Perioperative Management of Chronic Anticoagulation

Laura Chang Kit
PGY-5

At the end of this talk, you should

- know which of your patients needs to be anticoagulated perioperatively
- manage the basic perioperative anticoagulation for your patient based on current guidelines
- know what drugs to be cautious about during anticoagulation
Why is this increasingly important?

- Increased age of patients
- Many are chronically anticoagulated
  - Atrial fibrillation
  - Cardiac stents
  - Thromboembolic events
  - Mechanical heart valves
- Many require urological procedures, repeated procedures
- Increasing polypharmacy

The culprits...

- Warfarin
  - Atrial fibrillation
  - Mechanical heart valves
  - Venous thromboembolism

- Antiplatelet therapy – ASA, thienopyridines
  - Cardiovascular disease – CVA, MI, PAD
  - Cardiac stents
Warfarin management
Warfarin

Warfarin

Vitamin K \[\xrightarrow{\text{warfarin}}\] reduced vitamin K

\(\xrightarrow{\text{Vit KO reductase}}\)

Gamma carboxylation of newly synthesized factors

II (prothrombin), VII, IX, X
(extrinsic pathway)

Fibrinogen \[\xrightarrow{\text{Fibrin}}\] cross-linked clot

*Monitor PT/INR – sens to all vit K factors esp VII

Longest \(t_{1/2}=60\) hrs
Perioperative Management for Elective Procedures

- Need to stratify patients to assess risk of thrombosis peri-operatively vs risk of hemorrhage post operatively
Can we further stratify patients according to thrombosis risk?

YES
CHADS score

Assess thrombosis risk in patients with non-rheumatic AF

- C – CHF
- H – HTN
- A – Age > 75 yrs
- D – DM
- S – Stroke

Give 1 point each, 2 for stroke

*Validated
*Direct correlation to risk of thromboembolism from AF

<table>
<thead>
<tr>
<th>CHADS Score (points)</th>
<th>Adjusted Stroke Rate/100 Pt-Yrs</th>
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<td>5</td>
<td>12.5</td>
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<td>6</td>
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*One point each for congestive heart failure, hypertension, age >75 years and diabetes mellitus, and 2 points for stroke.
† Score range 0 to 6.

Thrombosis Risk with A Fib

High:
- CHADS score 5-6
- Recent (within last 3 months) stroke or TIA
- Rheumatic valvular heart disease

Moderate:
- CHADS 3-4

Low:
- CHADS 0-2
- No history of stroke or TIA
Thrombosis Risk with MHV

High:
- Any mitral MHV
- Older (caged-ball or tilting disk) aortic MHV
- Recent (within last 6 months) stroke or TIA

Moderate:
- Aortic bi-leaflet MHV with atrial fibrillation, prior stroke or TIA, hypertension, diabetes mellitus or age >75 years

Low:
- Aortic bi-leaflet MHV without atrial fibrillation and no additional risk factors

Thrombosis Risk with VTE

High:
- Recent (within last 3 months) VTE event
- Severe thrombophilia (protein C or S deficiency, antithrombin deficiency, anti-phospholipid antibodies, multiple defects)

Moderate:
- VTE event within last 3-12 months
- Non-severe thrombophilia (heterozygote factor V Leiden or prothrombin 20210 mutation)
- Recurrent VTE
- Active cancer treated in last 6 months or palliative

Low:
- Single VTE event >12 months ago and no additional risk factors
Low Risk Thrombosis

- No bridging required
- Discontinue warfarin (and ASA) 5 days prior to surgery
- Check INR day before surgery (usu <1.4)
- Restart warfarin at pre-op dose as soon as hemostasis adequate
Moderate or High Risk

- Bridging anticoagulation recommended pre and post op
- Unfractionated (UFH) or Low Molecular Weight Heparin (LMWH)

**Moderate Risk**
- CHADS 3-4
- VTE event within last 3-12 months
- Non-severe thrombophilia (heterozygote Factor V Leiden or prothrombin 20210 mutation)
- Recurrent VTE
- Active cancer treated in last 6 months or palliative
- Anti-Xa INR > 0.3 or clinical concern for bleeding
- Prior stroke or TIA
- Age: 75 years or older

**High Risk**
- CHADS 5-6
- Recent (within last 3 months) stroke or TIA
- Rheumatic valve or heart disease
- Recent (within last 6 months) VTE event
- Severe thrombophilia (protein C or S deficiency, antithrombin deficiency, anti-phospholipid antibodies, multiple defects)
- Any mitral valve
- Older (caged-ball or tilting disk) aortic valve
- Recent (within last 6 months) stroke or TIA

