Managing antiplatelet and antithrombotic medications in the setting of GI bleeding and endoscopic procedures

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Learning Objectives

1. Understand GI bleeding risk of antithrombotic regimens
   - Anticoagulants (warfarin, novel oral anticoagulant [NOAC])
   - Antiplatelets (aspirin, thienopyridine agents)
   - Combination therapy (complex antithrombotic therapy [CAT])

2. Strategies for common endoscopic situations
   - Stopping and restarting drugs in the elective setting
   - Antithrombotic management in the acute setting
   - Bridge therapy - what is the evidence?

3. Cardiogastroenterology tips
   - Pragmatic and actionable tips for your practice
By 2030, >40% of US adults will have ≥ 1 form of cardiovascular disease.

*Expected aggressive increase in antiplatelet and anticoagulant use for primary and secondary prevention.

Complex Antithrombotic Therapy (CAT) in Elderly Patients: GI Bleeding Outcomes

One-Year Number Needed to Harm (NNH); N=78,133

<table>
<thead>
<tr>
<th>1-Year NNH for CAT-related Events</th>
<th>Dual Therapy</th>
<th>Triple Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anticoagulant and Antiplatelet Agent</td>
<td>Aspirin and Anticoagulant</td>
</tr>
<tr>
<td>Upper GI Bleeding NNH (95% CI)</td>
<td>65 (24-379)</td>
<td>56 (22-231)</td>
</tr>
<tr>
<td>Lower GI Bleeding NNH (95% CI)</td>
<td>19 (11-37)</td>
<td>15 (9-30)</td>
</tr>
<tr>
<td>Transfusion NNH (95% CI)</td>
<td>43 (21-128)</td>
<td>16 (9-31)</td>
</tr>
<tr>
<td>Hospitalization* NNH (95% CI)</td>
<td>39 (18-121)</td>
<td>34 (16-89)</td>
</tr>
</tbody>
</table>

Antiplatelets
Decrease platelet aggregation and inhibit thrombus formation

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Aspirin (ASA)</th>
<th>P2Y_{12} Receptor-Antagonist</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Clopidogrel (Plavix)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prasugrel (Effient)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ticagrelor (Brilinta)</td>
</tr>
<tr>
<td>Irreversible inhibition of COX-1 and COX-2</td>
<td>Irreversible inhibition of P2Y_{12} receptor</td>
<td>Irreversible inhibition of P2Y_{12} receptor</td>
</tr>
<tr>
<td>Required time to recover adequate platelet function</td>
<td>7 days</td>
<td>5-7 days</td>
</tr>
</tbody>
</table>

CARDIOGASTROENTEROLOGY TIP #1
Management of ASA Monotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Antiplatelet Agent</th>
<th>Procedure</th>
<th>Case</th>
<th>Control</th>
<th>Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yousfi et al. 2004</td>
<td>ASA use within 3 days prior</td>
<td>Colonoscopy + polypectomy</td>
<td>40%</td>
<td>33%</td>
<td>OR 1.41 (0.68-3.04)</td>
</tr>
<tr>
<td>Hussain et al. 2007</td>
<td>ASA or clopidogrel within 10 days prior</td>
<td>Sphincterotomy</td>
<td>16%</td>
<td>17%</td>
<td>OR 0.41 (0.13-1.31)</td>
</tr>
</tbody>
</table>

It is reasonable to perform endoscopic procedures in patients taking ASA.

Indications: Dual Antiplatelet Therapy

Current AHA and ACC guidelines include clopidogrel, ticagrelor and prasugrel.

**Post-ACS**
- Up to 12 months following unstable angina or NSTEMI managed without PCI
- At least 14 days (12 months in some) following STEMI

**Post-Stent**
- ASA indefinitely and clopidogrel or ticagrelor for:
  - Up to 12 months after bare metal stent (BMS) placement
  - At least 12 months after drug-eluting stent (DES) placement


Risk of Clinical Events After Clopidogrel Cessation Among Patients with ACS

Significantly higher risk of adverse events (~2-fold increase) during first 0-90 days post-ACS with clopidogrel discontinuation

Ho et al. JAMA 2008.
CARDIOGASTROENTEROLOGY TIP #2
Stent Thrombosis Post-DES: Risk with Antiplatelet Cessation

Short-term discontinuation of thienopyridine is safe in patients with DES if ASA therapy maintained.

\[ \text{Patients with Thrombotic Event} \]

- ASA and thienopyridine discontinued simultaneously (n=33)
- ASA discontinued after thienopyridine previously discontinued (n=15)
- Only thienopyridine discontinued; ASA continued (n=94)

Eisenberg M et al. Circulation 2009

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Post-Polypectomy Bleeding With and Without Antithrombotic Therapy

Cessation of ASA/NSAID before colonoscopy/polypectomy is unnecessary.

