Bridging Therapy: Peri-operative Antithrombotic Management

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Perioperative Antithrombotic treatment

Anticoagulants

Warfarin (VKA)
Unfractionated Heparin
LMWH

Antiplatelet drugs

Aspirin
ADP-receptor P2Y12 antagonists:
  Clopidogrel,
  Ticlopidine
  Prasugrel
Integrin αIIbβ3 (GPIIb/IIIa) receptor antagonists:
  Tirofiban, Eptifibatide,
  Abciximab
Indications for long-term antithrombotic treatment

Anticoagulants
- Mechanical heart valve
- Atrial fibrillation
- VTE
  (PAD, DCM, PPH)

Antiplatelet drugs
- Acute coronary syndrome
  1° prevention of MI
  2° prevention of MI
- Coronary stents
- Stroke
Surgery and ATT
OR
SAFE SURGERY

What is the Risk of peri-operative Thrombosis?
What is the Risk of peri-operative bleeding?

DEFICIENCIES IN CURRENT EVIDENCE

- From descriptive studies and clinical experience
- Does not account for:
  - the added risk of thrombosis during surgery
  - the rebound theory
  - the heterogeneity in patients’ characteristics
  - the post-operative clinical course
SAFE SURGERY: Choosing the Best Approach

Must Answer three basic questions

1 - Is interruption of antithrombotic therapy in the perioperative period needed?

2 - If antithrombotic therapy is interrupted, is bridging anticoagulation needed?

3 - Which is the best bridging strategy (bridging medication, timing, outpatient vs. inpatient)
SAFE SURGERY: Choosing the Best Approach

Must DO three basic ASSESSMENTS

1- Assessment of Thromboembolic Risk After Interruption of Antithrombotic Therapy

2- Assessment of Bleeding Risk Associated With Surgery or Other Invasive Procedures

3- How to Balance Thromboembolic Risk and Bleeding Risk
Thromboembolism Risk Category

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Star-Edwards</td>
<td>Bjork-Shiley</td>
<td>Medtronic-Hall</td>
</tr>
<tr>
<td>Omnicarbon</td>
<td>St. Jude</td>
<td>Carbomedics</td>
</tr>
</tbody>
</table>

Patient Characteristics

| Stroke or TIA < 6 mo | Any MV | Caged-ball or single leaflet tilting disc AV |

Suggested Management

<table>
<thead>
<tr>
<th>Therapeutic dose SC LMWH/IV UFH</th>
</tr>
</thead>
</table>

| A Fib, CVA, TIA, emboli, LV dysfxn, >75 y/o, HTN, DM |

<table>
<thead>
<tr>
<th>Bileaflet tilting disc AV and ≥ 2 stroke/TIA</th>
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</table>

<table>
<thead>
<tr>
<th>Therapeutic dose SC LMWH/IV UFH or low dose SC LMWH</th>
</tr>
</thead>
</table>

| Bileaflet tilting disc AV No AF or any RF for Stroke |

| low dose SC LMWH or no bridge |

J.D. Douketis, Chest 2008; 133; 299S-339S
<table>
<thead>
<tr>
<th>Thromboembolism Risk Category</th>
<th>Patient Characteristics</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Stroke or TIA &lt; 3 mo CHADS$_2$ score 5/6 Rheumatic Valvular heart Disease</td>
<td>Therapeutic dose SC LMWH/IV UFH</td>
</tr>
<tr>
<td><strong>Moderate</strong></td>
<td>CHADS$_2$ score 3/4</td>
<td>Therapeutic dose SC LMWH/IV UFH or low dose SC LMWH</td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>CHADS$_2$ score 0/2 (and no Stroke/TIA)</td>
<td>low dose SC LMWH or no bridge</td>
</tr>
</tbody>
</table>

A Fib, CVA, TIA, emboli, LV dysfxn, >75 y/o, HTN, DM

J.D. Douketis, Chest 2008; 133; 299S-339S
Perioperative AC Rx in Patients With VTE

VTE Recurrence Risk

High

Moderate

Low

Patient Characteristics

Recent VTE (< 3 wks)
Severe thrombophilia (def Protein C/S/Antithrombin)
APL Ab or LA

VTE (3 to 12 months)
Recurrent VTE
Active Cancer

VTE > 12 mo ago or no RF

Suggested Management

Therapeutic dose SC LMWH/IV UFH

Therapeutic dose SC LMWH/IV UFH or low dose SC LMWH

low dose SC LMWH or no bridge

J.D. Douketis, Chest 2008; 133; 299S-339S
<table>
<thead>
<tr>
<th>Bleeding Risk</th>
<th>Type of Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk</strong></td>
<td>CABG/Valve Replacement, IC or spinal Sx, Ao aneurysm repair, peripheral artery bypass, other major vascular Sx, Prostate/bladder, Reconstructive plastic Sx, major cancer sx, renal/prostatic Bx, polypectomy,</td>
</tr>
<tr>
<td><strong>Moderate Risk</strong></td>
<td>Major abd, thoracic, and orthopedic Cardiac pacemaker/defib implantation</td>
</tr>
<tr>
<td><strong>Low Risk</strong></td>
<td>Catarct, cutaneous, laparascopic choly/hernia repair, cardiac cath</td>
</tr>
</tbody>
</table>
Three important decisions taken

