Perioperative Implications of New Anticoagulants and Platelet Inhibitors
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Objectives

• Review cell-based model of coagulation
• Review limitations of current agents
• Discuss three new drugs
  - Dabigatran (Pradaxa)
  - Rivaroxaban (Xarelto)
  - Prasugrel (Effient)
• Consider indications, mechanism, metabolism
• Consider perioperative management and reversal
• Discuss regional/neuraxial management (Dr. Schroeder)

Cell-based model of coagulation

![Cell-based model of coagulation diagram]

Ac#va#on
Amplifica#on
Propaga#on

Gayle JA, et al. An8coagulants: Newer		
ones, mechanisms, and periopera8ve	
updates. Anesthesiology Clin
Potential indications for anticoagulants and platelet inhibitors

- Perioperative VTE prophylaxis
- VTE treatment
- Stroke prevention in atrial fibrillation
- Prosthetic heart valve prophylaxis
- Ventricular assist device prophylaxis
- Acute coronary syndrome
- Thrombosis prevention in coronary stents

Why not just use heparin?

- Intravenous
- PTT monitoring
- Risk of HIT/Immunogenic
- Requires AT3 cofactor
- Free thrombin only

What is wrong with warfarin?

- Slow onset
- Variable dose response
- INR monitoring
- Narrow therapeutic index
- Drug/dietary interactions
What is wrong with clopidogrel?

PLT activation is central to ACS and silent thrombosis (ST)
Slow onset after oral loading dose
Highly variable activation of prodrug
High rate of clopidogrel “resistance”
Resistance is associated with increased risk of ACS and ST

Example case #1
A 64 yo female with acute ICH following a fall requires decompressive craniotomy. She has atrial fibrillation and takes dabigatran for stroke prevention. Timing of her last dose is unknown, but it is prescribed BID.

- Are there any coagulation assays that may be helpful?
- If her last dose was 6 hours ago, how long will she remain anticoagulated/coagulopathic?
- Is there anything I can do to reverse her anticoagulation?

Example case #2
A 55 yo male with atrial fibrillation is seen in the anesthesia clinic two weeks prior to elective TKA. He takes rivaroxaban for stroke prevention. He has normal renal function.

- When should he stop taking rivaroxaban preoperatively to minimize surgical bleeding?
- Should you order any preop coagulation assays?
- How long after his last dose of rivaroxaban would you consider performing a spinal anesthetic? Femoral nerve block?
Example case #3

A 55 yo male presents for trans-metatarsal amputation of his right foot for gangrene. He is obese, diabetic, and has a remote history of cervical spine fusion for traumatic injury. He had two drug-eluting stents placed in his LAD six months ago. He took aspirin and prasugrel yesterday morning.

- Would it be reasonable to perform spinal or epidural anesthesia?
- If not, how long would I need to delay the procedure to do so?
- What about popliteal sciatic (+/- saphenous) nerve block?

New Anticoagulants: Dabigatran, Rivaroxaban

Direct factor inhibitors
- Dabigatran – IIa/thrombin
- Rivaroxaban – Xa

Oral administration
- No routine monitoring
- Rapid onset
- Predictable pharmacologic profile
- Minimal drug and dietary interactions
Dabigatran

Dabigatran – Mechanism
Direct thrombin inhibitor
Prodrug, activated in liver
Inhibits free and clot-bound thrombin
Reversible binding

Dabigatran - Advantages
Oral administration
Rapid onset – peak effect 2 hours – no bridging
No need for routine monitoring
No significant dietary interactions
Limited drug interactions
Dose reduction with amiodarone
No risk of HIT
Dabigatran - Elimination

Predictable pharmacokinetics
80% renal elimination
Half life 12-17 hrs
Elimination prolonged with renal dysfunction
Dose reduced with moderate dysfunction (CrCl < 30-50)
Not advised with severe dysfunction (CrCl < 15-30)
BID dosing

Dabigatran - Monitoring

No routine monitoring required
Therapeutic ranges for coagulation tests are unknown
May be useful in case of overdose or acute hemorrhage

