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Endoscopic diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021

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MAIN RECOMMENDATIONS

1 ESGE recommends in patients with acute upper gastrointestinal hemorrhage (UGIH) the use of the Glasgow–Blatchford Score (GBS) for pre-endoscopy risk stratification. Patients with GBS ≤ 1 are at very low risk of rebleeding, mortality within 30 days, or needing hospital-based intervention and can be safely managed as outpatients with outpatient endoscopy.
Strong recommendation, moderate quality evidence.

2 ESGE recommends that in patients with acute UGIH who are taking low-dose aspirin as monotherapy for secondary cardiovascular prophylaxis, aspirin should not be interrupted. If for any reason it is interrupted, aspirin should be restarted as soon as possible, preferably within 3–5 days.
Strong recommendation, moderate quality evidence.

3 ESGE recommends that following hemodynamic resuscitation, early (≤ 24 hours) upper gastrointestinal (GI) endoscopy should be performed.
Strong recommendation, high quality evidence.

4 ESGE does not recommend urgent (≤ 12 hours) upper GI endoscopy since as compared to early endoscopy, patient outcomes are not improved.
Strong recommendation, high quality evidence.

5 ESGE recommends for patients with actively bleeding ulcers (FIa, FIb), combination therapy using epinephrine injection plus a second hemostasis modality (contact thermal or mechanical therapy).
Strong recommendation, high quality evidence.

6 ESGE recommends for patients with an ulcer with a nonbleeding visible vessel (FIIa), contact or noncontact thermal therapy, mechanical therapy, or injection of a sclerosing agent, each as monotherapy or in combination with epinephrine injection.
Strong recommendation, high quality evidence.

7 ESGE suggests that in patients with persistent bleeding refractory to standard hemostasis modalities, the use of a topical hemostatic spray/powder or cap-mounted clip should be considered.
Weak recommendation, low quality evidence.

8 ESGE recommends that for patients with clinical evidence of recurrent peptic ulcer hemorrhage, use of a cap-mounted clip should be considered. In the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE.
Strong recommendation, moderate quality evidence.

9 ESGE recommends high dose proton pump inhibitor (PPI) therapy for patients who receive endoscopic hemostasis and for patients with FIIb ulcer stigmata (adherent clot) not treated endoscopically.
(a) PPI therapy should be administered as an intravenous bolus followed by continuous infusion (e. g., 80 mg then 8 mg/hour) for 72 hours post endoscopy.
(b) High dose PPI therapies given as intravenous bolus dosing (twice-daily) or in oral formulation (twice-daily) can be considered as alternative regimens.
Strong recommendation, high quality evidence.

10 ESGE recommends that in patients who require ongoing anticoagulation therapy following acute NVUGIH (e. g., peptic ulcer hemorrhage), anticoagulation should be resumed as soon as the bleeding has been controlled, preferably within or soon after 7 days of the bleeding event, based on thromboembolic risk. The rapid onset of action of direct oral anticoagulants (DOACS), as compared to vitamin K antagonists (VKAs), must be considered in this context.
Strong recommendation, low quality evidence.

SOURCE AND SCOPE

This Guideline is an official statement from the European Society of Gastrointestinal Endoscopy (ESGE). It is an update of the previously published 2015 ESGE Clinical Guideline addressing the role of gastrointestinal endoscopy in the diagnosis and management of acute nonvariceal upper gastrointestinal hemorrhage (NVUGIH). The evidence statements and recommendations specifically pertaining to endoscopic hemostasis therapies are limited to peptic ulcer hemorrhage. Endoscopic hemostasis therapy recommendations for nonulcer NVUGIH etiologies, can be found in the 2015 ESGE Guideline.

Introduction

The most common causes of acute upper gastrointestinal hemorrhage (UGIH) are nonvariceal. These include gastric and duodenal peptic ulcers, mucosal erosive disease of the esophagus/stomach/duodenum, malignancy, Mallory–Weiss syndrome, Dieulafoy lesion, “other” diagnosis, or no identifiable cause [1]. This ESGE Guideline focuses on the pre-endoscopic, endoscopic, and post-endoscopic management of patients presenting with acute nonvariceal upper gastrointestinal hemorrhage (NVUGIH), specifically peptic ulcer hemorrhage.

ABBREVIATIONS

APA	antiplatelet agent
APC	argon plasma coagulation
ASA	American Society of Anesthesiologists
AUROC	area under receiver operating characteristic
DAPT	dual antiplatelet therapy
CHADS2	congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, and previous stroke or transient ischemic attack [risk score]
CI	confidence interval
DOAC	direct oral anticoagulant
ESGE	European Society of Gastrointestinal Endoscopy
FFP	fresh frozen plasma
GBS	Glasgow–Blatchford Score
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HR	hazard ratio
ICU	intensive care unit
INR	international normalized ratio
IRR	incident rate ratio
NBVV	nonbleeding visible vessel
NGT	nasogastric tube
NNT	number needed to treat
NVUGIH	nonvariceal upper gastrointestinal hemorrhage
OR	odds ratio
OTS	over-the-scope
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PICO	patients, interventions, controls, outcomes
PNED	Progetto Nazionale Emorragia Digestive
PPI	proton pump inhibitor
PUB	peptic ulcer bleeding
RBC	red blood cell
RCT	randomized controlled trial
RD	risk difference
RR	relative risk or risk ratio
TAE	transcatheter angiographic embolization
TTS	through-the-scope
TXA	tranexamic acid
UGIH	upper gastrointestinal hemorrhage
VKA	vitamin K antagonist

Methods

ESGE commissioned this Guideline (ESGE Guideline Committee chair, J.V.H.) and appointed a guideline leader (I.M.G.). The guideline leader established four task forces based on the statements of the previous 2015 Guideline [2], each with its own leader (M.C., A.J.S., J.M., J.L.).

Key questions (**Table 1 s**, see online-only in Supplementary material) were prepared by the coordinating team (I.M.G., M. C., A.S., J.M., J.L.) according to the PICO format (patients, interventions, controls, outcomes) and divided amongst the four task forces. Given this is an update of the 2015 ESGE Clinical Guideline on NVUGIH, each task force performed a structured systematic literature search using key words (**Table 2 s**) in English-language articles limited from January 1, 2014 to January 31, 2020, in Ovid MEDLINE, Embase, Google Scholar, and the Cochrane Database of Systematic Reviews. Additional topic-specific searches on timing of endoscopy and role of cap-mounted clips for hemostasis in peptic ulcer hemorrhage were conducted up to August 31, 2020. The hierarchy of studies included in this evidence-based guideline was, in decreasing order of evidence level, published systematic reviews/meta-analyses, randomized controlled trials (RCTs), prospective and retrospective observational studies, and case series. New evidence on each key question was summarized in evidence tables (**Table 3 s**), using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [3]. Grading of the evidence depends on the balance between the benefits and risk or burden of any health intervention. Further details on ESGE guideline development have been previously reported [4].

The results of the literature search and answers to PICO questions were presented to all guideline group members during two online face-to-face meetings conducted on June 27 and 28, 2020. Subsequently, drafts were made by each task force leader and distributed between the task force members for revision and online discussion. In September 2020, a draft prepared by I.M.G. and the four task force leaders was sent to all guideline group members. After agreement of all members was obtained, the manuscript was reviewed by two independent external reviewers. The manuscript was then sent for further comments to the 49 ESGE member societies and individual members. It was then submitted to the journal *Endoscopy* for publication. The final revised manuscript was agreed upon by all the authors. This ESGE Guideline was issued in 2021 and will be considered for update in 2025. Any interim updates will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

Evidence statements and Recommendations

Evidence statements and Recommendations are grouped according to the different task force topics: pre-endoscopy management (task forces 1 and 2), intraendoscopy management (task force 3), and postendoscopy management (task force 4). Each statement is followed by the strength of evidence based on GRADE and the discussion of the evidence that occurred during the two 3-hour online face-to-face meetings. ▶ **Table 1** summarizes all recommendations in this updated guideline.

▶ **Table 1** Summary of Guideline statements and recommendations.

Pre-endoscopy management	
Initial patient evaluation and hemodynamic resuscitation	
1	ESGE recommends immediate assessment of hemodynamic status in patients who present with acute upper gastrointestinal hemorrhage (UGIH), with prompt intravascular volume replacement initially using crystalloid fluids if hemodynamic instability exists. Strong recommendation, low quality evidence.
Red blood cell (RBC) transfusion strategy	
2	ESGE recommends, in hemodynamically stable patients with acute UGIH and no history of cardiovascular disease, a restrictive RBC transfusion strategy with a hemoglobin threshold of ≤ 7 g/dL prompting RBC transfusion. A post-transfusion target hemoglobin concentration of 7–9 g/dL is desired. Strong recommendation, moderate quality evidence.
3	ESGE recommends in hemodynamically stable patients with acute UGIH and a history of acute or chronic cardiovascular disease, a more liberal RBC transfusion strategy with a hemoglobin threshold of ≤ 8 g/dL prompting RBC transfusion. A post transfusion target hemoglobin concentration of ≥ 10 g/dL is desired. Strong recommendation, low quality evidence.
Patient risk stratification	
4	ESGE recommends in patients with acute UGIH the use of the Glasgow–Blatchford Score (GBS) for pre-endoscopy risk stratification. Patients with GBS ≤ 1 are at very low risk of rebleeding, mortality within 30 days, or needing hospital-based intervention and can be safely managed as outpatients with outpatient endoscopy. Strong recommendation, moderate quality evidence.
Management of antithrombotic agents (antiplatelet agents and anticoagulants)	
5	ESGE recommends that in patients with acute UGIH who are taking low dose aspirin as monotherapy for primary cardiovascular prophylaxis, aspirin should be temporarily interrupted. Aspirin can be re-started after careful re-evaluation of its clinical indication. Strong recommendation, low quality evidence.
6	ESGE recommends that in patients with acute UGIH who are taking low dose aspirin as monotherapy for secondary cardiovascular prophylaxis, aspirin should not be interrupted. If for any reason it is interrupted, aspirin should be re-started as soon as possible, preferably within 3–5 days. Strong recommendation, moderate quality evidence.
7	ESGE recommends that in patients with acute UGIH who are taking dual antiplatelet therapy (DAPT) for secondary cardiovascular prophylaxis, aspirin should not be interrupted. The second antiplatelet agent should be interrupted, but re-started as soon as possible, preferably within 5 days. Cardiology consultation is suggested. Strong recommendation, low quality evidence.
8	ESGE does not recommend routine platelet transfusion for patients with acute NVUGIH who are taking antiplatelet agents. Strong recommendation, low quality evidence.
9	ESGE does not recommend the use of tranexamic acid in patients with acute NVUGIH. Strong recommendation, high quality evidence.
10	ESGE recommends that in patients with acute UGIH taking vitamin K antagonists (VKAs), that the anticoagulant be withheld. Strong recommendation, low quality evidence
11	ESGE recommends that in patients with acute UGIH taking vitamin K antagonists (VKAs) who have hemodynamic instability, low dose vitamin K supplemented with intravenous prothrombin complex concentrate (PCC), or fresh frozen plasma (FFP) if PCC is not available, should be administered. However, this should not delay endoscopy or if required, endoscopic hemostasis. Strong recommendation, low quality evidence.
12	ESGE recommends that in patients with acute UGIH taking direct oral anticoagulants (DOAC), the anticoagulant should be withheld and endoscopy not delayed. In patients with severe ongoing bleeding, use of a DOAC reversal agent or intravenous PCC should be considered. Strong recommendation, low quality evidence.
Proton pump inhibitor (PPI) therapy	
13	ESGE suggests that pre-endoscopy high dose intravenous proton pump inhibitor (PPI) therapy be considered in patients presenting with acute UGIH, to downstage endoscopic stigmata and thereby reduce the need for endoscopic therapy; however, this should not delay early endoscopy. Weak recommendation, high quality evidence.

Somatostatin and somatostatin analogues	
14	ESGE does not recommend the use of somatostatin, or its analogue octreotide, in patients with NVUGIH. Strong recommendation, low quality evidence.
Nasogastric/orogastric tube aspiration and lavage	
15	ESGE does not recommend the routine use of nasogastric or orogastric aspiration/lavage in patients presenting with acute UGIH. Strong recommendation, moderate quality evidence.
Endotracheal intubation	
16	ESGE does not recommend routine prophylactic endotracheal intubation for airway protection prior to upper endoscopy in patients with acute UGIH. Strong recommendation, high quality evidence.
17	ESGE recommends prophylactic endotracheal intubation for airway protection prior to upper endoscopy only in selected patients with acute UGIH (i. e., those with ongoing active hematemesis, agitation, or encephalopathy with inability to adequately control the airway). Strong recommendation, low quality evidence.
Prokinetic medications	
18	ESGE recommends pre-endoscopy administration of intravenous erythromycin in selected patients with clinically severe or ongoing active UGIH. Strong recommendation, high quality evidence.
Endoscopic management	
Timing of upper GI endoscopy	
1	ESGE recommends adopting the following definitions regarding the timing of upper GI endoscopy in acute UGIH relative to the time of patient presentation: urgent ≤ 12 hours, early ≤ 24 hours, and delayed > 24 hours. Strong recommendation, moderate quality evidence.
2	ESGE recommends that following hemodynamic resuscitation, early (≤ 24 hours) upper GI endoscopy should be performed. Strong recommendation, high quality evidence.
3	ESGE does not recommend urgent (≤ 12 hours) upper GI endoscopy since as compared to early endoscopy, patient outcomes are not improved. Strong recommendation, high quality evidence.
4	ESGE does not recommend emergent (≤ 6 hours) upper GI endoscopy since this may be associated with worse patient outcomes. Strong recommendation, moderate quality evidence.
5	ESGE recommends that the use of antiplatelet agents, anticoagulants, or a predetermined international normalized ratio (INR) cutoff level, should not be used to define or guide the timing of upper GI endoscopy in patients with acute UGIH. Strong recommendation, low quality evidence.
On-call GI endoscopy resources	
6	ESGE recommends the availability of both an on-call GI endoscopist proficient in endoscopic hemostasis and on-call nursing staff with technical expertise in the use of endoscopic devices, to allow performance of endoscopy on a 24/7 basis. Strong recommendation, low quality evidence.
Endoscopic diagnosis	
7	ESGE recommends the Forrest (F) classification be used in all patients with peptic ulcer hemorrhage to differentiate low risk and high risk endoscopic stigmata. Strong recommendation, high quality evidence.
8	ESGE recommends that peptic ulcers with spurting or oozing bleeding (FIa and FIb respectively) or with a nonbleeding visible vessel (FIIa) receive endoscopic hemostasis because these lesions are at high risk for persistent bleeding or recurrent bleeding. Strong recommendation, high quality evidence.
9	ESGE suggests that peptic ulcers with an adherent clot (FIIb) be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding (FIa or FIb) or nonbleeding visible vessel (FIIa) should receive endoscopic hemostasis. Weak recommendation, moderate quality evidence.
10	ESGE does not recommend endoscopic hemostasis in patients with peptic ulcers having a flat pigmented spot (FIIc) or clean base (FIII), as these stigmata have a low risk of adverse outcomes. In selected clinical settings these patients may have expedited hospital discharge. Strong recommendation, moderate quality evidence.
11	ESGE does not recommend the routine use of Doppler endoscopic probe in the evaluation of endoscopic stigmata of peptic ulcer bleeding. Strong recommendation, low quality evidence.

12	ESGE does not recommend the routine use of capsule endoscopy technology in the evaluation of acute UGIH. Strong recommendation, low quality evidence.
Endoscopic therapy for peptic ulcer hemorrhage	
13	*FIa, FIb (active bleeding)* **(a)** ESGE recommends for patients with actively bleeding ulcers (FIa, FIb), combination therapy using epinephrine injection plus a second hemostasis modality (contact thermal or mechanical therapy). Strong recommendation, high quality evidence. **(b)** ESGE suggests that in selected actively bleeding ulcers (FIa,FIb), specifically those > 2 cm in size, with a large visible vessel > 2 mm, or located in a high-risk vascular area (e. g., gastroduodenal, left gastric arteries), or in excavated/fibrotic ulcers, endoscopic hemostasis using a cap-mounted clip should be considered as first-line therapy. Weak recommendation, low quality evidence.
14	*FIIa (nonbleeding visible vessel)* ESGE recommends for patients with an ulcer with a nonbleeding visible vessel (FIIa), contact or noncontact thermal therapy, mechanical therapy, or injection of a sclerosing agent, each as monotherapy or in combination with epinephrine injection. Strong recommendation, high quality evidence.
15	ESGE does not recommend that epinephrine injection be used as endoscopic monotherapy. If used, it should be combined with a second endoscopic hemostasis modality. Strong recommendation, high quality evidence.
16	ESGE recommends that persistent bleeding be defined as ongoing active bleeding refractory to standard hemostasis modalities. Strong recommendation, high quality evidence.
17	ESGE suggests that in patients with persistent bleeding refractory to standard hemostasis modalities, the use of a topical hemostatic spray/powder or cap-mounted clip should be considered. Weak recommendation, low quality evidence.
18	ESGE recommends that in patients with persistent bleeding refractory to all modalities of endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE. Strong recommendation, moderate quality evidence.
19	ESGE suggests considering the use of hemostatic forceps as an alternative endoscopic hemostasis option in peptic ulcer hemorrhage. Weak recommendation, moderate quality evidence.
Post-endoscopy management	
Proton pump inhibitor (PPI) therapy	
1	ESGE recommends high dose PPI therapy for patients who receive endoscopic hemostasis and for patients with FIIb ulcer stigmata (adherent clot) not treated endoscopically. **(a)** PPI therapy should be administered as an intravenous bolus followed by continuous infusion (e. g., 80 mg then 8 mg/hour) for 72 hours post endoscopy. **(b)** High dose PPI therapies given as intravenous bolus dosing (twice-daily) or in oral formulation (twice-daily) can be considered as alternative regimens. Strong recommendation, high quality evidence.
Second-look endoscopy	
2	ESGE does not recommend routine second-look endoscopy as part of the management of NVUGIH. Strong recommendation, high quality evidence.
Management of recurrent bleeding	
3	ESGE recommends that recurrent bleeding be defined as bleeding following initial successful endoscopic hemostasis. Strong recommendation, high quality evidence.
4	ESGE recommends that patients with clinical evidence of recurrent bleeding should receive repeat upper endoscopy with hemostasis if indicated. Strong recommendation, high quality evidence.
5	ESGE recommends that in the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE. Strong recommendation, high quality evidence.

6	ESGE recommends that for patients with clinical evidence of recurrent peptic ulcer hemorrhage, use of a cap-mounted clip should be considered. In the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE. Strong recommendation, moderate quality evidence.
Helicobacter pylori	
7	ESGE recommends, in patients with NVUGIH secondary to peptic ulcer, investigation for the presence of *Helicobacter pylori* in the acute setting (at index endoscopy) with initiation of appropriate antibiotic therapy when *H. pylori* is detected. Strong recommendation, high quality evidence.
8	ESGE recommends re-testing for *H. pylori* in those patients with a negative test at index endoscopy. Strong recommendation, high quality evidence.
9	ESGE recommends documentation of successful *H. pylori* eradication. Strong recommendation, high quality evidence.
Dual antiplatelet therapy and PPI co-therapy	
10	ESGE recommends that in patients who have had acute NVUGIH and require ongoing dual antiplatelet therapy (DAPT), PPI should be given as co-therapy. Strong recommendation, moderate quality evidence.
Re-starting anticoagulation therapy (vitamin K antagonists [VKAs], direct oral anticoagulants [DOACs])	
11	ESGE recommends that in patients who require ongoing anticoagulation therapy following acute NVUGIH (e. g., peptic ulcer hemorrhage), anticoagulation should be resumed as soon as the bleeding has been controlled, preferably within or soon after 7 days of the bleeding event, based on thromboembolic risk. The rapid onset of action of direct oral anticoagulants (DOACS), as compared to vitamin K antagonists (VKAs), must be considered in this context. Strong recommendation, low quality evidence.
12	ESGE recommends PPIs for gastroduodenal prophylaxis in patients requiring ongoing anticoagulation and with a history of NVUGIH. Strong recommendation, low quality evidence.

Pre-endoscopy management

Initial patient evaluation and hemodynamic resuscitation

RECOMMENDATION

ESGE recommends immediate assessment of hemodynamic status in patients who present with acute upper gastrointestinal hemorrhage (UGIH), with prompt intravascular volume replacement initially using crystalloid fluids if hemodynamic instability exists.

Strong recommendation, low quality evidence.

The goals of hemodynamic resuscitation are to correct intravascular hypovolemia, restore adequate tissue perfusion, and prevent multiorgan failure. Early intensive hemodynamic resuscitation of patients with acute UGIH has been shown to significantly decrease mortality [5]. However, uncertainty remains regarding the optimal rate of fluid resuscitation (aggressive vs. restrictive) [6–9]. A small RCT, including 51 participants presenting with acute UGIH and hemorrhagic shock, suggested that as compared to a conventional fluid resuscitation strategy, a restrictive fluid resuscitation regimen combined with an inotropic pharmacologic agent (dopamine hydrochloride) led to fewer adverse events [6]. A meta-analysis of 11 studies, including 3 studies specifically on UGIH, reported significant reductions in mortality (risk ratio [RR] 0.67, 95 %CI 0.56–0.81; $P<0.001$), postoperative complications (multiorgan dysfunction syndrome, RR 0.37, 95 %CI 0.21–0.66, $P<0.001$, and acute respiratory distress syndrome, RR 0.35, 95 %CI 0.21–0.6; $P<0.001$) in those patients receiving limited fluid resuscitation [8]. However, most of the patients in this meta-analysis suffered from trauma, and it is unclear whether the results can be extrapolated to patients with acute UGIH.

Moreover, there is ongoing uncertainty regarding the ideal crystalloid fluid type to be used in hemodynamic resuscitation for acute UGIH, either saline 0.9 % sodium chloride or balanced crystalloids [10–12]. The selection of fluid type in critically ill patients requires careful consideration, based on safety, effects on patient outcomes, and costs. In both a large RCT and a meta-analysis of critically ill patients (most without UGIH), as compared to saline, use of a balanced crystalloid solution (e. g., lactated Ringer's solution) was shown to reduce both mortality and major adverse renal events [11, 12]. However, there remains a lack of evidence for the subgroup of patients presenting with acute UGIH.

Red blood cell (RBC) transfusion strategy

RECOMMENDATION

ESGE recommends, in hemodynamically stable patients with acute UGIH and no history of cardiovascular disease, a restrictive red blood cell (RBC) transfusion strategy with a hemoglobin threshold of ≤ 7 g/dL prompting RBC transfusion. A post-transfusion target hemoglobin concentration of 7–9 g/dL is desired.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends, in hemodynamically stable patients with acute UGIH and a history of acute or chronic cardiovascular disease, a more liberal RBC transfusion strategy with a hemoglobin threshold of ≤ 8 g/dL prompting RBC transfusion. A post-transfusion target hemoglobin concentration of ≥ 10 g/dL is desired.

Strong recommendation, low quality evidence.

A restrictive red blood cell (RBC) transfusion strategy is considered standard of care in non-massive, acute UGIH [13–15]. A meta-analysis of five RCTs comprising 1965 patients with acute UGIH reported that, as compared to a liberal RBC transfusion strategy, a restrictive RBC transfusion strategy was associated with significantly lower mortality (RR 0.65, 95 %CI 0.44–0.97) and reduced rebleeding (RR 0.58, 95 %CI 0.40–0.84) [16]. This was true for patients with both variceal or nonvariceal bleeding. However, the hemoglobin thresholds that prompted RBC transfusion differed between RCTs and most of the data used in the meta-analysis came from two large RCTs, which could affect generalizability [13, 14].

A meta-analysis of 31 RCTs comprising 12 587 anemic patients with a variety of underlying comorbidities found that a restrictive RBC transfusion strategy did not adversely affect patient outcomes. In-hospital mortality was lower with a restrictive strategy, but 30-day mortality was not significantly different (RR 0.97, 95 %CI 0.81–1.16) [17]. The most common hemoglobin thresholds used to prompt RBC transfusion were ≤ 7 g/dL or ≤ 8 g/dL for the restrictive RBC transfusion strategy and ≤ 9 g/dL or ≤ 10 g/dL for the liberal transfusion strategy. Despite limited data, this meta-analysis concluded that a restrictive RBC transfusion strategy appeared to be safe in patients with underlying cardiovascular disease. However, there were no available data for patients with acute coronary syndrome.

In a separate meta-analysis examining the effects of a restrictive versus liberal RBC transfusion strategy on outcomes in patients with cardiovascular disease not undergoing cardiac surgery (11 RCTs including 3033 patients with cardiovascular disease), Docherty et al. found that it may not be safe to use a hemoglobin threshold of < 8 g/dL to prompt RBC transfusion in patients with ongoing acute coronary syndrome or chronic cardiovascular disease [18]. The authors reported that the risk of acute coronary syndrome in patients managed with a restrictive RBC transfusion strategy was significantly increased (RR 1.78, 95 %CI 1.18–2.70, $P = 0.01$). The authors concluded that until adequately powered, high quality RCTs become available for patients with cardiovascular disease, a more liberal hemoglobin threshold (> 8 g/dL) to prompt RBC transfusion should be used for patients with both acute or chronic cardiovascular disease.

Patient risk stratification

RECOMMENDATION

ESGE recommends, in patients with acute UGIH, the use of the Glasgow–Blatchford Score (GBS) for pre-endoscopy risk stratification. Patients with GBS ≤ 1 are at very low risk of rebleeding, mortality within 30 days, or needing hospital-based intervention and can be safely managed as outpatients with outpatient endoscopy.

Strong recommendation, moderate quality evidence.

Three risk stratification scores have been primarily studied in patients presenting with acute UGIH: the Glasgow-Blatchford Score (GBS), the pre-endoscopy Rockall Score, and the AIMS65 [19–21]. Risk stratification of patients presenting with acute UGIH can assist the triage of patients to in-hospital versus out-of-hospital management. Our updated systematic literature search identified several recent studies that provide additional evidence supporting pre-endoscopy risk stratification and identification of low risk patients. A retrospective study of 2305 consecutive patients admitted for suspected UGIH demonstrated that a GBS ≤ 1 identified a significantly higher proportion of true low risk patients compared with a GBS = 0 (24.4 % vs. 13.6 %, $P < 0.001$) [22]. A systematic review assessed the predictive value of pre-endoscopy risk scores for 30-day serious adverse events (the composite outcome included 30-day mortality, recurrent bleeding, and need for intervention) [23]. Overall, the predictive value of the GBS was superior (sensitivity and specificity of 0.98 and 0.16, respectively, as compared to 0.93 and 0.24, respectively, for the pre-endoscopy Rockall score, and 0.79 and 0.61, respectively, for the AIMS65). In a prospective, international cohort study including 3012 patients, Stanley et al. evaluated the accuracy of the Rockall pre-endoscopy and complete scores, and the AIMS65, GBS, and Progetto Nazionale Emorragia Digestive (PNED) [24]. The GBS was reported to have the highest accuracy (AUROC 0.86) for predicting need for hospital-based intervention (RBC transfusion, endoscopic treatment, arterial embolization, surgery) or death. Moreover, a GBS ≤ 1 was the optimal threshold to predict patient survival without need for hospital-based intervention, with a sensitivity of 98.6 % and specificity of 34.6 %. However, none of the evaluated risk scores were able to predict other outcomes with acceptable ability (AUROC ≤ 0.80).

The sensitivity of a risk stratification score (e. g., detecting patients at high risk) is important so as not to incorrectly classify high risk patients as low risk when deciding on early hospital discharge. In contrast, risk score specificity is less crucial, since

low specificity results in more low risk patients being admitted to hospital, but not in high risk patients being prematurely discharged. Moreover, the use of a validated risk stratification score (such as the GBS) with early discharge of low risk patients can reduce the need for endoscopy services, hospital admission, and resource utilization, without increasing patient risk. Two prospective studies found that implementation of GBS = 0 as a standard for non-admission was associated with a positive clinical effect in terms of reduced rates of hospital admission (15 % of all acute UGIH patients), shorter length of hospital stay (6 vs. 19 hours), and reduced resource utilization among the low risk patients [25, 26]. It should be noted that when the GBS is used to identify very low risk patients, discharged patients should be informed of the limited risk of recurrent bleeding and should be advised to maintain contact with the discharging hospital.

Pre-endoscopy management of antithrombotic agents (antiplatelet agents and anticoagulants)

RECOMMENDATION

ESGE recommends that in patients with acute UGIH who are taking low dose aspirin as monotherapy for primary cardiovascular prophylaxis, aspirin should be temporarily interrupted. Aspirin can be restarted after careful re-evaluation of its clinical indication.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends that in patients with acute UGIH who are taking low dose aspirin as monotherapy for secondary cardiovascular prophylaxis, aspirin should not be interrupted. If for any reason it is interrupted, aspirin should be restarted as soon as possible, preferably within 3–5 days.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that in patients with acute UGIH who are taking dual antiplatelet therapy (DAPT) for secondary cardiovascular prophylaxis, aspirin should not be interrupted. The second antiplatelet agent should be interrupted, but restarted as soon as possible, preferably within 5 days. Cardiology consultation is suggested.

Strong recommendation, low quality evidence.

Patients with NVUGIH (e. g., peptic ulcer hemorrhage) who take antiplatelet agents face a serious clinical challenge since the risk of maintaining the antiplatelet agent to avoid thrombotic events must be balanced against the risk of persistent or recurrent bleeding. Both events are associated with increased mortality. Thus, it is important to know whether the indication for antiplatelet therapy is for primary or secondary cardiovascular prophylaxis. Primary prophylaxis is defined as use of antiplatelet agents by individuals who are free of, but at potential risk of developing cardiovascular disease. Secondary prophylaxis is the use of antiplatelet agents to prevent a second event in individuals who have had a myocardial infarction or certain types of cerebrovascular event. The evidence here however is limited and mostly restricted to low dose aspirin monotherapy. In the only published RCT, 156 recipients of low dose aspirin for secondary cardiovascular prophylaxis who had peptic ulcer bleeding with high risk endoscopic stigmata were randomized after endoscopic therapy to receive continuous aspirin or placebo [27]. At 8-week follow-up, all-cause mortality was significantly lower in the patients randomized to aspirin than in those receiving placebo (1.3 % vs. 12.9 %; i. e., a difference of 11.6 percentage points, 95 %CI 3.7–19.5 percentage points; hazard ratio [HR] 0.20), with the difference being attributable to cardiovascular, cerebrovascular, or gastrointestinal complications. In a retrospective analysis of 118 low dose aspirin users who had been treated for peptic ulcer bleeding and who were followed up for a median of 2 years, 47 (40 %) patients stopped their aspirin [28]. Those who discontinued aspirin and those who continued aspirin had similar mortality rates (31 %). However, in the subgroup of patients with cardiovascular comorbidities, those who discontinued aspirin had an almost fourfold increase in the risk of death or an acute cardiovascular event ($P < 0.01$).

Three more recent observational studies reported similar results. One study reported on 544 patients with peptic ulcer bleeding, of whom 74 (13.6 %) were taking antithrombotic agents [29]. The HR for a thrombotic event when antithrombotic agents were discontinued was 10.9 (95 %CI 1.3–89.7). No significant differences in recurrent bleeding events were observed between the two groups. A similar conclusion was reported in another retrospective cohort study [30]. Using Cox regression analysis, the investigators showed that the HR for recurrent bleeding was 2.98 (95 %CI 0.67–8.36) in patients who continued their antithrombotic agent(s) (85.5 % aspirin). However, the HR for death or acute cardiovascular disease in those who stopped taking antithrombotic agents was 5.21 (95 %CI 1.03–26.3). Lastly, Siau et al. evaluated outcomes in 118 patients with acute upper GI bleeding who had their antithrombotic therapy stopped at hospital discharge [31]. These authors reported that cessation of antithrombotic therapy was associated with increased mortality (HR 3.3, 95 %CI 1.1–10.3), increased thrombotic events (HR 5.8, 95 %CI 1.3–26.4), and overall increased adverse events (HR 3.0, 95 %CI 1.3–6.7). However, there was no significant increase in post-hospital discharge bleeding rates. These observational studies appear to concur with the only available RCT on this topic [27].

The optimal timing for the resumption of aspirin and/or other antiplatelet agents in the setting of acute NVUGIH (e. g., peptic ulcer hemorrhage) has not been adequately studied. A meta-analysis reported that the time interval to develop acute coronary syndrome after antithrombotic discontinuation is estimated to be within 1 week, and to be within 2 weeks for a cerebrovascular event [32]. In the updated Asia-Pacific working group consensus on nonvariceal upper gastrointestinal

bleeding, it was recommended that in patients with peptic ulcer hemorrhage, antithrombotic agents could be restarted the same day or not be interrupted at all if endoscopy demonstrates a Forrest III (clean base) ulcer [33]. A recent retrospective cohort study, including 871 GI bleeding patients, of whom 25 % had peptic ulcer hemorrhage and all of whom were taking antithrombotic medications (52.5 % antiplatelet agents), showed that at long-term follow-up (mean 24.9 months), resumption of either antiplatelet or anticoagulant therapy was associated with a higher risk of rebleeding, but a lower risk of an ischemic event or death [34]. Moreover, the investigators reported that when compared to late resumption of antithrombotic therapy, early resumption (≤ 7 days) following the bleeding episode showed no difference in mortality, a lower rate of ischemic events (13.6 % vs. 20.4 %), yet a significantly higher rate of GI rebleeding (30.6 % vs. 23.1 %; $P = 0.04$).

After 5 days of aspirin interruption, 50 % of circulating platelets are new and therefore able to produce thromboxane which plays a key role in thrombotic events [35]. Therefore, aspirin can be temporarily interrupted and resumed within a 5-day window in patients considered at high risk for recurrent bleeding. Overall, there is good evidence to maintain, or at least to only temporarily interrupt and then quickly resume aspirin therapy after aspirin interruption in patients with known cardiovascular disease who develop peptic ulcer hemorrhage.

To date, no studies have specifically investigated outcomes of the interruption and/or timing of resumption of non-aspirin antiplatelet agents in patients with peptic ulcer hemorrhage. Moreover, the data that are available are limited to the use of aspirin for secondary cardiovascular prophylaxis. Therefore, recommendations to withhold aspirin that has been prescribed for primary cardiovascular prophylaxis in patients who develop peptic ulcer hemorrhage is based solely on clinical judgment. In such patients, the risk of persistent or recurrent bleeding should outweigh the risk of a cardiovascular event. However, in a recent study of 95 patients taking low dose aspirin for primary cardiovascular prevention who developed peptic ulcer hemorrhage, 18 (18.9 %) subsequently had a cardiovascular event during follow-up. This suggests that the actual cardiovascular risk and aspirin indication for these patients should be more adequately assessed before interrupting aspirin for longer periods of time [34].

No studies have evaluated the best management strategy for patients taking dual antiplatelet therapy (DAPT) who develop peptic ulcer hemorrhage. In general, patients taking DAPT have in the recent past undergone a percutaneous coronary intervention (PCI) with stent placement and are at high risk of stent thrombosis if antiplatelet agents are interrupted [36]. Therefore, in patients with a recent PCI and stent placement and NVUGIH, a cardiologist should be consulted and maintenance of both antiplatelet agents be considered if the risk of rebleeding is thought to be low. ▶ **Fig. 1 a, b** outlines the management of antiplatelet therapy in patients with acute NVUGIH.

RECOMMENDATION

ESGE does not recommend routine platelet transfusion for patients with acute NVUGIH who are taking antiplatelet agents.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE does not recommend the use of tranexamic acid in patients with acute NVUGIH.

Strong recommendation, high quality evidence.

There is no high quality evidence supporting the benefit of routine platelet transfusion in patients who have acute UGIH while taking antiplatelet agents. Moreover, endoscopic hemostasis appears safe in patients with thrombocytopenia [37]. Zakko et al. reported that platelet transfusion in patients with GI bleeding taking antiplatelet medication(s), and in the absence of thrombocytopenia, did not reduce rebleeding, but was associated with higher mortality [38]. However, it would appear reasonable to consider platelet transfusion in patients taking antiplatelet medication(s) and with thrombocytopenia who have severe bleeding.

Several small studies and meta-analyses [39–42] have suggested benefit from use of tranexamic acid (TXA) in GI bleeding. However, a recent international multicenter RCT (the HALT-IT study), comparing TXA versus placebo in acute GI bleeding, reported no mortality benefit from TXA. Mortality, defined as death due to bleeding within 5 days of randomization, was 4 % (222 patients) in the TXA group and 4 % (226) in the placebo group (RR 0.99, 95 %CI 0.82–1.18). Moreover TXA was associated with a higher number of venous thromboembolic events (48 [0.8 %] vs. 26 [0.4 %]; RR 1.85, 95 %CI 1.15–2.98) [43].

RECOMMENDATION

ESGE recommends that, in patients with acute UGIH taking vitamin K antagonists (VKAs) the anticoagulant be withheld.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends that, in patients with acute UGIH taking vitamin K antagonists (VKAs) who have hemodynamic instability, low dose vitamin K supplemented with intravenous prothrombin complex concentrate (PCC), or fresh frozen plasma (FFP) if PCC is not available, should be administered. However, this should not delay endoscopy or, if required, endoscopic hemostasis.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends that, in patients with acute UGIH taking direct oral anticoagulants (DOACs), the anticoagulant should be withheld and endoscopy not delayed. In patients with severe ongoing bleeding, use of a DOAC reversal agent or intravenous PCC should be considered.

Strong recommendation, low quality evidence.

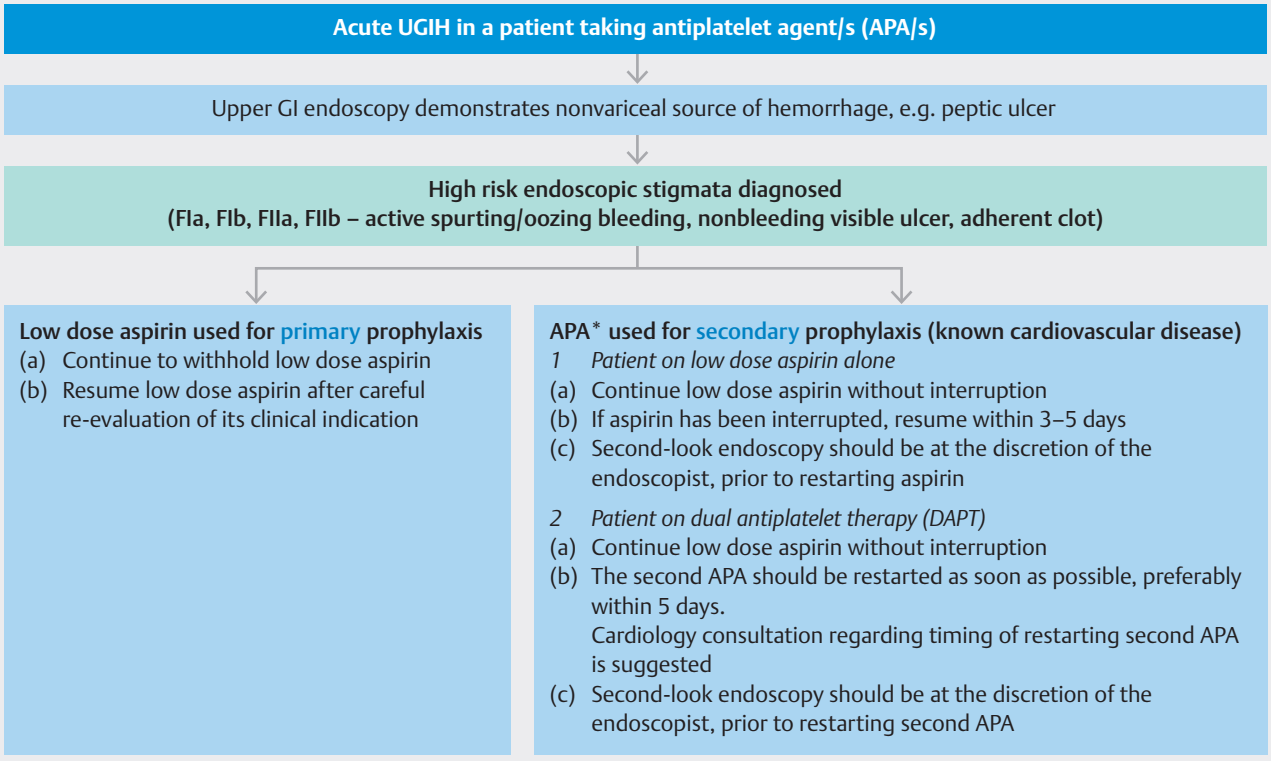
The management of patients taking anticoagulants (VKAs, DOACs) who develop acute UGIH (e.g., peptic ulcer hemorrhage) is clinically challenging since anticoagulant management must be addressed both prior to and following upper endoscopy [44]. Unfortunately, no studies have specifically addressed the optimal timing of endoscopy in patients receiving anticoagulants. Furthermore, since the pharmacokinetics and pharmacodynamic profiles of VKAs and DOACs are different, management is different. DOACs (factor Xa and thrombin inhibitors) have a rapid onset of action and a much shorter half-life than VKA, and routine tests for anticoagulant activity are lacking [45].

The anticoagulant effect of VKA is measured using the international normalized ratio (INR). Studies have shown that endoscopy outcomes in VKA-anticoagulated patients were similar in patients with normal INR compared with those with elevated INR at hospital admission, or in those where INR was corrected to a value <2.5 prior to endoscopy [44, 46–48]. More recent observational studies provide additional supporting evidence. Nagata et al. reported that in patients with acute upper (47%) or lower GI bleeding, early endoscopy (within 24 hours) in anticoagulant users (n = 157) was not associated with an increased risk of rebleeding (13.4% vs. 15.9%, P = 0.52) or thromboembolic events (5.7% vs. 3.2%, P = 0.68) when compared to matched controls not taking anticoagulants [49]. An INR >2.5 was seen in 22.9% of the anticoagulant users at the time of endoscopy. However rapid INR correction was associated with an increased risk of thromboembolism, as suggested in other studies [50, 51]. Another small study also suggested that the INR level did not affect rebleeding or endoscopy outcomes [52]. However, Peloquin et al. reported that in 134 patients with GI bleeding and a supratherapeutic INR of ≥3.5, therapeutic endoscopic intervention was less likely to be effective as the INR increased [53].

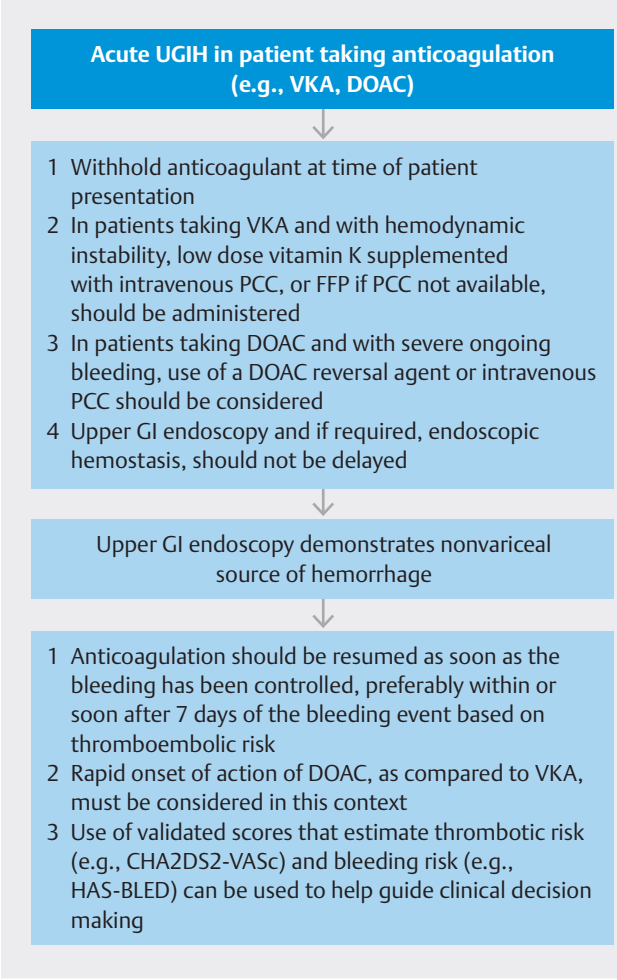
Reversal of the anticoagulant effect of VKAs in patients with acute UGIH can be achieved with low dose vitamin K, however, this takes time since the INR only starts to decrease within 2–4 hours and normalizes within 24 hours. Moreover, the anticoagulant reversal effect of vitamin K persists as compared to prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) [54]. Sin et al. reported that four-factor PCC appears to be associated with a significant thromboembolic risk; however it remains a useful agent for warfarin reversal [55]. That same study also suggested that in patients requiring reversal of warfarin anticoagulation, lack of concomitant vitamin K may contribute to "INR rebound," therefore concomitant low dose vitamin K may be appropriate in this situation. However, given the limited data, caution must be exercised when giving vitamin K since its persisting effect can impede re-coagulation efforts. Limitations of FFP include the requirement for a higher volume load to achieve a reversal effect, slower onset of action compared with PCC, and requirement for blood group typing. In addition, recent evidence suggests that use of FFP is associated with increased mortality in patients undergoing endoscopy for NVUGIH [56–58]. Three- or four-factor PCC or FFP can be used when the reversal of anticoagulation is urgent because of patient hemodynamic instability or life-threatening massive bleeding, irrespective of INR values. Recombinant factor VIIa is currently not recommended because of its high cost and higher risk of thromboembolism [59].

Patients who develop acute UGIH while taking DOACs must follow a similar protocol of early endoscopy and reversal of anticoagulation in cases of hemodynamic instability or life-threatening bleeding. However, there are particular considerations because of DOAC's specific pharmacodynamics and the availability of antidotes which rapidly block its anticoagulation effects. It is important to know the time of the last DOAC dose, since most DOACs have an 8–12-hour half-life and their effect usually disappears within 24 hours. Hemodialysis is effective to remove dabigatran from plasma and can help to prevent rebleeding [60]. PCC has also been shown to be effective for reversal of anticoagulation in patients with acute UGIH who are taking DOACs [61, 62]. However, the best potential therapeutic options rely on the availability of DOAC reversal agents that should be used in cases of life-threatening acute UGIH. The risk of thromboembolism with use of reversal agents is a concern, but very few data are available [63–67]. Idarucizumab is a specific antidote for dabigatran and works effectively within minutes. Thromboembolism and rebound effects have been reported in 6.8% and 23% of patients, respectively [63]. Other DOAC antidotes are being investigated but are not yet on the market [66, 67].

▶ **Fig. 2** outlines management of anticoagulant therapy in patients with acute NVUGIH.



▶ **Fig. 1** Management of antiplatelet therapy in patients with acute nonvariceal upper gastrointestinal hemorrhage (NVUGIH) with **a** high risk, and **b** low risk stigmata, diagnosed at endoscopy. *In patients using a nonaspirin antiplatelet agent (APA) as monotherapy (e. g. thienopyridine alone), low dose aspirin may be substituted for an interval period provided there is no contraindication or allergy to aspirin. Cardiology consultation is suggested for further APA recommendations. UGIH, upper gastrointestinal hemorrhage.