- ASA/NSAID (n=502)
- No ASA/NSAID (n=672)
- Clopidogrel (n=142)
- No Clopidogrel (n=1243)

**CARDIOGASTROENTEROLOGY TIP # 3**
Avoiding the Post-Polypectomy Bleed

- Cold snare technique for small lesions (< 5mm) *
- Saline/epi lifts to prevent excessive bleeding during hot snare procedures of sessile/flat lesions**
- Combined loop +clip can be considered for pedunculated lesions >2.0 cm ^^
- **Prophylactic clip placement following removal of large polyps (>1.0 cm) to close mucosal defects**
  - Reduces post-polypectomy bleeds (1.8% vs. 9.7%; p=0.001)^
  - Cost-effective in patients on antiplatelets and/or anticoagulants**
    - RCTs needed to confirm this finding
  - Avoid cautery alone for immediate post-polypectomy bleeding, due to risk of delayed bleeding with eschar sloughing*

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^^ Kouklakis et al. Surg Endosc 2009 ; ** anecdotal

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**Post-Polypectomy Bleeding:**

![Graph]

Significant delayed bleeding in 11.8% on DAPT with polyps >1.0 cm despite prophylactic hemoclip placement
CARDIOGASTROENTEROLOGY TIP #4
ASA After Endoscopic Control of Peptic Ulcer Bleeding

RCT
• Low-dose ASA (n=78) vs. placebo (n=78)
  • 30-day recurrent bleeding: 10.3% vs. 5.4%
    ▪ ARR: 4.9%; NNT=20
  • 30-day mortality: 1.3% vs. 9.0%
    ▪ ARI: 7.7%; NNH=13

Hospital-based cohort
• N=118
• Discontinued ASA therapy: Mortality and CV event HR 6.3 (1.3-31.3)

Discontinuation of ASA in CV patients is associated with increased mortality.


Second Generation Thienopyridine Drugs: Rates of Bleeding Events

<table>
<thead>
<tr>
<th>Major Bleeding (non-CABG) (%)</th>
<th>TRITON-TIMI 38 Trial</th>
<th>PLATO Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>2.4%</td>
<td>2.8%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1.8%</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

HR 1.32 (1.03-1.68) vs. HR 1.19 (1.02-1.38)


- 2nd generation thienopyridine agents
- Higher levels of platelet inhibition than clopidogrel → higher bleeding risk
- Most common bleeding location= GI
- Absolute increase greatest in elderly patients*
- Ticagrelor and Prasugrel unaffected by variants of CYP2C19 genotype
- Prasugrel unaffected by variants of ABCB1 genotype

CARDIOGASTROENTEROLOGY TIP #5
Peri-Endoscopic Antiplatelet Management

1. Avoid stopping all antiplatelets simultaneously after PCI with stent insertion.
2. You must maintain patient on ASA monotherapy when stopping thienopyridine agents.
3. Avoid cessation of thienopyridine agents (even when ASA is continued) within the first 30 days of DES or BMS placement.
4. Avoid stopping DAPT in the first 90 days post-ACS.
5. Defer elective endoscopic procedures until patients finishes appropriate course of thienopyridine agents, possibly up to 12 months following DES placement.
6. Perform elective high-risk endoscopic procedures 5-7 days after clopidogrel cessation, 7-9 days after prasugrel cessation, and 3-5 days after ticagrelor cessation.
7. Resume DAPT once hemostasis is achieved.

CARDIOGASTROENTEROLOGY TIP #6
Antiplatelet Pearls: Urgent Setting

- GIB in post-ACS patients associated with increased in-hospital mortality (OR 13.2 [4.3-40.5]) and 30-day mortality (OR 8.9 [3.7-22.5])
- GIB leading to ACS should be scoped
  - High likelihood of finding important lesions: HR 3.9 (1.8-8.5)
- Hematemesis or hemodynamic instability should be scoped
  - Faster cardiac catheterization in 43%
- Peri-procedural risks high (12%) in the first 24 hours after ACS but decline to 1-2% by 30 days
  - Time your urgent procedure accordingly
    - Within 48-72 hours if still oozing

## Oral Anticoagulants

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>New Generation Oral Anticoagulants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabigatran (Pradaxa)</td>
</tr>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Inhibition of Vitamin K-dependent γ-carboxylation</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Liver</td>
</tr>
<tr>
<td><strong>Time to maximum effect</strong></td>
<td>90 d for circulating drug; ~5-7 d for a therapeutic INR</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>36-42 h for circulating drug; ~5 d to normalize INR</td>
</tr>
<tr>
<td><strong>Excretion</strong></td>
<td>92% renal</td>
</tr>
</tbody>
</table>

