Learning Objectives

1. To clarify the CV risk of modifying antiplatelet therapy

2. To define strategies to reduce the risk for patients on antiplatelet therapy who are undergoing endoscopy

3. To review best-practice recommendations
Antiplatelets

- **Definition:** Pharmacotherapy that decreases platelet aggregation and inhibits thrombus formation

- **Includes:**
  - Aspirin (ASA)
  - Thienopyridine (P2Y<sub>12</sub> receptor antagonist):
    - Clopidogrel (Plavix<sup>®</sup>)
    - Prasugrel (Effient<sup>®</sup>)
    - Ticagrelor (Brilinta<sup>®</sup>)

Clinical Indications for Antiplatelet Therapy Use

- **Acute coronary syndrome (ACS)**
  - ST-segment elevation MI (STEMI)
  - Non-ST-segment elevation MI (NSTEMI)
- **Coronary revascularization**
  - Percutaneous coronary intervention (PCI)
  - Coronary artery bypass graft (CABG)
- **Acute cerebrovascular accident (CVA)**
- **Acute peripheral occlusion**
- **Secondary prevention**
  - Coronary artery disease (CAD)/ACS
  - CVA/TIA
  - Peripheral arterial disease (PAD)
- **Heart failure**
- **Atrial fibrillation**
- **Mechanical valve**
Antiplatelet Therapy Use in the United States: REACH Registry

**Antiplatelet Therapy**
- Aspirin (ASA)
- Thienopyridine (P2Y₁₂ receptor antagonist):
  - Clopidogrel (Plavix®)
  - Prasugrel (Effient®)
  - Ticagrelor (Brilinta®)

ASA only (69%)
ASA + thienopyridine (13%)
ASA + thienopyridine + anticoagulants (4%)
ASA + anticoagulants (4%)
ASA + thienopyridine + anticoagulants (1%)
Anticoagulant only (8%)
Thienopyridine + anticoagulant (1%)


ASA Monotherapy

**Arachidonic Acid**

COX-1 (constitutive)

COX-2 (inducible)

ASA

Thromboxane A₂ (TXA₂)

Prostacyclin (PGI₂)

Platelet Aggregation

Required Time to Recover Adequate Platelet Function: 7 days
AHA Recommendations for Primary and Secondary Prevention in CV Disease

**Indications for Primary Prevention:**
- 10-year CV risk >10%
- Diabetes and no previous history of vascular disease with 10-year CV risk >10% **AND** no increased risk for bleeding
- Women >65 years if benefit outweighs the risk of GI bleeding and hemorrhagic stroke.

**Indications for Secondary Prevention:**
- After coronary or cerebrovascular event

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ASA Monotherapy for Primary and Secondary Prevention: Meta-Analysis of RCTs

<table>
<thead>
<tr>
<th>Event</th>
<th>Rate Ratio (95% CI) (ASA monotherapy vs. control)</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular events: MI, stroke or vascular death</td>
<td>0.88 (0.82-0.94)</td>
<td><strong>0.06%</strong> <strong>(NNT = 1667)</strong></td>
<td>0.81 (0.75-0.87)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>0.77 (0.69-0.86)</td>
<td><strong>0.05%</strong> <strong>(NNT = 2000)</strong></td>
<td>0.69 (0.60-0.80)</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0.95 (0.85-1.06)</td>
<td><strong>0.01%</strong> <strong>(NNT = 10,000)</strong></td>
<td>0.87 (0.78-0.98)</td>
</tr>
<tr>
<td>Major GI bleeding</td>
<td>1.54 (1.30-1.82)</td>
<td><strong>0.03%</strong> <strong>(NNT = 3333)</strong></td>
<td>2.69 (1.25-5.76)</td>
</tr>
</tbody>
</table>

- Narrow threshold between efficacy and safety with ASA primary prevention (NNT = 1667 vs. NNT = 3333)
  - 2 vascular events prevented, ~1 GI bleeding would occur

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### Endoscopic Bleeding Risks in Patients on Monotherapy: Case-Control Studies

<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>

**Recommendation:** In the absence of a pre-existing bleeding disorder, it is reasonable to perform all elective procedures in patients taking ASA.


### Endoscopy-Related GI Bleeding Risks

Bleeding risk varies with procedure type and presence/absence of therapeutic interventions.