▶ **Fig. 2** Management of anticoagulants in acute nonvariceal upper gastrointestinal hemorrhage (NVUGIH) before and after upper GI endoscopy. UGIH, upper gastrointestinal hemorrhage; VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; GI, gastrointestinal.

Pre-endoscopy proton pump inhibitor (PPI) therapy

RECOMMENDATION

ESGE suggests that pre-endoscopy high dose intravenous proton pump inhibitor (PPI) therapy be considered in patients presenting with acute UGIH, to downstage endoscopic stigmata and thereby reduce the need for endoscopic therapy; however, this should not delay early endoscopy.

Weak recommendation, high quality evidence.

In the systematic literature search (from January 2014 to January 2020) for this updated NVUGIH guideline, we were unable to identify any systematic reviews, meta-analyses, RCTs, or observational studies evaluating pre-endoscopy PPI administration in patients presenting with acute UGIH. Although pre-endoscopy PPI therapy significantly reduces the prevalence of high risk endoscopic stigmata in peptic ulcer hemorrhage at the time of index endoscopy, and thereby reduces the need for endoscopic hemostasis, PPIs provide no significant impact on patient outcomes, including recurrent hemorrhage, need for surgery, or mortality [68]. In the 2015 ESGE NVUGIH guideline, initiation of high dose intravenous PPI was recommended for patients presenting with acute UGIH awaiting upper endoscopy, without delaying early endoscopy [1]. This was a strong recommendation based upon high quality evidence. However, the lack of a significant impact of pre-endoscopy PPI therapy on clinically relevant patient outcomes in acute NVUGIH has recently led to revised recommendations from several international evidence-based guideline bodies. In 2018, the Asia-Pacific working group consensus revised their earlier support for routine pre-endoscopy intravenous PPI administration in acute UGIH [33]. Since there is no proven impact on patient outcomes and costs are increased, the working group members voted to reject the indiscriminate use of pre-endoscopy intravenous PPIs in patients presenting in a stable condition with symptoms suggestive of acute UGIH. However, the working group noted that when endoscopy facilities or expertise in acute UGIH are not available within 24 hours, the downgrading of stigmata of recent hemorrhage and reducing the need for urgent endoscopy by use of intravenous PPIs could be justified. In 2019, the International Consensus Group on NVUGIH recommended that "pre-endoscopic PPI therapy may be considered to downstage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy" [15]. This was the same as their earlier recommendation in 2010 [69]. Lastly, the recently published United Kingdom consensus care bundle for early clinical management of acute UGIH did not recommend use of PPI prior to endoscopy [70].

Considering the available evidence, ESGE now "suggests" that pre-endoscopy, high dose intravenous PPI "be considered" in patients presenting with acute UGIH. This change is reflective of the lack of high level evidence for the impact of pre-endoscopy PPI on clinically relevant patient outcomes and remains consistent with other recent NVUGIH guideline recommendations.

Somatostatin and somatostatin analogues

RECOMMENDATION

ESGE does not recommend the use of somatostatin, or its analogue octreotide, in patients with NVUGIH.

Strong recommendation, low quality evidence.

Somatostatin, and its analogue octreotide, inhibit both acid and pepsin secretion while also reducing gastroduodenal mucosal blood flow [71]. However, they are not recommended in NVUGIH (e. g., peptic ulcer bleeding), either before endoscopy or as an adjunctive therapy following endoscopy, since published data show little or no benefit. A recently published retrospective cohort study including 180 patients with acute NVUGIH continues to show no significant differences in outcomes between patients receiving combination therapy (PPI plus octreotide infusion) and those receiving PPI alone (hospital

and intensive care unit [ICU] median length of stay, respectively, 6.1 vs. 4.9 days, $P=0.25$, and 2.3 vs. 1.9 days, $P=0.24$; rebleeding 9% vs. 12%, $P=0.63$; RBC units transfused 3 vs. 2 units, $P=0.43$; and mortality 6.7% vs. 5.6%, $P=1.00$) [72].

Nasogastric/orogastric tube aspiration and lavage

RECOMMENDATION

ESGE does not recommend the routine use of nasogastric or orogastric aspiration/lavage in patients presenting with acute UGIH.

Strong recommendation, moderate quality evidence.

A recent retrospective study and a review both concluded that nasogastric tube (NGT) aspiration does not differentiate upper from lower GI bleeding in patients with melena [73, 74]. Moreover, a randomized, single-blind, noninferiority study comparing NGT placement (with aspiration and lavage) to no NGT placement (n = 140 in each arm), failed to show that NGT aspiration could accurately predict the presence of a high risk lesion requiring endoscopic therapy (39% vs. 38%, respectively) [75]. In addition, adverse events (pain, nasal bleeding, or failure of NGT placement) occurred in 34% and there were no observed differences in rebleeding rates or mortality.

Endotracheal intubation

RECOMMENDATION

ESGE does not recommend routine prophylactic endotracheal intubation for airway protection prior to upper endoscopy in patients with acute UGIH.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends prophylactic endotracheal intubation for airway protection prior to upper endoscopy only in selected patients with acute UGIH (i.e., those with ongoing active hematemesis, agitation, or encephalopathy with inability to adequately control their airway).

Strong recommendation, low quality evidence.

It has been posited that prophylactic endotracheal intubation prior to upper endoscopy in unselected patients with acute UGIH could protect the patient's airway from potential aspiration of gastric contents and prevent cardiorespiratory adverse events. However, three recent systematic reviews/meta-analyses and a small retrospective case series show that prophylactic endotracheal intubation before upper endoscopy in patients with acute UGIH may be associated with a higher risk of aspiration and pneumonia, longer hospital stays, and potentially higher mortality [76–79]. In a meta-analysis by Almashhrawi et al., the authors reported that in patients with acute UGIH who received prophylactic endotracheal intubation prior to upper endoscopy, pneumonia within 48 hours was identified in 20 of 134 patients (14.9%) as compared with 5 of 95 patients (5.3%) not prophylactically intubated ($P=0.02$, OR 3.13) [78]. Despite observed trends, no significant differences were found for aspiration ($P=0.11$) or mortality ($P=0.18$). Alshamsi et al., in their meta-analysis including 10 observational studies (n = 6068 patients), reported that prophylactic endotracheal intubation was associated with a significant increase in aspiration (OR 3.85, 95%CI 1.46–10.25; $P=0.01$), pneumonia (OR 4.17, 95%CI 1.82–9.57; $P<0.001$) and hospital length of stay (mean difference 0.86 days, 95%CI 0.13–1.59; $P=0.02$) [77]. However, there was no observed effect on mortality (OR 1.92, 95% CI 0.71–5.23; $P=0.20$). Chaudhuri et al. included 7 observational studies (n = 5662 patients) in their meta-analysis and found that prophylactic endotracheal intubation was associated with significantly higher rates of pneumonia (OR 6.58, 95% CI 4.91–8.81), longer hospital length of stay (mean difference, 0.96 days, 95%CI 0.26–1.67), and increased mortality (OR 2.59, 95%CI 1.01–6.64) [76]. However, because of the observational design of the included studies, the data should be considered to be of low quality.

Prokinetic medications

RECOMMENDATION

ESGE recommends pre-endoscopy administration of intravenous erythromycin in selected patients with clinically severe or ongoing active UGIH.

Strong recommendation, high quality evidence.

In patients with acute UGIH, the quality of the endoscopic examination can be adversely affected by poor visibility in the upper GI tract due to blood, clots and fluids. It is reported that in 3% to 19% of UGIH cases, no obvious cause of bleeding is identified [80, 81]. This may in part be related to the presence of blood and clots impairing endoscopic visualization. Prokinetics may improve gastric mucosa visualization by inducing gastric emptying. Most studies assessing the use of pre-endoscopy prokinetics in UGIH have used erythromycin. Insufficient data were found to make recommendations for the use of metoclopramide [82–84].

Five published meta-analyses have evaluated the role of prokinetic agent infusion prior to upper GI endoscopy in patients presenting with acute UGIH [82–86]. The most recently published meta-analysis (n = 598 patients) by Rahman et al., showed that erythromycin infusion prior to upper endoscopy significantly improved gastric mucosa visualization (OR 4.14, 95%CI 2.01–8.53; $P<0.01$), reduced the need for a second-look endoscopy (OR 0.51, 95%CI 0.34–0.77; $P<0.01$), and reduced the length of hospital stay (mean difference –1.75, 95% CI –2.43 to –1.06; $P<0.01$) [86]. However other relevant outcomes, such as duration of the procedure, units of blood transfused, and need for emergency surgery showed no significant differences. Mortality was not assessed.

A single intravenous dose of erythromycin appears to be safe and generally well tolerated, with no adverse events reported in

the meta-analyses. Most studies that reported a significant improvement in endoscopic visualization with pre-endoscopic erythromycin infusion did include patients admitted to the intensive care unit because of acute UGIH with clinical evidence of active bleeding or hematemesis. These are the patients most likely to benefit from erythromycin infusion prior to endoscopy. The dose of erythromycin most commonly used is 250 mg, infused 30–120 minutes prior to upper GI endoscopy. A cost-effectiveness study found that pre-endoscopy erythromycin infusion in UGIH was cost-effective, primarily because of a reduction in the need for second-look endoscopy [87].

It should be noted that there have been difficulties accessing erythromycin in many countries. Furthermore, there are some contraindications to its administration. These include patient sensitivity to macrolide antibiotics and presence of a prolonged QT interval. Drug interactions such as erythromycin-induced digoxin toxicity have been reported to occur when erythromycin is repeatedly administrated, although the risk appears to be very low [88]. In addition, the combination of simvastatin and erythromycin may increase the risk of rhabdomyolysis [89].

Endoscopic management

Timing of upper GI endoscopy

RECOMMENDATION

ESGE recommends adopting the following definitions regarding the timing of upper GI endoscopy in acute UGIH relative to the time of patient presentation: urgent ≤ 12 hours, early ≤ 24 hours, and delayed > 24 hours.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that following hemodynamic resuscitation, early (≤ 24 hours) upper GI endoscopy should be performed.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE does not recommend urgent (≤ 12 hours) upper GI endoscopy since as compared to early endoscopy, patient outcomes are not improved.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE does not recommend emergent (≤ 6 hours) upper GI endoscopy since this may be associated with worse patient outcomes.

Strong recommendation, moderate quality evidence.

RECOMMENDATION

ESGE recommends that the use of antiplatelet agents, anticoagulants, or a predetermined international normalized ratio (INR) cutoff level, should not be used to define or guide the timing of upper GI endoscopy in patients with acute UGIH.

Strong recommendation, low quality evidence.

In patients with acute NVUGIH, upper GI endoscopy performed within 24 hours or after 24 hours of patient presentation are the commonly accepted definitions for “early” and “delayed” endoscopy [90–95]. Urgent upper GI endoscopy in the setting of acute UGIH has been variably defined as endoscopy performed between 6–12 hours of patient presentation [91, 96, 97]. There is no consensus definition of emergent endoscopy.

Early endoscopy (≤ 24 hours from the time of patient presentation) is associated with lower in-hospital mortality, shorter length of stay, and lower total hospital costs, and should be performed in patients with acute UGIH [92–94]. A beneficial role of urgent endoscopy (≤ 12 hours from the time of patient presentation) however, is not routinely demonstrated as published studies show conflicting results. While one recent study concluded that urgent endoscopy was an independent predictor of lower mortality [96], other studies have shown that urgent endoscopy was a predictor of worse patient outcomes [90, 97], or that clinical outcomes were not significantly different between urgent and early endoscopy [91]. Moreover, in a well-executed large RCT by Lau et al., the investigators reported that, at 30-day follow-up, as compared to “early” upper endoscopy (mean time to endoscopy 24.7 ± 9.0 hours), “urgent” upper endoscopy (mean time to endoscopy 9.9 ± 6.1 hours) performed in patients at high risk for further bleeding or death, was not associated with significantly lower rates of further bleeding (7.8 % vs. 10.9 %; HR 1.46, 95 %CI 0.83–2.58) or lower mortality (6.6 % vs. 8.9 %; HR 1.35, 95 %CI 0.72–2.54) [98]. Lastly, in a large prospective cohort study from Denmark, including 12 601 patients admitted to hospital with peptic ulcer bleeding, emergent endoscopy (performed < 6 hours from the time of patient presentation) was associated with higher in-hospital and 30-day mortality, particularly in hemodynamically unstable patients or in patients with an American Society of Anesthesiologists (ASA) score ≥ 3 [99]. In those patients, optimizing hemodynamic resuscitation and adequately attending to comorbidities prior to endoscopy may improve outcomes.

Although antiplatelet and anticoagulant therapies are usually interrupted or discontinued in patients with acute UGIH, it is now realized that complete reversal of the antithrombotic effect of those drugs is not necessary for performance of diagnostic and therapeutic endoscopy. One study evaluated the risk of rebleeding in patients receiving anticoagulants and concluded that an INR > 2.5 was not a risk factor for rebleeding in patients with acute UGIH [49]. This finding, combined with the fact that the antithrombotic effect of DOACs is not measured by INR, has led to the recommendation to avoid using a predetermined INR

cutoff value to define the timing of endoscopy in the setting of acute UGIH.

On-call GI endoscopy resources

RECOMMENDATION
ESGE recommends the availability of both an on-call GI endoscopist proficient in endoscopic hemostasis and on-call nursing staff with technical expertise in the use of endoscopic devices, to allow performance of endoscopy on a 24/7 basis.
Strong recommendation, low quality evidence.

Although a retrospective study from Japan concluded that the clinical outcomes of patients who underwent emergency endoscopic hemostasis for acute UGIH outside regular hours did not differ from those of patients treated during regular hours [100], two systematic reviews/meta-analyses found otherwise [95, 101]. Xia et al. reported that NVUGIH patients who were admitted out of hours had significantly higher mortality and received less timely endoscopy [95]. Shih and colleagues showed that the "weekend effect" was associated with increased mortality in UGIH patients, particularly in patients with NVUGIH [101].

Endoscopic diagnosis

RECOMMENDATION
ESGE recommends the Forrest (F) classification be used in all patients with peptic ulcer hemorrhage to differentiate low risk and high risk endoscopic stigmata.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE recommends that peptic ulcers with spurting or oozing bleeding (FIa or FIb, respectively) or with a nonbleeding visible vessel (FIIa) receive endoscopic hemostasis because these lesions are at high risk for persistent bleeding or recurrent bleeding.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE suggests that peptic ulcers with an adherent clot (FIIb) be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding (FIa or FIb) or nonbleeding visible vessel (FIIa) should receive endoscopic hemostasis.
Weak recommendation, moderate quality evidence.

RECOMMENDATION
ESGE does not recommend endoscopic hemostasis in patients with peptic ulcers having a flat pigmented spot (FIIc) or clean base (FIII), as these stigmata have a low risk of adverse outcomes. In selected clinical settings these patients may have expedited hospital discharge.
Strong recommendation, moderate quality evidence.

RECOMMENDATION
ESGE does not recommend the routine use of Doppler endoscopic probe in the evaluation of endoscopic stigmata of peptic ulcer bleeding.
Strong recommendation, low quality evidence.

RECOMMENDATION
ESGE does not recommend the routine use of capsule endoscopy technology in the evaluation of acute UGIH.
Strong recommendation, low quality evidence.

The Forrest (F) classification was developed more than 40 years ago to standardize the endoscopic characterization of peptic ulcers [102]. The Forrest classification is defined as follows: FIa spurting hemorrhage, FIb oozing hemorrhage, FIIa nonbleeding visible vessel, FIIb adherent clot, FIIc flat pigmented spot, and FIII clean base ulcer. This classification has been used in numerous studies to identify patients at risk of persistent ulcer bleeding, recurrent ulcer bleeding, and mortality. Most of these studies have shown that the presence of an ulcer endoscopically classified as FIa or FIb is an independent risk factor for persistent bleeding or recurrent bleeding [103]. A potential limitation of the Forrest classification is that recognition and identification of endoscopic stigmata and interobserver agreement may be less than optimal, although data are conflicting [104, 105].

The classification of FIb as a high risk stigma following endoscopic therapy is controversial. It is apparent that FIb stigmata require endoscopic hemostasis as there is active bleeding (i. e., oozing hemorrhage), but the response to endoscopic treatment may be different compared to that with other high risk endoscopic stigmata of hemorrhage (FIa, FIIa, and in some cases FIIb), specifically in peptic ulcer rebleeding rates. An RCT including 388 patients comparing PPI or placebo following successful endoscopic treatment of FIb ulcers found no apparent benefit on rebleeding rates with the addition of PPI (5.4 % vs. 4.9 %; OR 1.11, 95 %CI 0.42–2.95) [106]. In the placebo group, FIb ulcers had a lower risk of rebleeding (4.9 %) compared to FIa (22.5 %), FIIb (17.6 %), and FIIa (11.3 %). Studies using a Doppler endoscopic probe have shown rebleeding rates from FIb ulcers following endoscopic therapy to be lower than the rebleeding rates of FIa, FIIa and FIIb ulcers. This has led some to consider

a reassessment of the risk stratification of endoscopic stigmata of recent hemorrhage as follows: "high risk," FIa, FIIa, and FIIb; "medium risk," FIb and FIIc; and "low risk," FIII [106, 107]. A prospective study, that included two patient cohorts with 87 high risk stigmata (FIa, FIIa, FIIb) ulcers and 52 medium risk stigmata (FIb, FIIc) ulcers, demonstrated significantly higher Doppler signal-positive arteries in high risk stigmata ulcers compared to the medium risk stigmata ulcers, before endoscopic hemostasis (87.4% vs. 42.3%, $P<0.001$) as well as after endoscopic hemostasis (27.4% vs. 13.6%), and significantly higher 30-day rebleeding rates (28.6% vs. 0%, $P=0.04$). In addition, for spurting bleeding (FIa) versus oozing bleeding (FIb), baseline Doppler endoscopic probe arterial flow was 100% versus 46.7%, residual blood flow detected after endoscopic hemostasis was 35.7% versus 0%, and 30-day rebleed rates were 28.6% versus 0% (all $P<0.05$) [107]. However, given the low numbers of patients included in this study, larger size studies are needed before considering a change in endoscopic stigmata risk classification.

In addition to the Forrest classification, there are additional endoscopic features of peptic ulcers that can predict adverse outcomes and/or endoscopic treatment failure and recent publications continue to support this [108, 109]. These endoscopic features include large size of ulcer (>2 cm), large size of nonbleeding visible vessel, and ulcer location on the posterior duodenal wall or the proximal lesser curvature of the stomach.

The persistence of a positive Doppler probe signal following endoscopic hemostasis has been shown to predict recurrent bleeding [110]. The results of available studies have been disparate and limited by their methodology, the older endoscopic hemostasis therapies used, and the small numbers of patients included. However, two recent studies have used a through-the-scope (TTS) Doppler probe to guide endoscopic hemostasis. In an RCT with a subgroup of 86 patients with peptic ulcer bleeding, 53 were classified as "high risk" (FIa, FIIa, FIIb) and 23 as "medium risk" (FIb, FIIc). Patients were randomly assigned to standard endoscopic hemostasis or Doppler probe-guided hemostasis with repeat intervention until the Doppler signal was completely obliterated. Total rebleeding rates were significantly lower in the Doppler probe-guided hemostasis group (11.1% vs. 26.3%, $P=0.02$) but there were no significant differences in other outcomes [111]. In a study comprising 60 patients with FIa, FIb, and FIIa ulcers that were "assigned by chance" to standard endoscopic hemostasis (n=25) or Doppler probe-guided intervention (n=35) until the Doppler signal was obliterated, the Doppler probe-guided hemostasis group showed significantly lower rates for rebleeding (52% vs. 20%, $P=0.013$) and surgery (2% vs. 26%, $P=0.02$) [112]. A cost-minimization analysis suggests a per-patient cost-saving with the use of the Doppler endoscopic probe in patients with peptic ulcer bleeding, but cost-savings may be dependent on and limited to specific healthcare settings [113].

Since publication of the previous ESGE NVUGIH Guideline, five additional studies have been published that evaluate the role of capsule endoscopy technology (e.g., video capsule endoscopy, magnetically assisted capsule endoscopy, telemetric sensor capsule) in acute UGIH, namely one RCT, three prospective cohort studies, and one retrospective case series [114–118]. In the only RCT, Marya et al. reported on 87 patients with nonhematemesis GI hemorrhage who were randomized to early video capsule endoscopy or to "standard of care" whereby the gastroenterologist chose which procedures to perform and when to perform them based on the patient's presentation [114]. A source of GI bleeding was located in 64.3% of the patients in the early video capsule endoscopy arm and in 31.1% of the patients in the standard of care arm ($P<0.01$). Moreover, the likelihood of endoscopic location of bleeding over time was greater for patients receiving early video capsule endoscopy (adjusted hazard ratio 2.77, 95%CI 1.36–5.64). Overall, patients who received capsule endoscopy technology to evaluate their GI bleeding were more likely to undergo therapeutic procedures (e.g., balloon enteroscopy, colonoscopy, or surgery) than patients with standard of care treatment. Thus, capsule endoscopy technology may be helpful in the setting of acute UGIH, as it may assist in the clinical management plan. However, because data continue to be limited, including on costs and on availability of technology, the exact role for capsule endoscopy modalities in evaluating patients presenting with acute UGIH remains unknown. Additional high level studies are needed to further assess the diagnostic role of capsule endoscopy in this patient population.

Endoscopic therapy for peptic ulcer hemorrhage

RECOMMENDATION

FIa, FIb (active bleeding)

(a) ESGE recommends for patients with actively bleeding ulcers (FIa, FIb), combination therapy using epinephrine injection plus a second hemostasis modality (contact thermal or mechanical therapy) .

Strong recommendation, high quality evidence.

(b) ESGE suggests that in selected actively bleeding ulcers (FIa, FIb), specifically those >2 cm in size, with a large visible vessel >2 mm, or located in a high risk vascular area (e.g., gastroduodenal, left gastric arteries), or in excavated/fibrotic ulcers, endoscopic hemostasis using a cap-mounted clip should be considered as first-line therapy.

Weak recommendation, low quality evidence.

RECOMMENDATION

FIIa (nonbleeding visible vessel)

ESGE recommends, for patients with an ulcer with a nonbleeding visible vessel (FIIa), contact or noncontact thermal therapy, mechanical therapy, or injection of a sclerosing agent, each as monotherapy or in combination with epinephrine injection.

Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE does not recommend that epinephrine injection be used as endoscopic monotherapy. If used, it should be combined with a second endoscopic hemostasis modality.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE recommends that "persistent bleeding" be defined as ongoing active bleeding refractory to standard hemostasis modalities.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE suggests that in patients with persistent bleeding refractory to standard hemostasis modalities, the use of a topical hemostatic spray/powder or cap-mounted clip should be considered.
Weak recommendation, low quality evidence.

RECOMMENDATION
ESGE recommends that in patients with persistent bleeding refractory to all modalities of endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE.
Strong recommendation, moderate quality evidence.

Endoscopic hemostasis can be achieved using injection, thermal, and/or mechanical modalities, and it has been well demonstrated that any endoscopic hemostasis therapy is superior to pharmacotherapy alone in patients with FIa, FIb and FIIa ulcers [119, 120]. Meta-analyses show that thermal devices (contact and noncontact), injectable agents other than epinephrine (i. e., sclerosing agents, thrombin/fibrin glue), and clips are all effective methods for achieving durable hemostasis, with no single modality being superior [119–123]. Epinephrine injection therapy is effective at achieving primary hemostasis, but inferior to other endoscopic hemostasis monotherapies or combination therapy in preventing ulcer rebleeding [119, 120, 122]. Therefore, current evidence-based guidelines recommend that if epinephrine is used to treat peptic ulcer bleeding with high risk stigmata, it should only be used in combination with a second endoscopic hemostasis modality and not as monotherapy [1, 15].

▶ **Fig. 3 a–c** presents an algorithm, stratified according to the Forrest classification of endoscopic stigmata, for the endoscopic management of NVUGIH secondary to peptic ulcer.

Two recent meta-analyses support the superiority of combination endoscopic therapy (injection plus thermal therapy, and injection plus mechanical therapy) over epinephrine injection monotherapy in peptic ulcers with high risk stigmata [124, 125]. Baracat et al. performed a systematic review and meta-analysis of 28 RCTs that included 2988 adults with high risk peptic ulcer endoscopic stigmata. These authors reported that injection therapy alone, as compared to injection plus thermal therapy was inferior in terms of ulcer rebleeding (risk difference [RD] –0.08, 95 %CI –0.14 to –0.02) and need for emergency surgery (RD –0.06, 95 %CI –0.12 to 0.00). Moreover, they reported that injection therapy alone, as compared to injection plus mechanical therapy was also inferior in terms of rebleeding (RD –0.10, 95 %CI –0.018 to –0.03) and need for surgery (RD –0.11, 95 %CI –0.18 to –0.04) [124]. No significant difference in mortality between hemostasis modalities was observed. In a network meta-analysis, Shi et al. reported that the addition of mechanical therapy following epinephrine injection significantly reduced the probability of rebleeding and surgery (OR 0.19, 95 %CI 0.07–0.52 and OR 0.10, 95 %CI 0.01–0.50, respectively), while the addition of thermal therapy only reduced ulcer rebleeding rates (OR 0.30, 95 %CI 0.10–0.91) [125].

With respect to noncontact thermal therapy (e. g., argon plasma coagulation [APC]), limited data from three previous small RCTs suggest that in peptic ulcer hemorrhage, APC may provide similar efficacy to injection of a sclerosing agent (polidocanol) or contact thermal therapy (heater probe) [119]. More recently, a single RCT (noninferiority design) compared combination endoscopic therapies using epinephrine injection plus APC versus epinephrine injection plus soft coagulation using hemostatic forceps [126]. That study included 151 patients with high risk stigmata gastroduodenal ulcers (FIa, FIb, FIIa). The authors reported similar outcomes between APC and hemostatic forceps for rates of primary hemostasis (96.0 % vs. 96.1 %, $P = 1.00$), 7-day ulcer rebleeding (4.0 % vs. 6.6 %, $P = 0.72$) and 30-day ulcer rebleeding rates (6.7 % vs. 9.2 %, $P = 0.56$).

Clinicians must distinguish between two clinical scenarios in NVUGIH: persistent bleeding and recurrent bleeding. Persistent bleeding is defined as ongoing active bleeding (spurting, arterial pulsatile bleeding, or oozing) that is present at the end of index endoscopy and refractory to standard hemostasis modal-

▶ **Fig. 3** Algorithm for the endoscopic management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH) secondary to peptic ulcer, stratified by Forrest classification endoscopic stigmata: **a** FIa, FIb, FIIa; **b** FIIb; **c** FIIc, FIII. [1]Use of a large single-channel or double-channel therapeutic upper gastrointestinal endoscope is recommended. [2]Large-size 10-Fr probe recommended for contact thermal therapy. [3]Absolute alcohol, polidocanol, or ethanolamine injected in limited volumes. [4]The benefit of endoscopic hemostasis may be greater in patients at higher risk for recurrent bleeding, e. g., with older age, comorbidities, in-hospital UGIH. GI, gastrointestinal; PPI, proton pump inhibitor, TAE, transcatheter angiographic embolization.

Performance of upper GI endoscopy[1]

High risk endoscopic stigmata
FIa (active spurting, pulsatile arterial bleeding)
FIb (active oozing)
FIIa (nonbleeding visible vessel)

Perform endoscopic hemostasis

FIa and FIb stigmata
Combination therapy using dilute epinephrine injection + a second hemostasis modality (thermal[2], mechanical or sclerosant injection[3])

FIIa stigmata
Thermal[2], mechanical, or sclerosant injection[3] as monotherapy or in combination with dilute epinephrine injection

- High dose PPI (intravenous bolus + continuous infusion or minimum twice-daily intravenous bolus dosing for 72 hours or oral dosing)
- May start clear liquids soon after endoscopy
- Test for *Helicobacter pylori* at index endoscopy, treat if positive; document *H. pylori* eradication
- If negative *H. pylori* test at index endoscopy, repeat testing within 4 weeks following the acute bleeding episode to confirm initial test was true negative

If clinical evidence of rebleeding, repeat endoscopy with endoscopic hemostasis if indicated;
If endoscopic hemostasis still unsuccessful, refer for TAE if locally available, otherwise refer for surgery

a

Performance of upper GI endoscopy[1]

FIIb (adherent clot)

Consider performing clot removal followed by endoscopic hemostasis of underlying high risk stigmata[4]
OR
Medical management with high dose PPI (intravenous bolus + continuous infusion for 72 hours or minimum twice-daily intravenous bolus dosing for 72 hours or oral dosing)

If clot removal/endoscopic hemostasis performed:
- Dilute epinephrine injection circumferential to base of clot followed by clot removal using cold polyp snare guillotine technique
- If underlying high risk stigmata identified after clot removal, apply endoscopic hemostasis as described for FIa, FIb, FIIa stigmata
- High dose PPI (intravenous bolus + continuous infusion or minimum twice-daily intravenous bolus dosing for 72 hours or oral dosing)
- May start clear liquids soon after endoscopy
- Test for *H. pylori,* treat if positive; document *H. pylori* eradication
- If negative *H. pylori* test at index endoscopy, repeat testing within 4 weeks following the acute bleeding episode to confirm initial test was true negative

If clinical evidence of rebleeding, repeat endoscopy with endoscopic hemostasis if indicated;
If endoscopic hemostasis still unsuccessful, refer for TAE if locally available, otherwise refer for surgery

b

Performance of upper GI endoscopy[1]

Low risk stigmata
FIIc (flat pigmented spot)
FIII (clean base)

No endoscopic hemostasis required
In select clinical settings, these patients may have expedited hospital discharge

- Start oral PPI
- Start regular diet
- Test for *H. pylori,* treat if positive; document *H. pylori* eradication
- If negative *H. pylori* test at index endoscopy, repeat testing within 4 weeks following the acute bleeding episode to confirm initial test was true negative

c

ities. This is also referred to as "failed primary endoscopic hemostasis" [1]. Few RCTs have compared alternative treatment modalities in the management of patients with persistent ulcer bleeding. Meta-analyses and retrospective case series comparing transcatheter arterial embolization (TAE) and surgery suggest that patient outcomes following either approach are similar [127–129]. TAE, however, is associated with a higher failure rate in the control of bleeding [127–129]. A population-based cohort study compared outcomes in 282 patients (97 TAE and 185 surgery) and found a 34 % lower mortality among those in the TAE group (adjusted HR 0.66, 95 %CI 0.46–0.96). However, similarly to other cohort studies, rebleeding was higher after TAE (HR 2.48, 95 %CI 1.33–4.62), whereas following surgery adverse events were significantly higher (32.2 % vs. 8.3 %, $P<0.001$) [130].

Since publication of the original ESGE NVUGIH guideline in 2015, several additional studies have reported on the clinical efficacy of topical hemostatic agents (e. g., TC-325, Endoclot, and Inha University-Endoscopic Wound Dressing [UI-EWD]) in patients with GI bleeding secondary to peptic ulcer bleeding. These include case series, a multicenter patient registry, a pilot RCT, and a cost–effectiveness analysis [131–134]. A multicenter (12 sites) patient registry evaluated the effectiveness of TC-325 in upper and lower GI bleeding (167/314 [53 %] due to peptic ulcer) [132]. In the subgroup of peptic ulcer hemorrhage (most common stigmata, FIb), the authors reported an overall hemostasis rate of 86 %, an overall rebleeding rate of 12.7 %, and 7-day and 30-day all-cause mortality of 16.2 % and 24.6 %, respectively. These data however should be interpreted with caution because of the inherent limitations of a patient registry that included lack of randomization or sequential patient selection, multiple bleeding indications (with GI bleeding secondary to malignancy being over-represented in the cohort), along with patient selection bias and self-reported or unverified outcomes. In addition, a pilot RCT evaluated the clinical efficacy of TC-325 with/without epinephrine injection versus through-the-scope (TTS) clipping with/without epinephrine injection, in 39 patients with active NVUGIH (the majority of cases due to peptic ulcer, and 35/39 [89.7 %] with FIb oozing bleeding) [133]. The authors reported that primary hemostasis was achieved in all TC-325 cases and in 90 % of the mechanical therapy group ($P=0.49$). There was no difference in rebleeding, need for surgery, or mortality rates between the groups. This was a small pilot study with a limited number of patients enrolled, and thus not adequately powered to show a statistically significant difference between groups. Moreover, five patients in the TC-325 group required additional endoscopic intervention at the time of second-look endoscopy, while none in the clipping group required such therapy ($P=0.04$). These results should not be extrapolated to FIa bleeding lesions. Lastly, a decision analysis model compared the cost–effectiveness of traditional endoscopic hemostasis therapies alone, TC-325 alone, or these therapies in combination, when treating acute NVUGIH [134]. The authors reported that traditional endoscopic hemostasis complemented by TC-325 was more efficacious (97 % avoiding rebleeding) and less expensive than comparator treatments (mean cost per patient $ 9150). The second most cost-effective approach was TC-325 plus traditional endoscopic hemostasis (5.8 % less effective and $635 more costly per patient). The limitations of topical sprays/powders are that they only bind to sites with active bleeding and usually wash away within 12–24 hours; thus they are a temporary measure.

The role of cap-mounted clips (e.g, the Over the Scope Clip [OTSC], Ovesco, Tübingen, Germany; and the Padlock system, Steris Endoscopy, Mentor, Ohio, USA) in treating NVUGIH, used as first-line and second-line (e. g., rescue/salvage) therapy, continues to evolve. In a retrospective case series evaluating over-the-scope (OTS) clip technology as first-line treatment in NVUGIH (the FLETRock study), Wedi et al. reported on 118 patients with NVUGIH, including 60 patients (50.8 %) defined as high risk based upon a Rockall risk score ≥ 8 [135]. Primary clinical success (hemostasis by OTS clipping alone) was achieved in 107 patients (90.8 %) and secondary clinical success (hemostasis by OTS clipping in combination with adjunctive measures) in 7 patients (1.7 %). In 7.5 % of clip applications, the bleeding could not be stopped and treatment was defined as clinical failure. Patients with Forrest Ia active bleeding were at higher risk of rebleeding (11/31 patients, 35.5 %). Manta et al., in a multicenter retrospective study, also reported on the outcomes of 286 patients (74.8 % with NVUGIH) who were treated with OTS clipping as first-line endoscopic hemostasis therapy [136]. Of the 214 patients with NVUGIH, technical success was achieved in 208 (97.2 %), including 202/208 (97.1 %) achieving hemostasis with OTS clipping as monotherapy. Early rebleeding, within 24 hours, occurred in 9 patients (4.5 %), and no delayed bleeding (within 30 days) was reported. Technical failure of OTS clipping occurred in 6 patients, in ulcers located in the gastric fundus or posterior wall of the duodenal bulb. Brandler et al. reported an additional retrospective case series of 67 patients (60 patients with NVUGIH, including 49 due to peptic ulcer, 11 with Forrest Ia active bleeding) with bleeding lesions defined by the authors as being at "high risk of adverse outcome" (visible vessel > 2 mm; ulcer location in high risk vascular region, including gastroduodenal, left gastric arteries; penetrating, excavated or fibrotic ulcer with high risk stigmata) [137]. OTS clipping was performed as first-line therapy in 49 patients. The authors reported 100 % technical success, OTS clipping success (no bleeding related to OTS clipping requiring re-intervention) in 52 patients (81.3 %), and true success (no bleeding within 30 days) in 46 patients (71.8 %). They reported no adverse events.

In a systematic review and meta-analysis, Chandrasekar et al. examined the effectiveness of cap-mounted clip technology in achieving "definitive hemostasis" in GI bleeding, defined as successful primary hemostasis without rebleeding during the follow-up period (median 56 days) [138]. This meta-analysis included 21 studies (1 RCT, 20 observational) with 851 patients (687 with UGIH). In those patients with UGIH, OTS clipping was used as first-line endoscopic therapy in 75.8 % and definitive hemostasis was achieved in 86.6 % (95 %CI 81.9–91.3). The rebleeding rate in patients with UGIH was 11.0 % (95 %CI 6.8 %–15.2 %). The OTSC failure rate for UGIH was 6.2 % (95 %CI 3.1 %–9.2 %) and 16.9 % (95 %CI 9.3 %–24.5 %) for first- and second-line therapy, respectively. It must be noted that this meta-analysis is

limited, as all included studies but one were observational in design. Other observational studies have also reported on the efficacy and safety of OTSC used as either first-line or second-line hemostasis treatment, with similar findings [139–144].

Very recently, the first blinded RCT evaluating the efficacy and safety of a cap-mounted clip (OTS clip, n = 25) versus standard endoscopic hemostasis therapy (TTS clip or contact thermal therapy using multipolar electrocoagulation, n = 28) for first-line treatment of acute peptic ulcer or Dieulafoy bleeding was published by Jensen et al. [145]. The investigators reported that compared to standard endoscopic hemostasis, there was both significantly less recurrent bleeding within 30 days (1/25 [4.0 %] vs. 8/28 [28.6 %], $P = 0.017$) and fewer adverse events (0/25 [0 %] vs. 4/28 [14.3 %], $P = 0.049$) in the OTS clip group. There were no observed differences in need for surgery or mortality. However, a number of methodological limitations to this study must be noted, including the relatively limited number of patients, the inclusion of Dieulafoy lesions in addition to peptic ulcers, and the use of unconventional definitions of "major" endoscopic stigmata of recent hemorrhage that are not widely adopted.

In a multicenter RCT from Europe and Asia (the STING study), Schmidt et al. reported on 66 patients with recurrent peptic ulcer hemorrhage following initially successful endoscopic hemostasis, who were randomly assigned to undergo hemostasis with either OTS clipping (n = 33) or standard endoscopic therapy (using TTS clips, n = 31, or contact thermal therapy plus injection with dilute epinephrine, n = 2) [146]. By per-protocol analysis, persistent ulcer bleeding was observed in 14 patients (42.4 %) in the standard therapy group and 2 patients (6.0 %) in the OTS clip group ($P = 0.001$). Recurrent ulcer bleeding within 7 days occurred in 5 patients (16.1 %) in the standard therapy group versus 3 patients (9.1 %) in the OTS clip group ($P = 0.47$). Further bleeding occurred in 19 patients (57.6 %) in the standard therapy group and in 5 patients (15.2 %) in the OTS clip group (absolute difference 42.4 %, 95 %CI 21.6 %–63.2 %; $P = 0.001$). During 30 days of follow-up, 1 patient (3.0 %) in the standard therapy group and 1 patient (3.0 %) in the OTS clip group required surgery ($P = 0.99$), 2 patients (6.3 %) died in the standard therapy group and 4 patients (12.1 %) died in the OTSC group ($P = 0.67$).

To date, almost all evidence on the efficacy of OTS clipping is derived from case series or case series compared with historical controls. Randomized trials directly comparing topical agents and OTS clips/clamps with traditional hemostasis therapies are required to better define their true efficacies and safety in both first-line and second-line endoscopic management of acute NVUGIH, especially peptic ulcer bleeding.

RECOMMENDATION

ESGE suggests considering the use of hemostatic forceps as an alternative endoscopic hemostasis option in peptic ulcer hemorrhage

Weak recommendation, moderate quality evidence.

In 2015, the previously published ESGE guideline on NVUGIH reported on two small studies that compared the efficacy of mechanical therapy versus hemostatic forceps in peptic ulcer hemorrhage [147, 148]. The first was an RCT conducted in 96 patients with high risk bleeding gastric ulcers; it showed that use of monopolar, soft coagulation hemostatic forceps was as effective as mechanical therapy [147]. The second study was a prospective cohort study including 50 patients in whom use of bipolar hemostatic forceps was more effective than endoscopic clipping, for both initial hemostasis (100 % vs. 78.2 %, $P < 0.05$) and preventing recurrent bleeding (3.7 % vs. 22.2 %, P not significant) [148]. More recently, three additional RCTs have evaluated the efficacy of hemostatic forceps in peptic ulcer hemorrhage. Nunoe et al. reported on 111 patients with peptic ulcer hemorrhage; compared to contact thermal therapy (i. e., heater probe), hemostatic forceps achieved a significantly higher rate of primary hemostasis (96 % vs. 67 %, $P < 0.001$) and lower ulcer rebleeding rates (0 vs. 12 %) [149]. Kim et al, included 151 patients and failed to show any significant difference in rates of primary hemostasis, rebleeding, adverse events, or mortality between argon plasma coagulation (APC) and hemostatic forceps [150]. Finally, Toka et al. compared epinephrine injection plus hemostatic forceps to epinephrine injection plus mechanical therapy using TTS clips, in 112 patients, and demonstrated that as compared to mechanical therapy, hemostatic forceps achieved significantly higher rates of primary hemostasis (98.2 % vs. 80.4 %, $P = 0.004$) and significantly lower ulcer rebleeding (3.6 % vs. 17.7 %, $P = 0.04$) [151].

Box 1 presents a description of the endoscopic hemostatic modalities.

Post-endoscopy management

Proton pump inhibitor therapy

RECOMMENDATION

ESGE recommends high dose proton pump inhibitor (PPI) therapy for patients who receive endoscopic hemostasis, and for patients with FIIb ulcer stigmata (adherent clot) not treated endoscopically.

(a) PPI therapy should be administered as an intravenous bolus followed by continuous infusion (e. g., 80 mg then 8 mg/hour) for 72 hours post endoscopy.

(b) High dose PPI therapies given as intravenous bolus dosing (twice-daily) or in oral formulation (twice-daily) can be considered as alternative regimens.

Strong recommendation, high quality evidence.

Previously published evidence-based guidelines on NVUGIH recommended that PPI therapy, given as an 80 mg intravenous bolus followed by 8 mg/hour continuous infusion, be used to decrease ulcer rebleeding and mortality in patients with high risk endoscopic stigmata who had undergone successful endoscopic hemostasis [1, 15]. Meta-analyses of RCTs comparing low dose (80 mg/day or lower) to high dose PPI (> 80 mg/day), suggest that patient-centered outcomes were similar following

BOX 1 ENDOSCOPIC HEMOSTASIS TOOLBOX

Injection therapy

The primary mechanism of action of injection therapy is local tamponade resulting from a volume effect. Diluted epinephrine (1:10 000 or 1:20 000 with normal saline injected in 0.5–2-ml aliquots in and around the ulcer base) may also have a secondary effect that produces local vasoconstriction. Sclerosing agents such as ethanol, ethanolamine, and polidocanol produce hemostasis by causing direct tissue injury and thrombosis. Another class of injectable agents are tissue adhesives including thrombin, fibrin, and cyanoacrylate glues, which are used to create a primary seal at the site of bleeding.

Endoscopic injection is performed using needles which consist of an outer sheath and an inner hollow-core needle (19–25 gauge). The endoscopist or nursing assistant retracts the needle into the plastic sheath for safe passage through the working channel of the endoscope. When the catheter is passed out of the working channel and placed near the site of bleeding, the needle is extended out of the sheath and the solution injected into the mucosa using a syringe attached to the catheter handle.

Thermal therapy

Thermal devices are divided into contact and noncontact modalities. Contact thermal devices include heater probes that generate heat directly, multipolar/bipolar electrocautery probes that generate heat indirectly by passage of an electrical current through the tissue, and monopolar/bipolar hemostatic forceps. Noncontact thermal devices include argon plasma coagulation. Heat generated from these devices leads to edema, coagulation of tissue proteins, vasoconstriction, and indirect activation of the coagulation cascade, resulting in a hemostatic bond. Contact thermal probes also use local tamponade (mechanical pressure of the probe tip directly onto the bleeding site) combined with heat or electrical current to coagulate blood vessels, a process known as "coaptive coagulation."

Heater probes (available in 7-Fr and 10-Fr sizes) consist of a Teflon-coated hollow aluminum cylinder with an inner heating coil combined with a thermocoupling device at the tip of the probe to maintain a constant energy output (measured in joules, commonly delivering 15–30 J). Multipolar/bipolar electrocautery contact probes deliver thermal energy by completion of an electrical local circuit (no grounding pad required) between two electrodes on the tip of the probe as current flows through nondesiccated tissue. As the targeted tissue desiccates, there is a decrease in electrical conductivity, limiting the maximum temperature and depth and area of tissue injury. An endoscopist-controlled foot pedal activates the heater probe, controls the delivery of the energy (measured in watts) and provides waterjet irrigation. The standard setting for use in achieving hemostasis in peptic ulcer bleeding is 15–20 watts, which is delivered in 8–10-second applications (commonly referred to as tamponade stations).

Monopolar/bipolar hemostatic forceps are contact thermal devices widely used in the treatment of blood vessels or active bleeding during endoscopic submucosal dissection (ESD) and third-space endoscopy (e. g., peroral endoscopic myotomy [POEM]). However, studies evaluating the utility and safety of hemostatic forceps in the treatment of peptic ulcer bleeding are limited. Technically, hemostatic forceps are applied differently during treatment of bleeding in ESD/POEM and peptic ulcers. In ESD/POEM, the vessel is grasped and gently retracted by the forceps, then soft coagulation is applied. In the treatment of peptic ulcer bleeding, soft coagulation is applied directly by contacting the bleeding point with the closed tip of the hemostatic forceps. Potential disadvantages of hemostatic forceps should be considered, including a reduced coagulation effect in the presence of blood, clots, or water between the tip of the forceps and the bleeding point. Moreover, because of the monopolar nature of some hemostatic forceps, the mode of the cardiac device needs to be adjusted in patients with pacemakers and implantable cardioverter-defibrillators.

Argon plasma coagulation (APC), a noncontact thermal modality, uses high frequency, monopolar alternating current that is conducted to the target tissue without mechanical contact, resulting in coagulation of superficial tissue. The electrons flow through a stream of electrically activated ionized argon gas, from the probe electrode to the target, causing tissue desiccation at the surface. As the tissue surface loses its electrical conductivity, the plasma stream shifts to adjacent nondesiccated (conductive) tissue, which again limits the depth of tissue injury. If the APC catheter is not near the target tissue, there is no ignition of the gas and depression of the foot pedal results only in flow of inert argon gas. Coagulation depth is dependent on the generator power setting, duration of application, and distance from the probe tip to the target tissue (optimal distance 2–8 mm).

Mechanical therapy

Endoscopic mechanical therapies include clips (through-the-scope [TTS] and cap-mounted) and band ligation devices. TTS endoscopic clips are deployed directly onto a bleeding site and typically slough off within days to weeks after placement. Clips are available in a variety of jaw lengths and opening widths. The delivery catheter consists of a metal cable within a sheath enclosed within a Teflon catheter. After insertion of the catheter through the working channel of the endoscope, the clip is extended out of the sheath. The clip is then positioned over the target area and opened with the plunger handle. A rotation mechanism on the handle is available on some commercially available clips and this allows the endoscopist to change the orientation of the clip at the site of bleeding. The jaws of the clip

are applied with pressure and closed onto the target tissue by using the device handle. Some clips may be opened, closed, and repositioned, whereas others are permanently deployed and released upon clip closure. Similarly, some clips are automatically released on deployment, while others require repositioning of the plunger handle to release the deployed clip from the catheter. Hemostasis is achieved by mechanical compression of the bleeding site.