<table>
<thead>
<tr>
<th>Coagulation assay</th>
<th>Therapeutic ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin time (TT)</td>
<td>Sensitive and accurate</td>
</tr>
<tr>
<td>Ecarin clotting time (ECT)</td>
<td>Accurate but not available</td>
</tr>
<tr>
<td>ACT</td>
<td>Not dose dependent, qualitative only</td>
</tr>
<tr>
<td>aPTT</td>
<td>Not dose dependent, qualitative only</td>
</tr>
<tr>
<td>INR</td>
<td>Not sensitive, not recommended</td>
</tr>
</tbody>
</table>

Dabigatran Discontinuation before elective surgery

<table>
<thead>
<tr>
<th>Renal function (CLr m/minute)</th>
<th>Half-life (hours)</th>
<th>Timing of discontinuation after last dose of dabigatran before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 80</td>
<td>13 (1-2)</td>
<td>24 hours (standard risk of bleeding)</td>
</tr>
<tr>
<td>&gt; 50 to &lt; 80</td>
<td>15 (12-24)</td>
<td>24 hours (standard risk of bleeding)</td>
</tr>
<tr>
<td>&gt; 30 to &lt; 50</td>
<td>18 (15-23)</td>
<td>4 days (standard risk of bleeding)</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>27 (22-31)</td>
<td>4-5 days (standard risk of bleeding)</td>
</tr>
</tbody>
</table>

Suggest checking thrombin time to confirm normal coagulation
(May not be practical on DOS)
Dabigatran - Indications

Stroke prevention in atrial fibrillation (RE-LY trial)

Approved in EU/Canada but not US for perioperative VTE prophylaxis (RE-MOBILIZE trial)

Noninferior to coumadin for VTE treatment, but not approved for this indication (Re-COVER trial)

Not approved for mechanical valve prophylaxis. Currently in phase 2 trial.


Approved in EU/Canada but not US for perioperative VTE prophylaxis (RE-MOBILIZE trial)

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Not approved for mechanical valve prophylaxis. Currently in phase 2 trial.

Dabigatran – Stroke prevention

- RE-LY trial - 18,000 patients with AF, 2 year follow-up
- Randomized to dabigatran (150 mg or 110 mg BID) vs warfarin
- Primary outcome: Stroke or systemic embolism, noninferiority

- Coumadin: 1.69% per year (therapeutic INR achieved 64% of time)
- Dabigatran 110 mg: 1.53% per year (RR 0.91, p<0.001 noninferiority)
- Dabigatran 150 mg: 1.11% per year (RR 0.66, p<0.001 superiority)


Dabigatran – Risk of major bleeding

- Warfarin: 3.36% per year
- Dabigatran 110 mg: 2.71% per year (RR 0.8, p<0.003)
- Dabigatran 150 mg: 3.11% per year (RR 0.93, p<0.31)

Controversial – FDA only approved 150 mg BID dose

Dabigatran
Bleeding risk in the real world?

• Many reports of serious or fatal bleeding since FDA approval
  • Manufacturer reports rate of bleeding is not higher than in study
    (per 100,000 patient-treatment-years)
  • Concern has led to:
    • Safety advisories in Japan and Australia
    • Labeling updates in US and EU
    • May be related to inadequate monitoring of renal function
  • Genetic polymorphism present in 33% of Europeans affects
    rate of prodrug activation, increases bleeding risk
    • Pharmacokinetics/dynamics not as predictable as first thought?

Dabigatran – Reversal options
How to manage the patient with acute hemorrhage or emergent surgery?

No reversal agent!
Supportive care and time
Transfusion to correct anemia, dilutional coagulopathy, and
thrombocytopenia, but will not reduce drug effect
May consider oral charcoal if last dose < 2 hours
May consider hemodialysis to accelerate drug clearance
May consider FVIIa or prothrombin complex concentrate

No clinical data

Van Ryn, et al. Dabigatran etexilate – a novel, reversible, oral direct
thrombin inhibitor: Interpretation of coagulation assays and reversal of
Rivaroxaban

Rivaroxaban - Mechanism

Selective, direct Xa inhibitor
Inhibits free, clot-bound, and phospholipid-bound Xa
Reversible binding
Rivaroxaban - Advantages

Oral administration
Rapid onset – peak effect 1-4 hours
No need for routine monitoring
No significant dietary interactions
No risk of HIT
Few drug interactions
P450 and P-gp metabolism
Contraindicated with anti-HIV protease inhibitors and azole antifungals