<table>
<thead>
<tr>
<th>Low Risk (&lt;1%)</th>
<th>High Risk (&gt;1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Diagnostic + biopsy</td>
<td>➢ Polypectomy</td>
</tr>
<tr>
<td>➢ EGD (1.0%-0.1%)</td>
<td>➢ Gastric (7.2%)</td>
</tr>
<tr>
<td>➢ Double balloon enteroscopy (0.1%)</td>
<td>➢ Duodenal/ampullary</td>
</tr>
<tr>
<td>➢ Colonoscopy (0-0.02%)</td>
<td>➢ 1-3 cm (4.5%)</td>
</tr>
<tr>
<td>➢ Biliary/pancreatic stent without sphincterotomy (0.3%)</td>
<td>➢ &gt;3 cm (10.3%)</td>
</tr>
<tr>
<td>➢ ERCP without sphincterotomy*</td>
<td>➢ Colonic (0.7-3.3%)</td>
</tr>
<tr>
<td>➢ EUS without FNA</td>
<td>➢ Endoscopic mucosal resection (22%)</td>
</tr>
<tr>
<td>➢ Flexible sphincterotomy + biopsy*</td>
<td>➢ Biliary sphincterotomy (2.0-3.2%)</td>
</tr>
<tr>
<td>➢ Endosonography without FNA</td>
<td>➢ Pneumatic or bougie dilation (1.7%)</td>
</tr>
<tr>
<td>➢ Wireless capsule endoscopy*</td>
<td>➢ PEG placement (0.2-2.5%)</td>
</tr>
<tr>
<td></td>
<td>➢ Endosonography-guided FNA (0.5-2.9%)</td>
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<td></td>
<td>➢ Laser ablation and coagulation (1.1%)</td>
</tr>
<tr>
<td></td>
<td>➢ Treatment of varices (2.4-25.4%)</td>
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</table>

*Limited data, presumed negligible

Recommendation for Management in Primary Prevention

ASA Monotherapy

Primary Prevention (Low Thromboembolic Risk)

Low Endoscopic Bleeding Risk

Continue ASA

High Endoscopic Bleeding Risk

Continue ASA; *May elect to discontinue 7 days prior


Dual Antiplatelet Therapy

ASA

Arachidonic Acid

COX-1 (constitutive)

COX-2 (inducible)

ASA

Thromboxane A₂ (TXA₂)

Prostacyclin (PGI₂)

Platelet Aggregation

THIENOPYRIDINES

Clopidogrel

Prasugrel

Ticagrelor

ADP

P₂Y₁₁ Receptor

GP IIb/IIIa

↑ TXA₂

Platelet Aggregation

- Required Time to Recover Adequate Platelet Function:
  - ASA: 7 days
  - Clopidogrel: 5-7 days
  - Prasugrel: 7-9 days
  - Ticagrelor: 3 days
Case

- 65-year-old man with a family history of colorectal cancer
- STEMI with PCI and drug-eluting stent (DES) 13 months ago with history of stent occlusion
- Dual antiplatelet therapy: ASA + clopidogrel
- Asthma—Rx: Inhalers
- No other comorbidities/medications
- Normal labs
- PLAN: Elective screening colonoscopy

How should you manage his antiplatelet therapy?
Indication for antiplatelet therapy

Thromboembolic Risk
Probability of event depends on 3 factors

- Presence of additional thromboembolic risk factors
- Consequence of thromboembolic event


Low- vs. High-Risk Thromboembolic Conditions

<table>
<thead>
<tr>
<th>Low-Risk</th>
<th>High-Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated or paroxysmal nonvalvular atrial fibrillation</td>
<td>Atrial fibrillation associated with:</td>
</tr>
<tr>
<td>Bioprosthetic valve</td>
<td>- Valvular heart disease</td>
</tr>
<tr>
<td>Mechanical valve in the aortic position</td>
<td>- Prosthetic valves</td>
</tr>
<tr>
<td>Deep-vein thrombosis</td>
<td>- Active CHF</td>
</tr>
<tr>
<td></td>
<td>- LVEF &lt;35%</td>
</tr>
<tr>
<td></td>
<td>- History of thromboembolic event</td>
</tr>
<tr>
<td></td>
<td>- Hypertension</td>
</tr>
<tr>
<td></td>
<td>- Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>- Age &gt;75 yrs</td>
</tr>
<tr>
<td></td>
<td>- Mechanical valve in any position and previous thromboembolic event</td>
</tr>
<tr>
<td></td>
<td>- Recently (~1 yr) placed coronary stent</td>
</tr>
<tr>
<td></td>
<td>- Acute coronary syndrome</td>
</tr>
<tr>
<td></td>
<td>- Non-stented PCI after MI</td>
</tr>
</tbody>
</table>

