Endoscopy in the Era of Anti-Platelet and Anti-Coagulation

Larissa Fujii-Lau, MD
Assistant Professor of Medicine
University of Hawaii

Clinical Updates in Gastroenterology, Hepatology, and Nutrition
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Objectives

• Discuss 3 key questions to ask when managing antithrombotic agents in patients undergoing endoscopic procedures

• Review the newer antithrombotic agents

• Overview of antidotes & reversal agents

• Summarize recommendations on when to restart antithrombotics
Case 1

- 78M w/ nonvalvular atrial fibrillation (CHA$_2$DS$_2$-VASc score of 4) on dabigatran (Pradaxa) presents to the ICU with hypotension secondary to cholangitis. As the GI consult team, what would you recommend for management?
  - No ERCP, just medical management
  - ERCP w/ sphincterotomy
  - ERCP w/o sphincterotomy
  - ERCP w/ sphincterotomy if PT is normal
Case 2

- 62M w/ CAD on dual therapy w/ ASA + Prasugrel (Effient) for DES placed 13 months ago is found to have a pancreatic mass for which EUS FNA is anticipated. What would you recommend for his antiplatelet medications?
  - Continue both ASA & Prasugrel
  - Stop both ASA & Prasugrel
  - Continue ASA, stop Prasugrel 5 days prior to EUS
  - Continue ASA, stop Prasugrel 7 days prior to EUS
General Principles

• Individualized
• If in doubt, contact cardiologist or PCP
• Weigh risk of thromboembolism and bleeding
  ▫ Thromboembolic events are life-threatening, while GI bleeding can typically be treated
• Management differs for emergent & elective procedures
Key Questions to Ask in Every Patient
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1) Is this a high or low risk procedure (for bleeding)?

2) Is this a high or low risk patient (for thromboembolism)?

3) Is bridging therapy required?
3 Key Questions to Ask in Every Patient

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# High vs Low Risk Procedures

<table>
<thead>
<tr>
<th>High Risk (&gt;1.5% risk of bleed)</th>
<th>Low Risk (≤1.5% risk of bleed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ERCP w/ sphincterotomy</td>
<td>• ERCP w/o sphincterotomy</td>
</tr>
<tr>
<td>• EUS w/ FNA</td>
<td>• EUS w/o FNA</td>
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<tr>
<td>• Therapeutic BAE</td>
<td>• Push enteroscopy or diagnostic BAE</td>
</tr>
<tr>
<td>• Variceal treatment</td>
<td>• Diagnostic EGD, FS, colonoscopy ± mucosal biopsy</td>
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<tr>
<td>• EMR/ESD</td>
<td>• Capsule endoscopy</td>
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<tr>
<td>• Polypectomy</td>
<td>• Enteral stent deployment w/o dilation (controversial)</td>
</tr>
<tr>
<td>• Tumor ablation</td>
<td>• APC</td>
</tr>
<tr>
<td>• Cyst gastrostomy</td>
<td>• Barrett’s ablation</td>
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<tr>
<td>• PEG/J placement</td>
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<tr>
<td>• Endoscopic hemostasis</td>
<td></td>
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<tr>
<td>• Ampullary resection</td>
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<tr>
<td>• Pneumatic/bougie dilation</td>
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</table>

ASGE Guidelines 2016
Controversies

- Studies of bleeding risk exclude patients on complex antithrombotics
- Controversial procedures
  - Nonachalasia balloon dilation
  - Enteral stenting (0.5-5.3% risk)
3 Key Questions to Ask in Every Patient

1) Is this a high or low risk procedure (for bleeding)?

2) Is this a high or low risk patient (for thromboembolism)?

3) Is bridging therapy required?
High Risk Patients

- Valvular atrial fibrillation
- Nonvalvular atrial fibrillation
  - CHADS$_2$ or CHA$_2$DS$_2$-VASC score $\geq 2$
- Mechanical heart valves

- Venous thromboembolism

- Coronary artery disease
High Risk Patients

- Valvular atrial fibrillation
- Nonvalvular atrial fibrillation
  - CHADS2 or CHA2DS2-VASC score ≥ 2
- Mechanical heart valves
  - Type of prosthesis: caged-ball valve, tilting disc
  - Site: mitral valve
  - Number: ≥2
  - Other: h/o CVA/TIA, cardiac thrombi
- Venous thromboembolism
  - <3 months
  - Underlying thrombophilia or active cancer
  - Unprovoked
- Coronary artery disease
  - Acute coronary syndrome
  - Nonstented PCI after MI
  - Stents: BMS < 4 weeks or DES < 12 months

