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Williamsburg, Virginia

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Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
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ABIM Board Certified physicians need to complete their MOC activities by December 31, 2022 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2023 for this activity.

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Include specific strategies or changes that you plan to implement. THESE ANSWERS WILL BE REVIEWED.
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Faculty: Mark S. Riddle, MD, DrPH
Moderator: Freddy Caldera, DO, MS, FACG
Thursday, September 1st at Noon Eastern and NEW! 8pm Eastern!

Week 36 – Thursday, September 8, 2022
Perianal Crohn’s Disease – Evolutions in Management
Faculty: Miguel D. Regueiro, MD, FACG
Moderator: Jill K. J. Gaidos, MD, FACG
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Disclosures

Neena S. Abraham, MD, MSc (EPID) MACG
Disclosure Company: Role OR
No relevant financial relationships with ACCME ineligible companies.

Bryan G. Sauer, MD, MSc (Clin Res), FACG
Revolo Biotherapeutics: Data Safety Monitoring Board
Takeda: Consultant

*All of the relevant financial relationships listed for these individuals have been mitigated

Update on the Management of Anticoagulants and Antiplatelets Guideline

Neena S. Abraham MD, MSc (EPID), MACG
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Mayo Clinic Kern Center for the Science of Health Care Delivery Research

@NeenaSAbrahamMD
19 Recommendations

- Acute & Elective Endoscopy
- Rigorous GRADE methodology
- >500 pages of EtD* tables/data
- EBM principles addressing:
  1) Temporary interruption of anticoagulant and antiplatelet drugs
  2) Reversal of anticoagulant and antiplatelet drugs
  3) Periprocedural heparin bridging
  4) Post procedural drug resumption

*EtD = Evidence to Decision

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**Acute GIB Highlights**
- Vitamin K antagonist (VKA) reversal
- DOAC reversal
- Use of platelet transfusion

**Elective Procedural Highlights**
- VKA Interruption vs. continuation
- Bridge Anticoagulation
- DOAC temporary interruption & resumption
- DAPT Management
- ASA Monotherapy Management (Secondary Prevention)
Rigorous GRADE* approach

- GRADE-Light
- GRADE-Like
- GRADE-ish

*Grading of Recommendations, Assessment, Development, and Evaluations

ACG Midwest Regional Postgraduate Course
August 27-28, 2022      Indianapolis, IN

- Clinical questions framed \textit{a priori} using PICO
  - population/intervention/comparator/outcome
- Systematic literature search (not search of convenience)
- GRADE assessments quantify the “risk of bias” of studies
- Certainty of evidence-- very low, low, moderate, or high:
  - Limitations in design & execution of studies
  - Indirectness
  - Inconsistency
  - Imprecision
  - Publication bias

Evidence summaries discussed considering:

- **Magnitude & direction** of effect
- **Certainty of evidence** on the balance b/w desirable and undesirable outcomes
- **Patient values and preferences**
- **Feasibility** of intervention/outcome
- **Acceptability** of intervention/outcome
- **Resource utilization**

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**ACG-CAG CPG Recommendations: Interpretation**

**Types of Recommendations:**

- **Strong:** “*We recommend* that...” (strong evidence)
  - Most patients would choose this action
  - Clinicians should provide it

- **Conditional:** “*We suggest* that...” (weak or low certainty evidence)
  - Patients may or may not want this action
  - Multidisciplinary discussion
  - Help patients make decisions consistent with their values

@NeenaSAbrahamMD  
Abraham & Barkun et al, Am J Gastroent 2022
2022 Management Acute Anticoagulant GIB

Initial assessment

Severity of bleeding

Life-threatening bleed

No life-threatening bleed

Management based on the type of anticoagulant

Patient with acute GIB bleeding on an anticoagulant

Patient on VKA; consider PCC

Patient on a DOAC: consider DOAC-specific direct reversal agent or PCC

Patient on VKA: suggest against FFP or Vit K; cannot recommend for or against PCC

Patient on a DOAC: suggest against drug-specific reversal agent or PCC

Major clinically overt or apparent bleeding with:

