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Endoscopy for Your Patient on Anti-coagulants -- Is It Safe? And When to Stop?

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Objectives

- To accurately assess the risk of endoscopic procedures in patients on anti-thrombotic or anti-coagulant therapy
- To clarify the risk of modifying these therapies in the peri-endoscopic setting
- To understand the current practice recommendations for management in the urgent and non-urgent settings
Endoscopy and anticoagulation

- Procedure risk factors
- Patient risk factors
  - Underlying disease
  - Medications
    - Aspirin & NSAIDs
    - Warfarin
    - Novel oral anticoagulants
    - Thienopyridines

Procedural bleeding risks

<table>
<thead>
<tr>
<th>Low-risk Procedures (&lt;1.5%)</th>
<th>&lt;1/1000 Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGD +/- biopsy</td>
<td>✓</td>
</tr>
<tr>
<td>Colonoscopy +/- biopsy</td>
<td>✓</td>
</tr>
<tr>
<td>ERCP without sphincterotomy</td>
<td>✓</td>
</tr>
<tr>
<td>EUS without FNA</td>
<td>✓</td>
</tr>
<tr>
<td>Enteral stent without dilation</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Higher-risk Procedures (&gt;1.5%)</th>
<th>Estimated Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy with polypectomy</td>
<td>0.3 – 3.3%</td>
</tr>
<tr>
<td>Gastric polypectomy</td>
<td>7.2 %</td>
</tr>
<tr>
<td>Duodenal polyp/ampullectomy</td>
<td>4.5-10.3%</td>
</tr>
<tr>
<td>Endoscopic mucosal resection</td>
<td>5-22%</td>
</tr>
<tr>
<td>ERCP with sphincterotomy</td>
<td>2-3.2%</td>
</tr>
<tr>
<td>PEG</td>
<td>2.5%</td>
</tr>
<tr>
<td>Esophageal variceal band ligation</td>
<td>2.4-5.7%</td>
</tr>
<tr>
<td>EUS with FNA</td>
<td>1.3-6%</td>
</tr>
</tbody>
</table>

Management of anticoagulants: Patient risk stratification

“Low Risk Condition”
- Uncomplicated non-valvular atrial fibrillation
- Bioprosthetic valve
- Mechanical aortic valve
- Deep vein thrombosis

“High Risk Condition”
- Atrial fibrillation with:
  - Valvular/prosthetic disease
  - LVEF <35% or active CHF
  - HTN, diabetes
  - H/O thromboembolic event
  - Age > 75 years
- Mechanical mitral valve
- Mechanical valve with previous thrombotic event
- Recently placed coronary stent (<1 year)
- Acute coronary syndrome

ASGE Guidelines
Gastrointest Endosc 2009;70:1060-70

Medication related risk

- Aspirin & NSAIDs
- Warfarin
- Novel oral anticoagulants (NOAC)
- Thienopyridines (P2Y_{12} inhibitors)
Aspirin & NSAIDs

Aspirin
- Irreversible acetylation and inactivation of platelet cyclooxygenase
- Effect is for life of the platelet (7-10 days)
- Prolonged bleeding time for 48 hours and up to 8 days

NSAIDs
- Reversible binding to platelet cyclooxygenase
- Duration of effect related to time NSAID circulates in blood

Management of ASA & NSAIDs at time of endoscopy

694 patients
EGD/bx, Colon/bx, Colon/polypectomy

320 NSAIDs

374 Controls

Bleeding:
32 overall (4.9%)
Minor 28
Major 4

Minor bleeding:
20/320 (6%) NSAIDs
8/374 Controls (2%)
P=0.009

Major bleeding:
4/694 (0.58%)
2/320 NSAIDs
2/374 Controls

- Risk of significant GI bleeding after biopsy or polypectomy small
- Minor self limited bleeding increased after NSAIDs
- Major bleeding no different

Shiffman ML. Gastrointest Endoscopy 1994;40:458-62
Aspirin & NSAIDs: Effect on endoscopy

- In standard doses, aspirin and NSAIDs do not increase risk of significant bleeding
  - EGD with biopsy
  - Colonoscopy with biopsy or polypectomy
- Consider stopping ASA if given for primary prevention and known big polyp