CHA2DS2-VASC:
- CHF: 1 point
- Htn: 1 point
- Age ≥75: 2 points
- DM: 1 point
- Stroke: 2 points
- Vascular dz: 1 point
- Age 65-74: 1 point
- Female: 1 point

ASGE guidelines 2016, AHA Guidelines 2009
Cardiac Stent Occlusion

- Risk factors for stent occlusion >12 mths out
  - Prior stent occlusion
  - Active ACS
  - STEMI
  - Multivessel PCI
  - DM
  - Renal failure
  - Diffuse CAD
Low Risk Patients

- Uncomplicated or paroxysmal nonvalvular Afib
- Bioprosthetic valve
- Mechanical bileaflet aortic valve
- Venous thromboembolism >12 mths prior
Key Questions to Ask in Every Patient

1) Is this a high or low risk procedure (for bleeding)?

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Who Requires Bridging Therapy?

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<th>Procedure Risk</th>
<th>Patient Risk</th>
<th>Discontinue Antithrombotic</th>
<th>Bridging</th>
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Controversial

- Newer evidence showing higher risk of bleeding with no difference in thromboembolic events
  - BRUISE CONTROL study
    - High risk patients (>5% annual risk)
    - PPM or ICD surgery
    - RCT- continue warfarin vs heparin bridge
    - Thromboembolism uncommon
    - Bleeding more common (16% vs 3.5%) in heparin
  - BRIDGE investigators
    - RCT- LMWH bridge vs placebo
    - Arterial thromboembolism uncommon (0.3% vs 0.4%)
    - Major bleeding more common (3.2% vs 1.3%) in LMWH

Birnie et al NEJM 2013, Douketis et al. NEJM 2015
Anticoagulant Agents
Basic Principles

• Results of standard hemostatic tests do not reflect the degree of anticoagulation
  ▫ Vary in responsiveness to the new agents
  ▫ Useful if normal to indicate absence of effect

• To limit risk of bleeding, $3 \, t_{1/2}$ is the minimum amount of time to wait before the procedure
  ▫ $\sim 10\%$ of drug concentration
  ▫ $5 \, t_{1/2}$ is safer
Warfarin

- Inhibits vitamin K dependent clotting factors II, VII, IX, & X and proteins C & S
- Activity is measured with INR
- INR decreases to ≤1.5 in 93% of patients within 5 days of discontinuation
Heparins

- Activate antithrombin III and inhibit factor Xa
- Unfractionated heparin
  - Half life of 60-90 mins
  - Effects dissipate 3-4 hrs after discontinuation
- Low molecular weight heparins (LMWH):
  - Ardeparin, dalteparin, enoxaparin, tinzaparin
  - Duration of action is 10-12 hrs
  - Last dose should be given 24 hrs before the anticipated procedure at 50% of the total daily dose

New Anticoagulant Medications

Stage

Initiation

Tissue factor/VIIa

Drug inhibition

Propagation

X

IX

VIIIa

IXa

Xa

DXIs Rivaroxaban Apixaban

Fibrin formation

Fibrinogen

IIa

DTIs Dabigatran

Fibrin

Direct Factor Xa Inhibitors

- **Agents:**
  - PO- rivaroxaban (Xarelto), apixaban (Eliquis), edoxaban (Savaysa)
  - SQ- fondaparinux (Arixtra)

- **Lab monitoring:** None
  - Anti-factor Xa assays correlate w/ levels
  - PT, aPTT are insensitive
    - Normal test rule out high circulating drug levels
    - Ceiling effect of aPTT, so do not use in toxic levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Use</th>
<th>Pharmaco-kinetics</th>
<th>Discontinuation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>PO</td>
<td>Afib, DVT, THA</td>
<td>Onset: 1-3 h Peak: 2-4 h T₁/₂: 7-11 h</td>
<td>CrCl &gt;90: ≥1 d CrCl 60-90: 2 d CrCl 30-59: 3 d CrCl 15-29: 4d</td>
<td>66% renal excretion Avoid in cirrhosis</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>PO</td>
<td>Afib, THA, VTE</td>
<td>Onset: 1-3 h Peak: 1-3 h T₁/₂: 8-15 h</td>
<td>CrCl &gt;60: 1-2 d CrCl 30-59: 3 d CrCl 15-29: 4 d</td>
<td>25% renal excretion</td>
</tr>
<tr>
<td>Edoxaban (Savaysa)</td>
<td>PO</td>
<td>Afib, VTE</td>
<td>Onset: 1-2 h T₁/₂: 10-14 h</td>
<td>At least 24 hrs; no data on CrCl &lt;15</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux (Arixtra)</td>
<td>SQ</td>
<td>THA, DVT, PE</td>
<td>Peak- 2h</td>
<td>36 hrs</td>
<td>High affinity for anti-thrombin III</td>
</tr>
</tbody>
</table>

