Periprocedural Anticoagulation Strategies for Interruption, Resumption and Risk Avoidance

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Learning Objectives

1. **Anticoagulant-related GIB: the real risk**

- ❑ Proactive strategies to decrease risk & improve outcomes

2. **Management Paradigms: Case-Based**

- ❑ Resuscitation, reversal, and restarting drugs
- ❑ Preview upcoming ACG-CAG multidisciplinary guideline (4/2022)

3. **Clinical Pearls from the Mayo CardioGI clinic**

- ❑ Actionable tips you can use immediately in your practice

BY 2030…

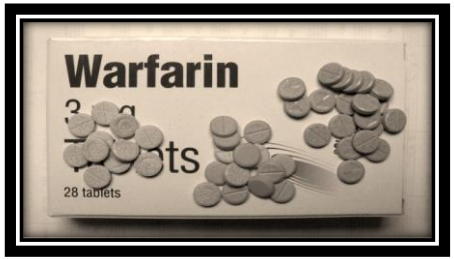
- Cardiovascular disease will increase by >10% as the population ages

- >40% of US adults with ≥1 form of cardiovascular disease
  - ❑Increased use of antiplatelet & anticoagulant drugs
  - ❑ Drug-related GIB hospitalization-Warfarin (#1) & Antiplatelets (#3)
  - ❑ Narrow therapeutic window in elderly cardiac patients & with multiple co-morbidities

Abraham NS, *Clinical Gastroenterol Hepatol* 2013; Heidenreich et al, *Circulation* 2011; Doyle et al. *J Am Coll Cardiol* 2009 ; Abraham NS. *J Am Gastrol* 2016; Budnitz et al. *NEJM* 2011; Koskinas et al. *Circ Cardiovasc Interv* 2015

MOST WANTED

THE ANTICOAGULANT BLEEDING GANG



GANG LEADER:
Warfarin

NEW MEMBERS:

Factor IIa Inhibitor (direct thrombin inhibitor):
Dabigatran (Pradaxa®)

Factor Xa Direct Inhibitor:
Rivaroxaban (Xarelto®)
Apixaban (Eliquis®)
Betrixaban (Bevyxxa®)

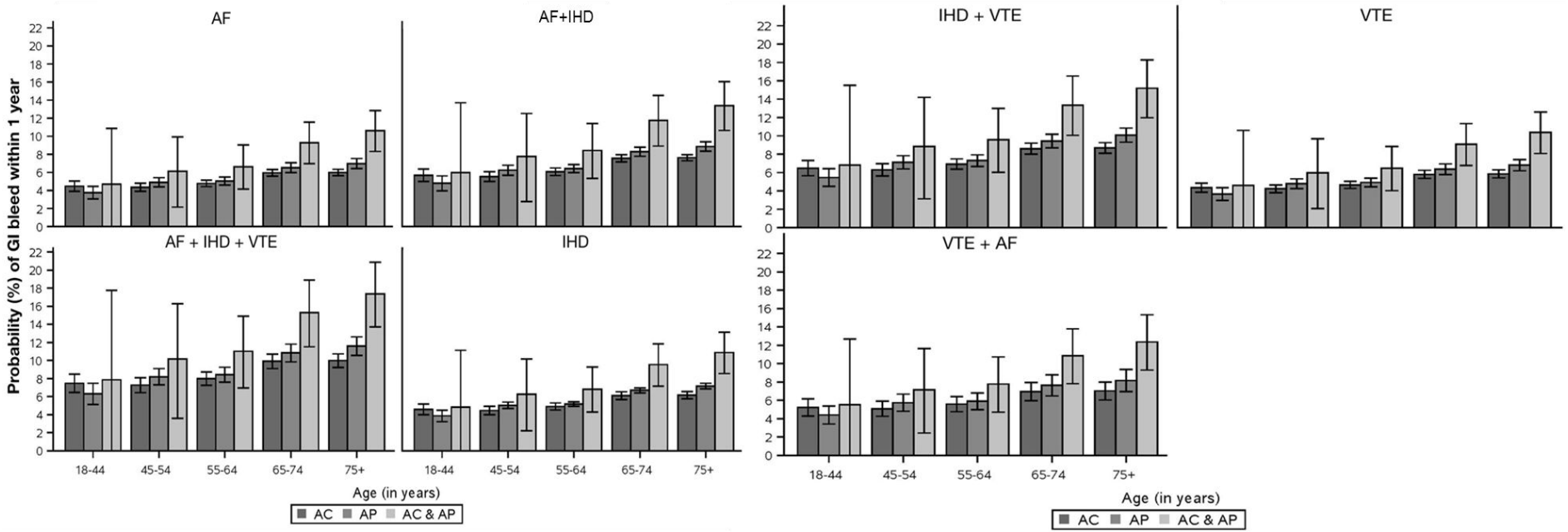
REWARD FOR CAPTURE

GIB Prediction Using Common Scores

	C statistic (95% CI) (N=39,539)
CHA_2DS_2-VASc	0.65 (0.63, 0.66)
$CHADS_2$	0.64 (0.62, 0.65)
HAS-BLED	0.64 (0.62, 0.66)
ORBIT	0.60 (0.58, 0.62)
ATRIA	0.60 (0.58, 0.62)

