BRIGHAM AND WOMEN'S HOSPITAL

Non-variceal Upper GI Bleeding: New approaches to management and endoscopic therapies

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Disclosure

- Chair, Scientific Advisory Board for Iterative Scopes (AI for colonoscopy)
- Consultant, 1Globe Healthcare

Objectives

- To understand the importance of resuscitation
- To know the timing and role of endoscopic therapy for control of GI bleeding
- To know the current endoscopic treatment options
- Be aware of recent advances in therapy
- Understand how to reduce rebleeding
- To learn about the new Consensus Guidelines

Non-variceal upper gastrointestinal bleeding

- 300,000 hospitalizations/year in USA
- 50% additional episodes of GI bleeding during hospitalizations for other reasons
- 2-14% mortality rate
- 80% stop bleeding spontaneously
- Endoscopic therapy is main bleeding treatment
- Higher mortality rate if re-bleed

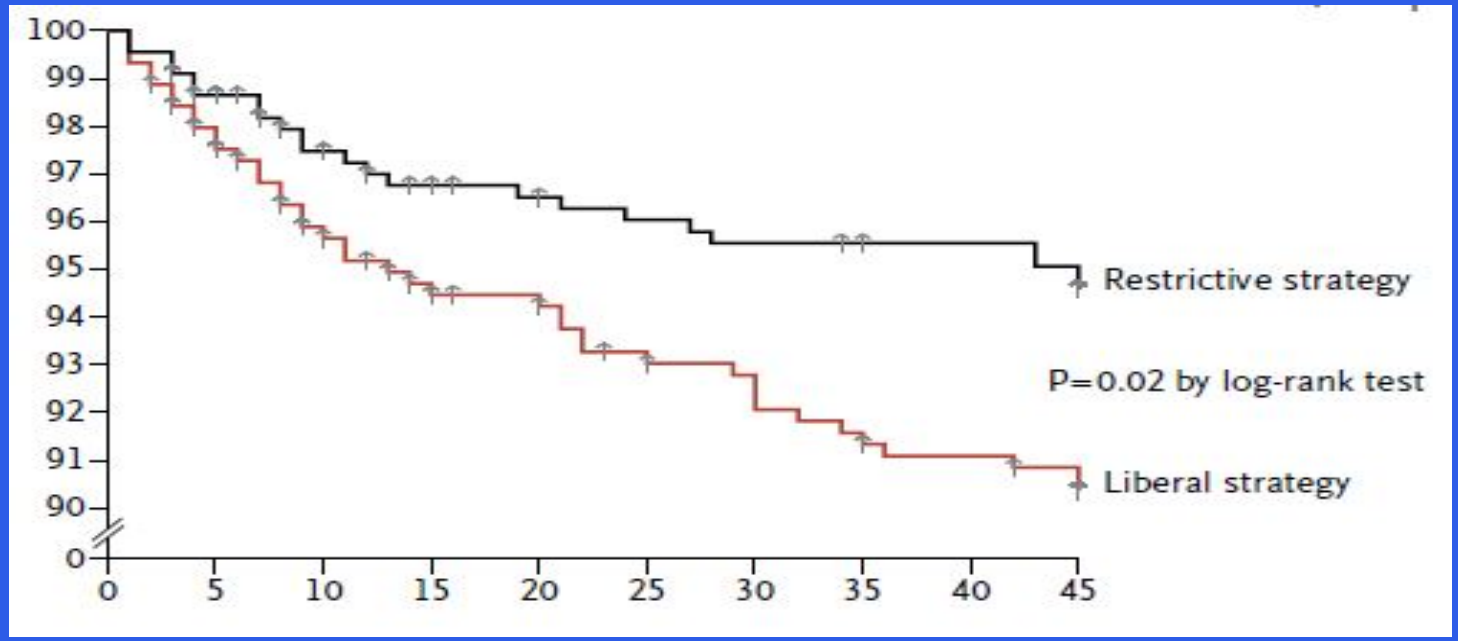
Initial UGIB management

- Assess hemodynamic status immediately
- Insert 2 large bore IVs and begin resuscitation
- Blood transfusions
  - Target hemoglobin ≥ 7 g/dl

  (≥ 9 g/dl if intravascular volume depletion or CAD)

Laine L, Jensen D. *Am J Gastroenterol* 2012;107:345-360

Survival according to transfusion strategy

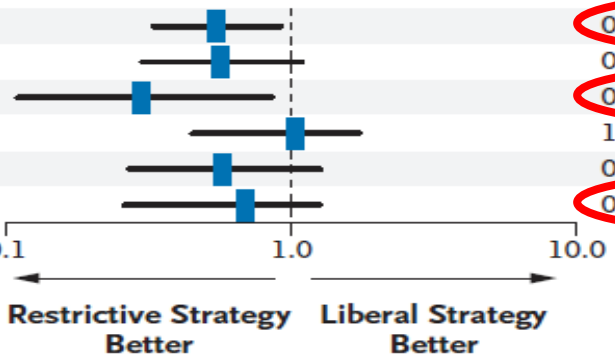


Villanueva C. *N Engl J Med* 2013;368(1):11-21

Restrictive vs. liberal strategy

B Death by 6 Weeks, According to Subgroup

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



New Transfusion Goals

- In patients with acute UGIB without underlying cardiovascular disease, we suggest giving blood transfusions for those with a hemoglobin level <8 g/dL
- Conditional recommendation, low-quality evidence
- In patients with acute UGIB with underlying cardiovascular disease we suggest giving blood transfusions at a higher hemoglobin threshold than for those without CV disease
- Conditional recommendation, very low-quality evidence

Barkun A et al. International Consensus Guidelines. *Annals Internal Medicine* in press

2012 ACG guidelines PPI recommendations

After successful endoscopic hemostasis, IV PPI therapy with 80 mg bolus followed by 8 mg/hour continuous infusion for 72 hours should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel, or an adherent clot.

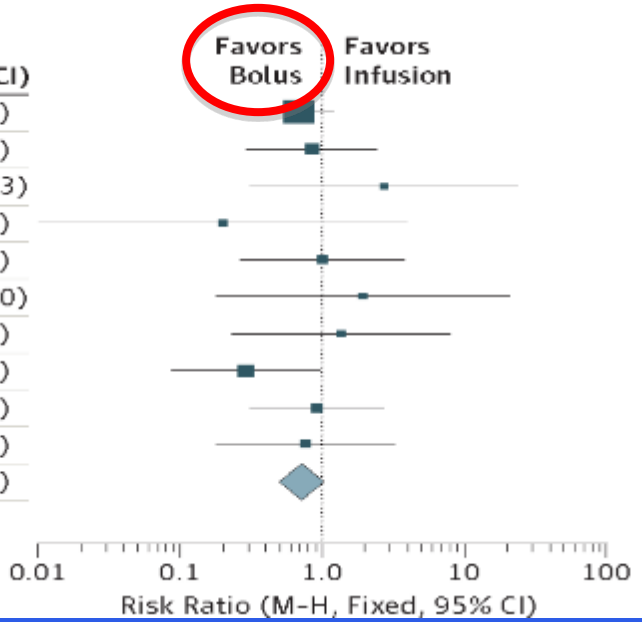
Strong recommendation

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

Continuous vs. intermittent PPIs

Source	Intermittent Bolus, No. Events	Intermittent Bolus, No. Total	Continuous Infusion, No. Events	Continuous Infusion, No. Total	Risk Ratio (M-H, Fixed, 95% CI)
Andriulli et al,[14] 2008	19	239	28	243	0.69 (0.40-1.20)
Chen et al,[16] 2012	6	101	7	100	0.85 (0.30-2.44)
Choi et al,[17] 2009	3	21	1	19	2.71 (0.31-23.93)
Jang et al,[24] 2006	0	19	2	19	0.20 (0.01-3.91)
Javid et al,[20] 2009	4	53	4	53	1.00 (0.26-3.79)
Kim et al,[21] 2012	2	54	1	52	1.93 (0.18-20.60)
Sung et al,[25] 2012	3	105	2	95	1.36 (0.23-7.95)
Ucbilek et al,[26] 2013	3	37	10	36	0.29 (0.09-0.97)
Yamada et al,[22] 2012	4	13	5	15	0.92 (0.31-2.73)
Yüksel et al,[23] 2008	3	49	4	50	0.77 (0.18-3.24)
Total (95% CI)	47	691	64	682	0.74 (0.52-1.06)

Heterogeneity: $\chi^2_9 = 5.96$ ($P = .74$) $I^2 = 0\%$
Test for overall effect: $z = 1.65$ ($P = .10$)



