Balancing Act: Managing Active Bleeding and Risk of Thrombosis in the Hospital

Neena S. Abraham MD, MSc (EPID), MACG

Professor of Medicine, Mayo Clinic

Cardio Gastroenterology Clinic, Mayo Clinic

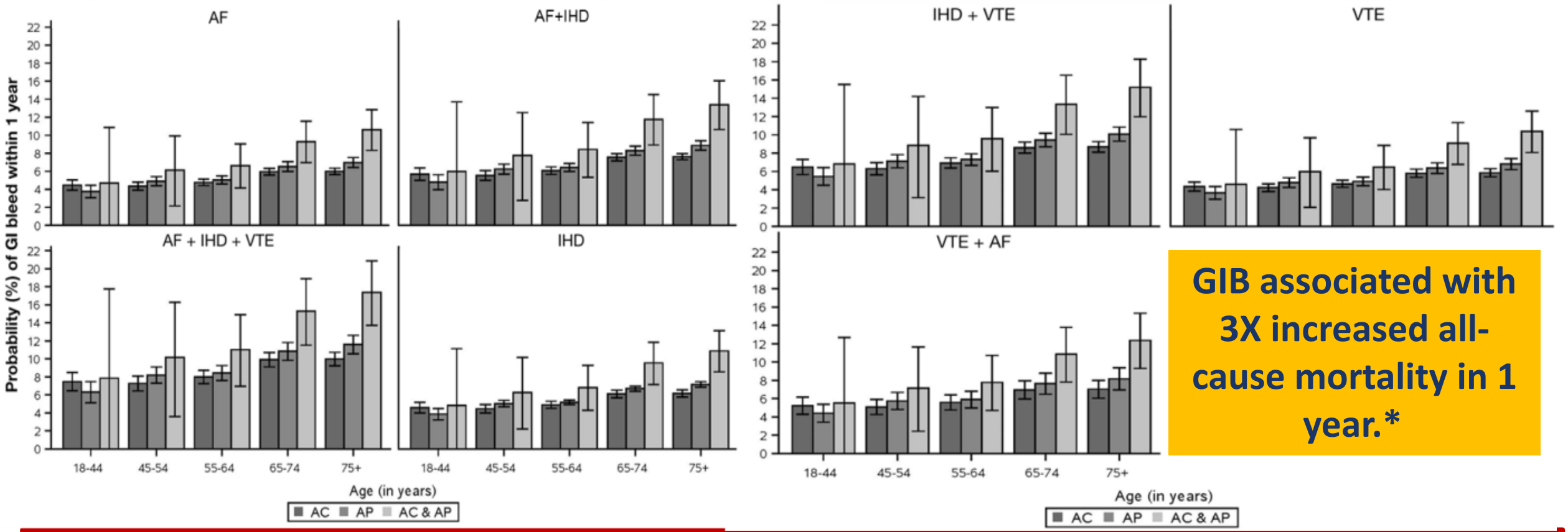
Division of Gastroenterology & Hepatology, Phoenix/Scottsdale, AZ

Division of Health Care Policy, Rochester, MN

Director, ACG Institute for Clinical Research & Education

X @NeenaSAbrahamMD

1- Year Risk of GIB: Age Stratified Analysis



GIB associated with 3X increased all-cause mortality in 1 year.*

- **GIB increases with age in all subgroups of cardiac patients (N=311,211).**
- **Patients aged >75 on concomitant anticoagulants & antiplatelets GIB risk increases from 10% to 17.5%.**

Abraham NS et al, *Clinical Gastroenterology and Hepatology* 2020; *Koskinas et al, *Circulation: Cardiovasc Interv 2015*

Higher thromboembolism (TE) risk	Higher recurrent GIB/transfusion
90 days from ACS, PCI, CVA	**Heparin/LMWH bridging** - mechanical heart valves, multiple co-morbidities, recent TE events
Extended temporary interruption - > 48 hours DOAC - > 7 days warfarin (from initial interruption)	**Rivaroxaban >> Apixaban** - Higher risk of recurrent GIB
Reversal agents **-** Vit K, PCC, DOAC-specific	**Warfarin with advanced age, low albumin and renal dysfunction >> DOAC users** with similar profile
Mechanical heart valves	
Clot with previous interruption (**thrombophilia**)	
30 days after **CV surgeries** (CABG etc.)	
Platelets transfusion increases mortality 5X	

Multidisciplinary discussion helpful for higher risk CV patients

GIB: Real Risk of Thromboembolism

- 30-day risk with temporary interruption <2 days: 0.7%
- 30-day mortality risk with temporary interruption: 0.5%
  - Risk is related more to underlying co-morbidities than interruption
- 30-day risk with temporary P2Y12 interruption risk: 1%
  - Critical you continue cardiac ASA during interruption
- **Increased risk associated with deviation from recommended protocols in the setting of acute GIB**

Case 1

- 83-year-old man with pancolonic diverticulosis, ischemic heart disease (remote NSTEMI), and atrial fibrillation on **apixaban & ASA**.
- 3 episodes of large volume, painless rectal bleeding; felt dizzy and faint, transported to ED.
- Admission labs: Hg of 6.6 g/dL (baseline of 12.1 g/dL), Hct 29.7%.
- Transfused 5 units PRBC and 3 L NS and remained tachycardic. Transferred to the ICU for further management.
- **How should you manage this patient's DOAC-related bleed?**