Yao X, Abraham NS, Noseworthy P et al, *American Journal of Cardiology* 2017

1- Year Risk of GIB: Age Stratified Analysis

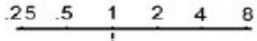


- **GIB increases with age in all subgroups of cardiac patients (N=311,211).**
- **Patients aged >75 on concomitant anticoagulants & antiplatelets GIB risk increases from 10% to 17.5%.**

Abraham NS et al, *Clinical Gastroenterology and Hepatology* 2020

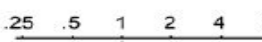
Mortality Predictors in Cardiac Patients

A Multivariate predictors of all-cause death at one year



	HR (95% CI)	P-value
Gastrointestinal bleeding	3.40 (1.67-6.92)	0.001
Age (per 10 years)	1.78 (1.57-2.03)	<0.001
Male sex	0.79 (0.62-1.01)	0.063
Current smoking	1.31 (0.98-1.76)	0.068
Diabetes Mellitus	1.39 (1.09-1.77)	0.007
Renal failure	1.93 (1.48-2.51)	<0.001
Peripheral artery disease	1.44 (1.06-1.94)	0.018
History of malignancy	1.66 (1.24-2.21)	0.001
Anemia	1.65 (1.26-2.16)	<0.001
STEMI	2.07 (1.54-2.80)	<0.001
Killip Class III-IV	5.12 (3.94-6.66)	<0.001
Any DES	0.57 (0.44-0.73)	<0.001

B Multivariate predictors of death, MI or stroke at one year



	HR (95% CI)	P-value
Gastrointestinal bleeding	3.75 (1.99-7.07)	<0.001
Age (per 10 years)	1.43 (1.30-1.56)	<0.001
Male sex	0.88 (0.73-1.07)	0.197
Current smoking	1.19 (0.96-1.49)	0.109
Diabetes Mellitus	1.36 (1.13-1.64)	0.001
Renal failure	1.67 (1.35-2.06)	<0.001
Peripheral artery disease	1.37 (1.07-1.75)	0.011
History of malignancy	1.33 (1.04-1.69)	0.021
Anemia	1.46 (1.18-1.80)	0.001
STEMI	1.49 (1.19-1.88)	<0.001
Killip Class III-IV	3.81 (3.02-4.80)	<0.001
Any DES	0.66 (0.54-0.81)	<0.001

All-Cause Mortality:

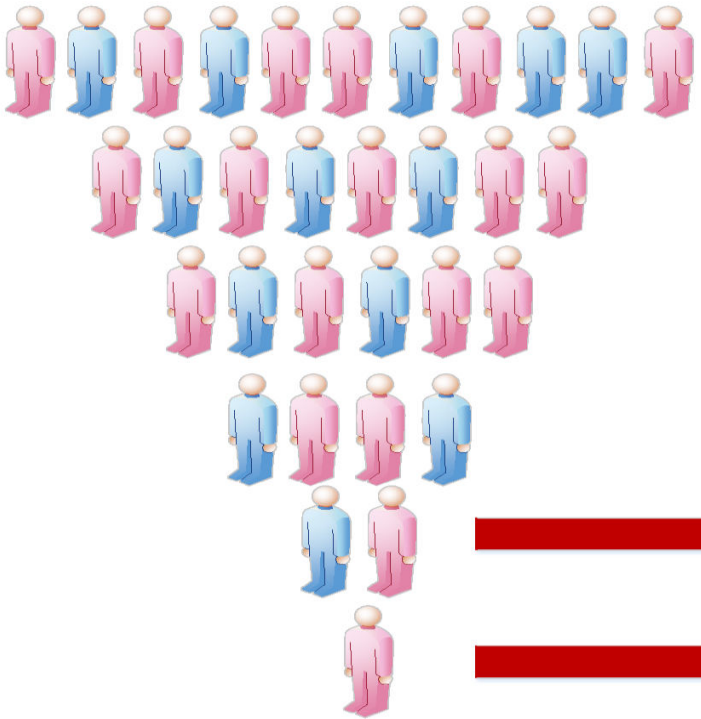
- **GIB associated with 3.4X increased risk at one year.**

Death, MI or Stroke:

- **GIB associated with 3.75X increased risk at one year.**

Koskinas et al, *Circulation: Cardiovascular Interventions* 2015

Mortality On Treatment With Antithrombotic Drugs



N = 24,044 patients

6.5% (5.7%-6.5%) died within 6 months of incident GIB

8.8% (8.3%-9.2%) died within 1 year of incident GIB

Abraham et al., *Am J Gastroenterol*, 2021

How To Decrease Anticoagulant GIB?