Currently two types of cap-mounted clip devices are commercially available for use in GI bleeding: the Ovesco Over The Scope Clip (OTSC) system (Ovesco Endoscopy, Tübingen, Germany) and the Padlock system (Steris Endoscopy, Mentor, Ohio, USA). These devices are similar in that they both utilize an applicator cap preloaded with a nitinol clip (either bearclaw-shaped with teeth or hexagonal in shape with circumferentially placed inner prongs) that fits onto the tip of the endoscope. However, there are some differences between these systems. In the Ovesco OTSC system, the applicator cap, with the preloaded nitinol clip, is affixed to the tip of the endoscope and incorporates a clip-release thread, which is pulled retrogradely through the working channel of the endoscope and fixed onto a handwheel mounted on the working channel access port of the endoscope. The clip is released by the endoscopist's turning the handwheel, in a manner similar to deploying a variceal ligation band. In contrast, the Padlock system deploys its hexagonally shaped clip using its "Lock-it" releasing mechanism. This is installed on the handle of the endoscope and connects to the clip by a linking cable delivery system on the outside of the endoscope. Thus, unlike the OTSC system, the Padlock does not take up the endoscope's working channel. The clips of both systems may remain attached to tissue for weeks. Deployment of a cap-mounted clip requires accurate positioning and adequate retraction of tissue into the cap of the device (either by suction or use of a retractor/anchoring device) before the clip can be properly deployed. Clipping of lesions located in difficult anatomic positions, such as the proximal lesser curvature of the stomach and the anatomic transition from the first to second part of the duodenum, can be technically challenging.

Finally, endoscopic band ligation devices, commonly used in esophageal variceal bleeding, have also been reported for treatment of NVUGIH (e. g., Dieulafoy lesions). These involve the placement of elastic bands over tissue to produce mechanical compression and tamponade.

Topical therapy

Topical agents are increasingly being used for nonvariceal upper gastrointestinal hemorrhage (NVUGIH). Advantages of noncontact, spray catheter delivery of hemostatic agents include ease of use, lack of need for precise lesion targeting, access to lesions in difficult locations, and the ability to treat a larger surface area. One example of a topical agent is TC-325, also known as Hemospray (Cook Medical, Winston-Salem, North Carolina, USA), which is a proprietary, inorganic, absorbent powder that rapidly concentrates clotting factors at the bleeding site, forming a coagulum. Hemospray is applied using a hand-held device consisting of a pressurized CO2 canister, a TTS delivery catheter, and a reservoir for the powder cartridge. The powder is delivered by the endoscopist by pushing a button in 1–2-second bursts until hemostasis is achieved. The maximum amount of TC-325 that can be safely administered during a single treatment session has not yet been established. The coagulum typically sloughs within 3 days and is naturally eliminated.

Other topical hemostatic sprays/powders include EndoClot, Ankaferd Blood Stopper, and Inha University-Endoscopic Wound Dressing (UI-EWD). EndoClot (EndoClot Plus, Santa Clara, California, USA) consists of absorbable modified polymers and is intended to be used as an adjuvant hemostatic agent to control bleeding in the GI tract. It is a biocompatible, nonpyogenic, starch-derived compound that rapidly absorbs water from serum and concentrates platelets, red blood cells, and coagulation proteins at the bleeding site to accelerate the clotting cascade. Hemostatic sprays/powders derived from plant products/extracts have also been evaluated, such as Ankaferd Blood Stopper (Ankaferd Health Products, Istanbul, Turkey). This topical agent promotes formation of a protein mesh that acts as an anchor for erythrocyte aggregation without significantly altering coagulation factors or platelets. It is delivered onto the bleeding site via an endoscopic spray catheter until an adherent coagulum is formed. The particles are subsequently cleared from the bleeding site within hours to days.

Finally, UI-EWD (NextBiomedical, Incheon, South Korea) is a biocompatible natural polymer in powder form using aldehyded dextran and succinic acid-modified L-lysine that is converted to an adhesive gel when in contact with water. The hemostatic powder is delivered via a spray catheter placed through the endoscope's working channel.

It should be noted that the overall efficacy of topical agents in brisk arterial bleeding (FIa) may be limited because of the rapid "wash-away" effect of the hemostatic agent by ongoing blood flow.

intermittent PPI administration (given either as intravenous bolus dosing or orally) [152, 153]. In their meta-analysis of 13 RCTs of high risk bleeding ulcers treated with endoscopic hemostasis, Sachar et al. compared intermittent PPI dosing (oral or intravenous) with the post-hemostasis PPI regimen of 80 mg intravenous bolus followed by 8 mg/hour continuous infusion [154]. The authors reported that the RR for recurrent ulcer bleeding within 7 days for intermittent infusion of PPI versus bolus plus continuous infusion of PPI was 0.72 (upper boundary of one-sided 95 %CI, 0.97), with an absolute risk difference of −2.64. RRs for other outcomes, including radiologic/surgical intervention and mortality, showed no differences between infusion regimens. These meta-analytic data indicate that intermittent PPI therapy may be comparable to intravenous bolus plus continuous PPI infusion following endoscopic hemostasis.

Given the pharmacodynamic profile of PPIs, consideration should be given to use of a higher dose of PPI (80 mg or more) given either intravenously or orally at least twice-daily [155]. These data appear to be supported by the results from an RCT (double-dummy, placebo-controlled design) that randomly assigned patients with peptic ulcer hemorrhage to high dose continuous infusion of esomeprazole versus 40 mg of oral esomeprazole twice-daily for 72 hours (118 vs. 126 patients, respectively) following endoscopic hemostasis [156]. In that study, recurrent ulcer bleeding at 30 days was reported in 7.7 % and 6.4 % of patients, respectively (difference −1.3 percentage points, 95 %CI −7.7 to 5.1 percentage points) [156]. However, it must be pointed out this study was conducted in an all-Asian population, was not a noninferiority study design, was stopped prematurely because of difficulty in patient recruitment, and lacks sufficient sample size to detect any small difference between low dose and high dose PPI regimens.

RECOMMENDATION
ESGE does not recommend routine second-look endoscopy as part of the management of NVUGIH.
Strong recommendation, high quality evidence.

Routine second-look endoscopy is defined as a scheduled repeat endoscopic assessment of a previously diagnosed bleeding lesion usually performed within 24 hours following the index endoscopy [1]. This strategy employs repeat endoscopy regardless of the type of bleeding lesion, perceived rebleeding risk, or clinical signs of rebleeding. However, second-look endoscopy should be reserved for selected patients considered to be at high risk of recurrent bleeding. Previous studies have failed to demonstrate either a clinical or economic benefit of routine second-look endoscopy [157, 158]. More recently, two RCTs from Asia both reported no benefit of routine second-look endoscopy in peptic ulcer hemorrhage [159, 160]. Chiu et al. showed similar rates of rebleeding within 30 days, in 10/153 (6.5 %) in a PPI infusion group and in 12/152 (7.9 %) in a second-look endoscopy group ($P = 0.646$). Moreover, ICU stay, transfusion requirements, need for surgery, and mortality were also not different between the groups. However, patients in the second-look endoscopy group were discharged from hospital 1 day earlier ($P < 0.001$) [159]. Park et al. found a higher rate of rebleeding within 30 days in those patients who underwent routine second-look endoscopy (16/158 (10.2 %) vs. 9/161 (4.5 %), $P = 0.13$) [160]. Thus, second-look endoscopy should be reserved for selected patients considered to be at high risk of recurrent bleeding. This includes patients in whom at index endoscopy there was an actively bleeding lesion, poor endoscopic visualization or an incomplete examination, or failure to identify a definitive source of hemorrhage, or when endoscopic hemostasis was considered by the endoscopist to be suboptimal.

Management of recurrent bleeding

RECOMMENDATION
ESGE recommends that recurrent bleeding be defined as bleeding following initial successful endoscopic hemostasis.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE recommends that patients with clinical evidence of recurrent bleeding should receive repeat upper endoscopy, including hemostasis if indicated.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE recommends that in the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE.
Strong recommendation, high quality evidence.

RECOMMENDATION
ESGE recommends that for patients with clinical evidence of recurrent peptic ulcer hemorrhage, use of a cap-mounted clip should be considered. In the case of failure of this second attempt at endoscopic hemostasis, transcatheter angiographic embolization (TAE) should be considered. Surgery is indicated when TAE is not locally available or after failed TAE.
Strong recommendation, moderate quality evidence.

As previously stated, recurrent bleeding is defined as bleeding following initial successful endoscopic hemostasis [161]. Clinical evidence for recurrent bleeding is commonly defined as follows: recurrent hematemesis or bloody nasogastric aspirate after index endoscopy; recurrent tachycardia or hypo-

tension after achieving hemodynamic stability; melena and/or hematochezia following normalization of stool color; or a reduction in hemoglobin ≥ 2 g/dL after a stable hemoglobin value has been attained [1, 15, 33].

In the management of patients with recurrent peptic ulcer bleeding after successful initial endoscopic control, an RCT comparing repeat endoscopic therapy with surgery showed that 35/48 (73 %) of patients randomized to endoscopic retreatment had long-term control of their peptic ulcer bleeding, avoided surgery, and had a lower rate of adverse events as compared to the surgery-treated patients. The remaining 13 patients underwent salvage surgery because of failed repeat endoscopic hemostasis (n = 11) or perforation due to contact thermal therapy (n = 2). It is generally recommended that patients with clinical evidence of recurrent bleeding undergo repeat endoscopy and further endoscopic treatment if indicated [162].

ESGE suggests the use of either a cap-mounted clip or a topical hemostasis spray/powder when there is recurrent bleeding and standard endoscopic treatments fail to control the bleeding. As previously detailed, limited RCT data suggest cap-mounted clipping may become the first-line hemostasis therapy in recurrent peptic ulcer hemorrhage [146].

In registries and case series, the success rate of primary hemostasis with the use of a topical hemostasis powder approaches 95 %. In the GRAPHE (Groupe de Recherche Avancé des Praticiens Hospitaliers en Endoscopie) registry, which included 202 patients with various upper GI bleeding etiologies (peptic ulcer in 75 patients [37.1 %], tumor in 61 [30.2 %], post-endoscopic therapy in 35 [17.3 %], or other in 31 [15.3 %]), the primary hemostasis success rate using a topical powder (TC-325) was 96.5 % [163]. The topical powder was used as a salvage therapy in 108 patients (53.5 %). The rate of further bleeding was high, 26.7 % by day 8 and 33.5 % by day 30. In a Spanish multicenter retrospective study of 261 patients, of whom 219 (83.9 %) presented with acute UGIH (most common causes were peptic ulcer [28 %], malignancy [18.4 %], and therapeutic endoscopy-related GIB [17.6 %]), TC-325 was used as rescue therapy in 191 patients (73.2 %) with a primary hemostasis success rate of 93.5 % (95 %CI 90 %–96 %). Failure at post-endoscopy days 3, 7, and 30 was 21.1 %, 24.6 %, and 27.4 %, respectively [164]. It must be noted that following successful application of a topical hemostatic powder such as TC-325, a follow-up treatment plan is required (e. g. second-look endoscopy or referral for TAE).

There is some evidence from an RCT that in patients predicted to be at high risk of further peptic ulcer bleeding following endoscopic hemostasis, prophylactic TAE may reduce recurrent bleeding [165]. In a subgroup analysis, prophylactic TAE in patients with ulcers 15 mm or more in size significantly reduced the rebleeding risk from 12/52 (23.1 %) to 2/44 (4.5 %) (P = 0.027). The number needed to treat with prophylactic TAE to prevent one ulcer rebleed was 5.

Helicobacter pylori

RECOMMENDATION

ESGE recommends, in patients with NVUGIH secondary to peptic ulcer, investigation for the presence of *Helicobacter pylori* in the acute setting (at index endoscopy) with initiation of appropriate antibiotic therapy when *H. pylori* is detected.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends re-testing for *H. pylori* in those patients with a negative test at index endoscopy.

Strong recommendation, high quality evidence.

RECOMMENDATION

ESGE recommends documentation of successful *H. pylori* eradication.

Strong recommendation, high quality evidence.

The value and cost–effectiveness of *H. pylori* eradication in patients with peptic ulcer bleeding is well established [166–168]. An updated Cochrane database systematic review, including 55 RCTs, that evaluated the benefits of eradication therapy in *H. pylori*-associated peptic ulcer was published by Ford and colleagues [169]. In duodenal ulcers, eradication therapy was found superior to both ulcer-healing drugs and no treatment. Furthermore, eradication therapy prevented recurrence of both gastric and duodenal ulcers more effectively compared to no treatment. However, results of this systematic review did not demonstrate superiority of eradication therapy in gastric ulcer healing and prevention of duodenal ulcer recurrence compared to ulcer-healing medications.

The consequences of delayed testing for *H. pylori* and initiation of eradication therapy in patients with peptic ulcer hemorrhage have been highlighted by several retrospective studies [170–172]. In the first study, a total of 1920 patients with peptic ulcer hemorrhage were classified into two groups depending on the time of initial eradication therapy administration after ulcer diagnosis. Results revealed that the late eradication group (with late being defined as a time lag ≥ 120 days after initial diagnosis) had an increased risk of re-hospitalization due to complicated recurrent ulcer compared to patients receiving earlier eradication therapy (HR 1.52, 95 %CI 1.13–2.04; P = 0.006) [170]. Another study of 830 peptic ulcer hemorrhage patients similarly displayed that adherence to the recommended *H. pylori* testing strategy (endoscopic biopsy, stool antigen testing or serology for *H. pylori* within 60 days of index endoscopy) correlated with a lower risk of hospital ICU admission (90 % of non-ICU patients tested vs. 66 % of ICU patients, P < 0.001; adjusted OR 0.42, 95 %CI 0.27–0.66) and a decreased compound risk of rebleeding or mortality 14–365 days after

index endoscopy (22 % vs. 47 %, $P<0.01$; adjusted HR 0.49, 95 % CI 0.36–0.67) [171]. However, delay in initiation of *H. pylori* eradication therapy, starting even from 8–30 days after peptic ulcer diagnosis, may time-dependently increase the risks of recurrence and development of a complicated ulcer, as shown by a nationwide population-based study including 29 032 patients [172]. Initiation of eradication therapy within 8–30, 31–60, 61–365, and >365 days of diagnosis was compared to immediate treatment within 7 days. Adjusted HRs for ulcer recurrence were 1.17 (95 %CI 1.08–1.25), 2.37 (95 %CI 2.16–2.59), 2.96 (95 %CI 2.76–3.16), and 3.55 (95 %CI 3.33–3.79), respectively, while HRs for complicated ulcer were 1.55 (95 %CI 1.35–1.78), 3.19 (95 %CI 2.69–3.78), 4.00 (95 %CI 3.51–4.55), and 6.14 (95 %CI 5.47–6.89), respectively. These results reaffirm the current view that testing for *H. pylori* and subsequent initiation of eradication therapy in the case of detection, should be performed as soon as possible in all patients presenting with acute NVUGIH secondary to peptic ulcer.

The higher rates of false-negative results linked to *H. pylori* testing in the acute setting (at index endoscopy) of NVUGIH constitutes an obstacle to the implementation of this testing strategy [173]. It is therefore advisable to repeat diagnostic testing in patients with an initially negative *H. pylori* test, within 4 weeks of the acute bleeding episode [174]. Interestingly, no recent meta-analyses or RCTs further examining either the diagnostic performance of testing in the acute setting or the concept of re-testing after the bleeding event, have been published. Re-testing for *H. pylori* is further supported only by the results of a 2014 prospective cohort study including 374 patients, in which retesting provided an additional diagnostic yield of 12.5 % (11 patients newly positive during delayed testing out of 88 initially negative patients, who repeated testing either through endoscopy or urea breath testing) [175]. Nevertheless, current evidence substantively justifies both the value of *H. pylori* testing in the acute setting as well as the role of delayed testing in minimizing the underestimation of *H. pylori* prevalence in peptic ulcer hemorrhage.

Dual antiplatelet therapy and PPI co-therapy

RECOMMENDATION

ESGE recommends that in patients who have had acute NVUGIH and require ongoing dual antiplatelet therapy (DAPT), PPI should be given as co-therapy.

Strong recommendation, moderate quality evidence.

Dual antiplatelet therapy (DAPT), combining low dose aspirin and a P2Y12 platelet receptor inhibitor (e. g., clopidogrel), is the cornerstone of management of patients with acute coronary syndromes and following coronary stent placement, but is associated with an increased risk of GI bleeding. PPIs substantially reduce this risk and their use as co-therapy with DAPT is recommended in patients with a previous GI bleeding event [1, 176–178]. Previous pharmacodynamic studies reported that the co-administration of PPIs with clopidogrel may reduce platelet inhibition, yet there is no high level evidence supporting the clinical significance of this interaction [179–181]. A recent meta-analysis again showed no significant difference between patients using clopidogrel alone and patients receiving the combination of clopidogrel and a PPI (n = 11 770), for all-cause mortality (OR 0.91, 95 %CI 0.58–1.40; $P=0.66$), acute coronary syndrome (OR 0.96, 95 %CI 0.88–1.05; $P=0.35$), myocardial infarction (OR 1.05, 95 %CI 0.86–1.28; $P=0.65$), or cerebrovascular accident (OR 1.47, 95 %CI 0.660–3.25; $P=0.34$) [182]. Moreover, the incidence of GI bleeding was significantly decreased in the group of patients who received PPI co-therapy (OR 0.24, 95 % CI 0.09–0.62; $P=0.003$).

Restarting anticoagulation therapy (VKAs, DOACs)

RECOMMENDATION

ESGE recommends that, in patients who require ongoing anticoagulation therapy following acute NVUGIH (e. g., peptic ulcer hemorrhage), anticoagulation should be resumed as soon as the bleeding has been controlled, preferably within or soon after 7 days of the bleeding event, based on thromboembolic risk. The rapid onset of action of direct oral anticoagulants (DOACs), as compared to vitamin K antagonists (VKAs), must be considered in this context.

Strong recommendation, low quality evidence.

RECOMMENDATION

ESGE recommends PPIs for gastroduodenal prophylaxis in patients requiring ongoing anticoagulation and with a history of NVUGIH.

Strong recommendation, low quality evidence.

There is only limited evidence to guide restarting anticoagulation therapy (e. g., VKAs, DOACs) following NVUGIH (e. g., peptic ulcer hemorrhage). The decision to restart anticoagulation therapy must balance the risk of recurrent bleeding with the risk of a thromboembolic event and/or the sequelae of these events, including death. Retrospective, observational studies have shown that resuming anticoagulation in patients following a GI bleed is associated with a lower risk of thrombosis and death [183–185] but a small increase in nonfatal GI bleeding events [34, 186]. Sostres et al. reported on 871 patients with GI bleeding, 25 % with peptic ulcer hemorrhage, while taking antithrombotic medications (38.9 % anticoagulants, 52.5 % antiplatelets, and 8.6 % both) [34]. Over an extended follow-up period (mean 24.9 months), the authors concluded that resumption of either antiplatelet or anticoagulant therapy (mean [standard deviation] 7.3 [5.9] days, median 5 days) was associated with a higher risk of rebleeding, yet a lower risk of ischemic events or death. Moreover, when compared to late resumption, earlier resumption of antithrombotic therapy (≤ 7 days) following the GI bleeding episode, was associated with a significantly lower rate of ischemic events (13.6 % vs. 20.4 %, $P=0.025$; adjusted HR 0.718, 95 %CI 0.487–1.061) and

a significantly higher rate of recurrent GI bleeding (30.6 % vs. 23.1 %, $P = 0.044$; adjusted HR 1.383, 95 %CI 1.001–1.910). A systematic review suggested that anticoagulation can be restarted between 7 and 15 days following the GI bleed event [187]. A risk modelling analysis, based on 121/207 patients (58.5 %) who restarted VKAs after an upper GI bleed, suggested that the optimal timing for the resumption of anticoagulation appears to be between 3–6 weeks after the index bleeding event, but that the decision must take into account thromboembolic risk and patient values and preferences [188]. In patients at high thrombotic risk for whom early resumption of anticoagulation within the first week following an acute bleeding event may be appropriate, bridging therapy using unfractionated or low molecular weight heparin should be considered. (Patients at high thrombotic risk include those with chronic atrial fibrillation with a previous embolic event; CHADS2 ≥ 3 [risk score including congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and previous stroke or transient ischemic attack]; mechanical prosthetic heart valve; recent deep venous thrombosis or pulmonary embolism [within past 3 months]; or with known severe hypercoagulable state.) This decision should be multidisciplinary involving a cardiologist and/or a hematologist. VKAs should be restarted earlier, as a loading dose is required and these medications take longer to achieve their anticoagulation effect.

Some experts suggest that a DOAC with less bleeding risk or a VKA with tight INR control should be prescribed. In an observational cohort study on post-hemorrhage anticoagulation resumption in patients with atrial fibrillation, the incidence of major recurrent bleeding was higher for patients on warfarin than for those on dabigatran (HR 2.31, 95 %CI 1.19–4.76) [189]. In the ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation) trial, the rate of major bleeding was 2.13 % per year with the use of apixaban and 3.09 % with that of warfarin (HR 0.69, 95 %CI 0.60–0.80; $P < 0.001$) [190]. However, no firm conclusion can be made as there is no direct comparison of DOACs or warfarin in patients after a major GI bleeding event.

The precise timing for restarting anticoagulation in patients who require anticoagulant therapy and who have had acute NVUGIH (e. g., peptic ulcer hemorrhage) remains undefined. However, evidence supports resuming anticoagulation within 7 days, provided that the GI bleeding has been controlled. In this context, clinicians must balance the thrombotic risk with the bleeding risk. Those patients at the highest thrombotic risk should restart anticoagulant therapy as soon as possible and the use of subcutaneous low molecular weight heparin as a bridge to oral anticoagulation may be a good option. Early consultation with a cardiologist and/or hematologist is desirable. It should be remembered that the timing for resumption of VKA is different from that for DOACs. Vitamin K antagonists should be started earlier since the time required to achieve adequate anticoagulation is much longer (up to 5 days) compared to that for DOACs which take only hours. The use of validated clinical prediction scores that estimate thrombotic risk (CHA(2)DS(2)-VASc) and bleeding risk (HAS-BLED) can be used to help guide clinicians in their decision making (▶ **Fig. 2**) [191–193].

Use of PPI in patients taking anticoagulants

The evidence for the protective effect of PPI in patients taking anticoagulants is limited. Unlike aspirin, anticoagulants do not cause mucosal breaks or ulcers, but they increase the risk of bleeding from pre-existing mucosal lesions or those induced by other agents or pathogenic mechanisms. Epidemiological studies have reported conflicting results [194–198]. However, we recommend the use of PPI in patients who require ongoing anticoagulation and have a history of previous peptic ulcer hemorrhage. This should be exclusive to patients who need to take anticoagulants and other gastrotoxic drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin [198]. The recent COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease) trial suggested that PPIs do not prevent gastrointestinal bleeding in patients receiving anticoagulants [199]. Patients with stable cardiovascular diseases were randomized to receive rivaroxaban (2.5 mg twice-daily) plus aspirin (100 mg once-daily), or rivaroxaban (5 mg twice daily) with an aspirin-matched placebo once-daily, or aspirin (100 mg once-daily) with a rivaroxaban-matched placebo (twice-daily). These patients were then further randomized to receive 40 mg pantoprazole or a placebo. There was no significant difference in upper GI events between the pantoprazole group 102/8791 (1.2 %) and the placebo group 116/8807 (1.3 %) (HR 0.88, 95 %CI 0.67–1.15). However, there were fewer occurrences of symptomatic gastroduodenal ulcers and acid-peptic related complications with the use of pantoprazole (8 vs. 17; HR 0.47, 95 %CI 0.20–1.09). In a retrospective Chinese cohort study (n = 5041), the use of PPI was associated with a reduced risk of GI bleeding in patients taking dabigatran and only in those with a prior history of peptic ulcer/GI bleed (incidence rate ratio [IRR] 0.14, 95 %CI 0.06–0.30) [200]. Risk factors for developing GI bleeding were patient age of 75 years or older, history of peptic ulcer/GI bleed and concomitant use of aspirin.

Disclaimer

The legal disclaimer for ESGE guidelines [4] applies to this Guideline.

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Competing interests

N. de Groot has worked with the NUMDL group on a national guideline on GI bleeding (January to June 2017). M. Dinis-Ribeiro has provided consultancy to Medtronic (October 2020); he is a Co-Editor-in-Chief of the journal *Endoscopy*. I.M. Gralnek is a consultant to Boston Scien-

tific, Medtronic, Motus GI, Vifor Pharma, Simbionix, and Neurogastrx; he is also on the medical advisory board of Motus GI and has received research funding from them and from OnePass, AstraZeneca and CheckCap; he has also been a speaker for Vifor Pharma and 3D Matrix. A. Lanas has provided consultancy to Bayer AG (2018 to 2020). A.J. Morris serves on an advisory board for Medtronic (October 2020, ongoing); he is an unpaid committee member and a guideline lead for the British Society of Gastroenterology (BSG); he has received a fee for a commissioned article in Medicine International journal (2019). I.S. Papanikolaou has received a consultancy fee from Boston Scientific (25 January 2018 and 21 October 2018); he has received travel grants from Takeda Hellas (10–13 October 2019 and 3–6 December 2020). F. Radaelli has served on an advisory board and been a speaker for Pfizer/BMS (2019 to 2020); he has been a speaker for Boehringer Ingelheim (2019 to 2020). A. Sanchez-Yague has received consultancy fees from Boston Scientific (2017 to 2019). J.E. van Hooft has received lecture fees from Medtronic (2014 to 2015, 2019) and Cook Medical (2019), and consultancy fees from Boston Scientific (2014 to 2017); her department has received research grants from Cook Medical (2014 to 2019), and Abbott (2014 to 2017). H. Awadie, G. Braun, M. Camus, T. Cúrdia Gonçalves, J. Lau, S.B. Laursen, Z. Neeman, A.J. Stanley, and M. Udd declare no competing interests.

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Thieme

Supplementary material

Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH): European Society of Gastrointestinal Endoscopy (ESGE) Guideline – Update 2021

Table 1s Key questions: acute nonvariceal upper gastriointestinal hemorrhage (NVUGIH)

1. **Patient presentation - hemodynamic resuscitation and risk assessment**
    a. How should the patient presenting with signs of acute upper GI bleeding (hematemesis, coffee ground emesis, melena) be initially hemodynamically resuscitated?
        i. what type of fluid(s) should be used? E.g., crystalloid fluids, plasma-expanders, red blood cell transfusions, fresh frozen plasma, platelets etc.?
    b. What are the evidence-based red blood cell transfusion recommendations?
        i. Restrictive vs liberal red blood cell transfusion policy?
        ii. Target hemoglobin for otherwsie healthy individuals?
        iii. Target hemoglobin for individuals with cardiovascular disease?
    c. How should patient risk assesssment / stratification be used?
    d. What risk stratification score(s) are reliable and valid? How / when should we apply validated risk stratification tools in clinical practice (pre-endoscopic scores, e.g., glasgow-blatchford score, clinical rockall score, AIMS65, something else)?
    e. Can we risk-stratify low-risk patients at presentation and recommend immediate hospital discharge, thus avoiding hospital admission?
    f. What's the role of endoscopic stigmata (Forresst classification) in risk stratification?

2. Pre-endoscopic management

a. How shoud we manage the patient using anti-platelet agents (single and/or dual) at the time of acute upper GI bleeding?
    i. continue them without interruption? stop them? If stopping, for how long? When to restart?
    ii. give reversal agents?
    iii. give fresh frozen plasma? Cryoprecipitate? Platelets? Tranxemic acid? Other?

b. How should we manage the patient using anti-coagulants (Vit K antagonists / DOACs) at the time of acute upper GI bleeding?
    i. continue them without interruption? stop them? If stopping, for how long? When to restart?
    ii. give reversal agents?
    iii. give fresh frozen plasma? Cryoprecipitate? Platelets? Tranxemic acid? Other?

c. What is the role of “early administration” (pre-endoscopy) PPI therapy (dose, timing, route)?

d. Is there a role for somatostatin therapy in acute NVUGIH?

e. Is there a role for nasogastric / orogastric tube aspiration?

f. Is there a role for prophylactic endotracheal intubation before upper endoscopy?
    i. Why to endotracheally intubate prophylactically?
    ii. When to endotracheally intubate prophylactically?
    iii. Who to endotracheally intubate prophylactically?

g. What is the role of prokinetic agents (e.g., metaclopramide, erythromycin) prior to upper endoscopy?
    i. When to use?
    ii. In whom to use?
    iii. When to give prior to upper endoscopy?

iv. What dose?

v. What are the contraindications to use?

3. **Endoscopic management of peptic ulcer hemorrhage**

a. Timing of endoscopy - What should be the timing of endoscopy in patients presenting with acute upper GI bleeding?

i. Define early/emergent/urgent/ delayed endoscopy?

ii. Which patients should undergo early/emergent/urgent/delayed endoscopy?

iii. What is the relationship between hemodynamic resuscitation and timing of endoscopy?

iv. Timing of endoscopy in patients using anti-platelet agents or anti-coagulants (does INR level matter)?

b. Which endoscopic classification should be used for describing low and high risk endoscopic stigmata in peptic ulcer bleeding? Forrest Class? Descriptive?

c. What ulcer stigmata require endoscopic hemostasis? Define high risk vs low risk endoscopic stigmata and their importance?

d. Which therapeutic endoscopic approach should be used (for peptic ulcer bleeding)?

i. Injection monotherapy? e.g., epinephrine, sclerosants, fibrin, thrombin

ii. Thermal contact monotherapy? e.g., bipolar, multi-polar, heat probe

iii. Thermal non-contact therapy? e.g., argon plasma coagulation

iv. Through-the-scope endoscopic clips?

v. Over-the-scope endoscopic clamps e.g., Ovesco OTSC?

vi. Topical powders / sprays?

vii. Coag grasper?

viii. Combination endoscopic therapy? e.g., injection + injection? injection + contact thermal therapy? injection + clips? Other?

e. Is there a role for Doppler US in helping to better evaluate endoscopic stigmata of recent hemorrhage for peptic ulcer bleeding? Its use pre and post endoscopic hemostasis therapy?

f. Is there a role for capsule endoscopy in the emergency department in evaluating acute UGI bleeding?

4. Post-endoscopic management

a. What are the recommendations for use of PPI post endoscopic hemostasis?

    i. Route? Timing? Continuous? Intermittant? Duration of therapy?

b. Is there a role for "scheduled" second-look endoscopy?

c. What to do with persistent bleeding / rebleeding / failed endoscopic hemostasis:

    i. What is the role of repeat upper endoscopy?

    ii. When is interventional radiology evaluation and treatment indicated? Using what? CTA? Angiopgraphy? Other?

    iii. When is surgery indicated?

d. Diagnois and treatment of H. Pylori in the acute setting of NVUGIH

    i. When?

    ii. In whom?

    iii. What if testing for h pylori in the acute setting of bleeding negative?

e. How should we manage the NVUGIH patient using anti-platelet and anti-coagulant drugs (anti-thrombotic agents) post endoscopy?

    i. When do we restart these medications post endoscopy?

Table 2s Key words used in systematic literature search

Key words
upper gastrointestinal hemorrhage, non-variceal upper gastrointestinal hemorrhage / bleeding, peptic ulcer hemorrhage, peptic ulcer bleeding, fluid resuscitation, fluid therapy, critical illness, crystalloid solutions, colloid solutions, plasma transfusions, red blood cell transfusion, platelet transfusion, hemoglobin, restrictive transfusion strategy, liberal transfusion strategy, risk stratification, mortality, rebleeding, anti-thrombotic agent, anti-platelet agent, dual anti-platelet therapy, anti-coagulation / anti-coagulant, coagulopathy, vitamin K inhibitor / antagonist, prokinetic agent, erythromycin, fresh frozen plasma, nasogastric tube, orogastric tube, proton pump inhibitor, prokinetic agent, erythromycin, endoscopic hemostasis, endotherapy, injection therapy, thermal therapy (contact, non-contact), mechanical therapy / endoscopic clipping, topical hemostasis therapy, second-look endoscopy, Doppler probe ultrasound, capsule endoscopy, video capsule endoscopy, helicobacter pylori, trans-catheter angiographic embolization, and surgery.

Table 3s Evidence tables

Patients with upper GI bleeding AND limited fluid resuscitation						
Reference	**Study design**	**Intervention**	**Participants**	**Outcome**	**Results**	**Level of evidence conclusion**
1) The Use of Limited Fluid Resuscitation and Blood Pressure Controlling Drugs in the Treatment of Acute Upper Gastrointestinal Hemorrhage Concomitant with Hemorrhagic Shock. ***Lu B, et al.*** ***Biochem Biophys. 2015 Jun;72(2):461-3.***	**RCT**	limited fluid resuscitation regimen combined with blood pressure-controlling drugs (dopamine) in treating acute upper gastrointestinal hemorrhage concomitant with hemorrhagic shock	n = 51; conventional group = 24 patients vs limited fluid resuscitation group (study group) = 27 patients	pre- and 12 h post-infusions, arterial blood samples for blood gas analysis, venous blood samples for routine blood analysis, blood lactate, base excess values, hemoglobin, amount of fluid resuscitation, mortality, complications	complication rates were lower in patients who received limited fluid resuscitation and drug-induced hypertension effective restoration of circulating blood volume and perfusion maintenance of vital organs	Limited fluid resuscitation combined with blood pressure-controlling drugs effective maintains blood perfusion of vital organs, improves whole body perfusion indicators, reduces the volume of fluid resuscitation, and achieves better bleeding control and resuscitation effectiveness Limit : single center - Chinese population - small sample size difficult to draw abovementioned conclusion from presented results

2) Efficacy of limited fluid resuscitation in patients with hemorrhagic shock: a meta-analysis. ***Duan C, et al. Int J Clin Exp Med 2015;8(7):11645-11656***	**Meta-analysis**	efficacy of limited fluid resuscitation during active hemorrhage compared with regular fluid resuscitation	11 studies and 1482 patients (3 studies upper GI bleeding patients) ; 752 in limited fluid resuscitation group vs. 757 in regular fluid resuscitation group	mortality, complication	reduction in mortality with limited fluid resuscitation (RR0.67; 95% CI=0.56-0.81, p<0.00001) reduction in occurrence of postoperative complication with limited fluid resuscitation (MODS: RR 0.37; 95% CI 0.21-0.66, p = 0.0008, ARDS RR = 0,35 (95% CI 0.21-0.6, p<0.0001)	Limited fluid resuscitation should be used in active hemorrhage in trauma setting Limit: Only Chinese population in upper GI bleeding series (3/11), not generalization to European population
Critically ill trauma patients and hypotensive resuscitation						
Reference	**Study design**	**Intervention**	**Participants**	**Outcomes**	**Results**	**Level of evidence conclusion**
3) Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma: Early termination of a randomized prospective clinical trial. ***Carrick MM, et al. J Trauma Acute Care Surg 2016;80:886-96.***	**RCT**	target minimum mean arterial pressure (MAP) of 50 mm Hg (experimental arm, LMAP; n= 86) or 65 mm Hg (control arm, HMAP; n = 82)	168 patients with trauma (gun shot stab wound)and hypotension (RRsyst<90mHg)and need of laparotomy	24h mortality 30d mortality complications	No significant survival advantage existed for the LMAP group at 30 days (p = 0.48) or 24 hours (p = 0.27). Acute renal injury occurred less often in the LMAP than in HMAP group (13% vs. 30%, p = 0.01).	hypotensive resuscitation at a target MAP of 50 mm Hg could NOT significantly improve 30-day mortality. limit: single center

Critically ill patients; comparison of crystalloids vs colloids						
Reference	**Study design**	**Intervention**	**Participants**	**Outcome**	**Results**	**Level of evidence conclusion**
4) Colloids versus crystalloids for fluid resuscitation in critically ill people ***Lewis SR et al. Cochrane Database of Systematic Reviews 2018;8:CD000567***	**Systematic Review**	comparison of four types of colloid (i.e. starches; dextrans; gelatins; and albumin or FFP) versus crystalloids	69 studies : 65 RCTs, 4 quasi-RCTs n= 30,020	mortality 30day, 90day	little or no difference in all-cause mortality at the end of follow-up, at 90 days, or at 30 days, between using colloids (starches; dextrans; or albumin or FFP) or crystalloids for fluid resuscitation in critically ill people	**little or no difference** in all-cause mortality moderate-certainty evidence of a slight increase in the need for blood transfusion or renal replacement therapy when starches were used for fluid resuscitation moderate-certainty data
Critically ill patients; comparison of crystalloids vs. saline						
5) Balanced Crystalloids Versus Saline in Critically Ill Adults: A Systematic Review and Meta-analysis. ***Hammond DA et al., Ann Pharmacother. 2020;54:5-13.***	**Review and Meta-analysis**	fluid resuscitation with balanced crystalloids or 0.9% sodium chloride (saline)	13 studies n = 30 950	28-30 day mortality	Balanced crystalloids demonstrated lower hospital or 28/30-day mortality (risk ratio [RR] = 0.86; 95% CI = 0.75-0.99; I^2 = 82%) overall odds of major adverse kidney events occurring in the first 30 days were less with balanced crystalloids than saline (OR = 0.78; 95% CI = 0.66-0.91; I^2 = 42%)	Balanced crystalloids should be preferred instead of saline in most critically ill adult patients

6) Balanced Crystalloids versus Saline in Critically Ill Adults. ***Semler M et al., N Engl J Med 2018;378:829-39***	**RCT**	saline 0.9% sodium chloride or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A)	n= 15 802 adult ICU patients	major adverse kidney event within 30 days a composite of death from any cause, new renal-replacement therapy, or persistent renal dysfunction	major adverse kidney event : balanced-crystalloids group: 1139 (14.3%) vs. saline group: 1211 (15.4%) (marginal OR, 0.91; 95% [CI], 0.84 - 0.99; conditional OR, 0.90; 95% CI, 0.82 - 0.99; p=0.04). Among patients with sepsis, 30-day inhospital mortality: 25.2% with balanced crystalloids; 29.4% with saline (adjusted OR, 0.80; 95% CI, 0.67 - 0.97; P=0.02)	balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction.

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
1) Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials ***Odutayo A et al.*** ***2017;2:354-360. Lancet Gastroenterol Hepatol***	**Systematic review and meta-analysis**	4 published and 1 unpublished randomised controlled trial 1965 participants 919 restrictive transfusion strategy and 1064 liberal transfusion strategy	Mortality Rebleeding Ischaemic events Mean RBC transfusion Comparison treatment effects between patient subgroups, including patients with liver cirrhosis, patients with non-variceal upper gastrointestinal bleeding, and patients with ischaemic heart disease at baseline (No statistically significant differences in the subgroups)	Number of RBC units transfused lower in the restrictive transfusion group (mean difference -1·73 units, 95% CI -2·36 to -1·11, p<0·0001). Restrictive transfusion associated with lower risk of all-cause mortality (RR 0·65, 95% CI 0·44-0·97, p=0·03) and rebleeding overall (0·58, 0·40-0·84, p=0·004) No difference in risk of ischaemic events	Differing transfusion thresholds used in the trials ➔reduce the validity of pooling data Most of the data came from two RCTs, which could affect the generalisability of our findings.	Restrictive strategy is safe in all subgroups of patients

2) Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. ***Jairath V, et al. Lancet. 2015;386:137-44***	**RCT** pragmatic, open-label, cluster randomised feasibility trial	patients aged 18 years or older with new presentations of acute upper gastrointestinal bleeding, irrespective of comorbidity, except for exsanguinating haemorrhage Restrictive: 80 g/L; liberal: 100 g/L 936 patients across six hospitals (403 patients in three hospitals with a restrictive policy and 533 patients in three hospitals with a liberal policy)	Feasibility (primary), mortality, rebleeding, acute myocardial infarction, stroke, transfusion reactions, acute kidney injury, bacterial infection, red blood cell FU : 28 days	Fewer patients received RBCs on the restrictive policy than on the liberal policy (restrictive policy 133 [33%] vs liberal policy 247 [46%]; difference –12% [95% CI –35 to 11]; p=0.23), with fewer RBC units transfused (mean 1.2 [SD 2.1] vs 1.9 [2.8]; difference –0.7 [–1.6 to 0.3]; p=0.12), although these differences were not significant. No significant difference in clinical outcomes	cluster randomised trials	Restrictive strategy is safe
3)Restrictive vs. Liberal transfusions strategy in patients With upper gastrointestinal bleeding — a randomized Controlled trial	Single-center, prospective, open-labeled, parallel arm; noninferiority **RCT**	Patients with sign of upper GI bleeding, 224 patients were included in the study, 112 each in group Both groups were comparable at admission Exclusion: massive	Mortality at 45 days Number of days from admission to death Cause of death Hb value before death Number of rebleeding episodes	The mortality rate within 45 days similar between the two groups (restrictive vs. liberal; 10/112 vs. 12/112; Hazard Ratio of 0.83; p=0.326). mean number of days from admission to death, hemoglobin before death,	Abstract, no full text available Single center Low effective (lack of power)	Restrictive transfusion did not increase the mortality, morbidity, re-bleeding rates and the need for interventions

Kate et al., ***Gastroenterology, 2018;154: 6, Abstract S-700 - S-701***		exsanguinating bleeding, transfusion within 90 days and a recent history of trauma or surgery Patients in restrictive group (Hb) threshold for transfusion of <7g/dl ; target Hb of 9 gm/dl liberal group <8g/dl and target Hb of 10gm/dl	Need for endoscopic intervention Requirement of Sengstaken Blakemore (SB) tube placement Length of hospital stay	number of rebleeding episodes, incidence of re-bleeding episodes, need for interventions, medical treatment, and cause of death during hospital stay due to variceal and nonvariceal causes were similar between the two groups.		
4) Target Level for Hemoglobin Correction in Patients With Acute Non-Variceal Upper Gastrointestinal Bleeding ***Lee, Jae Min et al.*** ***Gastroenterology, 2014;146: 5, Abstract S-321***	**RCT**	63 patients with acute NVUGIH restrictive transfusion, n=32 liberal transfusion, n=31 Restrictive: 80 g/L; liberal: 100 g/L Patients with liver cirrhosis, ischemic heart disease, and cerebrovascular disease were excluded	Rebleeding Hb level at 7 days and 45 days Clinical symptoms (general weakness, dizziness, and others)	Difference in re-bleeding rate restrictive transfusion group and liberal transfusion group (15.6% vs. 19.7%) No difference: Hb level at 7 days and 45 days after discharge, clinical symptoms	Abstract, no full text available Single center Low effective (lack of power)	Restrictive transfusion strategy is safe Less rebleeding rate
5)Transfusion thresholds and other	**Systematic review and**	All conditions	30-day mortality Other clinical	Transfusing at a restrictive haemoglobin concentration of	insufficient data to inform the safety of	Good evidence that

strategies for guiding allogeneic red blood cell transfusion. ***Carson JL, et al. Cochrane Database Syst Rev. 2016;10:CD002042.***	**meta-analysis**	A total of 31 trials, involving 12,587 participants The restrictive transfusion threshold most commonly 7 g/dL or 8 g/dL liberal transfusion threshold most commonly 9 g/dL to 10 g/dL	outcomes available in the RCT	between 7 g/dL to 8 g/dL decreased the proportion of participants exposed to RBC transfusion by 43% across a broad range of clinical specialities Overall, restrictive transfusion did not increase or decrease the risk of 30-day mortality compared with liberal transfusion strategies (RR 0.97, 95% CI 0.81 to 1.16, I^2 = 37%; N = 10,537; 23 trials; moderate-quality evidence) or any of the other outcomes assessed (i.e. cardiac events (low-quality evidence), myocardial infarction, stroke, thromboembolism)	transfusion policies in certain clinical subgroups, including acute coronary syndrome, myocardial infarction	transfusions with allogeneic RBCs can be avoided in most patients with haemoglobin thresholds above 7 g/dL to 8 g/dL.
6)Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis.	**Systematic review and meta-analysis**	patients with cardiovascular disease not undergoing cardiac surgery 11 trials enrolling patients with cardiovascular disease (n=3033) restrictive transfusion, n=1514 liberal transfusion,	30-day mortality, and cardiovascular events	The pooled risk ratio for the association between transfusion thresholds and 30-day mortality was 1.15 (95% confidence interval 0.88 to 1.50, P=0.50), with little heterogeneity (I2=14%). The risk of acute coronary syndrome in patients managed with restrictive compared with liberal transfusion was increased (nine trials; risk ratio 1.78, 95%	Our review has several limitations. There was clinical diversity between trial populations restrictive and liberal transfusion thresholds varied between trials, and the cut-off values	These data support the use of a more liberal transfusion threshold (>80 g/L) for patients with both acute and chronic cardiovascular disease until adequately

Docherty AB, et al. BMJ. 2016;352:i1351.		n=1519		confidence interval 1.18 to 2.70, P=0.01, I2=0%).	actually overlapped Definitions of cardiovascular disease varied, and inclusion criteria for some trials were restricted to ischaemic heart disease or acute coronary syndrome	powered high quality randomised trials have been undertaken in patients with cardiovascular disease.