Sachar H. *JAMA Intern Med* 2014 Nov;174(11):1755-62

Consensus PPI recommendations

- For patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy, we recommend using PPI therapy via IV loading dose followed by continuous-infusion IV
- Strong recommendation, moderate-quality evidence
- For patients who present with ulcer bleeding at high risk of rebleeding (ie, ulcer that required endoscopic therapy followed by 3 days of high-dose PPI therapy), we suggest using twice daily oral PPI (vs. once daily) through 14 days followed by once daily
- Conditional recommendation, very low-quality evidence

Barkun A et al. International Consensus Guidelines. *Annals Internal Medicine* in press

Timing of endoscopy

"Early endoscopy within 24 hours of presentation is recommended for most patients with acute upper gastrointestinal bleeding"

- International Consensus Guidelines 2010

"Patients with upper GI bleeding should generally undergo endoscopy within 24 hours of admission, following resuscitative efforts to optimize hemodynamic parameters"

- ACG Practice Guidelines 2012

ESGE guideline for time of endoscopy

- Following hemodynamic resuscitation, ESGE recommends early (≤24 hours) upper GI endoscopy
- Very early (<12 hours) upper GI endoscopy may be considered in patients with high risk clinical features, namely: hemodynamic instability (tachycardia, hypotension) that persists despite ongoing attempts at volume resuscitation; in-hospital bloody emesis/nasogastric aspirate; or contraindication to the interruption of anticoagulation

(strong recommendation, moderate quality evidence)

Gralnek IM. *Endoscopy* 2015;47:a1–a46

Emergent or urgent endoscopy?

- Emergent (<6-8 hours) endoscopy (EE) vs. urgent (8-24 hours) endoscopy (UE)
- Retrospective series (n=860)
- More endoscopic therapy in EE group
- No differences in:
  - Rebleeding rate
  - Length of stay, transfusions, surgery & mortality

Tai CM. *Am J Emerg Med* 2007;25:273-278
Targownik LE. *Can J Gastroenterol 2007;21:425-429*
Sarin N. *Can J Gastroenterol* 2009;23:489-493

Emergent endoscopy (< 12 hours)

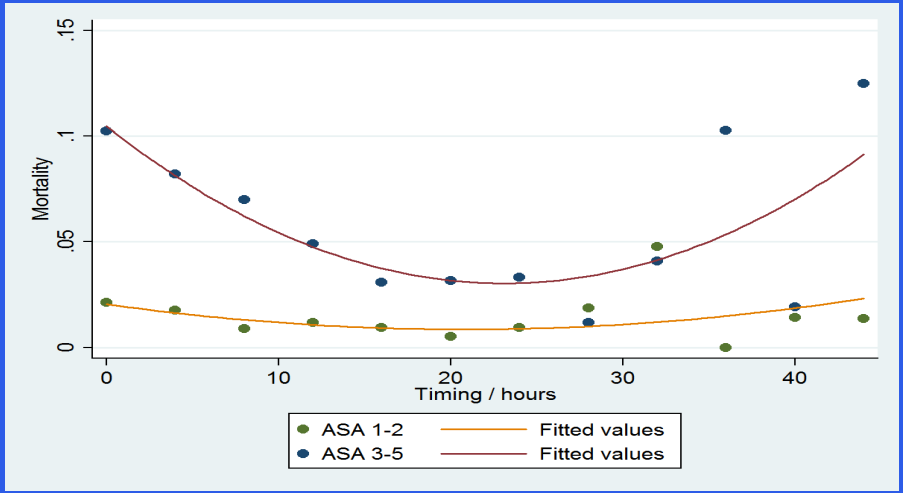
- Always after hemodynamic resuscitation and stabilization
- Hemodynamically unstable initially
- Hematemesis
- Suspected active bleeding
- Suspected variceal bleeding

Laine L, Jensen D. *Am J Gastroenterol* 2012;107:345-360;
Tsoi KKF. *Nat Rev Gastroenterol Hepatol* 2009; 6:463-469

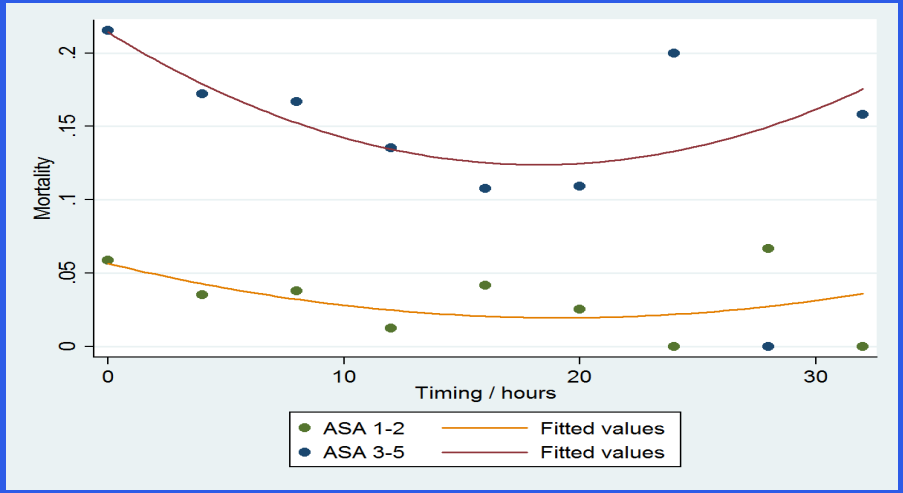
Worse outcomes may occur with emergent endoscopy

- Urgent endoscopy may have inadequate resuscitation
- Procedure may be done without usual supports (endoscopy nurses and techs)
- Procedure often done at off hours (i.e. 11 PM to 7 AM) and endoscopist may be fatigued and/or have a decrease in endoscopy performance quality
- Lack of back-up support immediately available (interventional radiology and surgery)

Mortality and time to endoscopy



Hemodynamically stable



Hemodynamically unstable

Laursen SB. *Gastrointest Endosc* 2017;85(5):936-944;
Kumar N. *Gastrointest Endosc* 2017;85(5):945-952

Increase in BUN at 24 hours predicts worse outcomes

TABLE 3. Outcomes in patients with an increased BUN versus decreased or unchanged BUN at 24 hours

	Increased BUN (n = 37)	Decreased or unchanged BUN (n = 320)	*P* value
Primary outcome			
Composite outcome	8 (22%)	28 (9%)	.014
Components of primary outcome			
Inpatient death	3 (8%)	4 (1%)	.004
Inpatient rebleeding	4 (11%)	16 (5%)	.15
Surgical intervention	1 (3%)	4 (1%)	.48
Interventional radiology intervention	1 (3%)	7 (2%)	.84
Endoscopic reintervention	2 (5%)	11 (3%)	.55
Secondary outcomes			
Endoscopic intervention	12 (32%)	90 (28%)	.58
Transfused	27 (73%)	251 (78%)	.45
No. of units transfused (per patient)	4 [0, 5]	3 [1, 4]	.45
Length of stay	4 [3, 5]	3 [2, 5]	.09

Proportions presented as percentages. Medians and interquartile range (IQR) presented as median [median − IQR, median + IQR].
BUN, Blood urea nitrogen.

Kumar NL. *Gastrointest Endosc* 2017;85:953-5

Summary of timing

Emergent endoscopy (within 12 hours)

- More endoscopic therapy performed
- No improvement in overall patient outcomes
- Benefits only patients with active bleeding
- May be associated with worse outcomes

Urgent / early endoscopy (within 24 hours)

- Decreases length of stay and costs
- Similar patient outcomes to early endoscopy

Consensus recommendations for timing of endoscopy

- For patients admitted with acute UGIB we suggest performing early endoscopy (within 24 hours of presentation).]
- Conditional recommendation, very low-quality evidence
- For patients with acute UGIB at high risk of rebleeding or mortality, the consensus group could not make a recommendation for or against performing endoscopy within 12 hours vs. performing endoscopy later
- No recommendation, very low-quality evidence

Barkun A et al. International Consensus Guidelines. *Annals Internal Medicine* in press

Stigmata of recent hemorrhage (SRH)

Stigmata	Forrest class	Prevalence (%)	Rebleeding w/o endotherapy (%)	Surgery (%)	Mortality (%)
Active bleeding	IA IB	12% (spurting and oozing)	55 (range 17-100%)	35	11
Nonbleeding visible vessel	IIA	8%	43	34	11
Adherent clot	IIB	8	22	10	7
Pigmented spot	IIC	16	10	6	3
Clean base	III	55	5	0.5	2

Laine L, Jensen D. *Am J Gastroenterol* 2012;107:345-360

Re-evaluation of the Forrest classification (SRH)

