Learning Objectives
At the conclusion of this presentation, the participant will be able to:
- Assess the risk of endoscopic procedures in non-bleeding patients on antithrombotic therapy (ATT)
- Clarify the cardiovascular (CV) risk of modifying ATT in the peri-endoscopic setting
- Understand best-practice recommendations for peri-endoscopic ATT management in the non-urgent and urgent settings.

Introduction
Prescription of ATT for CV conditions is common, with estimates of prevalence available from an international, prospective longitudinal study of >68,000 outpatients with vascular disease. In this cohort, most patients took aspirin monotherapy (~70%), 18% took dual antiplatelet therapy, and 6% took oral anticoagulant and aspirin therapy. Clinical indications for ATT are displayed in Table 1. In this session, we will review the best-practice recommendations for the peri-endoscopic antithrombotic period to minimize the risk of adverse gastrointestinal (GI) and CV outcomes.

Endoscopic Bleeding Risk
Bleeding risk varies with procedure type and presence/absence of therapeutic interventions. Low-risk procedures (<1% bleeding risk) include diagnostic procedures with or without mucosal biopsy, endoscopic retrograde cholangiopancreatography (ERCP) without sphincterotomy, diagnostic balloon-assisted enteroscopy, wireless capsule endoscopy, and endosonography without FNA. Higher-risk procedures are associated with a bleeding risk ≥1% and are listed in Table 2. In patients with normal hemostasis, risk of endoscopic bleeding is greatest after thermal ablation and endoscopic coagulation (5%), gastric polypectomy (7%) and mucosal resection (22%). The risk of postcolonoscopic polypectomy is fairly low, ranging from 0.3-3.6% overall and 0.6-6.1% per polyp but increases with polyp size >10 mm (odds ratio [OR] 4.5; 95% confidence interval [CI]: 2.0-10.3). Risk of bleeding may also be influenced by technique, morphology and location of the polyp. Patient-related factors associated with increased risk of bleeding include advanced age and chronic comorbid conditions (i.e., hypertension, diabetes, coronary artery disease, renal failure, cirrhosis, congenital and acquired coagulopathies, and thrombocytopenia). Elderly patients also have an increased likelihood of blood transfusion post-polypectomy. The risk of post-polypectomy bleed further increases with cautery (OR 6.7; 95% CI: 2.8-16.1), removal of more than 1 polyp (OR 12.1; 95% CI: 5.1-28.7), and pre-procedure anticoagulation with warfarin (OR 2.9; 95% CI: 1.2-7.0). A single-center, retrospective study evaluating the risk of post-polypectomy bleeding with and without clopidogrel found a higher rate of delayed bleeding (≤4 weeks post-procedure) in patients taking dual aspirin and clopidogrel therapy at colonoscopy compared to those taking aspirin alone (2.1% vs. 0.4%, p=0.04).

Thromboembolic Risk
An individual’s risk of thromboembolism from his/her prescribed ATT also varies, based on specific patient characteristics (Table 2). Prior to discontinuation of ATT, consider 3 factors: 1) indication for ATT (Table 1); 2) presence of additional thromboembolic risk factors; and 3) consequences of a thromboembolic event.

Anticoagulant therapy
Warfarin therapy substantially decreases risk of thrombotic events (66-80%); however, the absolute risk following interruption of anticoagulation of 4-7 days is very low at 1-2 per 1,000 patients among those with a low-risk thromboembolic condition. Among atrial fibrillation patients whose anticoagulation is adjusted (INR 1.3), 30-day risk for stroke is only 1.1%; however, this risk increases (3%) among elderly patients (>80 years) and those with a history of stroke, hyperlipidemia, hypertension, and family history of vascular disease. Most high-risk patients have valvular heart disease. Thromboembolic risk associated with prosthetic valves varies, based on position (mitral>aortic) and type (caged ball valves>tilting disk>bileaflet valves) and averages 4 per 1,000 patient-years with interruption of anticoagulation. The first month following an acute deep vein thrombosis poses the greatest risk, patient-related factors, and procedural characteristics are all important considerations for the clinician when deciding whether to proceed with anticoagulation.

