# Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

**Authors** Ian M. Gralnek[1,2], Jean-Marc Dumonceau[3], Ernst J. Kuipers[4], Angel Lanas[5], David S. Sanders[6], Matthew Kurien[6], Gianluca Rotondano[7], Tomas Hucl[8], Mario Dinis-Ribeiro[9], Riccardo Marmo[10], Istvan Racz[11], Alberto Arezzo[12], Ralf-Thorsten Hoffmann[13], Gilles Lesur[14], Roberto de Franchis[15], Lars Aabakken[16], Andrew Veitch[17], Franco Radaelli[18], Paulo Salgueiro[19], Ricardo Cardoso[20], Luís Maia[19], Angelo Zullo[21], Livio Cipolletta[22], Cesare Hassan[23]

**Institutions** Institutions listed at end of article.

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**Corresponding author**
***Ian M. Gralnek, MD, MSHS***
Institute of Gastroenterology and Liver Diseases, Ha'Emek Medical Center
Rappaport Faculty of Medicine, Technion-Israel Institute of Technology
Afula, Israel 18101
Fax: +972-4-6495314
ian_gr@clalit.org.il

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). It addresses the diagnosis and management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH).

## Main Recommendations

**MR1.** 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, moderate quality evidence).

**MR2.** ESGE recommends a restrictive red blood cell transfusion strategy that aims for a target hemoglobin between 7 g/dL and 9 g/dL. A higher target hemoglobin should be considered in patients with significant co-morbidity (e.g., ischemic cardiovascular disease) (strong recommendation, moderate quality evidence).

**MR3.** ESGE recommends the use of the Glasgow-Blatchford Score (GBS) for pre-endoscopy risk stratification. Outpatients determined to be at very low risk, based upon a GBS score of 0 – 1, do not require early endoscopy nor hospital admission. Discharged patients should be informed of the risk of recurrent bleeding and be advised to maintain contact with the discharging hospital (strong recommendation, moderate quality evidence).

**MR4.** ESGE recommends initiating high dose intravenous proton pump inhibitors (PPI), intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour), in patients presenting with acute UGIH awaiting upper endoscopy. However, PPI infusion should not delay the performance of early endoscopy (strong recommendation, high quality evidence).

**MR5.** ESGE does not recommend the routine use of nasogastric or orogastric aspiration/lavage in patients presenting with acute UGIH (strong recommendation, moderate quality evidence).

**MR6.** ESGE recommends intravenous erythromycin (single dose, 250 mg given 30 – 120 minutes prior to upper gastrointestinal [GI] endoscopy) in patients with clinically severe or ongoing active UGIH. In selected patients, pre-endoscopic infusion of erythromycin significantly improves endoscopic visualization, reduces the need for second-look endoscopy, decreases the number of units of blood transfused, and reduces duration of hospital stay (strong recommendation, high quality evidence).

**MR7.** Following hemodynamic resuscitation, ESGE recommends early (≤ 24 hours) upper GI endoscopy. Very early (< 12 hours) upper GI endoscopy may be considered in patients with high risk clinical features, namely: hemodynamic instability (tachycardia, hypotension) that persists despite ongoing attempts at volume resuscitation; in-hospital bloody emesis/nasogastric aspirate; or contraindication to the interruption of anticoagulation (strong recommendation, moderate quality evidence).

**MR8.** ESGE recommends that peptic ulcers with spurting or oozing bleeding (Forrest classification Ia and Ib, respectively) or with a nonbleeding visible vessel (Forrest classification IIa) receive endoscopic hemostasis because these lesions are at high risk for persistent bleeding or rebleeding (strong recommendation, high quality evidence).

**MR9.** ESGE recommends that peptic ulcers with an adherent clot (Forrest classification IIb) be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding (Forrest classification Ia or Ib) or nonbleeding visible vessel (Forrest classification IIa) should receive endoscopic hemostasis (weak recommendation, moderate quality evidence).

**MR10.** In patients with peptic ulcers having a flat pigmented spot (Forrest classification IIc) or clean base (Forrest classification III), ESGE does not recommend endoscopic hemostasis as these stigma-

ta present a low risk of recurrent bleeding. In selected clinical settings, these patients may be discharged to home on standard PPI therapy, e. g., oral PPI once-daily (strong recommendation, moderate quality evidence).

**MR11.** ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy. If used, it should be combined with a second endoscopic hemostasis modality (strong recommendation, high quality evidence).

**MR12.** ESGE recommends PPI therapy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. PPI therapy should be high dose and administered as an intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour) for 72 hours post endoscopy (strong recommendation, high quality evidence).

**MR13.** ESGE does not recommend routine second-look endoscopy as part of the management of nonvariceal upper gastrointestinal hemorrhage (NVUGIH). However, in patients with clinical evidence of rebleeding following successful initial endoscopic hemostasis, ESGE recommends repeat upper endoscopy with hemostasis if indicated. In the case of failure of this second attempt at hemostasis, transcatheter angiographic embolization (TAE) or surgery should be considered (strong recommendation, high quality evidence).

**MR14.** In patients with NVUGIH secondary to peptic ulcer, ESGE recommends investigating for the presence of *Helicobacter pylori* in the acute setting with initiation of appropriate antibiotic therapy when *H. pylori* is detected. Re-testing for *H. pylori* should be performed in those patients with a negative test in the acute setting. Documentation of successful *H. pylori* eradication is recommended (strong recommendation, high quality evidence).

**MR15.** In patients receiving low dose aspirin for secondary cardiovascular prophylaxis who develop peptic ulcer bleeding, ESGE recommends aspirin be resumed immediately following index endoscopy if the risk of rebleeding is low (e. g., FIIc, FIII). In patients with high risk peptic ulcer (FIa, FIb, FIIa, FIIb), early reintroduction of aspirin by day 3 after index endoscopy is recommended, provided that adequate hemostasis has been established (strong recommendation, moderate quality evidence).

## Abbreviations

| | |
|---|---|
| APC | argon plasma coagulation |
| ASA | American Society of Anesthesiologists |
| DAPT | dual antiplatelet therapy |
| $CHADS_2$ | 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 |
| INR | international normalized ratio |
| NBVV | nonbleeding visible vessel |
| NNT | number needed to treat |
| NOAC | non-VKA oral anticoagulant |
| NVUGIH | nonvariceal upper gastrointestinal hemorrhage |
| PAR | protease-activated receptor |
| PCC | prothrombin complex concentrate |
| PICO | patients, interventions, controls, outcomes |
| PPI | proton pump inhibitor |
| OR | odds ratio |
| PUB | peptic ulcer bleeding |
| RBC | red blood cell |
| RCT | randomized controlled trial |
| RR | relative risk *or* risk ratio |
| TAE | transcatheter angiographic embolization |
| UGIH | upper gastrointestinal hemorrhage |
| VCE | videocapsule endoscopy |
| VKA | vitamin K antagonist |

## Introduction

Acute upper gastrointestinal hemorrhage (UGIH) is a common condition worldwide that has an estimated annual incidence of 40–150 cases per 100 000 population [1, 2], frequently leads to hospital admission, and has significant associated morbidity and mortality, especially in the elderly. The most common causes of acute UGIH are nonvariceal [1, 2]. This includes peptic ulcers, 28 %–59 % (duodenal ulcer 17 %–37 % and gastric ulcer 11 %–24 %); mucosal erosive disease of the esophagus/stomach/duodenum, 1 %–47 %; Mallory–Weiss syndrome, 4 %–7 %; upper GI tract malignancy, 2 %–4 %; other diagnosis, 2 %–7 %; or no exact cause identified, 7 %–25 % [1, 2]. Moreover, in 16 %–20 % of acute UGIH cases, more than one endoscopic diagnosis may be identified as the cause of bleeding. The aim of this evidence-based consensus guideline is to provide medical caregivers with a comprehensive review and recommendations on the clinical and endoscopic management of NVUGIH.

## Methods

The ESGE commissioned this guideline on NVUGIH and appointed a guideline leader (I.M.G.) who in collaboration with the Chair of the ESGE Guidelines Committee (C.H.), invited the listed authors to participate in the guideline development and review. Key questions were prepared by the coordinating team (I.M.G. and C.H.) and reviewed and approved by all task force members. The coordinating team formed four task force subgroups, each with its own coordinator, and divided the key topics/questions amongst these four task force subgroups (see **Appendix e1**, online-only). Task force members included gastroenterologists/gastrointestinal endoscopists, an interventional radiologist, and a surgeon. Clinical questions were formulated using the PICO (patients, interventions, controls, outcomes) methodology.

Each task force subgroup performed a systematic literature search to identify the relevant literature that was subsequently used to prepare evidence-based, well-balanced statements on each of their assigned key questions. The Ovid MEDLINE, EMBASE, Google/Google Scholar, and the Cochrane Database of Sys-

tematic Reviews were searched for English-language articles including at a minimum the following key words: nonvariceal upper gastrointestinal (GI) hemorrhage/bleeding, peptic ulcer hemorrhage/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, aspirin, dual anti-platelet therapy (DAPT), anti-coagulation/anti-coagulant, direct/new oral anticoagulants (DOACs), coagulopathy, vitamin K inhibitor/antagonist, prokinetic agent, erythromycin, fresh frozen plasma, nasogastric tube, orogastric tube, proton pump inhibitor, prokinetic agent, erythromycin, endoscopic hemostasis, injection therapy, thermal therapy (contact, non-contact), mechanical therapy/endoscopic clipping, topical hemostasis therapy, second-look endoscopy, helicobacter pylori, *H. pylori*, transcatheter angiographic embolization (TAE), and surgery. The hierarchy of studies included as part of 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. All selected articles were graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [3,4].

Each task force subgroup proposed statements for each of their assigned key questions which were discussed and voted on during the NVUGIH task force guideline meeting held in Berlin, Germany in November 2014. In August 2015, a manuscript draft prepared by I.M.G. was sent to all task force members. After agreement on a final version, the manuscript was reviewed by two members of the ESGE Governing Board and sent for further comments to the National Societies and ESGE individual members. After agreement on a final version, the manuscript was submitted to the journal *Endoscopy* for publication. All authors agreed on the final revised manuscript.

This NVUGIH guideline will be considered for review and updating in 2020, or sooner if new relevant evidence becomes available. Any updates to this guideline in the interim will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

## Statements and recommendations

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See **Table 1**.

### Initial patient evaluation and hemodynamic resuscitation

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, moderate quality evidence).

The goals of hemodynamic resuscitation are to correct intravascular hypovolemia, restore adequate tissue perfusion, and prevent multi-organ failure. Early intensive hemodynamic resuscitation of patients with acute UGIH has been shown to significantly decrease mortality [5]. In an observational study of patients with acute UGIH and hemodynamic instability, patients who received intensive hemodynamic resuscitation had significantly fewer myocardial infarctions and lower mortality compared with those in the "observation group" ($P=0.04$ for both comparisons). However, there is no evidence from randomized controlled trials (RCTs), for or against early or large-volume intravenous fluid administration in uncontrolled hemorrhage [6,7]. Moreover, the selection of resuscitation fluid type in critically ill patients requires careful consideration based on safety, effects on patient outcomes, and costs. To date, there is ongoing uncertainty regarding the ideal fluid administration strategy in this clinical setting [8,9].

ESGE recommends a restrictive red blood cell transfusion strategy that aims for a target hemoglobin between 7 g/dL and 9 g/dL. A higher target hemoglobin should be considered in patients with significant co-morbidity (e.g., ischemic cardiovascular disease) (strong recommendation, moderate quality evidence).

The use of red blood cell (RBC) transfusions may be lifesaving following massive UGIH. However, the role of RBC transfusion in less torrential GI bleeding remains controversial, with uncertainty existing regarding the hemoglobin level at which blood transfusion should be initiated. This uncertainty reflects concerns from both the critical care and gastroenterology literature suggesting poorer outcomes in patients managed with a liberal RBC transfusion strategy [2,10,11]. In a recent RCT that included 921 patients presenting with all causes of acute UGIH, a restrictive RBC transfusion strategy (target hemoglobin, 7 to 9 g/dL) was compared with a more liberal transfusion strategy (target hemoglobin, 9 to 11 g/dL) [12]. The restrictive RBC transfusion group had significantly improved 6-week survival (95% vs. 91%; hazard ratio [HR] 0.55, 95% confidence interval [CI] 0.33–0.92) and reduced rebleeding (10% vs.16%; HR 0.68, 95%CI 0.47–0.98) [12]. In the subgroup of patients with NVUGIH (n=699), there was a statistical trend towards lower mortality in the restrictive vs. liberal RBC transfusion strategy (3.7% vs. 6.9%, $P=0.065$). Because the study was not powered to specifically evaluate NVUGIH, these findings should be interpreted with caution. Other limitations of this study include the exclusion of patients with massive exsanguinating bleeding and defined co-morbidities. Furthermore, all patients underwent endoscopy within 6 hours of presentation, which may not be feasible in everyday clinical practice. Coagulopathy at the time of NVUGIH presentation is another frequent and adverse prognostic factor [13]. Published data for the management of coagulopathy are limited and inconclusive. One small cohort study using an historical comparison group showed that aggressive volume resuscitation, including correction of coagulopathy (international normalized ratio [INR]<1.8), led to an improvement in mortality outcomes [5]. In a systematic review that evaluated the relevance of initial INR before correction in patients with NVUGIH, INR did not appear to predict rebleeding, yet after adjusting for potential confounders, an initial INR>1.5 predicted mortality (odds ratio [OR] 1.96, 95%CI 1.13–3.41) [14]. This may in part reflect the presence of underlying liver disease. There is however no available evidence to help guide coagulopathy correction in critically ill patients and wide variation in management exists in this area, indicating clinical uncertainty regarding optimal practice [15]. Platelet count has not been shown to be a predictor of either rebleeding or mortality. Currently, there is no high quality evidence to guide platelet transfusion thresholds, although a platelet transfusion threshold of $50\times10^9$/L has been proposed for most patients, with a target of $10\times10^9$/L for patients in whom platelet dysfunction is suspected [16].