Rebleeding post endoscopic therapy analysis from a large multicenter PPI study

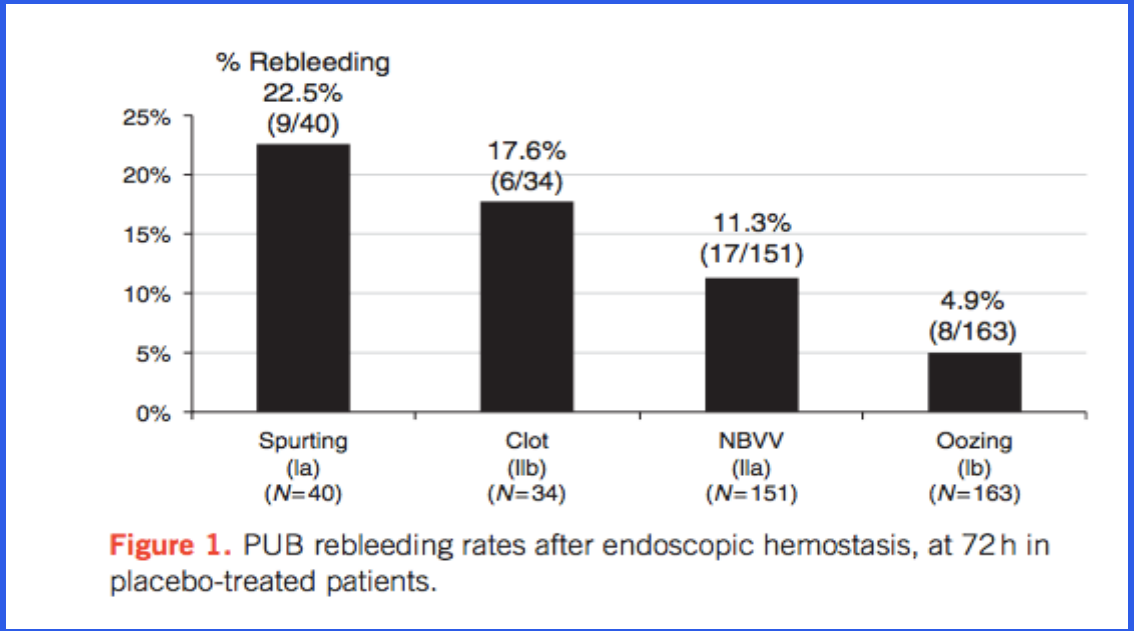


Figure 1. PUB rebleeding rates after endoscopic hemostasis, at 72 h in placebo-treated patients.

Jensen DM. *Am J Gastroenterol* 2017;112:441-46

Indications for endoscopic therapy

Stigmata	Endoscopic therapy?
Active bleeding	Yes
Non-bleeding visible vessel	Yes
Adherent clot	**+/-**
Flat spot	No
Clean ulcer base	No

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

Case: Upper endoscopy at 9 hours

Non-bleeding, large, cratered ulcer with a 6 mm pulsatile visible vessel at the GJ anastomosis

How would you treat this lesion?

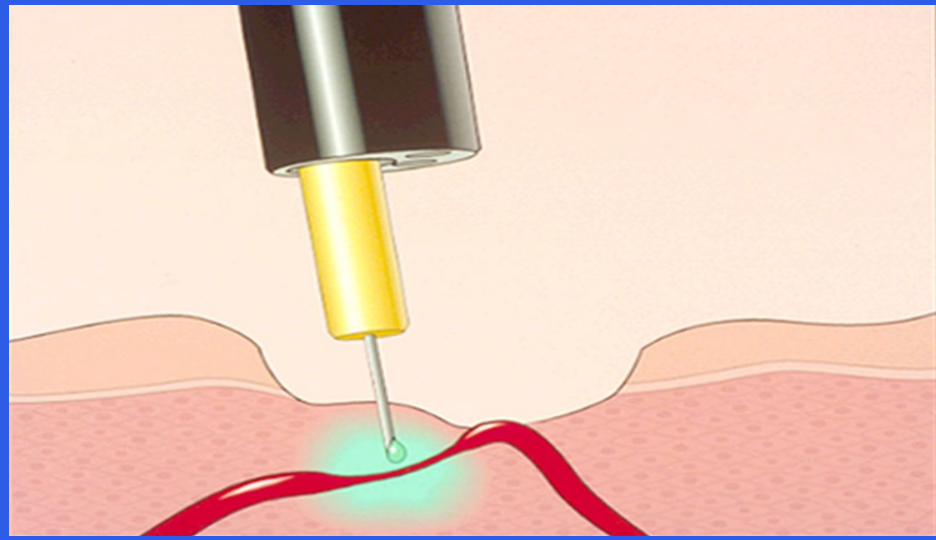
A. Epinephrine injection (1:10,000)
B. Epinephrine injection and bicap cautery
C. Hemoclips
D. Over the scope clip
E. Hemostatic spray

Traditional endoscopic therapies

- Injection
- Thermal (contact)
  - Bipolar probe
  - Monopolar
- Thermal (non-contact)
  - Argon plasma coagulation (APC)
- Mechanical
  - Hemoclips
  - Banding
- Combination

Injection

- Reduce blood flow by local tamponade
- Vasoconstricting agents reduce blood flow
  - Epinephrine 1:10,000 - 1:100,000
- Various agents can be injected
  - Ethanol
  - Sclerosants
    - Ethanolamine
    - Polidocanol
  - Tissue adhesives
    - N-butyl-2-cyanoacrylate
    - Fibrin glue
    - Thrombin



Epinephrine injection monotherapy not recommended

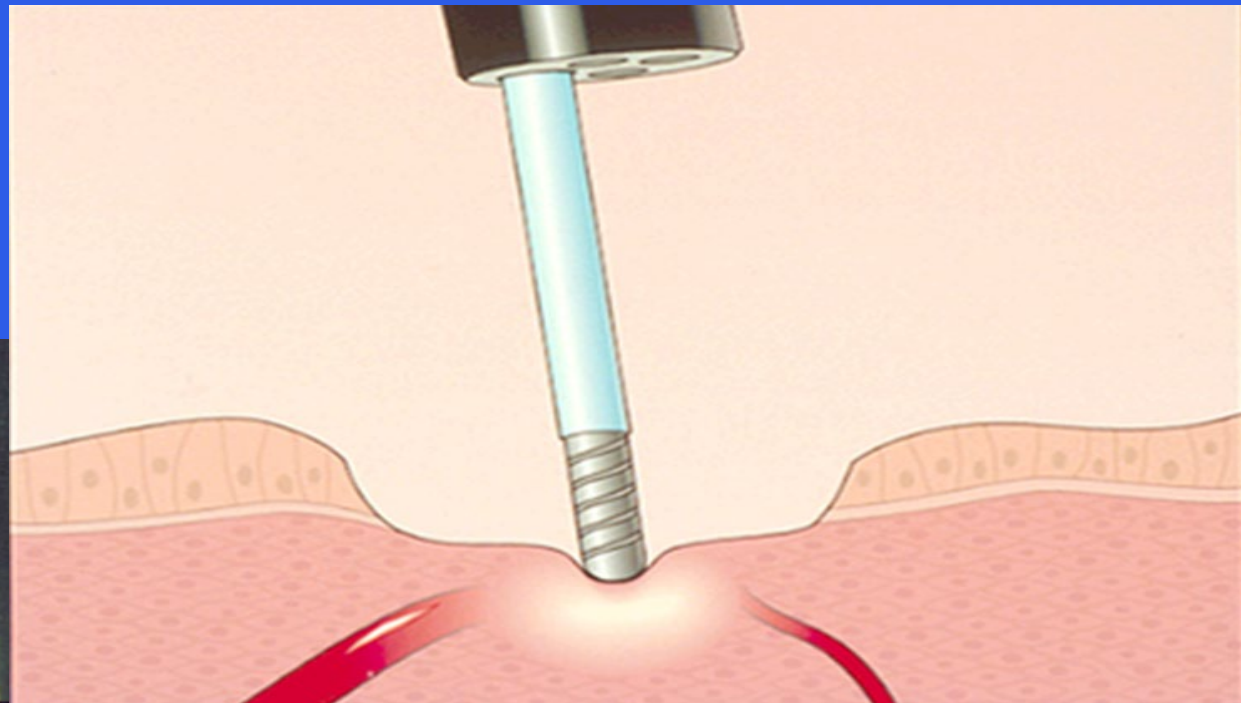
Park WG. *Gastrointest Endosc* 2007;66:343-54

Thermal therapy

- Bi-polar (Bicap) commonly used
- Coaptive coagulation: Compress vessel and then coagulate to seal vessel
- Larger 10 French probes more effective than smaller 7 French probes
- 10-15 Watts for multiple 8-12 second pulses
- Optimal therapy is 4-6 pulses