Table 1: Clinical indications for antithrombotic use

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome (ACS)</td>
<td>ST-segment elevation MI (STEMI), Non-ST-segment elevation MI (NSTEMI), Coronary revascularization (PCI/CABG)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Acute cerebrovascular accident (CVA), Transient ischemic attack (TIA)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Acute peripheral occlusion</td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>Coronary artery disease (CAD)/ACS, CVA/TIA, Peripheral artery disease (PAD)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Mechanical valve</td>
<td>Mechanical valve</td>
</tr>
</tbody>
</table>

Acknowledgments: Dr. Abraham is supported by a Merit Review Award from the Department of Veterans Affairs (VA IIR 08-028).
with a 40% chance of recurrence. This diminishes over time, and by the third month is <10%.12

Antiplatelet therapy
Among patients with clinical indications for aspirin and clopidogrel dual antiplatelet therapy, those patients post-coronary intervention (PCI) with placement of coronary stents (bare-metal stent [BMS] or drug-eluting stent [DES]) are at greatest potential risk for thrombotic event. Stent thrombosis is a real and significant risk in the post-PCI population, with gradual incline in risk over time after an initial magnified risk in the first 30 days post-implantation. Current guidelines advocate dual antiplatelet therapy for up to 12 months post-PCI with BMS and at least 12 months after DES.3 Early stent thrombosis (0-30 days post-PCI) has an estimated prevalence ~1% for both BMS and DES but varies, depending on individual clinical characteristics (i.e., prior stent thrombosis, acute coronary syndrome [ACS] or ST-segment elevation MI [STEMI], multi-vessel PCI, diabetes, renal failure, BMS implantation within last 30 days or DES implantation within last 12 months, non-cardiac surgery early after PCI), procedural (i.e., diffuse CAD, smaller post-PCI diameter, multiple stents, residual dissection, bifurcation stenting, large thrombus burden, first-generation DES), treatment and genetic risk factors.17,18 Late stent thrombosis, occurring 31-360 days post-PCI, is more common among patients with DES than among those with BMS.19 Among patients with DES, the estimated 3-year prevalence of late stent thrombosis is 2.9%, with a steady increase rate of 0.6% per year.20 The Dutch Stent Thrombosis Registry reported a high recurrent stent thrombosis and/or cardiac death event rates of 18.0% in the first 30 days, which continues up to 1, 2, and 3 years post-stent implantation (23.6%, 25.2%, and 27.9%, respectively).21 Furthermore, nearly 1 in 5 patients with first stent thrombosis will suffer a recurrent stent thrombosis.21

Stent thrombosis occurs shortly after discontinuing any antiplatelet, with a median interval of 7-14 days,22 which is extended to 122 days if only the thienopyridine is discontinued (i.e., changing dual antiplatelet therapy to aspirin monotherapy for a short time).23 These results suggest that short-term discontinuation of a thienopyridine while maintaining aspirin monotherapy is safer in patients with DES once the highest initial risk period for thrombosis (i.e., after 30 days post-implantation) has passed. A practical approach to minimize thromboembolic risk among this subset population is summarized in Table 3. Cessation of both clopidogrel and aspirin at any time in a post-PCI patient is associated with an increased risk over a brief period of time, especially if aspirin monotherapy is assured. Therefore, patients at high risk for thromboembolic events undergoing a high-risk endoscopic procedure should stop clopidogrel 5-7 days prior to the procedure and continue with aspirin therapy throughout the peri-endoscopic period.

Table 2: Procedures with low vs. high endoscopic bleeding risk and thromboembolic conditions

<table>
<thead>
<tr>
<th>Endoscopic Bleeding Risk</th>
<th>Thromboembolic Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Low Risk</td>
</tr>
<tr>
<td>High Risk</td>
<td>High Risk</td>
</tr>
</tbody>
</table>

- Diagnostic + biopsy
  - EGD
  - Double balloon enteroscopy
  - Colonoscopy
  - Biliary/pancreatic stent without sphincterotomy
  - ERCP with sphincterotomy
  - EUS without FNA
  - Flexible sphincterotomy + biopsy
  - Endosonography without FNA
  - Wireless capsule endoscopy
- Polypectomy
- Gastric
- Duodenal/ampullary
- Colonic
- Endoscopic mucosal resection
- Biliary sphincterotomy
- Pneumatic or bougie dilatation
- PEG placement
- Endosonography-guided FNA
- Laser ablation and coagulation
- Treatment of varices
- Uncomplicated or paroxysmal nonvalvular atrial fibrillation
- Bioprosthetic valve
- Mechanical valve in the aortic position
- Deep-vein thrombosis
- Atrial fibrillation with:
  - Valvular heart disease
  - Prosthetic valves
  - Active CHF
  - LVEF <35%
  - History of thromboembolic event
  - Hypertension
  - Diabetes mellitus
  - Age >75 years
- Mechanical valve in any position and previous thromboembolic event
- Recently (<1 yr) placed coronary stent
- Acute coronary syndrome
- Non-stented PCI after MI