• Continue VKA throughout Sx/procedure (minor dental/dermatological procedures)

• Interruption of VKAs Before Surgery with/without Bridging therapy
  ✓ no RCT, 3 observational studies compare interrup vs. partial interrup
  ✓ Retrospect cohort study 608 pt. (9.5% MAJOR BLEEDING)

RECOMMENDATION

• Resumption of VKAs After Surgery
Rationale For Bridging For Patients on VKAs

Cross Coverage to Therapeutic INR

- Requiring AC but have not achieved Therapeutic INR
- Peri-procedural
- Already Rxed w chronic AC and now documented drop in INR

- mechanical heart valves
- A Fib w risk factors for emboli
- recent VTE (< 3 months)
- hypercoaguable states
BENEFITS Supporting Need for Bridge Therapy

• High daily risk estimate for thrombosis when patients remain unprotected for several days peri-procedure
• Subtherapeutic INR offers little or no protection
• Possible rebound hypercoaguable state, especially when warfarin reinitiated leading to thrombosis
• Bleeding complications can be controlled while CVA or PE may have lasting effect
• New drugs and new data offer increased ease of therapy
“BRIDGING” STRATEGY
ACCP Evidence-based Clinical Practice Guidelines, 2008

- Hold Coumadin
- Start full Dose LMWH
- Prophylactic Dose LMWH
- Resume full dose LMWH
- Resume Coumadin

# Days pre-op

Day -7 - 5 - 4
√ INR

# Days post-op

+1 +2 +3 +5
√ INR
√ CBC

J.D. Douketis, Chest 2008; 133; 299S-339S
Current Standard in Bridge Therapy

Prospective Randomized Controlled Trials

Expert Opinion/Consensus
Prospective Randomized Trials
(Bridge Therapy)

None available for major Sx, but some in progress and others in the planning phase
Only few observational studies +nt
Expert Opinion on Bridge Therapy

- British Society of Hematology
- American College of Chest Physicians (ACCP)
- Kearon and Hirsh article; NEJM, May, 1997
- Pregnancy and Prosthetic Valve Clinical Consensus (PPCR)
- Douketis 2003
- ACCP Evidence-based Clinical Practice Guidelines, 2008
INR Pre-Op Day 3
Stop Warfarin +/- Vit K

UFH when INR < 2

Normal INR Range 1-1.3

therapeutic INR range

British Society of Haematology
INR Pre-Op Day

Stop Warfarin +/- Vit K

Low or full dose UFH or LMWH when INR < 2

American College of Chest Physicians
Limitations of Kearon and Hirsh Recommendations

- Discounts rebound phenomena
- Estimate 100-fold ↑ in VTE risk but no ↑ in ATE risk [versus Wahl’s review (5 of 493 patients had ATE, 4 died)]
- Low estimate ATE risk off warfarin (4.5%/year A fib, 8%/year mechanical valve)
- Estimate heparin bleeding risk of 3% per 2 days
- Recommends SC vitamin K, does not utilize LMWH
- Does not focus on patients’ characteristics (type of valve, risk factors for ATE in A Fib)
- SC (or no) heparin in A fib and mechanical valves??!!
• Better risk stratification of:
  - risk of post-procedural bleed
  - risk of peri procedure thrombotic complications

• Advocates normal or near normal INR at the time of surgery (earlier withdrawal of warfarin)

• Includes practical algorithms that guide perioperative management of AC
Regardless of thromboembolism risk category, patient’s characteristics take precedent!

- A Fib
- CVA
- TIA
- arterial emboli
- LV dysfxn
- >75 y/o
- HTN
- DM

Bridging strongly recommended

J.D. Douketis, Thrombosis Research; 108 (2003) 3-13
“BRIDGING” STRATEGY
ACCP Evidence-based Clinical Practice Guidelines, 2008

Day -7 -5 - 4
Hold Coumadin
√ INR

Start full Dose LMWH

Surgery
√ INR

Prophylactic Dose LMWH

Resume full dose LMWH
√ INR
√ CBC

Resume Coumadin

# Days pre-op
# Days post-op

J.D. Douketis, Chest 2008; 133; 299S-339S
In patients undergoing a minor surgical or other invasive procedure and who are receiving bridging anticoagulation with therapeutic-dose LMWH
Resume this regimen approximately 24 h after the procedure when there is adequate hemostasis over a shorter (eg, < 12 h) time interval

