Gastrointestinal Bleeding Etiologies, Management, and the Interplay with Anticoagulant and Antiplatelet Agents in the Peri-Procedural Period

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  - Cook Endoscopy

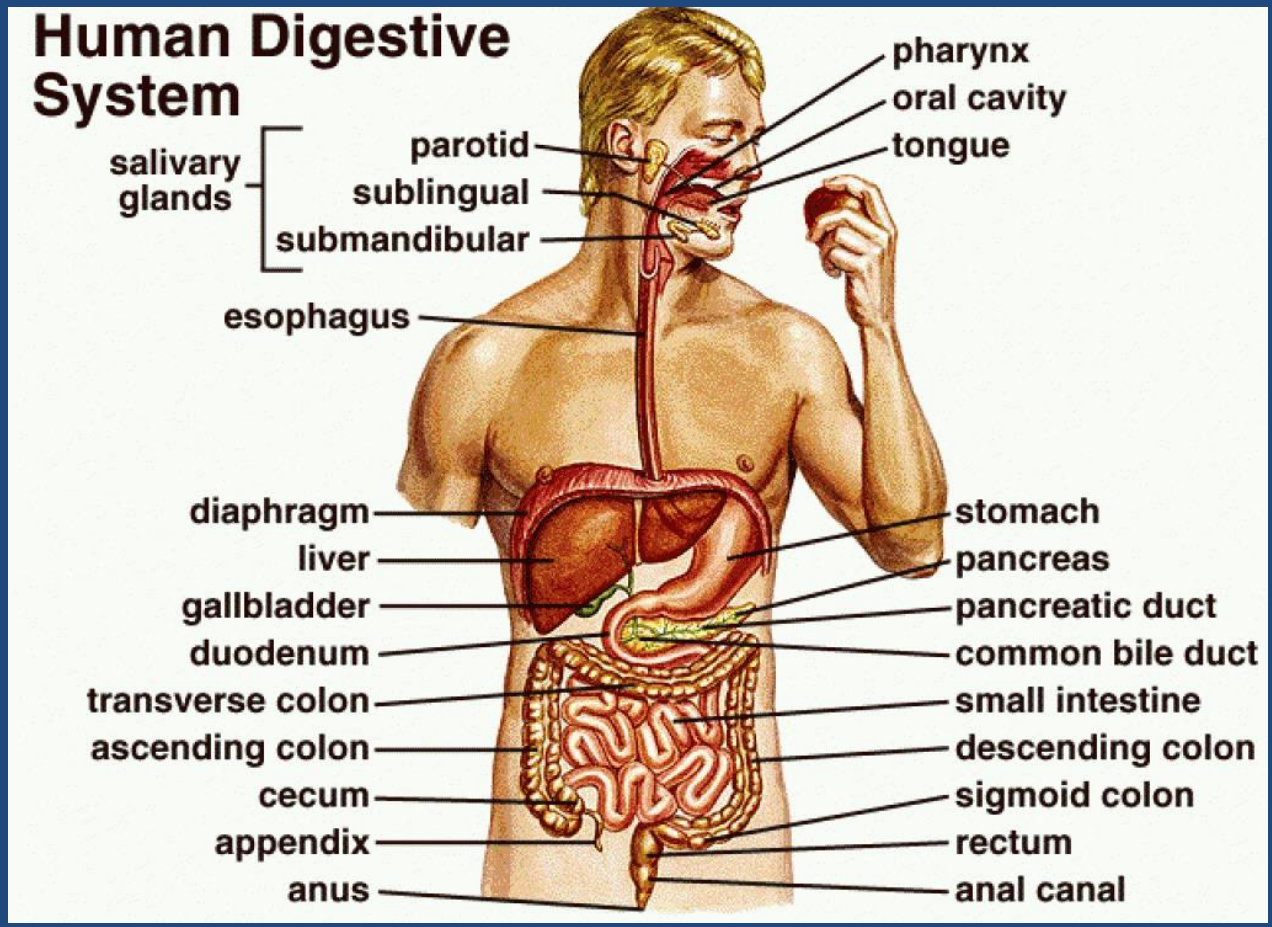
Learning Objectives

- Delineate the differential diagnoses of gastrointestinal bleeding, and differentiate upper GI bleeding, small bowel bleeding, and lower GI bleeding
- Explore management strategies in gastrointestinal bleeding, with a focus on non-variceal upper GI bleeding
- Recognize the different classes of anticoagulant and antiplatelet agents
- Understand patient and peri-procedural risk factors for bleeding and thrombosis
- Discuss appropriate antithrombotic agent management for elective and urgent GI procedures

Differential Diagnoses of Gastrointestinal Bleeding

Upper vs. Small Bowel vs. Lower GI Bleeding

- Upper: Esophagus to Ligament of Treitz
- Small Bowel: Ligament of Treitz to Terminal Ileum
- Lower: Cecum to Anus



https://detiina.com/simple-digestive-system/simple-digestive-system-simple-diagram-of-the-human-body-gi-tract-digestive-system/

Clinical Presentation of GI Bleeding

- Coffee-ground emesis
- Hematemesis
- Melena
- Hematochezia/Bright Red Blood Per Rectum

- Heme + stool, with or without iron deficiency anemia
- Iron deficiency anemia with or without heme + stools

NOT Acute GI Bleeding

Upper GI Bleeding Etiologies

Etiology	Estimated Percentage
Peptic Ulcer Disease	20-50%
Gastroduodenal Erosions	8-15%
Esophagitis	5-15%
Varices/Portal Hypertension	5-20%
Mallory-Weiss Tears	8-15%
Vascular Malformations (AVMs, GAVE, Dieulafoy's, Osler Weber Rendu)	≈ 5%
Other Conditions (i.e. Malignancy, etc.)	Remainder (Up to 5%)

Hwang JH, et al. Gastrointest Endosc 2012;75(6):1132-8.
Rockall TA, et al. BMJ 1995;311:222-6.
Boonpongmanee S, et al. Gastrointest Endosc 2004;59:788-94.
Savides TJ, et al. Endoscopy 1996;28:244-8.

Further Upper GI Bleeding Etiologies…

Etiology of Acute Upper Gastrointestinal Bleeding

Ulcerative or erosive
- Peptic ulcer disease
  - Idiopathic
  - Drug induced
    - Aspirin
    - Nonsteroidal antiinflammatory drugs
  - Infectious
    - Helicobacter pylori
    - Cytomegalovirus
    - Herpes simplex virus
  - Stress-induced ulcer
  - Zollinger Ellison Syndrome
- Esophagitis
  - Peptic
  - Infectious
    - Candida albicans
    - Herpes simplex virus
    - Cytomegalovirus
    - Miscellaneous
  - Pill-induced
    - Alendronate
    - Tetracycline
    - Quinidine
    - Potassium chloride
    - Aspirin
    - Nonsteroidal antiinflammatory drugs

Portal hypertension
- Esophageal varices
- Gastric varices
- Duodenal varices
- Portal hypertensive gastropathy

Arterial, venous, or other vascular malformations
- Idiopathic angiomas
- Osler-Weber-Rendu syndrome
- Dieulafoy's lesion
- Watermelon stomach (gastric antral vascular ectasia)
- Radiation-induced telangiectasia
- Blue rubber bleb nevus syndrome

Traumatic or post-surgical
- Mallory-Weiss tear
- Foreign body ingestion
- Post-surgical anastamosis
- Aortoenteric fistula
- Post gastric/duodenal polypectomy

Tumors
- Benign
  - Leiomyoma
  - Lipoma
  - Polyp (hyperplastic, adenomatous, hamartomatous)
- Malignant
  - Adenocarcinoma
  - Gastrointestinal stromal tumor
  - Lymphoma
  - Kaposi's sarcoma
  - Carcinoid
  - Melanoma
  - Metastatic tumor
- Miscellaneous
  - Hemobilia
  - Hemosuccus pancreaticus

http://utdol.com/online/content/image

Small Bowel Bleeding Etiologies

Common Causes

< 40 y/o	> 40 y/o
Inflammatory Bowel Disease	Angioectasias (AVMs)
Meckel's Diverticulum	NSAID Ulcers, Erosions, Diaphragms
Neoplasms	Neoplasms
Dieulafoy's Lesions	Dieluafoy's Lesions
Polyposis Syndromes	

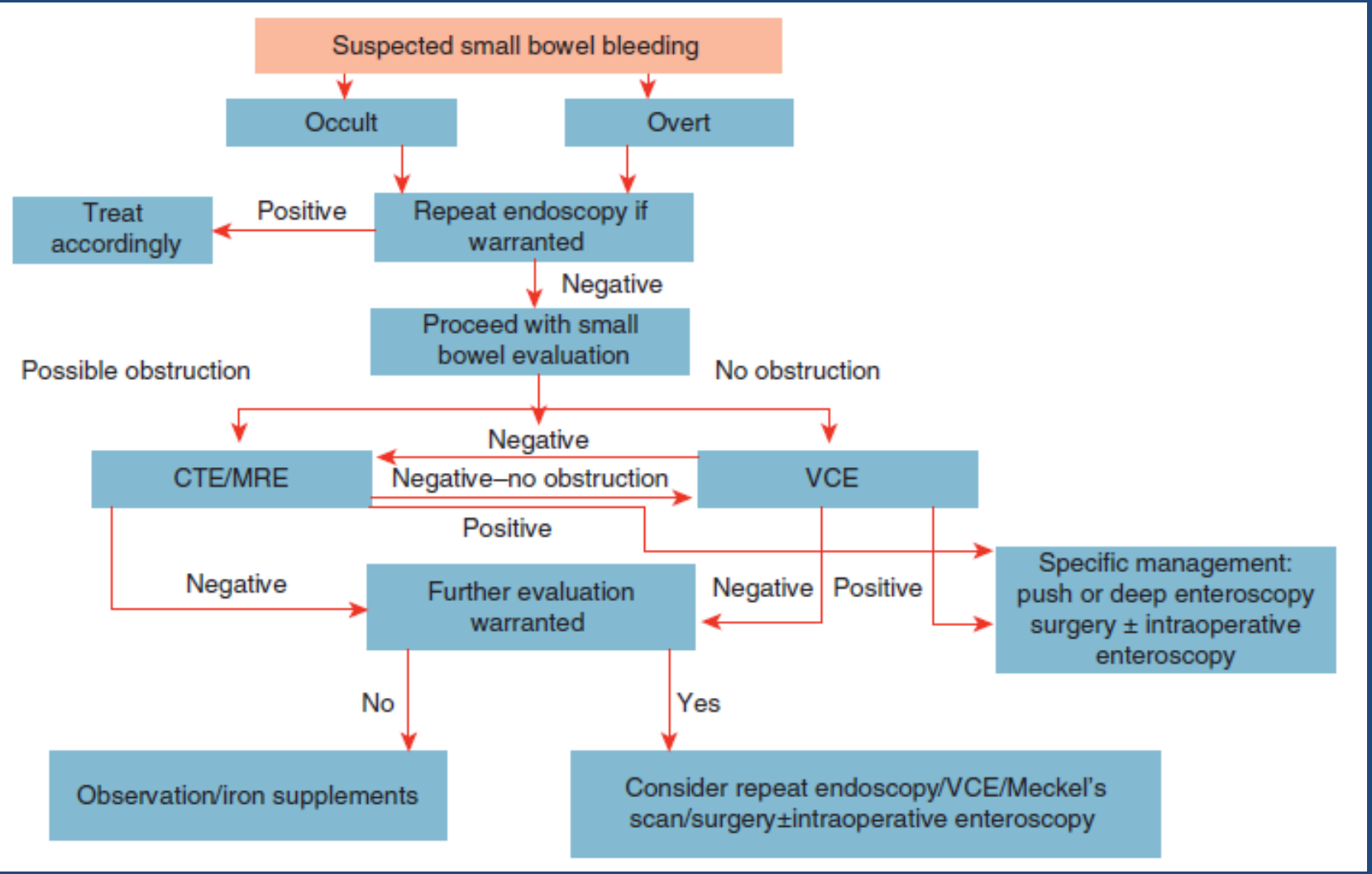
Malignant Neoplasm Types:

- Primary small bowel adenocarcinoma
- Primary neuroendocrine tumors (carcinoid, GIST)
- Small bowel lymphoma
- Metastases: melanoma, renal cell carcinoma, lung and breast

Rare Causes
Aorto-enteric Fistula
Radiation Enteritis
Celiac Disease
Autoimmune Enteropathy
Henoch-Schoenlein Purpura
Small Bowel Varices
Portal Hypertensive Enteropathy
Amyloidosis
Blue Rubber Bleb Nevus Syndrome
Pseudoxanthoma Elasticum
Osler-Weber-Rendu Syndrome
Kaposi's Sarcoma with AIDS
Plummer-Vinson Syndrome
Ehlers-Danlos Syndrome
Hemobilia & Hemosuccus Pancreaticus
Inherited Polyposis Syndromes (FAP, Peutz-Jeghers)