**Table 1** Summary of Guideline statements and recommendations. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

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|---|
| **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, moderate quality evidence). |
| 2 ESGE recommends a restrictive red blood cell transfusion strategy that aims for a target hemoglobin between 7 g/dL and 9 g/dL. A higher target hemoglobin should be considered in patients with significant co-morbidity (e. g., ischemic cardiovascular disease) (strong recommendation, moderate quality evidence). |
| **Risk stratification** |
| 3 ESGE recommends the use of a validated risk stratification tool to stratify patients into high and low risk groups. Risk stratification can aid clinical decision making regarding timing of endoscopy and hospital discharge (strong recommendation, moderate quality evidence). |
| 4 ESGE recommends the use of the Glasgow-Blatchford Score (GBS) for pre-endoscopy risk stratification. Outpatients determined to be at very low risk, based upon a GBS score of 0 – 1, do not require early endoscopy nor hospital admission. Discharged patients should be informed of the risk of recurrent bleeding and be advised to maintain contact with the discharging hospital (strong recommendation, moderate quality evidence). |
| **Pre-endoscopy management** |
| 5 For patients taking vitamin K antagonists (VKAs), ESGE recommends withholding the VKA and correcting coagulopathy while taking into account the patient's cardiovascular risk in consultation with a cardiologist. In patients with hemodynamic instability, administration of vitamin K, supplemented with intravenous prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) if PCC is unavailable, is recommended (strong recommendation, low quality evidence). |
| 6 If the clinical situation allows, ESGE suggests an international normalized ratio (INR) value < 2.5 before performing endoscopy with or without endoscopic hemostasis (weak recommendation, moderate quality evidence). |
| 7 ESGE recommends temporarily withholding new direct oral anticoagulants (DOACs) in patients with suspected acute NVUGIH in coordination/consultation with the local hematologist/cardiologist (strong recommendation, very low quality evidence). |
| 8 For patients using antiplatelet agents, ESGE recommends the management algorithm detailed in **Fig. 2** (strong recommendation, moderate quality evidence). |
| 9 ESGE recommends initiating high dose intravenous proton pump inhibitors (PPI), intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour), in patients presenting with acute UGIH awaiting upper endoscopy. However, PPI infusion should not delay the performance of early endoscopy (strong recommendation, high quality evidence). |
| 10 ESGE does not recommend the use of tranexamic acid in patients with NVUGIH (strong recommendation, low quality evidence). |
| 11 ESGE does not recommend the use of somatostatin, or its analogue octreotide, in patients with NVUGIH (strong recommendation, low quality evidence). |
| 12 ESGE recommends intravenous erythromycin (single dose, 250 mg given 30 – 120 minutes prior to upper GI endoscopy) in patients with clinically severe or ongoing active UGIH. In selected patients, pre-endoscopic infusion of erythromycin significantly improves endoscopic visualization, reduces the need for second-look endoscopy, decreases the number of units of blood transfused, and reduces duration of hospital stay (strong recommendation, high quality evidence). |
| 13 ESGE does not recommend the routine use of nasogastric or orogastric aspiration/lavage in patients presenting with acute UGIH (strong recommendation, moderate quality evidence). |
| 14 In an effort to protect the patient's airway from potential aspiration of gastric contents, ESGE suggests endotracheal intubation prior to endoscopy in patients with ongoing active hematemesis, encephalopathy, or agitation (weak recommendation, low quality evidence). |
| 15 ESGE recommends adopting the following definitions regarding the timing of upper GI endoscopy in acute overt UGIH relative to patient presentation: very early < 12 hours, early ≤ 24 hours, and delayed > 24 hours (strong recommendation, moderate quality evidence). |
| 16 Following hemodynamic resuscitation, ESGE recommends early ( ≤ 24 hours) upper GI endoscopy. Very early ( < 12 hours) upper GI endoscopy may be considered in patients with high risk clinical features, namely: hemodynamic instability (tachycardia, hypotension) that persists despite ongoing attempts at volume resuscitation; in-hospital bloody emesis/nasogastric aspirate; or contraindication to the interruption of anticoagulation (strong recommendation, moderate quality evidence). |
| 17 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, moderate quality evidence). |
| **Endoscopic therapy (peptic ulcer bleeding)** |
| 18 ESGE recommends the Forrest (F) classification be used in all patients with peptic ulcer hemorrhage in order to differentiate low and high risk endoscopic stigmata (strong recommendation, high quality evidence). |
| 19 ESGE recommends that peptic ulcers with spurting or oozing bleeding (Forrest classification Ia and Ib respectively), or with a nonbleeding visible vessel (Forrest classification IIa) receive endoscopic hemostasis because these lesions are at high risk for persistent bleeding or rebleeding (strong recommendation, high quality evidence). |
| 20 ESGE recommends that peptic ulcers with an adherent clot (Forrest classification IIb) be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding (Forrest classification Ia or Ib) or nonbleeding visible vessel (Forrest classification IIa) should receive endoscopic hemostasis (weak recommendation, moderate quality evidence). |
| 21 In patients with peptic ulcers having a flat pigmented spot (Forrest classification IIc) or clean base (Forrest classification III), ESGE does not recommend endoscopic hemostasis as these stigmata present a low risk of recurrent bleeding. In selected clinical settings, these patients may be discharged to home on standard PPI therapy, e. g., oral PPI once-daily (strong recommendation, moderate quality evidence). |
| 22 ESGE does not recommend the routine use of Doppler ultrasound or magnification endoscopy in the evaluation of endoscopic stigmata of peptic ulcer bleeding (strong recommendation, low quality evidence). |
| 23 For patients with actively bleeding ulcers (FIa, FIb), ESGE recommends combining epinephrine injection with a second hemostasis modality (contact thermal, mechanical therapy, or injection of a sclerosing agent). ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy (strong recommendation, high quality evidence). |

**Table 1** (Continuation)

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| **Initial patient evaluation and hemodynamic resuscitation** |
| 24 For patients with nonbleeding visible vessel (FIIa), ESGE recommends mechanical therapy, thermal therapy, or injection of a sclerosing agent as monotherapy or in combination with epinephrine injection. ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy (strong recommendation, high quality evidence). |
| 25 For patients with active NVUGIH bleeding not controlled by standard endoscopic hemostasis therapies, ESGE suggests the use of a topical hemostatic spray or over-the-scope clip as salvage endoscopic therapy (weak recommendation, low quality evidence). |
| **Endoscopic therapy (other causes of NVUGIH)** |
| 26 For patients with acid-related causes of NVUGIH different from peptic ulcers (e. g., erosive esophagitis, gastritis, duodenitis), ESGE recommends treatment with high dose PPI. Endoscopic hemostasis is usually not required and selected patients may be discharged early (strong recommendation, low quality evidence). |
| 27 ESGE recommends that patients with a Mallory – Weiss lesion that is actively bleeding receive endoscopic hemostasis. There is currently inadequate evidence to recommend a specific endoscopic hemostasis modality. Patients with a Mallory – Weiss lesion and no active bleeding can receive high dose PPI therapy alone (strong recommendation, moderate quality evidence). |
| 28 ESGE recommends that a Dieulafoy lesion receive endoscopic hemostasis using thermal, mechanical (hemoclip or band ligation), or combination therapy (dilute epinephrine injection combined with contact thermal or mechanical therapy) (strong recommendation, moderate quality evidence). Transcatheter angiographic embolization (TAE) or surgery should be considered if endoscopic treatment fails or is not technically feasible (strong recommendation, low quality evidence). |
| 29 In patients bleeding from upper GI angioectasias, ESGE recommends endoscopic hemostasis therapy. However, there is currently inadequate evidence to recommend a specific endoscopic hemostasis modality (strong recommendation, low quality evidence). |
| 30 In patients bleeding from upper GI neoplasia, ESGE recommends considering endoscopic hemostasis in order to avert urgent surgery and reduce blood transfusion requirements. However, no currently available endoscopic treatment appears to have long-term efficacy (weak recommendation, low quality evidence). |
| **Post endoscopy/endoscopic hemostasis management** |
| 31 ESGE recommends PPI therapy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. PPI therapy should be high dose and administered as an intravenous bolus followed by continuous infusion (80 mg then 8 mg /hour) for 72 hours post endoscopy (strong recommendation, high quality evidence). |
| 32 ESGE suggests considering PPI therapy as intermittent intravenous bolus dosing (at least twice-daily) for 72 hours post endoscopy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. If the patient's condition permits, high dose oral PPI may also be an option in those able to tolerate oral medications (weak recommendation, moderate quality evidence). |
| 33 In patients with clinical evidence of rebleeding following successful initial endoscopic hemostasis, ESGE recommends repeat upper endoscopy with hemostasis if indicated. In the case of failure of this second attempt at hemostasis, transcatheter angiographic embolization (TAE) or surgery should be considered (strong recommendation, high quality evidence). |
| 34 ESGE does not recommend routine second-look endoscopy as part of the management of NVUGIH. However, second-look endoscopy may be considered in selected patients at high risk for rebleeding (strong recommendation, high quality evidence). |
| 35 In patients with NVUGIH secondary to peptic ulcer, ESGE recommends investigating for the presence of *Helicobacter pylori* in the acute setting with initiation of appropriate antibiotic therapy when *H. pylori* is detected. Re-testing for *H. pylori* should be performed in those patients with a negative test in the acute setting. Documentation of successful *H. pylori* eradication is recommended (strong recommendation, high quality evidence). |
| 36 ESGE recommends restarting anticoagulant therapy following NVUGIH in patients with an indication for long-term anticoagulation. The timing for resumption of anticoagulation should be assessed on a patient by patient basis. Resuming warfarin between 7 and 15 days following the bleeding event appears safe and effective in preventing thromboembolic complications for most patients. Earlier resumption, within the first 7 days, may be indicated for patients at high thrombotic risk (strong recommendation, moderate quality evidence). |
| 37 In patients receiving low dose aspirin for primary cardiovascular prophylaxis who develop peptic ulcer bleeding, ESGE recommends withholding aspirin, re-evaluating the risks/benefits of ongoing aspirin use in consultation with a cardiologist, and resuming low dose aspirin following ulcer healing or earlier if clinically indicated (strong recommendation, low quality evidence). |
| 38 In patients receiving low dose aspirin for secondary cardiovascular prophylaxis who develop peptic ulcer bleeding, ESGE recommends aspirin be resumed immediately following index endoscopy if the risk of rebleeding is low (e. g., FIIc, FIII). In patients with high risk peptic ulcer (FIa, FIb, FIIa, FIIb), early reintroduction of aspirin by day 3 after index endoscopy is recommended, provided that adequate hemostasis has been established (strong recommendation, moderate quality evidence). |
| 39 In patients receiving dual antiplatelet therapy (DAPT) who develop peptic ulcer bleeding, ESGE recommends continuing low dose aspirin therapy. Early cardiology consultation should be obtained regarding the timing of resuming the second antiplatelet agent (strong recommendation, low quality evidence). |
| 40 In patients requiring dual antiplatelet therapy (DAPT) and who have had NVUGIH, ESGE recommends the use of a PPI as co-therapy (strong recommendation, moderate quality evidence). |

## Risk stratification

ESGE recommends the use of a validated risk stratification tool to stratify patients into high and low risk groups. Risk stratification can aid clinical decision making regarding timing of endoscopy and hospital discharge (strong recommendation, moderate quality evidence).

ESGE recommends the use of the Glasgow-Blatchford Score (GBS) for pre-endoscopy risk stratification. Outpatients determined to be at very low risk, based upon a GBS score of 0 – 1, do not require early endoscopy nor hospital admission. Discharged patients should be informed of the risk of recurrent bleeding and be advised to maintain contact with the discharging hospital (strong recommendation, moderate quality evidence).