In patients undergoing major surgery or a high bleeding risk surgery/procedure and for whom postoperative therapeutic-dose LMWH/UFH is planned
Delay the initiation of therapeutic-dose LMWH/UFH for 48 to 72 h after surgery when hemostasis is secured OR administer low-dose LMWH/UFH after surgery when hemostasis is secured, or completely avoid LMWH or UFH after surgery over the administration of therapeutic-dose LMWH/UFH in close proximity to surgery
In patients who are receiving bridging anticoagulation with LMWH

The routine use of anti-factor Xa levels to monitor the anticoagulant effect of LMWHs not required
Emergency Surgery in the Anticoagulated Patient

- D/C all anticoagulants
- If INR >2.5: Vit K +/- (plasma or factor concentrate)
- Prepare PRBC, platelet, and FFP
- Consider PRBC transfusion to “augment hematocrit” especially in pts with cardiac disease
- Watch for volume overload, dilutional thrombocytopenia and coagulaopathy
- Restart AC postop. as early as possible or start Bridging therapy
Newer anticoagulants and Bridging potential

**Fondaparinux (Arixtra)**

The role of fondaparinux in perioperative bridge therapy has not been established, and there are some important limitations to its use as a routine bridging agent


AC guidelines provide minimal direction on the periop use of fondaparinux

Fondaparinux's extended half-life of 17-21 h complicates its use as a periop bridging therapy.

The ideal time for discontinuation before surgery not known

Neuraxial blockade in patients with planned fondaparinux thromboproph may not be feasible in clinical practice.
Coronary stents: Perioperative hazards

PCI: Restenosis or Stent thrombosis

- Balloon angioplasty
  - Gruentzig, 1997
  - 15-60%
- Bare metal stents
  - 1986
  - 10-30%
- Drug eluting stents
  - 2003
  - 5-10%
Drug eluting stent

- Platform (stent)
- Carrier (Polymer)
- Drug to prevent neointimal hyperplasia
Drug eluting stents: Types

- Sirolimus DES
- Paclitaxel
- Zotarolimus
- Everolimus
- Biolimus

Stainless steel, tubular
Stainless steel, multiple rings
Chrome-Cobalt, tubular
Chrome-Cobalt, multiple rings
Antiplatelet drugs for Coronary stents

- **Aspirin**
  - Continue indefinitely

- **Integrin αIIbβ3 (GPIIb/IIIa) receptor antagonists:**
  - Tirofiban,
  - Eptifibatide,
  - Abciximab

- **ADP-receptor P2Y12 antagonists:**
  - Clopidogrel
  - Ticlopidine
  - Prasugrel

  - (Bare metal stent ≥6 wk)
  - (DES ≥ 12 mo)
# Risk factors for stent thrombosis

<table>
<thead>
<tr>
<th>Procedure-related</th>
<th>Patient and lesion-related</th>
<th>Stent-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent malposition</td>
<td>ACS</td>
<td>Delayed endothelisation</td>
</tr>
<tr>
<td>Stent underexpansion</td>
<td>Premature STOP APAs</td>
<td>Type of drug (DES)</td>
</tr>
<tr>
<td>Stent length</td>
<td>Drug resistance</td>
<td>Kinetic of drug release</td>
</tr>
<tr>
<td>Slow CBF</td>
<td>Low LVEF</td>
<td>Design</td>
</tr>
<tr>
<td>Positive remodeling</td>
<td>DM</td>
<td>Polymer vs. non polymer</td>
</tr>
<tr>
<td>Residual arterial dissection</td>
<td>Age&gt;75</td>
<td>Hypersensitive to polymer (Kounis syndrome)</td>
</tr>
<tr>
<td></td>
<td>Bifurcated lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Long lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complex lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Small vessels</td>
<td></td>
</tr>
</tbody>
</table>
Clinical risk score for Stent thrombosis

*(Baran et al)*

<table>
<thead>
<tr>
<th>Clinical Factors</th>
<th>Hazard Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel stop&lt;6 mo</td>
<td>5.28</td>
<td>5</td>
</tr>
<tr>
<td>DM (Insulin)</td>
<td>4.74</td>
<td>5</td>
</tr>
<tr>
<td>Left main stenting</td>
<td>2.73</td>
<td>3</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.63</td>
<td>3</td>
</tr>
<tr>
<td>Lesion length&gt;28 mm</td>
<td>2.35</td>
<td>2</td>
</tr>
<tr>
<td>Multiple stents</td>
<td>2.25</td>
<td>2</td>
</tr>
<tr>
<td>Mod to Severe Cal.</td>
<td>2.25</td>
<td>2</td>
</tr>
<tr>
<td>Ref vessel Dia.&lt; 3mm</td>
<td>1.72</td>
<td>2</td>
</tr>
<tr>
<td>Total score</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>