### CARDIOGASTROENTEROLOGY TIP #7

**Classic Supratherapeutic Warfarin Bleed**

**INR at time of endoscopy is not predictive of rebleeding**

![Flowchart](chart.png)

- Adjusted OR*: 0.50 (0.21-1.16)
  - Controlling for age, comorbidity, antiplatelet use, post-procedure heparin and PPI use, hypotension, ulcer as bleeding source, and active bleeding at endoscopy
  
- N=102 INR >1.3; Mean INR 1.8 (1.3-2.7)
  
- Rebleeding rate similar with and without reversal agent: 24.7% vs. 30.0% (p=0.54)
  
- Significant delay in endoscopy with normalization of INR: 20.9 h vs. 73.6 h (p<0.0001)
  
- Important stigmata identified in 83% of cases

**Normalizing INR does not reduce rebleeding but delays endoscopy**

**Endoscopic therapy is very effective— even in patients with moderately elevated INR.**

Choudari & Palmer. Gut 1994; Wolf A. Am J Gastroenterol
CARDIOGASTROENTEROLOGY TIP #8
Resuming Warfarin After GI Bleeding (GIB)

90-Day Thrombosis
Warfarin Resumption
HR: 0.05 (0.01-0.58)
P = 0.002

90-Day Recurrent GI Bleeding
Warfarin Resumption
HR: 1.32 (0.50-3.57)
P = 0.10

Patients with warfarin-associated GIB and indications for continued long-term antithrombotic therapy should resume anticoagulation within the first week (4-7 days) following hemorrhage.


Novel Oral Anticoagulants
High GI Bleeding Risk: Meta-Analysis

New Generation Oral Anticoagulants + Antiplatelet Therapy: GI Bleeding in Post-ACS Population

CV EVENTS

<table>
<thead>
<tr>
<th>Study</th>
<th>POOLED OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESTEEM (2003)</td>
<td>0.76 (0.59-0.98)</td>
</tr>
<tr>
<td>ATLAS ACS-TIMI 46 (2009)</td>
<td>0.78 (0.58-1.05)</td>
</tr>
<tr>
<td>APPRAISE (2009)</td>
<td>0.76 (0.50-1.16)</td>
</tr>
<tr>
<td>RUBY-1 (2011)</td>
<td>1.05 (0.56-1.90)</td>
</tr>
<tr>
<td>RE-DEEM (2011)</td>
<td>0.95 (0.81-1.12)</td>
</tr>
<tr>
<td>ATLAS ACS 2-TIMI 51 (2012)</td>
<td>1.30 (0.71-2.38)</td>
</tr>
</tbody>
</table>

Favors Anticoagulant Favors Placebo

MAJOR BLEEDS

<table>
<thead>
<tr>
<th>Study</th>
<th>POOLED OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESTEEM (2003)</td>
<td>1.98 (0.80-4.49)</td>
</tr>
<tr>
<td>ATLAS ACS-TIMI 46 (2009)</td>
<td>1.43 (0.24-8.58)</td>
</tr>
<tr>
<td>APPRAISE (2009)</td>
<td>15.68 (2.14-114.97)</td>
</tr>
<tr>
<td>RUBY-1 (2011)</td>
<td>2.55 (1.48-4.41)</td>
</tr>
<tr>
<td>RE-DEEM (2011)</td>
<td>2.05 (0.25-17.05)</td>
</tr>
<tr>
<td>ATLAS ACS 2-TIMI 51 (2012)</td>
<td>1.75 (0.25-14.24)</td>
</tr>
</tbody>
</table>

Favors Anticoagulant Favors Placebo

CARDIOGASTROENTEROLOGY TIP #9

Peri-Procedural Management of NOAC

Pre-Procedure
- Determine last NOAC dose and creatinine clearance

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>Half-life (h)</th>
<th>Timing of Discontinuation Before Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80</td>
<td>13 (11-22)</td>
<td>Moderate procedural bleeding risk (2-3 half-lives)</td>
</tr>
<tr>
<td>&gt;50 to &lt;80</td>
<td>15 (12-34)</td>
<td>High procedural bleeding risk (4-5 half-lives)</td>
</tr>
<tr>
<td>&gt;30 to &lt;50</td>
<td>18 (13-23)</td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>27 (22-35)</td>
<td></td>
</tr>
</tbody>
</table>

- Patients at high risk of bleeding: Perform aPTT day before procedure. Normal result= no clinically significant dabigatran effect.