Performance of new thresholds of the Glasgow Blatchford score in managing patients with upper gastrointestinal bleeding. ***Laursen SB, et al. Clin Gastroenterol Hepatol 2015;13:115-21.e2. study***.	Retrospective, international, cohort study Following scores were evaluated: GBS and two age-extended versions of GBS Different thresholds of each score were evaluated	Consecutive UGIB patients (n=2305)	Hospital-based intervention (transfusion, endoscopic treatment, interventional radiology, surgery) or in-hospital mortality Transfusion Haemostatic intervention (endoscopic treatment, surgery, interventional radiology) In-hospital mortality	GBS ≤ 1 had a high level of sensitivity (99.2%) and specificity (98.8%) for predicting need for hospital-based intervention or death. GBS ≤ 1identified a higher proportion of true low-risk patients compared with GBS = 0 (24.4 vs 13.6%; p<0.001) Among patients with GBS ≤ 2, 3% had adverse outcomes	Retrospective data collection in one centre No long-term follow-up Inpatients not included	Use of GBS ≤ 1 for identification of patients suitable for outpatient management seems safe and increases the number of identified patients suitable for outpatient management compared to GBS=0 A significant proportion of patients with GBS ≤ 2 experience adverse outcomes
Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study ***Stanley AJ, et al. BMJ***	Prospective, international, cohort study Following scores were evaluated: admission/full Rockall scores, AIMS65, Glasgow Blatchford score	Consecutive UGIB patients (n=3012)	Hospital-based intervention (transfusion, endoscopic treatment, interventional radiology, surgery), or 30-day mortality Endoscopic treatment 30 day mortality,	GBS had highest accuracy (AUROC: 0.86) for predicting need for hospital-based intervention or death compared with full Rockall score (0.70), PNED score (0.69), admission Rockall score (0.66), and AIMS65 (0.68). GBS ≤ 1 was the optimum threshold to predict survival without need for hospital-based	Many patients were not scoped (31%) Inpatients not included	GBS ≤ 1 had high accuracy at predicting need for hospital-based intervention or death within 30 days GBS had higher performance for predicting need for hospital-based intervention or death than Rockall scores, AIMS65 and PNED

2017;356:i6432.	(GBS), and PNED Different thresholds of each score were evaluated		rebleeding LOS	intervention with sensitivity 98.6% and specificity 34.6%. None of the evaluated scores were able to predict other outcomes with acceptable (AUROC ≤0.80) ability		None of the evaluated scores were able to predict need for transfusion, endoscopic therapy, or mortality with acceptable ability
Ramaekers R, et al. The predictive value of preendoscopic risk scores to predict adverse outcomes in emergency department patients with upper gastrointestinal bleeding: a systematic review. ***Ramaekers R, et al. Acad Emerg Med. 2016;23:1218-1227.***	Systematic review and meta-analysis predictive value of pre-endoscopic risk scores for 30-day serious adverse events UGIH	16 articles included: 3 studied Glasgow Blatchford Score (GBS), 1 clinical Rockall score (cRockall) and 2 AIMS65; 6 compared GBS and cRockall, 3 compared GBS, a modification of the GBS and cRockall and 1 compared the GBS and AIMS65.	Se and Spe for prediction a composite outcome included 30-day mortality, recurrent bleeding and need for intervention	sensitivity and specificity of the GBS was 0.98 and 0.16 respectively; for the cRockall it was 0.93 and 0.24 respectively; and for the AIMS65 it was 0.79 and 0.61 respectively. The GBS with a cut-off point of 0 had a sensitivity of 0.99 and a specificity of 0.08.	Future prospective studies are needed to develop robust new scores for use in ED patients with UGIB.	The GBS with a cut-off point of 0 was superior over other cut-off points and risk scores for identifying low-risk patients but had a very low specificity. None of the risk scores identified by our systematic review were robust and hence, cannot be recommended for use in clinical practice. Future prospective studies are needed to develop robust new scores for use in ED patients with UGIB.
Comparison of the Glasgow-Blatchford and Rockall Scores for prediction of nonvariceal upper gastrointestinal	Retrospective, multicenter cohort study from China.	Non-variceal UGIB Patients registered with a principal ICD-9	In-hospital mortality Surgery Rebleeding	Rockall scores were closer associated with in-hospital mortality compared with GBS (AUROCs 0.80-0.84 vs 0.62)	Only patients undergoing endoscopy were included	Rockall score was superior to GBS in predicting in-hospital mortality

bleeding outcomes in Chinese patients. ***Lu M, et al. Medicine (Baltimore). 2019;98:e15716***	Following scores were evaluated: GBS and Rockall scores	diagnosis associated with UGIB who were scoped (n=2,977)		All scores had low ability to predict rebleeding (AUROCs ≤0.66) and need for surgery (AUROCs ≤0.59)	Patients with variceal bleeding (12%) were excluded No long-term follow-up Retrospective design	

Reference & year/country	Study design	Patients & Intervention	Outcomes	Results	Level of evidence	Conclusions & Comments
Yang, Surg Endosc 2019; Taiwan	Prospective cohort study. To assess the risk of rebleeding in Forrest 2c lesions at a 2nd look endoscopy, by using the Rockall score	140 patients who had endoscopic therapy and at 2nd look had had Forrest 2c lesion; split by Rockall >=6 or <6.	PU rebleeding day 4-14, and day 4-28 after first bleed.	Rebleeding at 4-14 days for Rockall >=6 vs <6 was 18.6% vs 2.9% (p=0.003) and at 4-28 days was 24.3% vs 4.3% (p=0.001). KM curve showed lower rebleeding with Rockall <6 (p=0.01)	Very low -Cohort study	Combination of Rockall >=6 and Forrest 2c lesion at 2nd look endo identifies patients at risk of PUB rebleeding following initial endo & IV PPIs Rx. Used 2nd look endoscopy
Kim, Gut & Liver 2018; Korean	Multicentre cohort (registry data) from patients with PUB at 28 Korean medical centres 2014-15	904 patients with PUB (897 analysed)	Rebleeding and 30-day mortality	30-day rebleeding in 64 (7.2%) 30-day mortality in 1%. Multivariate risk factors for rebleeding were: comorbidities, multiple drugs, albumin, hematemesis/hematochezia (not the Forrest classification)	Very low -Prospective multicentre cohort study	Relatively low PUB 30-day rebleeding and mortality rate. Rebleeding related to comorbidities, drugs, albumin and presentation symptoms rather than endo findings
Kantowski, Scand J Gastro 2018; International	Non-randomised comparative study of use of endo-doppler probe (or not) pre-injection therapy in higher risk PUB patients	PUB patients with Forrest 1a-2a lesions and Rockall >=5. 35 allocated to endo-doppler and 25 no doppler	PU rebleeding	No differences were seen in patient or ulcer characteristics. Rebleeding in doppler vs no-doppler was 20% vs 52% (p=0.013) and fewer doppler patients (1/35 vs 6/25) needed surgery (p=0.017). Bleeding related (but not all cause) mortality was lower with doppler (1/35 vs 6/25; p=0.017	Low -Non randomised comparative study	Suggests that use of endoscopic doppler to guide injection therapy may reduce rebleeding, need for surgery and bleeding related mortality for Forrest 1a-2a Peptic ulcers. However small and non-randomised study.

Jensen, Am J Gastro 2017; International study	Post hoc analysis of RCT of PPIs post PUB – ie observational cohort study of the placebo group & comparing 1b with other stigmata, and comparing rebleeding in 1b given placebo vs PPIs	388 PUB patients in RCT treated with placebo – assess rebleeding by Forrest classification	PU rebleeding by Forrest classification	*Rebleeding:* Forrest 1a: 22.5% ***Forrest 1b: 4.9%*** Forrest 2a 11.3% Forrest 2b 17.6 & no difference for 1b given PPI or placebo	Moderate/low -Post hoc analysis of RCT data	**<u>Indicates that PUB with oozing blood (1b) have very low rebleeding risk- suggest they may not need to be considered high risk ie would not need post Rx IV PPIs</u>**
Kim, Dig Dis Sci, 2016; Korea	Multicentre, prospective cohort study	699 patients with PUB and high-risk lesions (Forrest 1a-2b) from Feb 2011-Dec 2013.	Rebleeding	Rebleeding seen in 64 (9.2%). 2nd look endo was performed more in the non-rebleeding group (82% vs 62%; p<0.001). On multivariate analyses, use of NSAIDs, larger transfusions (>=5 units) and non-performance of 2nd look endo were risk factors for rebleeding	Very low -Prospective multicentre cohort	Rebleeding seen in 9.2% of these higher risk PUB patients. Performing 2nd look endo seemed to lower risk of rebleeding. Results not focusing on impact of Forrest lesion classification
Martinez Ramirez, Endoscopia 2016; Mexico	Single centre Cohort study	70 PUB patients 2013-2015	Rebleeding, mortality and other endpoints	Forrest classification only risk assessment scale associated with need for endoscopic therapy (p=0.0000), but ?not rebleeding Not the case with GBS, Rockall, or AIMS65	Very low - single centre cohort study	Forrest associated with endo-therapy (unsurprisingly), but not rebleeding or other endpoints

Cheng, Endosc Open Int; Taiwan	Prospective single centre, non-randomised study comparing day 2 or day 3 2nd look endo after endoRx and PPIs for PUB	316 patients	Risk factors for early rebleeding & use of score (R2nd) to predict need for 2nd look endo were analysed	Persistent major stigmata seen more in day 2 vs dat 3 group (15.4% vs 4,8%; p=0.002). Independent risk factors for early rebleeding were use of epineph injection alone & low albumin. Risk factors for persistent najor stigmata on day 3 were Forrest 1a-1b lesions and low albumin.	Very low - non randomised single centre study	They created a new score to predict early and routine 2nd look endoscopies
Kim, Korean J Gastro, 2015;Korea	Multicentre cohort (registry data) from 8 Korean hospitals Feb 2011-Dec 2013 Aim to assess Forrest 2b lesions	1101 patients with PUB- 126 (11.4%) were Forrest 2b lesions and included.	To compare outcomes between endoRx and Medical Rx; & assess risk factors for rebleeding in Forrest 2b	Of Forrest 2b: 66.7% had endoRx & 33.3% medical Rx (which had higher GBS & Rockall) Mortality higher in medical Rx (all cause 20% vs 3.7%; p=0.005). No difference in rebleeding (9.5% vs 7.1%; P=0.641). prev aspirin/NSAID only factor predicting rebleeding on multivartiate analysis	Very low - Registry data	Non randomised comparison of endoRx vs medical Rx for Forrest 2b PUB lesions in 126 patients. Note baseline parameters were different between groups.
DeGroot, Endosc. 2014; Holland	Prospective registry data	397 patients with PUB	30-day rebleeding & all-cause mortality	Forrest 1a (4.5% of cohort) had rebleeding rate=59% OR for rebleeding for 1b-2c were similar. Forrest more reliable for predicting rebleeding in GUs than DUs. Not helpful at predicting mortality. A simplified Forrest classification was proposed:	Very low/low -Prospective cohort	***Rebleeding after 1b PUB is lower than previously thought.*** Mortality poorly predicted by Forrest classification. Simplified classification proposed: High risk – Forrest 1a Increased risk – Forrest 1b-2c Low risk- Forrest 3

Ajayi, Am J Med Med Sci; 2014; Nigeria	Observational study 2009-2011	52 patients with PUB	Rebleeding after initial stabilization	Forrest 1a (5.8%)- rebleeding 33% 1b (5.8%) - 66.7% 2a (9.6%) - 80% 2b (19.2%) - zero 2c (25%) -zero 3 (34.6% -zero	Very low -Prospective cohort	Authors conclude that Forrest still help prediction of rebleeding (but not mortality). Small single centre observational study from Nigeria.
Bai, J Dig Disease 2014	Prospective descriptive multicentre Chinese study	1006 patients with PUB (2010-2011)	Rebleeding, endo-therapy, need for surgery	43.4% had high risk ulcers (Forrest 1a-2b). Rebleeding in this group after endotherapy (day 1-5) was 14.5% and surgery 1.8%. Mortality of Forrest 1a-2b was 0.5%	Very low -Prospective cohort	Note many high risk patients did not receive endo-therapy

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
10.) Laursen SB, Dalton HR, Murray IA, et al. Performance of new thresholds of the Glasgow Blatchford score in managing patients with upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2015;13:115-21.e2. study.	Retrospective, international, cohort study Following scores were evaluated: GBS and two age-extended versions of GBS Different thresholds of each score were evaluated	Consecutive UGIB patients (n=2305)	- Hospital-based intervention (transfusion, endoscopic treatment, interventional radiology, surgery) or in-hospital mortality - Transfusion - Haemostatic intervention (endoscopic treatment, surgery, interventional radiology) - In-hospital mortality	GBS ≤ 1 had a high level of sensitivity (99.2%) and specificity (98.8%) for predicting need for hospital-based intervention or death. GBS ≤ 1identified a higher proportion of true low-risk patients compared with GBS = 0 (24.4 vs 13.6%; p<0.001) Among patients with GBS ≤ 2, 3% had adverse outcomes	Retrospective data collection in one centre No long-term follow-up Inpatients not included	Use of GBS ≤ 1 for identification of patients suitable for outpatient management seems safe and increases the number of identified patients suitable for outpatient management compared to GBS=0 A significant proportion of patients with GBS ≤ 2 experience adverse outcomes
11.) Mustafa Z, Cameron A, Clark E, Stanley AJ. Outpatient management of low-risk patients	Prospective single-center cohort study from UK	Consecutive UGIB-patients presenting to hospital	- Hospital-based intervention (transfusion, endoscopic treatment, interventional	GBS was closer associated with need for hospital-based intervention or death < 30 days compared with	Single-center study Only 31% of GBS≤1	GBS was superior to admission Rockall score in predicting need for hospital-based

with upper gastrointestinal bleeding: can we safely extend the Glasgow Blatchford Score in clinical practice? Eur J Gastroenterol Hepatol 2015;27:512-5.	Outpatient management were recommended in patients with GBS≤1 Patients not attending O/P EGD were followed up at least 6 month after study inclusion Following scores were evaluated: GBS, admission Rockall score	(n=514)	radiology, surgery) or death within 30 days	admission Rockall score (AUROCs: 0.91 vs 0.75) 22% of patients had GBS=0 36% of patients had GBS ≤ 1 48% of patients with GBS ≤ 1 (17% of total study population) avoided admission to hospital None of the patients with GBS ≤ 1 managed outside hospital developed adverse outcomes Among patients with GBS ≤ 1 admitted to	managed in the community attended planned O/P EGD No documented reason for hospital admission in 16% of admitted GBS≤1 patients	intervention or death < 30 days Patients with GBS≤1 can safely be managed as outpatients unless hospital admission is required for other reasons

				hospital, 2% (n=2) required intervention or died (death due to non-GI malignancy, transfusion due to a MW-tear) NPV of GBS≤1 in predicting adverse outcomes was 98.9%		
12.) Aquarius M, Smeets FG, Konijn HW, et al. Prospective multicenter validation of the Glasgow Blatchford bleeding score in the management of patients with upper gastrointestinal hemorrhage presenting at an emergency department. Eur J Gastroenterol Hepatol	Prospective multi-center study from the Netherlands Following scores were evaluated: GBS and Rockall scores	Consecutive patients presenting to EDs with UGIB (n=520)	- Need for treatment (transfusion, endoscopic treatment, surgery, embolisation) - Rebleeding - 30-day mortality - Readmission with UGIB	GBS was closer associated with need for treatment than both Rockall scores (AUROCs: 0.88 vs 0.70-0.77) GBS=0 had a sensitivity and specificity for predicting need for treatment of 99.5% and 23.1%, respectively GBS≤1 had a	16% of patients did not undergo endoscopy	GBS is superior to both Rockall scores in predicting need for treatment in UGIB Patients with GBS≤2 have low risk of needing treatment or dying < 30 days and are eligible for outpatient management

2015;27:1011-6.				sensitivity and specificity for predicting need for treatment of 99.5% and 35.2%, respectively GBS≤2 had a sensitivity and specificity for predicting need for treatment of 99.4% and 42.4%, respectively 26% of patients had GBS≤2 Among patients with GBS≤2 1/137 needed treatment (patient with known oesophageal carcinoma and GBS=0) and 1/137 died (death not bleeding related)		
13.) Yang HM, Jeon	Prospective	Consecutive	- Hospital-based	GBS and full-Rockall	Potential	GBS was better

SW, Jung JT, et al. Comparison of scoring systems for nonvariceal upper gastrointestinal bleeding: a multicenter prospective cohort study. J Gastroenterol Hepatol 2016;31:119-25.	multicentre cohort study from South Korea	patients presenting to hospital with non-variceal UGIB (n=1584)	intervention (transfusion, endoscopic treatment, interventional radiology, surgery) - Rebleeding - 30-day mortality	score had similar ability to predict need for hospital-based intervention (AUROCs: 0.71 vs 0.73) and performed better than admission Rockall score for this endpoint (AUROC: 0.60) Only 0.8% of patients had GBS=0 No patient with GBS=0 died or required haemostatic intervention (potential need for transfusion not specified in paper) Rockall scores were better than GBS (AUROCs: 0.75-0.76 vs 0.64) for	problems with overtreatment, as some patients with absence of stigmata of recent bleeding at EGD underwent endoscopic treatment (12% of patients with full-Rockall score=0) Very few low-risk patients indicating potential selection bias No data on transfusion in patients with low GBS	than Rockall scores to predict need for hospital-based intervention GBS had relatively low ability to predict need for hospital-based intervention in this South Korean/Asian population Only very few patients had GBS=0 (<1%) Patients with GBS=0 had low risk of poor outcome

				predicting 30-day mortality Fore predicting rebleeding all scores had AUROCs≤0.64		
14.) Park SM, Yeum SC, Kim BW, et al. Comparison of AIMS65 Score and Other Scoring Systems for Predicting Clinical Outcomes in Koreans with Nonvariceal Upper Gastrointestinal Bleeding. Gut Liver. 2016;10:526-31.	Single center retrospective cohort study from Korea Following scores were evaluated: AIMS65, GBS, Rockall scores	Patients presenting to hospital with non-variceal UGIB who underwent endoscopy (n=523)	- 30-day mortality - Rebleeding - Transfusion - Endoscopic treatment	AIMS65 (AUROC: 0.79) and Rockall scores (AUROC: 0.76-0,81) performed equally well and better than GBS (AUROC: 0.61) in predicting 30-day mortality Rockall scores (AUROC: 0.72-0.77) and GBS (AUROC: 0.71) were closer associated with rebleeding than AIMS65 (AUROC:0.61) GBS (AUROC:0.84) was superior in	Single-center study Retrospective design High exclusion rate due to exclusion of patients with: variceal bleeding (32%), who were not scoped (15%), had missing data (14%) or no source of bleeding at EGD (9%)	AIMS65 and Rockall scores were better than GBS for predicting 30-day mortality in UGIB Rockall scores and GBS were better than AIMS65 for predicting rebleeding GBS were better than Rockall scores and AIMS65 for predicting transfusion

				predicting transfusion compared with Rockall scores and AIMS65 (AUROCs:0.60-0.62) Only full Rockall score was able to predict need for endoscopic treatment (AUROC: 0.75 vs 0.52-0.59).		
15.) Park SW, Song YW, Tak DH, et al. The AIMS65 Score Is a Useful Predictor of Mortality in Patients with Nonvariceal Upper Gastrointestinal Bleeding: Urgent Endoscopy in Patients with High AIMS65 Scores. Clin Endosc 2015;48:522-7.	Retrospective, single-centre, cohort study Following scores were evaluated: AIMS65 and Rockall score (not clear if admission or full Rockall score was used)	Non-variceal UGIB (n=634) Patients bleeding from cancer, patients not scoped, and patients with incomplete data were excluded	- In-hospital mortality - Endoscopic haemostasis - Rebleeding - Blood transfusion - LOS - Timing of endoscopy	AIMS65 was better than Rockall score in predicting in-hospital mortality (AUROCs: 0.94 vs 0.87) 0/434 patients with AIMS65 < 2 died during hospital admission In-hospital mortality rate	Patients who were not scoped, had bleeding from varices or upper GI-cancer, or incomplete data were excluded No long-term follow-up Retrospective	AIMS65 may be useful in predicting mortality in UGIB Patients with AIMS65<2 have low risk of death during hospitalisation

				0.94%	design Very low mortality rate (0.9%) – external validity? Unclear if full or admission Rockall score was used	
16.) Taha AS, McCloskey C, Craigen T, Angerson WJ. Antithrombotic drugs and non-variceal bleeding outcomes and risk scoring systems: comparison of Glasgow Blatchford, Rockall and Charlson scores. Frontline Gastroenterol 2016;7:257-263.	Single-centre retrospective cohort study from UK Following scores were evaluated: GBS, Rockall scores, Charlson comorbidity index (CCI)	Patients presenting to hospital with an ICD-10 code associated with UGIB Performance of scores were compared between users and non-users of antithrombotic drugs (ATD)	- LOS - Transfusion - Rebleeding - 30-day mortality	41% were ATD-users GBS (AUROCs: 0.90 vs 0.85;p<0.005) and Rockall score (AUROCs: 0.77 vs 0.61;p<0.005) had lower ability to predict transfusion in users of ATD when compared with non-users There was a trend	Retrospective study Single-centre study Identification of patients based on administrative data Inpatients not	GBS and Rockall score were less effective in predicting outcome in ATD-users compared with non-users GBS was better than Rockall score and CCI for predicting need for transfusion or rebleeding

		(n=2071)		towards lower ability of GBS (AUROCs: 0.78 vs 0.72) and Rockall score (AUROCs: 0.84 vs 0.73) in predicting mortality in users of ATD when compared with non-users GBS (AUROCs: 0.86 vs 0.73;p<0.001) and Rockall score (AUROCs: 0.76 vs 0.57;p<0.001) had lower ability to predict rebleeding in users of ATD when compared with non-users	included	Rockall score was closer associated with mortality than GBS
17.) Thanapirom K, Ridtitid W, Rerknimitr R, et al. Prospective comparison of three risk scoring systems in non-variceal and variceal upper	Prospective, multicenter study from Thailiand Following scores were evaluated:	Consecutive patients with UGIB undergoing EGD (n=981)	- Need for treatment (transfusion, endoscopic/ radiological/ surgical haemostasis) - In-hospital	In non-variceal UGIB, GBS was closer associated with need for treatment than Rockall scores (AUROCs: 0.77 vs 0.0.61-0.69;	No data on mortality as an isolated endpoint No data on performance in overall group of	GBS had the best ability to predict need for treatment in non-variceal UGIB Full-Rockall score

gastrointestinal bleeding. J Gastroenterol Hepatol 2016;31:761-7.	GBS and Rockall scores		mortality or rebleeding - Transfusion - Endoscopic haemostasis	p<0.001) In non-variceal bleeding, full-Rockall score was superior (AUROC: 0.80) in predicting death or rebleeding (NB: considered as one endpoint) when compared with admission Rockall score and GBS (AUROCs 0.66-0.76) All scores had poor ability to predict need for treatment, or death or rebleeding, in patients with variceal bleeding (AUROCs ≤0.66) No deaths or rebleeding occured in patients with GBS ≤2	patients with UGIB No data on need for treatment among patients with low GBS No long-term follow-up Patients managed on an outpatient basis were not included	was superior in predicting in-hospital-mortality or rebleeding (combined endpoint) in non-variceal UGIB None of the evaluated scores could predict outcome in variceal-UGIB

18.) Lip HT, Heah HT, Huei TJ, et al. Rockall risk score in predicting 30 days non-variceal upper gastrointestinal rebleeding in a Malaysian population. Med J Malaysia 2016;71:225-230.	Retrospective single-center cohort study from Malaysia Following score was evaluated: Rockall score	Patients undergoing endoscopy for UGIB Patients with variceal bleeding were not included (n=1,323)	- Rebleeding - Surgery - 30-day mortality	Rockall score had low ability to predict rebleeding (AUROC: 0.63), surgery (AUROC: 0.67), and 30-day mortality (AUROC: 0.58)	Retrospective design Single-centre study Data limited to patients undergoing endoscopy	Rockall score had poor ability to predict outcome following NVUGIB in a Malaysian population
19.) Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ 2017;356:i6432.	Prospective, international, cohort study Following scores were evaluated: admission/full Rockall scores, AIMS65, Glasgow Blatchford score (GBS), and PNED Different	Consecutive UGIB patients (n=3012)	- Hospital-based intervention (transfusion, endoscopic treatment, interventional radiology, surgery), or 30-day mortality - Endoscopic treatment - 30 day mortality, rebleeding - LOS	GBS had highest accuracy (AUROC: 0.86) for predicting need for hospital-based intervention or death compared with full Rockall score (0.70), PNED score (0.69), admission Rockall score (0.66), and AIMS65 (0.68). GBS ≤ 1 was the optimum threshold to predict survival without need for	Many patients were not scoped (31%) Inpatients not included	GBS ≤ 1 had high accuracy at predicting need for hospital-based intervention or death within 30 days GBS had higher performance for predicting need for hospital-based intervention or death than Rockall scores,

	thresholds of each score were evaluated			hospital-based intervention with sensitivity 98.6% and specificity 34.6%. None of the evaluated scores were able to predict other outcomes with acceptable (AUROC ≤0.80) ability		AIMS65 and PNED None of the evaluated scores were able to predict need for transfusion, endoscopic therapy, or mortality with acceptable ability
20.) Budimir I, Stojsavljević S, Baršić N, et al. Scoring systems for peptic ulcer bleeding: Which one to use? World J Gastroenterol 2017;23:7450-7458.	Prospective single-centre cohort study from Croatia Following scores were evaluated: GBS, Rockall scores, Baylor bleeding score (BBS)	Consecutive patients with peptic ulcer bleeding (n=1012)	- Need for hospital-based intervention or death < 30 days - 30-day mortality - Transfusion - Surgery - Rebleeding	GBS was superior to the pre-endoscopic RS and BBS in predicting need for intervention or death (AUROCs: 0.84 vs 0.57-0.64) For predicting mortality, Rockall scores were better than GBS and BBS (AUROCs: 0.82 vs 0.63-0.67)	Single-centre study Inclusion limited to PUB-patients Inpatients not included	GBS was better than RS and BBS for predicting 1. need for hospital-based intervention or death < 30 days, 2. transfusion, 3. surgery and 4. rebleeding Rockall scores were better than GBS and BBS for predicting 30-day

				GBS were best at predicting need for blood transfusion (AUROC: 0.83), surgery (AUROC: 0.82) and rebleeding (AUROC: 0.75)		mortality
21.) Ko IG, Kim SE, Chang BS, et al. Evaluation of scoring systems without endoscopic findings for predicting outcomes in patients with upper gastrointestinal bleeding. BMC Gastroenterol 2017;17:159.	Retrospective single-center study from South Korea Following scores were evaluated: GBS, a modified GBS (excluding hepatic disease, cardiac failure, melaena, syncope, and age), admission Rockall score	UGIB-patients assessed in the ER (n=590)	- Need for intervention - 30-day mortality	GBS and mGBS had highest ability to predict need for intervention (AUROC: 0.73) compared with admission Rockall score (AUROC: 0.65; p<0.001) Admission Rockall score was closer associated with 30-day mortality than GBS and mGBS (AUROCs: 0.93 vs 0.65-0.66; p<0.001)	Single center study Retrospective design No data available on classified low-risk patients	GBS was moderate accurate in predicting need for intervention in UGIB Admission Rockall score was accurate in detechtion of patients in high risk of death wihtin 30 days
22.) Gu L, Xu F, Yuan J. Comparison	Retrospective single-center	UGIB-patients who were	- In-hospital mortality	AIMS65 was closer associated with in-	Patients who were not	AIMS65 was superior to full-

of AIMS65, Glasgow-Blatchford and Rockall scoring approaches in predicting the risk of in-hospital death among emergency hospitalized patients with upper gastrointestinal bleeding: a retrospective observational study in Nanjing, China. BMC Gastroenterol 2018;18:98.	study from China. Following scores were evaluated: AIMS65, GBS and full-Rockall score	scoped (n=799)		hospital mortality (AUROC: 0.91) than full-Rockal score (0.86) and GBS (0.71) AIMS65 performed well in both patients with non-variceal UGIB (AUROC: 0.89) and patients with variceal UGIB (AUROC: 0.94) Sensitivity and specificity for predicting mortality for AIMS65 ≥2 were 0.88 and 0.84, respectively	scoped or had missing data for any risk score were excluded Single center study Retrospective design No long-term follow-up	Rockall score and GBS in predicting in-hospital mortality in non-variceal and variceal UGIB
23.) Banister T, Spiking J, Ayaru L. Discharge of patients with an acute upper gastrointestinal bleed from the emergency	Retrospective dual-centre study from UK Following GBS-thresholds were	Patients presenting to the ED's with a primary diagnosis of UGIB	- Need for hospital-based intervention or death < 30 days	GBS was effective in predicting need for intervention or death < 30 days (AUROC: 0.89) 12% of patients had	Retrospective design Patients with missing data excluded	GBS ≤1 can safely be used to discharge patients with UGIB-symptoms from the ED without performance of

department using an extended Glasgow-Blatchford Score. BMJ Open Gastroenterol 2018;5(1):e000225.	evaluated: 0, ≤1, ≤2			GBS=0 26% of patients had GBS ≤1 71% of patients with GBS ≤1 were safely discharged to outpatient endoscopy None of the patients with GBS ≤1 needed intervention or died 8.1% of patients with GBS=2 had adverse outcomes		in-hospital endoscopy GBS ≤1 doubled the number of identified low-risk patients compared with GBS =0
24.) Oakland K, Kahan BC, Guizzetti L, et al. Development, Validation, and Comparative Assessment of an International	Retrospective, international, multicentre cohort study based on five international datasets (Canada, UK,	Mixture of datasets containing patients with non-variceal UGIB and datasets containing	- 30-day mortality - 30-day rebleeding - Surgical or radiological intervention	CANUKA-score and admission Rockall score had similar ability to predict 30-day mortality (AUROCs: 0.77-0.79) and were marginally closer	Differences in case-mix in included datasets Patients not scoped exluded	CANUKA had higher accuracy than GBS in identifying patients dying within 30 days

Scoring System to Determine Risk of Upper Gastrointestinal Bleeding. Clin Gastroenterol Hepatol 2019;17:1121-1129.e2.	Australia). Following scores were evaluated: CANUKA score, GBS and admission Rockall score	patients with both variceal and non-variceal UGIB Some datasets only included patients undergoing endoscopy Fase 1: Development of CANUKA score (n=10,639) Fase 2: Validation of CANUKA score and comparison with GBS and admission Rockall score (n=2,072)	- Endoscopic treatment - Blood transfusion - Poor outcome (one of the outpoints listed above)	associated with mortality than GBS (AUROC: 0.74; p=0.047) GBS was best at predicting poor outcome (AUROC: 0.92) compared with CANUKA score (0.90; p<0.001) and Rockall score (0.76; p<0.001) Patients with CANUKA≤1 (6.8%) had low risk of death (0%) and low risk of poor outcome (3,7%) within 30 days. Among patients with GBS≤1 (23.7%) 1.1% died < 30 days and 4.7% had a poor outcome.	in some datasets One dataset was based on administrative data Retrospective design	CANUKA and admission Rockall score had similar discriminative ability for predicting 30-day mortality Only 3.7% of patients with CANUKA≤1had a poor outcome compared with 4.7% of patients with GBS≤1, but GBS≤1 identified a considerable higher number of classified low-risk patients (23.7% vs 6.8%) GBS was best at predicting need for endoscopic treatment

				GBS was marginally best at predicting need for endoscopic treatment (AUROC: 0.78) compared with CANUKA score (0.77; p=0.047) and Rockall score (0.66; p<0.001) All scores performed poorly in predicting rebleeding (AUROCs ≤ 0.68)		
25.) Lu M, Sun G, Huang H, et al. Comparison of the Glasgow-Blatchford and Rockall Scores for prediction of nonvariceal upper gastrointestinal bleeding outcomes in Chinese patients. Medicine (Baltimore). 2019;98:e15716	Retrospective, multicenter cohort study from China. Following scores were evaluated: GBS and Rockall scores	Non-variceal UGIB Patients registered with a principal ICD-9 diagnosis associated with UGIB who were scoped (n=2,977)	- In-hospital mortality - Surgery - Rebleeding	Rockall scores were closer associated with in-hospital mortality compared with GBS (AUROCs 0.80-0.84 vs 0.62) All scores had low ability to predict rebleeding (AUROCs ≤0.66) and need for surgery (AUROCs ≤0.59)	Only patients undergoing endoscopy were included Patients with variceal bleeding (12%) were excluded No long-term follow-up Retrospective design	Rockall score was superior to GBS in predicting in-hospital mortality

26.) Shafaghi A, Gharibpoor F, Mahdipour Z, Samadani AA. Comparison of three risk Scores to predict outcomes in upper gastrointestinal bleeding; modifying Glasgow Blatchford with Albumin. Rom J Intern Med 2019. doi: 10.2478/rjim-2019-0016	Retrospective single-center study from Iran. Following scores were evaluated: AIMS65, a modified AIMS65 (albumin threshold changed from 3 to 3,5), GBS, a modified GBS (adding albumin to the score) and Full-Rockall score	UGIB-patients who were scoped Patients with missing data for all risk scores were excluded (n=563)	- In-hospital mortality - Rebleeding - Need for transfusion - Endoscopic treatment - Composite endpoint (one of the outcomes mentioned above)	AIMS65, GBS and full-Rockall scores all had low discriminative abilities for predicting in-hospital mortality (AUROCs: ≤0.67) 1.3% of patients with an AIMS65 of zero died during hospitalisation Sensitivity and specificity for predicting in-hospital mortality for AIMS65 ≥2 were 0.47 and 0.80, respectively Poor ability of all scores for predicting other outcomes (AUROCs ≤0.7)	High exclusion rate (30%) Single center study Retrospective design No long-term follow-up	None of the evaluated risk scores performed well in predicting any outcome

27.) Kim MS, Choi J, Shin WC. AIMS65 scoring system is comparable to Glasgow-Blatchford score or Rockall score for prediction of clinical outcomes for non-variceal upper gastrointestinal bleeding. BMC Gastroenterol 2019;19:136.	Retrospective single-center study from South Korea. Following scores were evaluated: AIMS65, GBS and Rockall scores	Non-variceal UGIB-patients who were scoped Patients with post-procedure bleeding af endoscopic resection (GIST) were excluded (n=512)	- In-hospital mortality - Composite endpoint (in-hospital mortality, ICU stay; rebleeding; blood transfusion; endoscopic treatment; embolisation or surgery) - Rebleeding - ICU stay - Transfusion	AIMS65 and Rockall scores had similar ability to predict in-hospital mortality (AUROCs: 0.84 vs 0.74-0.75) There was a trend towards better ability of AIMS65 to predict mortality compared with GBS (AUROCs: 0.84 vs 0.72; p=0.07) AIMS65 < 2 (71%) was associated with very low risk of death during hospital admission (0.6%) Sensitivity and specificity for predicting mortality for AIMS65 ≥2 were 0.88 and 0.73 All scores were poor in predicting the composite endpoint and rebleeding (AUROCs ≤0.7)	11% of patients were excluded (missing data, loss of follow-up or post-procedure bleeding) Low event rate (11 deaths) Single center study Retrospective design No long-term follow-up	AIMS65, Rockall scores and GBS have similar ability to predict in-hospital mortality Patients with AIMS65 < 2 have a very low risk of death during hospitalisation (0.6%)

				GBS performed well in predicting need for transfusion (AUROC: 0.87)		

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
1.) Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ 2017;356:i6432.	Prospective, international, cohort study Following scores were evaluated: admission/full Rockall scores, AIMS65, Glasgow Blatchford score (GBS), and PNED Different thresholds of each score were evaluated	Consecutive UGIB patients (n=3012)	Hospital-based intervention (Composite endpoint: transfusion, endoscopic treatment, interventional radiology, surgery, 30-day mortality), endoscopic treatment, 30 day mortality, rebleeding, length of hospital stay	GBS had highest accuracy (AUROC: 0.86) for predicting need for hospital-based intervention compared with full Rockall score (0.70), PNED score (0.69), admission Rockall score (0.66), and AIMS65 (0.68). GBS ≤ 1 was the optimum threshold to predict survival without need for hospital-based intervention with sensitivity 98.6% and specificity 34.6%. None of the	Many patients were not scoped (31%) Inpatients not included	GBS ≤ 1 has high accuracy at predicting need for hospital-based intervention or death within 30 days GBS has higher performance for predicting need for hospital-based intervention or death than Rockall scores, AIMS65 and PNED None of the evaluated scores were able to predict need for transfusion,

				evaluated scores were able to predict other outcomes with acceptable (AUROC ≤0.80) ability		endoscopic therapy, or mortality with acceptable ability
2.) Laursen SB, Dalton HR, Murray IA, et al. Performance of new thresholds of the Glasgow Blatchford score in managing patients with upper gastrointestinal bleeding. Clin Gastroenterol Hepatol 2015;13:115-21.e2. study.	Retrospective, international, cohort study Following scores were evaluated: GBS and two age-extended versions of GBS Different thresholds of each score were evaluated	Consecutive UGIB patients (n=2305)	Hospital-based intervention (Composite endpoint: transfusion, endoscopic treatment, interventional radiology, surgery, in-hospital mortality), transfusion, haemostatic intervention (endoscopic treatment, surgery, interventional radiology), in-hospital mortality	GBS ≤ 1 had a high level of sensitivity (99.2%) and specificity (98.8%) for predicting need for hospital-based intervention or death. GBS ≤ 1identified a higher proportion of true low-risk patients compared with GBS = 0 (24.4 vs 13.6%; p<0.001) Among patients with GBS ≤ 2, 3% had adverse outcomes	Retrospective data collection in one centre Inpatients not included	Use of GBS ≤ 1is safe and leads to increased number of identified low-risk patients suitable for outpatient management compared to GBS=0 A significant proportion of patients with GBS ≤ 2 experience adverse outcomes

3.) Stanley AJ,	Prospective	Consecutive	Hospital-based	Fase 1: GBS had	Retrospective	Use of GBS=0

Ashley D, Dalton HR, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. Lancet 2009 Jan 3;373(9657):42-7.	(retrospective data collection in one centre), multicentre, cohort study Following scores were evaluated: GBS and Rockall scores	UGIB patients Fase 1: Comparison of performance of GBS, admission (pre-endoscopy) and full Rockall scores (n=676) Fase 2: Implementation of outpatient management of patients with GBS=0 (n=572)	intervention (Composite endpoint: transfusion, endoscopic treatment, interventional radiology, surgery, in-hospital mortality)	higher ability to predict need for hospital-based intervention than both Rockall scores (0.92 vs 0.72-0.81) No interventions were required inpatients with GBS=0 Fase 2: 22% of patients fulfilled criteria for outpatient management (GBS=0). 15% of patients avoided hospital admission. Only 40% of patients offered outpatient endoscopy attended the procedure	data collection in one centre Inpatients not included	identifies UGIB-patients who can safely be managed as out-patients Implementation of a protocol for non-admission of patients with GBS=0 – unless necessary for other reasons – reduces the number of hospital admission with UGIB

4.) Stanley AJ, Dalton HR, Blatchford O. Multicentre comparison of the Glasgow Blatchford and Rockall Scores in the prediction of clinical end-points after upper gastrointestinal haemorrhage. Aliment Pharmacol Ther 2011;34:470-5.	Retrospective, multicentre cohort study Comparison of performance of GBS, admission (pre-endoscopy) and full Rockall scores	Consecutive UGIB patients (n=1555)	- Transfusion - Endoscopic treatment or surgery - In-hospital mortality	GBS were superior to both Rockall scores for prediction of transfusion (AUROCs: 0.92 vs 0.69-0.75) GBS performed better than admission Rockall score for prediction of endoscopic or surgical intervention (AUROCs: 0.79 vs 0.63) GBS performed similar to full Rockall score for prediction of endoscopic or surgical intervention (AUROCs: 0.79 vs 0.76)	Retrospective data collection in one centre Inpatients not included	GBS is as effective as both Rockall scores in predicting death after UGIB GBS is better than admission Rockall score for predicting need for endoscopic or surgical intervention

				GBS performed similar to admission and full Rockall scores for prediction of mortality (AUROCs: 0.74- 0.79)		
5.) Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996;38:316-21.	Prospective cohort study on a dataset collected as part of a national UK-audit Following scores were evaluated: Rockall scores	Consecutive UGIB patients Fase 1: Development of risk score (n=4185) Fase 2: Validation of risk score (n=1625)	- In-hospital mortality - Rebleeding	Rockall score was proportionally associated with risk of rebleeding and death during hospitalisation Full-Rockall score of ≤ 2 (26% of patients) is associated with very low risk of death during hospitalisation (0.1%) and low rate of rebleeding (4.5%)	Lacks external validation No long-term follow-up No clear definition of rebleeding	Rockall score can be used to estimate patients risk of rebleeding or death during hospitalisation A Full-Rockall score of ≤ 2 can be used to identify patients in low risk of poor outcome
6.) Saltzman JR, Tabak YP, Hyett BH, Sun X, Travis AC, Johannes RS. A simple risk	Retrospective cohort study Based on a	Patients registered with a principal diagnosis associated with	- In-hospital mortality - LOS - Costs	AIMS65 was proportional associated with in-hospital mortality, LOS and costs	No data on performance or findings at endoscopy	AIMS65 can be used to stratify UGIB-patients by predicting in-hospital mortality,

score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. Gastrointest Endosc 2011;74:1215-24.	clinical research database from US (187 participating hospitals) Following score was evaluated: AIMS65	UGIB Fase 1: Development of risk score (n=29,222) Fase 2: Validation of risk score (n=32,504)		AIMS65 has a discriminative ability corresponding to AUROC of 0.77 for prediction of in-hospital mortality Sensitivity and specificity for predicting mortality for AIMS65 ≥2 were 0.79 and 0.61 AIMS65=0 (19% of patients), low AIMS65 < 2 (60%), and high AIMS65 ≥2 (40%) were associated with in-hospital mortality rates of 0.3%, 0.9%*, and 5.3%, respectively	Identification of patients based on administrative data No long-term follow-up No data on rebleeding Lacks external validation	LOS and costs in UGIB Patients with AIMS65 <2 have low risk (0.9%*) of death during hospitalisation Patients with AIMS65 ≥2 have a high risk (5.3%) of death during hospitalisation
7.) Hyett BH, Abougergi MS, Charpentier JP,	Retrospective, single-centre, cohort study	Patients registered with a principal ICD-10	- In-hospital mortality - Hospital-based	AIMS65 was superior in predicting in-	Patients with missing data related to risk	AIMS65 is superior to GBS for predicting in-

Kumar NL, Brozovic S, Claggett BL, Travis AC, Saltzman JR. The AIMS65 score compared with the Glasgow-Blatchford score in predicting outcomes in upper GI bleeding. Gastrointest Endosc 2013;77:551-7.	Following scores were evaluated: AIMS65 and GBS	diagnosis associated with UGIB and complete dataset on risk scores available (n=278)	intervention (Composite endpoint: transfusion, endoscopic treatment, interventional radiology, surgery, in-hospital mortality) - Blood transfusion - ICU admission - Rebleeding - LOS - Timing of endoscopy	hospital mortality (AUROCs: 0.93 vs 0.68; p<0.001) compared with GBS Low AIMS65 <2 and high AISM65 ≥2 were associated with 0.5% and 21% risk of death during hospitalisation, respectively Sensitivity and specificity for predicting mortality for AIMS65 ≥2 were 0.94 and 0.76 GBS was better than AIMS65 in predicting treatment with blood transfusion (AUROCs: 0.85 vs 0.65; p<0.01)	scores were excluded (14.5%) Retrospective design Low sample size Data on findings at endoscopy are not presented Only patients with "confirmed UGIB" were included, but definition of "confirmed" is unclear No long-term follow-up	hospital mortality in UGIB Patients with AIMS65 <2 have low risk (0.5%) of death during hospitalisation Patients with AIMS65 ≥2 have a high risk (21%) of death during hospitalisation

				AIMS65 and GBS performed similar in predicing need for hospital-based intervention (AUROCs: 0.62 vs 0.68) and the other secondary outcomes	Identification of patients based on administrative data	
8.) Park SW, Song YW, Tak DH, Ahn BM, Kang SH, Moon HS1, Sung JK, Jeong HY. The AIMS65 Score Is a Useful Predictor of Mortality in Patients with Nonvariceal Upper Gastrointestinal Bleeding: Urgent Endoscopy in Patients with High AIMS65 Scores. Clin Endosc 2015;48:522-7.	Retrospective, single-centre, cohort study Following scores were evaluated: AIMS65 and Rockall score (not clear if admission or full Rockall score was used)	Non-variceal UGIB (n=634) Patients bleeding from cancer, patients not scoped, and patients with incomplete data were excluded	- In-hospital mortality - Endoscopic haemostasis - Rebleeding - Blood transfusion - LOS - Timing of endoscopy	AIMS65 was better than Rockall in predicting in-hospital mortality (AUROCs: 0.94 vs 0.87; p-value not listed) 0/434 patients with AIMS65 < 2 died during hospital admission In-hospital mortality rate 0.94%	Patients who were not scoped, had bleeding from varices or upper GI-cancer, or incomplete data were excluded No long-term follow-up Retrospective design Very low mortality rate	AIMS65 may be useful in predicting mortality in UGIB Patients with AIMS65<2 have low risk of death during hospitalisation.