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**Diagram:**

- **ATE/VTE Risk**
- **High**
  - **Procedure:** Stop Warfarin
    - Start LMWH or UFH at therapeutic dose
  - Surgery or Procedure
    - **PostOp:** Restart Warfarin
  - **Bleeding Risk:**
    - **High**
      - Restart LMWH or UFH at therapeutic dose
    - **Low**
      - Continue LMWH or UFH at therapeutic dose

- **Intermediate**
  - **Procedure:** Stop Warfarin
    - Start LMWH or UFH at prophylactic dose
  - Surgery or Procedure
    - **PostOp:** Restart Warfarin
  - **Bleeding Risk:**
    - **High**
      - Restart LMWH or UFH at prophylactic dose
    - **Low**
      - Continue LMWH or UFH at prophylactic dose

**Therapeutic dose preferred**

8th edn ACCP guidelines
Moderate and High Risk

- Discontinue warfarin (and ASA) 5 days before procedure (t ½ = 22hrs)
- Heparin contraindicated if hx of HIT
- Start therapeutic dose of UFH or LMWH
  - 36 hrs after discontinuation of warfarin OR
  - When INR < lower limit of goal INR range
- Check INR day prior to surgery

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LMWH

- Therapeutic dose
  - Enoxaparin 1.5mg/kg sc od
  - Dalteparin 200u/kg sc od
  - Usually for 3 days preop
- Last dose given 24hrs before procedure and is reduced
  - Enoxaparin 1mg/kg sc
  - Dalteparin 100u/kg sc

UFH

- Use if contraindication to LMWH
  - Morbidly obese
  - Cr Cl<30ml/min
- Admit and start infusion 2 days prior to surgery
  - Nomogram +/- bolus
- Discontinue 4-6 hrs before procedure
Post procedure bridging therapy

**When adequate haemostasis:**
- Start UFH or LMWH 12hrs after procedure
- Start warfarin at pre-op dose (usu 48hrs to attain goal INR)
- Monitor INR/PTT
- Maintain LMWH/UFH overlap until INR in therapeutic range for two consecutive days

- **If active clinically significant bleeding** OR indefinite contraindication to anticoagulation
- AND HIGH risk of recurrent VTE
  → consider IVC filter

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**Unfractionated Heparin**

Binds and activates Antithrombin III (ATIII)

Inactivates thrombin (IIa), IXa, Xa, XIa, XIIa (intrinsic pathway)

Decreased clot formation

*Monitor PTT – mainly Factor IIa*
Unfractionated Heparin

**PROS**
- Short half life (60 mins) – can be stopped and PTT normalized within 4-6hrs
- Easily reversed by protamine sulphate
- Recommended in patients with Cr Cl <30ml/min, or >190kg (monitored, safer)

**CONS**
- Continuous IV infusion – needs admission $\$\$
- Needs monitoring of PTT
- Less predictable dose response
- Inconvenient – out of town
- 1% risk of heparin induced thrombocytopenia (HIT)
- Risk of HI osteopenia with long term use
Low Molecular Weight Heparin

- Also activates ATIII
- Mainly affects anti-Xa activity (vs anti-IIa)
  - Can monitor anti-Xa activity in obese or renal failure
- Smaller molecules – less binding to circulating/cellular proteins
  - More predictable dose response
  - Better bioavailability at lower doses
  - Longer plasma half-life

PROS

- More predictable dose response – weight only
- No lab monitoring required
- Longer half life → OD or BID
- Slightly lower risk of HIT
- Allows outpatient bridging

CONS

- Expensive $$ - out of pocket
- Renal clearance – not for Cr Cl < 30ml/min
- Morbidly obese >190kg – proper dosing not clear
Alternatives

- Fondaparinux (Arixtra)
  - New heparinoid
  - Binds ATIII but selective anti-Xa activity
  - Advantage - low risk of HIT
  - No antidote

- Direct Thrombin Inhibitors (pure anti-IIa activity)
  - For pts with history of HIT
  - Argatroban, lepirudin (injectable)
  - Newest Dagibatran (oral – Pradax)
  - No antidote

Risk of Haemorrhage

- Patient vs Procedure
- Patient
  - Age $\geq$ 65
  - Stroke
  - GI bleed
  - DM
  - Renal insufficiency
  - Recent MI
  - Severe anemia
  - Hx of surgical bleeding
  - Liver disease with synthetic dysfunction
  - Hematological disorder
Risk of Haemorrhage

- Procedure
  - Approach (MIS vs open)
  - Length of procedure – increased risk of bleeding >45mins
  - Amt of blood loss
  - Hemostatic agents used