- Hypovolemic shock or severe hypotension requiring pressors or surgery
  - or associated with a decrease in Hg of >5 g/dL
  - or requiring transfusion of ≥ 5 units of packed red blood cells
  - or causing death
Warfarin: Acute Reversal

- **ASGE (2016)**
  - 4-factor prothrombin complex concentrate (PCC) with factors II, VII, IX and X
  - Vitamin K (5-10 mg by slow IV)
  - **No FFP**
    - Large volumes & transfusion-associated pulmonary edema

- **ACG-CAG CPG (2022)**
  - **No FFP**
  - **No Vitamin K**
  - PCC preferred over FFP with supratherapeutic INR/life-threatening GIB
    - Rapid & reliable correction of INR
    - **Conditional recommendation, very low certainty of evidence**

**@NeenaSAbrahamMD**

*Abraham & Barkun et al, Am J Gastroent 2022; Acosta & Abraham et al, Gastroint Endosc 2016*

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Wait, What?... NO Vitamin K?

**Vit K 1-2 mg used when INR ≥ 10 restores therapeutic-level anticoagulation (INR 2.0-3.0)***

**Clinically significant GI bleeding requiring therapeutic intervention:**
- Does not achieve rapid hemostasis
- Limited value in the acute setting

**When:**
- Use Vitamin K in the setting of supratherapeutic INR

**IF:**
- Plan = reverse anticoagulant effect slowly (2-weeks)
- Objective is to stop VKA altogether
- Do not use in this setting without consulting the patient’s hematologist or cardiologist

**ACG-CAG CPG:**
- We suggest against the use of vitamin K
  - **(conditional recommendation, very low certainty of evidence)**

**@NeenaSAbrahamMD**

*Abraham & Barkun et al, Am J Gastroent 2022*
Warfarin Resumption

What did ACG-CAG CPG guideline panel think?
- Limited high-certainty evidence (acute & elective setting)
- We could not reach a recommendation for or against resuming warfarin the same day as the procedure vs. 1-7 days after the procedure

What do I do?
- The heart always wins!
- Balance risk of thromboembolism & further bleeding
- Resume w/in 4-7 days from drug discontinuation; same day if diagnostic
  ➢ 1% embolic risk

Abraham & Barkun et al, Am J Gastroent 2022

No routine use of DOAC reversal agents

- Avoid andexanet alfa
  - Single published study with serious risk of bias & no control group; little GIB data
  - Higher risk of thromboembolism & cost of drug ($49,500)
  - Could be considered w/ life-threatening GIB in hospitalized patients if rivaroxaban or apixaban taken w/in last 24 hours
- Rarely need idarucizumab
  - Few patients taking dabigatran; could be considered w/ life-threatening GIB in hospitalized patients
- Possibly a role for PCC?
  - Two cohort studies* with comparator arms (no PCC); both with limitations
  - Systematic reviews of mainly low-quality, single arm cohort studies ^
  - “Better bad choice” in the setting of life-threatening hemorrhage?

*Schulman Thromb Res 2017; *Smythe J Thromb Thrombolysis 2015; ^da Luz Transfusion 2017
DOAC Resumption after GIB

- Not addressed in ACG-CAG CPG
  - No high-certainty data in the GIB setting

What do I recommend?
- Resume DOAC day after the procedure in MOST
  - Providing endoscopic hemostasis had been achieved
  - Would not hold DOAC post-procedure > 48-72 hours
    - Timing of resumption dictated by the risk of post-procedural bleeding & multidisciplinary discussion

^ Barkun et al. 2022 (DDW 2022); Abraham, Barkun et al. Am J Gastro 2022

Management Acute Antiplatelet GIB

Routine Platelet Transfusion
- Mortality increase with GIB (OR = 5.6, 95% CI: 1.5-27.1)
- Mortality increase with CABG (OR= 4.8, 95% CI: 1.7-13.7)
- Mortality increase with ICH (OR = 2.1, 95% CI: 1.2-3.6)

Interrupt Cardiac ASA Used for Secondary Prevention
- Reduced mortality with ASA continuation
- ASA discontinued at presentation? Resume w/in 24 hrs. of successful endoscopic hemostasis
- ASA for primary prevention- little CV benefit & high GIB risk

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Abraham & Barkun et al, Am J Gastroent 2022
**Elective Endo? Do No Harm**

*Defer elective exams until the patient is no longer high-risk*

Ex: CRC screening/surveillance, Family History CRC, FIT + (can wait up to 9 months); DGBI; GERD/Barrett's Esophagus or cirrhosis screening/surveillance, etc.

