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Endoscopy and the Anticoagulated Patient

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Objectives

- To accurately assess the risk of endoscopic procedures in patients on antithrombotic therapies
- To know the risk of thromboembolic events when withholding antithrombotic drugs
- To know how to manage these agents in patients with GI bleeding
- To understand the current practice recommendations for when to stop, how to reverse and when to restart these agents
Major considerations for endoscopy and antithrombotics

- Procedural risk factors
- Patient risk factors
  - Underlying disease
  - Medications
    - Aspirin
    - Thienopyridines
    - Warfarin
    - Direct oral anticoagulants

Procedural bleeding risks

<table>
<thead>
<tr>
<th>TABLE 3. Procedure risk for bleeding (overall)</th>
<th>Low-risk procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher-risk procedures</td>
<td></td>
</tr>
<tr>
<td>Polypectomy</td>
<td>Capsule endoscopy</td>
</tr>
<tr>
<td>Biopsy or pancreatic sphincterotomy</td>
<td>External stent deployment (Controversial)</td>
</tr>
<tr>
<td>Treatment of varices</td>
<td>Argon plasma coagulation</td>
</tr>
<tr>
<td>PEG placement</td>
<td>Endoscopic hemostasis</td>
</tr>
<tr>
<td>Therapeutic balloon-assisted enteroscopy</td>
<td>EUS with FNA</td>
</tr>
<tr>
<td>EUS with FNA</td>
<td></td>
</tr>
<tr>
<td>Endoscopic hemostasis</td>
<td></td>
</tr>
<tr>
<td>Tumor ablation</td>
<td></td>
</tr>
<tr>
<td>Gastrosopy</td>
<td></td>
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<tr>
<td>Ampullary resection</td>
<td></td>
</tr>
<tr>
<td>EUS</td>
<td></td>
</tr>
<tr>
<td>Endoscopic submucosal dissection</td>
<td></td>
</tr>
<tr>
<td>Pneumatic or bougie dilation</td>
<td></td>
</tr>
<tr>
<td>P/EJ</td>
<td></td>
</tr>
</tbody>
</table>

PEI: Percutaneous endoscopic sphincterotomy
*PEG: percutaneous endoscopic therapy is low risk. Does not apply to EUS/PEI.
**EUS with FNA: solid masses on EUS/PEI is low risk.

Acosta RD, Abraham NS, ASGE SOP. Gastrointest Endosc 2016:83:3-16
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

Risks for thromboembolic events

<table>
<thead>
<tr>
<th>Annual risk</th>
<th>Mechanical heart valve</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Any mitral valve prosthesis</td>
<td>Recent (within 3 months) VTE</td>
</tr>
<tr>
<td></td>
<td>Any caged-ball or tilting disk aortic valve prosthesis</td>
<td>Severe thrombophilia (deficiency of protein C, protein S, or antithrombin, antiphospholipid antibodies, multiple abnormalities)</td>
</tr>
<tr>
<td></td>
<td>Recent (within 6 months) OVA or TJA</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>Bileaflet aortic valve prosthesis and one or more of the following risk factors: AF, prior OVA or TJA, hypertension, diabetes, congestive heart failure, age ≥ 75 years</td>
<td>VTE within the past 3-12 months</td>
</tr>
<tr>
<td></td>
<td>+ Severe thrombophilia (heterozygous factor V Leiden or prothrombin gene mutation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Recurrent VTE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+ Active cancer (treated within 6 months or palliative)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Bileaflet aortic valve prosthesis without AF and no other risk factors for OVA</td>
<td>VTE &gt; 12 months previous and no other risk factors</td>
</tr>
</tbody>
</table>

Acosta RD, Abraham NS, ASGE SOP: Gastrointest Endosc 2016;83:3-16
Anti-thrombotic medications

- Anti-platelet agents
  - Aspirin
  - Thienopyridines (P2Y₁₂ inhibitors)
- Anti-coagulant medications
  - Warfarin
  - Direct oral anticoagulants (DOAC)
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

Management of ASA at endoscopy

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

320 ASA
374 Controls

Bleeding
32 overall (4.9%)
Minor 28
Major 4

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

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

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

Aspirin effect on endoscopy

- In standard doses, aspirin does not increase risk of significant bleeding
  - EGD with biopsy
  - Colonoscopy with biopsy or polypectomy

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

Risk of stopping ASA

- ASA withdrawal precedes 10% of acute vascular syndromes

- Time between stopping ASA and acute event
  - 14.3 days for CVA
  - 8.5 days for acute coronary syndrome
  - 25.8 days for peripheral ischemia

RCT of aspirin vs. placebo after peptic ulcer bleed

Sung JJ. *Ann Intern Med* 2010;152:1-9

**30-d Bleeding**

- Event rate (%)
- ASA: 12%
- Placebo: 4%

**Mortality**

- ASA: 10%
- Placebo: 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”

  Bhutt. *Circulation* 2008;118:1894;
  Laine L, Jensen DM. *Am J Gastroenterol* 2012;107:345
Thienopyridines (P2Y\textsubscript{12} inhibitors)