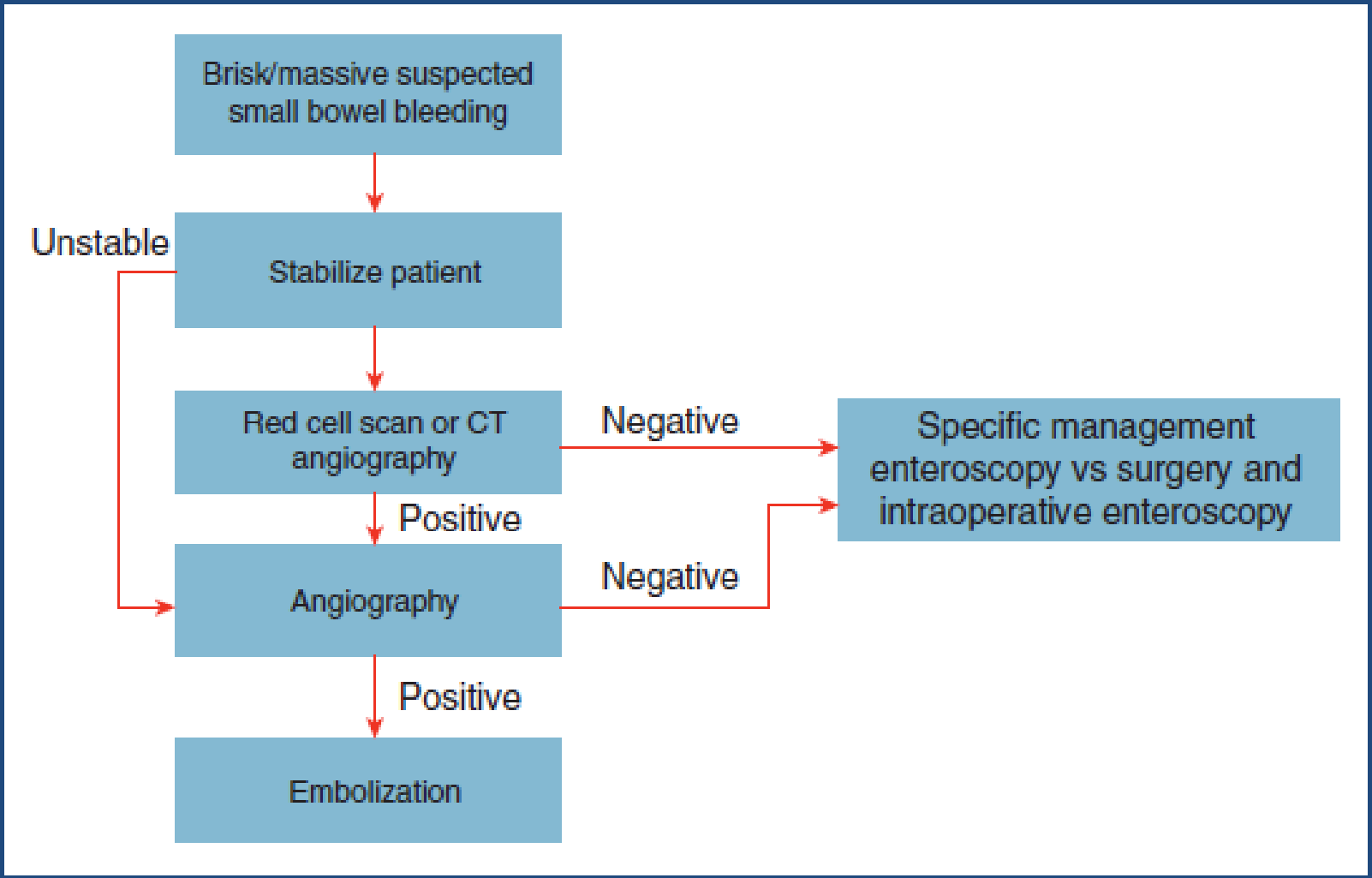
Barkin JA, et al. Gastroenterological Endoscopy, 3rd Ed. Thieme. 2017.
Gerson LB, et al. Am J Gastroenterol. 2015;110(9):1265-87.

Small Bowel Bleeding Management: ACG 2015



Gerson LB, et al. Am J Gastroenterol. 2015;110(9):1265-87.

Brisk or Massive Suspected Small Bowel Bleeding Management: ACG 2015



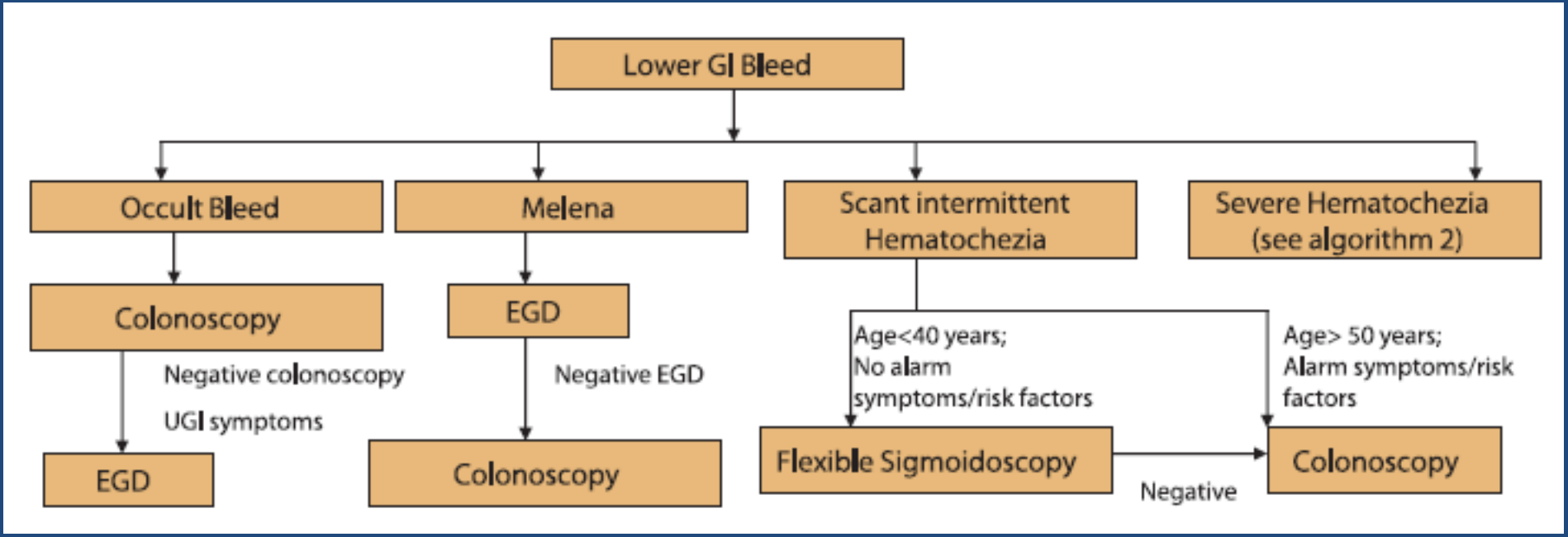
Gerson LB, et al. Am J Gastroenterol. 2015;110(9):1265-87.

Lower GI Bleeding Etiologies

Etiology
Diverticular Bleeding
Ischemic Colitis
Angioectasias (AVMs)
Hemorrhoids
Colorectal Neoplasia/Malignacy
Post-Polypectomy Bleeding
Inflammatory Bowel Disease
Infectious Colitis
NSAID Colopathy
Radiation Proctopathy
Stercoral Ulcer
Rectal Varices
Dieulafoy's Lesions

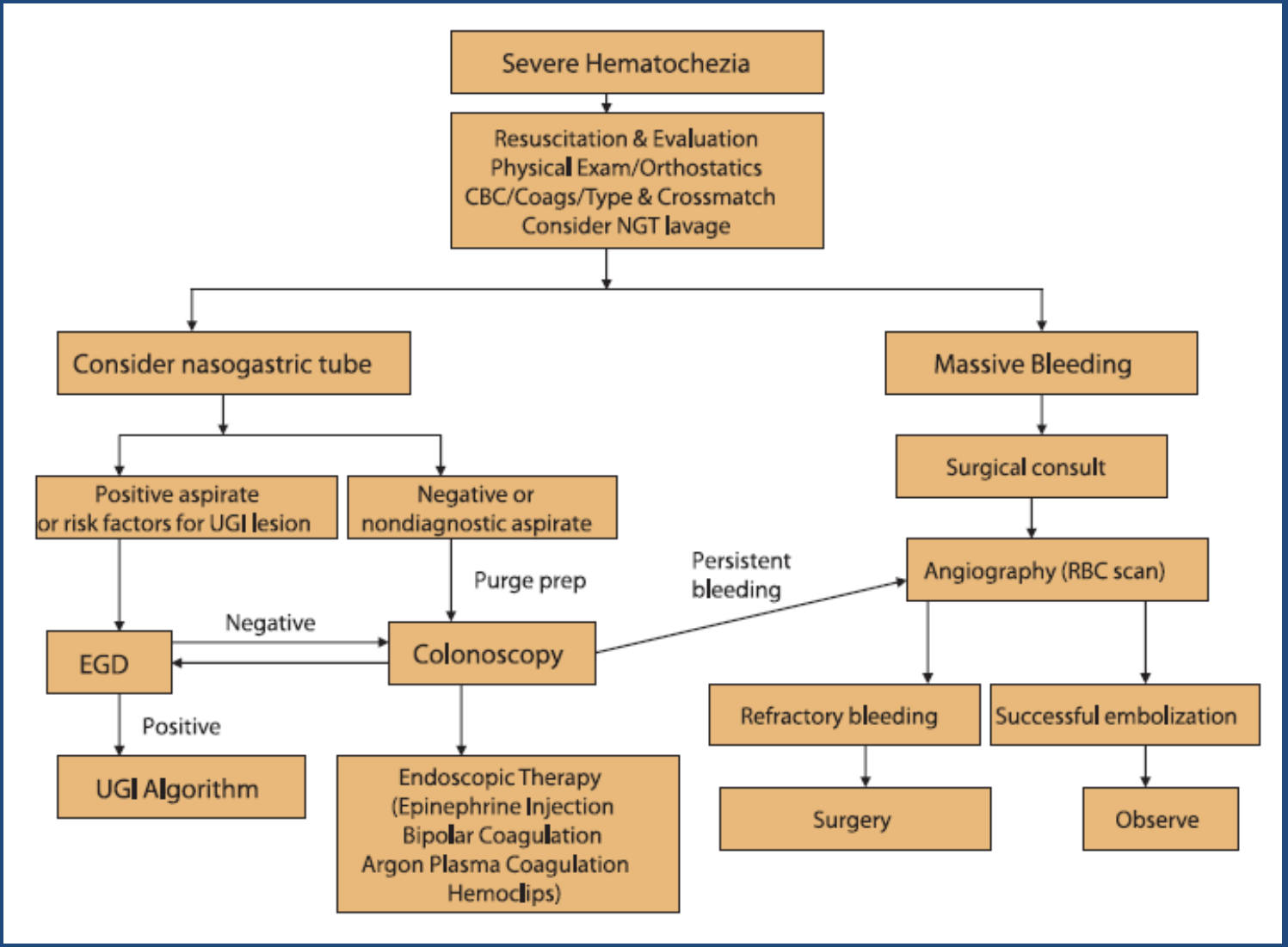
Pasha SF, et al. Gastrointest Endosc. 2014;79(6):875-85.

Lower GI Bleeding Management: ASGE 2014



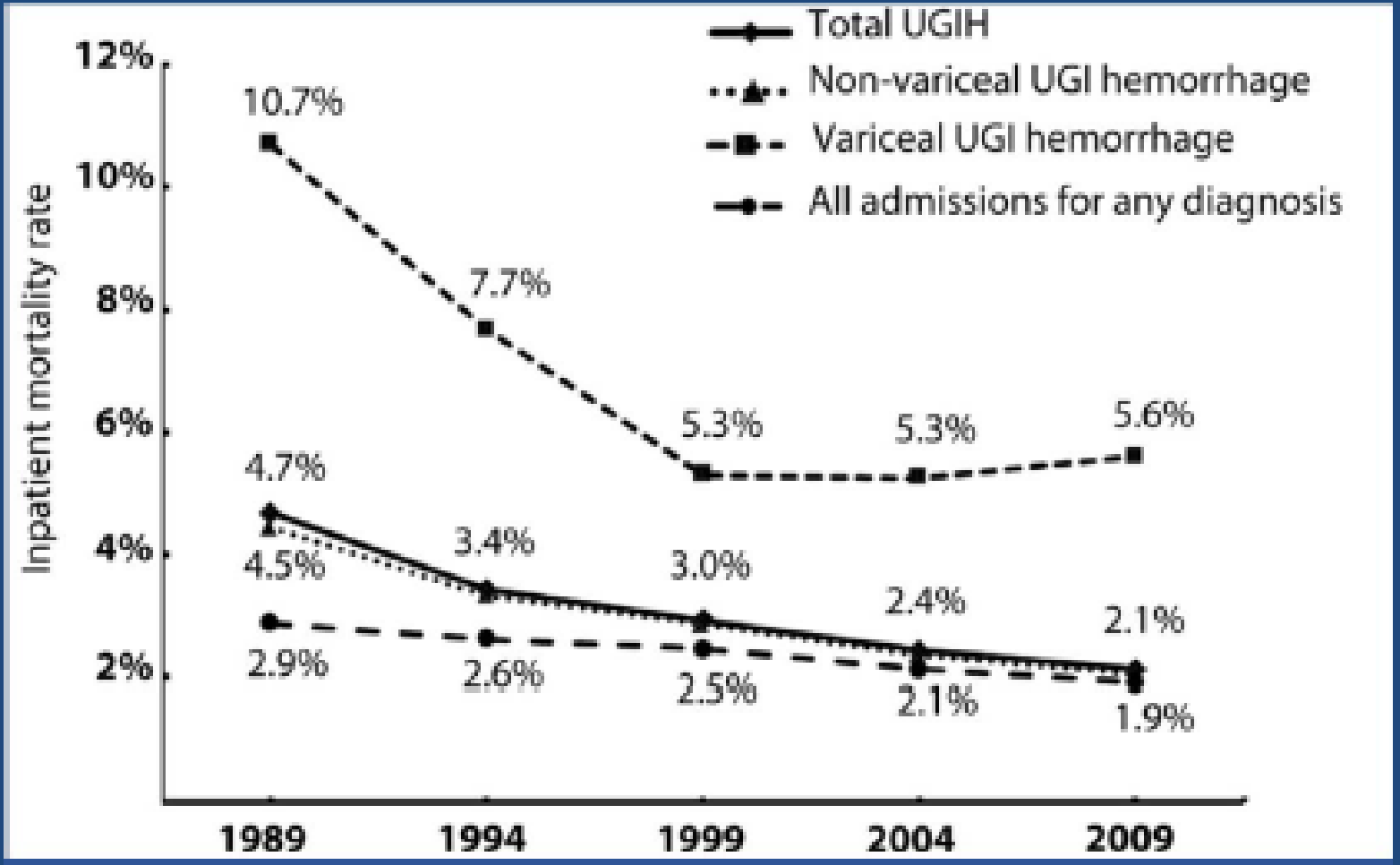
Pasha SF, et al. Gastrointest Endosc. 2014;79(6):875-85.

Severe Hematochezia Management: ASGE 2014



Pasha SF, et al. Gastrointest Endosc. 2014;79(6):875-85.

UGI Bleeding Incidence Has Decreased and Survival Has Improved



Non-Variceal UGI Hemorrhage Incidence: 108/100k (1994) → 78/100k (2009)

Abougergi, MS, et al. Gastrointest Endosc 2015;81(4):882-8.e1.

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Nationwide Trends in UGI Bleeding Hospitalizations and the Role of Endoscopy

	1989	2009
In-Hospital Upper Endoscopy Rate	70%	85%
Endoscopic Therapy Rate	10%	27%
Early Endoscopy Rate	36%	54%
Median Length of Hospital Stay	4.5 days	2.8 days
Median Total Hospitalization Charges	$9249	$20,370

Abougergi, MS, et al. Gastrointest Endosc 2015;81(4):882-8.e1.