"A drug is a poison with one good side effect"

➢ *Neena S. Abraham MD*

Pick a better bad choice

Comparative Safety of DOACS (N= 57,788 AFIB Patients)

Rivaroxaban vs Dabigatran (n=32,574)		ARR	NNH
2.74	2.02	0.72*** (0.27, 1.17)	139
Apixaban vs Dabigatran (n=13,084)			
1.38	2.73	-1.35*** (-2.03, -0.67)	74
Apixaban vs Rivaroxaban (n=13,130)			
1.34	3.54	-2.20*** (-3.00, -1.40)	45

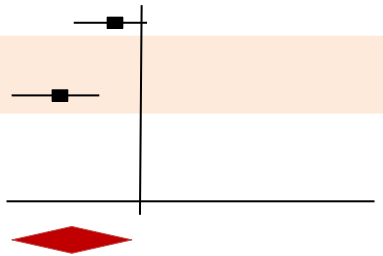
*p<0.05, **p<0.01, ***p<0.001

- Apixaban associated with 61% and 67% reduction in GIB when compared with dabigatran and rivaroxaban
- Benefit of apixaban persists in the very elderly (age≥75)

Abraham NS et al, *Gastroenterology* 2017

Apixaban vs VKAs :Gastrointestinal Hemorrhage

Study or Subgroup	log[Hazard Ratio]	SE	Apixaban Total	VKA Total	Weight	Hazard Ratio IV, Random, 95% CI
Halvorsen	-0.26136474	0.13965188	6506	11427	52.0%	0.77 [0.59, 1.01]
Yao	-0.67334455	0.16264728	7695	7695	48.0%	0.51 [0.37, 0.70]
Total (95% CI)			14201	19122	100%	0.63 [0.42, 0.95]



Heterogeneity: Tau² = 0.06; Chi² = 3.69, df= 1(P=0.05); I² = 73%

Test for overall effect: Z = 2.23 (P < 0.03)

Ntaios G et al, *Stroke* 2017

The Best Defense is a Smart Offense

An ounce of prevention is worth a ton of cure

- Aggressively manage risk factors

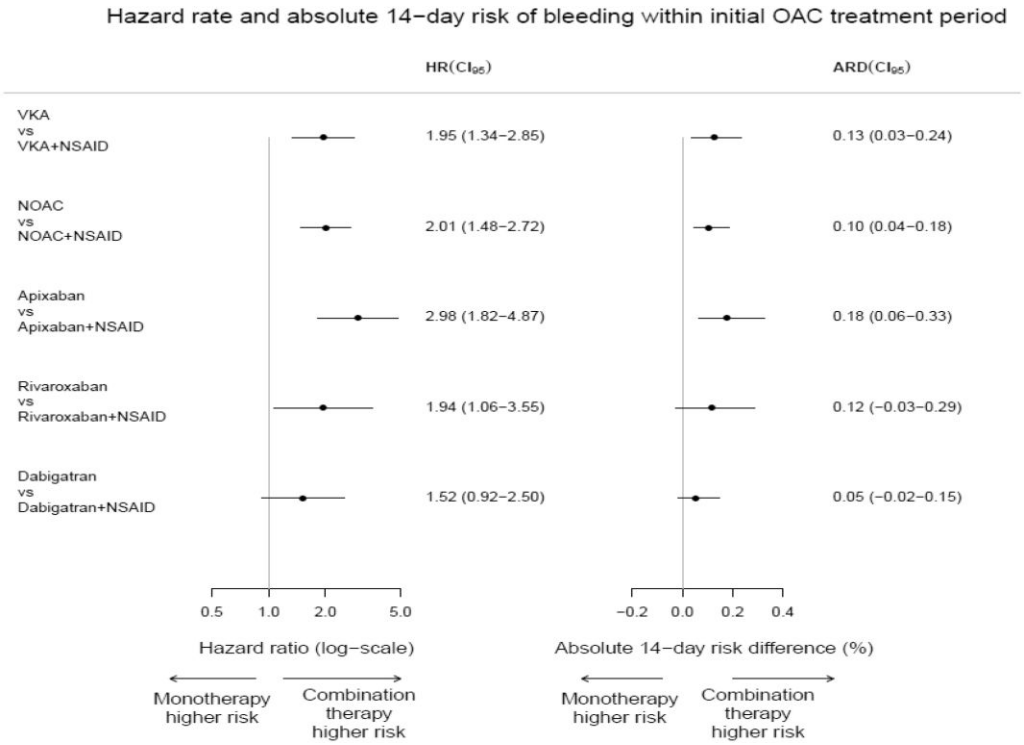
Anticoagulant GI Bleeding: Risk Minimization

- Document risk factors
- Luminal survey
  - Active DOAC in gut known to cause topical effect
- **Risks are synergistic**
  - Especially in the elderly & co-morbid, and with concomitant prescription of multiple antithrombotic agents
- **Modify these risk factors aggressively:**
  - ➢ Avoid NSAIDs
  - ➢ Lowest dose of ASA; if chronic = gastroprotection
  - ➢ Be aware of drug-drug & herbal interactions affecting P-gp or CYP3A4 (*warfarin and DOACs have similar profiles*)
  - ➢ Avoid triple antithrombotic strategies
  - ➢ Test and eradicate *H. pylori (Class 1 recommendation)*
  - ➢ PPI gastroprotection