Risk stratification of patients presenting with acute UGIH can assist in identifying those who may require more urgent intervention and help triage patients to in-hospital vs. out-of-hospital management. A number of scoring tools have been created for predicting outcomes following acute UGIH, with the Glasgow-Blatchford Score (GBS) (▶ **Table 2**) and Rockall score being the most widely evaluated and adopted [17 – 19]. However, no single scoring tool has been shown to excel at predicting all relevant

**Table 2** Glasgow-Blatchford Score (GBS).

| | Points |
|---|---|
| **Systolic blood pressure, mmHg** | |
| 100 – 109 | 1 |
| 90 – 99 | 2 |
| < 90 | 3 |
| **Blood urea nitrogen, mmol/L** | |
| 6.5 – 7.9 | 2 |
| 8.0 – 9.9 | 3 |
| 10.0 – 24.9 | 4 |
| ≥ 25.0 | 6 |
| **Hemoglobin for men, g/dL** | |
| 12.0 – 12.9 | 1 |
| 10.0 – 11.9 | 3 |
| < 10.0 | 6 |
| **Hemoglobin for women, g/dL** | |
| 10.0 – 11.9 | 1 |
| < 10.0 | 6 |
| **Other risk variables** | |
| Pulse ≥ 100 | 1 |
| Melena | 1 |
| Syncope | 2 |
| Hepatic disease | 2 |
| Cardiac failure | 2 |

**TOTAL GBS** _____

GBS restricted for use only in nonhospitalized, ambulatory patients
Risk variables measured at time of patient presentation
GBS = 0 – 1 denotes "low-risk"

outcomes in acute UGIH (e.g., rebleeding, need for intervention, mortality) [19]. This is not surprising as the most validated risk scores were derived to assess a specific UGIH outcome: that for the Rockall score being mortality and for the GBS being the need for intervention [17,18].

A recent systematic review evaluating the accuracy of the available UGIH risk stratification tools demonstrated substantial heterogeneity in predicted outcomes and highlighted that methodological quality of the prediction scores was less than optimal [19]. Regarding the need for intervention, retrospective and prospective studies have assessed the prognostic value of the GBS vs. the Rockall score. These studies showed that the GBS correctly identified 98 % (95 %CI 89 % – 100 %) of those patients who did not require any subsequent intervention while 83 % (95 %CI 71 % – 91 %) of those patients were identified using the Rockall score. Randomized controlled trials and observational studies consistently indicate that clinical, endoscopic, and social factors may identify patients who may be safely discharged for outpatient management [20 – 28]. The most frequent adverse event reported is rebleeding ranging between 0.5 % and 4 %, with no deaths or hospital readmissions for surgery reported. Moreover, studies consistently indicate that outpatient management of appropriately selected patients with acute UGIH reduces resource utilization [20, 21, 27]. Emergency department discharge without inpatient endoscopy (i.e., outpatient management) should be considered for patients if: systolic blood pressure ≥ 110 mmHg, pulse < 100 beats/minute, hemoglobin ≥ 13.0 g/dL for men or ≥ 12.0 g/dL for women, blood urea nitrogen < 18.2 mg/dL, along with the absence of melena, syncope, hepatic disease, and cardiac failure [18]. (See **Appendix e2**, online-only.)

## Pre-endoscopy management

### Initial management of antithrombotic agents (anticoagulants and antiplatelet agents)

For patients taking vitamin K antagonists (VKAs), ESGE recommends withholding the VKA and correcting coagulopathy while taking into account the patient's cardiovascular risk in consultation with a cardiologist. In patients with hemodynamic instability, administration of vitamin K, supplemented with intravenous prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) if PCC is unavailable, is recommended (strong recommendation, low quality evidence).

If the clinical situation allows, ESGE suggests an international normalized ratio (INR) value < 2.5 before performing endoscopy with or without endoscopic hemostasis (weak recommendation, moderate quality evidence).

GI bleeding represents a serious complication of VKA therapy, with an incidence of 1 % – 4 % per year [29,30]. Discontinuation of anticoagulants and correction of coagulopathy before endoscopy is the "standard of practice" in patients with clinically significant GI bleeding [31 – 33]. Because data are limited, specific strategies to reverse VKAs in a patient with acute overt UGIH vary [34]. Practice guidelines recommend urgent reversal in all patients presenting with serious, life-threatening bleeding (i.e., hemodynamic instability or shock), either in the case of therapeutic or supratherapeutic INR elevations [32,35]. For patients who are not actively bleeding and are hemodynamically stable, intravenous vitamin K administration may be an option. When more urgent reversal is required, administration of prothrombin complex concentrates (PCCs) or fresh frozen plasma (FFP) is necessary, with concomitant intravenous administration of 5 – 10 mg vitamin K to prevent "rebound coagulopathy" once the transfused factors have been cleared. Prothrombin complex concentrates contain clotting factors prepared from pooled and concentrated human plasma and are preferred over FFP because of several advantages, including no need to check the patient's blood group, less risk for volume overload because of smaller transfusion volume, faster onset of action, similar thrombotic risk profile, and minimal risk of infectious transmission, albeit at a higher cost [36 – 40]. A recent prospective, nonrandomized, comparative study of 40 warfarin users who presented with UGIH and an INR > 2.1 reported that patients who received PCC had a near normalized INR at 2 hours following infusion (INR = 1.5) while those who received FFP had an INR of 2.4 at 6 hours following infusion [38]. No patient in the PCC group had active bleeding at endoscopy compared with 7 in the FFP group (0 vs. 35 %, $P < 0.01$). The risk of thrombosis following PCC administration approximates 1 %, and is similar to that reported with FFP [39,40].

ESGE recommends temporarily withholding new direct oral anticoagulants (DOACs) in patients with suspected acute NVUGIH in coordination/consultation with the local hematologist/cardiologist (strong recommendation, very low quality evidence).

As an alternative to heparin and VKAs, the new non-VKA oral anticoagulants (NOACs; also referred to as direct oral anticoagulants [DOACs]) are being rapidly adopted worldwide, primarily for thromboembolic prevention in patients with nonvalvular atrial fibrillation and for prophylaxis or treatment of venous thromboembolism [41]. These pharmacological agents do however, present a risk of significant GI bleeding similar to or greater than that reported with warfarin [42,43]. Moreover, DOACs differ in comparison with heparin and VKA. Specifically, in the absence of renal or hepatic failure, DOAC clearance and the subsequent

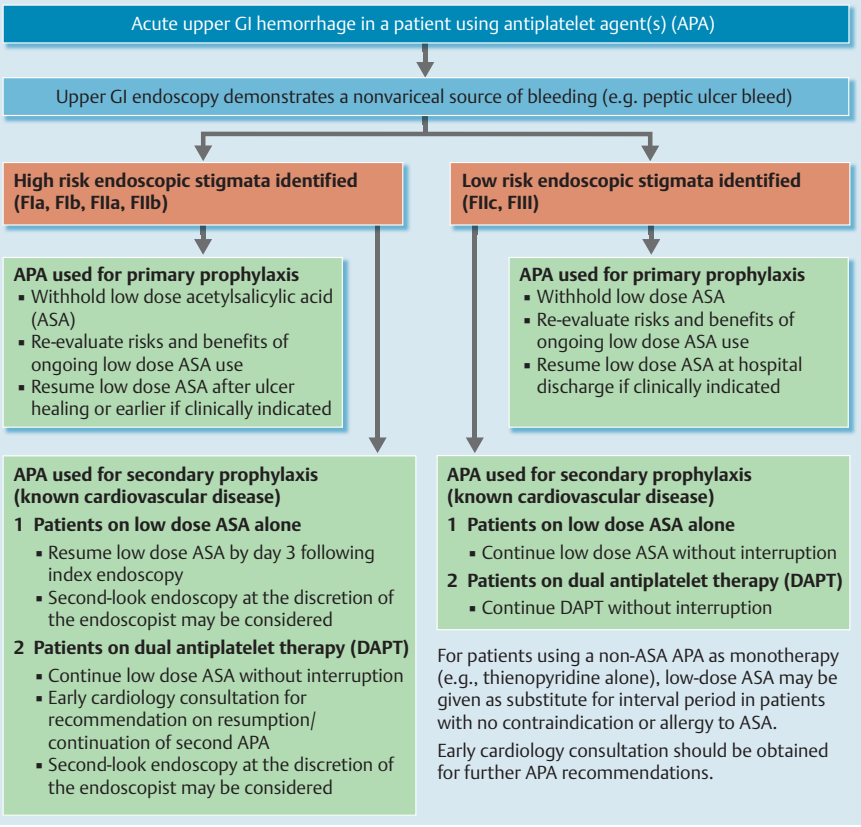


**Fig. 1** Algorithm for the management of patients with acute upper gastrointestinal hemorrhage who are using antiplatelet agent(s): European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

loss of anticoagulation effect is rapid and predictable (occurring gradually over 12–24 hours), routine laboratory tests are not sensitive for the quantitative assessment of their anticoagulant activity, and there is currently no specific reversal agent/antidote for emergency use with any DOAC, although potential agents are in development and may be commercially available in the next 1–2 years [44–46]. As there are no published clinical trials addressing the management of GI bleeding in patients using DOAC, current recommendations are based on expert opinion or laboratory end-points [47–49].

At the time of patient presentation with acute UGIH, DOACs should be temporarily withheld. Given their relatively short half-life, time is the most important antidote against DOACs. Strategies to accelerate anticoagulation reversal are supported only by data collected from healthy human volunteers, animal models, and in vitro studies [50]. Based on those data, vitamin K or FFP have no place as reversal agents for DOACs. Prothrombin complex concentrates or activated PCC may be considered in patients with severe or life-threatening bleeding, and hemodialysis can be used to reduce the blood concentration of dabigatran, but not that of rivaroxaban and apixaban which are more tightly bound to plasma proteins [48,49,51]. Additional data on the clinical effectiveness of these strategies in acutely bleeding patients are urgently needed.

For patients using antiplatelet agents, ESGE recommends the management algorithm detailed in **Fig. 1** (strong recommendation, moderate quality evidence).

Antiplatelet agents include low dose aspirin and thienopyridines (e.g., clopidogrel, prasugrel, ticlopidine) that irreversibly inhibit platelet aggregation, ticagrelor a reversible $P2Y_{12}$ receptor antagonist, and vorapaxar, a protease-activated receptor (PAR-1) antagonist that inhibits thrombin. The minimum duration of antiplatelet agent discontinuation that allows for restoration of normal platelet aggregation is 5–7 days [52].

Studies have shown that in patients taking low dose aspirin for secondary cardiovascular prophylaxis, all-cause mortality was lower if aspirin was not discontinued following peptic ulcer bleeding [53,54]. In an RCT, 156 recipients of low dose aspirin for secondary prophylaxis who had peptic ulcer bleeding were randomized to receive continuous aspirin or placebo [53]. At 8-week follow up, all-cause mortality was lower in the patients randomized to aspirin compared with placebo (1.3% vs. 12.9%, 95%CI 3.7%–19.5%; hazard ratio [HR] 0.20), with the difference being attributable to cardiovascular, cerebrovascular, or GI complications. The 30-day ulcer rebleeding rate was not significantly greater in the aspirin group. Patients who required dual antiplatelet therapy (DAPT) were excluded from this study. In a subsequent retrospective analysis that included 118 low dose aspirin recipients who had been treated for peptic ulcer bleeding and followed-up for a median of 2 years, 47 (40%) patients stopped aspirin [54]. Patients who discontinued aspirin and those who continued aspirin had similar mortality rates (31%). However, in a subgroup analysis limited to patients with cardiovascular comorbidities, those patients who discontinued aspirin had an almost fourfold increase in the risk of death or acute cardiovascular event ($P<0.01$) [54]. Randomized controlled trials have shown that neither aspirin nor clopidogrel use impede ulcer healing promoted by proton pump inhibitors (PPI) [55,56].

## Pharmacological therapy

ESGE recommends initiating high dose intravenous proton pump inhibitors (PPI), intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour), in patients presenting with acute UGIH awaiting upper endoscopy.

However, PPI infusion should not delay the performance of early endoscopy (strong recommendation, high quality evidence).

A Cochrane meta-analysis of 6 RCTs (n = 2223 patients) showed that administering PPIs before endoscopy significantly decreases the incidence of high risk stigmata of hemorrhage at the time of index endoscopy (37.2% vs. 46.5%; OR 0.67, 95%CI 0.54 – 0.84) and the need for endoscopic hemostasis (8.6% vs. 11.7%; OR 0.68, 95%CI 0.50 – 0.93), but has no effect on rebleeding, need for surgery, or mortality [57].

Cost – effectiveness studies suggest that high dose PPI infusion prior to endoscopy for patients with UGIH is more effective and less costly than placebo [58, 59]. (See **Appendix e3**, online-only.)

ESGE does not recommend the use of tranexamic acid in patients with NVUGIH (strong recommendation, low quality evidence).

Tranexamic acid reduces clot breakdown by inhibiting the fibrinolytic action of plasmin. A recent RCT demonstrated that tranexamic acid significantly reduces bleeding-related and all-cause mortality in trauma patients with significant hemorrhage [60]. A Cochrane meta-analysis evaluating the use of tranexamic acid in 1654 UGIH patients showed a beneficial effect of tranexamic acid on mortality when compared with placebo (relative risk [RR] 0.61, 95%CI 0.42 – 0.89), but not on other patient outcomes including bleeding, surgery, or transfusion requirements [61]. However, the beneficial effect on mortality did not persist in subgroup analysis. The studies included in this meta-analysis have important limitations that affect their generalizability including their methodological quality and the fact that the majority were conducted before the widespread use of therapeutic endoscopy and PPIs. To date, no controlled trial assessing the role of alternative antifibrinolytic agents (e.g., aminocaproic acid, aprotinin) in patients with acute UGIH has been reported. (See **Appendix e4**, online-only.)