Coagulation probes

- Bipolar
- Bipolar + injection
- Coagulation forcep
- ~~Heater probe~~



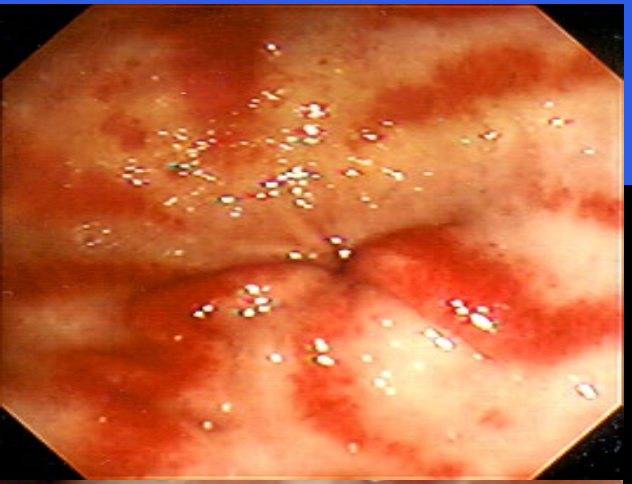
Monopolar cautery

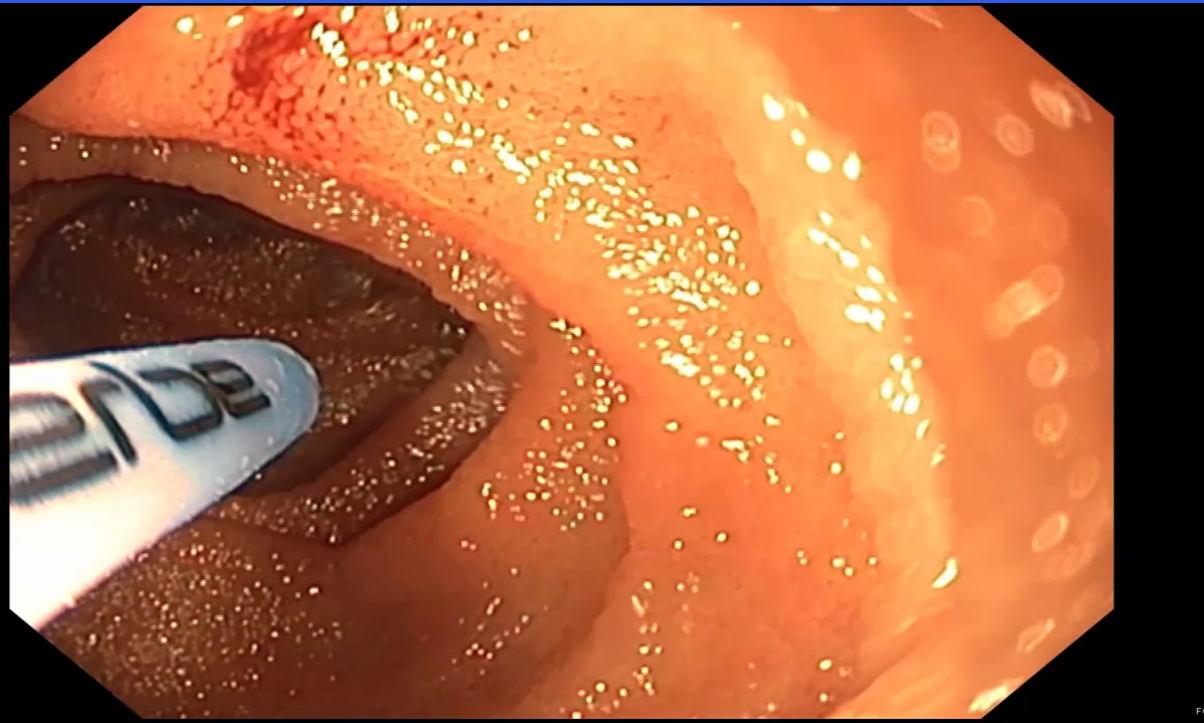
- Coagulation forceps and soft coag
- 3 small RCTs in patients with peptic ulcers
- Treatment with monopolar cautery with soft coagulation vs. hemoclips, heater probe or epi/fibrin injection
- Similar efficacy (initial control and rebleeding) compared to hemoclips
- Better efficacy compared to heater probe or injection

Nunoue T. *J Clin Gastroenterol* 2015;49(6):472-6
Arima S. *J Gastroenterol* 2010;45(5):501-5
Toka B. *Gastrointest Endosc* 2018 Oct 17