Cotton PB. GIE 1991;37:383-93
Hui AJ. GIE 2004;59:44-8
Shiffman ML. GIE 1994;40:458-62
Freeman M. NEJM 1996;335:909-18
Yousfi M. Am J Gastro 2004;99:1785-9
Hussain N. Aliment Pharmacol Ther 2007;25:579-84

RCT of aspirin vs. placebo after peptic ulcer bleed

Sung JJ. Ann Intern Med 2010;152:1-9
**Resumption of aspirin after GI bleeding**

- ACCF/ACG/AHA Consensus Document
  - “Reintroduction of anti-platelet therapy in high-CV-risk patients is reasonable in those who remain free of rebleeding after 3 to 7 days”

- ACG Guidelines
  - “If given for secondary prevention (i.e. established CV disease) then aspirin should be resumed as soon as possible after bleeding ceases in most patients: ideally within 1-3 days and certainly within 7 days”


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**Warfarin**

- Inhibits the production of the vitamin K dependent clotting factors:
  - II, VII, IX and X
- Inhibits proteins C and S
- Onset between 24 and 96 hours
- Transient reversal with fresh frozen plasma (duration based on half-life of factor VII, which is 4 to 6 hours)
- Duration of action is 2 to 5 days
**Warfarin: Effect on endoscopy**

- 41 patients with post-polypectomy bleeding (0.9% of total) with 132 controls
- Anticoagulation was resumed within one week in 34% of cases and 9% of controls (OR 5.2, p < 0.001)
- For every 1 mm increase in polyp size OR for bleeding of 1.09 (p = 0.008)
- Concomitant aspirin use did not increase risk of bleeding

Sawhney M. Endoscopy 2008:40:115-9

**Impact of anticoagulation and therapeutic endoscopy**

- 233 patients post successful therapeutic endoscopy
- 44% patients had an INR >1.3 (95% < 2.7)

**Rebleeding Rate**
- 23% in anticoagulated patients (INR >1.3)
- 21% in patients with normal coagulation (INR’s <1.3)

- INR is not a predictor of: rebleeding, length of stay, transfusions, surgery, or mortality

Endoscopic therapy is appropriate in mildly to moderately anticoagulated patients

Resuming warfarin after GI bleeding

Recommend patients with warfarin-associated GI bleed and indications for anticoagulation should restart within 4-7 days

Witt DM. Arch Intern Med. 2012;172(19):1484-1491

Removal of colorectal polyps (<1 cm) in anticoagulated pts

Horiuchi A. Gastrointest Endosc 2014;79(3):417-23
**ASGE recommendations**

- “Endoscopic evaluation and therapy in patients who have a GI bleed while using anti-thrombotic agents is both warranted and safe”
  - Data are very limited
- “Mechanical hemostasis (e.g. hemoclips) may provide therapeutic advantages in patients who must resume anticoagulated states”
  - This has not been rigorously studied

ASGE Guidelines Gastrointest Endosc 2009;70:1060-70

**Warfarin: recommendations**

- **Acute gastrointestinal hemorrhage**
  - Correct INR to 1.5 to 2.5
  - Do not delay endoscopy if INR < 2.5

- **Elective low-risk procedures**
  - If anticoagulation is temporary, delay procedure
  - **No** adjustment in anticoagulation, however, INR should not be above therapeutic range
  - Avoid administration of vitamin K
**Warfarin: recommendations for elective high risk procedure**

- **Low-risk conditions** (for an adverse thromboembolic event off anticoagulants)
  - Discontinue 3-5 days prior to procedure
  - Restart warfarin evening of procedure

- **High-risk conditions**
  - Discontinue 3-5 days prior to procedure
  - Bridge with heparin or LMWH (or NOAC)
  - Resume warfarin evening of procedure

**CHADS₂ score**

- Congestive heart failure (CHF), hypertension, age ≥ 75 years and diabetes mellitus are each = 1 point
- Prior CVA or transient ischemic attack (TIA) are = 2 points