Rivaroxaban - Elimination

Half life approximately 9 hours
Hepatic metabolism, 70% renal 30% fecal elimination

• Dose reduction in moderate renal impairment (CrCl < 50)
• Avoid use in severe renal impairment (CrCl < 30)
• Avoid use in hepatic disease with associated coagulopathy
Once daily dosing


Rivaroxaban - Monitoring

No monitoring required
Therapeutic ranges not established

<table>
<thead>
<tr>
<th>Coagulation assay</th>
<th>Probably most useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT</td>
<td>Prolonged, linear dose response</td>
</tr>
<tr>
<td>ACT</td>
<td>No data</td>
</tr>
<tr>
<td>Thrombin time</td>
<td>Not affected by rivaroxaban</td>
</tr>
<tr>
<td>INR</td>
<td>Not recommended with standard reagents</td>
</tr>
</tbody>
</table>

**Rivaroxaban - Indications**

**Stroke prevention in atrial fibrillation (ROCKET-AF trial)**
- 14000 pts, randomized, blinded
- Noninferior to warfarin for risk of stroke (1.7% vs 2.2%, p<0.001)
- Equivalent overall bleeding risk, but less ICH and fatal bleeding

**Perioperative VTE prophylaxis (RECORD-4 trial)**
- 3000 pts undergoing TKA, randomized, blinded
- Primary outcome DVT, PE, or death
- Superior to enoxaparin 30 mg BID (6.9% vs 10.1%, p=0.12)


**Rivaroxaban Discontinuation before elective surgery**

No formal recommendations
Similar half-life (9 hours) to dabigatran
Both are reversible inhibitors
Reasonable to adopt similar practice
- 24 hrs before low risk surgery
- 2-4 days before high risk (neuro/spine/cardiac) surgery
- Longer period in patients with renal dysfunction

**Rivaroxaban – Reversal options**

No reversal agent!
Supportive care, PRBC/plasma/PLT transfusion, and time

May consider FVIIa or PCC
- In-vitro and animal studies show partial reversal of coagulation assays
- Only animal study to assess clinical bleeding during rivaroxaban overdose showed no change
- No human clinical data

No benefit to oral charcoal or hemodialysis

Apixaban

- Oral direct Xa inhibitor
- Mechanism and characteristics similar to rivaroxaban
  - May be superior for patients with renal dysfunction
- Superior to coumadin for stroke prevention in AF with less bleeding (ARISTOTLE trial)
  - Awaiting FDA approval
  - Delayed in June 2012 for further review
- Approved in EU for perioperative VTE prophylaxis

Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) Versus Warfarin in Patients With Atrial Fibrillation

- Decreased risk of stroke (RR 0.78)
  - Ischemic stroke (RR 0.87)
  - Hemorrhagic stroke (RR 0.45)
- Decreased all cause mortality (RR 0.88)
- Decreased risk of intracranial bleeding (RR 0.49)

What does this mean for us?

- We will see many more patients on these agents in the near future
- We need to understand their duration of action, implications for regional anesthesia and surgical bleeding, and limited options for acute reversal

New platelet inhibitor: Prasugrel

Thienopyridine class
Inhibitor of P2Y₁₂ (ADP) receptor

Importance of platelets

- Platelet plug formation and clotting cascade occur simultaneously
- Platelets provide the phospholipid surface for clotting factor complexes
- Platelets are central to thrombus formation in ACS and stent thrombosis (ST)

Platelet function and inhibition

1. Platelets are activated by ADP at P2Y₁₂ receptor (also by TF, thrombin, epinephrine)
2. Activated platelets express Gp IIb/IIIa receptor
3. Platelets crosslink with fibrin via Gp IIb/IIIa and vWF

Platelet inhibition is central to the management of ACS and prevention of stent thrombosis (ST)
What's wrong with clopidogrel?