- Selectively inhibit ADP-induced platelet aggregation
- Inhibit the binding of ADP to P2Y\textsubscript{12} receptor 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>Irreversible</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</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>
Dual antiplatelet therapy (DAPT)

ASA

Arachidonic Acid

COX-1 (constitutive)\n\nCOX-2 (inducible)

ASA

Thromboxane A₂ (TXA₂)

Prostacyclin (PGI₂)

Platelet Aggregation

Thienopyridines

Clopidogrel

Prasugrel

Ticagrelor

ADP

P₂Y₁₂ Receptor

GP IIb/IIIa

↑ TXA₂

Platelet Aggregation

Required Time to Recover Adequate Platelet Function:

- ASA: 7 days
- Clopidogrel: 7 days
- Prasugrel: 7 days
- Ticagrelor: 2 days

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%, $P=0.25$)
- Delayed PPB occurred in 2.4% of patients receiving thienopyridines and in none of the controls ($P=0.01$)
- 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
Thienopyridines:
Recommendations

- **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 a thienopyridine and aspirin (preferably aspirin)

Strategies for the management of GI bleeding on thienopyridines

- Discontinue medication if possible
- Platelet transfusion if reversal needed
- Switch to clopidogrel if on a newer agent (e.g. prasugrel and ticagrelor)
- Clinical judgment is key and communication with cardiology critical
Vorapaxar

- New oral antiplatelet agent (Zontivity)
- 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

Anticoagulants
**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

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

<table>
<thead>
<tr>
<th>Immediate Bleeding</th>
<th>Delayed Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>25</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td></td>
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<tr>
<td>15</td>
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<tr>
<td>10</td>
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<tr>
<td>10</td>
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<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Cold  | Conventional

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

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**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 DOAC)
  - Resume warfarin evening of procedure
Risks/benefits of bridging

- Patients with atrial fibrillation who required warfarin interruption for an elective procedure assigned to either bridging anticoagulation or placebo
- Forgoing bridging was noninferior to bridging for arterial thromboembolism and superior for major bleeding

**Table 1. Study Outcomes.**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging [N=918]</th>
<th>Bridging [N=956]</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4%)</td>
<td>3 (0.3%)</td>
<td>0.05*</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (0.3%)</td>
<td>3 (0.4%)</td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>2 (0.2%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3%)</td>
<td>29 (3.2%)</td>
<td>0.001†</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5 (0.5%)</td>
<td>4 (0.4%)</td>
<td>0.84†</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>7 (0.8%)</td>
<td>14 (1.5%)</td>
<td>0.10†</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
<td>0.25†</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>12 (1.3%)</td>
<td>18 (1.9%)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

*P value for noninferiority. †P value for superiority.


Impact of anticoagulation and endoscopy in GI bleeding

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

**Rebleeding Rate**

- 23% in anticoagulated patients (INR $\geq$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

Wolf AT. *Am J Gastroenterol* 2007;102:290-6
Resuming warfarin after GI bleeding

90-Day Recurrent GI Bleeding

<table>
<thead>
<tr>
<th>Days</th>
<th>Warfarin stopped</th>
<th>Warfarin resumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>% without Recurrent GI</td>
<td>% without Recurrent GI</td>
<td></td>
</tr>
<tr>
<td>P=0.10</td>
<td>Warfarin Resumption HR: 1.32 (0.50-3.57)</td>
<td></td>
</tr>
</tbody>
</table>

90-Day Thrombosis

<table>
<thead>
<tr>
<th>Days</th>
<th>Warfarin stopped</th>
<th>Warfarin resumed</th>
</tr>
</thead>
<tbody>
<tr>
<td>% without Thrombosis</td>
<td>% without Thrombosis</td>
<td></td>
</tr>
<tr>
<td>P=0.002</td>
<td>Warfarin Resumption HR: 0.05 (0.01-0.58)</td>
<td></td>
</tr>
</tbody>
</table>

ASGE recommends warfarin-associated GI bleed and indications for anticoagulation should restart within 4-7 days; same day restart with low-risk endoscopic stigmata.

Witt DM. Arch Intern Med 2012;172(19):1484-1491; Acosta RD, Abraham NS, ASGE SOP. Gastrointest Endosc 2016;83:3-16

Warfarin reversal

- **American College of Chest Physicians (2012)**
  - 4-factor prothrombin complex (PCC) which contain factors II, VII, IX and X (Kcentra)
  - Vitamin K (5-10 mg by slow IV)
  - No FFP
  - No individual coagulation factors (recombinant factor VIIa)

- **American Heart Association/American College of Cardiology (2014): valvular heart disease**
  - 4 factor PCC or FFP
  - No Vitamin K (can cause hypercoagulable state)
ASGE recommendations

- “We suggest that endoscopic therapy not be delayed in patients with serious GI bleeding and an INR <2.5”
- “We recommend either (1) 4-factor PCC and vitamin K or (2) FFP be given for life-threatening GI bleeding in patients on warfarin anticoagulant therapy”
  - The ACCP only advocates option 1
  - The AHA/ACC supports options 1 or 2