- Advanced age
- History of GI bleeding
- Use of antiplatelets
- Use of anticoagulants
- Use of NSAIDs
- Use of chronic ASA
- Use of steroids
- *H. pylori* infection
- Non-GI co-morbidity
  - Cardiac & Renal

Abraham NS, *Am J Gastroenterol Suppl* 2016; Desai J et al, *Thromb Haemost* 2013; Bhatt DL et al, *Circulation* 2008; Lauffenburger JC et al, *Pharmacotherapy* 2015; Heidbuchel H et al, *Europace* 2013; Abraham NS et al, *Circulation* 2013

14-day Risk of Bleeding: Anticoagulant & NSAIDs

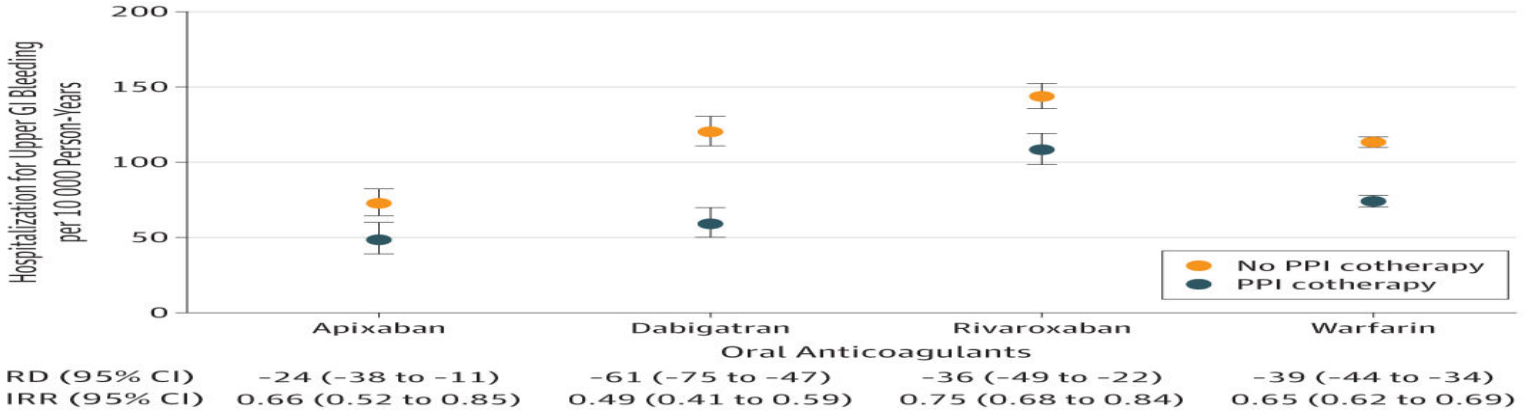


- **NSAIDs co-prescribed with warfarin or DOACs confer a substantial independent risk of bleeding in AF patients.**
- **NSAIDs were co-prescribed to 14.6% of people taking anticoagulants.**
- **NSAID prescribing was consistently higher among patients on DOACs than among those on VKA.**

Schjerning Olsen AM et al, *European Heart Journal – Cardiovascular Pharmacotherapy* 2019

Oral Anticoagulant, PPI Cotherapy & UGI Bleeding

Adjusted Incidence of Hospitalization for Upper Gastrointestinal (GI) Tract Bleeding by Individual Oral Anticoagulants



IRR indicates incidence rate ratio; PPI, proton pump inhibitor; RD, rate difference per 10 000 person-years. Error bars indicate 95% CIs.

Concomitant PPI prescription in all comers decreased the risk of GI bleeding

- **Regardless of the anticoagulant prescribed**

Ray W et al, *JAMA* 2018

Case 1

- 63-year-old woman with mitral valve prosthesis and chronic atrophic gastritis is on longstanding warfarin therapy and PPI.
- Recently diagnosed with an upper respiratory tract infection and given amoxicillin by her primary care doctor.
- Developed multiple episodes of melena over 48 hours; feels dizzy and faint; resuscitated with fluids. Remains tachycardic despite 3 L.
- Admission labs: Hg of 7.6 g/dL (baseline of 11.1 g/dL), Hct 32.7%, Cr 2.3, and INR 4.6.
- **How should you manage this patient's supratherapeutic INR before endoscopy?**