Delayed onset after oral loading dose
- Risk of acute ST

Prodrug requires two step p450 activation
- Considerable variability in amount of active drug produced
- Drug-drug interactions with PPIs and statins (7)

Clopidogrel resistance occurs in up to 30% of patients
- Preserved platelet function due to decreased active drug formation
- Patients are not monitored for clopidogrel resistance
- Clopidogrel resistance increases risk of ST and MI (RR 2.4)

Prasugrel - Advantages

Prasugrel Pharmacokinetics:
- Single step p450 activation of prodrug
- Greater concentration of active drug
- Reduction in ischemic events

Prasugrel Pharmacodynamics:
- Greater antiplatelet effects, higher levels of inhibition, lower levels of bleeding

Prasugrel Clinical Efficacy:
- Efficacy in various clinical scenarios, reduction in ischemic events, lower rates of bleeding

Prasugrel: Higher and more consistent level of platelet inhibition

Prasugrel: Fewer hypo-responders

![Graph showing platelet inhibition comparison between prasugrel and clopidogrel](image)

- **Graph Title**: Comparison of prasugrel and clopidogrel loading doses on platelet function. Maximum magnitude of platelet inhibition is shown in prasugrel vs. clopidogrel.

Prasugrel - Indications

**Patients with ACS undergoing planned PCI**

(Triton-TIMI 38 trial)

- 13,000 patients, randomized to prasugrel or clopidogrel
- Lower risk of CV death, MI, stroke (9.9% vs 12.1%, p<0.001)
- Lower rate of stent thrombosis over 15 mos (1.1 vs 2.4%, p<0.001)
- Increased rate of fatal and non-fatal bleeding

Contraindicated in patients with prior TIA or stroke

Prasugrel – Clinical considerations

- Elimination half life of active drug is 7 hours
- Platelet inhibition is irreversible, so effect will persist until platelets are regenerated (7-10 days)
- Platelet transfusion should be effective if last dose of prasugrel was > 24 hours
- Expect more bleeding with prasugrel than clopidogrel
- Continue at least aspirin, if not dual anti-platelet therapy, peripherally to reduce risk of stent thrombosis
Recommendations for new anticoagulants and regional anesthesia – the UW perspective

UW regional anesthesia section consensus recommendations

- Presented regional staff (4/5) with drug info and manufacturer, ASRA, and ESA rec’s for dabigatran, rivaroxaban, and prasugrel
- Dabigatran
  - 4/4 rec waiting 5 days prior to neuraxial intervention
- Rivaroxaban
  - 4/4 rec waiting 2 days prior to neuraxial intervention
- Prasugrel
  - 1/4 rec waiting 10 days prior to neuraxial intervention
  - 1/4 rec waiting 12 days prior to neuraxial intervention
  - 2/4 rec waiting 14 days prior to neuraxial intervention

Recommendations for regional anesthesia

- Dabigatran
  - Reversibly inhibits free and clot bound thrombin
  - Half life 8 hours after single dose, 17 hours after repeated doses
- Various Recomendations
  - ASRA – “cautious approach”
  - ESA – contraindicated prior to neuraxial manipulation. May start six hours after neuraxial manipulation.
  - Horlocker 2011 BJA – 7 day pause in therapy prior to neuraxial block
  - Manufacturer – advises against use of regional anesthesia in presence of dabigatran
  - (Penn 2 days for normal renal function, 5 days for impaired)
**Recommendations for regional anesthesia**

- **Rivaroxaban**
  - Selective and reversible activated factor Xa inhibitor
  - May be monitored by PT and aPTT
  - Half life 9 hours, prolonged to 13 hours in elderly and those with renal dysfunction
  - ASRA – “cautious approach”
  - ESA – 22-26 pause in therapy prior to neuraxial manipulation, may start drug therapy 4-6 hours following manipulation.
  - Horlocker 2011 BJA – 22-26 hours should elapse prior to neuraxial block. Longer intervals required in those with impaired renal function. Indwelling neuraxial catheters contraindicated due to the “boxed warning.”