<table>
<thead>
<tr>
<th>Patients &lt;3 months out from:</th>
<th>Patients with PTCA/PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Ischemic Attack</td>
<td>Drug-eluting stent (&lt;6 months)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Bare-metal stent (&lt;4 weeks)</td>
</tr>
<tr>
<td>Lower extremity deep vein thrombosis</td>
<td>ACS plus drug-eluting stent (&lt;6 months)</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>ACS plus bare-metal stent (&lt;2 months)</td>
</tr>
<tr>
<td>Acute Coronary Syndrome (ACS)</td>
<td></td>
</tr>
</tbody>
</table>

**Low Risk Procedures: Continue Warfarin**

- 5 cohort studies
  - **Favorable profile for continuation** *(very low certainty evidence)*
  - Limited Data: Imprecision, lack of standardized procedure technique & adjustment for confounders
- GI Bleeding
  - Estimating risk limited by few studies (w/ controls), small sample size & rare events
  - Pooled data (5 studies) – 0/239 bleeding events (95% CI; 0%-12.35%) with *continuous warfarin*
- Thromboembolic Events
  - Single small cohort study - **nonsignificant reduction of thromboembolic events with uninterrupted (0/43) vs. interrupted (1/19).**

### Procedural Risk of Bleeding

<table>
<thead>
<tr>
<th>High bleeding risk procedures (30-d risk of major bleed &gt;2%)</th>
<th>Low/moderate bleeding risk procedures (30-d risk of major bleed ≤2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polypectomy (≥1 cm)</td>
<td>Endoscopy with/without biopsy</td>
</tr>
<tr>
<td>PEG/PEJ placement</td>
<td>Colonoscopy with/without biopsy</td>
</tr>
<tr>
<td>ERCP with biliary or pancreatic sphincterotomy</td>
<td>Flexible sigmoidoscopy with/without biopsy</td>
</tr>
<tr>
<td>EMR/ESD</td>
<td>ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy, tissue sampling, or treatment of choledocholithiasis</td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>EUS without FNA</td>
</tr>
<tr>
<td>Endoscopic hemostasis (excluding APC)</td>
<td>Push enteroscopy and diagnostic balloon-assisted enteroscopy</td>
</tr>
<tr>
<td>Radiofrequency ablation</td>
<td>Enteral stent deployment</td>
</tr>
<tr>
<td>POEM</td>
<td>Argon plasma coagulation</td>
</tr>
<tr>
<td>Treatment of varices (including variceal band ligation)</td>
<td>Balloon dilation of luminal strictures</td>
</tr>
<tr>
<td>Therapeutic balloon-assisted enteroscopy</td>
<td>Polypectomy (&lt;1 cm)</td>
</tr>
<tr>
<td>Tumor ablation</td>
<td>ERCP without biliary or pancreatic sphincterotomy</td>
</tr>
<tr>
<td>Cystgastrostomy</td>
<td>Marking (including clipping, electrocoagulation, tattooing)</td>
</tr>
<tr>
<td>Ampullary resection</td>
<td>Video capsule endoscopy</td>
</tr>
<tr>
<td>Pneumatic or bougie dilation for achalasia or esophageal strictures</td>
<td></td>
</tr>
<tr>
<td>Laser ablation and coagulation</td>
<td></td>
</tr>
</tbody>
</table>

Abraham, Barkun et al. Am J Gastro 2022

### Advanced Procedures: Interrupt Warfarin

Absence of studies in advanced endoscopic procedures limits our ability to comment on safety of proceeding without interrupting warfarin.

For Advanced Endoscopic Procedures:
May be appropriate to temporarily interrupt warfarin for 5 days WITHOUT bridging heparin.