Direct Thrombin Inhibitors

• Agents
  ▫ PO- Dabigatran (Pradaxa)
  ▫ IV- Bivalirudin (Angiomax)
  ▫ SQ- Desirudin (Iprivask)

• Lab monitoring
  ▫ Thrombin generation time (not available in USA)
  ▫ PT & aPTT vary in their sensitivities
    • Normal aPTT effectively rules out a clinically significant circulating drug level
<table>
<thead>
<tr>
<th></th>
<th>Route</th>
<th>Indication</th>
<th>Pharmacokinetics</th>
<th>Discontinuation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td>PO</td>
<td>Afib</td>
<td>Onset: 1-3 hrs, $T_{1/2}$: 12-14 hrs</td>
<td>High risk procedure</td>
<td></td>
</tr>
<tr>
<td><strong>(Pradaxa)</strong></td>
<td></td>
<td></td>
<td></td>
<td>CrCl &gt;80: 2-3 d</td>
<td>80% renal excretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CrCl 50-80: 2-3 d</td>
<td>Shorter times in lower risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CrCl 30-49: 3-4 d</td>
<td>procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CrCl ≤29: 4-6 d</td>
<td></td>
</tr>
<tr>
<td><strong>Bivalirudin</strong></td>
<td>IV</td>
<td>HIT</td>
<td>Onset: mins, $T_{1/2}$: 30 mins</td>
<td>Immediately before</td>
<td></td>
</tr>
<tr>
<td><strong>(Angiomax)</strong></td>
<td></td>
<td></td>
<td></td>
<td>anesthesia induction</td>
<td></td>
</tr>
<tr>
<td><strong>Desirudin</strong></td>
<td>SQ</td>
<td>DVT proph s/p THA</td>
<td></td>
<td>10 hrs</td>
<td></td>
</tr>
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<td><strong>(Iprivask)</strong></td>
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Antiplatelet Agents
Antiplatelet Medications

Diagram showing the process of platelet aggregation and the role of antiplatelet medications in preventing it.
**COX inhibitors**

- **Aspirin**: irreversibly inactivates plt COX→ suppression of thromboxane A2 dependent aggregation
  - Effect lasts for plt’s life (7-10 days)
- **NSAIDS**: reversible inhibition
- May be continued safely in perioperative period
  - In the absence of a pre-existing bleeding disorder

Thienopyridines

- Bind to P2Y12 component of ADP receptors on plt surface → prevents activation of the GPIIb/IIIa receptor complex → ↓ plt activation
  - Only inhibits 40-60% of ADP-induced plt activation
- Indications: ACS ± PCI, CVA, PVD
- Medications
  - 1\textsuperscript{st} generation: ticlopidine (Ticlid)
  - 2\textsuperscript{nd} generation: clopidogrel (Plavix)
  - 3\textsuperscript{rd} generation: prasugrel (Effient), ticagrelor (Brilinta)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Notes</th>
<th>Half-life Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine (Ticlid)</td>
<td>Hematologic side effects (neutropenia, TTP, HUS) limit its use</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel (Plavix)</td>
<td>Prodrug that requires mutistep activation Dependent on ABCB1 and CYP2C19 genotypes for activation</td>
<td>7-8 hrs 5-7 days</td>
</tr>
<tr>
<td>Prasugrel (Effient)</td>
<td>Prodrug requiring activation in 1 step 10-100x more potent than clopidogrel FDA black box warning: should not be used in pt’s with active bleeding, h/o TIA/CVA, or likely to undergo urgent CABG</td>
<td>2-15 hours 5-7 days</td>
</tr>
<tr>
<td>Ticagrelor (Brilinta)</td>
<td>Reversible Quickly absorbed Does not require activation Rapid effect that closely parallels drug-exposure levels Avoid in hepatic impairment</td>
<td>7-8.5 hrs 3-5 days</td>
</tr>
</tbody>
</table>
Vorapaxar (Zontivity)