<table>
<thead>
<tr>
<th>CHADS₂ Score or Assessment</th>
<th>Risk of CVA</th>
<th>CVA rate/100 pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 1, or 2</td>
<td>Low</td>
<td>1.9-4.0</td>
</tr>
<tr>
<td>3 or 4</td>
<td>Moderate</td>
<td>5.9-8.5</td>
</tr>
<tr>
<td>5 or 6, or CVA or TIA within 3 months, or severe valvular heart disease</td>
<td>High</td>
<td>12.5-18.2</td>
</tr>
</tbody>
</table>
Approach to bridge therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Associated Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation (AF)</td>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; score &lt;4</td>
<td>No bridge required</td>
</tr>
<tr>
<td></td>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt; score of ≥ 4, history of CVA, VTE, or</td>
<td>Bridge therapy required</td>
</tr>
<tr>
<td></td>
<td>cardiac thrombus</td>
<td></td>
</tr>
<tr>
<td>Valvular Heart Disease</td>
<td>Mechanical bileaflet aortic valve</td>
<td>No bridge required</td>
</tr>
<tr>
<td></td>
<td>Mitral valve replacement, 2 or more mechanical valves,</td>
<td>Bridge therapy required</td>
</tr>
<tr>
<td></td>
<td>non bileaflet AV, or aortic replacement with other</td>
<td></td>
</tr>
<tr>
<td></td>
<td>risk factors</td>
<td></td>
</tr>
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</table>

Novel oral anticoagulants

- Factor Xa or IIa (thrombin) inhibitors
- At least as effective as warfarin in preventing CVA’s in atrial fibrillation
- Oral fixed dose without coagulation management are convenient
- Therapeutic anticoagulation within hours
- Normal coagulation within 24-48 hours after NOAC dose is held
Bleeding risk of novel anticoagulant vs. warfarin


Desai J. Gastrointest Endosc. 2013;7(2):227-239

* Statistically significant increased rate of gastrointestinal bleeding compared to warfarin
Renal insufficiency and NOAC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Recommended interval between last dose and procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>• 1-2 days for CrCl &gt;50 mL/min &lt;br&gt;• 3-5 days for CrCl &lt;50 mL/min</td>
</tr>
<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>• ≥ 1 day for normal renal function &lt;br&gt;• 2 days for CrCl 60-90 mL/min &lt;br&gt;• 3 days for CrCl 30-59 mL/min &lt;br&gt;• 4 days for CrCl 15-29 mL/min</td>
</tr>
<tr>
<td>Apixaban (Eliquis)</td>
<td>• 1-2 days for Cr CI &gt;60 mL/min &lt;br&gt;• 3 days for CrCl 50-59 mL/min &lt;br&gt;• 5 days for CrCl &lt;30-49 mL/min</td>
</tr>
</tbody>
</table>

Laboratory monitoring

- PT, PTT and thrombin time may be helpful
- Dabigatran—greater effect on PTT
  - If PTT normal, little anticoagulant effect
  - Only NOAC to affect thrombin time
- Riboraxaban and Apixaban greater effect on PT
  - If PT normal in patient on Rivaroxaban, little ongoing anticoagulant effect
Reversal of NOAC

- Consider oral charcoal if NOAC ingestion < 2 hours prior
- If poor renal function and dabigatran, consider hemodialysis
- If severe bleeding, consider prothrombin concentrate or recombinant factors
- No specific antidote

Edoxaban

- Oral reversible Factor Xa inhibitor
- Approved January 2015
  - Decreased CV events
  - 22% increased risk of GI bleeding, but 33% decreased overall bleeding
- 62% bioavailable, 50% renal excretion
- No data on peri-procedural outcomes

Thienopyridines (P2Y\textsubscript{12} inhibitors)

- Selectively inhibit ADP-induced platelet aggregation
- Inhibit the binding of ADP to P2 receptors and subsequent activation of the GP IIb/IIIa receptor
- Inhibition takes several days to develop
  - 40% to 60% inhibition of aggregation after 3 to 5 days
  - Some antiplatelet activity for 7-10 days

Thienopyridine class

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticlopidine</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>ADP (P2Y\textsubscript{12}) receptor antagonists</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
<td></td>
</tr>
<tr>
<td>Active vs. Inactive Pro-drug</td>
<td>Inactive prodrug: CYP2C19 activation</td>
<td>Inactive prodrug: CYP2C19 activation</td>
<td>Inactive prodrug: CYP3A4 activation</td>
<td>Active</td>
</tr>
<tr>
<td>Drug Half-life</td>
<td>6 hr</td>
<td>12 hr</td>
<td>3.7 h</td>
<td>6-12 h</td>
</tr>
<tr>
<td>Platelet inhibition</td>
<td>7-10 d</td>
<td>7-10 d</td>
<td>7-10 d</td>
<td>1-2 d</td>
</tr>
</tbody>
</table>
**Thienopyridines and colonoscopy with polypectomy**

