-27% per year
- Transient risk factor: 2-5% per year
- Increased risk:
  - cancer
  - chronic disease- cardiac or pulmonary
  - APLS

Douketis JD 2000
Risk stratification for VTE

<table>
<thead>
<tr>
<th>Risk</th>
<th>Patient characteristics</th>
<th>Bridging anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Recent (within 3 weeks) episode of VTE, active cancer, APLS, major chronic disease</td>
<td>Strongly recommended</td>
</tr>
<tr>
<td>Moderate</td>
<td>VTE within past 6 months, VTE recurring with previous warfarin interruption</td>
<td>Considered</td>
</tr>
<tr>
<td>Low</td>
<td>None of above</td>
<td>Optional</td>
</tr>
</tbody>
</table>
Perioperative management of anticoagulation
Stopping antithrombotic drug

- Anti-platelet drugs stopped at least 7 days before surgery
- Warfarin stopped 5 days
- INR on day before surgery
- If INR > 1.5, give oral vit K 1-2mg

ACCP 2008
Bridging anticoagulant therapy

- Indication: high risk category; consider for moderate risk
- Start LMWH 2 days after stopping warfarin
- Last therapeutic dose of LMWH 12h before op with bd dose or 24h before op with once-daily dose
- iv UFH stopped 4-6h before op
Safe INR

- Most surgical procedures: < 1.5

- Neurosurgery: < 1.2

Ansell J, Chest 2001
Neuraxial anaesthesia

- Insertion of epidural needle:
  - Prophylactic LMWH dose stopped 12 h before
  - Treatment LMWH dose stopped 24h before

- Removal of epidural catheter:
  - 10-12h after last dose of LMWH
  - Resume LMWH 2h after catheter removal

Horlocker RA, Reg Anesth Pain Med 2003
Resumption of anticoagulation
Resumption of anticoagulant

- Adequate post-op hemostasis
- Surgical procedure and bleeding risk
Assessment of bleeding risk

- Type of surgery
- Post-op haemostasis
- Clinical consequences
Bleeding risk stratification

• High risk:
  - Neurosurgery, genito-urinary, renal biopsy
  - Heart valve replacement, CABG
  - Major cancer surgery, bowel polypectomy

• Moderate risk:
  - Major intra-abdominal, intra-thoracic, orthopedic
  - Pacemaker insertion

• Low risk:
  - Cataract extraction, cutaneous surgery
  - Lap cholecystectomy, hernia repair
  - Coronary angiography
# Resumption of anticoagulation

<table>
<thead>
<tr>
<th>Bleeding risk</th>
<th>Suggested anticoagulant management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Warfarin</td>
</tr>
<tr>
<td></td>
<td>Low dose LMWH</td>
</tr>
<tr>
<td></td>
<td>Full dose LMWH</td>
</tr>
<tr>
<td></td>
<td>Evening of day after surgery</td>
</tr>
<tr>
<td></td>
<td>24-48h after surgery</td>
</tr>
<tr>
<td></td>
<td>48-72h after surgery</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>Evening of day of surgery</td>
</tr>
<tr>
<td></td>
<td>Evening of day of surgery</td>
</tr>
<tr>
<td></td>
<td>24-48h after surgery</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>Evening of day of surgery</td>
</tr>
<tr>
<td></td>
<td>Evening of day of surgery</td>
</tr>
<tr>
<td></td>
<td>24h after surgery</td>
</tr>
</tbody>
</table>

Stop LMWH once INR in therapeutic range  

*Duoketis JD 2003*
Case VN

- 40 years old lady
- L DVT 3 months ago - idiopathic
- On warfarin; target INR 2.5
- Fell and hurt her knee? meniscus tear
- Plan for arthroscopy
- No other risk factors or medical illness
Case VN

- What is the VTE risk?
  Moderate risk: VTE within 6 months

- How would you manage her?
Case VN

- Stop warfarin 5 days
- Admitted for LMWH- was it necessary?
- INR 1.6 the day before op
- What will you do?
Case VN

What actually happened..