Risk Factors for Upper GI Bleeding

- Peptic Ulcer Disease:
  - NSAIDs/ASA
  - *Helicobacter pylori* infection
  - Tobacco smoking = ??
  - Steroids and EtOH are NOT independent risk factors
  - Psychological stress = ??
- Stress Ulcers: intubation > 48h, increased intracranial pressure, burns >35% TBSA
- Esophagitis: supine position (especially in bedbound patients)
- Mallory Weiss Tears: after wretching
- Varices: risks for liver disease or portal hypertension

Rosenstock S, et al. Gut 2003;52(2)186-93.
Lee SP, et al. Clin Endosc 2017;50(6):578-84.
Deding U, et al. BMC Gastroenterol 2016;16:140.
https://medlineplus.gov/ency/article/000206.htm

Management of Gastrointestinal Bleeding

Diagnostic Tools for Localization of GI Bleeding

- Upper Endoscopy (EGD)*
- Video Capsule Endoscopy
- Enteroscopy*
- Colonoscopy*
- CT Angiography
- Nuclear Medicine Bleeding Scan
- Angiography*
- Surgery*

*May Be Therapeutic As Well

Initial Assessment of Upper Gastrointestinal Bleeding

GI Bleeding Initial Patient Assessment & Risk Stratification

- Immediate assessment of hemodynamics: Stable vs. Unstable
- Examine the patient (including digital rectal examination)
- Insert 2 large bore peripheral IVs and start volume resuscitation
- Labs: CBC (beware of false normals if hemoconcentrated), type and cross, CMP (BUN/Cr, LFTs), PT/INR/PTT
- Blood Transfusions:
  - Target Hgb ≥ 7 g/dL (≥ 10 g/dL if active cardiac conditions)
- Risk Stratification: High-Risk vs. Low-Risk
  - Patient Triage (ICU, Inpatient, Outpatient)
  - Timing of Endoscopy
- Consult appropriate colleagues: GI, ICU, IR, Surgery

Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60

Glasgow Blatchford Score (GBS) for UGI Bleed Management Risk Stratification

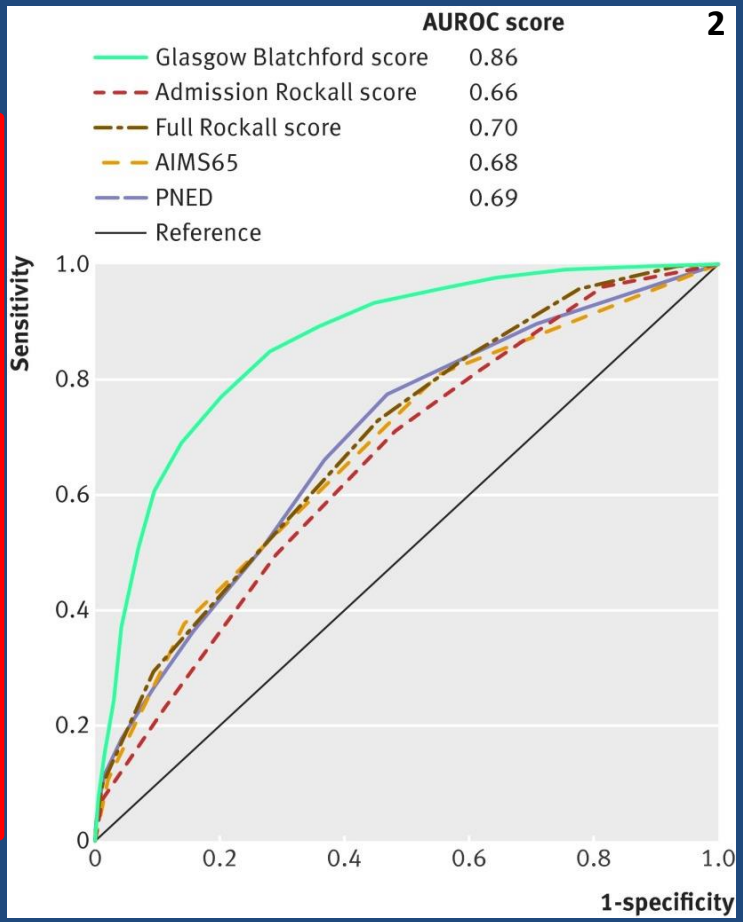
1

Admission risk marker	Score component value
Blood urea (mmol/L)	
⩾6·5 <8·0	2
⩾8·0 <10·0	3
⩾10·0 <25·0	4
⩾25	6
Haemoglobin (g/L) for men	
⩾120 <130	1
⩾100 <120	3
<10·0	6
Haemoglobin (g/L) for women	
⩾100 <120	1
<100	6
Systolic blood pressure (mm Hg)	
100–109	1
90–99	2
<90	3
Other markers	
Pulse ⩾100 (per min)	1
Presentation with melaena	1
Presentation with syncope	2
Hepatic disease	2
Cardiac failure	2

Table 1: **Admission risk markers and associated score component values**

Patients with presentation GBS ≤ 1 in UGI Bleed can be safely discharged from the Emergency Room[2]

2



GBS ≤ 1: Sens 98.6%, Spec 34.6%, PPV 96.6%, NPV 56.0%

1. Blatchford O. Lancet 2000;356:1318–21.
2. Stanley AJ. BMJ 2017;356:i6432.

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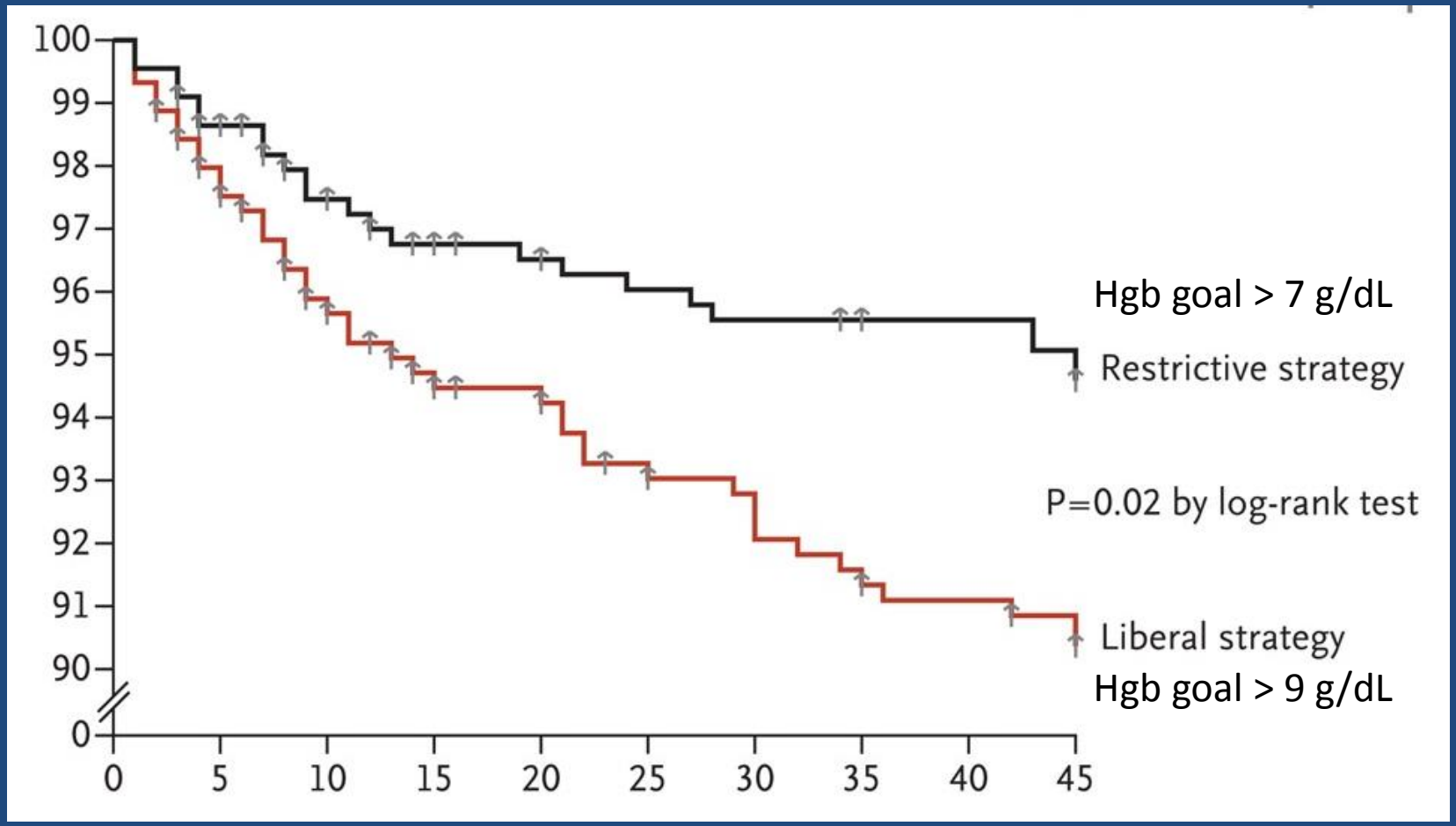
Pre-Endoscopic Management of Upper Gastrointestinal Bleeding

Pre-Endoscopic Medical Therapy for UGI Bleeding

- Volume Resuscitation
- Blood Transfusion
- Proton Pump Inhibitors
- Prokinetic Agents
- Nasogastric Tube and Lavage??
- Endotracheal Intubation??
- Special Scenario: Suspected Variceal Bleeding

Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
Hwang JH, et al. Gastrointest Endosc 2012;75(6):1132-8.

Improved Survival with Restrictive Transfusion Strategy for Acute UGI Bleeds



Villanueva C, et al. NEJM 2013;368(1):11-21.

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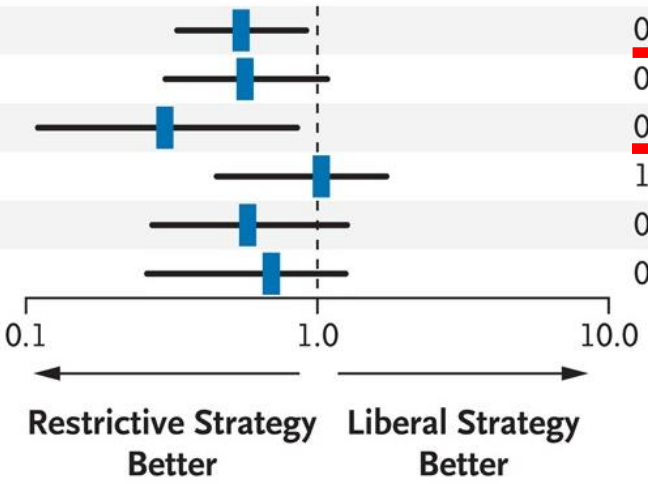
Improved Survival with Restrictive Transfusion Strategy for Acute UGI Bleeds

Subgroup	Restrictive Strategy	Liberal Strategy	Hazard Ratio (95% CI)	P Value
	no. of patients/total no. (%)			
Overall	23/444 (5)	41/445 (9)	0.55 (0.33–0.92)	0.02
Patients with cirrhosis	15/139 (11)	25/138 (18)	0.57 (0.30–1.08)	0.08
Child–Pugh class A or B	5/113 (4)	13/109 (12)	0.30 (0.11–0.85)	0.02
Child–Pugh class C	10/26 (38)	12/29 (41)	1.04 (0.45–2.37)	0.91
Bleeding from varices	10/93 (11)	17/97 (18)	0.58 (0.27–1.27)	0.18
Bleeding from peptic ulcer	7/228 (3)	11/209 (5)	0.70 (0.26–1.25)	0.26



- ACG Recommendation: Transfusion goal of Hemoglobin > 7 g/dL (> 10 g/dL if active cardiac disease)
- ***DON'T FORGET***: Platelets, Fresh Frozen Plasma, Cryoprecipitate if needed

Villanueva C, et al. NEJM 2013;368(1):11-21.
Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.

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The Benefit of Proton Pump Inhibitor Use Before Endoscopy

Outcome	PPI Group	Controls	Odds Ratio (95% CI)
Rebleeding Rate	13.9%	16.6%	0.81 (0.61-1.09)
Need for Surgery	9.9%	10.2%	0.96 (0.68-1.35)
Mortality	6.1%	5.5%	1.12 (0.72-1.73)
High-Risk Stigmata Lesions	37.2%	46.5%	0.67 (0.54-0.84)
Need for Endoscopic Treatment at Index Endoscopy	8.6%	11.7%	0.68 (0.50-0.93)

- ACG & ASGE Guidelines recommend IV PPI before Endoscopy
- PPI Dosage: 80 IV bolus x1 followed by 8 mg/hr IV drip
- IV PPI is also recommended to decrease further bleeding if endoscopy will be delayed or cannot be performed

Sreedharan A, et al. Cochrane Database Syst Rev 2010(7): CD005415.
Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
Hwang JH, et al. Gastrointest Endosc 2012;75(6):1132-8.

Prokinetic Agents: The Role and Benefit of Pre-Endoscopic Erythromycin

Erythromycin vs. No Erythromycin (N=598)	Difference (95% CI)
Adequate Gastric Mucosal Visualization	OR 4.14 (2.01-8.53); p<0.01
Need for Second Look Endoscopy	OR 0.51 (0.34-0.77); p<0.01
Length of Hospital Stay	Mean difference -1.75 days (-2.43 to -1.06); p<0.01

- ACG Guidelines (2012): Use erythromycin 250 mg IV 30-120 minutes before endoscopy
- ASGE Guidelines (2012): Use erythromycin if high-probability of fresh blood
- Limited data on Metoclopramide to suggest efficacy

Rahman R, et al. Ann Gastroenterol 2016;29(3):312-7.
Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
Hwang JH, et al. Gastrointest Endosc 2012;75(6):1132-8.

Myth Busters: Nasogastric Tube Placement and Lavage

- *NOT Recommended*

- NGT lavage not required to make diagnosis or as a prognosticator
  - Positive lavage: blood or coffee ground material
  - "Negative lavage": Presence of Bile (Not clear fluid)
  - High false negative rate

- Nasogastric aspiration/decompression of limited efficacy for clearance/visualization

- No documented therapeutic effect for hemostasis of ice cold water lavage

Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.