Table 3: Cessation of antiplatelets and thrombotic event risk

<table>
<thead>
<tr>
<th>Cessation of...</th>
<th>Time Period after PCI</th>
<th>Thrombotic Event Risk</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antiplatelet therapies</td>
<td>Any time, for any stent</td>
<td>Increase risk</td>
<td>Events likely to occur within 7-30 days of drug discontinuation</td>
</tr>
<tr>
<td>Clopidogrel alone</td>
<td>Early period (0-30 days) of DES/BMS placement</td>
<td>Increases risk</td>
<td>Avoid cessation of ATT</td>
</tr>
</tbody>
</table>
| Clopidogrel alone | >30 days from BMS placement | Does not increase risk | - Common in clinical practice  
- Does not confer increased risk over a brief period of time (i.e., <7 days) |
Management Strategies In The Non-Bleeding Patient

Management of antiplatelet therapy

Table 4 summarizes and compares the recommendations from three GI societies: The American College of Gastroenterology (ACG), The American Society of Gastrointestinal Endoscopy (ASGE), and The British Society of Gastroenterology (BSG). In general, low-risk endoscopic procedures require no adjustment in antiplatelet therapy. For high risk endoscopic procedures, the following are recommended: 1) Avoid cessation of all antiplatelet therapies after PCI with stent placement when possible; 2) Avoid cessation of clopidogrel (even when aspirin is continued) within the first 30 days of PCI and either DES or BMS placement when possible; 3) Defer elective endoscopic procedures, possibly up to 12 months, if clinically acceptable from the time of PCI and DES placement; 4) Perform endoscopic procedures, particularly those associated with high bleeding risk, 5–7 days after thienopyridine drug cessation. Aspirin therapy should be continued during the short period of thienopyridine cessation; 5) Resume thienopyridine and aspirin therapy after the procedure once hemostasis is achieved. A loading dose of thienopyridine should be considered for patients at risk for thrombosis; 6) Continue platelet-directed therapy as prescribed in patients undergoing elective endoscopic procedures associated with low risk for bleeding.

Management of anticoagulant therapy

As shown in Table 5, low-risk procedures require no adjustments. For high-risk endoscopic procedures, warfarin should be discontinued 3–5 days prior to the procedure and resumed the night of the procedure. It takes ~3 days after interruption for the INR to reach a level <2.0. Confirm INR is normal (INR<1.2) or near normal (1.3–1.4) the day before endoscopy. Patients with a high-risk thromboembolic condition for whom a high-risk endoscopy procedure is planned should be bridged with unfractionated heparin (UFH) or low molecular weight heparin (LMWH). For these patients, AHA/ACC guidelines recommend that warfarin should be held at presentation and bridging therapy initiated during the period in which the INR may become supratherapeutic. The incidence of major bleeding is low (<2%) when full dose bridging therapy is given before and/or after endoscopy. Following endoscopic hemostasis, warfarin can be reinitiated within 2–6 hours of intravenous heparin, and observation for rebleeding should precede readministration of warfarin. Intravenous heparin infusion has advantages over low molecular weight heparins as a bridge to re-warfarinization in this setting. With its rapid onset of action and short half-life, it can be ceased/reversed quickly with rebleeding.

Management Strategies In The Bleeding Patient

There is a strong association between ATT and increased GI bleeding, further increased when combining antiplatelets and anticoagulants. The risk of bleeding associated with anticoagulation is highest during the first month, when it is approximately 10 times greater than after the first year of therapy. Most patients have an identifiable source, usually a duodenal or gastric ulcer. An early diagnostic endoscopy should be performed, unless the patient has a supratherapeutic INR, in which case an identifiable source of bleeding is less likely to be found. Patients with clinically significant acute GI bleeding with a supratherapeutic INR (>2.5) should undergo correction of anticoagulation. Although there are few data regarding the ideal target INR in the urgent setting, limited data support administration of fresh frozen plasma to
partially correct the INR to 1.5-2.5.4,5,31 Table 6 shows reversal strategies for ATT if the clinical setting dictates. Reversal of platelet dysfunction associated with antiplatelets can be difficult. However, transfusion of platelets +/- desmopressin can be helpful in some situations (i.e., thienopyridines). Bleeding complications associated with LMWH range from 0-5%,32 and its anticoagulant effect may be reversed within 8 hours of the last dose. If quick reversal is required, protamine sulfate should be used with caution, as it can cause severe hypotension and anaphylactoid reactions.32 Recommendations for the management of ATT in the urgent endoscopic setting are displayed in Table 7.4

**REFERENCES**