- 2 u FFP requested for op- was it necessary?
- After op, FFP transfused
- Patient developed urticaria
- INR on op day: 1.3
Peri-op anticoagulation plan list

<table>
<thead>
<tr>
<th>Name:</th>
<th>Date of birth:</th>
<th>Address:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Anticoagulant drug</th>
<th>Indication</th>
<th>Thrombosis risk</th>
<th>Bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>High ☐ Intermediate ☐ Low ☐</td>
<td>High ☐ Intermediate ☐ Low ☐</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for categorization</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perioperative management</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop warfarin on date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Check INR on dates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start heparin on date</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type</th>
<th>Dose</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Stop heparin before surgery |                          |                |
| Date                        | Time                     |
|                            |                          |                |

| Restart heparin after surgery (check bleeding risk) |                          |                |
| Date                        | Time                     |
|                            |                          |                |

| Restart warfarin after surgery |                          |                |
| Date                        | Time                     |
|                            |                          |                |

Copies of the form given to anaesthetist ☐ preop. ward ☐ postop. ward ☐ anticoagulation clinic ☐

Thachil J, Br J Surg 2008
Summary

- Patients on warfarin undergoing surgery should have a planned management.

- Risk stratify them into low, moderate or high risk group.

- Balance risk of thrombosis and risk of bleeding.
Warfarin in Pregnancy
Anticoagulation in Pregnancy

- Acute VTE
- Thromboprophylaxis
- Mechanical heart valves
- Management of labour and delivery
Selection of Prosthetic Heart Valves

In women of childbearing age

- Tissue valves
  - High risk of structural valve deterioration

- Mechanical valves
  - Long-term durability
  - High risk of valve-thrombosis
Mechanical Heart Valves in Pregnancy

- Interests of the mother and the fetus are in conflict

- Warfarin is safest for mother

- UH / LMWH is safest for fetus
Problems with warfarin

- Teratogenic (5%)
- Increased risk of miscarriage
- Increased risk of stillbirth
- Maternal bleeding
- Fetal intracerebral haemorrhage

Cotrufo et al. Obst & Gynecol 2002; 99: 35-40
## Warfarin vs. UH

<table>
<thead>
<tr>
<th></th>
<th>Warfarin (N=792)</th>
<th>Heparin-warfarin (N=230)</th>
<th>Heparin (N=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal loss</td>
<td>33.6%</td>
<td>26.5%</td>
<td>16.3%</td>
</tr>
<tr>
<td>Embryopathy</td>
<td>6.4%</td>
<td>3.4%</td>
<td>0%</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>3.9%</td>
<td>9.2%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>1.8%</td>
<td>4.2%</td>
<td>15.0%</td>
</tr>
</tbody>
</table>

Chan, Arch Intern Med 2000
## LMWH vs UH

<table>
<thead>
<tr>
<th></th>
<th>TEC</th>
<th>MM</th>
<th>Fetal loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>UH (Chan)</td>
<td>33.3%</td>
<td>15.0%</td>
<td>16.3%</td>
</tr>
<tr>
<td>LMWH (Oran) n=81</td>
<td>13.4%</td>
<td>1.5%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

LMWH

- Monitor anti-Xa

- Maintain 4-6 hours post-injection anti-Xa >1.0 U/ml

- Adjunctive aspirin

Maternal mortality

- Main cause: valve thrombosis

- Risk factors:
  - Valve type: single leaflet / ball in cage
  - Valve position: mitral
  - LA size
  - Heparin
  - Hx previous thrombosis
  - no. of mechanical valves

Vongpatanasin NEJM ’96, Sadler BJOG ‘00
Elkayam J ACC ’99, Oakley et al EHJ ’03
Fetal loss

- Risk factors:
  - Mitral mechanical valve
  - Warfarin

Vongpatanasin NEJM '96, Sadler BJOG '00
Elkayam JACC '99, Oakley et al EJH '03
Not all valves are the same

- Bi-leaflet tilting disc
  St Jude/Carbomedics

- Ball in cage
  Starr Edwards

- Single tilting disc
  Bjork-Shiley

Aortic position
Large

Mitral position
Small

Increasing thrombogenicity
Which Anticoagulant Regimes for Mechanical Valves?

• Warfarin throughout
• Heparin until 12/40, Warfarin until 36/40, Heparin
• Heparin + aspirin throughout

Small mitral Bjork Shiley <5mg warfarin
Large aortic Bileaflet
1. Adjusted –dose bd LMWH throughout (keep peak 4h anti-Xa >1.0 U/mL)

2. Adjusted-dose bd UH s/c throughout (keep 2x APTT or anti-Xa 0.35 to 0.7 U/mL)

3. UH or LMWH until 13th week with warfarin substitution
ACCP 2008

- Very high risk:
  - Older generation prosthesis in mitral position
  - History of thromboembolism

  - Warfarin + aspirin throughout; with UH or LMWH close to delivery
Informed choice
Warfarin: reducing fetal risk

- Full counselling
- Stop before 6 weeks if changing to heparin
- Optimum dose < 5mg/day
  