Prophylactic Endotracheal Intubation in UGI Bleeds

Indications:

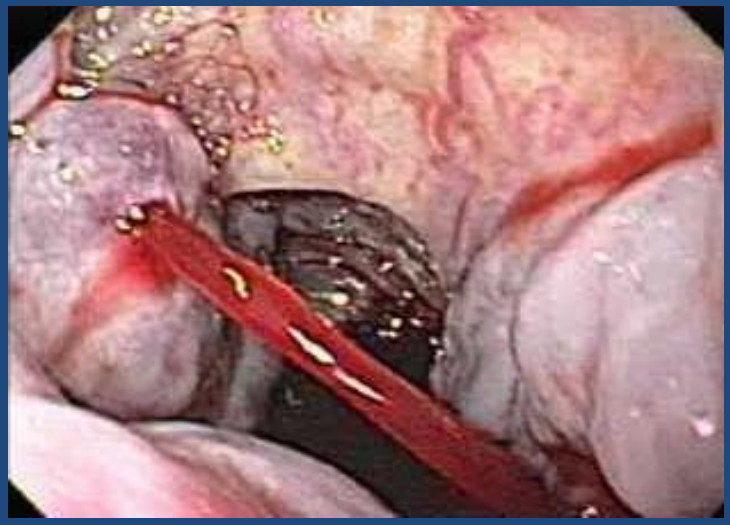
- Massive hematemesis
- Altered mental status
- Airway protection

Considerations:

- Potential risk of aspiration pneumonia
- Potential risk of cardiac adverse events (shock)

Hayat U. Gastrointest Endosc 2017;86:500-9

Special Scenario: Suspected Variceal Bleeding



- **Warning Signs**: cirrhosis/portal HTN, EtOH, elevated LFTs, jaundice, thrombocytopenia, coagulopathy, ascites, prior varices
- PPI: 80mg IV bolus x1 then drip 8 mg/hr
- Octreotide: 50mcg IV bolus x1 then drip 50 mcg/hr (continue for 3-5 days if variceal bleed on EGD)
- Antibiotics: IV ceftriaxone 1g q24h or quinolone or broader to start then may switch eventually to PO to complete 7 day course
- Platelets: Consider transfusion if < 50,000
- Correct Coagulopathy: Consider transfusing FFP if INR > 1.5-2.0
- Consider endotracheal intubation
- Consult colleagues early: GI, ICU, IR for possible TIPS

Hwang JH, et al. Gastrointest Endosc 2014;80(2):221-7.
https://www.gastrointestinalatlas.com/english/varices.html

Endoscopic Assessment and Management of Upper Gastrointestinal Bleeding

Endoscopic Management of UGI Bleeds: Factors to Consider

- Timing: When to Perform Endoscopy?
- Endoscopic Therapy:
  - Conventional Methods vs. New Techniques
- Methods to Decrease Rebleeding

Timing of Upper Endoscopy: The 24 Hour Window

ACG 2012 Guideline Recommendation :[1]

- "Patients with upper GI bleeding should generally undergo endoscopy within 24 hours of admission, following resuscitative efforts to optimize hemodynamic parameters and other medical problems."

Better Outcomes if EGD Within 24 Hours: [2]

- Study of 1.8 Million UGI Bleeds in NIS 2007-13
- 3x increased risk of death without EGD (3.0 vs. 8.5%)
- 50% lower mortality if EGD within 24 hours vs. later
- Early EGD (< 24 hours) → decreased morbidity, shorter LOS, and lower total hospital costs

1. Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.

2. Garg SK. Endoscopy International Open. 2017;05:E376-86.

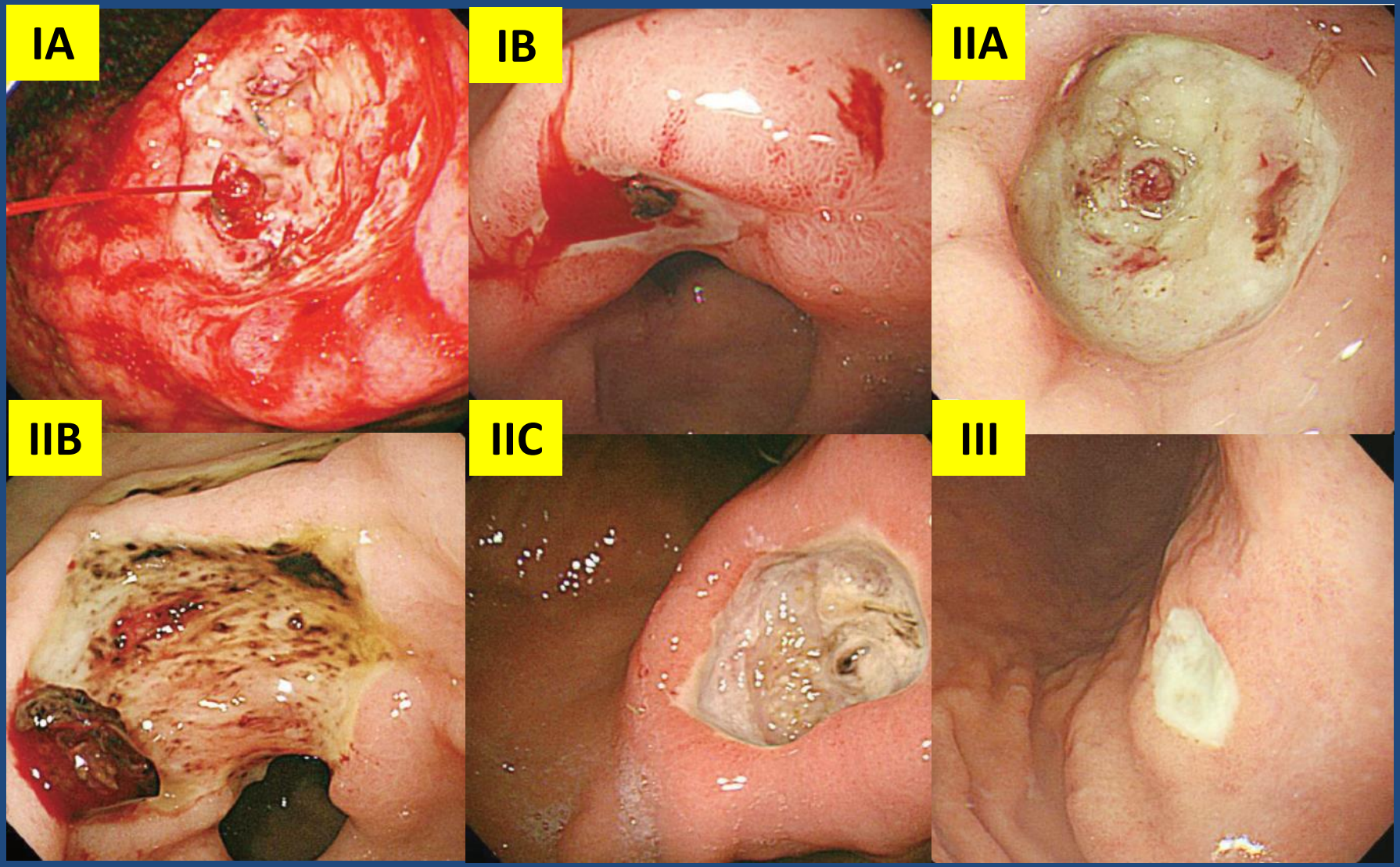
Optimal Timing of Endoscopy Within 24 Hours: Emergent vs. Urgent Endoscopy

- Emergent endoscopy (< 6-8 hours) vs. Urgent endoscopy (8-24 hours): [1-3]
  - Retrospective series of 860 patients
  - Increased endoscopic therapy in emergent group
  - No differences in rebleeding rate, length of stay, transfusion requirements, need for surgery, or mortality

- Emergent Endoscopy (<12 hours) if: [4-7]
  - Initial hemodynamic instability
  - Hematemesis or suspected active bleeding
  - AFTER stabilization and resuscitation
  - Potential benefit for high-risk patients (incl. variceal)[7]

1. Tai CM. Am J Emerg Med 2007;25:273-8.
2. Targownik LE. Can J Gastroenterol 2007;21:425-9.
3. Sarin N. Can J Gastroenterol 2009;23:489-93.
4. Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
5. Tsoi KKF. Nat Rev Gastroenterol Hepatol 2009;6:463-9.
6. Maggio D. Can J Gastroenterol 2013;27:454-8.
7. Lim LG, et al. Endoscopy 2011;43:300-6..

Forrest Classification of Peptic Ulcers



Kim SY, et al. Clin Endosc 2012;45(3):220-3

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Forrest Classification of Peptic Ulcers and Prevalence

Stigmata of Recent Hemorrhage	Forrest Classification	Prevalence
Active Spurting Bleeding	IA	12% (Spurting + Oozing)
Active Oozing Bleeding	IB	
Non-Bleeding Visible Vessel	IIA	8%
Adherent Clot	IIB	8%
Flat Pigmented Spot	IIC	16%
Clean Base	III	55%

Enestvedt BK, et al . Gastrointest Endosc 2008;67:422-9.

Natural History of Further Bleeding, Surgery and Mortality Based on Stigmata of Recent Hemorrhage

Stigmata	Further Bleeding (N=2994)	Surgery for Bleeding (N=1499)	Mortality (N=1387)
Active Bleeding	55% (17-100%)	35% (20-69%)	11% (0-23%)
Non-Bleeding Visible Vessel	43% (0-81%)	34% (0-56%)	11% (0-21%)
Adherent Clot	22% (14-36%)	10% (5-12%)	7% (0-10%)
Flat Pigmented Spot	10% (0-13%)	6% (0-10%)	3% (0-10%)
Clean Ulcer Base	5% (0-10%)	0.5% (0-3%)	2% (0-3%)

Laine L , et al. N Engl J Med 1994;331:717-27.

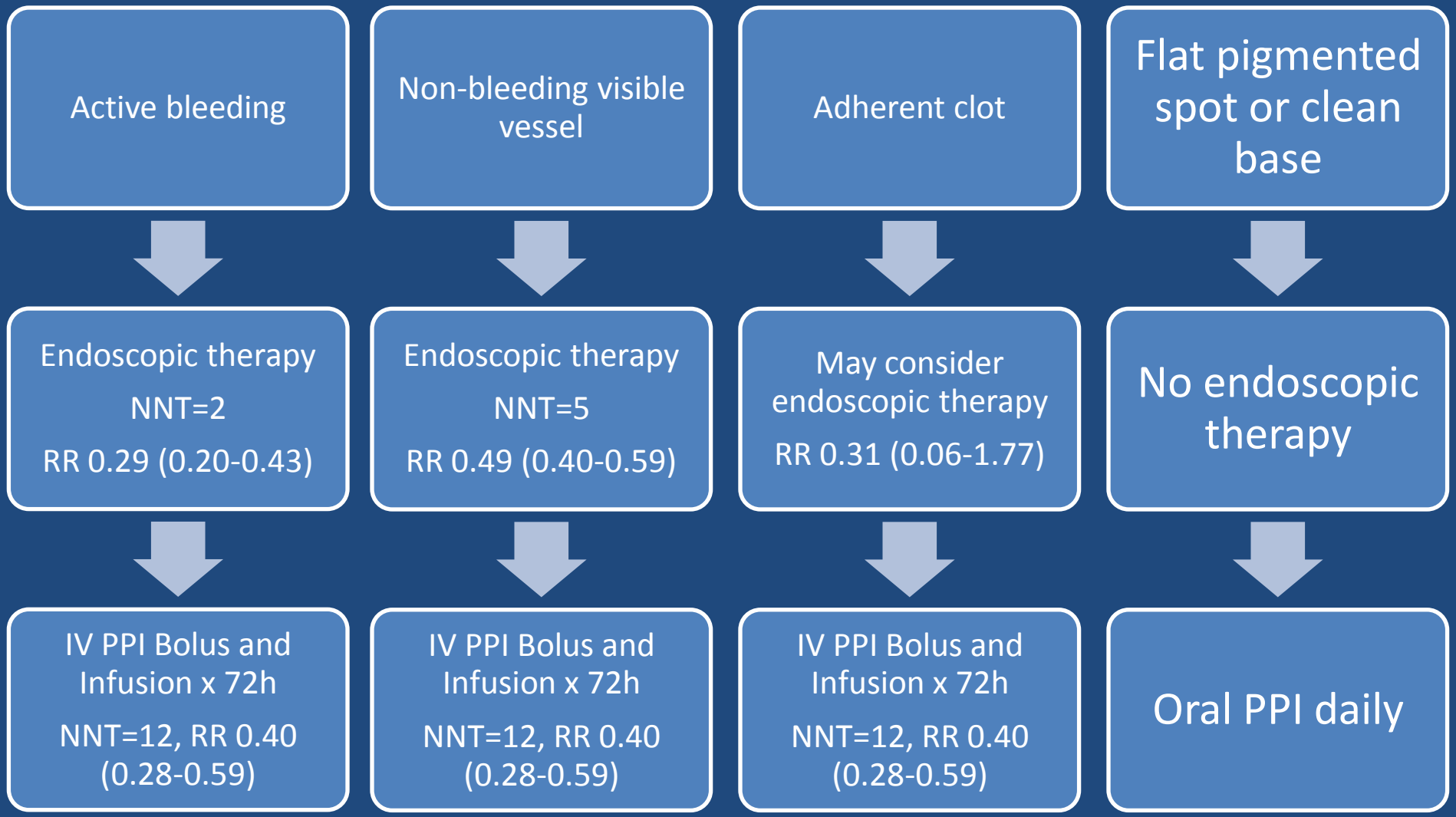
Risk of Recurrent Bleeding Without Endoscopic Therapy Based on Stigmata of Recent Hemorrhage

Stigmata	Risk of Recurrent Bleeding Without Therapy
Active Arterial Bleeding (Spurting)	Approaches 100%
Ulcer Oozing (Without other stigmata)	10-27%
Non-Bleeding Visible Vessel	Up to 50%
Non-Bleeding Adherent Clot	8-35%
Flat Spot/Pigmented Spot	< 8%
Clean Base	< 3%

Merit Endoscopic Therapy

Jensen DM. Can J Gastroenterol 1999;13:413-5.
Johnston JH. Gastrointest Endosc 1990;36:S16-S20.
Savides TJ, et al. Gastroenterol Clin N Am 2000;29:465-87.
Kovacs TO, et al. Curr Treat Options Gastroenterol 2007;10:143-8.
Sung JJ, et al. Ann Intern Med 2003;139:237-43.

Recommended Management Based on Ulcer Stigmata

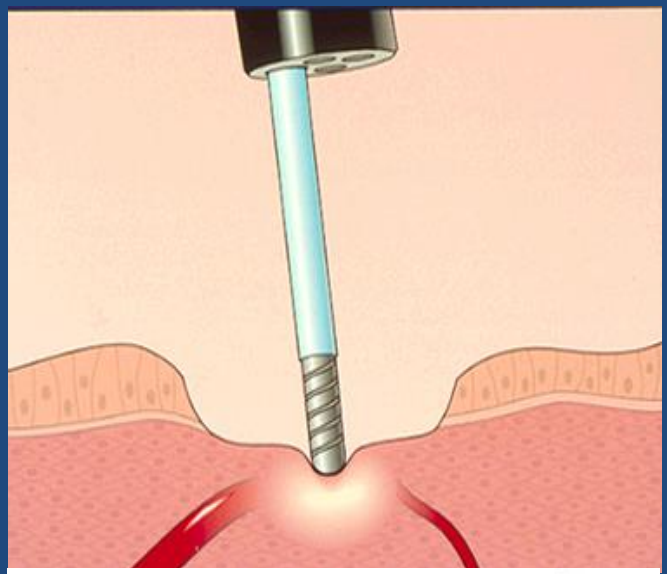


Post-EGD IV PPI: Surgery NNT=28, RR 0.43 (0.24-0.76); Mortality NNT= 45, (RR 0.41 (0.20-0.84)

Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
Laine L , McQuaid KR. Clin Gastroenterol Hepatol 2009;7:33-47.