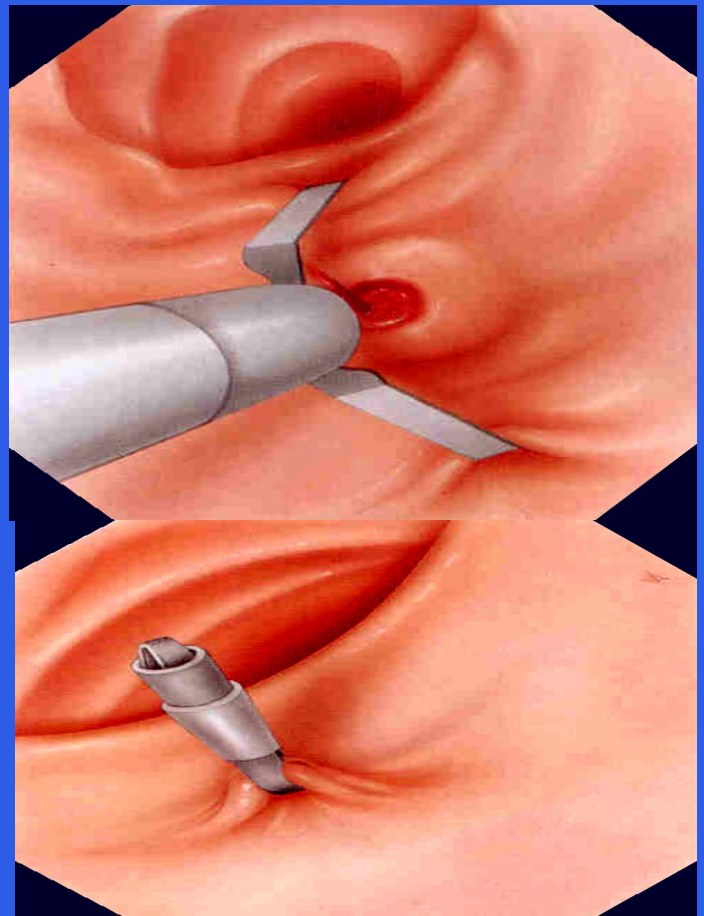
Argon plasma coagulation

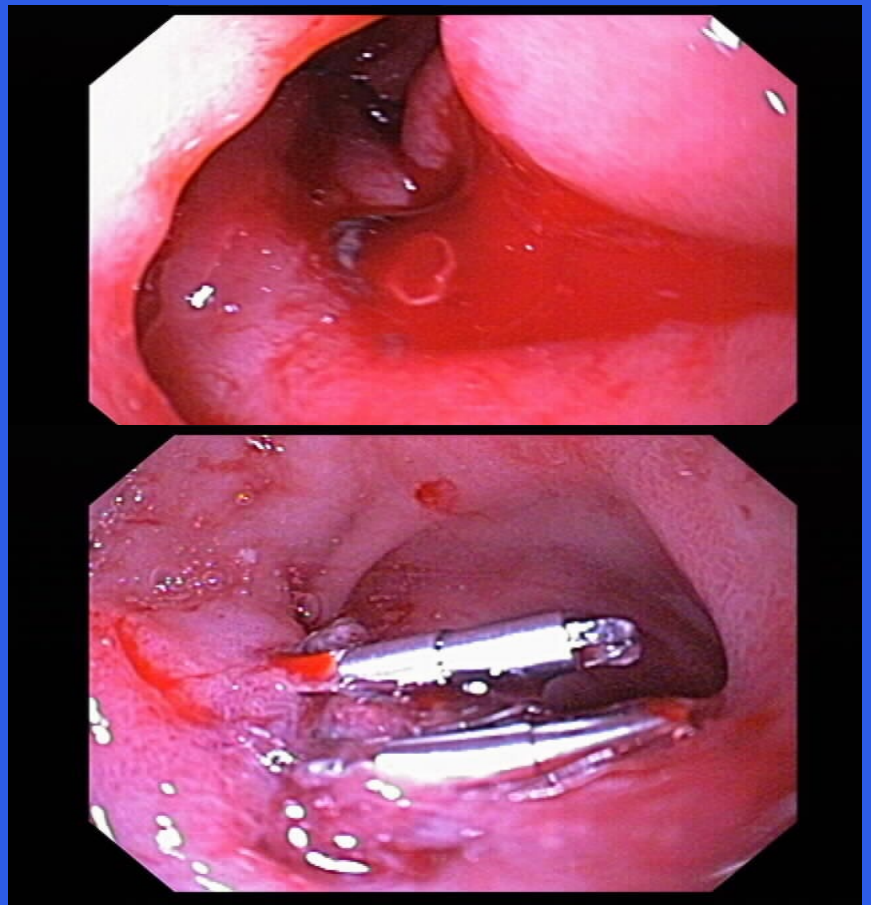
Best for AVM's and watermelon stomach



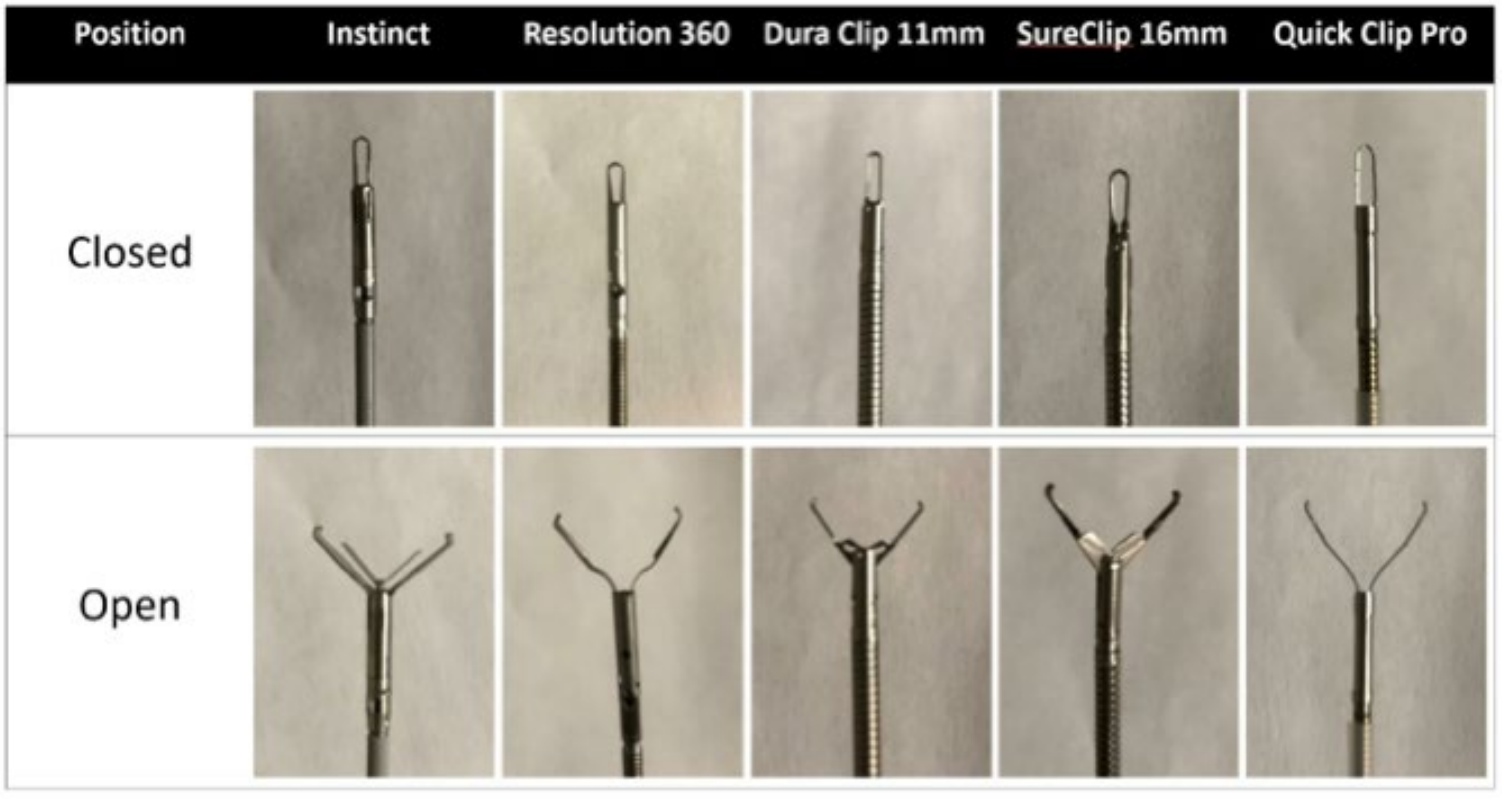


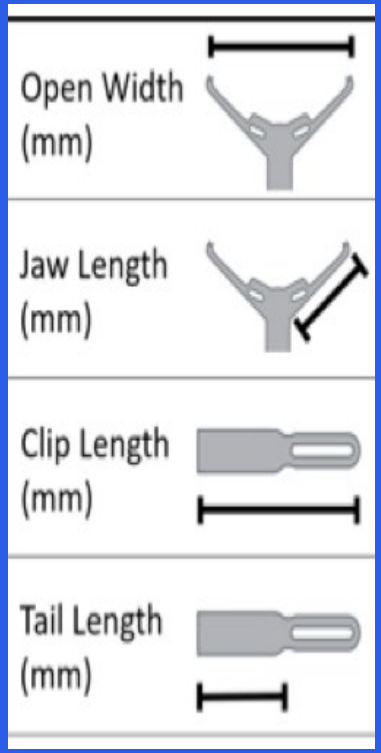
Hemoclips





Be familiar with available hemoclips





Wang TJ. *Gastrointest Endosc* 2019;89(1):77-86

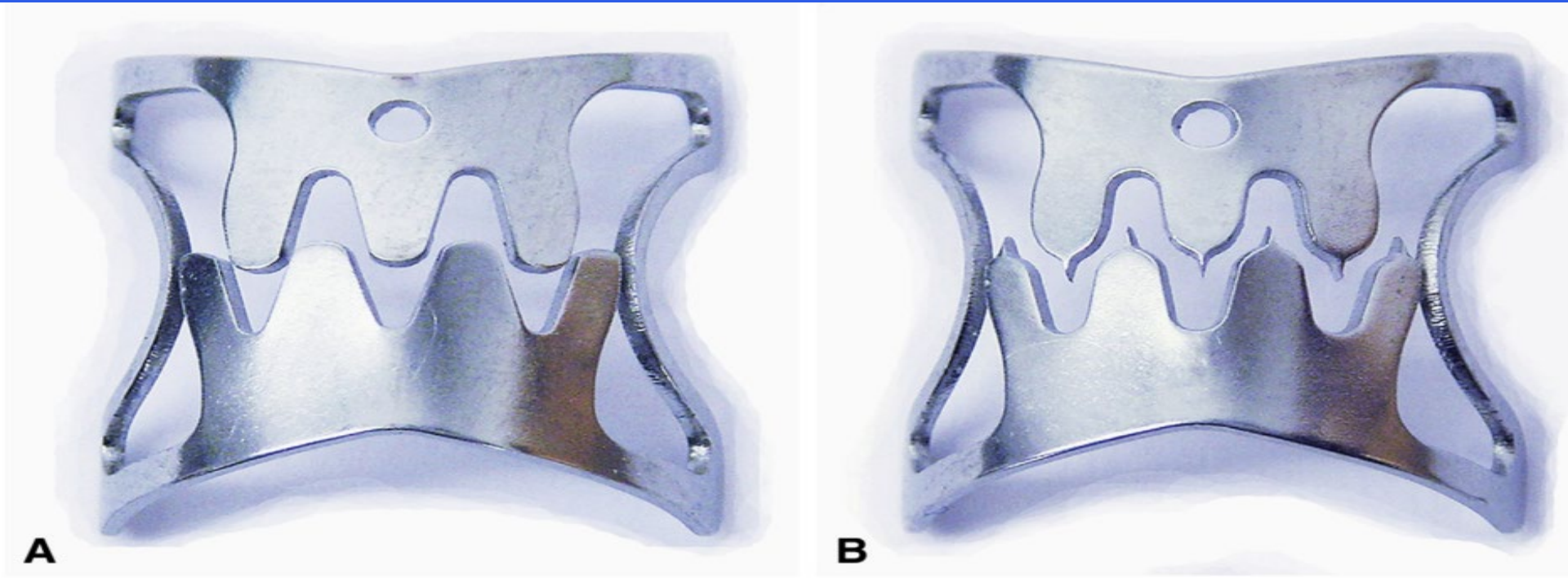
Consensus recommendations for endoscopic therapy