					(0.9%) – external validity? Unclear if full or admission Rockall score was used	
9.) Robertson M, Majumdar A, Boyapati R, Chung W, Worland T, Terbah R, Wei J, Lontos S, Angus P, Vaughan R. Risk stratification in acute upper GI bleeding: comparison of the AIMS65 score with the Glasgow-Blatchford and Rockall scoring systems. Gastrointest Endosc. 2016;83:1151-60.	Retrospective, single-centre, cohort study Following scores were evaluated: AIMS65, GBS, admission and full Rockall score	Patients registered with a principal ICD-10 diagnosis associated with UGIB who were scoped and had complete dataset on risk scores (n=424)	- In-hospital mortality - Hospital-based intervention (Composite endpoint: transfusion, endoscopic treatment, interventional radiology, surgery, in-hospital mortality) - Blood transfusion - ICU admission - Rebleeding - LOS	AIMS65 was better than GBS and admission Rockall scores in predicting in-hospital mortality (AUROCs: 0.80 vs 0.76 vs 0.74) AIMS65 and full-Rockall score performed similar in predicting mortality (AUROCs: 0.80 vs 0.78) At threshold ≥3, AIMS65 had a sensitivity of 0.72 and specificity of	Retrospective design Low sample size Patients with incomplete datasets were excluded. Only patients undergoing endoscopy were included No long-term	

				0.77 for predicting in-hospital mortality For predicting need for hospital-based itnervention, AIMS65, GBS and full Rockall score had similar low AUROCs ranging between 0.62-0.69 AIMS65 was best for predicting ICU stay (AUROC 0.74) compared with GBS (0.70) and Rockall scores (0.62-0.71) GBS was superior in predicting need for transfusion (AUROC 0.90) compared to AIMS65 (0.72) and Rockall scores	follow-up Identification of patients based on administrative data	

				(0.66-0.68) In-hospital mortality rate 4.2%		
10.) Marmo R, Koch M, Cipolletta L, et al. Predicting mortality in non-variceal upper gastrointestinal bleeders: validation of the Italian PNED Score and Prospective Comparison with the Rockall Score. Am J Gastroenterol 2010;105:1284-91.	Prospective, multicenter cohort study from Italy. Validation of PNED-score and comparison with (full?) Rockall score	Non-variceal UGIB Fase 1: Development of PNED (n=1,020) based on data from a previous publication (Marmo R, et al. Am Jr Gastroenterol 2008) Fase 2: Validation of PNED and comparison with (full) Rockall score (n=1,360)	- 30-day mortality	PNED was closer associated with 30-day mortality than Rockall score (AUROCs: 0.81 vs 0.66; p<0.001) Patients with PNED > 8 had high risk of death (32%) At threshold >8 PNED had a sensitivity of 21% and specificity of 98.7%	Only patients undergoing endoscopy were included Patients with variceal bleeding (12%) were excluded No true external validation Calculation of PNED requires data on rebleeding, which is unknown initially	PNED can be used to predict risk of death < 30days following non-variceal UGIB International validation of PNED is needed
11.) Lu M, Sun G,	Retrospective,	Non-variceal	- In-hospital	Rockall scores were	Only patients	Rockall score is

Huang H, et al. Comparison of the Glasgow-Blatchford and Rockall Scores for prediction of nonvariceal upper gastrointestinal bleeding outcomes in Chinese patients. Medicine (Baltimore). 2019;98:e15716	multicenter cohort study from China. Following scores were evaluated: GBS and Rockall scores	UGIB Patients registered with a principal ICD-9 diagnosis associated with UGIB who were scoped (n=2,977)	mortality - Surgery - Rebleeding	closer associated with in-hospital mortality compared with GBS (AUROCs 0.80-0.84 vs 0.62) All scores had low ability to predict rebleeding (AUROCs ≤0.66) and need for surgery (AUROCs ≤0.59)	undergoing endoscopy were included Patients with variceal bleeding (12%) were excluded No long-term follow-up Retrospective design	superior to GBS in predicting in-hospital mortality
12.) Gu L, Xu F, Yuan J. Comparison of AIMS65, Glasgow-Blatchford and Rockall scoring approaches in predicting the risk of in-hospital death among emergency hospitalized patients with upper	Retrospective single-center study from China. Following scores were evaluated: AIMS65, GBS and full-Rockall score	UGIB-patients who were scoped (n=799)	- In-hospital mortality	AIMS65 were closer associated with in-hospital mortality (AUROC: 0.91) than full-Rockal score (0.86) and GBS (0.71) AIMS65 performed well in both patients with non-variceal UGIB (AUROC: 0.89) and	Patients who were not scoped or had missing data for any risk score were excluded Single center study Retrospective	AIMS65 is superior to full-Rockall score and GBS in predicting in-hospital mortality in non-variceal and variceal UGIB

gastrointestinal bleeding: a retrospective observational study in Nanjing, China. BMC Gastroenterol 2018;18:98.				patients with variceal UGIB (AUROC: 0.94) Sensitivity and specificity for predicting mortality for AIMS65 ≥2 were 0.88 and 0.84	design No long-term follow-up	
13.) Kim MS, Choi J, Shin WC. AIMS65 scoring system is comparable to Glasgow-Blatchford score or Rockall score for prediction of clinical outcomes for non-variceal upper gastrointestinal bleeding. BMC Gastroenterol 2019;19:136.	Retrospective single-center study from South Korea. Following scores were evaluated: AIMS65, GBS and Rockall scores	Non-variceal UGIB-patients who were scoped Patients with post-procedure bleeding af endoscopic resection (GIST) were excluded (n=512)	- In-hospital mortality - Composite endpoint (in-hospital mortality, ICU stay; rebleeding; blood transfusion; endoscopic treatment; embolisation or surgery) - Rebleeding - ICU stay - Transfusion	AIMS65 and Rockall scores had similar ability to predict in-hospital mortality (AUROCs: 0.84 vs 0.74-0.75) There was a trend towards better ability of AIMS65 to predict mortality compared with GBS (AUROCs: 0.84 vs 0.72; p=0.07) AIMS65 < 2 (71%) was associated with very low risk of death during	11% of patients were excluded (missing data, loss of follow-up or post-procedure bleeding) Low power/event rate (11 deaths) Single center study Retrospective	AIMS65, Rockall scores and GBS have similar ability to predict in-hospital mortality Patients with AIMS65 < 2 have a very low risk of death during hospitalisation (0.6%)

				hospital admission (0.6%) Sensitivity and specificity for predicting mortality for AIMS65 ≥2 were 0.88 and 0.73 All scores were poor in predicting composite endpoint and rebleeding (AUROCs ≤0.7) GBS performed well in predicting need for transfusion (AUROC: 0.87)	design No long-term follow-up	
14.) Shafaghi A, Gharibpoor F, Mahdipour Z, Samadani AA. Comparison of three risk Scores to predict	Retrospective single-center study from Iran. Following scores were evaluated:	UGIB-patients who were scoped Patients with missing data for	- In-hospital mortality - Rebleeding - Need for transfusion	AIMS65, GBS and full-Rockall scores all had low discriminative abilities for predicting in-hospital mortality	High exclusion rate (30%) Single center study	None of the evaluated risk scores performed well in predicting any outcome

outcomes in upper gastrointestinal bleeding; modifying Glasgow Blatchford with Albumin. Rom J Intern Med. 2019. doi: 10.2478/rjim-2019-0016	AIMS65, a modified AIMS65 (albumin threshold changed from 3 to 3,5), GBS, a modified GBS (adding albumin to the score) and Full-Rockall score	all risk scores were excluded (n=563)	- Endoscopic treatment - Composite endpoint (one of the outcomes mentioned above)	(AUROCs: ≤0.67) 1.3% of patients with an AIMS65 of zero died during hospitalisation Sensitivity and specificity for predicting in-hospital mortality for AIMS65 ≥2 were 0.47 and 0.80 Poor ability of all scores for predicting other outcomes (AUROCs ≤0.7)	Retrospective design No long-term follow-up	
15.) Ko IG, Kim SE, Chang BS, et al. Evaluation of scoring systems without endoscopic findings for predicting outcomes in	Retrospective single-center study from South Korea Following scores were evaluated: GBS, a modified	UGIB-patients assessed in the ER (n=590)	- Need for intervention - 30-day mortality	GBS and mGBS had highest ability to predict need for intervention (AUROC: 0.73) compared with admission Rockall score (AUROC:	Single center study Retrospective design No data	GBS is moderate accurate in predicting need for intervention in UGIB Admission Rockall score is accurate in

patients with upper gastrointestinal bleeding. BMC Gastroenterol 2017;17:159.	GBS (excluding hepatic disease, cardiac failure, melaena, syncope, and age), admission Rockall score			0.65; p<0.001) Admission Rockall score was closer associated with 30-day mortality than GBS and mGBS (AUROCs: 0.93 vs 0.65-0.66; p<0.001)	available on classified low-risk patients	detechtion of patients in high risk of death wihtin 30 days
16.) Thanapirom K, Ridtitid W, Rerknimitr R, et al. Prospective comparison of three risk scoring systems in non-variceal and variceal upper gastrointestinal bleeding. J Gastroenterol Hepatol 2016;31(4):761-7.	Prospective, multicenter study from Thailiand Following scores were evaluated: GBS and Rockall scores	Consecutive patients with UGIB However, patients refusing EGD were excluded (n=981)	- Need for treatment (transfusion, endoscopic/ radiological/ surgical haemostasis) - In-hospital mortalty and rebleeding - Transfusion - Endoscopic haemostasis	In non-variceal UGIB, GBS were closer associated with need for treatment than Rockall scores (AUROCs: 0.77 vs 0.0.61-0.69; p<0.001) In non-variceal bleeding, full-Rockall score was superior (AUROC: 0.80) for predicting death **and** rebleeding when compared with admission Rockall score and GBS	No data on mortality as an isolated endpoint No data on performance in overall group of patients with UGIB No data on need for treatment among patients with low GBS	GBS has the best ability to predict need for treatment in non-variceal UGIB Full-Rockall score is superior in predicting in-hospital-mortality **and** rebleeding (combined endpoint) in non-variceal UGIB None of the evaluated scores could predict outcome in

				(AUROCs 0.66-0.76) All scores had poor ability to predict need for treatment, or death **and** rebleeding, in patients with variceal bleeding (AUROCs ≤0.66) No deaths or rebleeding occured in patients with GBS ≤2	No long-term follow-up Patients managed on an outpatient basis were not included	variceal-UGIB
17.) Bryant RV, Kuo P, Williamson K, et al. Performance of the Glasgow-Blatchford score in predicting clinical outcomes and intervention in hospitalized patients with upper GI bleeding. Gastrointest	Prospective single-center study from South Australia Following scores were evaluated: GBS and Rockall scores	Consecutive patients hospitalised with UGIB (including patients with in-hospital bleeding) (n=888)	- Endoscopic treatment - Need for further endoscopic treatment - Transfusion - Rebleeding - Surgery - Death	GBS and Rockall scores performed similar in predicting in-hospital mortality (AUROCs: 0.71-0.76) GBS and full-Rockall score were superior in predicting need for endoscopic therapy compared with admission-	High rate of non-performance of endoscopy (20%) Single-center study No long-term follow-up	GBS and Rockall scores perform similar in predicting in-hospital mortality when also including patients with in-hospital bleeding GBS was best for predicting transfusion and as

Endosc 2013;78:576-83.				Rockall score (AUROCs: 0.76 vs 0.66) GBS was best for predicting transfusion (AUROC: 0.81) compared with both Rockall scores (AOROCs: 0.68-0.70) All scores performed poorly in predicting rebleeding and surgery (AUROCs ≤0.71)		good as Full-Rockall score for predicting need for endoscopic therapy
18.) Pang SH, Ching JY, Lau JY, et al. Comparing the Blatchford and pre-endoscopic Rockall score in predicting the need for endoscopic	Prospective, single-center study Following scores were evaluated: GBS and admission-	Consecutive outpatients presenting with UGIB who underwent endoscopy (n=1087)	- Need for endoscopic treatment - Rebleeding - 30-day mortality	GBS is closer associated with need for endoscopic treatment (AUROC: 0.72) than admission Rockall-score (AUROC not presented in paper)	Patients who were not scoped were not included Single center study	GBS=0 can be used to identify low-risk patients who will not require an immediate EGD

therapy in patients with upper GI hemorrhage. Gastrointest Endosc 2010;71:1134-40.	Rockall score			No patient with GBS=0 (4,6%) required endoscopic treatment, rebled or died wihtin 30 days	No details regarding performance of scores for predicting rebleeding and mortality	
19.) Meltzer AC, Burnett S, Pinchbeck C, et al. Pre-endoscopic Rockall and Blatchford scores to identify which emergency department patients with suspected gastrointestinal bleed do not need endoscopic hemostasis. J Emerg Med. 2013;44:1083-7.	Retrospective, single-centre, cohort study from US Following scores were evaluated: GBS and admission Rockall score	Patients presenting to the ED who had a final ED-diagnosis associated with UGIB (n=690)	- Need for endoscopic haemostasis	2/15 (13%) of admitted patients with a GBS=0 required endoscopic treatment (both cases had MW-lesions) 9/67 (13%) of admitted patients with a Rockall score of zero required endoscopic treatment	No follow-up on patients who were not admitted to hospital (14%) Single center study Retrospective design Identification of patients based on administrative	Low GBS or Rockall score does not exclude potential need for endoscopic treatment in patients presenting to the ER with symptoms of UGIB

					data	
20.) Oakland K, Kahan BC, Guizzetti L, et al. Development, Validation, and Comparative Assessment of an International Scoring System to Determine Risk of Upper Gastrointestinal Bleeding. Clin Gastroenterol Hepatol. 2019;17:1121-1129.e2.	Retrospective, international, multicentre cohort study based on five international datasets (Canada, UK, Australia). Following scores were evaluated: CANUKA score, GBS and admission Rockall score	Mixture of datasets containing patients with non-variceal UGIB and datasets containing patients with both variceal and non-variceal UGIB Some datasets only included patients undergoing endoscopy Fase 1: Development of CANUKA score (n=10,639) Fase 2: Validation of CANUKA score	- 30-day mortality - 30-day rebleeding - Surgical or radiological intervention - Endoscopic treatment - Blood transfusion - Poor outcome (one of the outpoints listed above)	CANUKA-score and admission Rockall score had similar ability to predict 30-day mortality (AUROCs: 0.77-0.79) and were marginally closer associated with mortality than GBS (AUROC: 0.74; p=0.047) GBS was best at predicting poor outcome (AUROC: 0.92) compared with CANUKA score (0.90; p<0.001) and Rockall score (0.76; p<0.001) Patients with CANUKA≤1 (6.8%) had low risk of death (0%) and low risk of poor outcome (3,7%)	Differences in case-mix in included datasets Patients not scoped exluded in some datasets One dataset was based on administrative data Retrospective design	CANUKA has higher accuracy than GBS in identifying patients dying within 30 days CANUKA and admission Rockall score have similar discriminative ability for predicting 30-day mortality Only 3.7% of patients with CANUKA≤1had a poor outcome compared with 4.7% of patients with GBS≤1, but GBS≤1 identified a considerable higher number of classified low-risk patients (23.7% vs

		and comparison with GBS and admission Rockall score (n=2,072)		within 30 days (0%). Among patients with GBS≤1 (23.7%) 1.1% died < 30 days and 4.7% had a poor outcome. GBS was marginally best at predicting need for endoscopic treatment (AUROC: 0.78) compared with CANUKA score (0.77; p=0.047) and Rockall score (0.66; p<0.001) All scores performed poorly in predicting rebleding (AUROCs ≤ 0.68)		6.8%) GBS was best at predicting need for endoscopic treatment

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Na HK, et al. Erythromycin infusion prior to endoscopy for acute nonvariceal upper gastrointestinal bleeding: a pilot randomized controlled trial. Korean J Intern Med. 2017 Nov;32(6):1002-1009	Randomized controlled trial	43 patients were randomly assigned: 14 patients in the erythromycin group; 15 patients in the gastric lavage group; and 14 patients in the erythromycin + gastric lavage group	Primary outcome satisfactory visualization. Secondary outcomes - identification of a bleeding source - the success rate of hemostasis - duration of endoscopy - complications related to erythromycin infusion or gastric lavage - number of transfused blood units - rebleeding rate - bleeding-related mortality	Overall satisfactory visualization was achieved in 81% of patients: 92.8% in the erythromycin group; 60.0% in the gastric lavage group; and 92.9% in the erythromycin + gastric lavage group, respectively (p = 0.055). The identification of a bleeding source was possible in all cases. The success rate of hemostasis, duration of endoscopy, and number of transfused blood units did not significantly differ between groups. There were no complications.	- Small patient group - patients excluded with severe comorbidities or unstable vital signs	Intravenous EM infusion prior to emergency endoscopy for acute NVUGIB may be of help to provide satisfactory endoscopic visualization

				Rebleeding occurred in three patients (7.0%). Bleeding-related mortality was not reported.		
Rahman R, et al. Pre-endoscopic erythromycin administration in upper gastrointestinal bleeding: an updated meta-analysis and systematic review. Ann Gastroenterol. 2016 Jul-Sep;29(3):312-7	Systematic review and meta-analysis of six randomized controlled trials (search run on nov 2015)	n=598 Patients received 250mg or 3-4mg/kg erythromycin in 20-90min before endoscopy was performed	<u>Primary outcomes</u> - gastric visualization, - need for second-look endoscopy - units of blood transfused - length of endoscopy - length of hospital stay - need for emergent surgery.	Erythromycin administration showed statistically significant improvement in adequate gastric mucosa visualization (OR 4.14; 95% CI: 2.01-8.53, P<0.01) while reduced the need for a second-look endoscopy (OR 0.51; 95% CI: 0.34-0.77, P<0.01) and length of hospital stay (MD -1.75; 95% CI: -2.43 to -1.06, P<0.01). Duration of procedure (P=0.2), units of blood transfused	- the doses of erythromycin varied among the studies, ranging from 125 mg to 250 mg - two of the four outcomes (gastric visualization and units of blood transfused) demonstrated significant heterogeneity - data for gastric visualization, only adequate versus inadequate was utilized and degrees of visualization beyond that was	Erythromycin before endoscopy in patients with acute UGIB significantly improves gastric mucosa visualization while reducing hospital stay and the need for a second-look endoscopy

				(P=0.08), and need for emergent surgery (P=0.88) showed no significant differences.	not assessed.	

Study Ref.	Study Type	Patient Group	Key Outcomes	Key Results	Limitations	Conclusions
1) Chaudhuri D, Bishay K, Tandon P, et al. Prophylactic endotracheal intubation in critically ill patients with upper gastrointestinal bleed: a systematic review and meta-analysis. JGH Open 2019	Systematic review and meta-analysis	Studies including patients older than 16 years undergoing EGD for severe UGIB (defined as patients who needed immediate endoscopy or admission to an ICU), comparing prophylactic intubation (PI) to no PI.	Cardiac events (composite outcome of myocardial infarction and cardiac arrest), pneumonia, LOS (in hospital and ICU) and death.	7 studies (5662 patients) included in the meta-analysis (all retrospective): - PI was associated with increased mortality (OR 2.59) - hospital LOS was higher in the PI group - PI showed higher rates of pneumonia (OR 6.58) and cardiac events (OR 2.11), and a trend toward increased ICU LOS	- small number of studies included - retrospective nature of the studies	Prophylactic intubation in severe UGIB is associated with a greater risk of pneumonia, LOS, death, and cost compared to endoscopy without intubation.
2) Alshamsi F, Jaeschke R, Baw B, et al. Prophylactic endotracheal intubation in patients with upper gastrointestinal bleeding undergoing endoscopy: a	Systematic review and meta-analysis	Studies including patients with UGIB requiring emergent EGD,	Aspiration, pneumonia, mortality, hospital length of stay	10 studies (6068 patients) included in the meta-analysis: - PEI was	Lack of adjustment for the severity of clinical situation	Low to very low quality evidence from observational studies suggests that PEI in the

systematic review and meta-analysis. Saudi J Med Med Sci 2017; 5(3): 201–209		comparing those who underwent prophylactic endotracheal intubation (PEI) and those who did not undergo PEI.		associated with increased risk of aspiration (OR 3.85; 6 studies) - PEI was associated with increased risk of pneumonia (OR 4.17; 5 studies) - PEI did not affect mortality (8 studies) - PEI increased the hospital length of stay (6 studies) - No differences between		setting of UGIB may be associated with higher rates of respiratory complications and, less likely, with increased mortality.

				variceal vs. non-variceal bleeding		
3) Almashhrawi AA, Rahman R, Jersak ST, et al. Prophylactic tracheal intubation for upper GI bleeding: a meta-analysis. World J Metaanal 2015; 3(1): 4-10	Meta-analysis	Studies examining the impact of prophylactic endotracheal intubation (PEI) on UGIB outcomes	Pneumonia within 48 h, mortality, aspiration	4 studies (367 patients): - PEI associated with increased risk of pneumonia (OR 3.13; 3 studies) - PEI was not associated with higher mortality or aspiration, but sensitivity analyses demonstrated statistically	Small number of included studies; all studies were observational; significant heterogeneity was identified in 2 of the 3 outcomes (mortality and aspiration)	Pneumonia within 48 h is more likely in UGIB patients who received prophylactic endotracheal intubation prior to endoscopy. Trends showing higher odds of mortality and aspiration in those prophylactically intubated were noted but no statistically significant differences were seen

				significant worse outcomes in those undergoing prophylactic intubation		
4) Perisetti A, Kopel J, Shredi A, et al. Prophylactic pre-esophagogastroduodenoscopy tracheal intubation in patients with upper gastrointestinal bleeding. Proc (Bayl Univ Med Cent). 2019 15;32(1):22-25	Single-center retrospective study from 2000 to 2013	Adult (>18 years) patients admitted or transferred to the ICU who had acute UGIB, in whom endotracheal intubation (ETI) was performed within 48 hours before or during EGD for UGIB with an indication of airway protection or shock or respiratory	Primary outcome: pulmonary aspiration Secondary outcomes: myocardial infarction, pneumonia, acute respiratory distress syndrome, cardiogenic pulmonary edema, sepsis, mortality, hospital days	Of the 69 patients undergoing pre-EGD ETI 38% had pulmonary aspiration, 9% myocardial infarction, 9% ARDS, 7% pulmonary edema, the median length of hospital stay was 10 days, and the mortality rate was 22%.	Dependence of information recorded in the medical records; small sample size; the patients who were intubated could have been more critically ill; the diagnosis of aspiration in a critically ill patient can be difficult; single-center study	The incidence of pulmonary aspiration with pre-EGD tracheal intubation was high (38%). Cardiopulmonary complications including myocardial infarction, acute respiratory distress syndrome, and pulmonary edema were high in intubated patients.

		failure				

First author, year, ref	Study design, participants (n)	Intervention/ Exposure	Outcome	Remarks
Riha, 2019 [1]	R (180)	PPI+octreotide vs. PPI	Median hospital LOS: 6.1 vs. 4.9 days (NS) Median ICU LOS: 2.3 vs. 1.9 days (NS) Rebleeding rates: 9% vs. 12% (NS) Mortality: 6.7% vs. 5.6% (NS) Median units of pRBCs for blood transfusions: 3 vs. 2 (NS) Multivariate analysis: all remained NS	NS differences

Abbreviations: PPI, proton pump inhibitor; ICU, intensive care unit; LOS, length of stay; pRBCs, packed red blood cells; NS, nonsignificant.

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Nagata N, Sakurai T, Moriyasu S, Shimbo T, Okubo H, Watanabe K, et al. Impact of INR monitoring, reversal agent use, heparin bridging, and anticoagulant interruption on rebleeding and thromboembolism in acute gastrointestinal bleeding. PLoS One. 2017;12:e0183423.	Retrospective cohort study	314 patients with acute upper or lower GIB: 157 anticoagulant users and 157 age-, sex-, and important risk-matched non-users.	The risks of rebleeding and thromboembolism in anticoagulated patients with acute GIB	No differences seen in rates of rebleeding (13.4% vs. 15.9%, P=0.52) or thromboembolism (5.7% vs. 3.2%, P=0.68) between users and non-users. Among anticoagulant users, early endoscopy (<24 h post-onset) was not associated with rebleeding (OR, 0.7; 95% CI, 0.3-1.8), thromboembolic events (OR, 0.5; 95% CI, 0.1-2.1) or endoscopy-related adverse events (0%); rebleeding was also not associated with an INR ≥2.5 (OR, 0.7; 95% CI, 0.2 to 2.3)	Retrospective analysis Mixed patients for all types of bleeding	Endoscopy appears to be safe for anticoagulant users with acute GIB compared with nonusers. Patient background factors were associated with rebleeding, whereas anticoagulant management factors (e.g. INR correction, reversal agent use, and drug interruption) were associated with thromboembolism. Early intervention without reversal agent use, heparin bridge, or anticoagulant interruption may be warranted for acute GIB.

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Shingina A, Barkun AN, Razzaghi A, et al. Systematic review: the presenting international normalised ratio (INR) as a predictor of outcome in patients with upper nonvariceal gastrointestinal bleeding. Aliment Pharmacol Ther 2011;33:1010–8.	Systematic review	Non-variceal upper GI bleeding with INR values	To assess the usefulness of the initial INR in patients with NVUGIB.	Only 2 studies were valid, but reported disparate, and conflicting results on predictive ability. An INR >1.5, significantly predicted mortality (OR: 1.96; 95% CI: 1.13-3.41).	Only 2 studies were considered valid and had contradictory results	An elevated INR at initial presentation does not predict rebleeding in NVUGIB.
Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Sung JJ, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018 Gut 2018. PMID 29691276	Clinical Guideline	NA Patients with NVUGIB.	- PPI effect - Antiplatelet and anticoagulant effects - rebleeding - need for surgery	Statement 5: Patients with haemodynamic shock and signs of upper gastrointestinal bleeding should be offered urgent endoscopy after resuscitation and	NA	NA

			- mortality - need for intervention -	stabilization. Statement 13: In patients receiving dual antiplatelet agents, at least one antiplatelet agent should be resumed in cases of upper gastrointestinal bleeding Statement 14: Among direct oral anticoagulant (DOAC) or warfarin users with high cardiothrombotic risk who develop ulcer bleeding, DOAC or warfarin should be resumed as soon as haemostasis is established		

Sostres C, Marcén B, Laredo V, et al. Risk of rebleeding, vascular events and death after gastrointestinal bleeding in anticoagulant and/or antiplatelet users. *Aliment Pharmacol Ther*. 2019;50(8):919–929. doi:10.1111/apt.15441	Retrospective cohort analysis	871 patients with GIB (25% PUB) taking antithombotic drugs 52.5% used an antiplatelet ;93.1% interrupted treatment after GIB. and 80.5% restarted therapy. Median follow-up was 24.9 months (IQR: 7.0-38.0). -	Rebleeding, vascular events and death.	Resumption of therapy was associated with a higher risk of rebleeding (HR 2.184; 95% CI: 1.357-3.515) but a lower risk of an ischaemic event (HR 0.626; 95% CI: 0.432-0.906) or death (HR 0.606; 0.453-0.804) in a multivariable COX hazards proportional models -	Retrospective analysis Mixed patients for all types of bleeding	Resumption of anticoagulant or antiplatelet therapy after a gastrointestinal bleeding event was associated with a lower risk of vascular events and death and a higher rebleeding risk. The benefits of early reinstitution of anticoagulant/antiplatelet therapy outweigh the gastrointestinal-related risks.

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Barkun AN, Almadi M, Kuipers EJ, et al. Management of Nonvariceal Upper	Guideline	NA	- PPI effect - Antiplatelet and anticoagulant	In patients with previous ulcer bleeding receiving cardiovascular	NA	In patients with previous ulcer bleeding receiving cardiovascular

Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group [published online ahead of print, 2019 Oct 22]. *Ann Intern Med*. 2019;10.7326/M19-1795. doi:10.7326/M19-1795			effects - rebleeding - need for surgery - mortality - need for intervention -	prophylaxis with single or dual antiplatelet therapy, we suggest using PPI therapy vs. no PPI therapy.		prophylaxis with single or dual antiplatelet therapy, we suggest using PPI therapy vs. no PPI therapy.

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Staerk L, Lip GY, Olesen JB, et al. Stroke and recurrent haemorrhage	Retrospective cohort study	Danish cohort study (1996-2012) included	the risks of all cause mortality, thromboembolism,	Compared with non-resumption of treatment, a	Retrospective analysis Mixed patients	Among patients with atrial fibrillation who

associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2015;351:h5876. Published 2015 Nov 16. doi:10.1136/bmj.h5876 Format:		all patients (4602) with atrial fibrillation discharged from hospital after gastrointestinal bleeding while receiving antithrombotic treatment.	major bleeding, and recurrent gastrointestinal bleeding associated with restarting antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation	reduced risk of all cause mortality was found in association with restart of oral anticoagulation (HR 0.39, 95% CI 0.34-0.46), an antiplatelet agent (0.76, 0.68-0.86), and oral anti-coagulation plus an antiplatelet agent (0.41, 0.32 -0.52), and a reduced risk of thromboembolism was found in association with restart of oral anticoagulation (0.41, 0.31- 0.54), an antiplatelet agent (0.76, 0.61 - 0.95), and oral anticoagulation plus an antiplatelet agent (0.54, 0.36-0.82). Restarting oral anticoagulation alone was the only	for all types of bleeding	experience gastrointestinal bleeding while receiving antithrombotic treatment; subsequent restart of oral anticoagulation alone was associated with better outcomes for all cause mortality and thromboembolism compared with patients who did not resume treatment. This was despite an increased longitudinal associated risk of bleeding.

				regimen with an increased risk of major bleeding (1.37, 1.06- 1.77) compared with non-resumption of treatment;.		
			-	-	-	

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Prediction Model for Significant **Bleeding** in Patients with Supratherapeutic International Normalized Ratio After Oral **Administration** of Warfarin. Pourafkari L, Baghbani-Oskouei A, Savadi-Oskouei S,	Retrospective cohort study	medical records of patients taking warfarin with an international normalized ratio > 3.5.	bleeding episodes and the need for transfusion of blood products performance of new bleeding score predictor. New Bleeding Score (NBLDSCOR)	NBLDSCOR was the best predictor of significant bleeding in this population. Neither ATRIA nor ORBIT was a good predictor of significant bleeding, where the area under the curve for the receiver-operating	Retrospective analysis, no validation cohort, limited sample size Mixed patients for all types of bleeding	The NBLDSCOR including age, negative Rhesus factor, low hemoglobin, renal impairment, and concomitant peptic ulcer and disseminated cancer is a good predictor of significant bleeding in this

Ghaffari S, Parizad R, Tajlil A, Nader ND. Clin Drug Investig. 2019 Jun;39(6):533-542.				characteristic plot for ATRIA was 0.654 ± 0.034 and for ORBIT was 0.604 ± 0.033. The predictive power of NBLDSCOR was superior to ATRIA and ORBIT ($p < 0.001$),		patient population.
Management of Oral **Anticoagulation** Therapy After **Gastrointestinal Bleeding**: Whether to, When to, and How to Restart an **Anticoagulation** Therapy. Kido K, Scalese MJ. Ann Pharmacother. 2017 Nov;51(11):1000-1007	Systematic review	Articles referring to patients with GIB taking anticoagulants	To evaluate current clinical evidence for management of oral anticoagulation therapy after gastrointestinal bleeding (GIB) with an emphasis on whether to, when to, and how to resume an anticoagulation therapy.	9 studies were identified. Four retrospective cohort studies showed that resuming anticoagulation therapy was associated with significantly lower rate of thromb-oembolism (TE). Meta-analyses and prospective cohort studies also supported this finding. Two retrospective cohort studies indicated an	-	Anticoagulation therapy resumption is recommended, with resumption being considered between 7 and 14 days following GIB regardless of the therapy chosen.

				increase in GIB when anti-coagulation reinitiation occurred in less than 7 days without a decrease in TE. Resuming therapy between 7 and 15 days did not demonstrate a significant increase in GIB or TE. A large retrospective study showed that apixaban was associated with the significantly lowest risk of GIB compared with both rivaroxaban and dabigatran.		

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Peloquin, J.M.*, et al.* Diagnostic and Therapeutic Yield of Endoscopy in	Retrospective cohort	A total of 134 patients	Predictors of endoscopically	On multivariate logistic	Retrospective	This study demonstrates

Patients with Elevated INR and Gastrointestinal Bleeding. *Am J Med* **129**, 628-634 (2016).	analysis	treated with warfarin with INR 3.5 or greater (mean 5.5, range 3.5-17.1) who presented with symptoms of gastrointestinal bleeding, most commonly as melena or symptomatic anemia	identifiable lesions, interventions, and outcomes.	regression, concomitant antiplatelet therapy (odds ratio [OR] 2.59; 95% confidence interval [CI], 1.13-5.94), timing of EGD within 12 hours of presentation (OR 3.71; 95% CI, 1.05-13.08), and INR level (OR 0.79; 95% CI, 0.64-0.98) were the only significant independent predictors of identifying a source of bleeding.	analysis, limited sample size Mixed patients for all types of bleeding	that the relationship between INR elevation and identification of a bleeding source or endoscopic intervention at EGD are antiparallel.
Shim CN, Chung HS, Park JC, et al. Is Endoscopic Therapy Safe for Upper Gastrointestinal Bleeding in Anticoagulated Patients With Supratherapeutic International Normalized Ratios?. *Am J Ther*. 2016;23(4):e995–e1003. doi:10.1097/MJT.0000000000000002	Retrospective cohort analysis	192 anticoagulated patients who underwent endoscopic treatment for UGIB were enrolled in the	To evaluate the safety of endoscopic therapy for UGIB in anticoagulated patients with supratherapeutic	There were no significant differences in therapeutic outcomes between patients with INR within the	Retrospective analysis, limited sample size Mixed patients for all types of	We should consider endoscopic therapy for UGIB in anticoagulated patients, irrespective of

		study. Patients were divided into 2 groups based on the occurrence of rebleeding within 30 days of the initial therapeutic endoscopy: no-rebleeding group (n = 168) and rebleeding group (n = 24)	INR in terms of rebleeding and therapeutic outcomes.	therapeutic range and those with supratherapeutic INR. Supratherapeutic INR at the time of endoscopic therapy did not change rebleeding and therapeutic outcomes.	bleeding	INR at the time of endoscopic therapy.

Reference & year/country	Study design	Patients & Intervention	Outcomes	Results	limitations	Conclusions & Comments
Ramos, Gastrointest Endosc 2018;	Retrospective cohort study.	144 Patients with GI bleeding & platelets 20-50x10^9/L. Included cirrhotics & non-cirrhotics	Yields, procedure adverse events, Tx, rebleeding & mortality	Median platelet count was 41x10^9/L. Diagnostic yield 68% (p=0.04) & therapeutic yield 60% (NS). Initial haemostasis 94% and one adverse event. Median red cell & plt. Tx fell after intervention. Rebleeding 22% & 30% at 30 days & 1 year. INR >2 predicted rebleeding. All-cause mortality: 19% at 1 month & 30% at 1 year. GIB mortality only 3% & 4% respect. INR>2, APTT >38 secs, low BP, ITU admission & lung comorbidities predicted mortality	Retrospective design	Endo for GIB in patients with low platelets appears safe (cirrhosis & non-cirr.). There are moderated diag. & therap. yields, high haemostasis rates and reduced Tx requirements. Rebleeding and mortality are high
Zakko, Clin Gastroenterol Hepatol 2017; USA	Retrospective cohort study. Cases who received platelet transfusions were matched with controls. Multivariate analysis used.	204 GI bleeding (57% UGIB) patients taking antiplatelet meds. (and count >100x10^9/L admitted to Yale-New Haven (2008-2013)	Recurrent GI bleeding	Multivariate analyses showed higher mortality if platelets given (OR 5.57; 95% CIs 1.52-27.1). Higher proportion of major CVS events and also hospital stay >4 days in patients given platelets seen on univariate analysis, but not multivariate analysis.	Retrospective design	Platelet transfusion (in absence of thrombocytopenia) in UGIB patients on antiplatelet meds did not reduce rebleeding but **was associated with higher mortality**.
Li, Lancet	Prospective population-	3166 patients (50% >75yrs)	Bleeding type, severity, &	405 first bleeding events (218 GIB) during 13 509 patient yrs.	Cohort study (although	If on antiplatelet meds without routine PPI, risk of

2017; UK	based cohort study	with 1st TIA, ischaemic cva, or MI treated with antiplatelets	outcomes <10 years. Also assessed NNT to prevent UGIB with PPI	follow-up. 314 (78%) admitted to hospital. Risk of major bleeding increased with age (HR if >75ys: 3.10 (p<0.0001); and fatal bleeding 5.53 (p<0.0001) Risk of major GIB >75yrs: HR 4.13 (p<0.0001), esp if disabling or fatal (10.26; p<0.0001). If >75yrs, major GIB were mostly disabling or fatal. NNT for PPI to prevent fatal or disabling UGIB over 5 yrs was 25 if >85yrs vs 338 if <65yrs.	large)	major bleeding is high in older patients. Half the major bleeds in elderly are GIB, therefore data supports use of routine PPI in this group.

Reference & year/country	Study design	Patients & Intervention	Outcomes	Results	limitations	Conclusions & Comments
Connolly, NEJM 2019	Multicentre prospective cohort study	352 patients with acute major bleeding on factor Xa inhibitors given andexanet (bolus then 2-hour infusion)	Change in Xa activity, and hemostatic efficacy at 12 hrs.	Mean age 77yrs. IC bleeding in 64%, GIB in 26%. 92% reduction in Xa activity. Excellent or good hemostasis seen in 82%. 30-day mortality in 14%; thrombotic event in 10% at 30 days. Reduced Xa activity did not predict hemostatic efficacy (although modestly predictive in IC bleed	Cohort study	In major bleeding, Andexanet markedly reduced anti-Xa activity and 82% had good-excellent hemostasis at 12 hours.
Van der Wall,	Prospective	137 patients on	4-hr reversal	35% was proven UGUB. 84% of GIB was	Cohort	Idarucizumab showed

Circulation 2019	multicentre cohort study	dabigatran with uncontrollable GIB requiring reversal with Idarucizumab (2014-16)	of anticoag effect; also hemostasis, rebleeding, thrombo-embolic events and mortality	major/life-threatening. Complete reversal of effect seen in 97.5%. Hemostasis in 68.7% after 2.4 hrs. 4.4% had thrombo-embolic event <90 days. 14.6% died	design	rapid & complete reversal of dabigratan activity in nearly all patients with GIB.
Serengupta, 2018; Clin Gastroenterol Hepatol	Retrospective analysis (2010-2014) assessing rebleeding and thromboembolism in patients with GIB on DOACs	1338 patients on DOACs hospitalized with GIB	Rebleeding and thromboemb.	Not restarting DOAC ass with older patients, heart failure, Tx & ITU stay. Restarting DOAC <30 days was not associated with thrombo-emb. or rebleeding. On Multivariate, prev thrombo-embol. ass. with further thrombo-emb; and Thienopyridine use ass. with rebleeding. More patients resuming rivaroxaban had rebleeding compared with other DOACs (p=0.04)	Retrospective study	Resuming DOAC not associated with thrombo-embolism or rebleeding
Schulman , Thromb Haemost 2018; Canada	Prospective cohort study in 9 hospitals	66 patients on Xa inhibitors (apixaban or rivoroxaban) given 2000 units PCC for major bleeding (16 had GI bleeding)	Haemostatic effectiveness at day 1 and 30- day follow-up.	Haemostatic effectiveness good in 65% & poor or none in 15%. For GI bleeding the figures were 695 and 19% respectively. Overall 9 deaths at 30 days and 5 major thromboembolic events. Post hoc analysis: reversal effective in 68%, ineffective in 32% by Int Soc. Thromb/Haem criteria.	Observational study. Haemostatic effectiveness rather subjective. Post hoc assessment.	PCC may have a beneficial effect in major bleeding in patients taking Xa inhibitors, but risk of thromboembolism needs taken into account.
Nagata, Gut	Japanese	16977 patients	GI bleeding	In matched score analysis of 5046 pairs,	Database	Post endoscopy GI

2018; Japan	procedure database with propensity matching to compare bleeding & thrombotic events	undergoing 13 high risk endo procedures on peri-op warfarin or DOAC (2014-15)	and Thrombo-embolism	warfarin group had more GI bleeding than DOACs (12% vs 9.9%; p=0.002) with no difference in thrombo-embolism (5,4% vs 4.7%) or mortality (5.4% vs 4.7%). Risks of bleeding higher if warfarin or DOAC used + heparin bridging vs DOAC alone, also with higher thrombo-embo. Highest bleeding risk seen in ESD, EMR, VBL or injection sclerotherapy. Moderate in colonic polypectomy, ERCP & EUS-FNA	analysis	bleeding higher in warfarin than DOAC. Heparin bridging did not appear helpful.
Milling, Am J Emerg Med 2018; USA	Retrospective 5-centre review of cases of major bleeding with Xa inhibitors.	56 patients on Xa inhibitors and life-threatening bleeding (52% were GI bleeds)	Overall transfusions & other management; 30-day mortality	43% overall received various factor or plasma products. 30-day mortality was 21%. Re-anticoagulation <30 days in 41%.	Retrospective cohort study	Variable approach to management noted.
Pollack, NEJM 2017	Multicentre prospective cohort study	503 patients on dabigatran with uncontrolled bleeding (group A; 45% GIB, 33% IC bleed) or about to undergo an urgent procedure (group B)	Reversal of anticoagulant effect with idarucizumab; hemostasis, thrombotic events and mortality	301 and 202 in groups A and B respectively. Median max reversal was 100%. Median time to cessation of bleeding in group A was 2.5 hrs. Median time to procedure in group B was 1.6 hrs, with peri-procedural hemostasis assessed as normal in 93%. At 90 days, thromboitic events seen in 6.3% and 7.4% in groups A and B; with mortality 18.8% and 18.9%	Cohort study	In emergency situation, idarucizumab rapidly, durably and safely reversed anticoagulant effect of dabigratan.
Pannach, J	Prospective	143 patients on	Management,	Upper GI bleeding confirmed in 44.1% of	Cohort	GI bleeding in patients

Gastroenterol 2017; Germany	cohort study	DOACs with major GI bleeding.	length of stay and in-hospital mortality. Results compared with a historical cohort of patients with GI bleeding	DOAC patients. UGIB commoner in the 185 patients VKA patients and the 711 antiplatelet patients. PUB seen in 27% of the DOAC group vs 54% in VKA and 61% in antiplatelet groups. DOAC group had lower resource utilisation, shorter stay and lower mortality (1.6%) vs others	study with historical comparison group	on DOACs appears different from that on VKA or antiplatelet Rx and has better short-term prognosis
Nagata, PLoS One 2017; Japan.	Retrospective single centre cohort study	314 patients with UGIB (157 anticoag users and 157 matched controls	Rebleeding and thrombo-enbolism	No endo related adverse seen and no difference in rate of endoRx, Tx, rebleeding or thrombo-embol. Rebleeding associated with low platelets and low dose aspirin, but not HAS-Bled score, heparin bridge or INR>2.5. Thrombo-embolism associated with INR>2.5, reversal agent used, and anticoag interruption, but not CHA2DS2-VASc. Tx need was higher in warfarin than DOAC users.	Retrospective and single centre design	Endoscopy for UGIB appears safe for anticoag users. Rebleeding appears to be associated with patient factors, with thrombo-embolism associated with anticoag factors (INR correction, reversal agents, drug interruption). Therefore, early intervention without reversal agents or interruption may be best
Milling, Ann Emerg Med	Multicentre, retrospective	191 patients with dabigatran related major	Mortality and management	12 patients died (8 had GI bleeding). Red cell and plasma transfusion common, but only 11 (6%) were given purified	Retrospective chart	Use of reversal strategies was low,

2017; USA	study	bleeding (62% had GI bleeding)		coagulation factors.	review	although mortality low.
Sin, J Crit Care 2016; USA	Retrospective study	93 adults receiving 4-factor PCC for life-threatening bleeds (n=63) or emergency surgery (n=30)	Thrombo-embolism within 14 days (and effect on INR)	12% developed thrombo-emb. <14 days (median time 5 days). Risk increased by Heparin induced low platelets; major surgery <14 days; >6 risk factors for Thrombo-emb. For patients post warfarin reversal, INR corrected within 24hrs in 87%. INR "rebound" seen in 25% (mostly when no Vit K given).	Retrospective observational study	4-factor PCC associated with significant thrombo-embolic risk. However useful agent for warfarin reversal. Lack of concomitant Vit K may contribute to INR rebound
Subramamiam, Transfusion 2016; Australia	Retrospective cohort study in 3 centres	2228 patients having endo for NVUGIB (2008-2010)	30-day and 1-year mortality	30-day and 1-year mortality were 4.9% and 13.9%. Transfusion of ≥4 units associated with >10 times odds of rebleeding if Hb>9g/dL. Use of ≥5 units FFP associated with increased 30-day mortality (p=0.008) and 1-year mortality (p=0.005) after adjustment for confounders	Retrospective study	FFP administration associated with increased mortality; and red cell transfusion associated with further bleeding in a subset of patients
Fabricus, World J Surgery 2016; Denmark	Retrospectve analysis of Danish hospital admissions	5107 admitted patients with haemostatic endoscopic interventions for NVUGIB in Denmark 2011-13	Effect of transfusion policy on 30-day mortality; repeat endo; surgery (after correcting for confounders)	Red cell Tx associated with repeat endo, surgery, 30-day mortality. FFP use associated with risk for surgery, and 30-day mortality (OR 1.04; p<0.01). Platelet use associated with less need for repeat endo	Retrospective analysis of national data	Red cell and FFP transfusion associated with adverse events
Karaca, Am J Emerg Med	Prospective cohort study	40 patients with GI bleeding on	Efficacy of warfarin	Mean INR at 2 and 6 hours was lower in PCC group (p<0.01 for both). 7 patients had	Cohort non-	After GI bleeding on warfarin, INR levels

2014; Turkey		warfarin with INR>2.1 who had PCC or FFP (n=20 each)	reversal using PCC or FFP	active bleeding at endo in FFP group vs none in PCC group (p<0.01). ED stay lower in PCC group (p<0.01)	randomise d comparison	appeared to be reversed more quickly with PCC than FFP.
Stollings, J Crit Care 2018; USA	Retrospectiv e single centre observationa l study of TXA	36 GI bleeding (UGIB in 67%) patients admitted to ICU and given TXA (2012-2016)	Blood products transfusion and adverse events	Rebleeding in 14%, surgery or embolization in 16%. Prior heparin had been given to 7 patients, warfarin to 2 and DOAC to 1. No PCC was given. More red cell transfusions were given pre- than post TXA, but no difference seen between pre- and post- FFP or platelet transfusions. DVT in 6%, MI and acute renal failure in 3% each. 28-day mortality in 53%	Retrospecti ve single centre observatio nal study design	Lower red cell transfusion post TXA administration and relatively low risk of complications.
Tavakoli, UEGJ 2017, Iran	Double blind, single centre RCT of TXA	410 patients with UGIB randomised to IV TXA (n=138), topical TXA via ng (133) or placebo	Urgent endo, mortality rebleeding, blood transfusion, endo or surgical intervention & health status	Time to endo shorter in placebo group (p<0.001); need for urgent endo higher in placebo group (p<0,001). Other endpoints similar. No thromboembolic events seen within 1 week	Single centre; follow-up not robust and not complete in 61 patients	TXA appears promising for UGIB, especially to reduce need for urgent endoscopy

Saidi, Lioab 2017; Iran	Prospective double-blind placebo controlled single centre trial of TXA	131 patients with UGIB – ng TXA	Red cell transfusion	Reduced red cell Tx ($p<0.001$) and reduces rebleeding (6% vs 18.8%; p=0.033) in TXA group. Also, lower emergency endoscopy in TXA group (9% vs 22%; p=0.04). Similar mortality in both group	Single centre; Sample size calculation had limitations	Intragastric TXA safe, simple and well tolerated with reduction in transfusion requirements and rebleeding. Further data needed before this can be recommended.
Flores, Medwave 2015; Chile (Spanish with English abstract)	Combined meta-analysis of 5 systematic reviews including 8 RCTs using GRADE (identified by Epistemonikos database)	UGIB patients given TXA	Rebleeding; mortality and adverse events	*Article in Spanish with English abstract only*	Database search then results combined then assessed by GRADE. Cannot find English copy of full paper	TXA probably reduces rebleeding and mortality, without increasing thromboembolic adverse effects
Cochrane review: TXA for upper GI bleeding; 2014	Intervention review (Cochrane)	RCTs of patients with UGIB given TXA vs no intervention, placebo or other anti-ulcer drugs	All-cause mortality, bleeding and adverse events	8 RCTs included (control groups were placebo in 7 and no intervention in 1). Two also had control group assigned to anti-ulcer drugs. Mortality overall was lower in TXA group (RR0.60, 95%CI 0.42-0.87; p=0.007. This was not confirmed if missing data patients were included as Rx failures.	Analysed studies dated from 1973-2011	Suggests TXA had a beneficial effect, but high drop-out in the analysed studies limited accuracy

				No difference seen in thrombo-embolic events		

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Kim SY, Hyun JJ, Suh SJ, et al. Risk of Vascular Thrombotic Events Following Discontinuation of Antithrombotics After Peptic Ulcer Bleeding. *J Clin Gastroenterol*. 2016;50(4):e40–e44. doi:10.1097/MCG.0000000000000354	Retrospective cohort analysis	544 patients with PUB, 72 patients were taking antithrombotics and followed up for >2 months. Forty patients discontinued antithrombotics after ulcer bleeding (discontinuation group) and 32 patients continued antithrombotics with or without transient interruption (continuation group).	Association between discontinuation of antithrombotic drugs after ulcer bleeding and thrombotic events (ischemic heart disease or stroke) -	Thrombotic events developed more often in the discontinuation group than in the continuation group [7/32 (21.9%) vs. 1/40 (2.5%), P=0.019]. Hazard ratio for thrombotic event when antithrombotics were continuously discontinued was 10.9 (95% confidence interval, 1.3-89.7). There were no significant differences in recurrent bleeding events between the 2 groups.	Retrospective analysis Quite a limited number of patients exposed Unbalanced groups	Discontinuation of antithrombotics after peptic ulcer bleeding increases the risk of cardiovascular events

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Wang et al. Long-term Prognosis in Patients Continuing Taking Antithrombotics After Peptic Ulcer Bleeding World J Gastroenterol 23 (4), 723-729. 2017. PMID 28216980.	Retrospective cohort analysis	A total of 167 patients with PUB divided into either a continuing group to continue taking antithrombotic drugs (aspirin 85.7%) after ulcer bleeding or a discontinuing group to discontinue antithrombotic drugs (85.5% aspirin).	The primary outcome was recurrent bleeding. Secondary outcome were death or acute cardiovascular disease occurrence.	COX regression analysis showed that the hazard ratio (HR) for recurrent bleeding was 2.98 (95%CI: 1.06-8.35, *P* = 0.015) in the continuing group, while HR for death or acute cardiovascular disease in the discontinuing group was 5.21 (95%CI: 1.03-26.27, *P* = 0.028).	Small study, Retrospective analysis Unbalanced groups	Continuing antiplatelet drugs in patienst with PUB increases the risk of recurrent bleeding events, while discontinuing antithrombotics would increase the risk of death and developing cardiovascular disease.
K Siau et al. Stopping Antithrombotic Therapy After Acute Upper Gastrointestinal Bleeding Is Associated	Retrospective cohort study.	118 patients who underwent gastroscopy for UGIB while on antithrombotic	Cause-specific mortality, thrombotic events, rebleeding and	Stopping antithrombotic therapy at the time of discharge was associated with	Small study, Retrospective analysis Unbalanced	Discontinuation of antithrombotic therapy is associated with increased thrombotic events and reduced survival.