Traditional Endoscopic Therapeutic Modalities

- Injection (epinephrine 1:10,000)
  - NOT to be used as monotherapy
  - Further bleeding: RR 1.72 (1.08-2.78), NNT=9
- Thermal (contact): Bipolar (Gold) or Heater Probes
  - Further bleeding: RR 0.44 (0.36-0.54), NNT=4
  - Initial hemostasis: RR 11.70 (5.15-26.56)
  - Surgery/Mortality: RR 0.58 (0.34-0.98), NNT=33
- Thermal (non-contact): Argon Plasma Coagulation (APC)
- Mechanical: Hemoclips, Banding Devices if Varices
- **Combination Therapy Preferred**
  - **Epinephrine + Thermal or Mechanical**
  - **Further bleeding: RR 0.34 (0.23-0.50), NNT=5**



Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
Laine L , McQuaid KR. Clin Gastroenterol Hepatol 2009;7:33-47.
http://www.bostonscientific.com/en-US/products/clips/resolution-clip.html

Emerging Endoscopic Therapy Modalities

- New types of hemoclips and loop devices
- Over-the-scope clips
- Monopolar cautery
- Ablation
- Hemostatic Sprays
- Endoscopic Suturing
- Endoscopic Ultrasound Guided Therapies

https://hemospray.cookmedical.com
https://synecticsmedical.co.uk
https://apolloendo.com/overstitch/
http://medical.olympusamerica.com/products/curved-linear-array-eus

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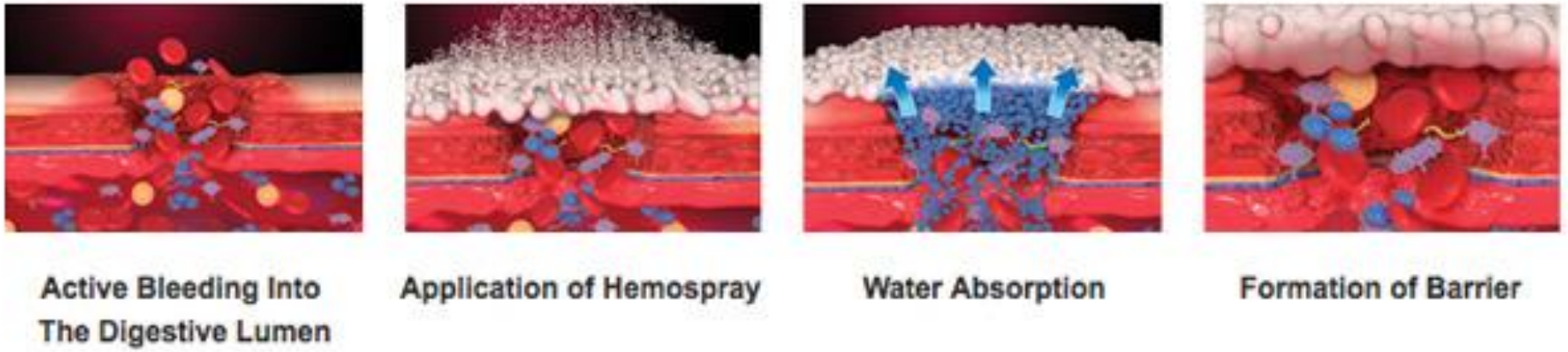
Hemospray© Mechanism and Efficacy



- Immediate Hemostasis Efficacy: 92.3% (95% in High-risk Forest 1a/1b lesions)
- Rebleeding Rate at 7 days: 20.6% overall (25% in high-risk lesions)

Chen Y. Gastrointest Endosc Clin N Am 2015;25:535-52
https://hemospray.cookmedical.com/

Hemospray© Performance Data

- "GRAPHE" Registry of 202 UGI bleed patients treated with Hemospray for first-line (46.5%) or rescue (53/5%) therapy[1]

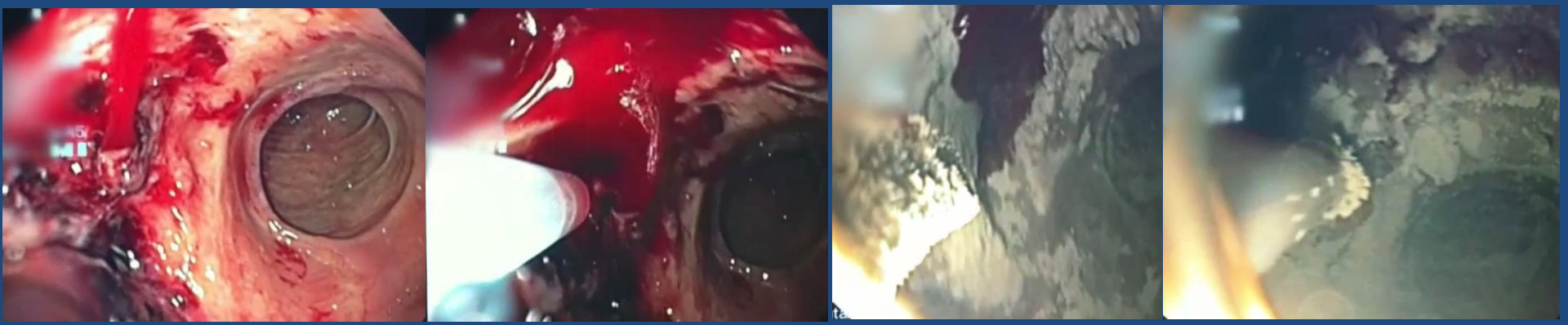
Lesion Type	Immediate Hemostasis	Recurrent Bleeding at Day 8	Need for Further Treatment
Ulcer: Forrest IA	93.3% (14/15)	66.7% (10/15)	60% (9/15)
Ulcer: Forrest IB	95.3% (41/43)	31.7% (13/41)	27.5% (11/40)
Sphincterotomy	100% (7/7)	28.6% (2/7)	28.6% (2/7)
Malignancy	95.1% (58/61)	25% (14/56)	27.8% (15/54)

- Prospective international multicenter study of 314 pts treated with Hemospray[2]

Clinical Outcome	Monotherapy	Combination Therapy	Rescue Therapy	P-Value
Immediate Hemostasis	92%	89%	86%	0.35
Rebleeding	7.3%	10%	19%	0.08
30-Day Mortality	25.4%	15%	22%	0.04

1. Haddara S, et al. Endoscopy 2016;48(12):1084-1095.
2. Alzoubaidi D, et al. DDW 2018 Abstract.

Hemospray© Additional Considerations



- Special expertise & equipment not required
- Potential uses in malignant bleeding and locations not amenable to endoscopic therapy
- Effective only in lesions with active bleeding (oozing or spurting)
- Second treatment modality or repeat endoscopy needed if high-risk lesion

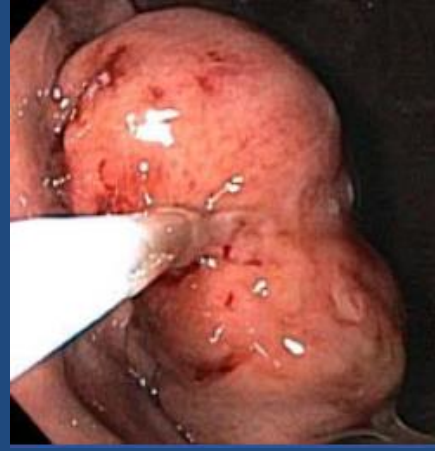
Photos courtesy of Cook Medical, Inc.

Over The Scope Clips (OTSC)

- OTSC is a cap-mounted device with clip deployed similar to banding device
- Potential Benefits: Larger mucosal defects or bleeding from a lesion in a difficult tposition
- Limited performance data to date:
  - Technical Success: approaches 100%
  - Clinical Success: approximately 70-90%
  - Improved performance if used as first-line as opposed to rescue therapy
  - RCT of 66 pts showing OTSC in treating recurrent bleeding peptic ulcers has decreased risk of rebleeding than "standard therapy" (6% vs. 42%; $p<0.001$)[1]

1. Schmidt A, et al. Gastroenterology 2018;155(3):674-686.
https://synecticsmedical.co.uk
R. Conigliaro, M. Frazzoni. Diagnosis and Endoscopic Management of Digestive Diseases, 2017; DOI 10.1007/978-3-319-42358-6_2.

Endoscopic Doppler Probe



- Doppler (sound-only) probe passed through the working channel of the endoscope
- Goal: localize vessels and confirm eradication of flow after endoscopic therapy

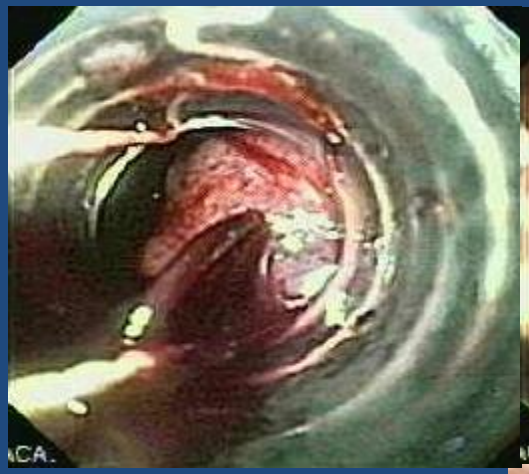
- RCT of 148 UGI bleeds comparing rebleeding rate of endoscopically (visually) guided only hemostasis (Control) vs. Doppler probe guided[1]

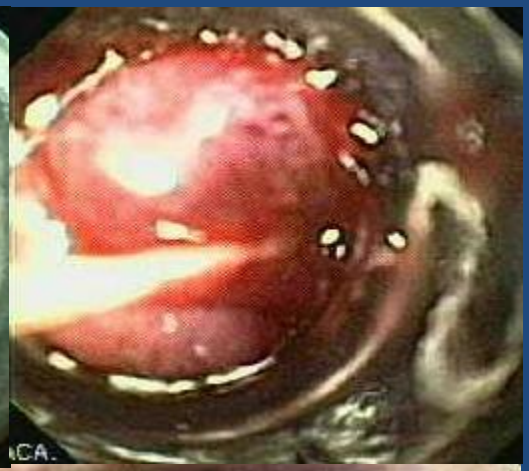
Forrest Classification	Control Rebleeding Rate	Doppler-Guided Rebleeding Rate	P-Value
Active arterial bleeding	5/10 (50%)	4/14 (28%)	
Non-bleeding visible vessel	7/27 (26%)	4/26 (15%)	
Adherent clot	4/16 (25%)	0/12 (0%)	
Flat pigmented spot	3/16 (19%)	0/16 (0%)	
Oozing arterial bleeding	1/7 (14%)	0/4 (0%)	
Total	**20/76 (26%)**	**8/72 (11%)**	**0.02**

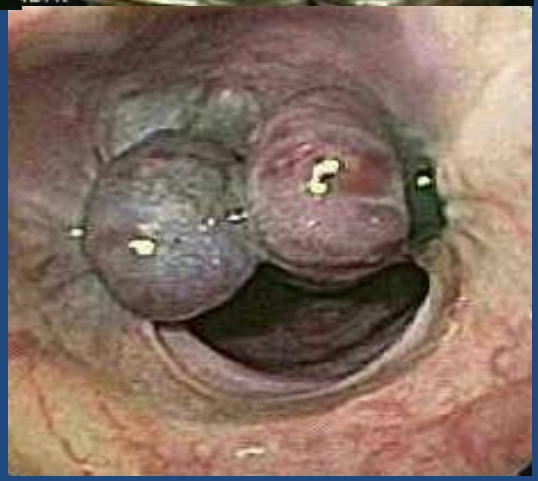
Jensen DM, et al. Gastroenterology 2017;152(6):1310-1318.e1
Wong RCK, et al. Gastrointest Endosc 2007;65(3):491-496.

Special Scenario: Esophageal Variceal Bleeding

- Endoscopic Variceal Ligation/Banding Ideal
- Endoscopic Injection of Sclerotherapy
- Medical Management:
  - IV PPI, Octreotide, Antibiotics
- Beta-blockers long-term
- Balloon Tamponade: temporize if endoscopic failure
- IR for TIPS/BRTO if treatment failure or gastric varices







Hwang JH, et al. Gastrointest Endosc 2014;80(2):221-7.
https://www.gastrointestinalatlas.com/english/variceal_banding_iv.html

Post-Endoscopic Management of Upper Gastrointestinal Bleeding

Post-Endoscopic Management: ACG 2012 Guidelines

- PPI IV Bolus and Infusion x 72h if high-risk stigmata present; oral daily PPI if flat spot/clean based ulcer
  - Question of benefit of PPI infusion (8mg/h) vs. intermittent 40mg IV q12h
  - Intermittent PPI (IV or oral) risk of further bleeding vs. placebo: RR 0.53 (0.35-0.78); no difference in surgery or mortality
- Routine second-look endoscopy 24h post-EGD with endoscopic therapy is not recommended
- Repeat endoscopy if clinical evidence of recurrent bleeding
- After second therapeutic EGD, if evidence of further bleeding, recommend interventional radiology angiography/embolization, or surgery

Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.

Rebleeding Predictors After Endoscopic Intervention

Predictor	# of Studies	Odds Ratio Range
Hemodynamic Instability	5	2.2-3.6
Comorbid Illness	2	7.6
Active Bleeding	5	1.6-14
Ulcer Size > 2 cm	4	1.8-4.6
Posterior Duodenal Ulcer	3	2.4
Lesser Curvature Gastric Ulcer	2	2.7

- Possible Signs of Rebleeding: Recurrent overt GI bleeding, drop in H/H, hemodynamic instability, drop in CVP, drop in urine output.