- Competitive & selective inhibitor of PAR-1
  - Major thrombin receptor on human plts
  - Inhibits plt aggregation
- Indications: MI, PAD
  - ↓ risk of MI, CVA, CV death, need for revascularization procedures
- FDA approved 1/2014
  - Black box warning- high risk of bleeding
  - Contraindications- h/o CVA/TIA, intracranial hemorrhage
- Effect remains up to 4 weeks after stopping
Emergent Procedures in the Acutely Bleeding Patient
Basic Principles

- Consider waiting to do the higher risk aspects at a later date (i.e. sphincterotomy, polypectomy)
- Minor bleeding
  - Hold antithrombotic
- Moderate-severe bleeding
  - Administer antidote if available
  - Transfuse blood components
  - Emergent hemostasis
- Life-threatening bleeding
  - Consider rapidly reversing agents (i.e. FFP, PCC)
# Antidotes: Anticoagulants

<table>
<thead>
<tr>
<th>Antidote</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Vitamin K (5-10 mg IV)</td>
</tr>
<tr>
<td>Direct Xa inhibitors</td>
<td>Activated charcoal (if overdosed within 1-2 hrs prior) Andexanet alfa (only in clinical trials) Others in development: aripazine, anivamersen</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>Dabigatran- idarucizumab, HD</td>
</tr>
</tbody>
</table>

Goal INR

- INR level prior to endoscopy has not been shown to be a predictor of rebleeding
- Effective hemostasis is achieved with moderately elevated INR
- ASGE guidelines: INR <2.5 is reasonable goal
  - Normalizing INR does not reduce rebleeding
  - Lower goals delay time to endoscopy
Reversal Agents: Warfarin

• Recombinant factor VIIa (rFVIIa)
  ▫ Restrict use to major GIB not adequately controlled by supportive care & endoscopy

• Prothrombin complex concentrates
  ▫ Clotting factors from pooled/concentrated plasma
  ▫ 3-factor PCCs (Bebulin, Profilnine): II, IX, X
    • With low dose rFVIIa if 4-factor PCC not available
  ▫ 4-factor PCCs (Kcentra): II, VII, IX, X + protein C, protein S, antithrombin
    • Less volume than FFP (consider in CHF/renal dz to reverse effects of warfarin)

ASGE guidelines 2016
Reversal Agents: DOAC

- No proven reversal agents
- 4-factor PCCs, rFVIIa
  - Used
  - Unclear role
  - No guarantee benefit
- Factor VIII inhibitor bypass activity (FEIBA)
  - Used for reversal of dabigatran
Reversal Agents: Antiplatelets

- Platelet transfusion
Resuming Antithrombotics
Resumption of Anticoagulants

- UFH: 2-6 hrs
- LMWH: 48-72 hrs if high risk procedure
- Coumadin: within 24 hrs
- DOACs: no recommendations
  - Rapid onset and offset of action
  - No good reversal agents
  - Consider 48 hours if low risk of bleeding, longer if higher risk of bleeding

ASGE guidelines 2016
Resumption of Antiplatelets

• Reinitiate as soon as hemostasis is achieved
• If aspirin was discontinued, resume ASAP
  ▫ Studies showing increased risk in 30-day mortality when aspirin not resumed
  ▫ No increase in postprocedural bleeding
• May consider the use of PPIs
  ▫ Patients with risk factor for GI bleed
Case 1

- 78M w/ nonvalvular atrial fibrillation (CHADS2 score 4) on dabigatran (Pradaxa) presents to the ICU with cholangitis. As the GI consult team, what would you recommend for management?
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Summary

• Always ask yourself the 3 questions when approaching antithrombotic agents
  ▫ Is the procedure high/low risk (bleeding)
  ▫ Is the patient high/low risk (thrombotic events)
  ▫ Is bridging required

• Thromboembolic events are life-threatening, while bleeding can usually be treated

• No good lab monitoring for newer agents

• No proven reversal agents
  ▫ If high risk patient, use older agents
Questions?
References

• ASGE Standards of Practice Committee. The management of antithrombotic agents for patients undergoing GI endoscopy. GIE 2016;83:3-16.