With Reduced Survival Postgrad Med J 94 (1109), 137-142. Mar 2018. PMID 29101296.		therapy , with median follow-up of 259 days.	serious adverse events	increased mortality (HR 3.32; 95% CI 1.07 - 10.31, P=0.027), thrombotic events (HR 5.77; 95% CI 1.26 to 26.35, P=0.010) and overall adverse events (HR 2.98; 95% CI 1.32 to 6.74, P=0.006). No significant differences in postdischarge bleeding rates between groups (HR 3.43, 0.36 to 33.04, P=0.255).	groups	
Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Sung JJ, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018 Gut 2018. PMID 29691276	Clinical Guideline	NA Patients with NVUGIB.	- PPI effect - Antiplatelet and anticoagulant effects - rebleeding - need for surgery - mortality - need for	Statement 12: Among patients with high cardiothrombotic risk receiving antiplatelet agents, these agents should be resumed as soon as haemostasis can be established. Statement 13: In patients receiving dual antiplatelet agents, at	NA	Among patients with high cardiothrombotic risk receiving antiplatelet agents, these agents should be resumed as soon as haemostasis can be established. In patients receiving dual antiplatelet agents, at

			intervention	least one antiplatelet agent should be resumed in cases of upper gastrointestinal bleeding		least one antiplatelet agent should be resumed in cases of upper gastrointestinal bleeding
Sostres C, Marcén B, Laredo V, et al. Risk of rebleeding, vascular events and death after gastrointestinal bleeding in anticoagulant and/or antiplatelet users. *Aliment Pharmacol Ther*. 2019;50(8):919–929. doi:10.1111/apt.15441	Retrospective cohort analysis	871 patients with GIB (25% PUB) taking antithombotic drugs 52.5% used an antiplatelet ;93.1% interrupted treatment after GIB. and 80.5% restarted therapy. Median follow-up was 24.9 months (IQR: 7.0-38.0). -	Rebleeding, vascular events and death.	Resumption of therapy was associated with a higher risk of rebleeding (HR 2.18; 95% CI: 1.35-3.51) but a lower risk of an ischaemic event (HR 0.62; 95% CI: 0.43-0.90) or death (HR 0.60; 0.45-0.80) in a multivariable COX hazards proportional models -	Retrospective analysis Mixed patients for all types of bleeding	Resumption of anticoagulant or antiplatelet therapy after a gastrointestinal bleeding event was associated with a lower risk of vascular events and death and a higher rebleeding risk. The benefits of early reinstitution of anticoagulant/antiplatelet therapy outweigh the gastrointestinal-related risks.

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**

Barkun AN, Almadi M, Kuipers EJ, et al. Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group [published online ahead of print, 2019 Oct 22]. *Ann Intern Med*. 2019;10.7326/M19-1795. doi:10.7326/M19-1795	Guideline	NA	- PPI effect - Antiplatelet and anticoagulant effects - rebleeding - need for surgery - mortality - need for intervention	In patients with previous ulcer bleeding receiving cardiovascular prophylaxis with single or dual antiplatelet therapy, we suggest using PPI therapy vs. no PPI therapy.	NA	In patients with previous ulcer bleeding receiving cardiovascular prophylaxis with single or dual antiplatelet therapy, we suggest using PPI therapy vs. no PPI therapy.

	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Hemara MH , et al. Endoscopic injection of autologous blood versus diluted epinephrine for control of actively bleeding gastroduodenal ulcers: a randomized-controlled study. Eur J Gastroenterol Hepatol. 2014;26:1267-1272	RCT, 100 patients	Injection therapy with 5-20mL autologous blood (n=50) Vs. Epinephrine injection (n=50)	- primary hemostasis - 30-day rebleeding - complications	no significant difference between the two groups for: - primary hemostasis (100% vs. 100%) - 10 day rebleeding (8% vs. 10%) - cardiovascular complications (0% vs. 4%)	Small sample size Unblinding	Autologous blood is effective as epinephrine for primary hemostasis and does not significantly reduce the rebleeding rate
Khodadoostan M et al. Endoscopic treatment for high-risk bleeding peptic ulcers: A randomized, controlled trial of epinephrine alone with epinephrine	RCT, 108 patients	Epinephrine injection alone (n=50) Vs. Epinephrine injection plus 8mL Fresh Frozen Plasma	- primary hemostasis - 30-day rebleeding	no significant difference between the two groups for: - primary hemostasis (94% vs. 98%) - rebleeding (14% vs. 8%)	Single vs. dual therapy Small sample size Unblinding	Injection of epinephrine plus FFP does not provide any benefit over epinephrine injection alone

plus fresh frozen plasma. J Res Med Sci. 2016;21:135.		(n=50)		- surgery (6% vs. 4%9 - mortality (10% vs. 6%)		
Nunoue T et al. A Randomized Trial of Monopolar Soft-mode Coagulation Versus Heater Probe Thermocoagulation for Peptic Ulcer Bleeding. J Clin Gastroenterol. 2015;49:472-476.	RCT, 111 patients	Soft coagulation (n=56) Vs. Heater probe (n=55)	- primary hemostasis - 30-day rebleeding - complications	primary hemostasis significantly higher in soft coagulation group (96% vs 67%, p<0.0001) - 30-day rebleeding (2% vs. 13%) - perforation (4% vs. 0%)	Small sample size Unblinding	Soft coagulation using monopolar hemostatic forceps is more effective than heater probe for achieving hemostasis
Wang HM, et al. Improvement of Short-Term Outcomes for High-Risk Bleeding	RCT, 116 patients	injection with distilled water plus APC (n=58) Vs. injection with	- primary hemostasis - 30-day rebleeding - 30-day mortality	Rebleeding rate significantly lower in APC group (3.6% vs. 16%, p=0.029)	Low-dose regiment of proton pump inhibitor (PPI), rather than high-dose PPI regiments was	Endoscopic therapy with APC following distilled water injection is more effective than distilled water injection alone for preventing rebleeding of peptic

Peptic Ulcers With Addition of Argon Plasma Coagulation Following Endoscopic Injection Therapy: A Randomized Controlled Trial. Medicine (Baltimore). 2015; 94: e1343.		distilled water only (n=58)	- hospital stay - units of blood transfused	no significant difference between the two groups for: - primary hemostasis (97% vs. 95%) - 30-day mortality (3.4% vs. 3.4%) - hospital stay (7.6 vs. 7.1) - units of blood transfused (4.4 vs 4.3)	used after endoscopy	ulcer
Kim JW et al. Comparison of hemostatic forceps with soft coagulation versus argon plasma coagulation for bleeding peptic ulcer--a randomized trial. Endoscopy. 2015; 47:680-7.	RCT, 151 patients	Epinephrine injection plus APC (n=75) Vs. epinephrine injection plus hemostatic forceps with soft coagulation (HFSC) (n=76)	- 30 day rebleeding - primary hemostasis - 7-day rebleeding - need for surgery or embolization - 30 day death - hospital stay - perforation	no significant difference between the two groups for: - 30 day rebleeding (6.7% vs. 9.2%) - primary hemostasis (96.0% vs. 96.1%) - 7 day rebleeding (4.0% vs. 6.6%) - need for surgery/ embolization (0% vs. 0%) - 30 day mortality: 2.7%	Small sample size Generalizability of HFSC procedure (single centre, expert endoscopists)	. The efficacy and safety of HFSc is not inferior to APC

				vs. 2.6% - hospital stay (9.7 vs. 7.8 days) - perforation (0% vs. 0%)		

Authors	Study type	Patient group	(n)	Intervention	endpoint	Outcomes	Conclusions
Jensen AmJ Gastro 2017	RCT	Group Ib Group Ia+IIa+IIb	388 Ib 163 Ia+IIa+IIb 225	PPI or placebo	rebleeding	PPI reduced rebleding in Ia+IIa+IIb but not Ib (5.4% vs 4.9%, n.s) Ib had lower risk of rebleeding (4.9%) compared to Ia(22.5%), IIb(17.6%) or IIa(11.3%)	PPI not recommended after successful treatment in Ib
Jensen GIE 2016	Prospective cohort	Patients with severe bleeding	High risk (Ia, IIa, IIb) 87 Med risk (Ib, IIc) 52 Low risk (III) 24	Doppler before and after Rx Comparison High vs med and Ia vs Ib	Doppler before Doppler after Rx Rebleeding 30d	High vs Med risk: - DEP+ before 87.4% vs 42.3% - DEP+ after 27,4% vs 13,6% Ia vs Ib - Dep+ before 100% vs 46.7% - DEP+after 35,7% vs 0% Rebleeding 28,6% vs 0%	DEP improves risk stratification Ia has higher DEP+ and rebleeding rates than Ib
Camus APT 2016	Prospective observa		1264	Ulcer size	rebleeding	Rebleeding: 17.7% increasing with size	Ulcer size independent risk factor for adverse outcome

	tional						
Lolle Scand J 2016	Prospective Observational	Duodenal ulcer Gastric ulcer	20059		Death Reintervention	Bleeding from DU vs GU: - all-cause mortality 90d (OR) 1.47 (1.30-1.67); p < 0.001 - all-cause mortality 30d OR 1.60 (1.43-1.77); p < 0.001 - re-intervention: adjusted OR 1.86 (1.68-2.06); p < 0.001	Duodenal location has worse all cause mortality and reintervention rate

Authors	Study type	Patient group	(n)	Intervention	endpoint	Outcomes	Conclusions
Jensen AmJ Gastro 2017	RCT	Group Ib Group Ia+IIa+IIb	388 Ib 163 Ia+IIa+IIb 225	PPI or placebo	rebleeding	PPI reduced rebleding in Ia+IIa+IIb but not Ib (5.4% vs 4.9%, n.s) Ib had lower risk of rebleeding (4.9%) compared to Ia(22.5%), IIb(17.6%) or IIa(11.3%)	PPI not recommended after successful treatment in Ib
Kim KJG 2015 (Korean translated with Google)	Retrospective	IIb	Total 1101 IIb 126	Endoscopic therapy 84 PPI 42	Rebleeding Mortality All cause mortality	Rebleeding endo vs PPI: - 7.1% vs. 9.5%; p=0.641 Mortality endo vs ppi: - 1.2%vs10%;p=0.018 All-cause mortality endo vsPPI - 3.7% vs. 20.0%; p=0.005	FIIb was associated with a significant reduction in bleeding related mortality and all cause mortality compared with medical therapy alone
Jensen Gastro 2017	RCT	Multiple NVUGIB Subgroup: SRH	High risk (Ia, IIa, IIb) 53 Med risk	Standard Doppler guided intervention.	Rebleeding 30d	Standard vs DEP guided: - Ia 50% vs 28,6% n.s - IIa 25.9% vs 15.4% n.s - IIb 25% vs 0% n.s.	Doppler shows a significant overall 30d rebleeding decrease but its

			(Ib, IIc) 23	Repeat intervention if DEP+ after intervention		- Ia 18.8% vs 0% n.s - IIc 14.3% vs 0% n.s - Total 26.3% v11.1%,p=0.0214	not significant in a case by case basis. Limitation: n is very low
Kantowski Scan J Gastro 2018	Prospective		Ia 6 Ib 41 IIa 13	Standard 25 Doppler guided intervention 35	Rebleeding Surgery Mortality	Rebleeding standard vs DEP: - 52% vs 20%, p=0.013 Surgery std vs DEP: - 2%vs 26%, p=0.017	Use of DEP associated with lower rebleeding, surgery and mortality Limitation: most patients Ib that already has a lw rebleeding rate after Rx Results not grouped by SRH

Authors	Study type	Patient group	(n)	Intervention	endpoint	Outcomes	Conclusions
Nunoue J Clin Gastro 2015	Prospective Randomized	PUB randomized to Group Soft coagulation with forceps Group heater probe	111 Group S 56 Group H 55	Soft coagulation with forceps Heater probe	Primary hemostasis Rebleeding Complications	Group S vs H - Primary hemostasis 96% vs 67%, p<0.0001 - Rebleeding 0 vs 12% - Complications 0 vs 2	
Kim Endoscopy 2015	RCT	PUB randomized to Group APC: Injection + APC Group HFSC: Injection + HFSC	Total 151 Group APC: 75 Group HFSC: 76	Injection + APC Injection + HFSC	Hemostasis Rebleeding 30d Adv events Mortality	APC vs HFSC: - Hemostasis 96% vs 96%, n.s. - Rebleeding 6.7% vs 9.2%, n.s - AE 1.3 % vs. 2.6 %, n.s - Mortality 2.7 % vs. 2.6 %	Coagulation forceps not inferior to APC
Toka GIE 2019	Prospective Randomized	MHFSC Hemoclip	112 MHFSC 56 Hemoclip 56	Injection + MHFSC Injection + hemoclip	Hemostasis Rebleeding 7d Time to hemostasis	MHFSC vs Hemoclip: - Hemostasis 98,2 vs 80,4, p=0.004 - Rebleeding 3.6% vs 17.7%, p=0.04	MHFSC is more effective achieving initial hemostasis

					Admission AE	- Time 302 ± 87.8 vs 568 ± 140.4 seconds - Admission 3.50 ± 1.03 vs 4.37 ± 1.86 days - AE none	provides a shorter procedure time and a lower rebleeding rate compared with Hemoclips

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
1 .Baracat et Al Surg Endosc 2016:	Meta Analysis of RCTs: 28 trials,2988 patients	Adult patients, Peptic Ulcer Bleeding: High risk Endoscopic stigmata: (Forrest 1a/b:II a/b) Hemoclip,Injection,Thermal Methods monotherapy or combination :	Initial haemostasis, rebleeding, surgery, death	Clip v Inj: Rebleeding :(RD -0.13,95% CI -0.19 - -0.08) NNT 7 Surgery: (RD-0.05 95% CI -0.09 - - 0.01)NNT 20 Clip /INJ v INJ: Rebleeding:(RD –0.10 95% CI -0.018 - - 0.03) NNT 10 Surgery(RD -0.11 95% CI -0.18 - - 0.04) NNT 9 Thermal/INJ v Thermal Rebleeding: NNT of 9 (RD -0.11, 95 % CI -0.21 to-	Low number of studies some comparisons Heterogeneity of injectates	No significant differences in initial haemostasis between methods,or mono v dual therapy Superior rebleeding rate and need for surgery for clip compared to injection, No benefit of combination clip/injection compared to clip alone Dual therapy (thermal or clip)favoured over monotherapy if

				0.02) Thermal/INJ v INJ NNT of 12 (RD -0.08, 95 % CI -0.14 to -0.02) Rebleeding: Clip v Clip /INJ:NS difference all comparisons Thermal mono v endoclip Mono :NS all comparisons		injection used as one modality in reducing rebleeding rate/surgery,but only rebleeding rate if thermal monotherapy compared to combination thermal /Injection No difference in mortality between modalities
2. Shi et al. BMC Gastroenterology (2017) 17:55	Seventeen eligible studies,1939 patients,were included in the network meta-analysis.	Adult patients, Peptic Ulcer Bleeding: High risk Endoscopic stigmata: (Forrest 1a/b: II a)		The addition of mechanical therapy (OR 0.19, 95% CrI 0.07–0.52 and OR 0.10, 95% CrI 0.01–	Small study sizes Blinding not accurately reported in all	Confirms that combination therapy is superior in reducing rebleeding rate after peptic ulcer

		Injection of Epinephrine monotherapy compared to combination Epinephrine with either Mechanical or Thermal methods of heamostasis		0.50, respectively) after epinephrine injection significantly reduced the probability of rebleeding and surgery. Similarly, patients who received epinephrine plus thermal therapy showed a significantly decreased rebleeding rate (OR 0.30, 95% CrI 0.10–0.91), as well as a non-significant reduction in surgery (OR 0.47, 95% CrI 0.16–1.20). Although differing, epinephrine plus mechanical therapy did not	studies Hetrogeneity of number of gastric v duodenal ulcer bleeds in component studies	bleed when compared to Epinephrine monotherapy alone. Although trend to favour Epi plus mechanical method compared to Epi plus thermal this was not significant.

				provide a significant reduction in rebleeding (OR 0.62, 95% CrI 0.19–2.22) and surgery (OR 0.21, 95% CrI 0.03–1.73) compared to epinephrine plus thermal therapy.		

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
1.) Brandler J, Buttar N, Baruah A et al. Efficacy of Over-the-Scope Clips in Management of High-Risk Gastrointestinal Bleeding. Clin Gastroenterol Hepatol 2018; 16(5):690-696	Case series with pre-test/post-test outcomes (IV)	67 patients with a "high-risk gastrointestinal bleeding" treated with OTSC; HR-AO-lesions (HR-AO= "high risk of adverse outcome") 60 patients with a NVUGIB, 49 patients with an ulcer bleeding, 11 patients with a Forrest-Ia-bleeding, primary-OTSC in 49 patients, 60% of patients with antiplatelet therapy or anticoagulant therapy HR-AO-lesions concerning NVUGIB: visible vessel >2mm, localization in high risk vascular	Effect of OTSC on rebleeding rate, need for re-intervention within 30 days Identifying risk factors associated with OTSC failure	Technical success 100% "True OTSC success": no bleeding related to OTSC requiring re-intervention in 52 patients (81,3%) OTSC success: no bleeding within 30 days in 46 patients (71,8%) Complications: None Risk factors for rebleeding: History of CAD, history of abdominal aortic aneurysm repair,	Low patient number; Case series with pre-test/post-test outcomes; Data from a highly specified centre	OTSC is effective in primary therapy of HR-AO-lesions

		territory (gastroduodenal, left gastric), penetrating, excavated or fibrotic ulcer Forrest Ia-IIb		length of hospital stay (?)		
2.) Goelder S, Messmann H, Neuhaus L et al. Over-the-scope clip in peptic ulcer bleeding: clinical success in primary and secondary treatment and factors associated with treatment failure. Endoscopy International Open 2019; 07:E846-E854	Case series with pre-test/post-test outcomes (IV)	100 patients with a peptic ulcer bleeding treated with OTSC 12/6t-OTSC primary-OTSC in 66 patients, secondary-OTSC in 34 patients in 75% duodenal ulcers 51 patients with Forrest-Ia-bleedings, 23 patients with Forrest-Ib-	Effect of OTSC on rebleeding rate, need for re-intervention Successful hemostasis: no rebleeding immediately after OTSC placement Recurrent bleeding: retreatment of the target lesion after initial successful endoscopic treatment required	Primary-OTSC: Successful hemostasis in 90,9%, recurrent bleeding in 16,7% Secondary-OTSC: Successful hemostasis in 94,1%, recurrent bleeding in 21,9% Factors associated with OTSC failure: localization: posterior duodenal wall, OR 8,11 (1,89 – 56,94), no	Low patient number; Case series with pre-test/post-test outcomes;	OTSC is effective in primary therapy and in recurrent ulcer bleeding

		bleedings 44 patients using anticoagulants Median RS of 7		significant influence of anticoagulants Complications: not mentioned		

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
3.) Kobara H, Hirohito M, Tsutomu M et al. Over-the-scope-clips: A review of 1517 cases over 9 years. DOI: 10.1111/jgh.14402	Review of case series with pre-test/post-test outcomes (IV)	1517 OTSC cases in 30 articles between 2010 and 2018 559 OTSC applications in order of hemorrhage: Mentioned case series after 2014: - Richter-Schrag HJ et	Clinical success rate CSR in refractory bleeding	CSR in refractory bleeding: 473/559 (84,6%) Complications: Severe complications in 0,59% (9/1517 cases): stenosis, (micro-)perforation,	Analysis of case series No discrimination between upper and lower GI-bleeding No discrimination between primary-OTSC and	OTSC is effective in therapy of GI-bleeding

		al., 2016, s. Study Ref. 4.) - Wedi E et al., 2016, s. Study Ref. 5.)			secondary-OTSC	
4.) Richter-Schrag HJ, Thimme R, Glatz T et al. First-line endoscopic treatment with over-the-scope clips significantly improves the primary failure and rebleeding rates in high-risk gastrointestinal bleeding: A single-center experience with 100 cases. World J Gastroenterol 2016. 22(41): 9162-9171	Historical control study (III-3)	Freiburg group: 93 patients, 100 OTSC applications in different severe acute UGIB and LGIB lesions, 63 patients with a NVUGIB Rockall-Score <7 in 33 patients, Rockall-Score ≥7 in 30 patients Primary-OTSC in 39 patients, secondary-OTSC in 33 patients 56 patients with active bleeding	Outcome concerning primary failure, rebleeding, rebleeding compared to the "original" Rockall group Primary failure: continued rebleeding immediately after OTSC placement Rebleeding: In-hospital-rebleeding after primary hemostasis with	Primary failure, overall: Primary-OTSC: 4,9%, secondary-OTSC: 23,1% (p = 0,008) Rebleeding, overall: Primary-OTSC: 8,2%, secondary-OTSC: 28,2% (p = 0,008) Rebleeding events with a Rockall-Score ≥7: "original" Rockall group: 46,8%	Historical control study with a control group from 1996	OTSC is effective in therapy of NVUGIB, in this study especially as first line treatment of high-risk-NVUGIB OTSC treatment is more effective in preventing rebleeding than standard therapy

		Median RS of 7 29 patients using anticoagulants Control group: "original" Rockall group	OTSC Technical success: Successful placement of the OTSC on the target lesion	Freiburg group: 18,6% (p = 0,0003) Factors associated with rebleeding: Secondary-OTSC (p = 0,008), no significant influence of anticoagulants		
5.) Wedi E, Hochberger J, Gonzalez S et al. One hundred and one over-the-scope-clip applications for severe gastrointestinal bleeding, leaks and fistula. World J Gastroenterol 2016. 22(5): 1844-1853	Case series with pre-test/post-test outcomes (IV)	84 patients treated with 101 OTSC, 41 patients with severe NVUGIB (Forrest Ia – IIb, Hb <7 g/dl) 12/6t-OTSC Primary-OTSC in 28 patients, secondary-OTSC in 13 patients 12 patients with a Forrest-Ia-bleeding, 3 patients with a	CSR in upper GI bleeding	CSR in upper GI bleeding: 35/41 (85,36%)	Low patient number; Case series with pre-test/post-test outcomes; definition of severe NVUGIB	OTSC is effective in primary therapy

		Forrest-Ib-bleeding				

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
6.) Asokkumar R, Ngu JH, Soetikno R et al. Use of over-the-scope-clip (OTSC) improves outcomes of high-risk adverse outcome (HR-AO) non-variceal upper gastrointestinal bleeding (NVUGIB). Endoscopy International Open 2018; 06:E789-E796.	Historical control study, prospective (III-3)	18 patients with 19 bleeding lesions treated with OTSC Primary-OTSC in 10 patients, secondary-OTSC in 9 patients 10 patients with an active bleeding 10 patients using anticoagulants Median RS 6,7 ± 1,3 n = 6: high-risk n = 12: intermediate-risk	Technical success Complete hemostasis: complete cessation of bleeding after OTSC placement Clinical success: no rebleeding within 30 days after placement of OTSC	Initial technical failure in 3 cases (!) Incomplete hemostasis after OTSC deployment in 6 patients (!), after applying additional techniques complete hemostasis was achieved Clinical success: 100% Comparison to the “original” Rockall group: Rebleeding rate significantly lower	Very low patient number; Case series with pre-test/post-test outcomes; control group from 1996;	OTSC is effective in primary therapy of HR-AO-lesions, but it can be tricky

		n = 1: low-risk HR-AO-lesions concerning NVUGIB: Bleeding due to a large-caliber (>2 mm) artery, localization within the major arterial territories (left gastric, gastroduodenal artery), bleeding from deeply penetrating, excavated or fibrotic ulcers with high-risk stigmata with risk of perforation when performing thermal therapy, bleeding when endoscopic therapy using mechanical approach or radiological approach was		in the high-risk-group (0% vs. 53%) and the intermediate-risk-group (0% vs. 24%) Comparison to the second control group: intermediate-to-high-risk: Rebleeding rate 0% vs. 21%, low-risk: n = 1: no statistical statement is to be made		

		unsuccessful, 20 – 40% complications, using standard therapy, Barkun AN et al., Gastrointest Endosc 2009; 69: 786-799 Control group: "original" Rockall group: Low-risk, n = 1206, RS ≤3, intermediate-risk, n = 1560, RS 4 – 7, high-risk, n = 190, RS ≥ 8 Second historical control group: n = 52, standard therapy, low-risk, n = 23, RS ≤ 3, intermediate-to-high risk, n = 29, RS ≥ 4, Stanley AJ				

		et al. BMJ 2017; 356:i6432				
7.) Schmidt A, Caca K, Goelder S et al. Over-the-Scope Clips Are More Effective Than Standard Endoscopic Therapy for Patients With Recurrent Bleeding of Peptic Ulcers. Gastroenterology 2018; 155:674-686.	RCT (II)	66 patients with recurrent ulcer bleeding after an initial successful hemostasis OTSC group: n = 33, active bleeding: n = 23, patients using anticoagulants: n = 15, RS ≥7: n = 19 Standard therapy group: n = 33 (TTSC: n = 31), cross over to OTSC is possible, active bleeding: n = 22, patients using anticoagulants: n = 12, RS ≥ 7: n = 19	Further bleeding: a composite endpoint of a persistent bleeding despite endoscopic therapy according to protocol or recurrent bleeding within 7 days after successful hemostasis Secondary endpoints: mortality, necessity of surgical or angiographic rescue therapy, …	Persistent bleeding: OTSC group: 2 patients, 6,0%, standard therapy group: 14 patients, 42,4%, p = 0,001 Recurrent bleeding within 7 days: OTSC group: 3 patients, 9,1%, standard therapy group: 5 patients, 16,1%, p = 0,468 Further bleeding as a composite endpoint: OTSC group: 5 patients, 15,2%, standard therapy	None	OTSC treatment as standard therapy in recurrent ulcer bleeding

				group: 19 patients, 57,6%, p = 0,001, CI 21,6 – 63,2 No significant differences in secondary endpoints		
8.) Wedi E, Richter-Schrag HJ, Fischer A et al. Multicenter evaluation of first-line endoscopic treatment with the OTSC in acute non-variceal upper gastrointestinal bleeding and comparison with the Rockall cohort: the FLETRock study. Surg Endosc 2017; 32(1): 307-314.	Historical control study (III-3)	FLET cohort: 118 patients Primary-OTSC: n = 121 Median RS of 7 65,3% were under antiplatelet therapy or anticoagulant therapy Low-risk: RS ≤3, n = 3,	Primary clinical success: hemostasis by OTSC alone Secondary clinical success: OTSC in combination with adjunctive measures Mortality in comparison with the “original” Rockall group Rebleeding rates in comparison	No technical failure Primary clinical success in 90,8% Secondary clinical success in 1,7% Clinical failure in 7,5% Presence of antiplatelet or anticoagulant therapy with no influence of	Low patient number; Case series with pre-test/post-test outcomes; control group from 1996;	Forrest-Ia-bleedings at higher risk of rebleeding Especially in the high-risk-group with RS ≥8 primary-OTSC seems to be effective

		moderate-risk: RS 4 – 7, n = 60, high-risk: RS ≥8, n = 55 Control group: “original” Rockall group	with the “original” Rockall group	outcome Forrest-Ia-bleedings at higher risk of rebleeding (11 patients from 31 patients) RS ≥8, n = 55: In-hospital-mortality overall: 29,1% (16 of 55 patients), bleeding-associated mortality: 10,9% (6 of 55 Patients, CI 4,1 – 22,2), predicted: 27,9%, p = 0,011 Rebleeding: 21,4% (12 of 56 clips, CI 11,6 – 34,4), predicted: 53,2%, p < 0,001		

9.) Manta R, Galloro G, Mangiafico S et al. First-line endoscopic treatment with over-the-scope clips in patients with either upper or lower gastrointestinal bleeding: a multicenter study. Endoscopy International Open 2018; 06:E1317-E-1321.	Case series with pre-test/post-test outcomes (IV)	286 patients in eleven tertiary endoscopic referral centres 112 patients with antithrombotic therapy (39,2%) 214 patients with NVUGIB Primary-OTSC 190 patients with active bleeding, 58 patients with a Forrest-Ia-bleeding, 73 patients with a Forrest-Ib-bleeding	Technical success Primary hemostasis: defined as bleeding stopping without additional endoscopic treatments Early rebleeding rate within 24 hours Delayed rebleeding rate within 30 days Management with non-endoscopic procedures following endoscopic failure	Technical success in 97,1% (208 patients from 214) Primary hemostasis in 97,1% (202 patients from 208) Early rebleeding rate 4,4% (9 patients from 202) Delayed rebleeding rate 0%	Low patient number; Case series with pre-test/post-test outcomes	Technical failure in six patients with ulcers in the fundus or posterior wall duodenal bulb Management of failure patients: Technical failure, primary hemostasis failure, early rebleeding

10.) Lamberts R, Halm U, Koch A et al. Use of over-the-scope-clips (OTSC) for hemostasis in gastrointestinal bleeding in patients under antithrombotic therapy. Endoscopy International Open 2017; 05:E324-E330.	Case series with pre-test/post-test outcomes (IV)	75 patients 68 patients with NVUGIB Primary-OTSC in 58,7%, Secondary-OTSC in 41,3% 69 patients with antiplatelet therapy, inhibitors of plasmatic coagulation or both Active bleeding in 51 patients				
11.) Chandrasekar VT, Sharma P, Desai M et al. Efficacy and safety of over-the-scope clips for gastrointestinal bleeding: a systematic review and metaanalysis.	Meta-analysis of 21 studies	n = 851, n = 687 (80,7%) with NVUGIB	Primary technical success: successful deployment of the clip over the lesion Primary clinical	Definitive hemostasis rate overall 87,8% (95%CI 83,7% - 92%), definitive hemostasis rate NVUGIB 86,6% (95%CI 81,9% - 91,3%), median	Only 8 studies with n >100, only 1 RCT Data from Augsburg (n = 100) not	The advantage here: investigation of the other trials I did not mention before Conclusion: primary OTSC:

Endoscopy 2019; 51:941-949			success: rate of hemostasis achieved after technical success Rebleeding rate: rate of patients with rebleeding after primary clinical success Definitive hemostasis: successful primary hemostasis, no rebleeding as *primary outcome*	follow-up 56 days Primary technical success rate 97,8% (95%CI 96,7% - 98,9%) Rebleeding rate 10,3% (95%CI 6,5% - 14,1%) Primary-OTSC failure rate 9% (95%CI 5,2% - 12,8%) Secondary-OTSC failure rate 26% (95%CI 16,1% - 36,0%) Only 2 adverse events in 851 reported (!)	included	large ulcers ≥ 2 cm, Forrest class 1 ulcers, for patients, who are on antithrombotic therapy

Study Ref.	Study type	Patient group	Key outcomes	Key results
1. Original article, pubmed Kantowski, M, Schoepfer AM, Settmacher U, Stallmach A, Schmidt C. 2018 Scandinavian Journal of gastroenterology German study	Retrospective Single center Comparative cohort study Patient were allocated in ED (Endoscopic Doppler) or ND (No Doppler) based on where they had the endoscopy. The endoscopic unit has one endoscopic suite with Doppler, the other one did not have the Doppler. There was no randomization or matching Endoscopies performed by only one experienced endoscopist The study period is not mentioned in the	High risk peptic bleeding ulcer Patients of at least 18 years of age, with clinical signs of bleeding (hematemesis, hematochezia, oe melena), classified as Forrest I-IIa and a Rockall score of 5 or higher. Total of 60 patients 35 ED group 25 ND group Two groups were comparable for ulcer size, localization, Forrest classification,	- Doppler technical success - Rebleeding rate - Surgery rate - Mortality	- Doppler technical success: 34/35 patients - Rebleeding rate ND group: 52% (13/25) ED group: 20% (7/35) p=0.01 - Surgery rate ND group: 24% (6/25) ED group: 3% (1/35) p=0.012 - Mortality Significantly lower in the ED group compared to the ND group (1/35 vs. 6/25, p Value=0.017), while all-cause mortality not significantly different between the two groups (7/35 vs 8/25, p value =0.367)

	article			
Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**
2. RCT Jensen DM ; Kovacs TOG, Ohning GV, Ghassemi K, Machicado GA, Dulai GS, Sedarat A, Jutabha R, Gornbein J Gastroenterology, 2017 USA study	Randomized controlled trial Single-blind study : Endoscopists were not blinded. Patients, families and managing teams were blinded 2 referral centers 8 doppler-trained endoscopists sample size calculation (estimation of 75 patients per group)	148 patients All stigmata of recent haemorrhage (SRH) were included (Forrest classification), even low SRH Severe non-variceal upper GI bleeding Clinically defined as presence of hematemesis, melena or hematochezia, signs or symptoms of hypovolemia (tachycardia, hypotension, othostatic change in pulse and blood pressure, dizziness or syncope) along with hemoglobine decrease from baseline of 2grams per decilitre or more or transfusion of 1 or more units of RBC 125 ulcers, 19 Dieulafoy's lesions, 4 Mallory Weiss	- Primary outcome: 30-day rebleeding rate - Secondary outcomes: complications, death, need for transfusions, surgery, or angiography	One difference at inclusion between 2 groups: more aspirin users in Doppler group (54.2% vs. 36.8%, p=0.034). <u>Significant difference in rates of lesion rebleeding</u> <u>26.3% control group vs. 11.1% Doppler group; p=0.0214.</u> Odds ratio for rebleeding with Doppler monitoring was 0.35 (95%CI 0.143-0.8565). <u>However, for each individual stigmata of recent haemorrhage (SRH), there were no significant difference in rebleed rates</u> No significant difference in rates of surgery and major complications (5.3% control group vs. 0% Doppler group, p=0.048), and in angiograohy for rebleeding, length of hospitalization, intensive care unit stay, need for transfusions, or mortality Strong association between residual blood flow after endoscopic hemostasis and rebleeding rates 8 of 9 (88.9%) patients in the Doppler

		Randomization n=76 control group n=72 doppler group All received Pantoloc infusion x 72 hours, then PPI po BIDx 30 d		group with residual blood flow that was not obliterated later rebled, compared with 0 of 8 (0%) in patients whose residual blood flow was obliterated with additional hemostasis (p=0.0004, Fisher exact test).
Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**
3. cost-effectiveness study AN Barkun, V Adam, RC Wong Clin Gastroenterol Hepatol. 2019	USA cost-effectiveness study based on RCT A decision tree representing the choice between Doppler probe examination (DPE) and traditional endoscopic visual assessment (TEA) approaches for patients undergoing an index endoscopy for active nonvariceal upper gastrointestinal bleeding.	Probabilities were provided by 2 previous randomized trials. 1)Jensen et al. 2017 (see above) and 2) Kohler B, Maier M, Benz C, et al. Acute ulcer bleeding. A prospective randomized trial to compare Doppler and Forrest classifications in endoscopic diagnosis and therapy. Dig Dis Sci 1997;42:1370–1374.	- Cost of the 2 different approaches with or without Doppler The adopted time horizon was 30 days after the index Endoscopy Costs expressed in 2017 US dollars A third-party payer perspective adopted	DPE is more efficacious 92.6% of patients avoiding rebleeding vs 78.6% for TEA and less expensive ($8502 vs $9104 for TEA).

	Deterministic and probabilistic sensitivity analyses			

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
1.) Brandler J, Buttar N, Baruah A et al. Efficacy of Over-the-Scope Clips in Management of High-Risk Gastrointestinal Bleeding. Clin Gastroenterol Hepatol 2018; 16(5):690-696	Case series with pre-test/post-test outcomes (IV)	67 patients with a "high-risk gastrointestinal bleeding" treated with OTSC; HR-AO-lesions (HR-AO= "high risk of adverse outcome") 60 patients with a NVUGIB, 49 patients with an ulcer bleeding, 11 patients with a Forrest-Ia-bleeding, primary-OTSC in 49 patients, 60% of patients with antiplatelet therapy or anticoagulant therapy HR-AO-lesions concerning NVUGIB: visible vessel >2mm, localization in high risk vascular	Effect of OTSC on rebleeding rate, need for re-intervention within 30 days Identifying risk factors associated with OTSC failure	Technical success 100% "True OTSC success": no bleeding related to OTSC requiring re-intervention in 52 patients (81,3%) OTSC success: no bleeding within 30 days in 46 patients (71,8%) Complications: None Risk factors for rebleeding: History of CAD, history of abdominal aortic aneurysm repair,	Low patient number; Case series with pre-test/post-test outcomes; Data from a highly specified centre	OTSC is effective in primary therapy of HR-AO-lesions

		territory (gastroduodenal, left gastric), penetrating, excavated or fibrotic ulcer Forrest Ia-IIb		length of hospital stay (?)		
2.) Goelder S, Messmann H, Neuhaus L et al. Over-the-scope clip in peptic ulcer bleeding: clinical success in primary and secondary treatment and factors associated with treatment failure. Endoscopy International Open 2019; 07:E846-E854	Case series with pre-test/post-test outcomes (IV)	100 patients with a peptic ulcer bleeding treated with OTSC 12/6t-OTSC primary-OTSC in 66 patients, secondary-OTSC in 34 patients in 75% duodenal ulcers 51 patients with Forrest-Ia-bleedings, 23 patients with Forrest-Ib-	Effect of OTSC on rebleeding rate, need for re-intervention Successful hemostasis: no rebleeding immediately after OTSC placement Recurrent bleeding: retreatment of the target lesion after initial successful endoscopic treatment required	Primary-OTSC: Successful hemostasis in 90,9%, recurrent bleeding in 16,7% Secondary-OTSC: Successful hemostasis in 94,1%, recurrent bleeding in 21,9% Factors associated with OTSC failure: localization: posterior duodenal wall, OR 8,11 (1,89 – 56,94), no	Low patient number; Case series with pre-test/post-test outcomes;	OTSC is effective in primary therapy and in recurrent ulcer bleeding

		bleedings 44 patients using anticoagulants Median RS of 7		significant influence of anticoagulants Complications: not mentioned		

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
3.) Kobara H, Hirohito M, Tsutomu M et al. Over-the-scope-clips: A review of 1517 cases over 9 years. DOI: 10.1111/jgh.14402	Review of case series with pre-test/post-test outcomes (IV)	1517 OTSC cases in 30 articles between 2010 and 2018 559 OTSC applications in order	Clinical success rate CSR in refractory bleeding	CSR in refractory bleeding: 473/559 (84,6%) Complications:	Analysis of case series No discrimination between upper and lower GI-	OTSC is effective in therapy of GI-bleeding

		of hemorrhage: Mentioned case series after 2014: - Richter-Schrag HJ et al., 2016, s. Study Ref. 4.) - Wedi E et al., 2016, s. Study Ref. 5.)		Severe complications in 0,59% (9/1517 cases): stenosis, (micro-)perforation,	bleeding No discrimination between primary-OTSC and secondary-OTSC	
4.) Richter-Schrag HJ, Thimme R, Glatz T et al. First-line endoscopic treatment with over-the-scope clips significantly improves the primary failure and rebleeding rates in high-risk gastrointestinal bleeding: A single-center experience with 100 cases. World J Gastroenterol 2016. 22(41): 9162-9171	Historical control study (III-3)	Freiburg group: 93 patients, 100 OTSC applications in different severe acute UGIB and LGIB lesions, 63 patients with a NVUGIB Rockall-Score <7 in 33 patients, Rockall-Score ≥7 in 30 patients Primary-OTSC in 39 patients, secondary-	Outcome concerning primary failure, rebleeding, rebleeding compared to the "original" Rockall group Primary failure: continued rebleeding immediately after OTSC placement	Primary failure, overall: Primary-OTSC: 4,9%, secondary-OTSC: 23,1% (p = 0,008) Rebleeding, overall: Primary-OTSC: 8,2%, secondary-OTSC: 28,2% (p = 0,008)	Historical control study with a control group from 1996	OTSC is effective in therapy of NVUGIB, in this study especially as first line treatment of high-risk-NVUGIB OTSC treatment is more effective in preventing rebleeding than standard

		OTSC in 33 patients 56 patients with active bleeding Median RS of 7 29 patients using anticoagulants Control group: "original" Rockall group	Rebleeding: In-hospital-rebleeding after primary hemostasis with OTSC Technical success: Successful placement of the OTSC on the target lesion	Rebleeding events with a Rockall-Score ≥7: "original" Rockall group: 46,8% Freiburg group: 18,6% (p = 0,0003) Factors associated with rebleeding: Secondary-OTSC (p = 0,008), no significant influence of anticoagulants		therapy
5.) Wedi E, Hochberger J, Gonzalez S et al. One hundred and one over-the-scope-clip applications for severe gastrointestinal bleeding, leaks and fistula. World J Gastroenterol 2016. 22(5): 1844-1853	Case series with pre-test/post-test outcomes (IV)	84 patients treated with 101 OTSC, 41 patients with severe NVUGIB (Forrest Ia – IIb, Hb <7 g/dl) 12/6t-OTSC Primary-OTSC in 28 patients, secondary-	CSR in upper GI bleeding	CSR in upper GI bleeding: 35/41 (85,36%)	Low patient number; Case series with pre-test/post-test outcomes; definition of severe NVUGIB	OTSC is effective in primary therapy

		OTSC in 13 patients 12 patients with a Forrest-Ia-bleeding, 3 patients with a Forrest-Ib-bleeding				

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
6.) Asokkumar R, Ngu JH, Soetikno R et al. Use of over-the-scope-clip (OTSC) improves outcomes of high-risk adverse outcome (HR-AO) non-variceal upper gastrointestinal bleeding (NVUGIB). Endoscopy International Open 2018; 06:E789-E796.	Historical control study (III-3)	18 patients with 19 bleeding lesions treated with OTSC Primary-OTSC in 10 patients, secondary-OTSC in 9 patients 10 patients with an active bleeding 10 patients using anticoagulants	Technical success Complete hemostasis: complete cessation of bleeding after OTSC placement Clinical success: no rebleeding within 30 days after placement of OTSC	Initial technical failure in 3 cases (!) Incomplete hemostasis after OTSC deployment in 6 patients (!), after applying additional techniques complete hemostasis was achieved Clinical success: 100%	Very low patient number; Case series with pre-test/post-test outcomes; control group from 1996;	OTSC is effective in primary therapy of HR-AO-lesions, but it can be tricky

		Median RS 6,7 ± 1,3 n = 6: high-risk n = 12: intermediate-risk n = 1: low-risk HR-AO-lesions concerning NVUGIB: Bleeding due to a large-caliber (>2 mm) artery, localization within the major arterial territories (left gastric, gastroduodenal artery), bleeding from deeply penetrating, excavated or fibrotic ulcers with high-risk stigmata with risk of perforation when performing		Comparison to the “original” Rockall group: Rebleeding rate significantly lower in the high-risk-group (0% vs. 53%) and the intermediate-risk-group (0% vs. 24%) Comparison to the second control group: intermediate-to-high-risk: Rebleeding rate 0% vs. 21%, low-risk: n = 1: no statistical statement is to be made		

		thermal therapy, bleeding when endoscopic therapy using mechanical approach or radiological approach was unsuccessful, 20 – 40% complications, using standard therapy, Barkun AN et al., Gastrointest Endosc 2009; 69: 786-799 Control group: "original" Rockall group: Low-risk, n = 1206, RS ≤3, intermediate-risk, n = 1560, RS 4 – 7, high-risk, n = 190, RS ≥ 8 Second historical				

		control group: n = 52, standard therapy, low-risk, n = 23, RS ≤ 3, intermediate-to-high risk, n = 29, RS ≥ 4, Stanley AJ et al. BMJ 2017; 356:i6432				
7.) Schmidt A, Caca K, Goelder S et al. Over-the-Scope Clips Are More Effective Than Standard Endoscopic Therapy for Patients With Recurrent Bleeding of Peptic Ulcers. Gastroenterology 2018; 155:674-686.	RCT (II)	66 patients with recurrent ulcer bleeding after an initial successful hemostasis OTSC group: n = 33, active bleeding: n = 23, patients using anticoagulants: n = 15, RS ≥7: n = 19 Standard therapy group: n = 33 (TTSC: n = 31),	Further bleeding: a composite endpoint of a persistent bleeding despite endoscopic therapy according to protocol or recurrent bleeding within 7 days after successful hemostasis Secondary endpoints: mortality, necessity of surgical or	Persistent bleeding: OTSC group: 2 patients, 6,0%, standard therapy group: 14 patients, 42,4%, p = 0,001 Recurrent bleeding within 7 days: OTSC group: 3 patients, 9,1%, standard therapy group: 5 patients, 16,1%, p = 0,468	None	OTSC treatment as standard therapy in recurrent ulcer bleeding

		cross over to OTSC is possible, active bleeding: n = 22, patients using anticoagulants: n = 12, RS ≥ 7: n = 19	angiographic rescue therapy, …	Further bleeding as a composite endpoint: OTSC group: 5 patients, 15,2%, standard therapy group: 19 patients, 57,6%, p = 0,001, CI 21,6 – 63,2 No significant differences in secondary endpoints		
8.) Wedi E, Richter-Schrag HJ, Fischer A et al. Multicenter evaluation of first-line endoscopic treatment with the OTSC in acute non-variceal upper gastrointestinal bleeding and comparison with the Rockall cohort: the FLETRock study. Surg	Historical control study (III-3)	FLET cohort: 118 patients Primary-OTSC: n = 121 Median RS of 7 65,3% were under antiplatelet	Primary clinical success: hemostasis by OTSC alone Secondary clinical success: OTSC in combination with adjunctive measures	No technical failure Primary clinical success in 90,8% Secondary clinical success in 1,7% Clinical failure in	Low patient number; Case series with pre-test/post-test outcomes; control group from 1996;	Forrest-Ia-bleedings at higher risk of rebleeding Especially in the high-risk-group with RS ≥8 primary-OTSC seems to be effective

