Objectives

- Review Bleeding Risk: Endoscopic Procedures and Interventions
- Risk Stratification of Low & High risk Thrombotic Conditions Encountered in Clinical Practice
- Review Newer AntiPlatelet Therapy Options and Novel Oral AntiCoagulants
- Discuss current concepts & best practice principles based on available data/guidelines
Balancing Risk of GI Bleeding vs Risk of Thromboembolic Events

**Bleed after endoscopy**

**Thromboembolic Event**

**Anti-Thrombotic Agents**

- **Anticoagulants**
  - Warfarin
  - Heparin
  - Low molecular weight heparin
  - Novel Oral AntiCoagulants (NOAC)

- **Anti-platelet agents**
  - Aspirin
  - Non-steroidal anti-inflammatory agents (NSAID)
  - Thienopyridine (clopidogrel, ticlopidine)
  - Glycoprotein IIb/IIIa receptor inhibitors
Focus On

- Aspirin
- Warfarin (vit K: II, VII, IX, X)
- Clopidogrel
- NOACs
  - Apixaban (Xa)
  - Rivaroxaban (Xa)
  - Dabigatran (Thrombin)
So How Should We Approach This?

- What do we know right now? (questions that have been answered)
- What to do with anti thrombotic agents pre and post elective endoscopy?
- What to do with anti thrombotic agents in a patient with GI bleeding?
- Review best practices for now… while we gain more experience with newer agents/more data becomes available

Surgical Interventions: Risk Stratification By Bleeding Risk

**Low risk**
- Endoscopy with biopsy
- Prostate or bladder biopsy
- EP study/RFA (including left sided ablation via single transseptal puncture)
- Angiography
- Pacemaker or ICD implantation (except complex anatomical setting e.g. congenital heart disease)

**High risk**
- Complex left-sided ablation: pulmonary vein isolation, VT ablation
- Spinal or epidural anesthesia; lumbar diagnostic puncture
- Thoracic surgery
- Abdominal surgery
- Major orthopedic surgery
- Liver biopsy
- Transurethral prostate resection
- Kidney biopsy

www.escardio.org/EHRA
Endoscopic Procedures: Bleeding Risk

<table>
<thead>
<tr>
<th>Higher-risk procedures</th>
<th>Low-risk procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypectomy</td>
<td>Diagnostic (EGD, colonoscopy, flexible sigmoidoscopy) including biopsy</td>
</tr>
<tr>
<td>Biliary or pancreatic sphincterotomy</td>
<td>ERCP without sphincterotomy</td>
</tr>
<tr>
<td>Pneumatic or bougie dilation</td>
<td>EUS without FNA</td>
</tr>
<tr>
<td>PEG placement</td>
<td>Enteroscopy and diagnostic balloon-assisted enteroscopy</td>
</tr>
<tr>
<td>Therapeutic balloon-assisted enteroscopy</td>
<td>Capsule endoscopy</td>
</tr>
<tr>
<td>EUS with FNA</td>
<td>Enteral stent deployment (without dilation)</td>
</tr>
<tr>
<td>Endoscopic hemostasis</td>
<td>Tumor ablation by any technique</td>
</tr>
<tr>
<td>Cystogastrostomy</td>
<td>Cystogastrostomy</td>
</tr>
<tr>
<td>Treatment of varices</td>
<td>Treatment of varices</td>
</tr>
</tbody>
</table>

Risk Factors: GI Bleeding

- Older age
- Cigarette smoking
- Sleep apnea
- Male gender
- CVA, DVT
- Prior GI bleeding
- Renal Insufficiency
Cardiovascular Conditions: Risk Status