Urgent Setting: Resuscitation, Reversal, Restart

- A– airway
- B– breathing
- C– call GI? No.. CIRCULATION

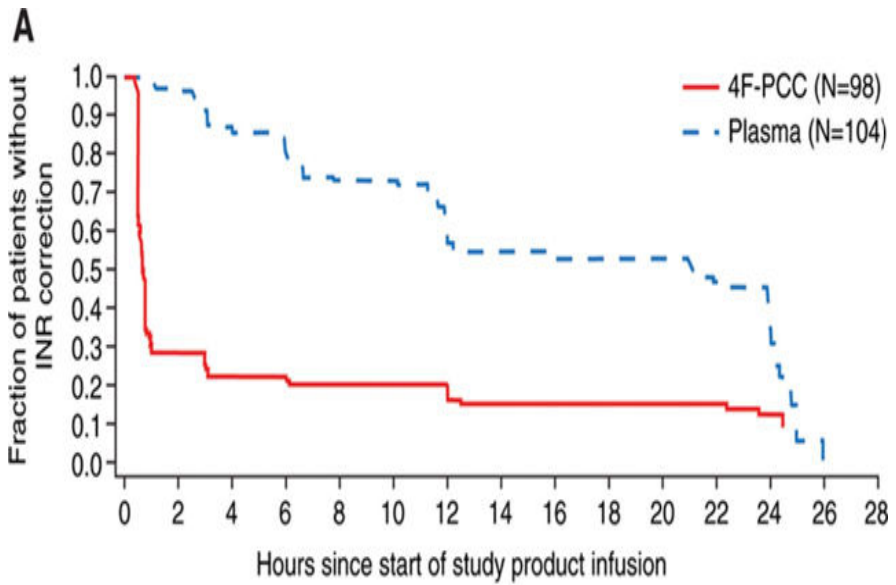
- GI -- Remember 3Rs…
  - Reverse Anticoagulant Effect
  - Rapid Endoscopy for Hemostasis
  - Restart Anticoagulant

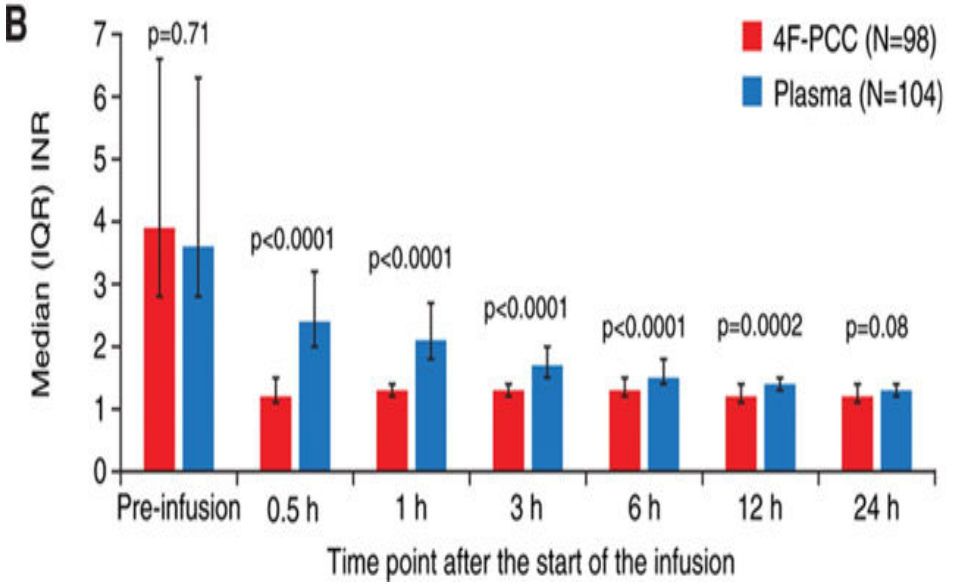
Warfarin: Acute Reversal

- **ASGE (2016)**
  - 4-factor prothrombin complex (PCC) with factors II, VII, IX and X
  - Vitamin K (5-10 mg by slow IV)
  - No FFP
    - large volumes required and transfusion is slow (Ex: 5 units X 9 hours to decrease INR from 3.95 to 2.0)
    - transfusion-associated pulmonary edema
- **ACG-CAG CPG (2021-2022)**
  - 4 factor PCC preferred over FFP with supratherapeutic INR/life-threatening GIB
    - Rapid & reliable correction of INR
  - No Vitamin K
  - *Conditional recommendation, very low certainty of evidence*

Abraham & Barkun et al, *Am J Gastroent* 2021; Acosta & Abraham et al, *Gastroint Endosc* 2016

Safety of PCC for Warfarin Reversal





*64% of bleeds were GIB

No increased thromboembolic risk with PCC
Rate is comparable to plasma (7%-8%)*

Sarode R et al, *Circulation* 2013; *Goldstein JN et al, *Lancet* 2015

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:

- Vit K 2-5 mg (po or IV) reverses anticoagulant effect (INR ≤ 1.3) in 24-48 hours
- Does not achieve rapid hemostasis; limited value in 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***)

Holbrook et al, *Chest* 2012 ; Abraham & Barkun et al, *Am J Gastroenterol* *(in press)*

Timing to Endoscopy: Do Not Wait to Normalize INR

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

Canadian Registry on Upper Gastrointestinal Bleeding and Endoscopy (RUGBE) – N=1869

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

Normalizing INR does not reduce re-bleeding but delays endoscopy

N=102 INR >1.3; Mean INR 1.8 (1.3-2.7)

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

Endoscopic therapy effective with moderately elevated INR (≤2.5)

Barkun A et al, *Am J Gastroenterol* 2004; Choudari & Palmer et al, *GUT* 1994; Wolf A, *Am J Gastroenterol* 2007; Shingina et al, *Aliment Pharmacol Ther 2011;* Acosta & Abraham et al, *Gastrointest Endosc* 2016

Anticoagulant 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?