- Case control study of 142 patients on clopidogrel and 1243 patients not on clopidogrel undergoing colonoscopy with polypectomy
- Acute bleeding rates similar (2.1% vs. 2.1%)
- Delayed bleeding rate higher with clopidogrel (2.1% vs. 0.4%, P = 0.04)
- Clopidogrel alone not a risk factor
- Risk factors associated with bleeding:
  - Combination of aspirin/NSAIDs and clopidogrel, OR 3.7
  - Number of polyps removed, OR 1.3

Singh M. Gastrointest Endosc 2010;71:998-1005
Thienopyridines, polypectomy and bleeding

- 516 patients not taking warfarin who received polypectomies
  - 219 were receiving thienopyridines
  - 297 were not (controls)
- Immediate PPB developed in 16 patients in the thienopyridine group (7.3%) and in 14 in the control group (4.7%, \( P = .25 \))
- Delayed PPB occurred in 2.4% of patients receiving thienopyridines and in none of the controls \( (P = .01) \)
- The rate of PPB for patients
  - 0 of 178 for taking neither aspirin or a thienopyridine
  - 0 of 119 for those taking aspirin only
  - 0 of 27 for those taking a thienopyridine only
  - 5 of 192 (2.6%) for those taking both

Feagins LA. Clin Gastro Hepatol 2013;10:1325-1332

Hemoclips for polyps > 2 cm

<table>
<thead>
<tr>
<th>TABLE 1. Delayed bleeds, perforations, and postpolypectomy syndromes according to whether clipping was performed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Not clipped</td>
</tr>
<tr>
<td>Partly clipped</td>
</tr>
<tr>
<td>Fully clipped</td>
</tr>
</tbody>
</table>

Liaquat H. Gastrointest Endosc 2013:77:401-7
Model of prophylactic hemoclip cost effectiveness

Parikh NH. Clin Gastro Hepatol 2013;11(10):1319-24

Algorithm for prophylactic clips post-polypectomy

Borodyansky L, Saltzman JR. Clin Gastro Hepatol 2013;11(10):1333-4
Thienopyridines: Recommendations

- **Acute gastrointestinal hemorrhage**
  - Discontinue medication if possible
  - Must consider risks of stopping agents
  - Platelet transfusion if quick reversal needed
  - Clinical judgment is critical

- **Elective low-risk procedures**
  - No adjustments

- **Elective high-risk procedures**
  - No firm recommendations
  - If stopping, do so 7 days prior to procedure
  - May be appropriate to restart next day
  - Consider single agent if on clopidogrel and aspirin (preferably aspirin)
Vorapaxar

• New oral antiplatelet agent
• Protease-activated receptor-1 (PAR-1) inhibitor
  • First in class antiplatelet medication
  • Approved January 2014 and prescribed with DAPT
  • Decreased CV events, but increased risk of bleeding
• Peak antiplatelet effects occur 1-2 hours after oral loading dose
• Very little data on peri-procedural outcome
• Discontinue 5-13 days prior to high-risk procedure

Bhatt DL. Circulation Research 2014;114:1929-1943

Factors to consider

- Is the procedure urgent or elective?
- Is the planned procedure low-risk or high-risk?
- Is the patient anticoagulated for a low-risk or a high-risk condition?
- Have you consulted the cardiologist/physician who prescribed the med?
Summary

- Endoscopic procedures may be performed on patients taking ASA and NSAIDs in standard dose.
- For patients on warfarin:
  - Low risk procedure, continue warfarin.
  - High risk procedure, DC and bridge if high (clot) risk pt.
- NOACs are potent anticoagulants with a rapid onset and offset, but an increased GI bleed risk.
- Hold thienopyridines if possible for high risk procedures but OK to continue ASA use.
- Consider prophylactic clips post polypectomy for polyps > 1 cm if on anticoagulants/antithrombotics.