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Abraham & Barkun et al, Am J Gastroent 2022
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**ACG-CAG CPG:**

**We suggest against bridging anticoagulation for patients** holding warfarin undergoing elective/planned endoscopic GI procedures

*(conditional recommendation, very low certainty of evidence)*

**CONSIDER IN***:

- Patients with mechanical valves
- AF with CHADS2 score >5
- History of thromboembolism during temporary interruption of VKAs
- Certain CV surgery (i.e., cardiac valve replacement, carotid endarterectomy, major vascular surgery).

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**Elective Endo: Timing of Warfarin Resumption**

- We could not reach a recommendation for or against resuming warfarin on the same day vs 1-7 days after the procedure.
  - No studies comparing same-day resumption of warfarin with a resumption in 1-7 days after an elective endoscopic procedure.
- Published literature limited by:
  - Lack of a comparator group
  - Lack of diversity of populations & endoscopic procedures
  - Use of bridging therapy
  - Outcomes assessment occurring at variable follow-up times

- Balance risk of thromboembolism & further bleeding
- Resume w/in 4-7 days from drug discontinuation; same day if diagnostic
  - 1% embolic risk
**Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) Cohort Study (N=3007)**

- 23 clinical centers in Canada, the United States, and Europe; n = 3007 atrial fibrillation patients

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Surgical Procedure-Associated Bleeding Risk</th>
<th>Preoperative DOAC Interruption Schedule</th>
<th>Postoperative DOAC Resumption Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean total temporary interruption of 3.9 days ± 1.6 day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>High</td>
<td>Day -5, Day -4, Day -3, Day -2</td>
<td>Day -1</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolagatran trebbinilate ( fondaparinux sodium)</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran etexilate (2 mg/kg)</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- No DOAC on shaded days & the day of the elective surgery or procedure.
- **ALL endoscopic procedures are considered low-risk (like the BRIDGE Trial^).**

Douketis JD et al, JAMA Internal Medicine 2019;^ Douketis JD et al, NEJM 2015

**PAUSE Post-Hoc Analysis of GI Data (n= 556 endoscopic procedures*)**

DOACs: Mean total temporary interruption of 3.9 days ± 1.6 day

- Pre-procedure- 2.0 ± 0.5 days (including the day of procedure)
- Post-procedure- 1.9 ± 1.5 days (including post-endo time elapsed on the day of the procedure)

**30-Day Outcomes:**

- GI bleeding – 2.5% (95% CI: 1.4% to 4.2%); N=14
  - 50% (n=7) major bleeding episodes (hospitalization/endo/blood)
- Thromboembolism – 0.7% (95% CI: 0.2% to 1.6%)
- Mortality - 0.5% (95% CI: 0.2% to 1.6%)

*Mostly EGD & colonoscopy with/without biopsy & polypectomy; very few advanced procedures

^ Barkun et al. 2022 (DDW 2022); Douketis JD et al, JAMA Internal Medicine 2019
How to Operationalize Recommendations

1. Hold DOAC for 2-3 days (including the day of the procedure)
   • 1 day before + day of procedure = 2 days in MOST
   • 2 days before + day of procedure = 3 days for advanced procedures

2. Resume DOAC day after the procedure in MOST
   • No studies comparing same-day resumption of DOAC with the resumption in 1-7 days after a temporary interruption in the elective endoscopic setting.
   • DOAC resumption post-procedure was 1.9 days ± 1.5 days providing endoscopic hemostasis achieved^ 
   • Would not hold DOAC post-procedure for more than 48-72 hours considering:
     ➢ Short half-life of the drug
     ➢ Risk of bleeding vs. risk of thrombosis with extended interruption

^ Barkun et al. (Am J Gastroenterol; in review); Abraham & Barkun et al., Am J Gastroenterol; Douketis JD et al, JAMA Internal Medicine 2019

No Change: DAPT Management

DAPT for secondary cardiovascular prevention - we suggest temporary interruption of the P2Y12 inhibitor while continuing ASA (conditional recommendation, very low certainty of evidence)