- **No tug of war between the heart and the GI tract, the heart always wins!**
- **Balance risk of thromboembolism and further bleeding**
- **Resume w/in 4-7 days from drug discontinuation; same day if diagnostic**
- **1% embolic risk**

Abraham & Barkun et al., *Am J Gastroenterol (in press)*

Case 2

- 76-year-old man with non-valvular atrial fibrillation on rivaroxaban & low-dose aspirin; hypertension, and hyperlipidemia admitted with congestive heart failure precipitated by 24 hours of melena.
- After appropriate resuscitation, melena & tachycardia continues. ER doctor calls to discuss use of a reversal agent.
- You suggest measuring the anticoagulant effect of rivaroxaban *before* using a reversal agent. Your lab does not have a drug-specific toxicity assay for rivaroxaban.
- **What other serum assay can be used to exclude a toxic level (i.e., excessive anticoagulant effect) of rivaroxaban?**

DOAC: Acute Reversal

- **HOLD drug** -- Short half-lives (<12-15 hours)

- **Perfuse kidneys**– maximize renal excretion
  - Dabigatran 80%
  - Rivaroxaban 50%
  - Edoxaban 40%
  - Apixaban 40%

- **Charcoal for toxic ingestion (<2-4 hours)**

Paradigm Shift: Is DOAC Level High?

- Measurement of anticoagulation effect desirable *before* reversal
- **Dabigatran**
  - Normal TT excludes clinically relevant levels
  - Dilute TT (more sensitive) and ECT useful for quantification across a broad range of levels
  - Normal APTT excludes excess levels
- **FXa Inhibitors**
  - Drug specific calibration required to assess toxicity
  - Normal PT excludes excess levels of rivaroxaban and edoxaban but not apixaban (toxic APIX possible even with normal PT)

Cuker et al, *J Am Coll Cardiol* 2014; Cuker et al, *J Thromb Thrombolysis* 2015; Douxfils et al, *Thromb Haemost* 2013; Becker et al, *J Thromb Thrombolysis* 2011; Zafar et al, *Thromb Haemost 2007*

DOAC Reversal Agents

- **Idarucizumab (Praxbind®)**
  - ❑ REVERSE-AD Trial^: Eliminates dabigatran effect within 5 minutes of two IV doses of 2.5g; $3,500/dose
  - ❑ *30-day thromboembolism of 5%*

- **Andexanet alpha (AndexXA®)**

  ANNEXA-4 Trial*: T ½= 1 hour w/ rapid onset; $49,500/dose
  - ❑ Reduced rivaroxaban by 89% & apixaban by 93% in patients with hemorrhage
  - ❑ *Anticoagulant reversal for 1 hour after infusion then rebound increase in anti-XA activity from unbound Xa inhibitor.*
  - ❑ FDA Approved 2018; *30-day thromboembolism of 12.7%*

- **Aripazine (PER977) *FDA continuing review**
  - ❑ Whole blood clotting time (*in vitro*) show reduction of edoxaban effect within 10 minutes of IV infusion (restoration to 10% over baseline); ongoing RCT

- **4- Factor PCC (Kcentra®)**
  - ❑ Factors II, VII, IX & X -- Reverses ⁺rivaroxaban, ^^apixaban and **edoxaban within 2-4 hours of one dose (50 IU/kg)
  - ❑ Thromboembolic risk is similar to FFP (5% to 7%)
  - ❑ $1,500/dose

^ Pollack et al, *NEJM* 2017; *Connolly et al, *NEJM* 2016; ⁺Levy JH et al, *J Thromb Haemost* 2017; ^^Song Y et al, *J Thromb Haemost* 2017; **Zahir H et al, *Circulation* 2015

What did the ACG-CAG CPG panel think?

Use of Reversal Agents:

- For patients on rivaroxaban or apixaban who are hospitalized or under observation with acute GIB, **we suggest against andexanet alfa administration** (*conditional recommendation, very low certainty of evidence*)
- For patients on dabigatran who are hospitalized or under observation with acute GIB, **we suggest against the administration of idarucizumab** (*conditional recommendation, very low certainty of evidence*)
- For patients on DOACs who are hospitalized or under observation with acute GIB, **we suggest against PCC administration** (*conditional recommendation, very low certainty of evidence*)