The Cardiac Patient: Indications for ASA+Clopidogrel

Acute Coronary Syndrome (ACS)

- Up to 12 months following unstable angina or NSTEMI managed without intervention
- At least 14 days (12 months in some) following STEMI
- Up to 12 months after bare metal stent (BMS) placement
- At least 12 months after 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.
The Cardiac Patient: Indications for ASA+Clopidogrel

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

Post-Stent
- Up to 12 months after bare metal stent (BMS) placement
- At least 12 months after drug-eluting stent (DES) placement

Stent Thrombosis: Risk of Cardiac Death
N=431 STEMI Patients, Post-PCI on Antiplatelet Therapy

1 in 5 patients who experience a first definite stent thrombosis experience a second stent thrombosis.

More common among patients with DES (vs. BMS):
- 3-year rate = 2.9%
- Steady incidence over 3 years → rate of 0.6% per year
**Duration of Dual Antiplatelet Therapy (DAPT) Post-PCI**

**Primary Endpoint**
- **EXCELLENT Trial:** 6 vs. 12 mo post-DES
  - No difference in ↓ cardiac risk (p=0.60)
- **PRODIGY Trial:** 6 vs. 24 mo post-DES or BMS
  - No difference in ↓ cardiac risk (p=0.91)

**Safety Endpoint**
- **EXCELLENT**
  - P=NS
  - No difference in major bleeding (p=0.64)
- **PRODIGY**
  - 24-mo: 7.4%
  - 12-mo: 3.5%
  - P=0.002

↑ GI bleeding at 2 years.
24 vs. 6-mo: HR 2.2 (1.4-3.2)

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**Summary: Duration of DAPT**

- DAPT for 6 mo post-stent likely sufficient for most
  - Benefit of reducing late-stent thrombosis may not outweigh risk of bleeding with longer-term DAPT
- Higher-risk patients need prolonged DAPT
  - Unstable disease presentation
  - Extensive/complex CAD
  - Diabetes
    - Diabetes is a prothrombotic condition
    - Diabetics are more frequently resistant to aspirin
- Logical approach → continue DAPT for a minimum of 12 mo post-DES and 6 mo post-BMS
  - Longer durations reserved for patients with complex presentations, difficult stent procedures or diabetes
  - Earlier termination should be assessed on a case-by-case basis with input from the cardiologist

Risk Factors for Early Stent Thrombosis (0-30 days)  
(Prevalence ≈ 1%)

**Clinical**
- Prior stent thrombosis
- Presentation with ACS or STEMI
- Multivessel PCI
- Diabetes
- Renal failure
- BMS implantation within last 30 days or DES implantation within last 12 months
- Noncardiac surgery early after PCI

**Procedural**
- Diffuse CAD
- Smaller post-PCI diameter
- Multiple stents
- Residual dissection
- Bifurcation stenting
- Large thrombus burden
- First-generation DES

Genotypes associated with impaired clopidogrel metabolism and platelet function
- Independent risk factors for early stent thrombosis

Prevalence of Genotypes and 1-Year Risk of Death, Stroke or MI: FAST-MI Trial (N=2208 French Patients)

**ABCB1 Alleles**
- 1 variant allele: 26.2%
- 2 variant alleles: 25.8%
- No variant alleles: 48.0%

**CYP2C19 Loss-of-Function Alleles**
- *2, *3, *4, and *5: 28.7%
- *2 variant alleles: 26.1%
- *2 & *3 variant alleles: 2.6%
- *4 variant alleles: 26.1%
- *5 variant alleles: 2.6%

Genotypes associated with impaired clopidogrel metabolism and platelet function
- Independent risk factors for early stent thrombosis

Prevalence of 1 *CYP2C19*2 Allele: U.S. Data

- African Americans: 33%
- Caucasians: 24%
- Mexican Americans: 18%
- Asians: 51%

Reduction in clopidogrel efficacy associated with *CYP2C19*2:
- 1 copy of allele = 47% reduction
- 2 copies = 65% reduction