- For patients with acutely bleeding ulcers with high-risk stigmata, we recommend endoscopic therapy with thermocoagulation or sclerosant injection.
- Strong recommendation, low-quality evidence
- For patients with acutely bleeding ulcers with high-risk stigmata, we suggest endoscopic therapy with (through the scope) clips.
- Conditional recommendation, very low-quality evidence

Barkun A et al. International Consensus Guidelines. *Annals Internal Medicine* in press

New therapies

The over-the-scope clip (OTSC)



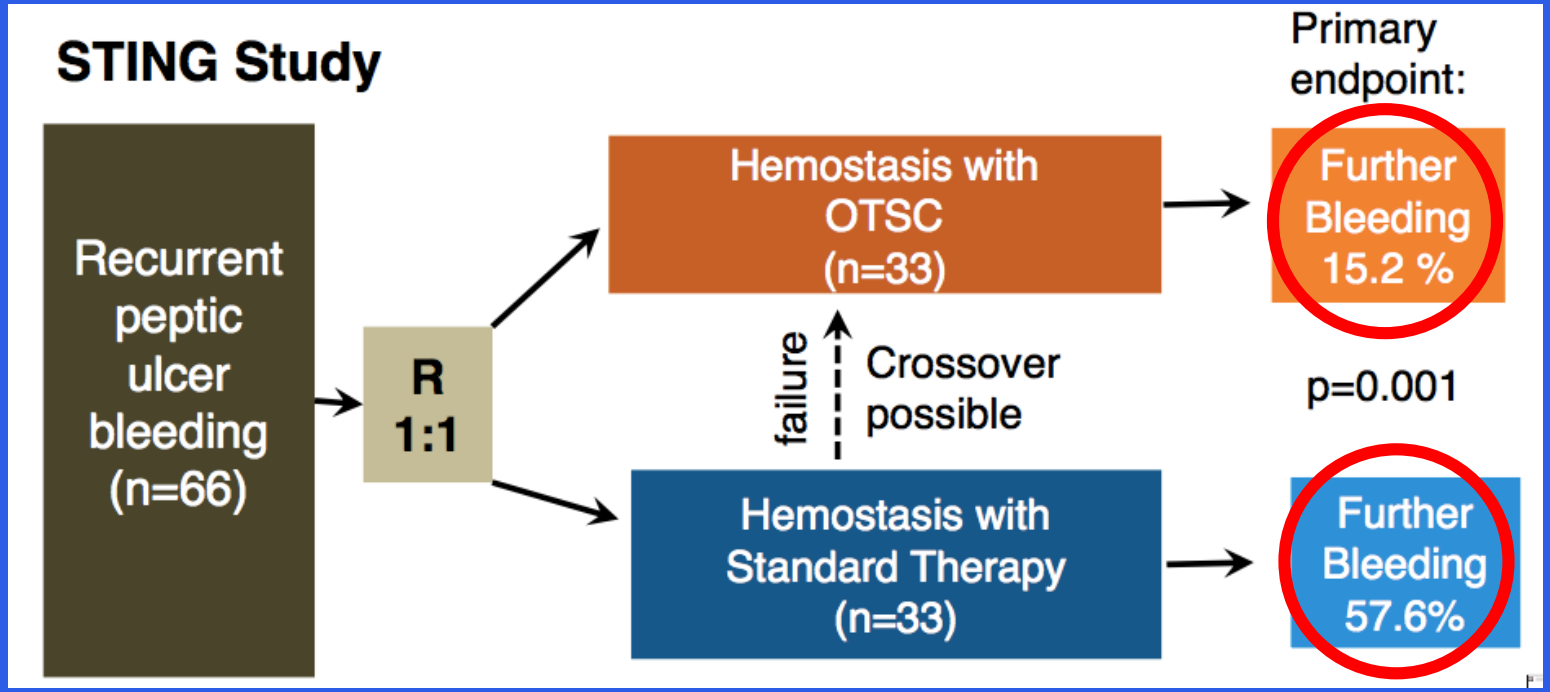
Kirschniak A. *Gastrointest Endosc* 2007;66:162-167

OTSC for primary control

- **40 patients**
  - Gastric and duodenal ulcers with large vessels and Dieulafoy's lesions
  - Technical success and primary hemostasis achieved in all patients (100%) and no rebleeding at 30 days
- **118 patients**
  - Technical success achieved in 92.4%
  - Mortality with estimated rebleeding reduced from 27.9% to 10.9%
- OTSC clips may be an alternative to standard hemostasis in high-risk patients for primary control of bleeding

Wedi E. *Surg Endosc* 2017:June 27;
Manno M. *Surg Endosc* 2016:30(5):2026-9

OTSC for rebleeding



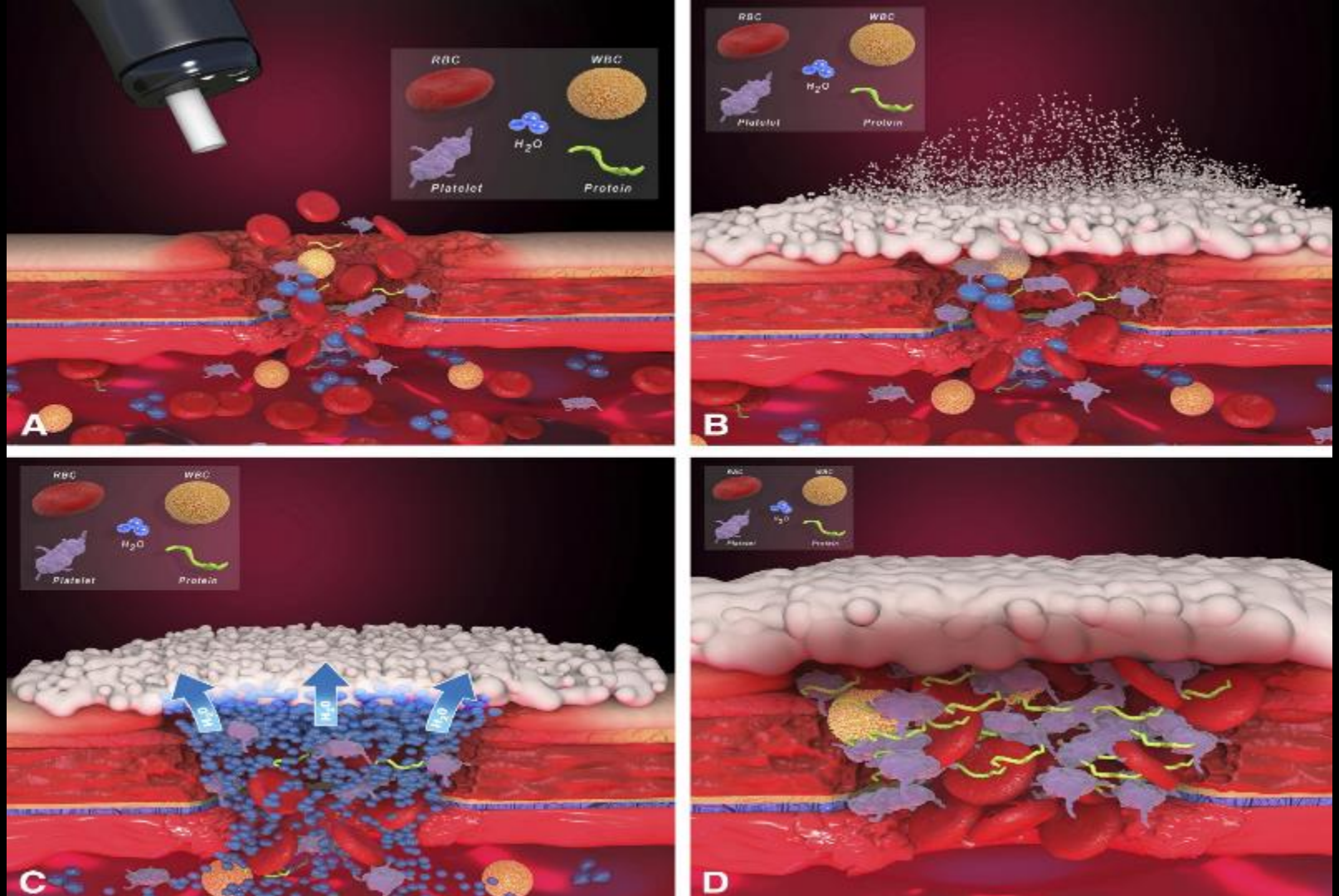
Schmidt A. Gastroenterology 2018; May 21

Topical hemostatic agents

Agent	Trade Name	Composition	Mechanism of action	Approved human application	Formulation
	Ankaferd BloodStopper	Standardized herbal mixture	Forms protein network, aggregates RBCs, activates clotting cascade	Dental procedures, ambulance, first aid services, schools, fast hemostasis	Tampons, sprays, ampoules
TC-325	Hemospray	Granular mineral-based	Adsorbs H_2O, mechanical tamponade, activates clotting cascade	Recently approved for nonvariceal GI bleed in Canada, Hong Kong, Europe	CO_2 pressurized handheld canister (20 g)
EndoClot	EndoClot	Absorbable modified polymers	Absorbs H_2O and concentrates cells, activates clotting cascade	Intended for adjuvant hemostatic therapy	Pressurized air compressor

RBCs, Red blood cells.