Overall, studies of peri-procedure anticoagulation management show that rates of post-procedure hemorrhage are at least as high as peri-procedure thrombosis complications!!!
TRUS biopsy
- Trend towards not stopping anticoagulation
- 1022 pts undergoing TRUS biopsy given survey to fill at day 10
- 1000 respondents
  - 49 on warfarin, 220 on ASA, 731 on no anticoagulation
  - Clinically significant outcomes
    - 18 (36.7%) on warfarin vs 440 (60.2%) not anticoagulated had hematuria
    - 4 (8.2%) on warfarin vs 153 (21%) had hematospermia
    - 7 (14.3%) on warfarin vs 95 (13%) had rectal bleeding (not significant)
    - NO association between severity of bleeding and anticoagulation

TURP
- Evidence equivocal
- Chakravarti et al Br J Urol 1998
  - 11 patients on long term warfarin underwent 12 TURPs, UFH bridging
  - 220 patients no anticoagulation undergoing TURPs
  - Average gland size 23cc - Mean tissue resected ??
  - Transfusion rate 11% non-anticoagulated vs 9.1% warfarin

- Dotan et al J Urol 2002
  - 20 pts on warfarin, LMWH bridging, 20 pts non-anticoagulated undergoing TURP
  - Mean tissue resected 26gm
  - No difference in transfusion requirement, but ~ 20%!!
  - Pts on LMWH bridging had longer hospital stay due to delays in removal or reinsertion of catheters for bleeding
Laser prostatectomy

- KTP
  - May not need to interrupt warfarin therapy
  - Several small studies
  - Ruszat et al Eur Urol 2007
    - 36 pts on warfarin vs 92 non-anticoagulated pts
    - Gland size 60cc
    - No significant difference in Hb decrease, no transfusions

Holmium Laser Enucleation of the Prostate in Patients on Anticoagulant Therapy or With Bleeding Disorders
Ehab Elzayat, Enmar Habib and Mostafa Elhilali*
From the Division of Urology, McGill University School of Medicine, Montreal, Quebec, Canada

- HOLEP
  - Can be done without stopping anticoagulation – with risk
  - 81 pts on oral anticoagulation undergoing HOLEP
    - 14 did not stop anticoagulation
    - 34 bridged with LMWH
    - 33 withheld anticoagulation temporarily without bridging
  - Average tissue resected 55gm
  - Mean enucleation time 86.5mins, morcellation 20.1 mins
  - 8 (9.6%) pts needed transfusion within 2-5 days post op (avg 3.7u)
    - 2 (14.2%) pts who were fully anticoagulated
      - 1 had mucosal bladder injury
    - 5 (14.7%) who were bridged
    - 1 (3%) without bridging
  - No major thromboembolic complications
Safety and Efficacy of Flexible Ureterorenoscopy and Holmium:YAG Lithotripsy for Intrarenal Stones in Anticoagulated Cases

Burak Turna, Robert J. Stein, Marc C. Smaldone, Bruno R. Santos, John C. Kefer, Stephen V. Jackman, Timothy D. Averch and Mihir M. Desai

From the Glickman Urological Institute, Cleveland Clinic Foundation, Cleveland, Ohio and Department of Urology, University of Pittsburgh Medical Center (MCN, SVJ, TDA), Pittsburgh, Pennsylvania

- Can be done without stopping of anticoagulation
- J Urol April 2008
- 37 anticoagulated patients vs 37 controls
  - Matched for stone size, location, number, bilaterality and concomitant ureteral stones
  - 14 on coumadin
  - 5 on clopidogrel
  - 18 on ASA

- No difference in thromboembolic or hemorrhagic events
- No transfusions necessary
- Stone free rates same

Safety and Efficacy of Percutaneous Nephrolithotomy in Patients on Anticoagulant Therapy

John C. Kefer, Burak Turna, Robert J. Stein and Mihir M. Desai

- 27 patients undergoing PCNL on chronic anticoagulation
- 16 (59%) warfarin – bridging therapy with LMWH
- 1 (4%) enoxaparin
- 9 (33%) clopidogrel
- 1 (4%) cilostazol (PDE III inhibitor)
- Outcomes
  - 2 (7%) had significant bleeding
    - 1 on clopidogrel – angioembolization for lower pole vessel, 5 u
    - 1 on warfarin at home (wrong dose) – clot evacuation, no transfusion
  - 1 (4%) had DVT/PE on POD4 – needed UFH, then IVC filter
  - All stone free at 1 month
Emergent Surgery