Acosta RD, Abraham NS, ASGE SOP. Gastrointest Endosc 2016;83:3-16

Strategies for management of GI bleeding on warfarin

- Continue the warfarin if mild bleeding
  - Reduce target INR to 2.0-2.5
  - Monitor INR levels closely
- Consider a switch to a DOAC
  - Consider if difficulty controlling INR level (not indicated for mechanical valves and some AF)
  - Switch to a DOAC with a lower bleed risk
- If bleeding occurred on both warfarin and ASA
  - Stop warfarin if possible and use low-dose ASA
Direct 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 DOAC dose is held
Mechanism of action of DOACs

Pharmacodynamics of DOACs and warfarin
Bleeding risk of direct anticoagulants vs. warfarin


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

* Statistically significant increased rate of gastrointestinal bleeding compared to warfarin
Stopping DOACs before endoscopy

<table>
<thead>
<tr>
<th>Drug (Creatinine Clearance)</th>
<th>Last dose prior to low-risk endoscopic procedure</th>
<th>Last dose prior to high-risk endoscopic procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran (&gt;50 mL/min)</td>
<td>1 day</td>
<td>2 days</td>
</tr>
<tr>
<td>Dabigatran (31-50 mL/min)</td>
<td>2 days</td>
<td>4 days</td>
</tr>
<tr>
<td>Dabigatran (&lt;30 mL/min)</td>
<td>4 days</td>
<td>6 days</td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban/Edoxaban (&gt;50 mL/min)</td>
<td>1 days</td>
<td>2 days</td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban/Edoxaban (31 to 50 mL/min)</td>
<td>1-2 days</td>
<td>3-4 days</td>
</tr>
<tr>
<td>Rivaroxaban/Apixaban/Edoxaban (&lt;30 mL/min)</td>
<td>2 days</td>
<td>4 days</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 DOAC to affect thrombin time
- **Rivaroxaban and edoxaban**—greater effect on PT
  - If PT normal in patient on rivaroxaban, little ongoing anticoagulant effect
Management of DOAC

- Consider oral charcoal if ingestion <2 hours prior
- Perfuse kidneys– maximize renal excretion
  - Dabigatran 80%
  - Rivaroxaban 50%
  - Apixaban 40%
  - Edoxaban 40%
- Consider hemodialysis for severe GI bleeding
  - Dabigatran (poorly protein bound; 35%)
  - Rival/Apix/Edox (highly protein bound; 87%-95%)
- If severe bleeding, consider prothrombin complex concentrate (PCC)
- No specific antidotes until recently

Dabigatran reversal agents

- Idarucizumab (Praxbind)
  - Humanized monoclonal antibody with high affinity for dabigatran
  - REVERSE-AD trial (interim analysis): Eliminates dabigatran effect within 5 minutes with two IV doses of 2.5 g given 15 minutes apart (ecarin clotting time and dilute thrombin time) in 88%-98% of subjects $3,500/dose
  - Accelerated review by FDA (approved October 16, 2015) for “life threatening hemorrhage/need for emergency surgery or procedures”

Dabigatran reversal agent

Andexanet alfa

- A recombinant protein specifically designed to reverse the anticoagulant activity of both direct and indirect Factor Xa inhibitors
- RCT of healthy older volunteers were given 5 mg of apixaban twice daily or 20 mg of rivaroxaban daily
  - Anti-factor Xa activity was reduced by >90% among those who received an andexanet bolus vs. 20% placebo (p<0.001)
  - Thrombin generation was fully restored in 96-100% versus 10% of the participants within 2 to 5 minutes (P<0.001)
  - These effects were sustained when andexanet was administered as a bolus plus an infusion with no serious adverse events
- FDA review issued a complete response letter (8/17/206)

Anti–Factor Xa activity before and after administration of Andexanet

Factor Xa inhibitor reversal agent
Strategies for management of GI bleeding and DOACs

- Be aware of the possible reversal agents
  - Dabigatran can be reversed
  - Xa inhibitor inhibitors will soon be available
- Measure the anticoagulation effect
  - Dabigatran—greater effect on PTT
  - Ecarin clotting time and dilute thrombin time
  - Xa inhibitors—greater effect on PT
- Switch to an alternative DOAC
  - Apixaban has a lower risk of GI bleeding

Factors to consider

- Is the procedure urgent?
- Is the planned endoscopy procedure low-risk or high-risk?
- Does the anti-thrombotic effect the bleeding risk of the procedure?
- Is the patient on an anti-thrombotic 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 standard dose ASA
- For high risk procedures on dual anti-platelet agents, hold thienopyridine but continue ASA
- For patients on warfarin
  - Low risk procedure, continue warfarin
  - High risk procedure, DC and consider bridge if high risk for thrombosis
- DOACs have a rapid onset and offset, but an increased GI bleed risk and new reversal drugs
- For high risk patients for thromboembolism, restart meds when bleeding controlled (within 1-7 days)