Barkun A. *Gastrointest Endosc* 2013;77:692-700


RBC
WBC
H_2O
Platelet
Protein
A
B
C
D

Hemostatic spray review

- Immediate hemostasis: 92.3% (180/195)
- Rebleed rate at 7 days: 20.6%
- High risk lesions (Forrest 1a, 1b)
  - Immediate hemostasis: 95% (53/56)
  - Rebleed rate at 7 days: 25% (13/53)
- Safety (243 cases)
  - 5 reported complications:
    - Pain (under-reported?), biliary obstruction (post-sphincterotomy bleed), perforation, hemo-peritoneum, splenic emboli (on day 29)

Chen Y. *Gastrointest Endosc Clin N Am* 2015;25:535-552

Data at the time of FDA approval

Study	N	Hemostasis on Index Endoscopy (%)	Re-bleed Rate (%)	30-day Mortality (%)	Bowel Perforation (%)	Powder Impaction (%)	Thromboembolic Event
Feasibility Study	**20**	95	10	0	0	0	0
SEAL Survey	**89**	100	19	5.6	3.4	0	0
HALT Study	**64**	97	20	3.2	3.1	0	0
APPROACH Study	**50**	100	10	2	0	0	0
Hemospray® Literature *	**522**	97.4	22	10.7	0.4	0	0
Emergency Use	**5**	100	0	20	0	0	0
Total	**750**	97.8	20.2	11.6	0.9	0	0

***Includes patients from the Feasibility Study and SEAL survey**

www.cookmedical.com/products/35a4a7f2-867b-4c81-a983-44ea06277852/

Hemospray in malignant bleeding

- Prospective, multicenter RCT in Canada in malignant bleeding
- 20 patients randomized 1:1 to TC-325 or SOC
  - Upper GI malignancy in 85% and bleeding was active oozing in 95%

Results:

- Immediate hemostasis was achieved in 90% of patients treated initially with Hemospray versus 40% in the SOC group (P = 0.057)
- In SOC group 5/6 patients crossed over to Hemospray, with hemostasis then achieved in 80% (4/5 patients)
- Hemostasis at index endoscopy (before or after crossover) was obtained in 87% of patients treated with Hemospray
- Rebleeding in Hemospray arm in 20% at 6 months (60% in SOC)

Barkun AN. *GIE in press*

Hemospray considerations

- Does not require special expertise
- May be effective in difficult locations
- Can be rapidly used if bleeding occurs after polypectomy or sphincterotomy
- Role in malignant bleeding
- Effective only in actively oozing or spurting bleeding lesions
- Second treatment modality needed if high risk of rebleeding

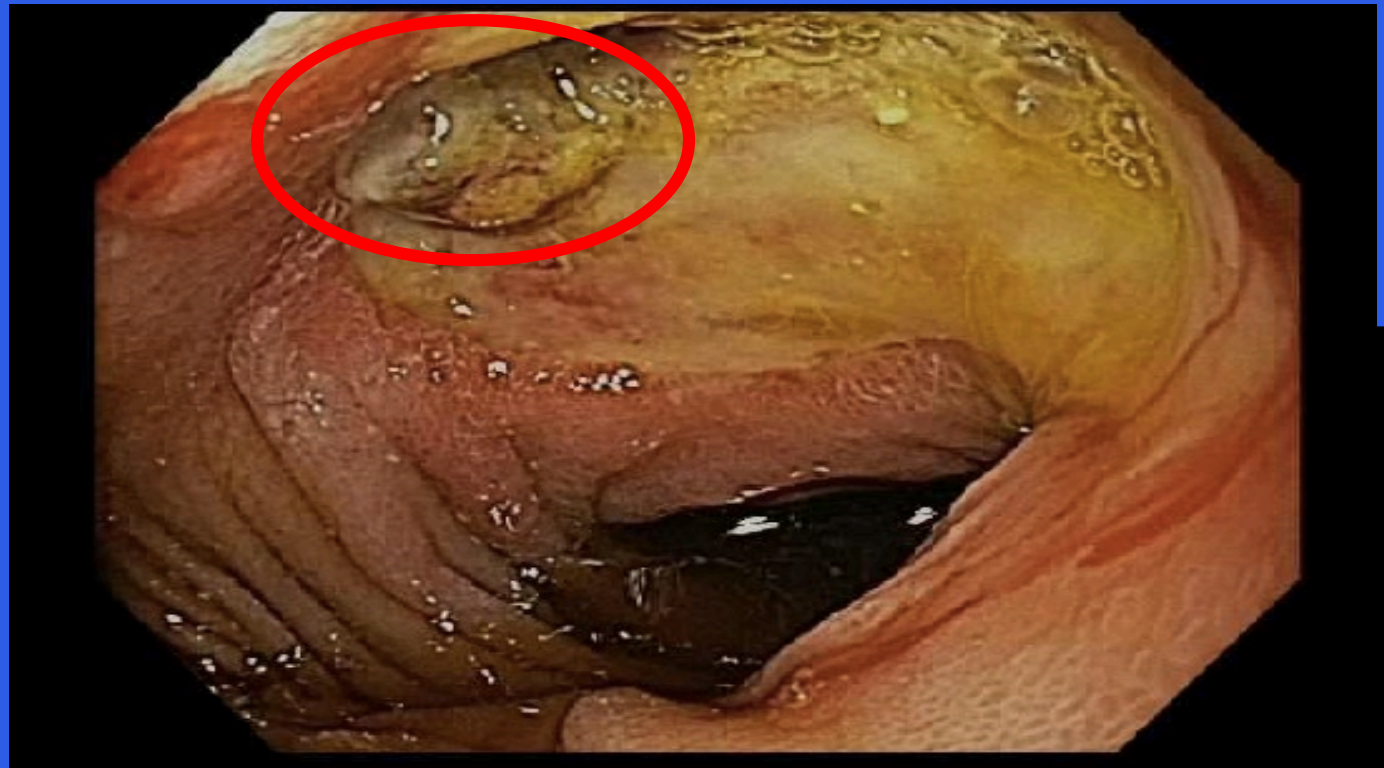
Approved by FDA for upper and lower GI bleeding

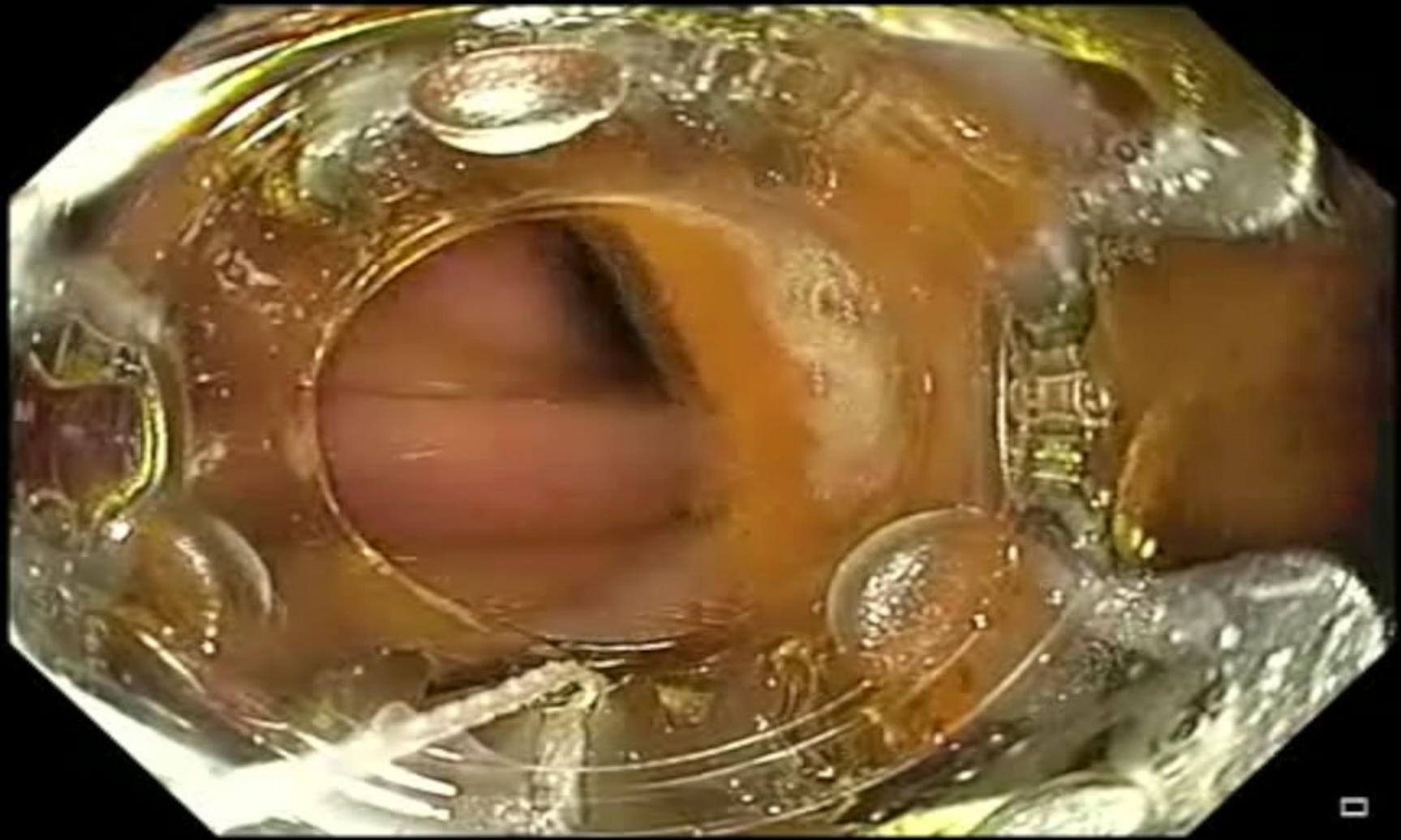
Consensus recommendations for TC-325 endoscopic therapy