Step 1: Triage

Major clinically overt or apparent bleeding with (any):

- **Hypovolemic shock or severe hypotension requiring pressors** or surgery
- **Decrease in Hg of >5g/dL***
- Requiring **transfusion of ≥5 units*** of packed red blood cells
- At risk of causing death

The rule of 5

Life-Threatening GIB? DOAC reversal agents

- **Andexanet alfa**
  - Higher risk of thromboembolism (10% -12%) and costly ($22,500)
  - Consider with life-threatening GIB if rivaroxaban or apixaban w/in 24 h
- **Idarucizumab**
  - On dabigatran- could be considered with life-threatening GIB w/in 24 h
  - Thromboembolism risk 5%-6%
- **Prothrombin Complex Concentrate (PCC)**
  - Clotting factors II, VII, IX, and X, Protein C and Protein S
  - Cohort studies with comparator arms (no PCC) & Systematic reviews
  - **“Better choice” in the setting of a life-threatening hemorrhage**
  - Low risk of thromboembolism (3%-5%)

Management of Acute Antiplatelet (APA) GIB

NO Routine Platelet Transfusion

- ❑ Mortality increase with GIB (OR = 5.6, 95% CI: 1.5-27.1)
- ❑ Consider if platelets <50K with multidisciplinary discussion

NO Interruption of Cardiac ASA (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*

Case 2

- A 63-year-old woman with **mechanical mitral valve** on **warfarin therapy and PPI**. Given amoxicillin by her primary care doctor.
- Copious melena over 48 hours. Resuscitated with fluids but remains tachycardic.
- Hg of 7.2 g/dL (baseline of 13.7 g/dL), Hct 30.7%, Cr 2.3, and INR 4.6.
- **How should you manage this patient's supratherapeutic INR before endoscopy?**

Warfarin: Acute Reversal

- **ACG-CAG CPG (2022)**
  - **No** FFP -- Large volumes and transfusion-associated pulmonary edema
  - **No** Vitamin K--- does not work fast enough (endoscopy within 24 hours)
  - **PCC preferred over FFP with supratherapeutic INR/life-threatening GIB**
    - **Rapid and reliable correction of INR**

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

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

Don’t Wait to Normalize INR

INR at time of endoscopy is not predictive of re-bleeding

- **INR >1.5 associated with 2X increased mortality but not re-bleeding risk (mortality related to co-morbidity, not bleeding)**

Normalizing INR does not reduce re-bleeding but delays endoscopy

Mean INR 1.8 (1.3-2.7)

- **Rebleeding rate similar with and without reversal: 24.7% vs 30.0% (p=0.54)**
- **Delay in endoscopy: 20.9 h vs 73.6 h (p<0.0001)**
- **Important stigmata in 83% of cases**

Endoscopic therapy effective with moderately elevated INR (≤ 2.5)*

Barkun A et al, Am J Gastroenterol 2004; Acosta and Abraham et al, Gastrointest Endosc 2016*

Who Needs to be Bridged?

LMWH bridging during warfarin interruption increases post-procedural bleeding without reducing thromboembolism.

- **BRIDGE RCT (n=1813) & PERIOP-2 RCT (n=1471)**
- **5 Observational Studies**

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).**

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

Warfarin, DOAC and APA Resumption

- No high-certainty data in the setting of GIB
- Next day in most
- Would not hold warfarin, DOAC or APA post-procedure >48-72 hours
- Timing of resumption dictated by the risk of post-procedural bleeding and multidisciplinary discussion

Decrease Future GI Bleeding Risk

- **PPI**
  - Teach them how to take them
- **Switch rivaroxaban to apixaban**
  - Decreases GIB by 64%
- **Check for *H.pylori* and eradicate**
  - Confirm eradication
- **No NSAIDs indefinitely**

Case 3

- A 58-year-old man with uncontrolled HTN, hyperlipidemia, T2DM, CKD (eGFR <30 mL/min) had a PEA arrest and NSTEMI.
- PTCA showed a mid-LAD lesion, and DES was placed; DAPT was initiated.
- In ICU, the patient developed hematemesis with a 3 gm drop in Hg. Resuscitated with fluids and 3 units PRBCs.
- **How should you manage this patient's DAPT before the urgent EGD?**

What are the clinical issues to consider?

- Recent NSTEMI with PEA on DAPT for DES (4 weeks ago)
- Acute UGIB with hemodynamic instability, transfusions
- Needs urgent EGD and hemostasis
- **What are the options for safely interrupting DAPT while minimizing the risk of DES occlusion?**
  - Multidisciplinary conference– CV, GI, Hematology

Wouldn't it be nice if there was a way to "bridge DAPT"??