Post-Procedure
- Consider rapid onset of action (1.5 h) when restarting.
- Consider prophylaxis (i.e., enoxaparin bridge) until hemostasis established so full dose can be resumed.
CARDIOGASTROENTEROLOGY TIP #10
Management of NOAC Bleeding

Initial Assessment and Risk Stratification: The ABC’s
A= Airway; B= Breathing; C= Circulation

Mild Bleeding
- Delay next dose
- Anticoagulant effect dissipates 24 h (with no renal failure)
- T1/2 = 12-17 h

Moderate-Severe Bleeding
- Correct hemodynamics to perfuse kidneys
- Blood-product transfusion
- Endoscopic evaluation
- +/- hemodialysis with renal failure
- Oral charcoal (if ingestion <2h)*; PPI probably helpful if recent ingestion (decreases absorption)

Life-Threatening Bleeding
- Consider rFVIIa or **PCC
- Charcoal filtration

* Recommendations based on limited nonclinical data
** PCC = prothrombin concentrate complex

Bridge Therapy – Who?

<table>
<thead>
<tr>
<th>Thromboembolic Risk Category</th>
<th>Atrial Fibrillation</th>
<th>Mechanical Heart Valve</th>
<th>Venous Thromboembolism (VTE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Risk &gt;10%</td>
<td>CHADS2 - 5 or 6</td>
<td>Mechanical Mitral Valve</td>
<td>VTE within 3 mos High-risk thrombophlebitis</td>
</tr>
<tr>
<td>CVA/TIA w/ in 3 mos Rheumatic valvular disease</td>
<td>Caged-ball or tilting disk aortic valve CVA/TIA w/ in 3 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annual risk 5-10%</td>
<td>CHADS2 - 3 or 4</td>
<td>Bileaflet Aortic Valve in high-risk patient</td>
<td>VTE 3-12 mos ago</td>
</tr>
<tr>
<td>Annual Risk &lt;5%</td>
<td>CHADS2 - ≤ 2</td>
<td>Bileaflet Aortic Valve in low risk patient</td>
<td>VTE &gt; 12 mos ago</td>
</tr>
<tr>
<td>No prior CVA/TIA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Bridge Tx– Evidence?

<table>
<thead>
<tr>
<th>Mechanical Heart Valve Studies</th>
<th>Clot (%)</th>
<th>Bleed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis 2004 (n=215)</td>
<td></td>
<td>1.2 %</td>
</tr>
<tr>
<td>Pengo 2009 (n=190)</td>
<td></td>
<td>2.7%</td>
</tr>
<tr>
<td>Kovacs 2004 (n=112)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammerstingl 2007 (n=116)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daniels 2009 (n=556)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL (n=1189)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AFIB/VTE/Vascular Bypass Graft Studies</th>
<th>Clot (%)</th>
<th>Bleed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis 2004 (n=346)</td>
<td></td>
<td>0.9 %</td>
</tr>
<tr>
<td>Pengo 2009 (n=663)</td>
<td></td>
<td>2.0%</td>
</tr>
<tr>
<td>Kovacs 2004 (n=112)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dunn 2007 (n=76)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wysokinski 2008 (n=345)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL (n=1532)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No thrombotic protection but increased bleeding risk*


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### My Top 10 Cardiogastroenterology Tips

1. It is safe to perform endoscopy on ASA monotherapy.
2. Avoid stopping thienopyridine in first 90 days post-ACS.
3. Continue ASA therapy when stopping thienopyridine.
4. GIB leading to ACS should be scoped 48-72 h post-ACS.
   - ↑ chance of finding high-risk endoscopic stigmata
   - Leads to faster cardiac catheterization in 43%
5. Endoscopic therapy is effective in patients with moderately elevated INR (≤ 2.7). No need to normalize INR.
My Top 10 Cardiogastroenterology Tips

6. Warfarin should be resumed within 4-7 days post-GIB.
7. New oral anticoagulants have ↑ GIB risk.
8. DAPT + new oral anticoagulants (triple antithrombotic therapy) associated with 3-fold ↑ risk of GIB.
9. NOAC-related bleeding → Support hemodynamics to promote renal excretion of drug.
10. Elective peri-procedural NOAC management depends on patient’s CrCl:
    - With normal CrCl:
      o High-risk endoscopy → Hold 2-3 days prior to case
      o Low-risk endoscopy → Hold 1-2 days prior to case
    - With impaired CrCL:
      o High-risk endoscopy → Hold 4-6 days prior to case
      o Low-risk endoscopy → Hold 2-3 days prior to case