- Stop warfarin
- Give
  - Vitamin K (po or IV) – reversal within 24hrs
  - fresh frozen plasma – more immediate reversal, effect weans in 6hrs
- Check INR pre-procedure
- Protamine sulphate to reverse heparin
- No antidotes for LMWH

Antiplatelet therapy management
Antiplatelet agents

- Thromboxane A₂ inhibitors
  - Acetylsalicylic acid (ASA)
  - Ibuprofen
- ADP-receptor antagonists (thienopyridines)
  - Clopidogrel (Plavix)
  - Ticlopidine (Ticlid)
- Phosphodiesterase Inhibitor
  - Dipyrimadole (Persantine)
  - ASA-dipyrimadole (Aggrenox)
- Glycoprotein IIb/IIIa blockers
  - Abciximab (ReoPro)
  - Tirofiban (Aggrastat)
  - Eptifibatide (Integrilin)

ASA and Thienopyridines

- Both inhibit platelet aggregation **irreversibly**

- ASA – inhibits COX-1 enzyme
  - Prevents formation of prostaglandins and TXA₂
- Plavix/Ticlid – binds to P2Y 12 platelet receptor
  - Prevents binding of ADP and subsequent platelet activation and aggregation

- Effects last 7-10 days after discontinuation
Indications

Treatment and prevention of cardiovascular diseases

- Stroke
- MI
- Peripheral arterial disease
- Stratification of risk difficult
Risk of thrombosis

- **Low risk**
  - Primary prevention of CAD (e.g., DM, HTN)

- **Intermediate risk**
  - Secondary prevention of CAD (e.g., previous MI or ischemic stroke)
    - ASA decreases risk of stroke 25%, risk of CV event 21% long term
    - Dual antiplatelet therapy further decreases risk of MI or CVA by 20% vs ASA

- **High risk**
  - Recent MI or stroke
    - ASA decreases risk of death post MI immediately
  - Coronary stents
    - Drug-eluting lumen (sirolimus or paclitaxel) > bare metal lumen

Management for Elective Procedures

- **Low risk**
  - Temporary interruption is safe
  - Stop drug 7 days prior to procedure
  - Restart when adequate hemostasis

- **Intermediate risk**
  - Consult with GP, internist or cardiologist to assess risks of discontinuation
  - As above
High risk

- Consult internist, cardiologist
- Recent MI or stroke
- Cardiac stent thrombosis
  - Risk highest until endothelialization of lumen occurs
    - 0.5-1% incidence of thrombosis – most within 1st month (BM ~ DES)
    - 0.7% risk of thrombosis at 1 year follow-up for DES
    - Increased frequency of late thrombosis (>30 days) with DES
      - DES takes longer time to endothelialize than BM
  - Combination ASA and thienopyridine essential

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**Incidence, Predictors, and Outcome of Thrombosis After Successful Implantation of Drug-Eluting Stents**

Joanne Iakoucou, MD; Thomas Schmidt, MD; Emilia Bonizzoni, PhD; Lai Ge, MD; Giuseppe M. Sangiorgi, MD; Goran Stankovic, MD; Elke Airoldi, MD; Alvise Cheffo, MD; Matteo Marrofre, MD; Mauro Carlini, MD; Iassen Michev, MD; Nicole Corazza, MD; Carla Brigooni, MD; Ulrich Geckens, MD; Elberth Glabe, MD; Antonio Columbo, MD

(JAMA. 2005;293:2126-2130)

- Prospective observational cohort study
  - 2229 patients with either sirolimus or paclitaxel –eluting stents
  - Pre-treated with ASA and either clopidogrel or ticlopidine
  - Continued combination treatment for at least 3 months (sirolimus) or at least 6 months (paclitaxel)
  - Outcomes measured at 9 months – subacute thrombosis (<30 days), late thrombosis (>30 days), cumulative thrombosis

- Results
  - 1.3% (29 pts) cumulative stent thrombosis
    - 0.6% (14 pts) – subacute thrombosis
    - 0.7% (15 pts) – late thrombosis
  - Post thrombosis mortality rate – 45% (13 pts died)
  - Most important risk factor of thrombosis
    – premature discontinuation of antiplatelet therapy
2007 ACC/AHA Guidelines

Recommendations post stent

- Elective Non-Cardiac Procedures
  Defer until following periods of antiplatelet therapy completed (increased risk of life-threatening thrombosis):
  - Bare metal stents – 4-6 weeks
  - Drug-eluting stents – 12 months
    - Consider continuing ASA throughout peri-operative period