Abraham & Barkun et al., *Am J Gastroenterol (in press)*

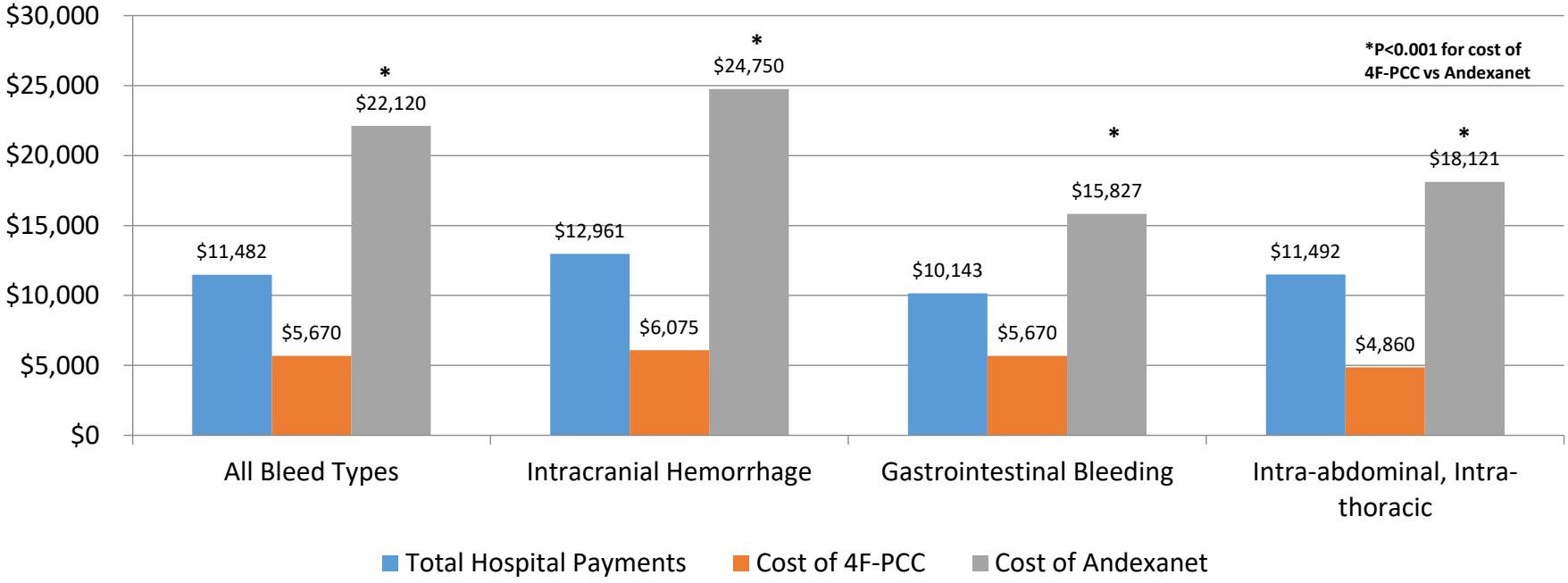
Why were these recommendations made?

*** No routine use of a reversal agent in patients with GIB ***

- **Avoid andexanet alfa**
  - Single published study with serious risk of bias & no control group; little GIB data
  - Higher risk of thromboembolism & high-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**

Cost of Reversal Agent Compared to Reimbursement Per Hospitalization



The projected cost of andexanet for the reversal of FXa-related life-threatening hemorrhage would exceed the national average hospital reimbursement/patient in nearly 75% of patients by over $7500/hospitalization.

Frontera JA et al, *Journal of Thrombosis and Thrombolysis* 2020

Case 3

- 66-year-old man referred for colonoscopy to remove 1.2 cm polyp seen on CT colonography.
- Occasional small volume hematochezia; no family history of colon cancer; no previous colonoscopy.
- Meds: metoprolol, simvastatin, and apixaban for paroxysmal non-valvular atrial fibrillation.
- Otherwise well with normal labs (no anemia or impaired kidney function).
- **How should you manage apixaban before and after the procedure?**