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 [62]. However, they are not routinely recommended in NVUGIH (e.g., peptic ulcer bleeding), either pre-endoscopy or as an adjunctive therapy post endoscopy, since published data show little or no benefit attributable to these pharmacological agents. (See **Appendix e5**, online-only.)

ESGE recommends intravenous erythromycin (single dose, 250 mg given 30 – 120 minutes prior to upper GI endoscopy) in patients with clinically severe or ongoing active UGIH. In selected patients, pre-endoscopic infusion of erythromycin significantly improves endoscopic visualization, reduces the need for second-look endoscopy, decreases the number of units of blood transfused, and reduces duration of hospital stay (strong recommendation, high quality evidence).

It has been reported that in 3% to 19% of UGIH cases, no obvious cause of bleeding is identified [63, 64]. This may in part be related to the presence of blood and clots impairing endoscopic visualization. There are four published meta-analyses evaluating the role of prokinetic agent infusion prior to upper GI endoscopy in patients presenting with acute UGIH [65 – 68]. The most recently published meta-analysis (n = 558 patients) showed that erythromycin infusion prior to endoscopy significantly improved gastric mucosa visualization (OR 3.43, 95%CI 1.81 – 6.50; $P < 0.01$), and decreased the need for second-look endoscopy (OR 0.47, 95%CI 0.26–0.83, $P = 0.01$), RBC units transfused (weighted mean difference −0.41, 95%CI −0.82 to −0.01, $P = 0.04$), and duration of hospital stay (weighted mean difference −1.51 days, 95%CI −2.45 to −0.56, $P < 0.01$) [68].

A single intravenous dose of erythromycin is safe and generally well tolerated, with no adverse events reported in the meta-analyses. Studies that found a significant improvement in endoscopic visualization with pre-endoscopic erythromycin infusion included patients admitted to the intensive care unit because of UGIH with clinical evidence of active bleeding or hematemesis or blood seen on nasogastric lavage. These patients are most likely to benefit from erythromycin infusion prior to endoscopy. The dose of erythromycin most commonly used is 250 mg and is infused 30 to 120 minutes prior to upper GI endoscopy. A cost – effectiveness study found that pre-endoscopy erythromycin infusion in UGIH was cost-effective, primarily due to a reduction in the need for second-look endoscopies [69]. Contraindications to erythromycin administration include sensitivity to macrolide antibiotics and prolonged QT interval.

Metoclopramide has been less studied, it has been assigned a "black box warning" by the United States Food and Drug Administration because of the risk of neurologic side effects, and caution should therefore be advised with the use of this prokinetic agent.

(See **Appendix e6**, online-only.)

## Role of gastric lavage and prophylactic endotracheal intubation

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 number of studies, including a meta-analysis, have evaluated the role of nasogastric aspiration/lavage in patients presenting with acute UGIH [70 – 73]. In distinguishing upper from lower GI bleeding, nasogastric aspiration has low sensitivity 44% (95%CI 39% – 48%) yet high specificity 95% (95%CI 90% – 98%). In identifying severe UGIH, its sensitivity and specificity are 77% (95%CI 57% – 90%) and 76% (95%CI 32% – 95%), respectively [70]. This meta-analysis also found that as compared to nasogastric aspiration/lavage, clinical signs and laboratory findings (e.g., hemodynamic shock and hemoglobin < 8 g/dL) had similar ability to identify severe UGIH [70]. Others have reported that nasogastric aspiration/lavage failed to assist clinicians in correctly predicting the need for endoscopic hemostasis, did not improve visualization of the stomach at endoscopy, or improve clinically relevant outcomes such as rebleeding, need for second-look endoscopy, or blood transfusion requirements [71 – 73]. It also should be noted that nasogastric aspiration/lavage is a very uncomfortable procedure that is not well tolerated or desired by patients [74].

In an effort to protect the patient's airway from potential aspiration of gastric contents, ESGE suggests endotracheal intubation prior to endoscopy in patients with ongoing active hematemesis, encephalopathy, or agitation (weak recommendation, low quality evidence).

It has been hypothesized that pre-endoscopic endotracheal intubation may prevent cardiorespiratory adverse events in patients with acute UGIH. However, between those patients who were prophylactically intubated prior to upper GI endoscopy as com-

pared to those patients not intubated, published data show no significant difference in patient outcomes (e.g., pulmonary aspiration, in-hospital mortality) [75–77]. One study suggested that aspiration was actually more frequent in those patients who had undergone endotracheal intubation prior to upper GI endoscopy [75]. At this time, endotracheal intubation prior to upper GI endoscopy in patients with UGIH does not seem to make a difference in patient outcome but published data are limited with small numbers of subjects and low methodological quality.

## Timing of endoscopy

ESGE recommends adopting the following definitions regarding the timing of upper GI endoscopy in acute overt UGIH relative to patient presentation: very early < 12 hours, early ≤ 24 hours, and delayed > 24 hours (strong recommendation, moderate quality evidence).

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

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, moderate quality evidence).

Performance of upper GI endoscopy within 24 hours of patient presentation with suspected NVUGIH and no contraindication to endoscopy has been proposed as a key quality indicator in the management of upper GI bleeding [78]. In a large European observational study that included 123 centers in 7 countries, there was wide variation in practice where anywhere from 70% to 93% of 2660 unselected patients with UGIH underwent upper endoscopy within 24 hours of hospital admission [79].

Two systematic reviews evaluating the timing of upper GI endoscopy demonstrated improved risk assessment and reduction in hospital length of stay if endoscopy was performed within 24 hours of patient presentation, yet the impact on need for surgery and in-hospital mortality was variable [80, 81]. More recently, a retrospective analysis of risk factors for mortality in more than 400 000 patients with NVUGIH found an increased mortality in patients who failed to receive upper endoscopy within 1 day of hospital admission (OR 1.32, 95%CI 1.26–1.38) [82]. (See **Appendix e7**, online-only.)

With respect to very early upper GI endoscopy, an RCT that included 325 patients with peptic ulcer bleeding showed that upper GI endoscopy performed within 12 hours of admission (as compared with 12–24 hours) resulted in a significant reduction in transfusion requirements in patients with bloody nasogastric lavage ($P < 0.001$). No such reduction was observed in patients with "coffee grounds" or clear lavage [83]. A retrospective analysis that included 934 UGIH patients showed that in the subset of patients having a GBS ≥ 12 (n = 97, 10.4%), the time lapse between presentation to endoscopy was the lone independent risk factor associated with all-cause in-hospital mortality [84]. In this study, a cutoff time of 13 hours in delay to endoscopy best discriminated between patient survival and nonsurvival.

In patients who are hemodynamically stable and without serious co-morbidities, RCTs have shown that performing endoscopy without hospital admission facilitates discharge in up to 46% of patients and reduces costs/resource utilization [20, 85]. Discharging low risk suspected NVUGIH patients (GBS = 0) directly from the emergency department without undergoing upper GI endoscopy has been proposed as a safe and cost-saving option in multiple studies in various clinical settings [18, 86–89]. Some investigators have suggested that using a GBS ≤ 1 (see **Table 2**) could double the number of patients eligible for ambulatory management while maintaining safety [89].

There are four published studies, one RCT and three prospective case series, that have evaluated the test characteristics and accuracy parameters of video capsule endoscopy (VCE) in risk stratification of patients presenting with acute UGIH [90–93]. The overall sensitivity, specificity, positive predictive value, and negative predictive value of VCE for detecting blood in the upper GI tract in patients suspected of acute UGIH are 75%, 76%, 67%, and 82% respectively. Because the data are limited, at this time there is no role for VCE in the emergency department setting in evaluating acute upper GIH. However, additional studies are needed to further assess VCE in this patient population since, for low to moderate risk UGIH patients, VCE may be a cost-effective modality if post-VCE low risk patients are discharged directly home from the emergency department and hospital admission is avoided [94, 95].

## Endoscopic management

### Endoscopic diagnosis

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

ESGE recommends that peptic ulcers with spurting or oozing bleeding (Forrest classification Ia and Ib, respectively) or with a nonbleeding visible vessel (Forrest classification IIa) receive endoscopic hemostasis because these lesions are at high risk for persistent bleeding or rebleeding (strong recommendation, high quality evidence).

ESGE recommends that peptic ulcers with an adherent clot (Forrest classification IIb) be considered for endoscopic clot removal. Once the clot is removed, any identified underlying active bleeding (Forrest classification Ia or Ib) or nonbleeding visible vessel (Forrest classification IIa) should receive endoscopic hemostasis (weak recommendation, moderate quality evidence).

In patients with peptic ulcers having a flat pigmented spot (Forrest classification IIc) or clean base (Forrest classification III), ESGE does not recommend endoscopic hemostasis as these stigmata present a low risk of recurrent bleeding. In selected clinical settings, these patients may be discharged to home on standard PPI therapy, e.g., oral PPI once-daily (strong recommendation, moderate quality evidence).

The Forrest (F) classification was developed more than 40 years ago in an attempt to standardize the characterization of peptic ulcers [96]. The Forrest classification is defined as follows: FIa spurting hemorrhage, FIb oozing hemorrhage, FIIa nonbleeding visible vessel, FIIb an adherent clot, FIIc flat pigmented spot, and FIII clean base ulcer [97–99]. This classification has been used in numerous studies that aimed to identify patients at risk of persistent ulcer bleeding, rebleeding 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 rebleeding [100–107]. A potential limitation of the Forrest classification is that stigmata recognition and identifica-

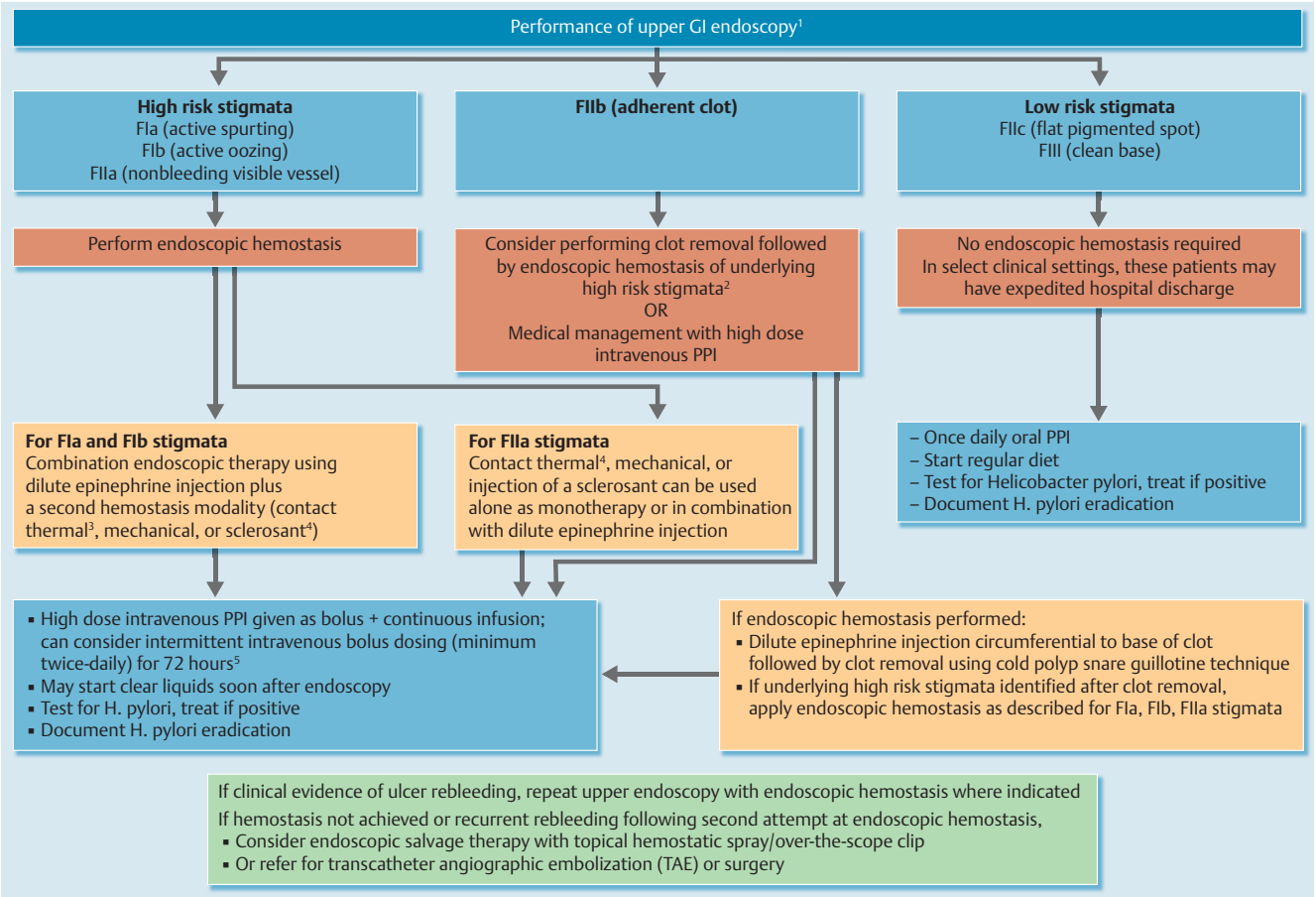


**Fig. 2** Algorithm for the endoscopic management of patients with nonvariceal upper gastrointestinal hemorrhage (NVUGIH) secondary to peptic ulcer, stratified by endoscopic stigmata: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. GI, gastrointestinal; PPI, proton pump inhibitor.
[1] Use of a large single-channel or double-channel therapeutic upper GI endoscope is recommended.
[2] The benefit of endoscopic hemostasis may be greater in patients at higher risk for rebleeding, e. g., older age, co-morbidities, in-hospital UGIH.
[3] Large size 10-Fr probe recommended.
[4] Absolute alcohol, polidocanol, or ethanolamine injected in limited volumes.
[5] High dose oral PPI may be an option in those able to tolerate oral medications.

tion, as well as interobserver agreement, may be less than optimal, although the data are conflicting [108, 109].