Elmunzer BJ, et al. Am J Gastroenterol 2008;103:2625-32

When to Discharge and When to Feed?[1]

High-Risk Stigmata (active bleeding, visible vessels, clots):

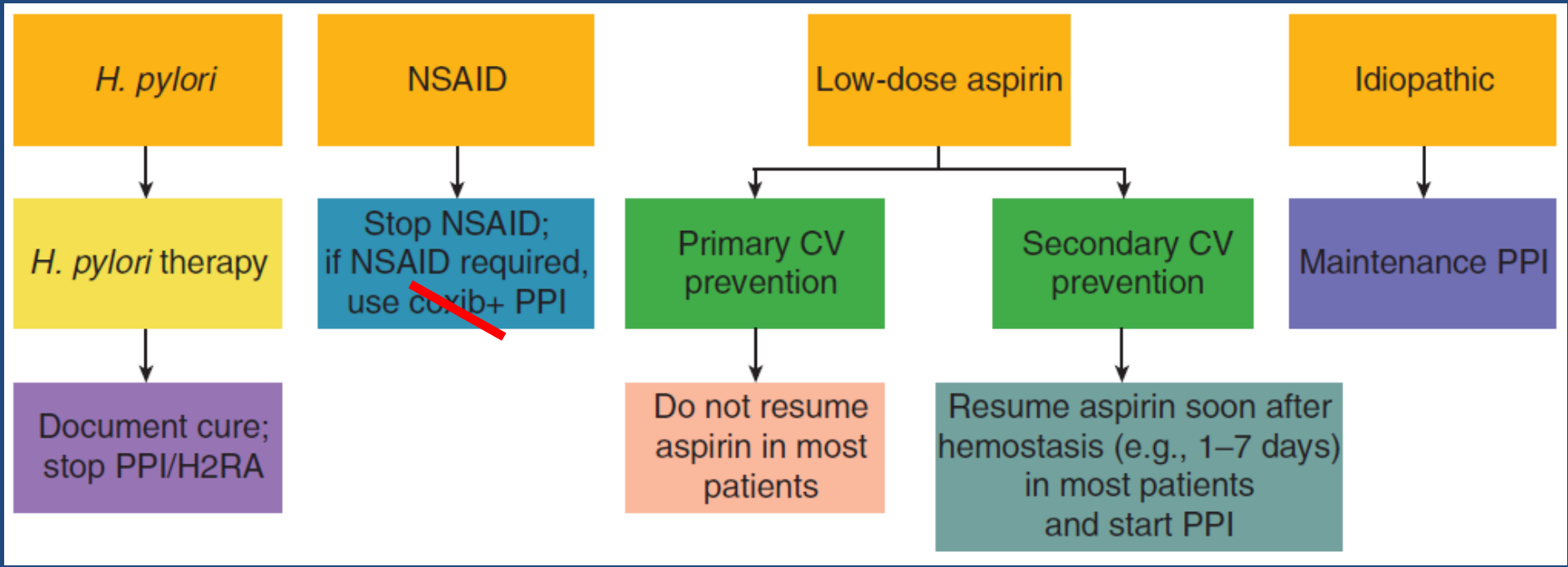
- Hospitalize: 3 days (72h of IV PPI) if no rebleeding
  - RCT of 764 pts at 91 centers in 16 countries with ulcer bleed with high-risk stigmata: 24% rebled after 3 days, 6% rebled after 7 days[2]
- Diet: Clear liquids after endoscopy x 48h
  - Guidelines vs. Practice??

Clean-Based Ulcers, Erosive Disease, Mallory-Weiss Tears (Lack of data on pigmented spots):

- Hospitalize: Discharge after EGD if:
  - H/H and Vitals stable
  - No other significant comorbidities
  - Safe/monitored environment to be discharged to
- Diet: Regular diet after endoscopy
  - RCT of 258 pts with immediate refeeding of regular diet vs. delayed refeeding (clear liquids at 36h and regular diet at 48 h) with no significant differences (rebleeding rate 4% vs. 5%)[3]

1. Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
2. Sung JJ , et al. Ann Intern Med 2009;150:455-64.
3. Laine L , et al. Gastroenterology 1992;102:314-6.

Management to Prevent Recurrent Ulcer Bleeding[1]

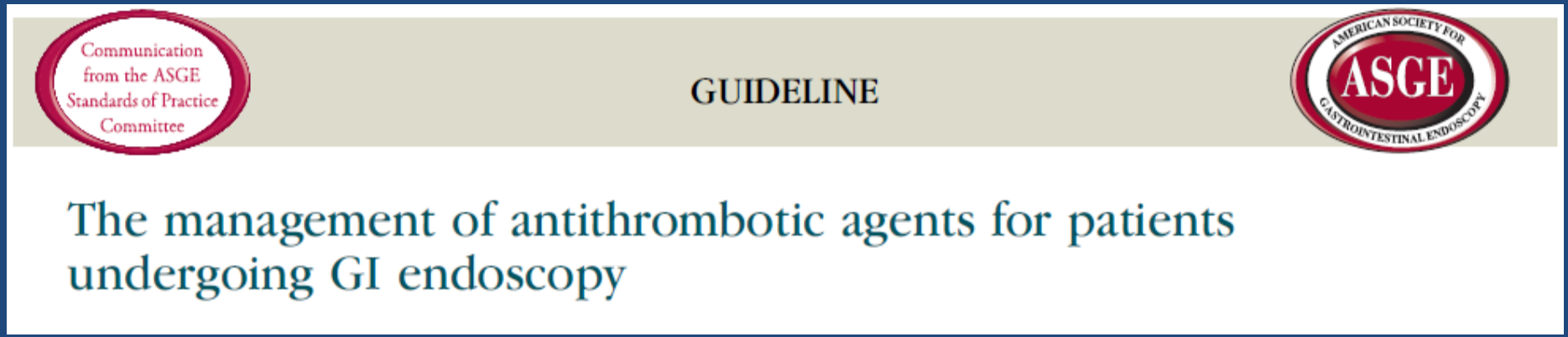


- Rebleeding Rates without Therapy (follow up range of 6 months – 7 years): 15-42%[2-10]

1. Laine L, Jensen D. Am J Gastroenterol 2012;107:345-60.
2. Jensen DM, et al. N Engl J Med 1994;330:382-6.
3. Gisbert JP, et al. Aliment Pharmacol Ther 2004;19:617-29.
4. Jaspersen D, et al. Gastrointest Endosc 1995;41:5-7.
5. Rokkas T, et al. Gastrointest Endosc 1995;41:1-4.
6. Vcev A, et al. Acta Fam Med Flum 1996;21:59-65.
7. Bataga S, et al. Gut 1997;41 (Suppl 3):A167.
8. Chan FKL, et al. N Engl J Med 2001;344:967-73.
9. Lai KC, et al. N Engl J Med 2002;346:2033-8.
10. Wong GLH, et al. Gastroenterology 2009;137:525-31.

Anticoagulant and Antiplatelet Agent Classes and Characteristics

2016 ASGE Guidelines



Acosta RD, et al. Gastrointest Endosc 2016;83(1):3-16.
http://dx.doi.org/10.1016/j.gie.2015.09.035
PubMed ID: 26621548

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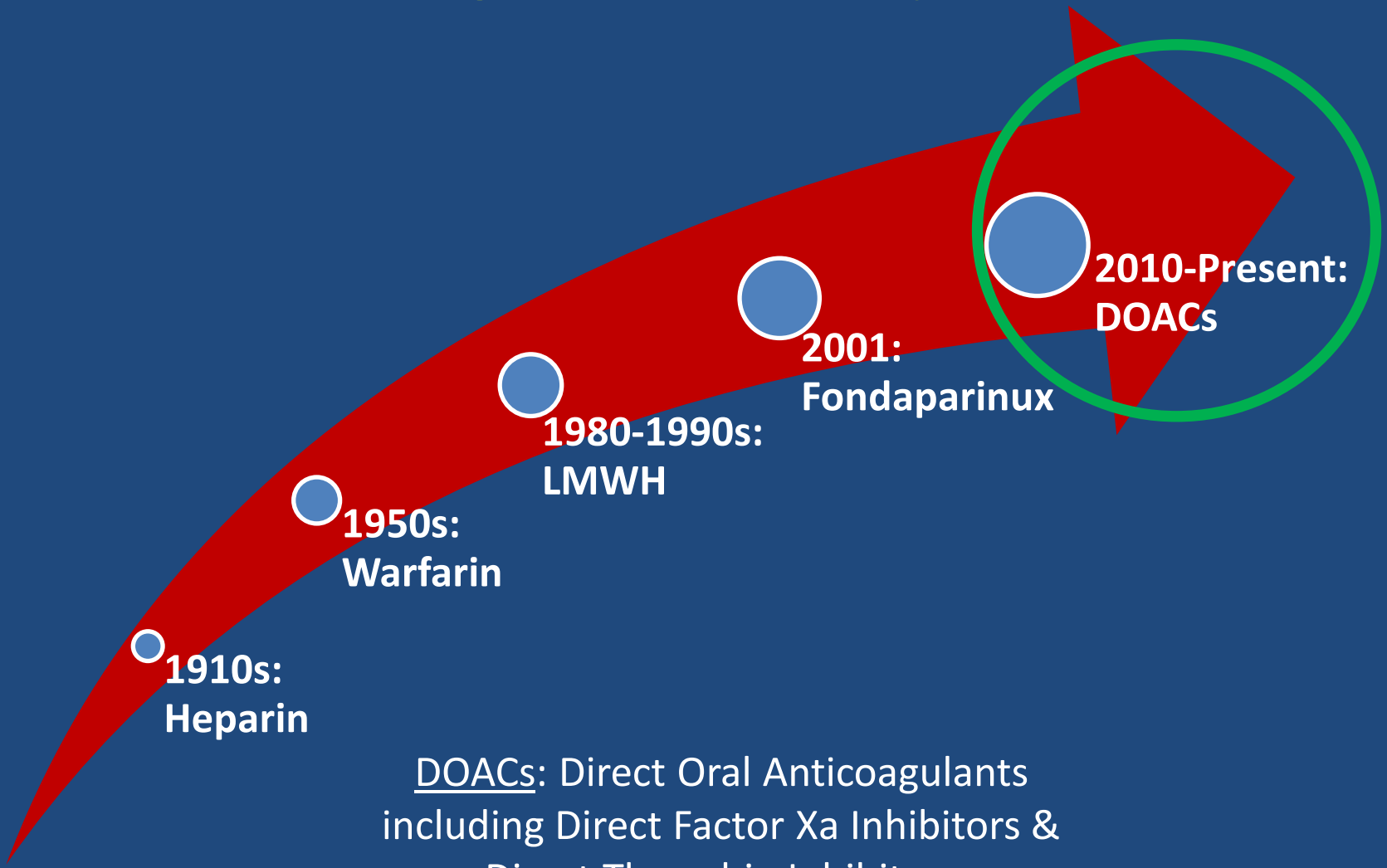
Anticoagulant Use Is Frequent and Increasing

- Prevalence of Atrial Fibrillation in the United States:
  - 2.6 million → 12 million by 2050[1]
- 900,000 incident or recurrent, fatal and nonfatal Venous thromboembolism (VTE) events annually in the U.S.[2]
- Total annual cost from VTE (including lost earnings from premature morality): $13-27 billion as of 2011[3]
- Over 30 million warfarin prescriptions annually in the U.S. → $158 million per quarter in 2010[4]
- Direct Oral Anticoagulants (DOACs): 62% of new anticoagulant Rx by 2013 → approximately $10 billion annually by 2016[5,6]

1. Lloyd-Jones D, et al. Circulation 2010.
2. Heit JA. Arterioscler Throm Vasc Biol 2008.
3. Mahan CE, et al. Thromb Haemost. 2012.
4. Raji MA, et al. Ann Pharmacother 2013.
5. Desai NR, et al. Am J Med 2014.
6. Frost & Sullivan Research Service. http://www.researchmarkets.com/reports/2020184/analysis_of_the_anticoagulant_market 2015.

Anticoagulant Development



DOACs: Direct Oral Anticoagulants including Direct Factor Xa Inhibitors & Direct Thrombin Inhibitors

Types of Anticoagulant Agents

Goal: Interfere with the Native Clotting Cascade

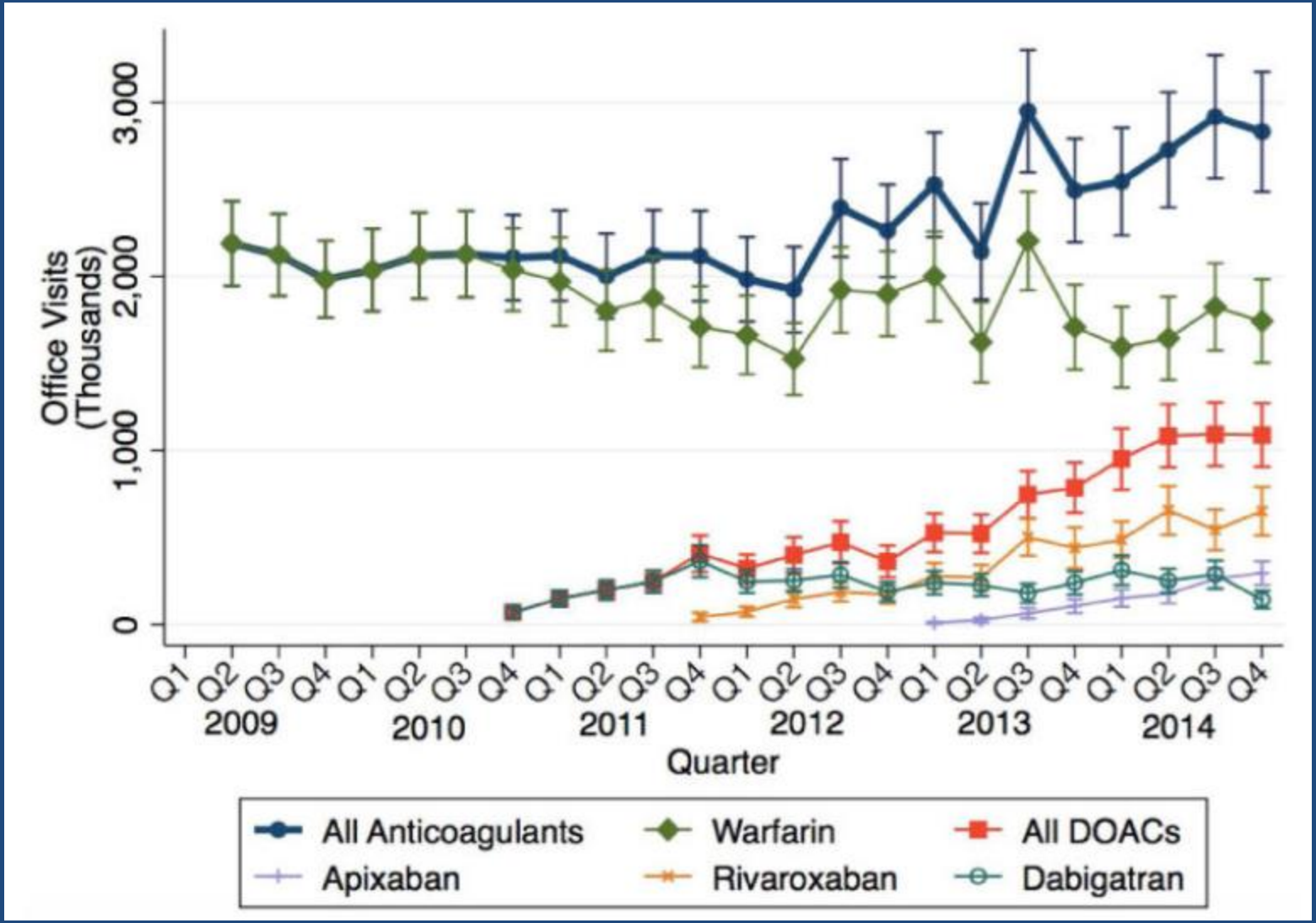
- Vitamin K Antagonists
  - Warfarin (Coumadin)
- Direct Factor Xa Inhibitors
  - Rivaroxaban (Xarelto)
  - Apixaban (Eliquis)
  - Edoxaban (Savayasa)