Options for APA "Bridging"

- **Options*:**
  - **IV Bivalirudin– a direct thrombin inhibitor (anticoagulant)**
    - High risk of bleeding, especially in patients with eGFR <30 ml/min, uncontrolled HTN, and a history of bleeding (OUR PATIENT!)
  - **IV Cangrelor– an adenosine triphosphate analog (antiplatelet)**
    - Selectively blocks $P2Y_{12}$ receptor-mediated platelet activation (like clopidogrel, prasugrel, and ticagrelor); adjunct to PCI
    - Blockade is direct, reversible, and competitive; short $T_{1/2}$ (3-6 minutes)
    - No renal excretion (safe for CKD)
    - Stable antiplatelet effect with infusion; platelet recovery in 30-60 min with discontinuation.

***No studies in the setting of acute GIB/Endoscopy. Extrapolation from post PCI bleeding studies. Multidisciplinary discussion recommended.**

CardioGI Pro Tips: CV Devices and GIB

- **LVADs**
  - **Thromboembolism & bleeding risk with HeartMate 3 << HeartMate 2**
  - Can lower target INR in HeartMate 3 to 2.0-2.5 safely
  - Drop ASA from 325 mg to 81 mg; PPI is critical
  - Start with push enteroscopy & colonoscopy for bleeds/IDA, then VCE
  - Tend to recurrently form AVMs in the same place (Heyde's syndrome); target approach
  - **No need to hospitalize, safely done as an outpatient, need a perfusionist**
- **LAAO/ Watchman**
  - Consider with any AFIB patient with **recurrent GIB after VKA to apixaban switch and/or dose reduction**
  - Post insertion after 6-week echo, can **tailor AT approach** (AC mono, AP mono, none)
- **TAVR**
  - Consider in any patient with Aortic Stenosis and recurrent GIB secondary to AVMs
  - Non-critical stenosis still benefit
  - After 6 weeks of DAPT, can reduce to AP monotherapy (clopidogrel/ASA) or none

To TEG or Not to TEG?

- **Thromboelastography (TEG) and rotational thromboelastometry (ROTEM*) cannot be reliably used* to predict or monitor anticoagulant reversal in patients with gastrointestinal bleeding.**
  - No validated sensitive or specific thresholds to guide reversal decisions
  - The sensitivity varies by agent, particularly for direct oral anticoagulants (DOACs).

- **The American College of Cardiology and the American College of Gastroenterology recommend using standard laboratory tests (INR for vitamin K antagonists and drug-specific anti-Xa levels for DOACs) to guide reversal**

- TEG/ROTEM-guided transfusion strategies may reduce unnecessary blood product use in certain populations (e.g., patients with cirrhosis)
  - ***BUT these assays do not reliably predict bleeding control, the need for reversal, or major clinical outcomes in gastrointestinal bleeding.***

Hemostatic Methods

- **Thermal therapy safe and effective**
  - 91% durable hemostasis; 95% technical success
  - No increased risk of rebleeding
  - OK in AC patients with INR ≤ 2.5; OK in APA patients with drug interruption
- **APC is safe & effective for AVM bleeding**
  - Low risk of post-procedural bleeding
  - Obliterate non-bleeding AVMs in patients who require chronic antithrombotic therapy; *may change clinical course with drug resumption*
- **Mechanical Hemostasis**
  - 100% primary hemostasis
  - Both OTSC and TTS have 35% re-bleeding rate (technical failure)
- **TC-325?**
  - First choice with malignant bleeding
  - Insufficient data in patients on chronic APA/ACA

Take Home Points (1): GIB Management

- **Anticoagulant? TRIAGE**
  - Life Threatening = Hospitalized, Pressors, Rule of 5
  - **Limit the use of reversal agents to life-threatening bleeds**
- **Warfarin Supratherapeutic Bleed**
  - No FFP or Vit K-- Choose PCC
- **DOAC GIB**
  - No routine reversal agents
  - Life-threatening GIB? Consider DOAC-specific or PCC if DOAC was taken within 24 hours
- **Platelet transfusions increase mortality 5X in GIB**

Resume drug with immediate hemostasis. Next day in most.
Avoid holding >48 hours without multidisciplinary discussion

Take Home Points (2): GIB Management

- **Pro Tips for CV devices (LVADs, TAVRs, and LAAOs) worth knowing**
- **NO thromboelastography (TEG)/rotational thromboelastometry (ROTEM)**
  - Do not reliably predict anticoagulant level, predict rebleeding or need for reversal agent.
  - Do NOT predict GIB outcomes.
- **Aggressively mitigate risk factors for re-bleeding**
  - Switch from Rivaroxaban to Apixaban
  - PPI (teach them how to take it!)
  - Eradicate *H.pylori;* NO NSAIDS
- **Hemostatic methods**
  - Thermal and Mechanical safe and effective
  - Insufficient data for TC-325

TAKE HOME POINTS (3)
Errors Increasing Thromboembolism

- Routine use of a reversal agent
- Platelet transfusion
- Discontinuation of cardiac ASA
- Failure to promptly restart antithrombotic agent when immediate hemostasis is achieved
- Multidisciplinary discussions for very high-risk cardiac patients
  - Recent ACS event
  - LVAD bleeders
  - History of a clot with drug interruption
- **ALWAYS err on the side of safety** *** **the heart always wins** ***