  BUT
- Maintain INR 2-4 depending on valve type
- Detailed and serial fetal scans
- Stop 10 days before delivery or 36 weeks
- Restart at least 3 days post partum
Any strategy carries risk
Women should participate in the choice of anticoagulation

Women should be fully informed of risks and benefits of all options

Decision should be individualized and ideally made pre-pregnancy

Care should be multidisciplinary
Breastfeeding

- Both warfarin and heparin are safe
Summary

- Warfarin in pregnancy is only indicated with mechanical heart valve

- Higher risk of embryopathy and fetal loss

- Lower risk for valve thrombosis
Summary

- Several choices - each with it’s own risk

- Informed choice - mum decides
Anticoagulation in Paediatrics
Paediatrics

- VTE rare
- Haemostasis is dynamic
  - AT levels low at birth (adult level at 3 mo)
  - Reduced and delayed thrombin generation (25% less than adults)
  - Reduced vitamin K-dependent factors at birth
- Distribution, binding, clearance are age-dependent
- Response to anticoagulants differs
Paediatrics

- Illnesses vary with age
- The need for GA to perform many diagnostic studies
- Vascular access (drug administration, blood taking)
- No specific pediatric formulation, weight-adjusted dosing difficult
- Dietary differences (breast milk and infant formulas have different vitamin K levels makes oral a/c difficult)
Paediatrics

- Prolonged APTT in neonates
- APTT therapeutic ranges are calculated using adult plasma?valid
- Heparin doses are age-dependent; highest <2mo
  - Larger volume of distribution
  - Altered pharmacokinetics
  - Low AT levels
# Developmental Haemostasis: Coagulation

## Normal Values

<table>
<thead>
<tr>
<th>Test</th>
<th>21 wk</th>
<th>26 wk</th>
<th>35 wk</th>
<th>Term</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (secs)</td>
<td>32</td>
<td>32</td>
<td>23</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>PTT (secs)</td>
<td>169</td>
<td>154</td>
<td>105</td>
<td>44</td>
<td>33</td>
</tr>
<tr>
<td>TT (secs)</td>
<td>34</td>
<td>26</td>
<td>21</td>
<td>20</td>
<td>14</td>
</tr>
</tbody>
</table>
Developmental Haemostasis: vitamin K dependent factors

Factor VII in fetal life

Factor IX

Factor X

Factor II

Gestational age (weeks)

I. Roberts
Neonatal thrombosis

- VTE in paediatrics most commonly occur in neonates
- Often occur in sick and preterm infants
- Risk factors:
  - Indwelling central line
  - Asphyxia
  - Septicaemia
  - Dehydration
  - Congenital heart disease
  - Maternal diabetes
Neonatal thrombosis

- Diagnosis: contrast angiography remains gold standard
- Treatment
  - Supportive: silent thrombosis
  - Anticoagulant: organ or limb dysfunction
  - Thrombolytic: limb viability threatened
  - Prophylactic a/c: indwelling umbilical artery catheters, cardiac catheterisation
## Neonatal anticoagulation

<table>
<thead>
<tr>
<th>Clinical indication</th>
<th>Medication</th>
<th>Traditional dosing</th>
<th>Current recommended dosing</th>
</tr>
</thead>
</table>
| Asymp or symp thrombus non-limb threatening | UH         | 75u/kg iv bolus, then 28u/kg/h                          | <28 wk: 25u/kg iv bolus, then 15u/kg/h  
28-37 wk: 50u/kg iv bolus, then 15u/kg/h  
>37 wk: 100u/kg iv bolus, then 28u/kg/h |
| Asymp or symp thrombus non-limb threatening | LMWH       | 1.5mg/kg SQ per 12h                                     | Term neonates: 1.7mg/kg SQ per 12h  
Preterm: 2.0mg /kg SQ per 12h                                  |
| Limb/life-threatening thrombus              | r-tPA      | NA                                                     | 0.06 mg/kg/h  
UFH at 10u/kg/h                                                 |
UH vs. LMWH

- Short half-life BUT
- Target-range achievement: poor
  - 14% within 6 hrs; 68% at 24hrs
- Increased bleeding risk: 12.5%
- Increased HIT: 3%
- Need iv access
- Need frequent blood taking for monitoring

Andrew M, REVIVE Study 1994
Future trends
Future trends in anticoagulation

- Alternatives to VKA; shorter-acting LMWH
- No monitoring required
- Safe and efficacious
- Antidote for reversal
- Paediatric formulation
- Safe in pregnancy
Thank you