In addition to the Forrest classification, there are other endoscopic features of peptic ulcers that can predict adverse outcomes and/or endoscopic treatment failure. These include large-size ulcer (>2 cm), large-size nonbleeding visible vessel, presence of blood in the gastric lumen, and ulcer location on the posterior duodenal wall or the proximal lesser curvature of the stomach [100, 101, 103, 105, 110, 111].

A meta-analysis of RCTs that evaluated endoscopic hemostasis vs. no endoscopic hemostasis demonstrated that endoscopic hemostasis was effective in preventing persistent or recurrent bleeding in actively bleeding ulcers (FIa, FIb: RR 0.29, 95 %CI 0.20 – 0.43; number needed to treat [NNT] 2, 95 %CI 2 – 2) as well as in ulcers with a nonbleeding visible vessel (FIIa: RR 0.49, 95 %CI 0.40 – 0.59; NNT 5, 95 %CI 4 – 6) [112].

**Fig. 2** presents an algorithm for the endoscopic management of bleeding peptic ulcer, stratified by endoscopic stigmata.

With respect to the incremental benefit of acid suppression in addition to endoscopic hemostasis, an RCT and a subsequent meta-analysis found a clear advantage for endoscopic hemostasis combined with PPI therapy over PPI therapy alone in preventing recurrent ulcer bleeding and need for surgery in patients with FIIa and FIIb ulcers [113, 114].

The indication for endoscopic treatment of FIIb ulcers (adherent clot) remains controversial because of conflicting data. In evaluation of the natural history of FIIb ulcers (that did not receive endoscopic hemostasis), it was found that 25 % of patients rebled within 30 days of follow-up [115]. In patients with FIIb ulcers, RCTs and a meta-analysis comparing medical therapy alone with endoscopic hemostasis demonstrated a significant advantage for endoscopic hemostasis in reducing ulcer rebleeding (8.2 % vs. 24.7 %, $P<0.01$, yet there was no difference in need for surgery or mortality [116 – 118]. In contrast, in a separate RCT, Sung and colleagues reported no ulcer rebleeding in those patients with adherent clots who received medical therapy alone; however the numbers of such patients in the trial were quite limited (n = 24) [113]. Moreover, a meta-analysis restricted only to RCTs showed no benefit for endoscopic hemostasis in patients with an adherent clot (RR 0.31, 95 %CI 0.06 – 1.77) [112].

In patients with peptic ulcers having a flat pigmented spot (FIIc) or clean base (FIII), rebleeding is rare and therefore endoscopic hemostasis does not provide a significant advantage [97 – 99].

ESGE does not recommend the routine use of Doppler ultrasound or magnification endoscopy in the evaluation of endoscopic stigmata of peptic ulcer bleeding (strong recommendation, low quality evidence).

The persistence of a positive Doppler signal following endoscopic hemostasis has been shown to predict recurrent bleeding [119]. The results of available studies have been disparate and limited by their methodology, older endoscopic treatments applied, and small numbers of subjects included; thus there is currently no consensus as to the advantage for the routine use of Doppler ultrasound in patents with NVUGIH [120–123]. A cost-minimization analysis did however demonstrate per-patient cost savings with use of Doppler ultrasound in patients with peptic ulcer bleeding [124].

With respect to magnification endoscopy, one study suggested that FIIa ulcers can be classified as low risk or high risk and that some visible vessels classified as low risk using conventional endoscopy can be reclassified as high risk using magnification endoscopy [125]. However, the classification used has not been validated and no clinical benefit of this approach has been demonstrated.

## Endoscopic therapy

For patients with actively bleeding ulcers (FIa, FIb), ESGE recommends combining epinephrine injection with a second hemostasis modality (contact thermal, mechanical therapy, or injection of a sclerosing agent). ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy (strong recommendation, high quality evidence).

For patients with nonbleeding visible vessel (FIIa), ESGE recommends mechanical therapy, thermal therapy, or injection of a sclerosing agent as monotherapy or in combination with epinephrine injection. ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy (strong recommendation, high quality evidence).

For patients with active NVUGIH bleeding not controlled by standard endoscopic hemostasis therapies, ESGE suggests the use of a topical hemostatic spray or over-the-scope clip as salvage endoscopic therapy (weak recommendation, low quality evidence).

Endoscopic hemostasis can be achieved using injection, thermal, and mechanical modalities (see Box 1), and any endoscopic therapy is superior to pharmacotherapy in patients with FIa, FIb and FIIa ulcers [112, 126]. 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 hemostasis, with no single modality being superior [112, 126, 137–141].

Epinephrine injection therapy is effective at achieving primary hemostasis, but inferior to other endoscopic hemostasis monotherapies or combination therapy in preventing ulcer rebleeding [112, 126, 139]. In the most recently published meta-analysis (19 RCTs, 2033 patients), epinephrine plus any second hemostasis modality significantly reduced rebleeding (OR 0.53, 95 %CI 0.35–0.81) and emergency surgery (OR 0.68, 95 %CI 0.50–0.93) but not mortality as compared with epinephrine injection monotherapy for high risk peptic ulcers [140]. Therefore, it is recommended 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 [97–99, 141].

With respect to contact thermal therapy (e.g., bipolar electrocoagulation, heater probe), a meta-analysis restricted only to RCTs found that contact thermal therapy was significantly more effective than no endoscopic hemostasis in achieving primary hemostasis (RR 11.7, 95 %CI 5.2–26.6), reducing recurrent bleeding (RR 0.44, 95 %CI 0.36–0.54; NNT = 4), need for urgent surgery (RR 0.39, 95 %CI 0.27–0.55; NNT = 8) and mortality (RR 0.58, 95 %CI 0.34–0.98) [112]. With respect to noncontact thermal therapy (e.g., argon plasma coagulation), limited data from three small RCTs suggest it is similar in efficacy to injection of a sclerosing agent (polidocanol) or contact thermal therapy (heater probe) [112].

Mechanical therapy using through-the-scope clips was found to be superior to injection monotherapy in four of five meta-analyses [112, 126, 137, 139, 142]. Mechanical therapy significantly reduced the risk of recurrent bleeding by 78 % (RR 0.22, 95 %CI 0.09–0.55) [112]. Compared with thermal coagulation, mechanical therapy provided no significant improvement in definitive hemostasis (RR 1.00, 95 %CI 0.77–1.31) [137]. However, a separate meta-analysis [126] found through-the-scope clips to be significantly more effective than thermal therapy in reducing the risk of recurrent bleeding (OR 0.24, 95 %CI 0.06–0.95). Two small studies from Japan compared the efficacy of clips versus hemostatic forceps [143, 144]. The first was an RCT conducted in 96 patients with high risk bleeding gastric ulcers and showed that use of monopolar, soft coagulation hemostatic forceps was as effective as clipping [143]. The second was an observational prospective cohort study on 50 patients in which use of bipolar hemostatic forceps was more effective than endoscopic clipping for both initial hemostasis (100 % vs. 78.2 %) and preventing recurrent bleeding (3.7 % vs. 22.2 %) [144]. Unlike thermal therapies and sclerosing agents, mechanical therapy using clips has the theoretical benefit of inducing only limited tissue injury, and therefore may be preferred in patients on antithrombotic therapy and those patients undergoing repeat endoscopic hemostasis for rebleeding. A multidisciplinary expert panel developed an explicit set of evidence-based quality indicators for NVUGIH [78]. Among them, it was felt that patients with ulcer-related bleeding with high risk stigmata and elevated INR (> 1.5–2.0), should receive endoscopic hemostasis using endoscopic clips or a combination of epinephrine injection plus clips.

Meta-analyses have shown that combination endoscopic hemostasis therapy (dilute epinephrine injection combined with a second hemostasis modality including injectable, thermal contact probe, or clips) is superior to injection therapy alone, but not to clips or contact thermal therapy alone [126, 139]. There may be practical reasons to pre-inject dilute epinephrine before other therapies for high risk endoscopic stigmata. Injection of epinephrine may slow or stop bleeding allowing improved visualization for application of subsequent therapy. Adverse events associated with combination endoscopic hemostasis are low and include induction of bleeding (1.7 %) and perforation (0.6 %) [139]. Recent international consensus guidelines endorse combination therapy (dilute epinephrine injection combined with contact thermal therapy, clips, or injection of a sclerosant [e.g., absolute ethanol]) as appropriate treatment in patients with peptic ulcer bleeding with high risk endoscopic stigmata [98, 99, 145].

New endoscopic hemostasis modalities (topical hemostatic sprays and over-the-scope clips) are emerging as possible alternative endotherapies for primary hemostasis when bleeding is refractory or not amenable to standard endoscopic hemostasis therapies [136, 146]. Moreover, several small retrospective studies have reported that an over-the-scope clip (OVESCO), may have a role as rescue hemostasis therapy for severe NVUGIH when conventional endoscopic treatment modalities fail [133,

134,147]. An inert nanopowder (Hemospray) that causes immediate hemostasis when sprayed onto active bleeding [136, 148] has recently been used as a primary hemostasis agent or as a second-line salvage therapy. Several prospective uncontrolled studies, a large European registry [149–154] and a systematic review of the current limited data suggests that Hemospray is safe and effective and may be best used in high risk cases as a temporizing measure or a bridge toward more definitive treatment [136]. Other topical agents, such as the starch-derived polysaccharide hemostatic system (EndoClot) and the Ankaferd blood stopper are also emerging [136]. However, RCTs directly comparing topical agents with traditional hemostasis methods are required to better define their optimal role and safety in the endoscopic management of NVUGIH.

For patients with acid-related causes of NVUGIH different from peptic ulcers (e.g., erosive esophagitis, gastritis, duodenitis), ESGE recommends treatment with high dose PPI. Endoscopic hemostasis is usually not required and selected patients may be discharged early (strong recommendation, low quality evidence).

ESGE recommends that patients with a Mallory–Weiss lesion that is actively bleeding receive endoscopic hemostasis. There is currently inadequate evidence to recommend a specific endoscopic hemostasis modality. Patients with a Mallory–Weiss lesion and no active bleeding can receive high dose PPI therapy alone (strong recommendation, moderate quality evidence).

ESGE recommends that a Dieulafoy lesion receive endoscopic hemostasis using thermal, mechanical (hemoclip or band ligation), or combination therapy (dilute epinephrine injection combined with contact thermal or mechanical therapy) (strong recommendation, moderate quality evidence). Transcatheter angiographic embolization (TAE) or surgery should be considered if endoscopic treatment fails or is not technically feasible (strong recommendation, low quality evidence).

In patients bleeding from upper GI angioectasias, ESGE recommends endoscopic hemostasis therapy. However, there is currently inadequate evidence to recommend a specific endoscopic hemostasis modality (strong recommendation, low quality evidence).

In patients bleeding from upper GI neoplasia, ESGE recommends considering endoscopic hemostasis in order to avert urgent surgery and reduce blood transfusion requirements. However, no currently available endoscopic treatment appears to have long-term efficacy (weak recommendation, low quality evidence).

Erosive esophagitis, gastritis and duodenitis are common causes of NVUGIH and generally have a benign course and excellent prognosis [2,64,155–158]. Meta-analyses show that acid suppression therapy is effective, with high dose PPI therapy being significantly more effective than H2-receptor antagonists and no observed differences in effectiveness amongst PPIs [159,160]. Endoscopic hemostasis is usually not required in this patient population and selected patients are candidates for early hospital discharge.

Although spontaneous resolution of bleeding is frequent, observational studies have demonstrated that acute UGIH secondary to Mallory–Weiss syndrome has a mortality similar to that of peptic ulcer bleeding [161,162]. Risk factors for adverse outcomes include older age, medical co-morbidities, and active bleeding at the time of endoscopy. The latter supports early endoscopy to stratify risk and to perform endoscopic hemostasis if active bleeding is identified [162–166]. Despite suggestions that mechanical methods (clips and band ligation) are more effective than epinephrine injection, this has not been found in all studies [164,167,168]. Mechanical therapy appears to be safe, yet data are insufficient to make a clear recommendation of one hemostasis modality over another [164,167,169,170].