Endosc 2017; 32(1): 307-314.		therapy or anticoagulant therapy Low-risk: RS ≤3, n = 3, moderate-risk: RS 4 – 7, n = 60, high-risk: RS ≥8, n = 55 Control group: “original” Rockall group	Mortality in comparison with the “original” Rockall group Rebleeding rates in comparison with the “original” Rockall group	7,5% Presence of antiplatelet or anticoagulant therapy with no influence of outcome Forrest-Ia-bleedings at higher risk of rebleeding (11 patients from 31 patients) RS ≥8, n = 55: In-hospital-mortality overall: 29,1% (16 of 55 patients), bleeding-associated mortality: 10,9% (6 of 55 Patients, CI 4,1 – 22,2), predicted: 27,9%,		

				p = 0,011 Rebleeding: 21,4% (12 of 56 clips, CI 11,6 – 34,4), predicted: 53,2%, p < 0,001		
9.) Manta R, Galloro G, Mangiafico S et al. First-line endoscopic treatment with over-the-scope clips in patients with either upper or lower gastrointestinal bleeding: a multicenter study. Endoscopy International Open 2018; 06:E1317-E-1321.	Case series with pre-test/post-test outcomes (IV)	286 patients in eleven tertiary endoscopic referral centres 112 patients with antithrombotic therapy (39,2%) 214 patients with NVUGIB Primary-OTSC 190 patients with active bleeding, 58 patients with a Forrest-Ia-bleeding, 73	Technical success Primary hemostasis: defined as bleeding stopping without additional endoscopic treatments Early rebleeding rate within 24 hours Delayed rebleeding rate within 30 days	Technical success in 97,1% (208 patients from 214) Primary hemostasis in 97,1% (202 patients from 208) Early rebleeding rate 4,4% (9 patients from 202) Delayed rebleeding rate 0%	Low patient number; Case series with pre-test/post-test outcomes	Technical failure in six patients with ulcers in the fundus or posterior wall duodenal bulb Management of failure patients: Technical failure, primary hemostasis failure, early rebleeding

		patients with a Forrest-Ib-bleeding	Management with non-endoscopic procedures following endoscopic failure			
10.) Lamberts R, Halm U, Koch A et al. Use of over-the-scope-clips (OTSC) for hemostasis in gastrointestinal bleeding in patients under antithrombotic therapy. Endoscopy International Open 2017; 05:E324-E330.	Case series with pre-test/post-test outcomes (IV)	75 patients 68 patients with NVUGIB Primary-OTSC in 58,7%, Secondary-OTSC in 41,3% 69 patients with antiplatelet therapy, inhibitors of plasmatic coagulation or both Active bleeding in 51 patients				

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation
1. Using Hemospray Improves the Cost-effectiveness Ratio in the Management of Upper Gastrointestinal Nonvariceal Bleeding Barkun A N	compared the cost-effectiveness of traditional recommended endoscopic hemostatic therapies and Hemospray alone or in combination when treating nonvariceal upper gastrointestinal bleeding (NVUGIB). Costs in 2014 US$ were based on the US National Inpatient Sample.	A decision tree of patients with NVUGIB assessed 4 possible treatment strategies: traditional therapy alone (T), Hemospray alone (H), traditional therapy completed by Hemospray if needed (T+H), or Hemospray completed by traditional therapy if needed (H+T).	Patients flow through the decision model until the final health state of having rebled (failure) or not (success) is reached.	T+H was more efficacious (97% avoiding rebleeding) and less expensive (average cost per patient of US$9150) than all other approaches. The second most costeffective approach was H+T (5.57% less effective and US$635 more per patient). Sensitivity analyses showed T+H followed by a strategy of H+T remained more cost-effective than H or T alone.	US healthcare costs Uncertainty of benefit in disease subgroup Limited high quality outcomes data in AUGIB for Hemospray Death no included in outcome analysis Assumes costs comparable to embolization as gold standard to achieve hemostasis Relies on DRG data,uncertain how to extrapolate to individual decision making
2. Comparison of Hemospray and Endoloot for the	Single centre retrospective cohort	Study of short term (ST-within 72 h-) and long term (LT-within	Study compared the rate of successful initial hemostasis ,	HP was applied a total of 239 times in	No randomisation or clear inclusion

treatment of gastrointestinal bleeding Vitali F et Al	study	30 d-) success for achieving hemostasis with HP (hemostatic podwers)and to directly compare the two agents Hemospray (HS) and Endoclot (EC).	rebleeding and mortality rates at 1 month,also complications	154 patients Clinical FU for at least one month was performed in 134 patients (87%) with a mean FU of 3.2 SD 5.5 mo (range 1-29). in 20 patients FU was not completed as they died from other causes than GI bleeding within 30 d after the first HP application Overall ST success was achieved in 125 patients (81%) and LT success in 81 patients (67%).	/exclusion criteria or information on sequential treatment allocation not given HP used prophylactically in some patients at high risk of bleeding Majority Forrest 1b lesions but some low risk Forrest III included (4%) Incomplete follow up data in 20 patients due to deaths

				Re-bleeding occurred in 27% of all patients. In 72 patients (47%), HP was applied as a salvage hemostatic therapy, here ST and LT success were 81% and 64%, with re-bleeding in 32%. As a primary hemostatic therapy, ST and LT success were 82% and 69%, with re-bleeding occurring in 22%. Perforation occurred in1.3% HS patents	
3. Randomized controlled trial of hemostatic powder versus endoscopic clipping for	Prospective single blind Randomised trial	Study of the use of TC-325 (associated with epinephrine injection) compared with the combined	Study compared the rate of successful initial hemostasis , rebleeding and mortality rates	Thirty-nine patients enrolled. Peptic ulcer was the most frequent etiology.	Small numbers/pilot study Epinephrine injected in

non-variceal upper gastrointestinal bleeding Baracat F et Al		technique of endoscopic clipping and epinephrine injection for the treatment of patients with NVUGIB		Primary hemostasis was achieved in all Hemospray cases and in 90% of Hemoclip group (p = 0.487). Five patients in Hemospray group underwent an additional hemostatic procedure during second-look endoscopy, while no patient in the Hemoclip group needed it (p = 0.04). Rebleeding, emergency surgery and mortality rates were similar in both groups. No toxicity, allergy events, or	hemospray group after hemospray,?targetted? non standard use epinephrine between groups The majority of patients presented with oozing bleeding (35/39–89.7%). Therefore cannot exptrapolate to Forrest 1a bleeding Non blinded decision making during second look endoscopy, non bleeding high risk stigmata in Hemospray group caused second intervention

				gastrointestinal obstruction signs were observed in Hemospray group.	
4. Outcomes from an international multicenter registry of patients with acute gastrointestinal bleeding undergoing endoscopic therapy with Hemospray Alzoubaidi D et Al	International disease registry Non cohort study	314 cases in 12 international centres Computerised database entry 167/314 patients (53%) peptic ulcer disease Forrest 1b most frequent lesion reported 100/167.	Study compared the rate of successful initial hemostasis , rebleeding and mortality rates	The rate of immediate hemostasis (89.5%),rebleeding (10.3%) 7-day and 30-day mortality 11.5% and 20.1% respectively	No randomisation or sequential selection Multiple indications ,cancer bleeds over represented? Selection bias Self reported /verified outcomes
5. Effectiveness of the polysaccharide hemostatic powder in non-variceal upper gastrointestinal bleeding: Using propensity score matching	Prospective,single centre sequential cohort and case control (after matching using Propensity scoring for GBS/Forrest classification)	40 patients with UGIB treated with PHP(endoclot) therapy between April 2016 and January 2017 (PHP group) and 303	Study compared the rate of successful hemostasis and the rebleeding between the two groups after as well as before propensity score matching using the	The rate of immediate hemostasis and 7-day and 30-day rebleeding were also similar in the two groups before and	More peptic ulcers in conventional therapy group (43.2% vs 75.5% for PHP vs conventional therapy), prevalence of

Park JC et Al	Forrest I/IIa included	patients with UGIB treated with conventional therapy between April 2012 and October 2014 Thirty patients treated with the PHP and 60 patients treated with conventional therapy were included in the matched groups.	Glasgow– Blatchford score and Forrest classification. Results:	after matching. After PS matching, the 7-day rebleeding rate remained similar between the groups (3.3% vs 3.3% for PHP vs conventional therapy group, respectively; P $\geq$ 0.999). Moreover, the 30-day rebleeding rates between two groups also did not show significant difference (3.3% vs 8.3% for PHP vs conventional therapy group, respectively; P = 0.180). No complication reported in using	tachycardia (heart rate over 100 beats per minute) was higher in the conventional therapy group, both before and after PS matching (P = 0.004 and P = 0.016, respectively). GBS higher in conventional group therefore groups not immediately comparable,corrected after matching. Small sample size Retrospective analysis of prospectively collected data, very low rebleeding rate with either modalities

				PHP Sequential time periods for enrollment	
6. Early clinical experience of the safety and efficacy of EndoClot in the management of non-variceal upper gastrointestinal bleeding Beg S et Al	Single centre ,retrospective cohort study	EndoClot was used in 21 patient of 173 AUGIB patients rebleeding after endoscopic therapy,(43/173 only received monotherapy) Standard endotherapy plus EndoClot was required to achieve hemostasis in 21 patients: 2nd agent in 7 cases, 3rd agent in 9 cases, 4th agent in 5 cases.	End points of this study included immediate hemostasis, 30-day rebleed rate, 30- day mortality rate, and adverse events.	Immediate hemostasis achieved in all cases, a 30-day rebleed rate of 4.8% (95% confidence interval [95 %CI]–4.34% to 3.94 %), and a 30-day mortality rate of 19.0% (95 %CI 2.29%–35.91 %). Fisher's exact test demonstrated no significant difference between their 30-day mortality rate (P=0.51) and rebleed rate (P=0.31) and those of the patients	Only 14/21 pts peptic ulcer bleeds Different hierarchy of when endoclot used Non randomised/blinded No details of how data on outcomes collected

		Rebleed: 4.8% Mortality: 19.0%		treated with standard endoscopic hemostatic techniques.	
7. Results of a EndoClot Polysaccharide Hemostatic System in Nonvariceal Gastrointestinal Bleeding Prospective Multicenter Observational Pilot Study Preiss_JC et Al	prospective observational pilot cohort study	Patients with acute GIB Seventy patients with acute GI bleeding were recruited into the study. Forrest IB, 38/58, (66%),	Efficacy of endoclot haemostasis assessed at 72/h and 1 week	Eighty-three percent (58/70) of the patients had upper and 17% (12/70) had lower GI bleeding. In the upper GI tract treatment success was achieved in 64% (30/47, 95% confidence interval, 50%-76%) after primary use and in all patients, when used after established techniques had failed (95% confidence interval, 70%-100%).	Non randomised,non blinded No inclusion/exclusion criteria Short follow up(72h)

Author, publication year , journal	Country	Study Objective	Participants/ Setting	Intervention	Outcome	Study Type	Results	Conclusion
Marya et al, Jan 2019, GIE	USA	To asses the benefits of deployment of a VCE soon after admission in the management of patients presenting with melena, hematochezia, or severe anemia compared with standard of care management.	Patients presented to ER or admitted to ward with non-hematemesis UGIB.	Patients were randomly assigned to early capsule arm or standard of care.	The rate of localization of bleeding during hospitalizatio n.	Parallel, randomiz ed, controlled trial.	Eighty-seven patients were included in this study: 45 randomized to the standard of care arm and 42 to the early capsule arm. A bleeding source was localized in 64.3% of the patients in the early capsule arm and in 31.1% of the patients in the standard of care arm ($P < .01$).	Early capsule endoscopy is a safe and effective alternative for the detection of the source of bleeding.
Robles et al, 2015, dig endo	Mexico	To evaluate emergency DBE and capsule endoscopy (CE) in patients with overt OGIB.	Patients who had CE and DBE due to OGIB from 2004 to 2014.	Patients with high suspicion of active OGIB were given CE If. The fresh blood was seen within 100min an emergent anterograde DBE was performed If fresh blood was seen after 100min then a	Analyzing the feasibility of this combined approach.	Retrospec tive study	Dieulafoy's lesion (DL; n = 11, 40.7%), angioectasia (n = 7, 25.9%), tumors (n = 4, 14.8%), diverticulum (n = 3, 11.1%), ulcers (n = 2, 7.4%). We diagnosed 23 lesions amenable to endoscopic hemostasis and successfully treated 21 of them (77.8%). DL detection rate was statistically higher in the emergency DBE group	Combined approach with RT viewing by CE is especially useful to identify recurrent bleeding vascular lesions such as DL.

				retrograde DBE was planned following bowel prep.			than in OGIB patients with DBE done 24 h after symptom onset (40.7% vs 0.9%, respectively, P < 0.001). Combined approach with RT viewing by CE correctly modified DBE management in four patients (25%).	
Schlag et al, 2015, GIE	Germany	To evaluate the impact of VCE when performed on patients with acute severe GI bleeding immediately after an initial negative upper endoscopy result.	Between December 2011 and February 2014 at a single university hospital ,Patients with melena, dark-red or maroon stool, hemodynamic instability, drop of hemoglobin level R 2 g/dL/day, and/or need of transfusion R 2 units of packed red blood cells per day.	After a negative upper endoscopy result, emergency VCE was performed by immediate endoscopic placement of the video capsule into the duodenum.	Rate of patients in whom emergency VCE correctly guided further diagnostic and therapeutic procedures.	Prospective study	Upper endoscopy showed the source of bleeding in 68 of 88 patients (77%). In the remaining 20 patients (23%), emergency VCE was performed, which was feasible in 19 of 20 patients (95%; 95% confidence interval [CI], 75%-99%). Emergency VCE correctly guided further diagnostic and therapeutic procedures in 17 of 20 patients (85%; 95% CI, 62%-97%) and showed a diagnostic yield of 75% (95% CI, 51%-91%).	In patients with acute severe GI bleeding and negative upper endoscopy results, emergency VCE can be useful for the immediate detection of the bleeding site and is able to guide further therapy.
Ching et at,	UK	To compare the	Patients presenting	Patients	Patient	Prospectiv	Thirty-three patients	MACE had

2019, GIE		diagnostic yields of MACE and EGD in patients with suspected acute upper GI bleeding.	to the emergency department with suspected acute upper GI bleeding, defined as having hematemesis (fresh blood or coffee ground vomiting) and/or melena within the previous 48 hours.	swallowed 1 L of water containing 40 mg of simethicone to distend and optimize gastric mucosal views immediately before MACE, which was performed using the MiroCam Navi.	tolerance, mucosal visibility by MACE, and frequency of small-bowel bleeding were assessed.	e, single-blinded, cohort study	were included for analysis (median age, 60 years; 75.8% male). MACE detected more focal lesions than EGD (40 versus 25, respectively, P = .02) but statistical significance was not reached for significant lesions (considered to be the bleeding source; 14 vs 13, respectively, P =1). Capsule endoscopy identified an additional cause for bleeding in the small bowel in 18%. Visualization by MACE was excellent in most areas; views of the esophagus, gastroesophageal junction, fundus, and duodenal bulb were suboptimal. MACE was better tolerated than unsedated EGD and correctly identified patients who were safe for discharge.	higher diagnostic yield for focal lesions and was better tolerated than EGD. It also correctly predicted safe discharge for patients with acute upper GI bleeding.

Schmidt et L, 2019, EIO	Germany	To investigate feasibility and safety of the novel sensor capsule in patients with symptoms of UGIB.	Patients presenting to the emergency department with acute UGIB were screened for eligibility.	From April 2015 to February 2016, 104 consecutive patients who presented with symptoms of UGIB were screened. Thirty patients were included in the study.	The primary aim was to investigate feasibility and safety of the device in a clinical setting.	Prospective nonrandomized, single center, open-label study.	Capsule ingestion was well tolerated in all patients and there were no device-related adverse events. Endoscopy showed blood or hematin in the upper gastrointestinal tract of 10 of 27 patients; in 2 of 10 patients it was estimated to be more than 20 mL; in 4 of 8 patients it was between 5 and 20mL and in 4 of 8 it was estimated to < 5mL. The sensor capsule was positive in 2 of 2 patients (100 %) with > 20mL of blood or hematin and in 1 of 8 patients (12.5 %) between 5 and 20mL.	Both device and procedure proved to be safe and feasible.

Authors	Study type	Patient group	(n)	Intervention	endpoint	Outcomes	Conclusions
Nunoue J Clin Gastro 2015	Prospective Randomized	PUB randomized to Group Soft coagulation with forceps Group heater probe	111 Group S 56 Group H 55	Soft coagulation with forceps Heater probe	Primary hemostasis Rebleeding Complications	Group S vs H - Primary hemostasis 96% vs 67%, p<0.0001 - Rebleeding 0 vs 12% - Complications 0 vs 2	
Kim Endoscopy 2015	RCT	PUB randomized to Group APC: Injection + APC Group HFSC: Injection + HFSC	Total 151 Group APC: 75 Group HFSC: 76	Injection + APC Injection + HFSC	Hemostasis Rebleeding 30d Adv events Mortality	APC vs HFSC: - Hemostasis 96% vs 96%, n.s. - Rebleeding 6.7% vs 9.2%, n.s - AE 1.3 % vs. 2.6 %, n.s - Mortality 2.7 % vs. 2.6 %	Coagulation forceps not inferior to APC
Toka GIE 2019	Prospective Randomized	MHFSC Hemoclip	112 MHFSC 56 Hemoclip 56	Injection + MHFSC Injection + hemoclip	Hemostasis Rebleeding 7d Time to hemostasis	MHFSC vs Hemoclip: - Hemostasis 98,2 vs 80,4, p=0.004 - Rebleeding 3.6% vs 17.7%, p=0.04	MHFSC is more effective achieving initial hemostasis

					Admission AE	- Time 302 ± 87.8 vs 568 ± 140.4 seconds - Admission 3.50 ± 1.03 vs 4.37 ± 1.86 days - AE none	provides a shorter procedure time and a lower rebleeding rate compared with Hemoclips

Authors	Study type	Patient group	(n)	Intervention	endpoint	Outcomes	Conclusions
Jensen AmJ Gastro 2017	RCT	Group Ib Group Ia+IIa+IIb	388 Ib 163 Ia+IIa+IIb 225	PPI or placebo	rebleeding	PPI reduced rebleding in Ia+IIa+IIb but not Ib (5.4% vs 4.9%, n.s) Ib had lower risk of rebleeding (4.9%) compared to Ia(22.5%), IIb(17.6%) or IIa(11.3%)	PPI not recommended after successful treatment in Ib
Jensen GIE 2016	Prospective cohort	Patients with severe bleeding	High risk (Ia, IIa, IIb) 87 Med risk (Ib, IIc)	Doppler before and after Rx Comparison High vs med	Doppler before Doppler after Rx	High vs Med risk: - DEP+ before 87.4% vs 42.3%	DEP improves risk stratification Ia has higher DEP+ and

			52 Low risk (III) 24	and Ia vs Ib	Rebleeding 30d	- DEP+ after 27,4% vs 13,6% Ia vs Ib - Dep+ before 100% vs 46.7% - DEP+after 35,7% vs 0% Rebleeding 28,6% vs 0%	rebleeding rates than Ib
Camus APT 2016	Prospective observational		1264	Ulcer size	rebleeding	Rebleeding: 17.7% increasing with size	Ulcer size independent risk factor for adverse outcome
Lolle Scand J 2016	Prospective Observational	Duodenal ulcer Gastric ulcer	20059		Death Reintervention	Bleeding from DU vs GU: - all-cause mortality 90d (OR) 1.47 (1.30-1.67); $p < 0.001$ - all-cause mortality 30d OR 1.60 (1.43-1.77);	Duodenal location has worse all cause mortality and reintervention rate

						p < 0.001 - re-intervention: adjusted OR 1.86 (1.68-2.06); p < 0.001	

Authors	Study type	Patient group	(n)	Intervention	endpoint	Outcomes	Conclusions
Jensen AmJ Gastro 2017	RCT	Group Ib Group Ia+IIa+IIb	388 Ib 163 Ia+IIa+IIb 225	PPI or placebo	rebleeding	PPI reduced rebleding in Ia+IIa+IIb but not Ib (5.4% vs 4.9%, n.s) Ib had lower risk of rebleeding (4.9%) compared to Ia(22.5%), IIb(17.6%) or IIa(11.3%)	PPI not recommended after successful treatment in Ib
Kim KJG 2015 (Korean translated with Google)	Retrospective	IIb	Total 1101 IIb 126	Endoscopic therapy 84 PPI 42	Rebleeding Mortality All cause mortality	Rebleeding endo vs PPI: - 7.1% vs. 9.5%; p=0.641 Mortality endo vs ppi: - 1.2%vs10%;p=0.018 All-cause mortality endo vsPPI - 3.7% vs. 20.0%;	FIIb was associated with a significant reduction in bleeding related mortality and all cause mortality

						p=0.005	compared with medical therapy alone
Jensen Gastro 2017	RCT	Multiple NVUGIB Subgroup: SRH	High risk (Ia, IIa, IIb) 53 Med risk (Ib, IIc) 23	Standard Doppler guided intervention. Repeat intervention if DEP+ after intervention	Rebleeding 30d	Standard vs DEP guided: - Ia 50% vs 28,6% n.s - IIa 25.9% vs 15.4% n.s - IIb 25% vs 0% n.s. - Ia 18.8% vs 0% n.s - IIc 14.3% vs 0% n.s - Total 26.3% v11.1%,p=0.0214	Doppler shows a significant overall 30d rebleeding decrease but its not significant in a case by case basis. Limitation: n is very low
Kantowski Scan J Gastro 2018	Prospective		Ia 6 Ib 41 IIa 13	Standard 25 Doppler guided intervention 35	Rebleeding Surgery Mortality	Rebleeding standard vs DEP: - 52% vs 20%, p=0.013 Surgery std vs DEP: - 2%vs 26%, p=0.017	Use of DEP associated with lower rebleeding, surgery and mortality Limitation: most patients Ib that already has a lw rebleeding rate after Rx Results not grouped by

							SRH

Kyaw, M., Tse, Y., Ang, D., Ang, T., & Lau, J. (2014). Embolization versus surgery for peptic ulcer bleeding after failed endoscopic hemostasis: A meta-analysis. Endoscopy International Open, 2(1), 14. doi:10.1055/s-0034-1365235	**Meta-analysis/ Systematic review**	**From 1234 citations, 6 retrospective comparative studies were included that involved 423 patients (TAE, 182; surgery, 241).** **TAE patients were older (mean age, TAE 75, surgery, 68).** **2 studies from Asian populations and 4 studies from European populations.**	**Outcome measures included rebleeding rate, all-cause mortality rate, and need for additional interventions to secure hemostasis.**	**The risk of rebleeding was significantly higher in TAE patients compared with surgically treated patients (relative risk [RR] 1.82, 95 % confidence interval [95 %CI] 1.23 – 2.67), with no statistically significant heterogeneity among the included studies (P = 0.66, I^2 = 0.0 %).** **No significant difference in mortality (RR 0.87, 95 %CI 0.59 – 1.29) or requirement for additional interventions (RR 1.67, 95 %CI 0.75 – 3.70) was shown between the two groups.**	**No RCT** **Observational studies with selection bias.** **Patients with higher surgical risk offered TAE.**	**surgery more definitively secured hemostasis,** **no significant difference in mortality rate or requirement of additional interventions.**

Beggs, Andrew D., Dilworth, Mark P., Powell, Susan L., Atherton, Helen, & Griffiths, Ewen A. (2014). A systematic review of transarterial embolization versus emergency surgery in treatment of major nonvariceal upper gastrointestinal bleeding. Clinical and Experimental Gastroenterology, 7(1), 93-104.	systematic review and meta-analysis	9 studies, n=711 patients, 347 patients in the TAE group and 364 in the surgery group. Patients in the TAE group were more likely to have ischemic heart disease (odds ratio [OR] =1.99; 95% confidence interval [CI]: 1.33, 2.98; P=0.0008; I (2)=67% [random effects model]) and be coagulopathic (pooled OR =2.23; 95% CI: 1.29, 3.87; P=0.004; I (2)=33% [fixed effects model]).	The primary outcomes were rebleeding rates and all-cause mortality. The secondary outcomes were rates of medical postoperative complications (pneumonia, myocardial infarction [MI], kidney injury, and stroke) and length of hospital stay.	Compared with TAE, surgery was associated with a lower risk of rebleeding (OR =0.41; 95% CI: 0.22, 0.77; P<0.0001; I (2)=55% [random effects]). There was no difference in mortality (OR =0.70; 95% CI: 0.48, 1.02; P=0.06; I (2)=44% [fixed effects]) between TAE and surgery.	The studies reviewed mainly comprised of retrospective cohort data, with no age, sex or comorbidity matching, due to the limitations of the type of study being undertaken. It could be argued that there was severe selection bias in these studies as patients with greater comorbidity were selected for TAE.	When compared with surgery, TAE had a significant increased risk of rebleeding rates after TAE; however, there were no differences in mortality rates. These findings are subject to multiple sources of bias due to poor quality studies.

Tarasconi, A., Baiocchi, G., Pattonieri, V., Perrone, G., Abongwa, H., Molfino, S., . . . Catena, F. (2019). Transcatheter arterial embolization versus surgery for refractory non-variceal upper gastrointestinal bleeding: A meta-analysis. World Journal of Emergency Surgery, 14(1), 1-13.	Systematic review and meta-analysis	Adult patients with refractory NVUGIB (defined as failure of endoscopic hemostasis or rebleeding after successful endoscopic hemostasis). Direct comparison of TAE and surgery	All-cause mortality with no time limit; rebleeding or continued bleeding; complications, both procedure-related and not procedure-related; need for further intervention for any reason	Only 13 studies were included for a total of 1077 patients (TAE group 427, surgery group 650). All selected papers were non-randomized studies: ten were single-center and two were double-center retrospective comparative studies, while only one was a multicenter prospective cohort study. No comparative randomized clinical trial is reported in the literature. Mortality. Pooled data (1077 patients) showed a tendency toward improved mortality rates after TAE, but this trend was not statistically significant (OD = 0.77; 95% CI 0.50, 1.18; P = 0.05; I^2 = 43% [random effects]). Significant heterogeneity was found among the studies. Rebleeding rate. Pooled data (865 patients, 211 events) showed that the incidence of rebleeding was significantly higher for patients undergoing TAE (OD = 2.44; 95% CI 1.77, 3.36; P = 0.41; I^2 = 4% [fixed effects]). Complication rate. Pooling of the data (487 patients, 206 events) showed a sharp reduction of complications after TAE when compared with surgery (OD = 0.45; 95% CI 0.30, 0.47; P = 0.24; I^2 = 26% [fixed effects]).	The retrospective nature of the majority of included studies leads to selection bias. Furthermore, the decision of whether to proceed with surgery or refer to TAE was made on a case-by-case basis by each attending surgeon. Thus, external validity is low. Another limitation involves the variability in etiology of the refractory bleeding. TAE techniques and surgical procedure also differ consistently between different studies. Frame time for mortality detection differs between the studies.	The present study shows that TAE is a safe and effective procedure; when compared to surgery, TAE exhibits a higher rebleeding rate, but this tendency does not affect the clinical outcome as shown by the comparison of mortality rates (slight drift toward lower mortality for patients undergoing TAE). The present study suggests that TAE could be a viable option for the first-line therapy of refractory NVUGIB and sets the foundation for the design of future randomized clinical trials.

				Need for further intervention. Pooled data (698 patients, 165 events) revealed a significant reduction of further intervention in the surgery group (OD = 2.13; 95% CI 1.21, 3.77; P = 0.02; I^2 = 56% [random effects]). A great degree of heterogeneity was found among the studies.		
Lau, J., Sung, J., Lam, Y., Chan, A., Ng, E., Lee, D., . . . Chung, S. (1999). Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. The New England Journal of Medicine, 340(10), 751-6.	Prospective randomized trial	3473 patients with bleeding peptic ulcers admitted to the hospital were included in the study if they have recurrent bleeding in the 72-hour period after endoscopic treatment. 1169 of 3473 adults underwent endoscopy to	Outcome variables included the duration of hospitalization after treatment, the need for hospitalization in the intensive care unit, the need for blood transfusion,	Of the 48 patients who were assigned to endoscopic retreatment, 35 had long-term control of bleeding. Thirteen underwent salvage surgery, 11 because retreatment failed and 2 because of perforations resulting from thermocoagulation. Five patients in the endoscopy group died	The results of randomized studies have been limited by the inclusion of small numbers of patients or the use of suboptimal	In patients with peptic ulcers and recurrent bleeding after initial endoscopic control of bleeding, endoscopic retreatment reduces the need for surgery without increasing the risk of death and is associated with fewer complications than surgery.

		reestablish hemostasis. Of 100 patients with recurrent bleeding, 7 patients with cancer and 1 patient with cardiac arrest were excluded from the study; 48 patients were randomly assigned to undergo immediate endoscopic retreatment and 44 were assigned to undergo surgery.	treatment-related complications, and 30-day mortality. Treatment-related complications included any complications that developed after endoscopic retreatment and subsequent salvage surgery.	within 30 days, as compared with eight patients in the surgery group (P=0.37). Seven patients in the endoscopy group (including 6 who underwent salvage surgery) had complications, as compared with 16 in the surgery group (P=0.03). The duration of hospitalization, the need for hospitalization in the intensive care unit and the resultant duration of that stay, and the number of blood transfusions were similar in the two groups. In multivariate analysis, hypotension at randomization (P=0.01) and an ulcer size of at least 2 cm (P=0.03) were independent factors predictive of the failure of endoscopic retreatment.	treatment at primary endoscopy.	
Schmidt A, Gölder S, Goetz	Prospect	Adult patients with	Primary	Persistent bleeding	Recruitme	In prospective

M, Meining A, Lau J, von Delius S, Escher M, Hoffmann A, Wiest R, Messmann H, Kratt T, Walter B, Bettinger D, Caca K. Over-the-Scope Clips Are More Effective Than Standard Endoscopic Therapy for Patients With Recurrent Bleeding of Peptic Ulcers. Gastroenterology. 2018;155:674–686.e6.	ive, randomized, controlled multicenter study	recurrent peptic ulcer bleeding following initially successful hemostasis (66 patients in the intent-to-treat analysis) were randomly assigned to groups (1:1) that underwent hemostasis with either OTSC or standard therapy.	endpoint of the study was "further bleeding," a combined endpoint of (1) persistent bleeding despite endoscopic therapy according to the protocol or (2) recurrent bleeding within 7 days after initial successful endoscopic therapy. Secondary endpoints were as follows: mortality (hospital	after per-protocol hemostasis was observed in 14 patients (42.4%) in the standard therapy group and 2 patients (6.0%) in the OTSC group (P = .001). Recurrent bleeding within 7 days occurred in 5 patients (16.1%) in the standard therapy group vs 3 patients (9.1%) in the OTSC group (P = .468). Further bleeding occurred in 19 patients (57.6%) in the standard therapy group and in 5 patients (15.2%) in the OTSC group (absolute difference 42.4%; 95% confidence interval 21.6–63.2; P = .001) Within 30 days of follow-up, 1 patient in the standard therapy group (3.0%) and 1 patient in the OTSC group (3.0%) required surgical therapy (P = .999). Within 30 days of the procedure, 2	nt duration was relatively long (3.5 years) and recruitment rates of the participating centers were inhomogeneous, most likely because rebleeding from peptic ulcers is rare. Standard therapy options in the control group were strictly limited per protocol	randomized trial, we found endoscopic treatment with OTSCs to be superior to standard therapy with TTSCs for patients with recurrent peptic ulcer bleeding.

			and 30-day mortality), necessity of surgical or angiographic salvage therapy, duration of hospital and ICU stay, number of blood units transfused, number of repeat endoscopies, or necessity of >2 endoscopic treatment modalities for successful hemostasis and complications associated with endoscopic	patients died in the standard therapy group (6.3%) and 4 patients died in the OTSC group (12.1%) (*P* = .672). There were no significant differences in the other secondary endpoints.	and did not allow for other alternatives like use of fibrin glue or hemostatic powders. This may have contributed to the high rate of further bleeding in this group. Furthermore, the crossover design, implemented for ethical reasons, with possible immediate switch to OTSC after	

			therapy.		failure of standard therapy may have reduced efforts of the endoscopist to achieve hemostasis conventionally. Additionally, any outcomes “downstream” of the crossover, such as rebleeding, surgery, angiographic treatment, and mortality cannot be correlated with the index	

					treatment and also make the study results difficult to compare with non-crossover studies. The study was unblinded and there was no protocol definition of how many clips and how much volume of epinephrine should be used. Moreover, we did not predefine how much time the endoscopist should	

					spent on hemostasis until it was considered as unsuccessful. Another limitation of our study may be heterogeneity in PPI treatment. According to the study protocol, all patients received 80 mg pantoprazole bolus, but choice of PPI regimen after initial bolus	

					administration was left to the choice of the investigators.	
Kyaw, Moe, Tse, Yee, Ang, Daphne, Ang, Tiing, and Lau, James. "Embolization versus Surgery for Peptic Ulcer Bleeding after Failed Endoscopic Hemostasis: A Meta-analysis." 2.1 (2014): E6-E14. Web.	Systematic review	There were two studies from Asian populations and four studies from European populations. All 6 studies were published as full papers. A total of 423 patients were included in the analysis, of whom 182 patients underwent TAE (56% male) and 241 patients received surgery (68% male). All 4 studies reported the TAE cohort to have patients with higher procedure-related risks.	Outcome measures included rebleeding rate, all-cause mortality rate, and need for additional interventions to secure hemostasis.	From 1234 citations, 6 retrospective comparative studies were included that involved 423 patients (TAE, 182, 56% male; surgery, 241, 68% male). TAE patients were older (mean age, TAE 75, surgery, 68). The risk of rebleeding was significantly higher in TAE patients compared with surgically treated patients (relative risk [RR] 1.82, 95% confidence interval [95%CI] 1.23–2.67), with no statistically significant heterogeneity among the included studies	Although numerous case studies exist on the use of TAE to treat NVUGIB, there are few published articles that compare TAE with surgery. To date there are no prospective data comparing the role of	A higher rebleeding rate was observed after TAE, suggesting surgery more definitively secured hemostasis, with no significant difference in mortality rate or requirement of additional interventions. The TAE patients were older and in poorer health, thus future randomized studies are needed for accurate comparison of the two modalities.

				($P = 0.66$, $I^2 = 0.0\%$). After sensitivity analysis excluding studies with a large age difference between the two groups, a higher risk of bleeding remained in the TAE group (RR 2.64, 95 %CI] 1.48 – 4.71). No significant difference in mortality (RR 0.87, 95 %CI 0.59 – 1.29) or requirement for additional interventions (RR 1.67, 95 %CI 0.75 – 3.70) was shown between the two groups.	TAE and surgery as a salvage therapy for patients with NVUGIB. After exclusion of any studies that did not compare TAE with surgery, only 6 studies were eligible for the meta-analysis. These studies are all retrospective observational comparative studies.	

					The main problem with such observational studies was patient selection bias. Conventional statistical approaches used in observational analyses have limited ability to address the influence of unmeasured confounders on the overall effect estimate.	

Walia, Sukhpreet S, Aadesh Sachdeva, John J Kim, Donald J Portocarrero, Terence D Lewis, and Yan S Zhao. "Cyanoacrylate Spray for Treatment of Difficult-to-control GI Bleeding." Gastrointestinal Endoscopy 78.3 (2013): 536-39. Web.	Case series.	This study involved consecutive patients with overt GI bleeding who were treated with n-butyl-2-cyanoacrylate spray during endoscopy for persistent bleeding d espite conventional hemostatic therapies.	Hemostasis, rebleeding, adverse events, and technical failure associated with cyanoacryla te spray.	Five patients were treated with cyanoacrylate spray during endoscopy for persistent bleeding (duo denal ulcer in 3, gastric vascular ectasia in 1, rectal postpolypectomy bleedi ng in 1) after failed conventiona l therapies. Immediate hemostasis a nd technical success were achieved in all patients. At a median follow-up of 42 days (range 38-120 days), 2 patients developed recurrent bleeding. One patient experienced rebleeding 2 days after the procedure, subsequently requiring radiographic intervention and surgery. Another patient had recurrent bleeding from a different bleeding sourc e 18 days after the	Small number of patients.	In patients with difficult-to-control GI bleeding failing conventional endoscop ic therapies, cyanoacrylate spray was effective in achieving immediate hemostasis. Prospective studies with a larger number of patients to evaluate the role of the cyanoacrylate spray technique during endoscopy for GI bleeding are needed.

				procedure. No adverse events attributed to the cyanoacrylate spray were observed.		
Katano, Takahito, Tsutomu Mizoshita, Kyoji Senoo, Satoshi Sobue, Hiroki Takada, Tomoyuki Sakamoto, Hisato Mochiduki, Takanori Ozeki, Akihisa Kato, Kayoko Matsunami, Kazuyuki Ito, and Takashi Joh. "The Efficacy of Transcatheter Arterial Embolization as the First-choice Treatment after Failure of Endoscopic Hemostasis and Endoscopic Treatment Resistance Factors." Digestive Endoscopy 24.5 (2012): 364-69. Web.	Retrospective study	There were 554 patients who required endoscopic hemostasis for bleeding gastric or duodenal ulcer. There were 397 patients with bleeding gastric ulcer, and 157 patients with bleeding duodenal ulcer. Initial endoscopic hemostasis failed in six patients, and TAE was performed; one of these six patients underwent surgery after TAE. Of the 548 patients in whom initial endoscopic hemostasis was successful, 33 patients experienced rebleeding. Rebleeding was	Successful hemostasis; successful TAE; need for emergent salvage surgery	TAE was attempted in 15 patients (2.7%). In 12 (80.0%) of 15 patients, embolization with coils was successful. In one patient (6.7%), embolization was ineffective. This patient underwent emergent salvage surgery. In two (13.3%) of 15 patients, no extravasation was observed during arteriography. These patients were cured with medication. In two patients, ulcer perforation was observed during endoscopy after rebleeding. These patients underwent surgery. In total, 3 (0.5%) of 554 patients underwent surgery. No recurrent bleeding was observed after TAE.	Further investigation is needed to determine whether emergent salvage surgery should be performed when blind embolization fails.	TAE is a safe and effective first-choice treatment for patients in whom endoscopic hemostasis has failed.

		defined as hematemesis or melena with hypotension. Of the 33 patients who experienced rebleeding, four died. In these four patients, rebleeding led to cardiopulmonary arrest before endoscopic therapy or TAE was performed. Second or third endoscopic treatments were performed in 29 of the patients who experienced rebleeding; the second or third endoscopic hemostasis failed in 11 of these patients. Of these 11 patients, 9 underwent TAE. There were two patients in whom perforation was observed during the second endoscopic		Hemoglobin level <8 g/dL at presentation (*P*=0.02), Rockall score ≥7 at presentation (*P*=0.002), and Forrest class Ia/Ib at initial endoscopic hemostasis (*P*<0.001) were found to be independent significant endoscopic treatment resistance factors.		

		treatment, and these patients underwent surgery.				
Lee, Han Hee, Jae Myung Park, Ho Jong Chun, Jung Suk Oh, Hyo Jun Ahn, and Myung-Gyu Choi. "Transcatheter Arterial Embolization for Endoscopically Unmanageable Non-variceal Upper Gastrointestinal Bleeding." Scandinavian Journal of Gastroenterology 50.7 (2015): 809-15. Web.	Retrospective study	Visceral angiography was performed in 66 patients (42 men, 24 women; mean age, 60.3 ± 12.7 years) who experienced acute non-variceal upper GI bleeding that failed to be controlled by endoscopy during a 7-year period. Among the 66 patients who had received angiography, 59 (89.4%) underwent embolization (Table II). Emergency (within 24 h) and urgent (24 h to 7 days) embolization was performed in 21 (35.6%) and 30 (50.8%) patients,	Outcomes included technical success rates, complications, and 30-day rebleeding and mortality rates.	TAE was feasible in 59 patients. The technical success rate was 98%. Rebleeding within 30 days was observed in 47% after an initial TAE and was managed with re-embolization in 8, by endoscopic intervention in 5, by surgery in 2, and by conservative care in 12 patients. The 30-day overall mortality rate was 42.4%. In the case of initial endoscopic hemostasis failure (n = 34), 31 patients underwent angiographic embolization, which was successful in 30 patients (96.8%). Rebleeding occurred in 15 patients (50%), mainly because of malignancy. Two factors were independent predictors	First, this study was designed as a retrospective study and was not randomized. Second, long-term follow up was not included in this study. Third, as we mentioned previously, almost half of the patients had bleeding from upper GI malignancies.	TAE controlled acute non-variceal upper GI bleeding effectively. TAE may be considered when endoscopic therapy is unavailable or unsuccessful. Correction of coagulopathy before TAE is recommended.

		respectively.		of rebleeding within 30 days by multivariate analysis: coagulopathy (odds ratio [OR] = 4.37; 95% confidence interval [CI]: 1.25-15.29; p = 0.021) and embolization in ≥2 territories (OR = 4.93; 95% CI: 1.43-17.04; p = 0.012). Catheterization-related complications included hepatic artery dissection and splenic embolization.		
Chiu, Philip, Henry Joeng, Catherine Choi, Kelvin Tsoi, Kwok Kwong, Siu Lam, and Joseph Sung. "High-dose Omeprazole Infusion Compared with Scheduled Second-look Endoscopy for Prevention of Peptic Ulcer Rebleeding: A Randomized Controlled Trial." 48.8 (2016): 717-22. Web.	Prospective randomized controlled noninferiority trial	Consecutive patients who received endoscopic treatment for bleeding peptic ulcers (actively bleeding, with nonbleeding visible vessels) were randomized to two treatment groups following hemostasis. One group (second-look endoscopy group) received the proton pump	The primary outcome was the rebleeding rate within 30 days after initial hemostasis.	A total of 153 patients were randomized to the PPI infusion group and 152 to the second-look endoscopy group. Rebleeding occurred within 30 days in 10 patients (6.5%) in the PPI infusion group and in 12 patients (7.9%) in the second-look endoscopy group (P = 0.646). Surgery was required for rebleeding in six patients from the PPI infusion group and	First, the study could not be conducted as a double-blind trial because one of the treatment arms involved additional endoscopy.	After endoscopic hemostasis, high-dose PPI infusion was not inferior to second-look endoscopy with bolus PPI in preventing peptic ulcer rebleeding.

		inhibitor (PPI) omeprazole as an intravenous bolus every 12 hours for 72 hours and a second endoscopy within 16 - 24 hours with retreatment for persistent stigmata of bleeding. The other group (PPI infusion group) received continuous high-dose omeprazole infusion for 72 hours. Patients who developed rebleeding underwent surgery if repeat endoscopic th erapy failed. A total of 153 patients were randomized to the PPI infusion group and 152 to the second-look endoscopy group.		three patients in the second-look endoscopy group (P = 0.32). Intensive care unit stay, transfusion requirements, and mortality were not different between the groups. Patients in the second-look endoscopy group were discharged 1 day earlier than those in the PPI infusion group (P < 0.001).	Conventio nally, a larger heat probe of 3.2 mm would be selected for standard thermal therapy. In the current study, a 2.3-mm heat probe was used because a combinati on of injection and thermal therapy could be achieved without changing the endoscope . Moreover,	

					patients were stratified to receive therapeutic endoscopy based on endoscopic stigmata of recent hemorrhage alone. With the current sample size, we could only declare that the rebleeding risk of high-dose PPI infusion is not inferior to that of scheduled second-look	

					endoscopy.	
Chiu, Philip Wai Yan, Enders Kwok Wai Ng, Simon Kin Hung Wong, Anthony Yuen Bun Teoh, Frances Ka Yin Cheung, Man-Yee Yung, Joseph Jao Yiu Sung, and James Yun Wong Lau. "Surgical Salvage of Bleeding Peptic Ulcers after Failed Therapeutic Endoscopy." Digestive Surgery 26.3 (2009): 243-48. Web.	Retrospective cohort study	Patients with a bleeding peptic ulcer recruited from the database were divided into two 5-year cohorts: the 1st cohort was from January 1993 to December 1998 and the 2nd cohort was from January 1999 to December 2004. The division between the 2 cohorts is according to the timing of the introduction of PPI infusion after endoscopic hemostasis in our unit. Patients who first developed rebleeding were managed by a repeated attempt at endoscopic hemostasis. Those who failed hemostasis after a	Clinical outcomes (including ulcer rebleeding and mortality), performance of minimal against definitive surgery and rate of complications	One hundred and twenty-three patients received salvage surgery in the 1st cohort, while 42 patients received surgical hemostasis for the bleeding peptic ulcer in the 2nd cohort. Patients in the 2nd cohort consisted of a larger proportion of in-hospital bleeders (cohort 1: 12.2%, cohort 2: 42.9%; $p < 0.005$) and had a significantly higher proportion of comorbidities. A larger number of patients received minimal surgery in cohort 2 (cohort 1: 42.3%, cohort 2: 73.8%; $p < 0.005$).	Our study is limited by the retrospective review of a prospectively collected database and the limited number of patients recruited. It is difficult to conduct a prospective randomized trial comparing minimal or definitive surgery after failed endoscopic	With advances in therapeutic endoscopy, patients who developed failed endoscopic hemostasis are likely to be poor surgical candidates with multiple comorbidities. The approach to salvage surgery has inclined towards minimal surgery to hasten surgical hemostasis among these fragile patients.

		repeated endoscopy or those who had a 2nd rebleeding were subjected to surgical hemostasis. The type of salvage surgery performed for uncontrolled ulcer bleeding was either minimal or definitive surgery. One hundred and twenty-three patients received salvage surgery in the 1st cohort, while 42 patients received surgical hemostasis for the bleeding peptic ulcer in the 2nd cohort.			hemostasis for bleeding peptic ulcers because of the low rate of uncontrolled rebleeding, limited number of candidates and the logistical problem of randomizing patients in their exsanguinations.	
Wong, Tiffany C.L, Wong, Ka-Tak, Chiu, Philip W.Y, Teoh, Anthony Y.B, Yu, Simon C.H, Au, Kim W.L, and Lau, James Y.W. "A Comparison of Angiographic Embolization	Retrospective study.	Patients with peptic ulcer bleeding in whom endoscopic hemostasis failed.	All-cause mortality, rebleeding, reintervention, and complicatio	Thirty-two patients underwent TAE and 56 underwent surgery. In those who underwent TAE, the bleeding vessels were gastroduodenal	Retrospective study.	In patients with ulcer bleeding after failed endoscopic hemostasis, TAE reduces the need for surgery without increasing the overall

with Surgery after Failed Endoscopic Hemostasis to Bleeding Peptic Ulcers." Gastrointestinal Endoscopy 73.5 (2011): 900-08. Web.			n rate.	artery (25 patients), left gastric artery (4 patients), right gastric artery (2 patients), and splenic artery (1 patient). Active extravasation was seen in 15 patients (46.9%). Embolization was attempted in 26 patients, and angiographic coiling was successful in 23 patients (88.5%). Bleeding recurr ed in 11 patients (34.4%) in the TAE group and in 7 patients (12.5%) in the surgery group (P=.01). More complications were observed in patients who underwent surgery (40.6% vs 67.9%, P=.01). There was no difference in 30-day mortality (25% vs 30.4%, P=.77), mean length of hospital stay (17.3 vs 21.6 days, P=.09), and need for transfusion (15.6 vs 14.2 units, P=.60) between the TAE and		mortality and is associated with fewer complications.