No reliable monitoring tests currently

- Heparin Derivatives
  - Unfractionated
  - Low molecular weight: Enoxaparin (Lovenox), Dalteparin (Fragmin)
  - Fondaparinux (Arixtra)
- Direct Thrombin Inhibitors
  - Dabigatran (Pradaxa)
  - Hirudins
  - Argatraban (Acova)

Acosta RD, et al. Gastrointest Endosc 2016;83(1):3-16

Direct Oral Anticoagulants Are Being Increasingly Used



Barnes GD, et al. Am J Med 2015

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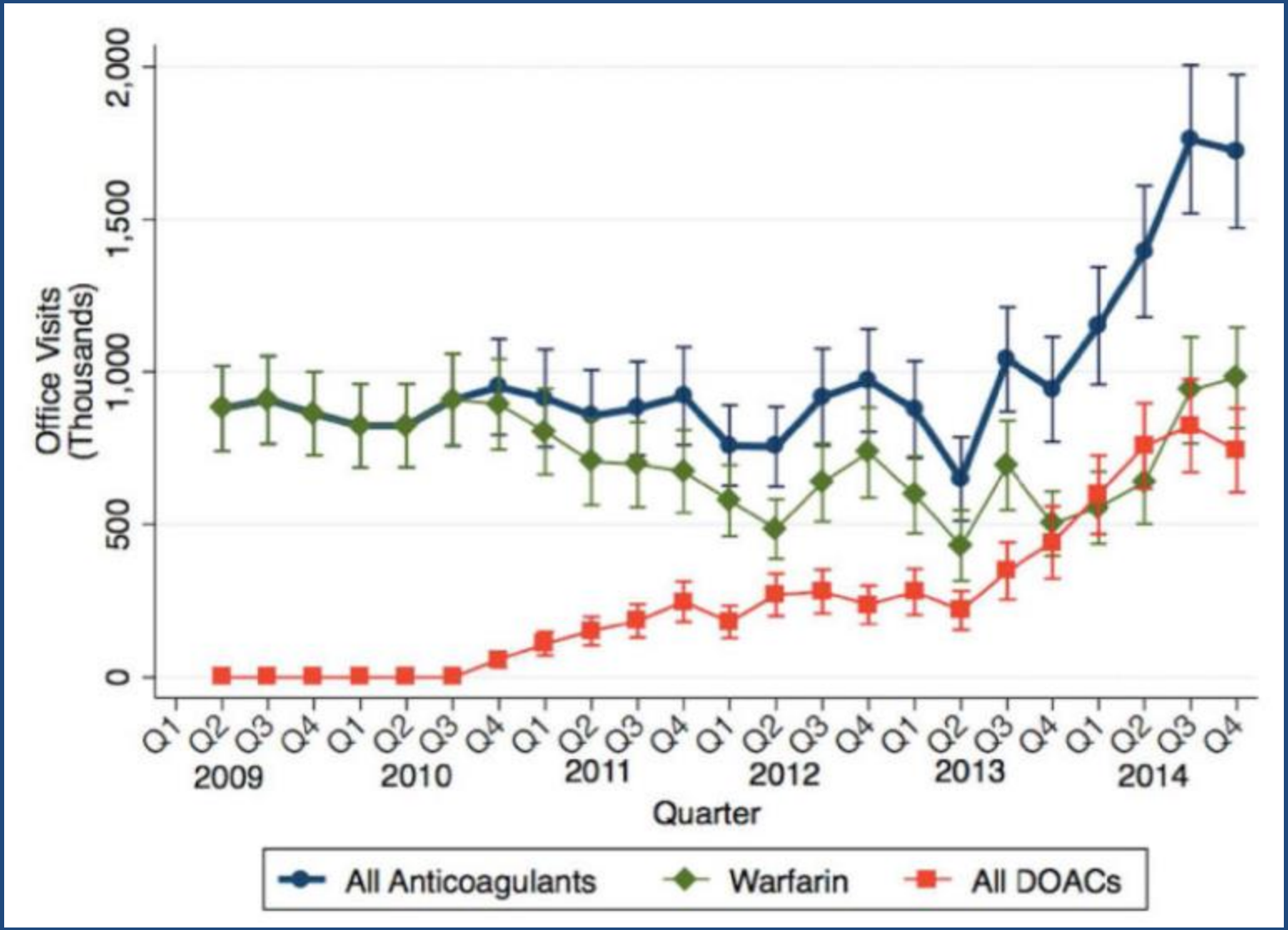
Use of Direct Oral Anticoagulants vs. Warfarin in A-Fib



Barnes GD, et al. Am J Med 2015

Anticoagulant Agents: Duration of Action & Reversal Options

Specific Agent(s)	Duration of Action	Reversal for Elective Procedure	Reversal for Urgent Procedure
Warfarin			
Unfractionated Heparin			
Low Molecular Weight Heparin			consider rVIIa
Fondaparinux	36-48 hours	Hold for at least 36 hours	Protamine sulfate; consider rVIIa
Direct Factor Xa Inhibitors	Onset: 1-4 h	Hold 1-4 days pending CrCl	Charcoal (if intake within 2-3h); nonactivated or activated PCC
Direct Thrombin Inhibitors	Onset: 1-3 h T½: 13-27 h	Hold 1-6 days pending CrCl & Proc. Bleed Risk	Charcoal (if intake within 2-3h); nonactivated or activated PCC; Hemodialysis

New Antidotes:
Dabigratran (Pradaxa): Idarucizumab (Praxbind)
Apixaban (Eliquis): Andexanet Alpha → FDA Fast Track
Edoxaban: Aripazine (PER 977) → FDA Fast Track

PCC: prothrombin complex concentrate. rVIIa: Recombinant Factor VIIa.

Acosta RD, et al. Gastrointest Endosc 2016;83(1):3-16

Types of Antiplatelet Agents

Goal: Decrease platelet aggregation → prevent thrombus formation

- Thienopyridines
  - Clopidogrel (Plavix)
  - Prasugrel (Effient)
  - Ticlodipine (Ticlid)
  - Ticagrelor (Brillinta)
- Aspirin/NSAIDs
- Protease-Activated Receptor-1 (PAR-1) Inhibitors
  - Vorapaxar (Zontivity)
- Glycoprotein IIb/IIIa Receptor Inhibitors
  - Abciximab (ReoPro)
  - Eptifibatide (Integrillin)
  - Tirofiban (Aggrastat)

Acosta RD, et al. Gastrointest Endosc 2016;83(1):3-16

Antiplatelet Agents: Duration of Action & Reversal Options

Specific Agent(s)	Duration of Action	Reversal for Elective Procedure	Reversal for Urgent Procedure
Aspirin	7-10 days	N/A	Hold; can give platelets
NSAIDS	Variable	N/A	Hold
Dipyridamole (Persantine)	2-3 days	Hold	Hold
Cilostazol (Pletal)	2 days	Hold	Hold
Thienopyridines	3-14 days (Clopidogrel 5-7 days)	Hold	Hold
GP IIb/IIIa Inhibitors	1-2 seconds – 24 hours	N/A	Hold; Hemodialysis (Tirofiban)
PAR-1 Inhibitor	5-13 days	Hold	Hold

Acosta RD, et al. Gastrointest Endosc 2016;83(1):3-16

Antithrombotic Agents and Endoscopy: Risk of GI Bleeding

Risk of GI Bleeding in Complex Antithrombotic Therapy

- Complex Antithrombotic Therapy: ASA + thienopyridine (i.e. clopidogrel) and/or warfarin[1]
- GI bleeding in patients on Complex Antithrombotic Therapy: **NNH = 42**[2-5]
- Further increased risk of GI bleeding in patients on triple therapy: ASA + clopidogrel + warfarin: **NNH = 12.5**[6,7]
- Risk of bleeding with adding direct oral anticoagulants (DOACs) to patients on dual antiplatelet therapy after acute coronary syndromes (ACS) is high[8]:
  - Systematic review & Meta-analysis of 7 placebo-controlled RCTs of 31,286 pts
  - Pooled Odds ratio 3.03; 95% CI 2.20-4.16
  - Absolute Risk 0.9%; 95% CI 0.7%-1.1%

1. Abraham NS. Clin Gastroenterol Hepatol 2013.
2. BMJ 1994;308:81-106.
3. Anand SS, et al. Circulation 1998.
4. Diener HC, et al. Lancet 2004.
5. Yusuf S, et al. NEJM 2001.
6. Sorensen R, et al. Lancet 2009.
7. Abraham NS, et al. Gastroenterology 2012.
8. Komocsi A, et al. Arch Intern Med 2012.

GI Bleeding in Elderly Patients with Complex Antithrombotic Therapy (78,133 Patients)

CAT-Related Events: 1 Year NNH	Anticoagulant + Antiplatelet Agent (Not Aspirin)	Aspirin + Anticoagulant	Aspirin + Antiplatelet Agent (DAPT)	Aspirin + Antiplatelet Agent + Anticoagulant
Upper GI Bleeding NNH (95% CI)	65 (24-379)	56 (22-231)	93 (34-544)	52 (20-210)
Lower GI Bleeding NNH (95% CI)	19 (11-37)	15 (9-30)	18 (10-37)	23 (13-49)
Transfusion NNH (95% CI)	43 (21-128)	16 (9-31)	51 (24-182)	25 (14-50)
Hospitalization NNH (95% CI)	39 (18-121)	34 (16-89)	67 (30-214)	45 (21-126)

1. Abraham NS, et al. Circulation 2013.

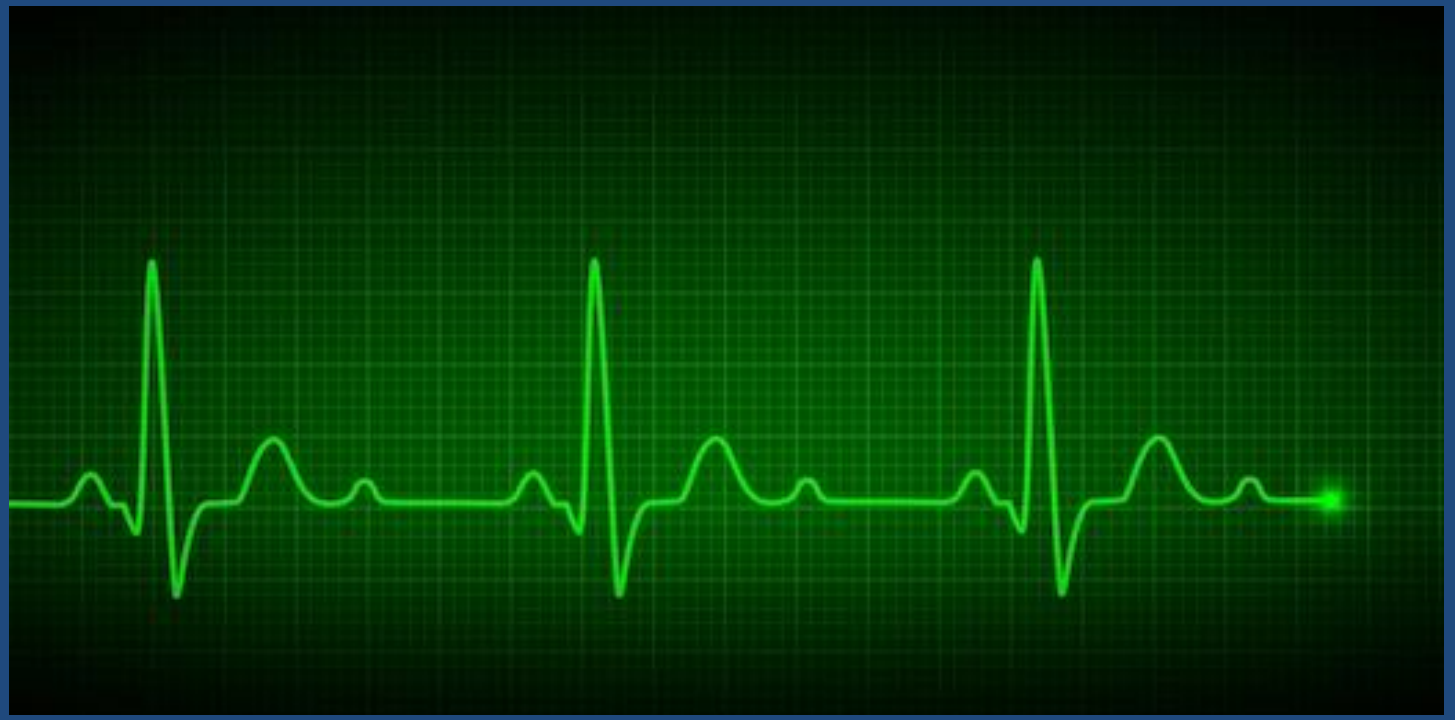
DOAC-Related GI Bleeding

Patient characteristics elevating risk of DOAC-Related bleeding:

- Age > 65 (vs. warfarin matched cohort) with further increase if Age > 75[1]
- Renal impairment: DOACs have partial renal clearance so decreased GFR increases DOAC half-life[2]
  - Dose adjustments for renal impairment unclear[3]
- Hepatic Disease: all DOACs have partial hepatic clearance[4]
  - Do not use if baseline coagulopathy
  - No dose adjustment for dabigatran or apixaban if Child-Pugh A; caution if Child-Pugh B
- Low body weight < 50kg[5]
- **Estimated 13,600 – 23,800 DOAC-related GI bleeds annually**[4]

1. Abraham NS, et al. BMJ 2015.
2. Salem JE, et al. Fundam Clin Pharmacol 2015.
3. Harper P, et al. NEJM 2012.
4. Abraham NS. Am J Gastroenterol 2016.
5. Gong IY, et al. Can J Cardiol 2013.