<table>
<thead>
<tr>
<th>Higher-risk condition</th>
<th>Low-risk condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation associated with valvular heart disease, prosthetic valves, active</td>
<td>Uncomplicated or paroxysmal nonvalvular</td>
</tr>
<tr>
<td>congestive heart failure, left ventricular ejection fraction &lt; 35%, a history of a</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>thromboembolic event, hypertension, diabetes mellitus, or age &gt; 75 y.</td>
<td>Bioprosthetic valve</td>
</tr>
<tr>
<td>Mechanical valve in the mitral position</td>
<td>Mechanical valve in the aortic position</td>
</tr>
<tr>
<td>Mechanical valve in any position and previous thromboembolic event</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td>Recently (&lt; 1 y) placed coronary stent</td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
</tr>
<tr>
<td>Nonstented percutaneous</td>
<td></td>
</tr>
</tbody>
</table>

High Risk of Thromboembolic Event in Peri-endoscopic Period

- Atrial Fibrillation with h/o embolic events or valve disease
- Prosthetic Valve
- Coronary artery disease and stents
- Deep Venous Thrombosis/Pulmonary Embolus
- Stroke/Transient Ischemic Attack
- Hypercoagulable states
What Do We Know About Aspirin?

• **ASGE Guideline**: Continue ASA for GI procedures

• **Numerous studies**: ASA (and NSAIA) no significant increase in risk of GI bleeding for routine GI procedures

• **For High Risk** GI procedures: may elect to hold for 5-7 days if patient at low risk for CV/CNS event (or could continue it)

What About ADP Antagonists (Thienopyridines)?

• Block ADP-dependent aggregation of platelets -inhibit P2Y-12 receptor.

• **Clopidogrel, Prasugrel**

• Similar to Aspirin antiplatelet effect: can last for 5-7 days after the drug has been withdrawn

• No reversal agent
Coagulation Cascade: Warfarin & NOAC Sites of Action

• NOAC's work in one of 2 ways:
  - Rivaroxaban, Edoxaban and Apixaban: factor Xa inhibitors.
  - Dabigatran: directly inhibiting thrombin—DTI

Rivaroxaban, Edoxaban
Apixaban
Factor Xa
Inhibitors

Dabigatran
Directly inhibiting thrombin—DTI
NOACs
(Novel Oral Anticoagulation Agents)

• Used globally
• Stroke prevention in AF
• Prevention of DVT
• Treatment of DVT
• Preferred over Warfarin
  • Quick on/quick off
  • No monitoring needed
  • Fewer interactions

NOAC vs Warfarin

• NOAC: Proven “non-inferior” or superior
• No monitoring needed
• Faster onset of action (2-4 hrs)
  • Faster out of system (normal renal/hepatic function)
• Decreased risk of intracranial bleeding
• Apixaban 110 mg BID dose:
  • Decreased risk of bleeding into “any” site
• NOACs: associated with increased GI bleeding
Upper GI Bleeding: NOAC Rx

Lower GI Bleeding: NOAC Rx
Management Guidelines

- Elective Endoscopic Procedures

- Acute GI Bleeding

General Approach to Patients on Antithrombotics Who Need ELECTIVE Endoscopy

- Delay ELECTIVE endoscopy until patient at lower risk for thromboembolism

- Discuss with patient’s cardiovascular or neurovascular physician whether (or when) drugs can be stopped

- Guidelines from ASGE, ESGE are only suggestions - Need to weigh the risks and benefits for each individual patient
Aspirin

• Stop it Rarely, if ever…

How To Manage Warfarin Prior to Endoscopic Procedures?

• Avoid Vitamin K before elective procedures: delays therapeutic re-anticoagulation after procedure

• Warfarin can usually be stopped for 4-7 days and then be restarted the following day

• 1% risk of thromboembolic events after temporary warfarin cessation

• High risk patients for thromboembolic events: Bridge with LMW heparin.
NOACs

• No definitive guidelines… yet

• However, the fast onset and fast offset make cessation and resumption easier

• Usually 24 hours is enough time to hold, unless renal insufficiency or high risk procedure, in which 48 hours may be better.