3rd-Generation Thienopyridine

- Includes prasugrel and ticagrelor
- Achieves significantly higher levels of platelet inhibition than clopidogrel
- Prasugrel and ticagrelor unaffected by variants in the *CYP2C19* genotype
- Prasugrel unaffected by variants in the *ABCB1* genotype

Rates of Bleeding Events in Antiplatelet Drug Trials for ACS

TRITON-TIMI 38 Trial

- Prasugrel: 2.4%
- Clopidogrel: 1.8%
- HR 1.32 (1.03-1.68)

PLATO Trial

- Ticagrelor: 2.8%
- Clopidogrel: 2.2%
- HR 1.19 (1.02-1.38)

Most common bleeding location = Gastrointestinal


Thromboembolic Risk

Endoscopic Bleeding Risk
Endoscopy-Related GI Bleeding Risks

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  • Laser ablation and coagulation (1.1%)  
  • Treatment of varices (2.4-25.4%)  
  • Colonic (0.7-3.3%) |

Risk ↑ 2-12x:
• ↑ Age
• Polypectomy with cautery
• Removal of >1 polyp
• Pre-procedural warfarin


*Limited data, presumed negligible

Post-Polypectomy Bleeding
With and Without Clopidogrel Therapy

**Single-site (VAMC), retrospective case-control**

<table>
<thead>
<tr>
<th>Clopidogrel (n=142)</th>
<th>No Clopidogrel (n=1243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.6%</td>
</tr>
<tr>
<td>Immediate (at endoscopy)</td>
<td>P=0.1</td>
</tr>
<tr>
<td>Delayed (≤ 4 weeks)</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

100% on ASA

Continuation of ASA After Endoscopic Control of Peptic Ulcer Bleeding

Low-dose ASA (n=78)
- 10.3% (3.4-17.2%)
- ARR 4.9% (NNT=20)

Placebo (n=78)
- 5.4% (0.3-10.5%)
- ARI 7.7% (NNH=13)

30-day Recurrent Bleeding

30-day All-Cause Mortality


Management of Platelet-Directed Pharmacotherapy in Patients With Atherosclerotic Coronary Artery Disease Undergoing Elective Endoscopic Gastrointestinal Procedures

Richard C. Becker, MD, James Schermer, MD, Harold L. Dauerman, MD, Frederick Spencer, MD, Satish Rao, MD, Marc Sabatine, MD, David A. Johnson, MD, Frances Chan, MD, Neera S. Abraham, MD, and Eamonn M. Quigley, MD in collaboration with the American College of Cardiology and the American College of Gastroenterology
Current Best-Practice Recommendations for Secondary Prevention

1. Avoid cessation of all antiplatelet therapies after PCI with stent placement, when possible.
2. Avoid cessation of clopidogrel (even when ASA 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. In patients on dual therapy, ASA should be continued.
5. Resume thienopyridine and ASA drug therapy after the procedure once hemostasis is achieved.

EXCELLENT and PRODIGY Trial data suggest up to 6 months DAPT in most patients is sufficient.


Guidance on Stopping or Continuing Antiplatelet Therapy: Questions to Ask

- Why is the patient taking the drug?
  - Primary or secondary prevention?
- Is the patient at-high risk?
  - DES vs. BMS
  - Diabetes
  - Multivessel PCI
- Are there other known high-risk factors?
  - Genetic polymorphisms
  - Prior stent occlusion
Antiplatelet Pearls: Urgent Setting

- Patients who present with GIB leading to ACS should be scoped.
  - There is a high likelihood of finding an important lesion (HR 3.9; 95% CI: 1.8-8.5).
- Patients who present with hematemesis or hemodynamic instability should be scoped.
  - Leads to faster cardiac catheterization in 43%
- Peri-procedural risks are high in the first 24 hours of an ACS event but decline to 1-2% by 30 days.


Clinical Summary

- To minimize risk: One size does not fit all.
  - Primary vs. secondary cardioprotective regimen
  - Acute vs. elective
- Balance real risk of thrombosis with short-term cessation vs. endoscopic bleeding risk.
- Consult with cardiologist
  - Regarding early cessation of thienopyridine after 6 months of DAPT
  - Always continue ASA monotherapy with thienopyridine cessation
- Unknown “real-life” magnitude of GI bleeding risk associated with 3rd-generation thienopyridines.
  - Guidelines have yet to address this class of drugs

Discuss recommendations with your patient.