Temporary Interruption of DOAC & Resumption of DOAC

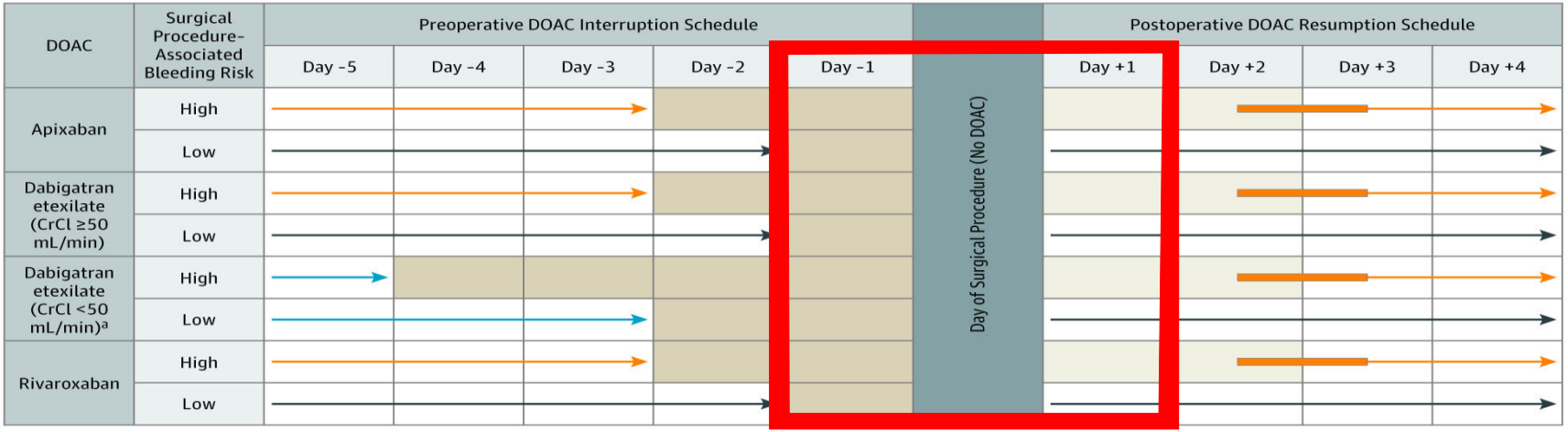
Factor Xa Inhibitor						Direct Thrombin Inhibitor	
Rivaroxaban		Apixaban		Edoxaban		Dabigatran	
CrCl (ml/min)	Last Dose (days)	CrCl (ml/min)	Last Dose (days)	CrCl (ml/min)	Last Dose (days)	CrCl (ml/min)	(days)
>90	≥1					>80	1-3
60-90	2	>60	1-2	>60	≥1	50-80	1-3
30-59	3	30-59	3	30-60	≥1	30-49	1.5-4
15-29	4	15-29	4	15-30	≥1	≤29	2-6

Restart when hemostasis achieved; usually next day at full dose

Acosta & Abraham et al, *GIE* 2016

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



- No DOAC on shaded days & on the day of the elective surgery or procedure.
- Dark blue arrows refer to patients with a low-bleed-risk surgical procedure**.
- **ALL endoscopic procedures considered as low-risk (similar to the BRIDGE Trial^).

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

PAUSE Cohort Study (n=3007)

Procedure-associated bleeding risk	Apixaban cohort (n=1257)	Dabigatran etexilate cohort (n=668)	Rivaroxaban cohort (n=1082)
Low bleeding risk			
No. (%)	851 (67.7)	440 (65.9)	709 (65.5)
30-d postoperative rate of major bleeding, % (95% CI)	0.59 (0-1.20)	0.91 (0-2.01)	1.27 (0-2.17)
High bleeding risk			
No. (%)	406 (32.3)	228 (34.1)	373 (34.5)
30-d postoperative rate of major bleeding, % (95% CI)	2.96 (0-4.68)	0.88 (0-2.62)	2.95 (0-4.76)

- Standardized management strategy *did not require heparin bridging or coagulation function testing*
- Low rates of perioperative major bleeding (<2%) and arterial thromboembolism (<1%)
- >90% overall had a minimal or no residual anticoagulant level at the time of the procedure.

Douketis JD et al, *JAMA Internal Medicine* 2019

What did the ACG-CAG CPG panel think?

- For patients on DOACs who are undergoing elective/planned endoscopic procedures, **we suggest temporarily interrupting DOAC rather than continuing DOAC** (*conditional recommendation, very low certainty of evidence*)

➢ Absolute risk of increased delayed bleeding with continuous DOAC could not be reliably calculated from current evidence

➢ Published GI literature limited by:

- ❑ Lack of adjustment for known confounders
- ❑ Limited sample sizes and low event rates
- ❑ Diversity of GI procedure types & endoscopic techniques
- ❑ Variable protocols for DOAC interruption

Abraham & Barkun et al., *Am J Gastroenterol (in press)*

How to operationalize recommendations

- **Hold DOAC for 2-3 days (including 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

- **Resume DOAC day after the procedure in MOST**
  - DOAC resumption post-procedure was 1.9 days ± 1.5 days providing endoscopic hemostasis had been achieved ^

  - **Would not hold DOAC post-procedure for more than 48-72 hours**
    - ➢ Timing of resumption dictated by risk of post-procedural bleeding

^ Douketis and Barkun (personal communication); Abraham & Barkun et al., *Am J Gastroenterol (in press*)

Summary: CardioGI Idiomatic Pearls

- **"A drug is a poison with one good side effect"**
  - ❑ Increased death 1-year after GIB; risk is 8-10% in most studies
  - ❑ Age is the most important risk factor
- **"Pick a better bad choice"**
  - ❑ Apixaban is the safest AC for the GI tract
  - ❑ Avoid concomitant prescription of antithrombotic agents; ASA 81 mg/day (if necessary)
- **"Welcome the new" (paradigms) – Acute & elective settings**
  - ❑ Resuscitation, reversal, and restarting drugs
  - ❑ Role of reversal agents
- **"The best defense is a smart offense"**
  - ❑ Aggressive risk minimization ALWAYS yields favorable results (Yes to PPI; No to NSAIDs)