Risk Stratification

<table>
<thead>
<tr>
<th>Risk Stratification</th>
<th>ST rate%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-6 (0.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>7-13 (3.6)</td>
</tr>
<tr>
<td>High</td>
<td>14-24 (12.6)</td>
</tr>
</tbody>
</table>
# Proposed stratification of hemorrhagic and thrombotic risk

<table>
<thead>
<tr>
<th>Minor</th>
<th>Moderate</th>
<th>Major</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemorrhagic risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion not req: Minor plastic/GS/OS Biopsies, Dental, Eye (Ant. chamber)</td>
<td>Transfusion usually needed: Cardiac surgery; major OS/visceral/ENT/urology or reconstructive sx</td>
<td>Possible bleeding in an enclosed space; cranial/spinal sx; sx of the posterior segment of eye; TURP</td>
</tr>
<tr>
<td><strong>Thrombotic risk</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 mo after AMI or CABG, percut. coronary angiography or BMS, coronary surgery; and CVS (&gt;12 mo if high-risk patient or associated complications)</td>
<td>&gt;12 mo after DES; 6–36 wks after AMI or CABG; BMS; and CVS (6–12 mo if high-risk patient or associated complications)</td>
<td>&lt;12 mo after DES; &lt;6 wks after AMI; CABG; BMS; and CVS (&lt;6 mo if high-risk patient or associated complications)</td>
</tr>
</tbody>
</table>
Relative contribution of key hazards associated with major adverse cardiac events in patients with Coronary stents
Periop management of APA in DES

DES < 12 Mo

Elective Sx. Can be deferred?

Yes

Postpone Sx ≥ 12 mo after DES

No

Multidisciplinary Consultation:
Anesthetist+Surgeon+Cardiologist+Hematologist

DES ≥12 Mo

Replace Aspirin ≥200mg by ≤100mg
Maintain Aspirin ≤100mg
Stop Clopidogrel ≥5 d + substitute Aspirin ≤100mg
High risk of bleeding: stop aspirin 2-5 d

Llau et al. Vascular Health and Risk Management 2010
Multidisciplinary Consultation: Anesthetist+Surgeon+Cardiologist+Hematologist

Bleeding risk

High

- DES stent thrombosis risk score (Baran et al)

Moderate

- Time elapsed from DES implantation
  - DES ≥ 6 mo
    - Stop Clopidogrel 5d
    - Maintain Aspirin
  - DES ≤ 6 mo
    - Maintain dual APAs

Low

- Surgery

• Replace aspirin >200 mg by ≤100 mg
• Maintain Aspirin dose ≤100 mg
• Stop Clopidogrel 5d
  - vs
• Stop Clopidogrel ≥ 5d ± bridge therapy
• If necessary stop aspirin 2–5d ± bridge therapy
Role of bridging treatment in Coronary stents

- Unmet need
- UFH: no antiplatelet activity
- LMWH: no antiplatelet activity
- Tirofiban infusion +/- heparin (t1/2 life 2hr, BT return to normal 4 hr after stopping with 50% recovery of platelet funct)

(Saonitto et al. Stop Clopidogrel 5d before Sx,
Start Tirofiban 4d before Sx.
Stop inf 4 hr before Sx and restart 2 hr after Sx.
Reload patient with Clopidogrel on D1
Continue Aspirin throughout)

Godet et al., Broad et al.
New APAs

- Cangrelor (t1/2 life 3-5 min, full recovery of platelet activity in 60 min)
  Phase III trials
- Ticagrelor (reversible, rapid onset, and short half-life) phases of pre-marketing testing
Use of thromboelastography as an adjunct to bridging therapy

- MA of conventional thromboelastography (TEGw) is not sensitive enough to detect the presence of thienopyridines or salicylates.
- May be used to monitor the antiplatelet effects of GPIIb/IIIa inhibitors.
- Routine use of PFAs to monitor Asp/Clopidogrel ✗
Modified TEG

- Uses reptilase (a proteolytic enzyme from snake venom) and Factor XIII to produce a cross-linked clot through which platelets can interact.
- Produces MA that is sensitive to the presence of thienopyridines and salicylates.
- Early results suggest good correlation with gold standard laboratory-based tests, such as optical platelet aggregometry.
- Could be useful in monitoring the antiplatelet effects of cangrelor during bridging therapy, allowing its rate of infusion to be titrated against a pre-determined mTEG MA during the perioperative period.
Future stents

- Coated with APA
- Enhanced drug-eluting profile
- Bio-resorbable stents made from Mg alloys or poly-L-lactic acid
Many Thanks