➢ Clopidogrel & Ticagrelor - 5 days*; Prasugrel – 7 days *

➢ Similar rates of delayed post-polypectomy bleeding
  ➢ 2 RCTs (Chan et al. & Won et al.)
  ➢ Systematic Review Observational Studies (Eisenberg et al.)
  ➢ Trend toward fewer cardio-thromboembolic events with thienopyridine interruption in patients who took concomitant ASA

*FDA Recommendations

**DAPT Interuption vs. Continuation**

- Systematic review of observational studies examining periprocedural AP regimens in patients with DES on DAPT
  - 6% late stent thrombosis (6/94) with thienopyridine interruption, but continued ASA occurred within 10 days, while only 2/94 (2%) occurred within 5 days.
  - High rates of late stent thrombosis (79%) with discontinuation of both agents or discontinuation of ASA (67%).

Eisenberg MJ et al, *Circulation* 2009

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**Elective Endo: Thienopyridine (P2Y12) Resumption**

- We could not reach a recommendation for or against resuming the P2Y12 inhibitor on the same day vs 1-7 days after the procedure.
  - Theoretically, earlier resumption would reduce thrombotic events and increase post-procedural bleeding— but no studies providing relevant evidence were identified.

- Prudent to resume thienopyridine with immediate endoscopic hemostasis ^ after considering:
  - Risk of delayed postprocedural bleeding, thrombosis, and patient preferences
  - Decisions regarding procedural timing and drug resumption in high-risk thromboembolic patients are ideally ascertained on a case-by-case basis in a multidisciplinary fashion.

ASA Monotherapy*

- For patients on ASA 81-325 mg/d (monotherapy) for *secondary CV prevention, we suggest against interruption of ASA* (conditional recommendation, very low certainty of evidence).
  - Bleeding risk is very low in diagnostic endoscopic procedures, biopsies, and most polypectomies.

- Interruption of ASA could be considered in the removal of larger and more complex polyps, and procedures with the highest bleeding risk.
  - With consideration of:
    - Patient CV risk
    - Patient preference regarding cardiovascular vs bleeding events
    - Patients on ASA as primary prevention should have ASA stopped before higher-risk endoscopic procedures.

Abraham & Barkun et al, *Am J Gastroent* 2022

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Take Home Points: Acute GIB

**Triage based on life-threatening GIB vs. not**
- Life Threatening = Hospitalized, Pressors, Rule of 5

**VKA Supratherapeutic Bleed**
- No FFP
- No Vit K
- Choose PCC over FFP

**DOAC GIB**
- No routine use of reversal agents
- Life-threatening GIB? Consider reversal agent if DOAC is taken w/in 24 hours (DOAC-specific or PCC)

**Antiplatelet GIB**
- No routine platelet transfusion (consider if platelets <100,000 per microliter)
- Continue ASA prescribed for secondary prevention

Abraham & Barkun et al, *Am J Gastroent* 2022
Take Home Points: Elective Endo (1)

Do no harm!
- Know the high-risk CV patient
- Defer elective procedures until a patient is no longer high-risk
- Multidisciplinary discussions/shared decision-making useful

VKA management
- Low post-procedural bleeding risk? Continue VKA
- High post-procedural bleeding risk? Hold X 5 days & resume with immediate hemostasis

Bridge anticoagulation with LMWH
- Unnecessary for most patients when VKA interrupted
- Consider with mechanical valves and in select patients at high thromboembolic risk
- Unnecessary for patients on DOACs

Abraham & Barkun et al, Am J Gastroent 2022

Take Home Points: Elective Endo (2)

DOAC management
- Temporary Interruption 2 days (incl. procedure day) in most
- Advanced procedure 3 days of interruption (incl. procedure day)
- Resume the day after the procedure
- Multidisciplinary discussions/shared decision-making

DAPT management
- Hold thienopyridine pre-procedure & continue cardiac ASA
  - Clopidogrel & Ticagrelor - 5 days; Prasugrel – 7 days
- Resume DAPT with immediate hemostasis

ASA monotherapy (secondary prevention)
- Continue in the peri-procedural setting

Abraham & Barkun et al, Am J Gastroent 2022
Questions and Answers

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