• ALWAYS CHECK FIRST WITH PRESCRIBER

NOAC: Risk Mitigation Strategies

• Ensure NOAC indicated
• Modifiable risk factors
  • ETOH
  • NSAIDS
  • Antiplatelet agents
  • H. pylori
• PPI cover
• Colon and EGD screen
• Renal function adjustment
• BREAKING NEWS !!!!

NOAC: FIRST REVERSAL AGENT
RECENTLY APPROVED BY FDA !!

“...In trials, a five-minute infusion of Idarucizumab was able to reverse the blood thinning effects of Dabigatran in young adults, elderly patients and in those with mild renal/hepatic dysfunction...”

Glund S, Lancet 2015
Drugs, Dec 2015
Algorithm for the ELECTIVE Endoscopy Setting

- **Aspirin/NSAID**
  - Low Thrombotic Risk: Continue
  - High Thrombotic Risk: Consider Discontinuing

- **Thienopyridines (e.g., Clopidogrel)**
  - Low Bleeding Risk: Continue
  - High Bleeding Risk: Discontinue

- **Warfarin**
  - Low Thrombotic Risk: Continue
  - High Thrombotic Risk: Consider Discontinuing 1-3 Days Prior
  - High Bleeding Risk: Discontinue

- Patients on Dual Antiplatelet Therapy: Continue Aspirin
- Patients on Clopidogrel Monotherapy: Add Aspirin (when d/c Clopidogrel)

Management of Anti Thrombotic Agents in the Patient with GI Bleeding and Urgent/Emergent Endoscopy
Stopping or Reversing Antithrombotic Agents in the Acutely GI Bleeding Patient

• **Warfarin**
  - Consider holding warfarin
  - Consider vitamin K, FFP, Factor VIIa
    - AHA/ACC recommendations
      - Fresh frozen plasma (FFP) >>>>> high dose Vitamin K
      - Avoid high-dose Vitamin K (10 mg) in mechanical valves as may cause hypercoag state
        - Low dose Vitamin K (1-2 mg) may be fine

• **Antiplatelet agents**
  - Consider stopping drug
  - Consider platelet transfusion

Restarting Antithrombotic Agents s/p Endoscopic Hemostasis

• Resumption of aspirin + PPI has lower rate of recurrent peptic ulcer bleeding than switching to clopidogrel *(Chan, NEJM 2005)*

• Continuation of low dose aspirin after endoscopic hemostasis results in lower all cause mortality (12.9% vs 1.3%) and higher rebleed rate (10.3% vs 5.4%) *(Sung JJ, Ann Int Med 2010)*
Compared with holding warfarin for 30 days, restarting warfarin after 7 days was NOT associated with increased risk of GIB and was associated with decreased risk of mortality and thromboembolism.

Qureshi et al, Am J Cardiol 2013.

Asia-Pacific Working Group Consensus on Non-Variceal Bleeding (Sung JJ, Gut 2011)

- Among aspirin users with high cardiothrombotic risk & PUD bleeding, resume aspirin ASAP
  
- Because risk of rebleeding is greatest in 1st 72 hours, consider restart aspirin ~ 3 days after hemostasis

- Uncertain about clopidogrel, but perhaps restart in 3-5 days

- If dual therapy: No data; depends on type of stent and when placed
Patients on Dual Antiplatelet Therapy: Continue Aspirin
Patients on Clopidogrel Monotherapy: Add Aspirin (when d/c Clopidogrel)
What About Endoscopic Therapy?

• After all, we are endoscopists……

• We should be able to fix all bleeding!!!
Vivek Kaul, MD, FACG

Endoclips

What is the Efficacy of Endoscopic Therapy in This Setting?

• Retrospective studies suggest endoscopic therapy seems safe and effective (even with INR >4)

• Mechanical hemostasis (i.e. clips) preferred
  • Especially if will resume antithrombotic meds

• Colonoscopy with polypectomy was safe in a large cohort of consecutive patients while on Clopidogrel (Singh et al GIE 2009)
A retrospective study that included 123 patients receiving anticoagulants reported an acceptable PPB rate (2.5%) after resection of 225 polyps (mean and maximum sizes, 5 and 15 mm, respectively) followed in all cases by prophylactic endoclip placement.