Are We Becoming



Cardio-Gastroenterologists?

http://www.shutterstock.com

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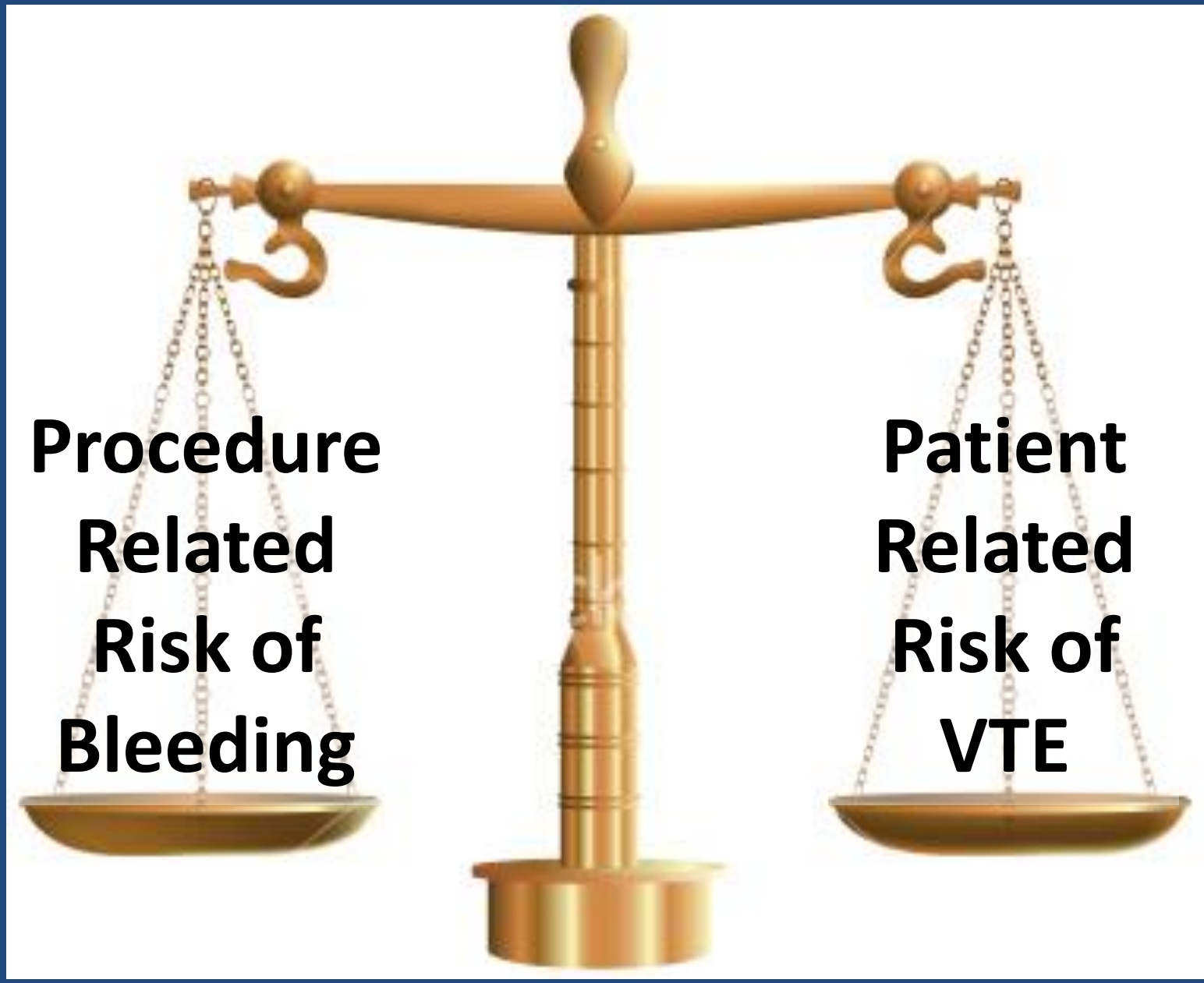
Key Factors to Consider

1. Urgency of the Procedure
2. Bleeding Risk of the Procedure
3. Effect of the Antithrombotic Agent on Bleeding Risk
4. Risk of Thromboembolism due to Peri-Procedural Interruption of the Antithrombotic Agent



Higher Risk Procedures	Low Risk Procedures
Polypectomy	Diagnostic EGD/colonoscopy with Biopsy
Endoscopic Mucosal Resection	Push Enteroscopy
Endoscopic Submucosal Dissection	Diagnostic Balloon-Assisted Enteroscopy
Ampullary Resection	Capsule Endoscopy
Sphincterotomy: Biliary or Pancreatic	ERCP (including Stenting & Dilation) without Sphincterotomy
Treatment of Varices	Argon Plasma Coagulation
Endoscopic Hemostasis	Barrett's Ablation
Tumor Ablation	
Therapeutic Balloon-Assisted Enteroscopy	
EUS with FNA*	EUS without FNA
Cystgastrostomy	
Pneumatic or Bougie Dilation	Enteral Stent Placement***
PEG Placement**	
PEJ Placement	

Acosta RD, et al. Gastrointest Endosc 2016;83(1):3-16

Risk of Thromboembolism Varies by Patient & Anticoagulation Indication

- Atrial Fibrillation: CHADS-VASc Score of ≥2 (high-risk for thromboembolism > 2.2%/year)[1]
- Mechanical heart valves[2]
- Venous thromboembolism[2]
- Cardiac Stents[3]: High-risk to stop Antiplatelet if:
  - Drug-eluting stent placement ≤ 12 months
  - Bare metal stent (BMS) placement ≤ 1 month
  - Acute coronary syndrome with BMS ≤ 12 months

1. Lip GY, et al. Chest 2010.
2. Acosta RD, et al. Gastrointest Endosc 2016.
3. Jneid H, et al. JACC 2012.

Antithrombotic Agent Management for Elective GI Procedures

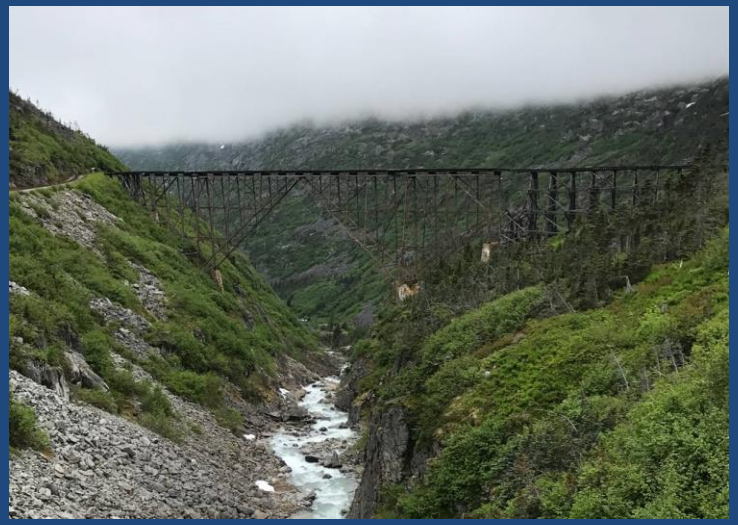
Anticoagulation Cessation for Elective Procedures

- If finite short period of time for anticoagulation (i.e. s/p Bare Metal Stenting or after VTE), **delay** elective procedures until anticoagulation is no longer indicated[1]
- Carefully weigh risks/benefits and consult specialists in patients needing longer-term anticoagulation (i.e. s/p Acute Coronary Syndrome or Drug-Eluting Stent)[2,3]
- Anticoagulation may be unable to be stopped in some patients
- Absolute risk of embolic event when stopping anticoagulation for 4-7 days: 1%[2,4]
- Re-initiate of anticoagulation (if with warfarin) within 4-7 days of cessation to prevent additional thromboembolic risk[5]
- **ASGE Recommendation: Continue anticoagulation in low-risk (of bleeding) procedures and stop for high-risk procedures (with bridge therapy if patient at high-risk for thromboembolism)[1]**

1. Acosta RD, et al. Gastrointest Endosc 2016.
2. Iakovou I, et al. JAMA 2005.
3. Mauri L, et al. NEJM 2007.
4. Blacker DJ, et al. Neurology 2003.
5. Witt DM, et al. Arch Intern Med 2012.

Bridge Therapy for Elective Procedures

- Patients on warfarin may be bridged with unfractionated heparin or LMWH
- RCT of 1884 pts with non-valvular A-Fib (low VTE risk) of heparin bridge vs. no bridge:[1]
  - Major Bleeding Events: 3.2% vs. 1.3%
  - Arterial Thromboembolism: 0.3% vs. 0.4%
- Patients who do not require bridge therapy:[2,3]
  - A-fib with CHADS-VASC < 2, bileaflet mechanical aortic valve
- Patients at high-risk for VTE should be bridged:[1-3]
  - A-fib with CHADS-VASC ≥2
  - Valvular A-fib
  - A-fib with history of CVA
  - Mechanical heart valves
  - LVAD
  - Recent VTE
  - A-fib with CHF
  - Post-ACS



1. Douketis JD, et al. NEJM 2015.
2. January CT, et al. J Am Coll Cardiol 2014.
3. Nishimura RA, et al. Circulation 2014.

Anti-Platelet Agent Cessation for Elective Procedures: Joint Recommendations from ACC/ACG[1]

- Avoid stopping antiplatelet agents after cardiac cath with stenting
- Avoid stopping clopidogrel (even if ASA continued) within first 30 days post-PCI with DES or BMS
- Defer elective procedures up to 12 months post-DES placement if clinically acceptable
- Perform endoscopic procedures with higher bleeding risk 5-7 days post-clopidogrel cessation, while continuing ASA
- Resume clopidogrel and ASA once procedural hemostasis achieved. Consider loading dose of clopidogrel if high-risk patient.
- Continue anti-platelet therapy if planned procedure is low bleeding risk

1. Becker RC, et al. Am J Gastroenterol 2009.

Antithrombotic Re-Initiation Post-Elective Procedures

- Weigh risk of bleeding post-procedure, the specific antithrombotic agent and its onset of action
- Resume anticoagulants ASAP, and antiplatelet agents once hemostasis achieved[1]
- Re-initiation of warfarin or heparin after colonoscopy associated with increased risk of bleeding within 1 week of polypectomy (OR 5.2; 95% CI 2.2-12.5)[2]
- AHA/ACC guidelines recommend restarting warfarin within 24 hours post-procedure if valvular heart disease and low thromboembolic risk, and heparin bridging if high risk[3]
- Limited data on re-initiation of DOACs post-GI procedures
  - Maximal drug effect within 2-4 hours
- If DOACs cannot be restarted within 24 hours and high thromboembolic risk, consider heparin bridge[4,5]

1. Acosta RD, et al. Gastrointest Endosc 2016.
2. Sawhney MS, et al. Endoscopy 2008.
3. Nishimura RA, et al. Circulation 2014.
4. Weitz JL, et al. Circulation 2012.
5. Dzik WS. Transfusion 2012.

Endoscopy for Acute Bleeding
and
Acute Coronary Syndromes (ACS)

Endoscopy for Acute Bleeding on Anticoagulation

- Endoscopic therapy for UGI bleeds is effective in anticoagulated patients
  - 95% initial success rate in 246 patients with INR of 1.3-2.7[1]
- Normalization of INR prior to endoscopy does NOT reduce risk of rebleeding but delays time to procedure[1,2]
- INR at time of endoscopy is not predictive of rebleeding[3]
  - Systematic review of 1869 non-Variceal UGI bleeds
- Reversal of warfarin with FFP or Prothrombin Complex +/- vitamin K[2,4,5]
- **Recommendation: Reasonable to perform endoscopy in bleeding patients with INR < 2.5**[2]

1. Wolf AT, et al. Am J Gastroenterol 2007.
2. Acosta RD, et al. Gastrointest Endosc 2016.
3. Shingina A, et al. Aliment Pharmacol Ther 2011.
4. Hollbrook A, et al. Chest 2012.
5. Nishimura RA, et al. Circulation 2014.

Reversal of Antiplatelet Agents in Acute GI Bleeding

- If serious or life-threatening bleeding: can stop agent or give platelets
- Resumption needed in most patients after endoscopic bleeding control
- ASA induced PUD: Restarting ASA + PPI better than clopidogrel monotherapy for recurrent GI bleed prevention[1,2]
- Resumption of cardiac ASA after PUD bleeding: RCT of 156 patients on PPI + ASA 80mg vs. Placebo[3]:
  - No significantly increased 30-day rebleeding risk (10.3% vs. 5.4%; 95%CI -3.6-13.4)
  - Increased 30-day mortality if ASA not resumed (1.3% vs 12.9%)
- **Recommendation: Resume antiplatelet agents once hemostasis achieved**[4,5]

1. Chan FK, et al. NEJM 2005.
2. Lai KC, et al. Clin Gastroenterol Hepatol 2006.
3. Sung JJ, et al. Ann Intern Med 2010.
4. Becker RC, et al. Am J Gastroenterol 2009.
5. Bhatt DL, et al. Circulation 2008.

Role of Urgent Endoscopy in Patients with Acute Coronary Syndromes or Recent Stenting

- 1-3% of patients with ACS will have a GI bleed during their index hospitalization[1-4]
- 4- to 7-fold increased risk of in-hospital mortality if GI bleed in ACS patients vs. ACS without GI bleed[2,3]
- Patients with UGI bleed leading to acute MI are more likely to require endoscopic therapy vs. patients with GI bleed after an acute MI (OR 3.9; 95% CI 1.8-8.5, $p<0.004$)[4]
- EGD for significant overt GI bleeding in setting of acute MI prior to cardiac catheterization[5]:
  - Decreased mortality if EGD prior to Cath: 97 vs. 600 per 10,000 pts
  - Fewer non-fatal complications if EGD before Cath: 1271 vs. 6000 per 10000 pts
  - Endoscopy 1st not beneficial in occult GI bleeding and acute MI

1. Moscucci M, et al. Eur Heart J 2003.
2. Al-Mallah M, et al. J Thromb Thrombo 2007.
3. Abbas AE et al. Am J Cardiol 2005.
4. Lin S, et al. Dig Dis Sci 2006.
5. Yachimski P, et al. Dig Dis Sci 2009.

Take Home Points

1. Recognize the different types of gastrointestinal bleeding

2. Appreciate the importance of initial volume resuscitation, medical therapy, and endoscopic therapy in the diagnosis and management of acute upper GI bleeds

3. Understand the urgency and bleeding risk of the planned GI procedure

4. Identify the effect of the antithrombotic agent on bleeding risk and the effect of stopping that agent on the patient's risk of thromboembolism

5. This is a team effort: When in doubt, consult the appropriate colleague

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