- **Prasugrel**
  - Irreversible inhibition of platelet function
  - ASRA = Other thienopyridine therapies (14 days for ticlopidine, 7-10 days for clopidogrel)
  - ESA – Rec 7-10 day pause in drug therapy prior to neuraxial manipulation. May start 6 hours after neuraxial manipulation.
  - Horlocker 2011 BJA – 7-10 day pause in therapy prior to neuraxial technique

**Regional anesthesia**

- Must be sure of every medication on patient med list
- ASRA guidelines are currently outdated and incomplete for newer anticoagulants (last published in 2010).
- ASRA guidelines do not adequately address peripheral techniques.
  - 11.0 Anaesthetic Management of the Patient Undergoing Plexus or Peripheral Block
    - 11.1 For patients undergoing deep plexus or peripheral block, we recommend that recommendations regarding neuraxial techniques be similarly applied (Grade 1C).
- Little motivation for drug companies to compile safety data in setting of regional anesthesia
- Patients are complicated and difficult choices often need to be made
Summary

Dabigatran and rivaroxaban
- Oral direct IIa and Xa inhibitors
- Predictable pharmacokinetics (?), no monitoring or dose adjustment
- Prolonged in renal failure
- No reversal agents
- Stop 24hrs–4 days before surgery depending on type

Prasugrel
- Thienopyridine P2Y12 (ADP) antagonist
- More effective and more consistent platelet inhibition than clopidogrel
- Similar time to termination of effect (7-10 days)
- Lower rate of MI and stent thrombosis, but more bleeding

Look for these drugs on your patients’ medication lists!

Summary

<table>
<thead>
<tr>
<th></th>
<th>Low risk surgery</th>
<th>High risk surgery</th>
<th>Neuraxial anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran*</td>
<td>≥ 24 hrs</td>
<td>2-4 days</td>
<td>5 days</td>
</tr>
<tr>
<td>Rivaroxaban*</td>
<td>≥ 24 hrs</td>
<td>2-4 days</td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td></td>
<td>R/B of surgical bleeding vs ST</td>
<td>10-14 days</td>
</tr>
</tbody>
</table>

* Longer interval required with renal dysfunction
Suggestions only, there are no formal practice guidelines.

Mount Washington, NH
Example case #1
A 64 yo female with acute ICH following a fall requires emergent decompressive craniotomy. She has atrial fibrillation and takes dabigatran for stroke prevention. Timing of her last dose is unknown, but it is prescribed BID.

- Are there any coagulation assays that may be helpful?
  - No tests should delay surgical treatment of her ICH.
  - Serial thrombin time assays may be useful to assess magnitude and observe resolution of anticoagulation effect.

- If her last dose was 6 hours ago, how long will she remain anticoagulated/coagulopathic?
  - If renal function is normal, coagulation will return to normal in 24-48 hours from last dose.

- Is there anything I can do to reverse her anticoagulation?
  - There is no antidote. Surgical decompression/control and supportive transfusion are required until bleeding stops. Transfusion will not reverse coagulopathy. Hemodialysis may speed drug clearance, but is impractical at this point. Factor concentrates may be considered.

Example case #2
A 55 yo male with atrial fibrillation is seen in the anesthesia clinic two weeks prior to elective TKA. He takes rivaroxaban for stroke prevention. He has normal renal function.

- When should he stop taking rivaroxaban preoperatively to minimize surgical bleeding?
  - He should stop taking it at least 24-48 hours before surgery.
  - With normal renal function, drug levels will fall to 25% of therapeutic concentration in 24 hrs.

- Should you order any preop coagulation assays?
  - No tests are necessary, but anti-Xa assay would confirm normal coagulation.

Example case #3
A 55 yo male presents for trans-metatarsal amputation of his right foot for gangrene. He is obese, diabetic, and has a remote history of cervical spine fusion for traumatic injury. He had two drug-eluting stents placed in his LAD six months ago. He took aspirin and prasugrel yesterday morning.

- Would it be reasonable to perform spinal or epidural anesthesia?
  - No, neuraxial techniques are contraindicated due to risk of spinal/epidural hematoma.

- If not, how long would I need to delay the procedure to do so?
  - 7-10 days following last dose of prasugrel.

- What about popliteal sciatic (+/ saphenous) nerve block for primary surgical anesthesia?
  - This is a reasonable alternative to GA for this patient because of his risk of airway difficulty and myocardial ischemia.
  - However, ASRA guidelines recommend similar caution with neuraxial and peripheral techniques.
Suggested references


Horlocker TT. Regional anaesthesia in the patient receiving antithrombotic and antiplatelet therapy. British J Anaes 2011;107 (S1):96-108.