The proximal stomach and duodenum are the most common locations for Dieulafoy lesions [171]. Endoscopic hemostasis is warranted if technically feasible. Observational studies have reported the superiority of combined, thermal and mechanical methods over injection monotherapy, in achieving primary hemostasis, preventing rebleeding, and in reducing the need for rescue therapy, yet with no proven mortality benefit [172–180]. All endoscopic hemostasis modalities (e.g., band ligation, through-the-scope clips, over-the-scope clips, contact thermal coagulation, and argon plasma coagulation) appear safe and have similar reported outcomes [171–180]. Selective TAE has been described as an effective rescue therapy if endoscopic hemostasis fails or in patients who are poor surgical candidates [181, 182]. If both endoscopic and angiographic therapies fail, surgery should be considered.

Studies on endoscopic hemostasis therapy of angioectasias of the upper GI tract are observational and include only a limited number of subjects. In two recent meta-analyses, endoscopic hemostasis therapy (e.g., argon plasma coagulation, heater probe, bipolar coagulation, monopolar coagulation, band ligation, YAG laser) is reported to be initially effective and safe, yet bleeding recurrence rates are significant [183,184]. Given the low quality of evidence and scarcity of comparative data, a recommendation on a specific endoscopic hemostasis treatment is not permitted at this time.

There are limited published data on the role of endoscopic hemostasis in bleeding due to upper GI tract neoplasia and evidence to support a specific modality is scarce [185–188]. Numerous endoscopic hemostasis modalities (e.g., injection, thermal, mechanical, topical spray/powder) have been reported, generally with limited impact on primary hemostasis, prevention of rebleeding, or mortality. However, endoscopic treatment may avert urgent surgery, reduce transfusion requirements, and may provide a temporary bridge to oncologic therapy and/or selective embolization [185–188].

## Management following endoscopy/ endoscopic hemostasis

ESGE recommends PPI therapy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. PPI therapy should be high dose and administered as an intravenous bolus followed by continuous infusion (80 mg then 8 mg/hour) for 72 hours post endoscopy (strong recommendation, high quality evidence)

ESGE suggests considering PPI therapy as intermittent intravenous bolus dosing (at least twice-daily) for 72 hours post endoscopy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. If the patient's condition permits, high dose oral PPI may also be an option in those able to tolerate oral medications (weak recommendation, moderate quality evidence).

Based upon previously published meta-analytic data, evidence-based guidelines on NVUGIH have recommended that PPI therapy be given as an 80 mg intravenous bolus followed by 8 mg/hour continuous infusion to reduce rebleeding, surgery, and mortality in patients with high risk ulcers that had undergone successful endoscopic hemostasis [98,99,189,190]. More recently however, a meta-analysis of RCTs of high risk bleeding ulcers treated with endoscopic hemostasis compared intermittent PPI dosing (oral or intravenous) with the currently recommended

post hemostasis PPI regimen of 80 mg intravenous bolus followed by 8 mg/hour continuous infusion [191]. In that meta-analysis, Sachar et al reported that the risk ratio of recurrent ulcer bleeding within 7 days for intermittent infusion of PPI vs. 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 %. Risk ratios for other outcomes, including radiologic/surgical intervention and mortality, showed no differences between infusion regimens. These meta-analytic data indicate that intermittent PPI therapy appears comparable to the currently recommended regimen of intravenous bolus plus continuous PPI infusion post endoscopic hemostasis. It should be noted however, that intermittent PPI bolus dosing is associated with a somewhat higher risk of rebleeding that in general can be managed endoscopically. Given the pharmacodynamic profile of PPIs, consideration should be given to use of high dose PPI infusion given at least twice-daily, and using high dose oral PPIs in patients able to tolerate oral medications [191]. The concept of high dose PPI varies between the different studies used in the meta-analysis conducted by Sachar et al. However, it appears that an 80 mg oral PPI dose followed by 40 – 80 mg orally every 12 hours for 72 hours yields an intragastric pH similar to that reported with continuous intravenous PPI infusion following successful endoscopic hemostasis of high risk peptic ulcers [192]. This is but one study, and therefore we need more data to confirm these findings before drawing firm practical conclusions for the post-endoscopy management of patients with NVUGIH. These data are in agreement with an RCT that randomized patients to high dose continuous infusion of esomeprazole vs. 40 mg of oral esomeprazole twice-daily for 72 hours (118 vs. 126 patients respectively) [193]. Recurrent 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). However, this study was conducted in an Asian population (e. g., PPI slow metabolizers) and its findings may not be generalizable to Western NVUGIH populations. Moreover, this study was stopped prematurely since it was not designed as an equivalency trial, and based on the preliminary data, thousands of patients would have been required in order to complete the study. (See **Appendix e8**, online-only.)

In patients with clinical evidence of rebleeding following successful initial endoscopic hemostasis, ESGE recommends repeat upper endoscopy with hemostasis if indicated. In the case of failure of this second attempt at hemostasis, transcatheter angiographic embolization (TAE) or surgery should be considered (strong recommendation, high quality evidence).

An RCT comparing endoscopic therapy with surgery for recurrent peptic ulcer bleeding after successful initial endoscopic control of bleeding showed that 35/48 (73 %) of patients randomized to endoscopic re-treatment 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 [194]. The remaining 13 patients underwent salvage surgery because of failed repeat endoscopic hemostasis (n = 11) or perforation due to contact thermal therapy (n = 2).

If further bleeding occurs following a second endoscopic treatment, surgery for low risk patients or interventional radiology for high risk patients should be considered [195]. In recent systematic reviews and meta-analyses comparing TAE with surgery for peptic ulcer bleeding after failed endoscopic hemostasis, a higher rebleeding rate was observed following TAE. No significant difference in mortality or need for additional interventions was shown between treatments [196, 197]. Hemostatic powder and over-the-scope clips may also be considered as rescue/salvage therapy. Although limited, emerging data suggest that hemostatic powder may be successfully employed as salvage hemostasis therapy [154, 198]. The over-the-scope clip (OTSC) has also proven an effective and safe therapeutic option for severe acute GI bleeding when conventional endoscopic treatment modalities fail [134, 147].

(See **Appendix e9**, online-only.)

ESGE does not recommend routine second-look endoscopy as part of the management of NVUGIH. However, second-look endoscopy may be considered in selected patients at high risk for rebleeding (strong recommendation, high quality evidence).

Routine second-look endoscopy is defined as a scheduled repeat endoscopic assessment of the previously diagnosed bleeding lesion usually performed within 24 hours following the index endoscopy [98]. This strategy employs repeat endoscopy regardless of the type of bleeding lesion, perceived rebleeding risk, or clinical signs of rebleeding. A meta-analysis that evaluated the effectiveness of routine second-look endoscopy in NVUGIH reported a significant reduction in rebleeding (OR 0.55, 95 %CI 0.37 – 0.81) and need for emergency surgery (OR 0.43, 95 %CI 0.19 – 0.96), but not mortality (OR 0.65, 95 %CI 0.26 – 1.62) [199]. However, only one included study in that meta-analysis utilized high dose intravenous PPI, and in that study no benefit for second-look endoscopy was observed, while any protective effect was limited only to high risk patients (e. g., those with active bleeding at index endoscopy). Similarly, scheduled second-look endoscopy does not appear to be cost-effective outside the subgroup of patients thought to be at high risk for recurrent ulcer bleeding [200]. Thus, the clinical utility and cost – efficiency of routine second-look endoscopy in unselected patients remains to be proven.

In patients with NVUGIH secondary to peptic ulcer, ESGE recommends investigating for the presence of *Helicobacter pylori* in the acute setting with initiation of appropriate antibiotic therapy when *H. pylori* is detected. Re-testing for *H. pylori* should be performed in those patients with a negative test in the acute setting. Documentation of successful *H. pylori* eradication is recommended (strong recommendation, high quality evidence).

Peptic ulcer remains the most frequent cause of acute NVUGIH with *H. pylori* infection remaining the primary cause of peptic ulcer disease [201, 202]. Indeed, when *H. pylori* is eradicated, the risk of ulcer rebleeding is reported to be extremely low [203, 204]. However, the false-negative rate of *H. pylori* diagnostic testing is higher if the test is performed at the time of the acute bleeding episode as compared to later follow-up [205]. A meta-regression analysis including 8496 bleeding peptic ulcer patients found an *H. pylori* prevalence of 72 %, with the infection rate being significantly higher when diagnostic testing was delayed until at least 4 weeks following the bleeding event (OR 2.08, 95 % CI 1.10 – 3.93; $P = 0.024$) [206]. Therefore, it is advisable to re-test at a later time those patients who had a negative *H. pylori* test in the acute setting.

When *H. pylori* infection is found, eradication therapy should be initiated and guided by patient and local factors [98, 99]. Documentation of successful *H. pylori* eradication is strongly recommended given the high risk of recurrent ulcer bleeding in the presence of persistent *H. pylori* infection [98, 99]. (See **Appendix e10**, online-only.)

ESGE recommends restarting anticoagulant therapy following NVUGIH in patients with an indication for long-term anticoagulation. The timing for

resumption of anticoagulation should be assessed on a patient by patient basis. Resuming warfarin between 7 and 15 days following the bleeding event appears safe and effective in preventing thromboembolic complications for most patients. Earlier resumption, within the first 7 days, may be indicated for patients at high thrombotic risk (strong recommendation, moderate quality evidence).

Retrospective, observational data have shown that resuming anticoagulation in patients with GI bleeding is associated with a lower risk of thrombosis and death [207–209]. Restarting warfarin therapy within 7 days of the index bleeding event was associated with an approximately twofold increased risk of rebleeding [207,209]. Conversely, as compared with resuming warfarin beyond 30 days, resuming warfarin between 7 and 30 days did not increase the risk of rebleeding, but did significantly decrease the risk of thromboembolism and improved survival [209]. These data appear to support that resumption of anticoagulation after 7 days of interruption is safe and effective in preventing thromboembolic complications for most patients. However, in patients at high thrombotic risk (e.g., chronic atrial fibrillation with previous embolic event, $CHADS_2$ score ≥3, mechanical prosthetic heart valve, recent [within past 3 months] deep venous thrombosis or pulmonary embolism, and patients with known severe hypercoagulable state), for whom early resumption of anticoagulation within the first week following an acute bleeding event might be appropriate, bridging therapy using unfractionated or low molecular weight heparin may be considered [210]. No data are currently available to guide the management of DOACs following NVUGIH. Yet caution in the early resumption of DOACs is required because of their rapid onset of action and the current lack of reversal agents. (See **Appendix 11**, online-only.)

In patients receiving low dose aspirin for primary cardiovascular prophylaxis who develop peptic ulcer bleeding, ESGE recommends withholding aspirin, re-evaluating the risks/benefits of ongoing aspirin use in consultation with a cardiologist, and resuming low dose aspirin following ulcer healing or earlier if clinically indicated (strong recommendation, low quality evidence). See **Fig. 1**.

In patients receiving low dose aspirin for secondary cardiovascular prophylaxis who develop peptic ulcer bleeding, ESGE recommends aspirin be resumed immediately following index endoscopy if the risk of rebleeding is low (e.g., FIIc, FIII). In patients with high risk peptic ulcer (FIa, FIb, FIIa, FIIb), early reintroduction of aspirin by day 3 after index endoscopy is recommended, provided that adequate hemostasis has been established (strong recommendation, moderate quality evidence). See **Fig. 1**.

In patients receiving dual antiplatelet therapy (DAPT) who develop peptic ulcer bleeding, ESGE recommends continuing low dose aspirin therapy. Early cardiology consultation should be obtained regarding the timing of resuming the second antiplatelet agent (strong recommendation, low quality evidence). See **Fig. 1**.

Discontinuing low dose aspirin therapy in the setting of secondary cardiovascular prophylaxis significantly increases the risk of an adverse cardiovascular event, usually occurring within the first week of discontinuation [211–214]. In a retrospective cohort study, patients with cardiovascular disease who discontinued low dose aspirin following peptic ulcer bleeding had an almost twofold increase in risk for death or an acute cardiovascular event in the first 6 months after hospital discharge, as compared with patients who continued aspirin therapy [54]. In an RCT evaluating continuous vs. interrupted aspirin treatment in patients with high risk peptic ulcers and at high cardiovascular risk, those receiving continuous aspirin had a twofold increased risk of early, nonfatal, recurrent bleeding (10.3% vs. 5.4% at 4 weeks; difference 4.9 percentage points, 95%CI −3.6 to 13.4 percentage points; HR 1.9, 95%CI 0.6–6.0), yet a 10-fold reduced risk of all-cause mortality at 8 weeks (1.3% vs. 12.9%; difference 11.6 percentage points, 95%CI 3.7–19.5 percentage points; HR 0.2 95%CI 0.06–0.60) and a lower mortality rate related to cardiovascular, cerebrovascular, or gastrointestinal events (1.3% vs. 10.3%; difference 9 percentage points, 95%CI 1.7–16.3 percentage points; HR 0.2, 95%CI 0.05–0.70), compared with those patients in whom aspirin was withheld [53]. Patients who required DAPT were excluded from this study. The antiplatelet effect of aspirin lasts for approximately 5 days (although new active platelets increase in number each day), and the risk of early recurrent bleeding is high in the first 3 days [53]. Therefore, restarting aspirin on day 3 in patients with high risk endoscopic stigmata is a reasonable trade-off between the risks of rebleeding and thrombosis. In patients with peptic ulcer bleeding with no high risk endoscopic stigmata, aspirin can be resumed immediately as RCTs have shown that neither aspirin nor clopidogrel use impede ulcer healing promoted by PPIs [53,55,56]. No high level evidence helps guide the timing for resumption of $P2Y_{12}$ platelet receptor inhibitors (e.g., clopidogrel) following NVUGIH. However, in view of its similar antiplatelet activity, it seems reasonable to apply a similar management strategy. Moreover, there is no evidence in the literature to help guide the management of patients receiving DAPT in the setting of NVUGIH. The overriding principle of balancing bleeding and thrombotic event risks requires close collaboration between the gastroenterology and cardiology teams.