				surgery groups.		
Skinner M, Gutierrez JP, Neumann H, Wilcox CM, Burski C, Mönkemüller K. Over-the-scope clip placement is effective rescue therapy for severe acute upper gastrointestinal bleeding. *Endosc Int Open*. 2014;2(1):E37–E40. doi:10.1055/s-0034-1365282	Retrospective case series	All patients who underwent placement of an OTSC for severe recurrent upper gastrointestinal bleeding over a 14-month period was studied. Twelve consecutive patients (67 % men; mean age 59, range 29 – 86) with ongoing upper gastrointestinal bleeding despite previous endoscopic management were included.	Outcome data for the procedure included achievement of primary hemostasis, episodes of recurrent bleeding, and complications.	Twelve consecutive patients (67 % men; mean age 59, range 29 – 86) with ongoing upper gastrointestinal bleeding despite previous endoscopic management were included. They had a mean ASA score of 3 (range 2 – 4), a mean hemoglobin of 7.2 g/dL (range 5.2 – 9.1), and shock was present in 75 % of patients. They had all received packed red blood cells (mean 5.1 units, range 2 – 12). The etiology of bleeding was: duodenal ulcer (n = 6), gastric ulcer (n = 2) Dieulafoy lesion (n = 2), anastomotic ulceration (n = 1), Mallory – Weiss tear (n = 1). Hemostasis was achieved in all patients. Rebleeding occurred in two patients 1 day and 7 days after OTSC	First, it is retrospective and therefore has the limitations of any such study. Second, it reflects the experience of a tertiary-care center; however, the scopes used are present in most hospitals.	The novel over-the-scope clip (OTSC) use represents an effective, easily performed, and safe endoscopic therapy for various causes of severe acute gastrointestinal bleeding when conventional endoscopic techniques have failed. This therapy should be added to the armamentarium of therapeutic endoscopists.

				placement. There were no complications associated with OTSC application.		
Repici, A., Ferrari, De Angelis, Caronna, Barletti, Paganin, Musso, Carucci, Debernardi-Venon, Rizzetto, and Saracco. "Adrenaline plus Cyanoacrylate Injection for Treatment of Bleeding Peptic Ulcers after Failure of Conventional Endoscopic Haemostasis." Digestive and Liver Disease 34.5 (2002): 349-55. Web.	Retrospective study	Between January 1995 and March 1998, 18 out of 176 patients, referred to our Unit for non-variceal upper gastrointestinal bleeding, were treated with intralesional injection of adrenaline plus undiluted cyanoacrylate. Persistent bleeding after endoscopic haemostasis or early rebleeding were the indications for cyanoacrylate treatment.	Hemostasis, Rebleeding, months of follow-up	Definitive haemostasis was achieved in 17 out of 18 patients treated with cyanoacrylate. One patient needed surgery. No early or late rebleeding occurred during the follow-up. No complications or instrument lesions related to cyanoacrylate were recorded.	Due to the retrospective nature, the small number of patients and the absence of randomisation, in our study, no definitive conclusions could be drawn concerning the use of the cyanoacrylate in the treatment of severe ulcer bleeding.	In our retrospective series, cyanoacrylate plus adrenaline injection was found to be a potentially safe and effective alternative to endoscopic haemostasis when conventional treatment modalities fail in controlling bleeding from gastroduodenal ulcers.
Loffroy R, Guiu B, Mezzetta L, et al. Short- and long-term results of	Retrospective	60 consecutive emergency embolization	Success rate of embolizatio	Embolization was feasible and successful in 57 patients. Sandwich	Although rates of procedural	Selective angiographic embolization is safe and effective for

transcatheter embolization for massive arterial hemorrhage from gastroduodenal ulcers not controlled by endoscopic hemostasis. *Can J Gastroenterol*. 2009;23(2):115–120. doi:10.1155/2009/795460	review	procedures in hemodynamically unstable patients. Patients were referred for selective angiography between 1999 and 2008 after failed endoscopic treatment of massive bleeding from gastrointestinal ulcers. Mean follow-up was 22 months.	n, rebleeding, complications, mortality, cause of mortality(recurrent bleeding vs underlying illness)	coiling of the gastroduodenal artery was used in 34 patients, and superselective occlusion of the terminal feeding artery (with glue, coils or gelatin particles) was used in 23 patients. Early rebleeding occurred in 16 patients and was managed with endoscopy (n=8), reembolization (n=3) or surgery (n=5). No major embolization-related complications occurred. Sixteen patients died within 30 days after embolization (including three who died from rebleeding) and 11 died thereafter. No late bleeding recurrences were reported.	success (95%) and early clinical success (71.9%) were high in our study, 26.7% of patients died within the first month.The impact of medications associated with increased bleeding on the one-month mortality rate was not clear in our study. Unfortunately, the	controlling life-threatening bleeding from gastroduodenal ulcers. The procedure usually obviates the need for emergency surgery in these high-risk patients. Survival depends chiefly on underlying conditions.

					postprocedural morbidity rate was not compared between the two techniques. Few data are available regarding postsurgical morbidity, most notably complications related to the surgical method and infectious complications.	
Roy A, Kim M, Hawes R, Varadarajulu S. The clinical and cost implications of	Systematic review	The study population consisted of all patients who had	The outcomes evaluated	The MedPAR claims data evaluated 13,501 hospitalizations, of	There are several limitations	Failure to achieve hemostasis at the index endoscopy has

failed endoscopic hemostasis in gastroduodenal ulcer bleeding. *United European Gastroenterol J*. 2017;5(3):359–364. doi:10.1177/2050640616663570		claims for receiving a blood transfusion and underwent an UGI endoscopy for gastroduodenal ulcer bleeding.	compared all-cause mortality during hospitalization, hospital LOS, hospital costs and hospital payments for patients who underwent blood transfusion and required one endoscopy, >1 endoscopy, IRH following failed endoscopy or surgical hemostasis following failed endoscopy of	which 12,242 (90.6%) reported one UGI endoscopy, 817 (6.05%) reported >1 UGI endoscopy, 303 (2.24%) reported IRH after failed endoscopy and 139 (1.03%) reported surgeries after failed endoscopy. All cause-mortality was significantly lower for patients who underwent only one UGI endoscopy (3%) compared to patients requiring >1 endoscopy (6%), IRH (9%) or surgery (14%), $p < 0.0001$. The median LOS was significantly lower for patients who underwent only one UGI endoscopy (four days) compared to patients requiring >1 endoscopy (eight days), IRH (nine days) or surgery (15 days), $p < 0.0001$. The median hospital costs	to this study. One, the database does not capture individual components of a treatment and hence the specific nature or timing of interventions undertaken are unknown. Two, details of pharmacological treatment or blood transfusion that is administered is unknown. Finally, the	significant clinical and cost implications. When feasible, a repeat endoscopy must be attempted followed by IRH. Surgery should preferably be reserved as a last resort for patients who fail other treatment measures.

			gastroduodenal ulcer bleeding. A secondary analysis was then conducted to analyze the demographics of the hospitals in which the procedures were performed.	were significantly lower for patients who underwent one UGI endoscopy ($10,518) compared to patients requiring >1 endoscopy ($20,055), IRH ($34,730) or surgery ($47,589), $p < 0.0001$.	database also precludes propensity score matching or any modeling based on patient comorbidities.	
Taina Nykänen, Erno Peltola, Leena Kylänpää & Marianne Udd (2017) Bleeding gastric and duodenal ulcers: case-control study comparing angioembolization and surgery, Scandinavian Journal of Gastroenterology, 52:5, 523-530, DOI: 10.1080/00365521.2017.1288756	Retrospective cohort study	The study population received treatment for BGDUs in Helsinki University Hospital (HUH) after failed endoscopic hemostasis during 2000–2015. Patients requiring additional hemostatic interventions (TAE or surgery) for high-risk ulcers (Forrest Ia–IIb), independent of ulcer etiology,	30-d mortality and rebleeding rates were the primary outcomes. Postoperative complications, blood transfusion rate, and the durations of	During the study period, bleeding gastric and duodenal ulcers (BGDUs) lead to 1583 hospital admissions. TAE or surgery was necessary on 85 (5.4%) patients, 43 receiving surgery and 42 TAE. Out of 42, 16 received prophylactic TAE. Two underwent angiography and TAE to localize the bleeding. The remaining 24 received TAE for	The study has all the known weaknesses of a retrospective study. As randomization did not occur, selection bias is evident, patients	Mortality and rebleeding rates did not differ between TAE and surgery. With less postoperative complications, TAE should be the preferred hemostatic method when endoscopy fails.

		comprised the study group.	intensive care and hospital admissions were the secondary outcomes.	active or recurrent bleeding after endoscopy. The comparison of TAE (n = 24) and surgery (n = 43) included only patients with active or recurrent bleeding. Mortality rate was 12.5% after TAE and 25.6% after surgery (p = 0.347). Rebleeding rate was 25% after TAE and 16.3% after surgery (p = 0.641). Postprocedural complications were less frequent after TAE than surgery (37.5 vs. 67.4%, p = 0.018). Other secondary outcomes did not differ. Out of 85 procedures, 14 (16.5%) took place between midnight and 8 a.m., all nighttime interventions being surgeries.	with active bleeding dominating in surgical group.	
Yen, Hsu-Heng, Yang, Chia-Wei, Su, Pei-Yuan, Su, Wei-Wen, and Soon, Maw-Soan. "Use of Hemostatic Forceps	Retrospective study	From January to October 2010, four hundred twenty-seven patients	Successful hemostasis or need for surgery	In 5 patients hemostasis was achieved with hemostatic forceps as a rescue therapy after	First, this study only included limited	In this study, we have demonstrated that hemostatic forceps can be a useful alternative

as a Preoperative Rescue Therapy for Bleeding Peptic Ulcers." Surgical Laparoscopy, Endoscopy & Percutaneous Techniques 21.5 (2011): 380-82. Web.		underwent endoscopic therapy for bleeding peptic ulcers. A retrospective analysis of the endoscopy database identified 5 patients who had received endoscopic therapy with hemostatic forceps (Coagrasper: FD-410LR; Olympus) during this period.		standard endoscopic therapy had failed. In 4 patients successful hemostasis was achieved, whereas 1 patient had to undergo emergency surgery.	cases and was retrospective in nature. We are unable to provide firm evidence to show the advantage of hemostatic forceps over other conventional endoscopic techniques. Second, the use of hemostatic forceps is easier in the case of ESD	method for controlling peptic ulcer bleeding after failure of conventional endoscopic techniques. Patients may benefit from this new technique. Further prospective and large-scale studies are required to confirm our observations.

					because the vessels are easier to identify and coagulate during the procedure. In a situation with bleeding peptic ulcers, there is no standard recommendation for the use of this device. The bleeding vessels are less easily caught by the forceps in bleeding peptic ulcers, and in some	

					cases we need to coagulate the vessel with forceps closed. While dealing with monopolar coagulation with hot biopsy forceps, the endoscopist should be aware of the necessity to avoid excessive coagulation, which might lead to delayed perforation. Third, the	

					cost of hemostatic forceps is relatively high compared with other endoscopic hemostatic devices. This may limit their use as a first line endoscopic therapeutic technique.	

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Valizadeh Toosi SM, et al. Comparison of Oral versus Intravenous Proton Pump Inhibitors in Preventing Re-bleeding from Peptic	Single center, prospective, randomized trial	178 patients with active upper gastrointestinal bleeding due to a peptic ulcer with stigmata	comparing the rate of re-bleeding or mortality, and the need for blood transfusion or	There were not significant statistical differences between the two groups in the volume of blood transfusion, mean duration of hospital stay,	The endoscopies had been performed by six gastroenterologists. This	This study showed no statistically significant difference between the two groups

Ulcer after Successful Endoscopic Therapy. Middle East J Dig Dis. 2018 Oct;10(4):236-241		of high risk for re-bleeding entered the study Received either high dose oral pantoprazole (80 mg stat and 80 mg twice daily for 3 days) or high dose intravenous pantoprazole (80 mg IV infusion within 30 minutes and 8 mg per hour for 3 days)	surgery during the first month	need to surgery, or mortality rates. However, the rates of re-bleeding were 2.3% (2:88) in the IV group and 3.3% (3:90) in the oral group (p = 0.6)	might have interfered with the same interpretation of the ulcers	of IV or oral PPI in the outcomes of high risk peptic ulcers after therapeutic endoscopy. Therefore, it seems that high dose oral PPI can be a good alternative to high dose IV PPI in ptients with bleeding peptic ulcer disease. Furthermore, due to the lower cost (approximately 30 times) and avail-ability of oral PPI, its use can be economically much more

						affordable
Sgourakis G, et al. High-dose vs. Low-dose Proton Pump Inhibitors post-endoscopic hemostasis in patients with bleeding peptic ulcer. A meta-analysis and meta-regression analysis. Turk J Gastroenterol. 2018 Jan;29(1):22-31	meta-analysis and meta-regression analysis . 10 RCTs concerning low- versus high-dose PPI administration post-endoscopic hemostasis published until December 2016 were identified.	a total of 1.651 participants allocated to high dose PPI versus low dose (range 20-160mg PPI per day)	Primary outcomes were rebleeding rates, need for surgical intervention, and mortality.	Here were significantly less cases of rebleeding in the low-dose PPI treatment arm (p=0.003). All but one study provided data concerning need for Surgical Intervention and Mortality. The respective effect sizes were [odds ratio (OR), 95% confidence intervals (CI): 1.35, 0.72-2.53] and [OR, 95% CI: 1.20, 0.70-2.05]. Both treatment arms were comparable considering the aforementioned outcomes (p=0.35 and p=0.51, respectively). Meta-regression analysis likewise unveiled comparable outcomes between studies using pantoprazole versus lansoprazole concerning all three outcomes [rebleeding (p=0.944), surgical inter- vention (p=0.884), and mortality	- There was a noteworthy discrepancy in the definition of rebleeding - Different dosing of High dose and low dose PPI between studies	low-dose PPI is equally effective as a high- dose PPI administration following endoscopic bleeding arrest in bleeding peptic ulcer patients

				(p=0.961)].		
Tringali A, et al. Comparing intravenous and oral proton pump inhibitor therapy for bleeding peptic ulcers following endoscopic management: a systematic review and meta-analysis. Br J Clin Pharmacol. 2017 Aug;83(8):1619-1635	Systematic review and meta-anlaysis. Search conducted Feb 2016. 9 RCTs were included	1036 subjects were allocated to receive oral PPIs (n = 518) or IV PPIs (n = 518).	recurrent bleeding, blood transfusion requirement, duration of hospital stay, a need for repeat endoscopy, surgery and 30-day mortality	No differences in the rebleeding rates [odds ratio (OR) 0.93, 95% confidence interval (CI) 0.60, 1.46; P = 0.77], need for surgery (OR 0.77, 95% CI 0.25, 2.40; P = 0.65), need for repeat endoscopy (OR 0.69, 95% CI 0.39, 1.21; P = 0.19), need for blood transfusion [(MD) –0.03, 95% CI –0.26, 0.19; P = 0.76], duration of hospital stay (MD –0.61, 95% CI –1.45, 0.23; P = 0.16) or 30-day mortality (OR 0.89, 95% CI 0.27, 2.43; P = 0.84) according to the route of administration. subgroup analysis showed that high-dose IV PPIs were equivalent to low-dose IV PPIs for all outcomes considered. A subgroup analysis comparing a high-dose oral PPI to a high-dose IV PPI demonstrated no statistically significance	-diferent regimens of dosing the PPIs between the groups - included some low-risk patients with Forrest classification IIc or III. These patients may have a lower risk of recurrent bleeding, which could explain the comparable efficacy of oral and IV PPIs. - Fifty per cent of the trials included in the meta-analysis were at a high risk of performance and detection	oral and IV PPIs have a similar efficacy after endoscopic treatment in controlling recurrent bleeding, the requirement for surgery and mortality in patients with peptic ulcer bleeding from dif-ferent stigmata.

				difference for any of the outcomes considered, except for the need for a blood transfusion, which favoured the high- dose oral PPI.	bias. Furthermore, the sample size in some of the RCTs included was too small, resulting in studies that were underpowered to demonstrate a statisti- cally significant difference between the two groups (oral vs. IV), leading to unreliable conclusions which would have limited the strength of the meta-analysis	
Chwiesko A, et al. Effects of different omeprazole dosing on gastric pH in non-variceal	Randomized controlled trial	50 patients with NVUGIB were prospectively	The intragastric pH was recorded for 72	The median percentage of time at an intragastric pH > 4.0 was higher in the IV	- unclear clinical	In patients with NVUGIB,

upper gastrointestinal bleeding: A randomized prospective study. J Dig Dis. 2016 Sep;17(9):588-599		enrolled, after achievement of endoscopic hemostasis, were randomized to 40-mg IV OME bolus injection bid or 80-mg IV bolus injection + 8-mg/h continuous IV infusion for 72 hours Forty-one Caucasians (n = 18 for IV infusion group; n = 23 for IV bolus group) were analysed	hours	infusion group than in the IV bolus group over 48 hours (100% vs. 96.6%, respectively; P = 0.009) and 72 hours (100% vs. 87.6%, respectively; P = 0.006), and that at an intragastric pH > 6.0 was higher in the IV infusion group compared to the IV bolus group over 72 hours (97.9% vs. 63.5%, P = 0.04).	relevance	OME IV bolus followed by continuous infusion was more effective than OME IV bolus bid in maintaining higher intragastric pH, regardless of CYP2C19 genetic polymorphisms. H. pylori infection accelerated the initial elevation of intragastric pH.
Chiu PW, Joeng HK, Choi CL, Tsoi KK, Kwong KH, Lam SH, Sung JJ. High-dose omeprazole infusion compared with scheduled	Non-inferiority randomized controlled trial	305 patients included. One group (second-look endoscopy group) received the proton pump inhibitor (PPI)	Rebleeding rate within 30 days after initial hemostasis. The margin for noninferiority	A total of 153 patients were randomized to the PPI infusion group and 152 to the second- look endoscopy group. Rebleeding occurred		High-dose omeprazole infusion was not inferior to scheduled second-look

second-look endoscopy for prevention of peptic ulcer rebleeding: a randomized controlled trial. Endoscopy. 2016 Aug;48(8):717-22		omeprazole as an intra-venous bolus every 12 hours for 72 hours and a second endoscopy within 16 – 24 hours with re-treatment for persistent stigmata of bleeding. The other group (PPI infusion group) received continuous high-dose omeprazole infusion for 72 hours.	was set at 5 %.	within 30 days in 10 patients (6.5 %) in the PPI in- fusion group and in 12 patients (7.9 %) in the sec-ond-look endoscopy group (P = 0.646). Surgery was required for rebleeding in six patients from the PPI infusion group and three patients in the second-look endoscopy group (P = 0.32). Intensive care unit stay, transfusion requirements, and mortality were not different between the groups. Patients in the second-look endoscopy group were discharged 1 day earlier than those in the PPI infusion group (P < 0.001).		endoscopy in the prevention of ulcer rebleeding. High-dose omeprazole infusion is the preferred postendosco py management strategy to avoid unnecessary endoscopic surveil- lance and discomfort for the patient. Scheduled second-look endoscopy demonstrate d an advantage by leading to earlier discharge from hospital

						after confirmation of secured hemostasis, and may be considered for selective patients at high risk of re- bleeding and mortality.
Lu Y, et al. Timing or Dosing of Intravenous Proton Pump Inhibitors in Acute Upper Gastrointestinal Bleeding Has Low Impact on Costs. Am J Gastroenterol. 2016 Oct;111(10):1389-1398	Cost-effectiveness analysis		For each, continuous or intermittent dosing regimens were assessed with associated incremental costs. Deterministic and probabilistic sensitivity analyses were performed.		Furthermore, indirect costs related to the administration of PPI (i.e., equipment and nursing time) were not included, which may have differed for continuous vs. intermittent dosing;	The incremental costs of using different IV PPI regimens are modest compared with total per patient costs.
Rodriguez E.A., Donath E., Waljee A.K., Sussman D.A. Value of oral proton pump inhibitors in acute,	systematic review and network meta-	Overall, 7767 patients were included, with the mean number of	Risk of rebleeding, length of stay (LOS), surgery	No difference was observed between IV PPI drip and scheduled IV PPI for mortality (relative	- were unable to perform subgroup analyses	Scheduled IV PPIs were as effective as IV PPI drip

nonvariceal upper gastrointestinal bleeding: A network meta-analysis. Journal of Clinical Gastroenterology. 51 (8) (pp 707-719), 2017	analysis A total of 39 studies using IV PPI drip, IV scheduled PPI, oral PPI, H2-receptor antagonists, and placebo	patients per study 193	(ROS), mortality, and total units of blood transfused (UBT)	risk=1.11; 95% credibility interval, 0.56-2.21), LOS (0.04, -0.49 to 0.44), ROS (1.27, 0.64-2.35) and risk of rebleeding within 72 hours, 1 week, and 1 month [(0.98, 0.48-1.95), (0.59, 0.13-2.03), (0.82, 0.28-2.16)]. Oral PPIs were as effective as IV scheduled PPIs and IV PPI drip for LOS (0.22, -0.61 to 0.79 and 0.16, -0.56 to 0.80) and UBT (-0.25, -1.23 to 0.65 and -0.06, -0.71 to 0.65) and superior to IV PPI drip for ROS (0.30, 0.10 to 0.78).	accounting for the high-risk features of the lesions or the interventions performed at endoscopy - The included studies also used a variety of weight-based or standard PPI dosage, making it a challenge to draw a conclusion as to the appropriate dosage of PPI to prevent the evaluated end-points.	for most outcomes. Oral PPIs were comparable to scheduled IV for LOS and UBT and superior to IV PPI drip for ROS. Conclusions should be tempered by low frequency endpoints such as ROS, but question the need for IV PPI drip in ANVGIB
Jiang M, Chen P, Gao Q. Systematic Review and Net-Work Meta-Analysis of Upper Gastrointestinal Hemor- rhage Interventions. Cell Physiol Biochem	Meta-analysis and systematic review. 47 articles included	9528 subjects	Rebleeding, mortality, need for surgery, hospital stay, blood transfusion		Did not perform any stratified analysis with respect to dose and administration	PPI is an effective medication for UGH patients and intravenous PPI exhibits

2016;39:2477- 91					route	equivalent effectiveness and safety in comparison to oral PPI. H2RA is not recommended for UGH patients as patients treated with H2RA are associated with an increased risk of adverse events including rebleeding, need for surgery and all-cause mortality.

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Staerk L, Lip GY, Olesen JB, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation:	Danish retrospective cohort study	4602 patients with atrial fibrillation discharged from hospital after gastrointestinal	Risks of all cause mortality, thromboembolism, major bleeding, and	Compared with non-resumption of treatment, a reduced risk of **all cause mortality** was	Not limited to PUB Main outcomes analysed	Among patients with atrial fibrillation who experience gastrointestinal

nationwide cohort study. *BMJ*. 2015;351:h5876. Published 2015 Nov 16. doi:10.1136/bmj.h5876 Format:		bleeding while receiving antithrombotic treatment. Restarted treatment regimens were single or combined antithrombotic drugs with oral anticoagulation and antiplatelets. Follow-up started 90 days after discharge to avoid confounding from use of previously prescribed drugs on discharge.	recurrent gastrointestinal bleeding were estimated with competing risks models and time dependent multiple Cox regression models.	found in association with restart of oral anticoagulation (HR 0.39, 95% CI 0.34 to 0.46), an antiplatelet agent (0.76, 0.68 to 0.86), and oral anticoagulation plus an antiplatelet agent (0.41, 0.32 to 0.52), and a reduced risk of **thromboembolism** was found in association with restart of oral anticoagulation (0.41, 0.31 to 0.54), an antiplatelet agent (0.76, 0.61 to 0.95), and	after a 90 days of blanking period after hospital discharge	bleeding while receiving antithrombotic treatment; subsequent restart of oral anticoagulation alone was associated with better outcomes for all cause mortality and thromboembolism compared with patients who did not resume treatment. This was despite an increased longitudinal associated risk of bleeding

				oral anticoagulation plus an antiplatelet agent (0.54, 0.36 to 0.82). Restarting oral anticoagulation alone was the only regimen with an increased risk of major bleeding (1.37, 1.06 to 1.77) compared with nonresumption of treatment;		
Witt DM, Delate T, Garcia DA, et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med*. 2012;172(19):1484–1491. doi:10.1001/archinternmed.20	Retrospective cohort stduy	Administrative and clinical databases, patients experiencing GIB during warfarin therapy were categorized according to whether they	Incidence of thrombosis, recurrent GIB, and death, as well as the time to resumption of anticoagulant therapy, during the 90 days following a	442 patients with warfarin-associated index GIB included in the analyses. 260 patients (58.8%) resumed	not all factors that affect clinical decision making could be collected.	he decision to not resume warfarin therapy in the 90 days following a GIB event is associated with increased risk for thrombosis

12.4261 Format:		resumed warfarin therapy after GIB and followed up for 90 days.	GIB event.	warfarin therapy. Warfarin therapy resumption after the index GIB was associated with a lower adjusted risk for thrombosis (hazard ratio [HR], 0.05; 95% CI, 0.01-0.58) and death (HR, 0.31; 95% CI, 0.15-0.62), without significantly increasing the risk for recurrent GIB (HR, 1.32; 95% CI, 0.50-3.57). Median (IQR) time to resumption of warfarin was 4 days (2-9 days).	Underesti mation of warafarin effect on TE and GIB, Not PUB	and death. For many patients who have experienced warfarin-associated GIB, the benefits of resuming anticoagulant therapy will outweigh the risks

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Sung JJ, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018 Gut 2018. PMID 29691276	Clinical Guideline	NA Patients with NVUGIB.	- PPI effect - Antiplatelet and anticoagulant effects - rebleeding - need for surgery - mortality - need for intervention	Statement 14: Among direct oral anticoagulant (DOAC) or warfarin users with high cardiothrombotic risk who develop ulcer bleeding, DOAC or warfarin should be resumed as soon as haemostasis is Established. Statement 13: In patients receiving dual antiplatelet agents, at least one antiplatelet agent should be resumed in	NA	NA

				cases of upper gastrointestinal bleeding		
Sostres C, Marcén B, Laredo V, et al. Risk of rebleeding, vascular events and death after gastrointestinal bleeding in anticoagulant and/or antiplatelet users. *Aliment Pharmacol Ther*. 2019;50(8):919–929. doi:10.1111/apt.15441	Retrospective cohort analysis	871 patients with GIB (25% PUB) taking antithombotic drugs 52.5% used an antiplatelet ;93.1% interrupted treatment after GIB. and 80.5% restarted therapy. Median follow-up was 24.9 months (IQR: 7.0-38.0). -	Rebleeding, vascular events and death.	Resumption of therapy was associated with a higher risk of rebleeding (HR 2.184; 95% CI: 1.357-3.515) but a lower risk of an ischaemic event (HR 0.626; 95% CI: 0.432-0.906) or death (HR 0.606; 0.453-0.804) in a multivariable COX hazards proportional models	Retrospective analysis Mixed patients for all types of bleeding	Resumption of anticoagulant or antiplatelet therapy after a gastrointestinal bleeding event was associated with a lower risk of vascular events and death and a higher rebleeding risk. The benefits of early reinstitution of anticoagulant/antiplatelet therapy outweigh the gastrointestinal-related risks.

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Barkun AN, Almadi M, Kuipers EJ, et al. Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group [published online ahead of print, 2019 Oct 22]. *Ann Intern Med*. 2019;10.7326/M19-1795. doi:10.7326/M19-1795	Guideline	NA	- PPI effect - Antiplatelet and anticoagulant effects - rebleeding - need for surgery - mortality - need for intervention -	In patients with previous ulcer bleeding receiving cardiovascular prophylaxis with single or dual antiplatelet therapy, we suggest using PPI therapy vs. no PPI therapy.	NA	In patients with previous ulcer bleeding receiving cardiovascular prophylaxis with single or dual antiplatelet therapy, we suggest using PPI therapy vs. no PPI therapy.

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Qureshi W, Mittal C, Patsias I, et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation [published correction appears in Am J Cardiol. 2015 Jul 1;116(1):166]. *Am J Cardiol*. 2014;113(4):662–668.	Retrospective cohort stduy	Patients who developed major GIB while taking warfarin Henry Ford Health System with a large catchment area serving all socioeconomic strata, covering majority of Southeast Michigan, United States.	Time-to-event adjusted analyses were performed to find an association of restarting warfarin and recurrent GIB, arterial thromboembolism, and mortality.	1,329 patients developed major GIB. Warfarin was restarted in 653 cases (49.1%). Restarting warfarin was associated with decreased thromboembolism (HR 0.71, 95% CI; 0.54 to 0.93, p [0.01) and reduced mortality (HR 0.67, 95% CI 0.56 to 0.81, p <0.0001) but not recurrent GIB (HR 1.18, 95% CI 0.94 to 1.10, p[0.47). When the outcomes were stratified by duration of warfarin interruption, restarting	Based on claims No able to enunciate all the factors that affect the clinical decision making Detection bias survivorship bias	Decision to restart warfarin after an episode of major GIB is associated with improved survival and decreased thromboembolism without increased risk of GIB after 7 days of interruption.

				warfarin after 7 days was not associated with increased risk of GIB but was associated with decreased risk of mortality and thromboembolism compared with resuming after 30 days of interruption.		

Study Ref.	**Study type**	**Patient group**	**Key outcomes**	**Key results**	**Limitation**	**Conclusion**
Ray WA, Chung CP, Murray KT, Smalley WE, Daugherty JR, Dupont WD, et al. Association of proton pump inhibitors with reduced risk of warfarin-related	retrospective cohort study	97,430 patients beginning warfarin treatment in Tennessee Medicaid and the 5% National Medicare Sample with 75,720 person-	hospitalizations for upper gastrointestinal bleeding potentially preventable by PPIs and for bleeding at other sites.	The risk of hospitalizations due to upper GIB decreased by 24% among patients who received PPI co-therapy (HR, 0.76; 95% CI, 0.63-0.91). There was no significant	Potential misclassification of ASA, NSAID and PPI use.	Overall PPI co-therapy was associated with reduced risk of warfarin-related upper gastrointestinal bleeding; the greatest reduction

serious upper gastrointestinal bleeding. Gastroenterology. 2016;151:1105-12 e10.		years of follow-up.		reduction in the risk of other gastrointestinal bleeding hospitalizations (HR, 1.07; 0.94-1.22) or non-gastrointestinal bleeding hospitalizations (HR, 0.98; 0.84-1.15) in this group. Among patients concurrently using antiplatelet drugs or NSAIDs, the risk decreased by 45% (HR, 0.55; 95% CI, 0.39-0.77) with PPI co-therapy. PPI co-therapy had no significant protective effect for warfarin patients not using antiplatelet drugs or NSAIDs (HR, 0.86; 95% CI, 0.70-1.06). Findings were similar in both study		occurred in patients also taking antiplatelet drugs or NSAIDs.The ffect was not seen in patients with NSAID or antiplatelet use.

				populations.		
Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, et al. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: A population based study. Gastroenterology. 2015;149:586-95 e3.	Retrospective cohort stduy	population-wide database managed by the Hong Kong Hospital Authority. Patients newly prescribed dabigatran (5041 patients) from 2010 through 2013 were included in the analysis.	Risk of GIB in dabigatran users by incidence rate ratio (IRR), adjusted for patient characteristics, comorbidities, and concurrent medications.	The risk of GIB in this population increased among patients 75 years and older (IRR, 2.47; 95% CI, 1.66–3.68), patients with a history of peptic ulcers or GIB (IRR, 2.31; 95% CI, 1.54–3.46), and patients who used aspirin (IRR, 1.52; 95% CI, 1.03–2.24). Concomitant use of gastroprotective agents was associated with a reduced risk of GIB , but it was significant for only upper GIB (IRR, 0.29; 95% CI, 0.15–0.54), and only for patients with a prior history of peptic ulcers or	Potential residual confounding No comparator group or control	The use of gastroprotective agents was associated with a reduced risk of GIB in patients taking dabigatran. The association was stronger for upper GIB than lower GIB, and in patients with a prior history of peptic ulcers or GIB.

				GIB (IRR, 0.14; 95% CI, 0.06–0.30).		

Study Ref.	Study type	Patient group	Key outcomes	Key results	Limitation	Conclusion
Kido K, Scalese MJ. Management of Oral **Anticoagulation** Therapy After **Gastrointestinal Bleeding**: Whether to, When to, and How to Restart an **Anticoagulation** Therapy. Ann Pharmacother. 2017 Nov;51(11):1000-1007	Systematic review	Articles referring to patients with GIB taking anticoagulants	To evaluate current clinical evidence for management of oral anticoagulation therapy after gastrointestinal bleeding (GIB) with an emphasis on whether to, when to, and how to resume an anticoagulation therapy.	9 studies were identified. Four retrospective cohort studies showed that resuming anticoagulation therapy was associated with significantly lower rate of thromboembolism (TE). Meta-analyses and prospective cohort studies also supported this finding. Two retrospective cohort studies indicated an increase in GIB when anti-	Heterogeneous studies and conclusions based on very few studies	Anticoagulation therapy resumption is recommended, with resumption being considered between 7 and 14 days following GIB regardless of the therapy chosen.

				coagulation reinitiation occurred in less than 7 days without a decrease in TE. Resuming therapy between 7 and 15 days did not demonstrate a significant increase in GIB or TE. A large retrospective study showed that apixaban was associated with the significantly lowest risk of GIB compared with both rivaroxaban and dabigatran.		
Moayyedi P, et al Pantoprazole to Prevent Gastroduodenal Events in Patients Receiving Rivaroxaban and/or Aspirin in a Randomized, Double-Blind,	3 × 2 partial factorial double-blind trial	17,598 participants with stable cardiovascular disease and	The primary outcome was time to first upper gastrointestinal	There was no significant difference in upper gastrointestinal	Significance was achieved in post-hoc comparison but not for the	In a randomized placebo-controlled trial, we found that routine use of

Placebo-Controlled Trial. Gastroenterology. 2019 Aug;157(2):403-412		peripheral artery disease. Participants were randomly assigned to groups given pantoprazole 40 mg daily or placebo, as well as rivaroxaban 2.5 mg twice daily with aspirin 100 mg once daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg alone.	event, defined as a composite of overt bleeding, upper gastrointestinal bleeding from a gastroduodenal lesion or of unknown origin, occult bleeding, symptomatic gastroduodenal ulcer or ≥5 erosions, upper gastrointestinal obstruction, or perforation.	events between the pantoprazole group and the placebo group (hazard ratio, 0.88; 95%CI, 0.67-1.15). Pantoprazole significantly reduced bleeding of gastroduodenal lesions (HR 0.52; 95% confidence interval, 0.28-0.94; P = .03); when a post-hoc definition of bleeding gastroduodenal lesion was used (HR 0.45; 95% confidence interval, 0.27-0.74), athe NNT was 982; 95% CI, 609-2528).	primary outcome. The number of bleeding upper GI events was still small.	proton pump inhibitors in patients receiving low-dose anticoagulation and/or aspirin for stable cardiovascular disease does not reduce upper gastrointestinal events, but may reduce bleeding from gastroduodenal lesions.
Hernandez I, Zhang Y, Brooks MM, et al. Anticoagulation use	Retrospective cohort	2010 to 2012 Medicare Part D	To evaluate anticoagulation	Resumption of anticoagulation	No information about the INR,	Dabigatran was associated with

and clinical outcomes after major bleeding on dabigatran or warfarin in atrial fibrillation. Stroke 2017;48:159–66.	study	data, we identified atrial fibrillation patients who experienced a major bleeding event while using warfarin (n=1135) or dabigatran (n=404) and categorized them by their posthemorrhage use of anticoagulation.	use after a first major bleed on warfarin or dabigatran and, second, to compare effectiveness and safety outcomes between patients discontinuing anticoagulation after a major bleed and patients restarting warfarin or dabigatran	with warfarin (hazard ratio [HR] 0.76; 95% CI 0.59–0.97) or dabigatran (HR 0.66; 95% CI 0.44–0.99) was associated with lower combined risk of ischemic stroke and all-cause mortality than anticoagulation discontinuation. The incidence of recurrent major bleeding was higher for patients prescribed warfarin after the event than for those prescribed dabigatran (HR 2.31; 95% CI 1.19–4.76) or whose anticoagulation	which may have affected the decision to restart anticoagulation therapy in patients who bled on warfarin. **No stratified by the anatomic location of the index bleeding** **event.** No stratified by the dose of dabigatran used.	a superior benefit/risk ratio than warfarin and anticoagulation discontinuation in the treatment of atrial fibrillation patients who have survived a major bleed.

				ceased (HR 1.56; 95% CI 1.10–2.22), but did not differ between patients restarting dabigatran and those discontinuing anticoagulation (HR 0.65; 95% CI 0.32–1.33).		
Sengupta N, Marshall AL, Jones BA, Ham S, Tapper EB. Rebleeding vs Thromboembolism After Hospitalization for Gastrointestinal Bleeding in Patients on Direct Oral Anticoagulants. *Clin Gastroenterol Hepatol*. 2018;16(12):1893–1900.e2. doi:10.1016/j.cgh.2018.05.005	Retrospective cohort study	Medical claims data from the Truven Health Marketscan Commercial Claims and Encounters Database, from January 1, 2010, through December 31, 2014. 1338 adults treated with DOACs and hospitalized for GIB (dabigatran, n = 679; rivaroxaban, n =	Frequency at which patients resume DOAC therapy following hospitalization for GIB in a real-world setting, and the risks and benefits.	Higher proportions of patients who did not resume DOAC had heart failure, received blood, and required intensive care. Restarting DOAC therapy within 30 days was not associated with thromboembolism within 90 days (HR, 0.98; 95% CI, 0.37–2.21) or recurrent GIB	They may not have captured all follow-up rebleeding and thromboembolic events, or outpatient adverse outcomes It does not capture outpatient mortality Events They did not	Resuming DOAC therapy was not associated with thromboembolism within 90 days or recurrence of GIB; a history of venous thromboembolism and thienopyridine use were associated with a risk of subsequent thromboembolism and GIB

		608, apixaban, n = 51).		(HR, 1.44; 95% CI 0.72–2.68).). A higher proportion of patients who resumed treatment with rivaroxaban, compared with other DOACs, had recurrence of GIB . The median time to refilling a claim for DOAC after GIB was 40 days (IQR, 17–88 d)	search claims for warfarin after index discharge, some patients were switched from DOAC to warfarin, and consequently were categorized as not having a DOAC resumed	respectively.
Sengupta N, Feuerstein JD, Patwardhan VR, et al. The risks of thromboembolism vs. recurrent gastrointestinal bleeding after interruption of systemic anticoagulation in hospitalized inpatients with gastrointestinal bleeding: a prospective study [published correction appears in Am J	Propsective cohort study	197 Patients admitted to the hospital who had GIB while on systemic anticoagulation.	Safety and risk of continuation of anticoagulation after GIB	Anticoagulation continuation was independently associated on multivariate regression with a lower risk of major thrombotic	Residual confounding by indication There is also a significant amount of heterogeneity in the cohort. Survival bias	Restarting anticoagulation at discharge after GIB was associated with fewer thromboembolic events without a significantly increased risk of

Gastroenterol. 2015 Mar;110(3):480]. *Am J Gastroenterol*. 2015;110(2):328–335. doi:10.1038/ajg.2014.398 Format:				episodes within 90 days (hazard ratio (HR)=0.121, 95% CI =0.006-0.812, P=0.03). Patients with any malignancy at time of GIB had an increased risk of thromboembolism in follow-up (HR=6.1, 95% CI=1.18-28.3, P=0.03). Anticoagulation continuation at discharge was not significantly associated with an increased risk of recurrent GIB at 90 days (HR=2.17, 95% CI=0.861-6.67, P=0.10) or death within 90 days (HR=0.632, 95% CI=0.216-1.89, P=0.40)	may have affected the primary outcome. Patients lost to follow-up	recurrent GIB at 90 days. The benefits of continuing anticoagulation at discharge may outweigh the risks of recurrent GIB.

Chai-Adisaksopha C, Hillis C, Monreal M, Witt DM, Crowther M. Thromboembolic events, recurrent bleeding and mortality after resuming anticoagulant following gastrointestinal bleeding. A meta-analysis. *Thromb Haemost*. 2015;114(4):819–825. doi:10.1160/TH15-01-0063	Systematic review of phase III randomised controlled trials and cohort studies	patients with atrial fibrillation or venous thromboembolism who received oral anticoagulant.	Risk of thromboembolism, recurrent GI bleeding and mortality for patients on long-term anticoagulation who experience GI bleeding based on whether anticoagulation therapy was resumed.	Three studies were included in the meta-analysis. The resumption of warfarin was associated with a significant reduction in thromboembolic events (HR 0.68, 95% CI 0.52 - 0.88, p<0.004, I^2=82%). There was a not statistically significant increase in recurrent GI bleeding in patients who restarted warfarin compared to those who did not (HR 1.20, 95% CI 0.97 to 1.48). Resumption of warfarin was associated with significant	Few studies in the meta-analysis. Heterogeneity of patients and intervention. Serious risk of bias	This meta-analysis demonstrates that resumption of warfarin following interruption due to GI bleeding is associated with a reduction in thromboembolic events and mortality without a statistically

				reduction in mortality (HR 0.76, 95% CI 0.66 to 0.88).		
Little D, Chai-Adisaksopha C, Hillis C, et al. Resumption of anticoagulant therapy after anticoagulant-related gastrointestinal bleeding: A systematic review and meta-analysis. *Thromb Res*. 2019;175:102–109. doi:10.1016/j.thromres.2019.01.020	Systematic review and meta-analysis	EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials for new references from January 2014 to September 2017. Randomized controlled trials and observational studies involving adults with OAC-related GI bleeding were included.	Risks of recurrent GI bleeding, thromboembolism, and death in patients who resumed OAC compared to those who did not.	12 observational studies involving 3098 patients. There was an increased risk of recurrent GI bleeding (RR 1.91, 95% CI 1.47-2.48, and a reduced risk of thrombo-embolism (RR 0.30, 95% CI 0.13-0.68,) and death (RR 0.51, 95% CI 0.38-0.70, I^2 = 71.8%, 8 studies) in patients who resumed OAC compared to those who did not.	11 of 12 studies were judged to be at serious risk of bias due to confounding	Resuming OAC after OAC-related GI bleeding appears to be associated with an increase in recurrent GI bleeding, but a reduction in thromboembolism and death.

Majeed A, Wallvik N, Eriksson J, et al. Optimal timing of vitamin K antagonist resumption after upper gastrointestinal bleeding. A risk modelling analysis. *Thromb Haemost*. 2017;117(3):491–499. doi:10.1160/TH16-07-0498	Risk Modelling Analysis	Data on the bleeding location, timing of VKA resumption, recurrent GI bleeding and thromboembolic events were collected from a cohort of patients with upper GIB taking Vit K anticoagulants	'total risk', based on the sum of the cumulative rates of recurrent GI bleeding and thromboembolic events, depending on the timing of VKA resumption	121 (58 %) of 207 patients with VKA-associated upper GI bleeding were restarted on anticoagulation after a median (interquartile range) of one (0.2-3.4) week after the index bleeding. Restarting VKAs was associated with a reduced risk of thromboembolism (HR 0.19; 95 % CI, 0.07-0.55) and death (HR 0.61; 95 % CI, 0.39-0.94), but with an increased risk of recurrent GI bleeding (HR 2.5; 95 % CI, 1.4-4.5). The composite risk obtained from the combined	Modelling risk analysis based on very few cases	The optimal timing of VKA resumption after VKA-associated upper GI bleeding appears to be between 3-6 weeks after the index bleeding event but has to take into account the degree of thromboembolic risk, patient values and preferences

				statistical model of recurrent GI bleeding, and thromboembolism decreased if VKAs were resumed after three weeks and reached a nadir at six weeks after the index GI bleeding.		

First author, year, ref	Study design, participants (n)	Intervention/ Exposure	Outcome	Remarks
Ford, 2016 [4]	MA (34 RCTs, 3,910)	ET+UHD vs. UHD for DU healing	12.4% vs 18.7% ulcer persistence, RR 0.66; 95% CI 0.58-0.76	ET+UHD superior to DU healing (low quality evidence)

	MA (2 RCTs, 207)	ET vs. NT for DU healing	21.7% vs. 58.5% ulcer persistence, RR 0.37; 95% CI 0.26-0.53	ET superior to NT for DU healing (low quality evidence)
	MA (15 RCTs, 1,974)	ET+UHD vs. UHD for GU healing	16.0% vs. 13.0% ulcer persistence, RR 1.23; 95% CI 0.90-1.68	Imprecise differences (very low quality evidence)
	MA (4 RCTs, 319)	ET vs. UHD for DU recurrence prevention	11.9% vs. 16.3% ulcer recurrence, RR 0.73; 95% CI 0.42-1.25	Imprecise differences (very low quality evidence)
First author, year, ref	**Study design, participants (n)**	**Intervention/ Exposure**	**Outcome**	**Remarks**

Ford, 2016 [4]	MA (27 RCTs, 2,509)	ET vs. NT for DU recurrence prevention	12.9% vs. 64.4% ulcer recurrence, RR 0.20; 95% CI 0.15-0.26	ET superior to NT for DU recurrence prevention (very low quality evidence)
	MA (12 RCTs, 1,476)	ET vs. NT for GU recurrence prevention	16.3% vs. 52.4% ulcer recurrence, RR 0.31; 95% CI 0.22-0.45	ET superior to NT for GU recurrence prevention (very low quality evidence)
Chang, 2015 [5]	R (1,920)	ET initiation within >120 vs. ≤ 120 days after PUB diagnosis	HR 1.52; 95% CI 1.13-2.04; p= 0.006	ET better initiated within 120 days of PUB diagnosis
Hung, 2019 [6]	R (830)	Hp testing in acute NVUGIH (within first 60 days) vs. no testing	ICU hospitalization: OR, 0.42; 95% CI, 0.27-0.66. Rebleeding and mortality in first	Hp testing better in acute setting of NVUGIH

			year: 22% vs. 47%, p<0.01; HR, 0.49; 95% CI, 0.36-0.67	
First author, year, ref	**Study design, participants (n)**	**Intervention/ Exposure**	**Outcome**	**Remarks**
Sverdén, 2018 [7]	R (29,032)	ET initiation within 8-30, 31-60, 61-365, >365 days vs. 7 days after PUB diagnosis	Ulcer recurrence HRs: 1.17 (95% CI, 1.08-1.25), 2.37 (95% CI, 2.16-2.59), 2.96 (95% CI, 2.76-3.16) and 3.55 (95% CI, 3.33-3.79) Complicated ulcer HRs: 1.55 (95% CI, 1.35-1.78), 3.19 (95% CI, 2.69-3.78), 4.00 (95% CI, 3.51-4.55) and 6.14, (95% CI, 5.47-6.89)	ET better initiated within 7 days of PUB diagnosis