Let’s simplify a bit and review some scenarios...
Thienopyridines (Clopidogrel)

- Always check with cardiologist/prescriber
- TYPE of stent
- AGE of stent
- Stroke history
- Usually if stopped is stopped for 5-7 days
- In nearly every instance, continue or substitute aspirin

GI Bleeding Management: NOAC Anemia/Guaiac + stools

- Semi-elective evaluation reasonable (~1-2wks)
- Colonoscopy +/- EGD
- Small bowel evaluation if needed
- Typically would continue NOAC (high risk condition)
- Monitor Hb/Hct
- Monitor for overt GI bleeding
GI Bleeding Management: NOAC

Overt/Major GI Bleeding

- Best managed as inpatient in hospital
- Standard resuscitation protocols
- NOAC should be held
- Antiplatelet Rx: review need per case
- Multidisciplinary consultation
- Urgent Endoscopic evaluation
- Angiographic embolization when needed
- **Reversal Agent for severe/life threatening bleeding**

Uncontrolled NOAC Associated GI Bleeding

- Topical thrombin & fibrin sealant
- Topical hemospray powder (n/a in USA)
- Systemic Tranexamic acid
- Prothrombin complex concentrate
- Recombinant activated factor VII
- Hemodialysis & Hemoperfusion (Dabigatran)
- **Reversal Agent for severe/life threatening bleeding**
- IR/Surgery
ANTIDOTES!

- Aspirin: Platelet transfusion
- Warfarin: Vit K, FFP
- Heparin: Protamine Sulfate
- Clopidogrel: Platelet Transfusion
- Dabigatran: Idarucizumab
- Other NOACs: none yet

Especially Difficult Scenarios!!

- Jehovah’s Witness patient
- The “recalcitrant Cardiologist”
- The Cardiologist cannot be found!
- LVAD patients
- The patient with acute MI
Endoscopy in the Setting of Acute Coronary Syndrome

• 1-3% of patients with ACS will have GIB
• GIB in setting of ACS has 4-7 fold increased risk of in-hospital mortality
• Risk of EGD and Colonoscopy 1-2% in setting of ACS
• Using intravenous PPI: reduced emergent need for EGD in mild-moderate UGI bleeding

Endoscopy in the Setting of Acute Coronary Syndrome

Which Risk Are We Willing to Take?

- Continue
  - Recurrent bleeding
  - Continuing bleeding
- Stop
  - ACS/stent thrombosis
  - CVA
  - DVT/PE

We can almost always stop GI bleeding while CVA/ACS are usually irreversible and devastating !!
Vivek Kaul, MD, FACG

Summary

• Low risk Endoscopy AND High risk for CVS/CNS event favors **continuing** antithrombotic agent

• High risk Endoscopy AND Low risk for CVS/CNS event favors **holding** antithrombotic agent

• High risk Endoscopy/High risk for CVS/CNS event?
  • Well, that’s what LEGENDS are made of !!!

• **Variables:** Duration of action of agent, availability of reversing agents, ability to more ‘easily’ control bleeding endoscopically, local expertise/resources all weigh in considerably

• Don’t under-estimate the efficacy of endoscopic therapy!

“...It is therefore strongly **recommended** that the gastroenterologist/endoscopist **never** be the one to instruct the patient to stop any anticoagulant or antiplatelet therapy. This should be a recommendation pending the patient finalizing approval by the prescriber of these agents — typically the cardiologist, neurologist, and vascular surgeon or primary care provider.”

Parth J. Parekh, MD, Jonathan Merrell, MD, Meredith Clary, MD, John E. Brush, MD, FACC, and David A. Johnson, MD, FACS, FASGE

*Am J Gastroenterol* 2014, 109:9 – 19
All Bleeding Eventually Stops....!!!!!

Thanks!!!

Interventional Endoscopy Team @ URMC