In patients requiring dual antiplatelet therapy (DAPT) and who have had NVUGIH, ESGE recommends the use of a PPI as co-therapy (strong recommendation, moderate quality evidence.

Dual antiplatelet therapy, combining low dose aspirin and a $P2Y_{12}$ 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 [215–217]. Proton pump inhibitors substantially reduce this risk and their use is recommended in patients with a previous GI bleeding event [218–220]. Pharmacodynamic studies have shown that the co-administration of PPIs with clopidogrel reduces platelet inhibition, but the clinical significance of this interaction has been extensively debated [221–225]. Previous meta-analyses suggest that concomitant clopidogrel and PPI use may be associated with increased adverse cardiovascular events and myocardial infarction, but no effect on mortality [226,227]. However, the presence of significant heterogeneity in the included studies indicates that this evidence is at best, inconsistent, and at worst, potentially biased or confounded. A recent meta-analysis included a subanalysis limited to RCTs and propensity-matched studies evaluating the interaction between PPI and clopidogrel; the subanalysis showed no significant differences 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), and cerebrovascular accident (OR 1.47, 95%CI 0.660–3.25; $P$ = 0.34) [228]. The incidence of GI bleeding was significantly decreased in the group of patients who received a PPI (OR 0.24, 95% CI 0.09–0.62; $P$ = 0.003). Current evidence does not support a clinically relevant interaction between PPIs and clopidogrel. (See **Appendices e12** and **e13**, online-only.)

**Box 1 Endoscopic hemostasis modalities: a primer**

**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 [126]. Sclerosing agents such as absolute ethanol, ethanolamine, and polidocanol produce hemostasis by causing direct tissue injury and thrombosis. It should be noted that when using a sclerosing agent in nonvariceal upper gastrointestinal hemorrhage (NVUGIH), the volume injected should be limited because of concerns about tissue necrosis, perforation, or pancreatitis. Another class of injectable agents is 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 can retract the needle into the 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 submucosa using a syringe attached to the catheter handle [126].

**Thermal therapy**

Thermal devices used in the treatment of upper gastrointestinal (UGI) bleeding are divided into contact and noncontact modalities. Contact thermal devices include heater probes which generate heat directly and bipolar electrocautery probes which generate heat indirectly by passage of an electrical current through the tissue. Noncontact thermal devices include argon plasma coagulation (APC) tools. Heat generated from these devices leads to edema, coagulation of tissue proteins, contraction of vessels, and indirect activation of the coagulation cascade, resulting in a hemostatic bond [126, 127].

Contact thermal probes 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 15 – 30 joules of thermal energy are delivered). An endoscopist-controlled foot pedal activates the heater probe and provides waterjet irrigation. Multipolar/bipolar electrocautery contact probes (7-Fr and 10-Fr sizes) 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, depth, and area of tissue injury. An endoscopist-controlled foot pedal controls the delivery of the energy [127]. 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) [96].

APC, a noncontact thermal modality, uses high frequency, monopolar alternating current conducted to the target tissue through a stream of ionized gas, without mechanical contact, resulting in coagulation of superficial tissue [128]. As the tissue surface loses its electrical conductivity, the argon plasma stream shifts to adjacent nondesiccated (conductive) tissue, which again limits the depth of tissue injury [126]. 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 (flow rates of 0.5 – 0.7 L/min). 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) [129, 130].

**Mechanical therapy**

Endoscopic mechanical therapies include clips (through-the-scope and over-the-scope) and band ligation devices. Endoscopic clips are deployed directly onto a bleeding site and typically slough off within days to weeks after placement [131]. Hemostasis is achieved by mechanical compression of the bleeding site.

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, 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. Some clips are provided with a reusable delivery sheath, greatly reducing costs. Similarly, some clips are automatically released on deployment, while others require repositioning of the plunger handle to release the deployed clip from the catheter [131].

The over-the-scope clip device includes an applicator cap, a nitinol clip, and a hand wheel [132, 133]. The applicator cap, with the mounted nitinol clip, is affixed to the tip of the endoscope in a manner similar to that of a variceal band ligation device. Caps are available in three sizes to accommodate various endoscope diameters: 11 mm, 12 mm, and 14 mm. Caps are also available in two lengths (3 mm and 6 mm) to allow variation in the amount of tissue grasped. Clips come in three different shapes of teeth: rounded, pointed and long-pointed. Clips with rounded teeth are used where the goal is tissue compression to achieve hemostasis. The applicator cap incorporates a clip release thread, which is pulled retrogradely through the working channel of the endoscope and fixed onto a hand wheel mounted on the working-channel access port of the endoscope. The clip is released by turning the hand wheel, in a manner similar to deploying a variceal ligation band [134].

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

**Topical therapy**

Topical hemostatic sprays have been used in acute NVUGIH with promising results, but thus far in a limited number of patients and without any comparative data regarding standard endoscopic hemostasis therapies [135,136]. 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 large surface area.

Topical hemostatic sprays include TC-325, (Hemospray, Cook Medical Inc, 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 comes in a hand-held device consisting of a pressurized CO2 canister, a through-the-scope delivery catheter, and a reservoir for the powder cartridge. The powder is delivered via pushbutton 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 [135,136]. The coagulum typically sloughs within 3 days and is naturally eliminated. Hemospray has received regulatory clearance in some countries.

Additional topical hemostatic sprays include EndoClot and the Ankaferd Blood Stopper [135,136]. EndoClot (EndoClot Plus Inc, Santa Clara, California, USA) is a 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 derived from plant products/extracts have also been evaluated. Clinical experience with these agents for endoscopic hemostasis is currently limited to the off-label use of the Ankaferd Blood Stopper (Ankaferd Health Products Ltd, 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 and 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 later. The overall efficacy of these topical agents is unknown in brisk arterial bleeding and may be limited because of the rapid "wash-away" effect of the hemostatic agent by ongoing blood flow.

ESGE guidelines represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability. Further controlled clinical studies may be needed to clarify aspects of these statements, and revision may be necessary as new data appear. Clinical consideration may justify a course of action at variance to these recommendations. ESGE guidelines are intended to be an educational device to provide information that may assist endoscopists in providing care to patients. They are not rules and should not be construed as establishing a legal standard of care or as encouraging, advocating, requiring, or discouraging any particular treatment.

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**Institutions**

[1] Institute of Gastroenterology and Liver Diseases, Ha'Emek Medical Center, Afula, Israel
[2] Rappaport Faculty of Medicine Technion-Israel Institute of Technology, Haifa, Israel
[3] Gedyt Endoscopy Center, Buenos Aires, Argentina
[4] Departments of Internal Medicine and Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands
[5] University of Zaragoza, Aragon Health Research Institute (IIS Aragon), CIBERehd, Spain
[6] Department of Gastroenterology, Sheffield Teaching Hospitals, United Kingdom
[7] Division of Gastroenterology and Digestive Endoscopy, Maresca Hospital, Torre del Greco, Italy
[8] Department of Gastroenterology and Hepatology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic
[9] Department of Gastroenterology, IPO Porto, Portugal and CINTESIS, Porto Faculty of Medicine, Portgal
[10] Division of Gastroenterology, Hospital Curto, Polla, Italy
[11] First Department of Internal Medicine and Gastroenterology, Petz Aladar, Hospital, Gyor, Hungary
[12] Department of Surgical Sciences, University of Torino, Torino, Italy
[13] Institute and Polyclinic for Diagnostic Radiology, University Hospital Dresden-TU, Dresden, Germany
[14] Department of Gastroenterology, Ambroise Paré Hospital, Boulogne, France
[15] Department of Biomedical and Clinical Sciences, University of Milan, Gastroenterology Unit, Luigi Sacco University Hospital, Milan, Italy
[16] Department of Medical Gastroenterology, Rikshospitalet University Hospital, Oslo, Norway
[17] Department of Gastroenterology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, United Kingdom
[18] Department of Gastroenterology, Valduce Hospital, Como, Italy
[19] Department of Gastroenterology, Centro Hospitalar do Porto, Portugal
[20] Department of Gastroenterology, Centro Hospitalar e Universitário de Coimbra, Portugal
[21] Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy
[22] Gastroenterology and Endoscopy Department, Antonio Cardarelli Hospital, Naples, Italy
[23] Digestive Endoscopy Unit, Catholic University, Rome, Italy

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**Appendix e1** Nonvariceal upper gastrointestinal hemorrhage (NVUGIH): task forces and key questions.

| Topics and key questions | Task forces (leader in bold) |
|---|---|
| **Task force 1:** Initial patient evaluation/hemodynamic resuscitation/risk stratification | **David S. Sanders**<br>Jean-Marc Dumonceau<br>Matthew Kurien<br>Gilles Lesur<br>Riccardo Marmo |
| How should the patient be initially hemodynamically resuscitated? | |
| Who should receive blood product transfusion? What target for hemoglobin? | |
| How should patient risk stratification be used? | |
| What risk stratification score(s) are reliable and valid? Pre-endoscopy risk score? Post-endoscopy risk score? | |
| How should risk stratification tools be applied? | |
| **Task force 2:** Pre-endoscopic management | **Jean-Marc Dumonceau**<br>Ian Gralnek<br>Cesare Hassan<br>Angel Lanas<br>Gilles Lesur<br>Istvan Racz<br>Franco Radaelli<br>Gianluca Rotondano |
| How to manage the patient using antiplatelet and anticoagulant drugs (known collectively as antithrombotic agents) at the time of acute upper gastrointestinal (UGI) bleeding? | |
| Need to also consider the current data on potential adverse events related to antiplatelet/anticoagulant drug interruption (i. e. atrial fibrillation, cardiac stent thrombosis, cardiac ischemic event, neurovascular event) | |
| What is the role of pre-endoscopy proton pump inhibitor (PPI) therapy? | |
| What is the role of pre-endoscopy somatostatin therapy? | |
| What is the role of naso-/orogastric tube aspiration/lavage? | |
| What is the role of endotracheal intubation before upper endoscopy? | |
| Is there a role for antifibrinolytic medications? | |
| What is the role of prokinetic agents prior to upper endoscopy? | |
| Is there a role for capsule endoscopy in the emergency department in evaluating acute UGI bleeding? | |
| What is appropriate timing for upper endoscopy? | |
| **Task force 3:** Endoscopic management | **Ernst J. Kuipers**<br>Ricardo Cardoso<br>Livio Cipolletta<br>Mário Dinis-Ribeiro<br>Luís Maia<br>Gianluca Rotondano<br>Paulo Salgueiro |
| Which endoscopic classification should be used for describing high and low risk endoscopic stigmata of recent hemorrhage in peptic ulcer bleeding? What are high risk vs. low risk endoscopic stigmata and their importance in risk stratification? | |
| Is there a role for doppler ultrasonography, magnification endoscopy, chromoendoscopy in helping to better evaluate endoscopic stigmata of recent hemorrhage for peptic ulcer bleeding? | |
| Which ulcer stigmata require endoscopic hemostasis? Which do not? | |
| Which endoscopic hemostasis modality should be used (with focus on peptic ulcer bleeding)? | |
| Injection therapy? | |
| Thermal contact therapy? | |
| Thermal noncontact therapy? | |
| Mechanical therapy? | |
| Combination therapy? | |
| Topical spray/powder therapy | |
| What to do in situations of nonvariceal, nonulcer bleeding lesions? | |
| **Task force 4:** Post-endoscopic management | **Angel Lanas**<br>Lars Aabakken<br>Alberto Arezzo<br>Roberto de Franchis<br>Cesare Hassan<br>Ralf-Thorsten Hoffmann<br>Tomas Hucl<br>Gilles Lesur<br>Franco Radaelli<br>Andrew Veitch<br>Angelo Zullo |
| What is the medical management post endoscopic hemostasis? | |
| What to do when rebleeding occurs? What is the role of repeat upper endoscopy? | |
| Is there a role for scheduled second-look endoscopy? | |
| Rebleeding/failed endoscopic hemostasis: When should the interventional radiologist be involved/when should the surgeon be involved? | |
| Diagnosis and treatment of Helicobacter pylori? When? In whom? What if testing for H. pylori in the acute setting of bleeding is negative? Documentation of eradication? | |
| How to manage the NVUGIH patient using antiplatelet and anticoagulant drugs (collectively known as antithrombotics agents) post endoscopy? How and when to reinstitute these medications? | |
| When to discharge patients home? | |