- In patients with actively bleeding ulcers, we suggest using TC-325 as a temporizing therapy to stop bleeding when conventional endoscopic therapies are not available or fail
  Conditional recommendation, very low-quality evidence
- In patients with actively bleeding ulcers, we suggest AGAINST using TC-325 as a single therapeutic strategy vs. conventional endoscopic therapy (clips alone, thermocoagulation alone, or combination therapy)
- Conditional recommendation, very low-quality evidence

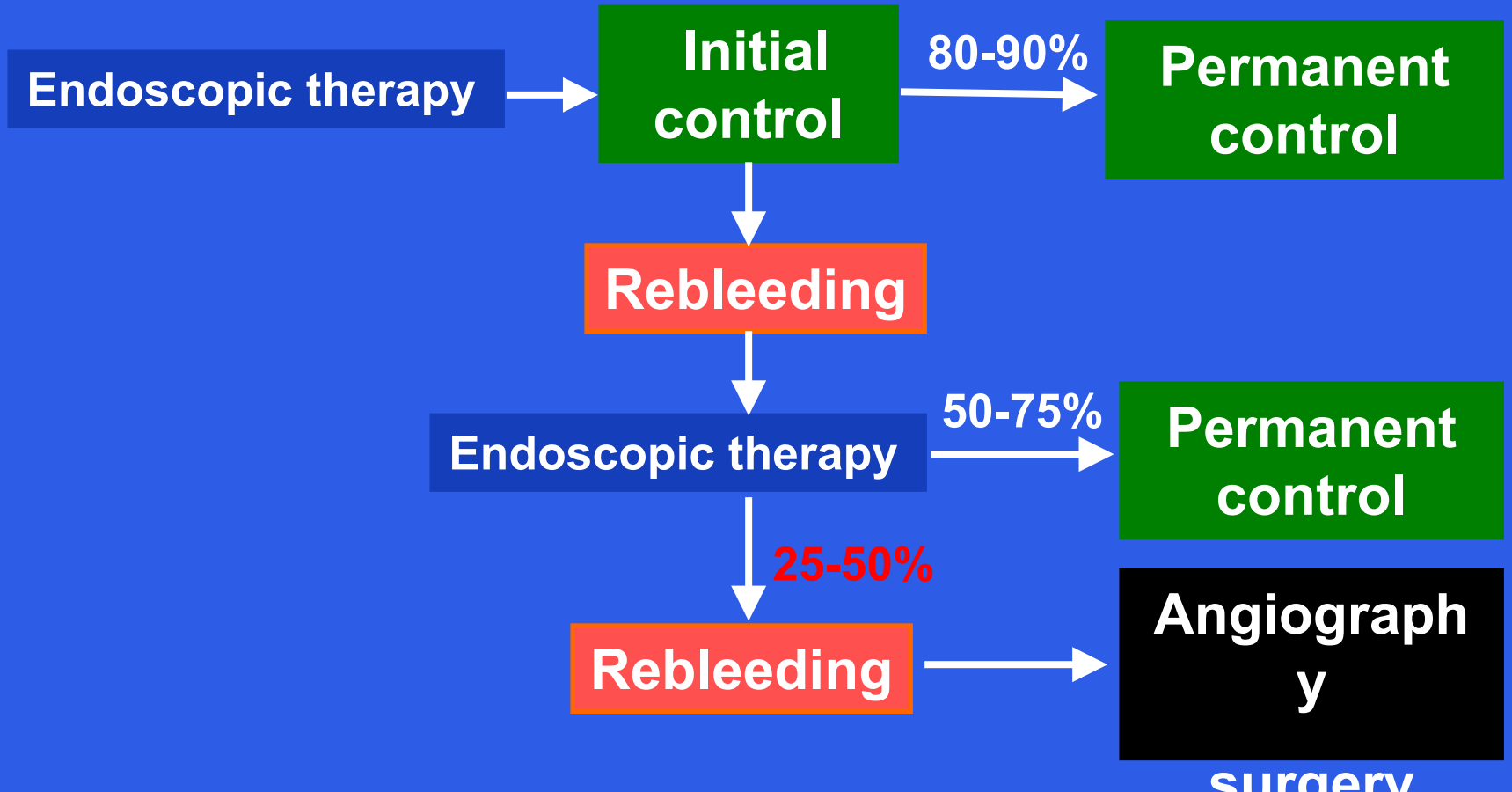
Barkun A et al. International Consensus Guidelines. *Annals Internal Medicine* in press

Case conclusion



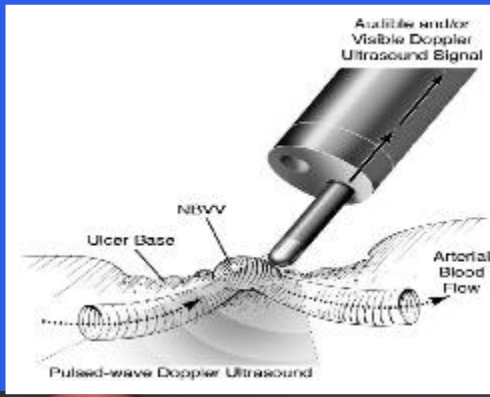


Repeat endoscopy for rebleeding



Reducing rebleeding: Doppler probes

- First report in upper GI bleeding in 1986
- Easy to learn and use with auditory signal
- Relatively inexpensive devices
- Ulcers with a positive Doppler signal at higher risk of rebleeding



Jensen DM. *Gastrointest Endosc* 2016;83(1):129-36;
Nayor J, Saltzman JR. *Gastrointest Endosc* 2016;83(1):137-139

RCT of Doppler-guided endoscopic therapy in upper GI bleeding

- 148 patients with severe non-variceal UGI bleeding
  - Standard visually guided hemostasis
  - Doppler guided hemostasis
- **Results**
  - Rebleeding within 30 days in 20/76 (26.3%) standard group vs. 8/72 (11.1%) in Doppler group (p=0.02, NNT = 7)
  - Decreased surgery and major complications in Doppler group (p=0.048)

Jensen DM. *Gastroenterology* 2017;152(6):1310-1318

Consensus statement on the use of Doppler probes

- In patients with acutely bleeding ulcers who have undergone endoscopic therapy, the consensus group could not make a recommendation for or against using Doppler endoscopic probe (DEP) vs. no DEP to assess the need for further endoscopic therapy
- No recommendation, very low-quality evidence

Barkun A et al. International Consensus Guidelines. *Annals Internal Medicine* in press

Take home points

- Resuscitate your patients adequately
- Perform endoscopy in within 24 hours
- IV PPI drip x 72 hours given if endoscopic therapy done
- Standard endoscopic therapies are cautery and hemoclips
- Monopolar cautery is a promising alternative therapy
- OTSCs are useful for large vessels and for rebleeding
- Hemospray is useful to treat active GI bleeding
- Use of Doppler probes may decrease rebleeding rates
- International consensus upper GI bleeding guidelines updated