- Urgent or Emergent Non-Cardiac Procedures
  - Can stop thienopyridine
  - Continue ASA throughout peri-operative period
  - Restart thienopyridine as soon as possible

- No evidence for bridging with warfarin, glycoprotein IIb/IIIa, antithrombotics after discontinuation of oral antiplatelet drugs
Risk of Haemorrhage

TRUS biopsy – minimal risk on ASA
- Maan et al BJU Int 2003 – retrospective study
  - 36 pts on low dose ASA – not withheld
  - 141 pts on no antiplatelet therapy
  - Sextant biopsy
  - Outcomes
    - No increase in self-reported bleeding complications (hematuria, rectal bleeding or hematospermia)
    - No major bleeding complications
- Giannarini et al Urology 2007 – RCT
  - 200 consecutive men taking low dose ASA, prostate biopsy – 3 arms
  - No discontinuation of ASA
  - Discontinuation of ASA and bridging with LMWH
  - Discontinuation of ASA without bridging
  - No difference in frequency of bleeding complications
  - Median duration of hematuria and rectal bleeding higher in groups 1 & 2 by ~2-3 days

Early Initiation of Aspirin After Prostate and Transurethral Bladder Surgeries is Not Associated With Increased Incidence of Postoperative Bleeding: A Prospective, Randomized Trial

Y. Ehrlich,* O. Yossepowitch, D. Margel, D. Lask, P. M. Livne and J. Daniël
From the Department of Urology, Rabin Medical Center, Petach Tikva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

- JU 2007, Randomized trial ASA
- 120 pts on ASA referred for TURBT, TURP or open retropubic prostatectomy (OP)
- ASA withheld 5 days before surgery
- Randomized to early ASA initiation (within 24hrs of discontinuation of CBI) or late (3 weeks post op)
- Outcomes
  - Predischarge hematuria requiring CBI reinitiation
  - Late hematuria requiring admission
  - NO significant differences between the two groups or amongst the surgical procedures
  - In early initiation group - 2 had MI 2 months post op, 1 had CVA 3 weeks post op
- Early ASA initiation does not increase bleeding risk for TURBT, TURP, OP - consider in high risk CVD pts
Thienopyridine therapy

- Few small studies
- Ruszat et al Eur Urol 2007 KTP laser
  - 116 patients on oral anticoagulation, including 9 on clopidogrel vs 92 patients with no anticoagulation
  - 80W KTP laser for photoselective vaporisation
  - Average size gland 60cc, average duration of resection 65mins
  - No transfusions required, post op Hb drop same
  - No difference in bleeding between both groups, including on clopidogrel

Safety and Effectiveness of Photoselective Vaporization of the Prostate (PVP) in Patients on Ongoing Oral Anticoagulation

Robin Ruszat\(^{a, b}\), Stephen Wyles\(^{a}\), Thomas Forster\(^{a}\), Oliver Reich\(^{a}\), Christian G. Stief\(^{a}\), Thomas C. Gasser\(^{a}\), Tullio Sulser\(^{a}\), Alexander Bachmann\(^{a, b}\)

\(^{a}\) Department of Urology, University Hospital Basel, Basel, Switzerland
\(^{b}\) Department of Urology, Ludwig Maximilian University of Munich, Munich, Germany

JU 2008, retrospective review

- 37 patients anticoagulated, 5 on clopidogrel compared to 37 patients matched, not anticoagulated
- Ho:YAG lithotripsy during flexible URS
- No procedure had to be terminated for poor visibility
- No difference in stone free rate, intraop or post op complications, bleeding or thromboembolic complications
## Warfarin
### Drugs that alter effect

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<tr>
<th>Increase anticoagulation</th>
<th>Decrease anticoagulation</th>
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<tr>
<td>• ASA</td>
<td>• Drugs that induce CYP450</td>
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<tr>
<td>• Disulfiram (antabuse)</td>
<td>• Rifampin</td>
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<td>• Cimetidine</td>
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<td>• High dose vit C, K</td>
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<td>• Septra</td>
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## Heparin
### Drugs that alter action

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Antiplatelet therapy
Drug Interactions

- ASA
  - Increased risk of GI ulcer – EtOH, steroids, NSAIDs
  - Decreases diuretic effect of spironolactone
  - Increases plasma level of methotrexate

- Ticlopidine
  - Impaired absorption with antacids

Conclusion

- Anticoagulant and antiplatelet medications are common and use is increasing
- More patients undergoing urological procedures are likely to be on these medications
- Urologists should be able to assess patients according to risk of thrombosis and risk of hemorrhage on these medications to make treatment decisions about perioperative anticoagulation