**Appendix e2** Criteria for outpatient management of patients with nonvariceal upper gastrointestinal hemorrhage (NVUGIH).

| First author, year [ref.] | Study design, study objective | Participants | Patients, n (%) | | Outcomes | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Observed | Out-patients | Transfusion required | Re-bleeding | Need for surgery | Death |
| Longstreth, 1995 [229] | Prospective | Absolute criteria.<br>Absence of: high risk endoscopic findings (arterial bleeding, adherent clot, or visible vessel); varices; and portal hypertensive gastropathy<br>Nonabsolute criteria.<br>No debilitation; no orthostatic vital sign change; no severe liver disease; no serious concomitant disease; no anticoagulation therapy or coagulopathy; no fresh, voluminous hematemesis or multiple episodes of melena on the day of presentation; no severe anemia (hemoglobin < 8.0 g/dL); adequate support at home | 141 | 34 (24 %) | | 1 (2.9 %) | 0 | 0 |
| Longstreth, 1998 [230] | Retrospective | As above | Not done | 176 | | 1 (0.5 %) | 0 | 0 |
| Cebollero-Santamaria, 1999 [231] | Prospective | Clinical criteria.<br>Absence of: severe cardiac disease/recent myocardial infarction; severe respiratory failure; decompensated cirrhosis; severe coagulopathy (international normalized ratio [INR] ≥ 1.5); poor social support; requirement for blood transfusion; recent cerebrovascular accident<br>Endoscopic criteria.<br>Clean base ulcer < 1.5 cm in diameter; erosive mucosal disease (esophagus, stomach, or duodenum); nonbleeding Mallory – Weiss tear; portal hypertensive gastropathy | 84 | 24 (28 %) | | 1 (4.1 %) | 0 | 0 |
| Brullet, 2004 [232] | RCT | Clinical criteria.<br>Absence of signs of hypovolemia (defined as systolic blood pressure < 100 mmHg and pulse rate > 100 beats/minute with peripheral signs of circulatory failure);<br>Absence of severe associated diseases (defined as American Society of Anesthesiologists [ASA] classification III – V);<br>No anticoagulant drug therapy; and<br>Appropriate sociofamilial support.<br>The latter was defined as the following: (i) living within a family whose members were able to comprehend the clinical condition of the patient and capable of providing adequate care; (ii) having a telephone; and (iii) residing less than 20 minutes by car from the hospital.<br>Endoscopic criteria.<br>(1) peptic ulcer with an nonbleeding visible vessel;<br>(2) ulcer size smaller than 15 mm | 297 endoscopically treated patients | 40 (13 %) | 7 | 2 | 0 | 0 |

**Appendix e2** (Continuation)

| First author, year [ref.] | Study design, study objective | Participants | Patients, n (%) | | Outcomes | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Observed | Out-patients | Transfusion required | Re-bleeding | Need for surgery | Death |
| Lai, 1997 [233][1] | Prospective | Inclusion criteria were as follows:<br>(1) Presence of melena and/or hematemesis;<br>(2) Presence of duodenal ulcer and absence of other upper gastrointestinal pathology to account for gastrointestinal bleeding;<br>(3) Hemoglobin level greater than 10 gm/dL on admission;<br>(4) Systolic blood pressure above 100 mmHg and pulse less than 100 beats/minute on admission before any resuscitation with fluids, and orthostatic blood pressure drop of less than 10 mmHg (patient excluded if abnormal vital signs developed after admission);<br>(5) No concurrent serious medical illness (absence of heart failure, chronic obstructive airway disease, hepatic cirrhosis, hematologic malignancies, chronic renal failure, and strokes);<br>(6) no stigmata of recent hemorrhage on endoscopy, which was carried out within 24 h of admission;<br>(7) Age 60 years or younger; and<br>(8) Normal coagulation findings. | 305 | 75 (24 %) | 0 | 0 | 0 | 0 |
| Lee, 1999 [234][2] | RCT | Clinical criteria.<br>Absence of:<br>Co-morbid illness requiring intensive care (e. g., myocardial ischemia);<br>Hemodynamic instability after resuscitation by infusion of 2 L of fluid (heart rate greater than 115 beats/min, systolic blood pressure less than 90 mmHg, or diastolic blood pressure less than 60 mmHg);<br>Known or suspected variceal source, coagulopathy (use of any anticoagulant or thrombolytic agent within the preceding week, platelet count less than 50 000, INR < 1.5, or any other known coagulopathy);<br>Upper GI bleeding within the preceding 1 month; and<br>Age less than 18 years.<br>Endoscopic criteria.<br>No clot obscuring complete visualization;<br>Clean ulcer base;<br>Mallory-Weiss tear;<br>Esophagitis, gastritis, duodenitis, or other benign findings.<br>Hemodynamically stable, alert, wanted to go home | 56 | 26 (46 %) | | 1 (3.8 %) | 0 | 0 |
| Gralnek, 2004 [235] | Retrospective | Complete Rockall scores (after endoscopy) of ≤ 2 | 175 | 53 (30 %) | | 2 (3.7 %) | 0 | 0 |

**Appendix e2** (Continuation)

| First author, year [ref.] | Study design, study objective | Participants | Patients, n (%) | | Outcomes | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Observed | Out-patients | Transfusion required | Re-bleeding | Need for surgery | Death |
| Cipolletta. 2002 [236][2] | RCT | Clinical criteria.<br>Absence of hypovolemic shock, orthostatic change in vital signs, and need for blood transfusion;<br>Normal coagulation findings;<br>Absence of serious concurrent medical illness;<br>Easy accessibility to hospital; and<br>Adequate sociofamial support at home.<br>Endoscopic criteria.<br>Absence of varices and signs of portal hypertension, high risk stigmata of recent hemorrhage (active bleeding, visible vessel, or adherent clot);<br>Patients having a clean ulcer base or flat spot, gastritis or duodenitis, Mallory – Weiss tear, or other benign findings. | 244 | 95 (39%) | | 2 (2.%) | 0 | 0 |

GI, gastrointestinal; INR, international normalized ratio; RCT, randomized controlled trial.
[1] Only patients with peptic ulcer
[2] The hospital stay and the costs of care were significantly less for early endoscopy

**Appendix e3** Role of proton pump inhibitors (PPIs) prior to upper endoscopy in acute upper gastrointestinal hemorrhage.

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitations | Conclusions |
|---|---|---|---|---|---|---|
| Sreedharan, 2012 [237] | Cochrane meta-analysis of 6 RCTs<br>Searches were re-run in Feb 2006 and Oct 2008 | Total of 2223 patients were included with unselected upper GI bleeding.<br>Prior to endoscopy patients were given PPI (oral or intravenous) or H2RA or placebo | – 30-day mortality<br>– Rebleeding<br>– Surgery<br>– Stigmata of recent hemorrhage (SRH) at index endoscopy<br>– Need for endoscopic therapy<br>– Need for transfusion | No significant difference between PPI and control treatment for:<br>– Mortality: 6.1 % vs. 5.5 %; OR 1.12, 95 %CI 0.72 – 1.73<br>– Rebleeding rates: 13.9 % vs. 16.6 %; OR 0.81, 95 %CI 0.61 – 1.09<br>– Surgery: 9.9 % – 10.2 %; OR 0.96, 95 %CI 0.68 – 1.35<br>Significant reduction:<br>– Proportion with SRH: 37.2 % – 46.5 %; OR 0.67, 95 %CI 0.54 – 0.84<br>– Need for endoscopic therapy: 8.6 % – 11.7 %; OR 0.68, 95 %CI 0.50 – 0.93 | Oral and intravenous PPI studies are mixed<br>– No data regarding the length of pre-emptive PPI and placebo treatment<br>– Variceal and nonvariceal bleeding sources are not analyzed selectively | PPI treatment initiated before endoscopy for upper GI bleeding might reduce the proportion of patients with SRH at index endoscopy and significantly reduces requirement for endoscopic therapy during index endoscopy.<br>However, there is no evidence that PPI treatment affects clinically important outcomes, namely mortality or need for surgery. |
| Lau, 2007 [238] | Double-blind, placebo-controlled, randomized trial | Omeprazole group (n = 319): 80 mg omeprazole intravenous bolus + 8 mg/h control infusion until endoscopy<br>Placebo group (n = 319): placebo bolus + placebo infusion until endoscopy<br>Endoscopies were performed next morning.<br>Mean duration of infusion before endoscopy:<br>– Omeprazole group 14.7 ± 6.3 h<br>– Placebo group 15.2 ± 6.2 h | Primary:<br>– Need for endoscopic therapy at the first endoscopic examination<br>Secondary:<br>– Signs of bleeding<br>– Need for urgent endoscopy<br>– Emergency surgery<br>– Recurrent bleeding | Among patients with peptic ulcer bleeding, endoscopic treatment required in:<br>– Omeprazole group 22.5 %<br>– Placebo group 36.8 %<br>– OR 0.61, 95 %CI 0.44 – 0.84; $P = 0.002$<br>Active ulcer bleeding seen less frequently in omeprazole group than in placebo group: 6.4 % vs. 14.7 %; $P = 0.001$.<br>Rebleedings: 3.5 % in omeprazole group vs. 2.5 % in placebo group; $P = 0.49$ | Long-term aspirin users were excluded | Pre-emptive omeprazole appears to accelerate the resolution of signs of bleeding.<br>Fewer cases of actively bleeding ulcers were seen among patients receiving omeprazole than among those who received placebo.<br>In patients awaiting endoscopy pre-emptive use of high dose intravenous omeprazole is recommended. |
| Liu, 2012 [239] | Randomized, single-center, prospective, double-blind | PPI parenteral (either omeprazole or esomeprazole) started prior to endoscopy ("early" endoscopy ≤ 24 h, "late" > 24 – 72 h)<br>Intensive regimen, 80 mg + 8 mg/h infusion: 410 patients<br>Standard regimen, 2 × 40 mg PPI/day: 456 patients | Rebleeding rate<br>Need for endoscopic therapy at first endoscopy | Rebleeding:<br>11 % in standard regimen group vs. 6.4 % in intensive regimen group ($P = 0.03$)<br>Early endoscopy therapy need: 16.7 % vs. 10.0 % ($P = 0.05$)<br>Rebleeding rates at late endoscopies: 7.5 % in standard vs. 4.0 % in intensive PPI group ($P = 0.03$) | Both omeprazole and esomeprazole were used<br>Endoscopic therapy was not standardized<br>No detailed data about the timing of endoscopy (how many hours after the initiation of pre-emptive PPI therapy) | High dose intravenous PPI initiated before endoscopy reduces rebleeding rates, blood transfusion volume and hospital stay, especially when endoscopy is delayed beyond 24 h of presentation.<br>No alteration on need for endoscopic treatment. |

**Appendix e3** (Continuation)

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitations | Conclusions |
|---|---|---|---|---|---|---|
| Barkun, 2010 [240] | International Consensus Guideline | NA<br>Patients receiving pre-emptive PPI before endoscopy. | Rebleeding<br>Need for surgery<br>Mortality<br>Need for intervention<br>Supportive cost-effective analysis | Pre-endoscopic PPI treatment significantly reduced the proportion of patients with high risk stigmata (OR 0.67, CI 0.54 – 0.84), and the need for pre-endoscopic therapy (OR 0.68, CI 0.50 – 0.93) compared with the control group (placebo or H2RA).<br>Economic dominance of pre-endoscopic high dose intravenous PPI therapy. | NA | Pre-endoscopic PPI therapy may be considered in order to downstage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy.<br>Comment: ESGE Board endorsed the consensus recommendation. |
| Tsoi, 2008 [241] | Decision analysis model<br>Cost-effectiveness comparison | Omeprazole group (80 mg bolus intravenous + 8 mg/h infusion):<br>n = 314 patients<br>187 peptic ulcer cases<br>– initiated prior to endoscopy<br>Placebo group:<br>n = 317 patients<br>190 peptic ulcer cases<br>– initiated prior to endoscopy | Number of patients who avoided endoscopic therapy within the follow-up period<br>Direct costs of medical treatment, diagnostic endoscopy, hemostasis, emergency surgery, hospitalization | 248 patients in the PPI group and 227 patients in the placebo group avoided endoscopic therapy.<br>Overall direct costs: 2813 US dollars (USD) in the PPI group vs. 2948 USD in the placebo group<br>Costs were reduced by 7.4 % with pre-emptive PPI therapy | The estimated values were based on an assumed linear relationship | The use of high dose PPI before an endoscopy is shown to be an effective and cost-saving way to treat patients with upper GI bleeding. |
| Barkun, 2008 [242] | Editorial | NA | Key questions:<br>To contrast the pre-endoscopic with post-endoscopic hemostatic uses of PPI (in high dose intravenous administration) in patients with peptic ulcer bleeding<br>Almost no data about the time elapsed until endoscopy (i. e., the duration of intravenous PPI administration before gastroscopy)<br>What is the optimal duration of pre-emptive high dose intravenous PPI therapy regarding cost-effectiveness<br>Which subgroups of ulcer patients benefits most from pre-endoscopy PPI therapy | NA | NA | The earlier the endoscopy is performed, the less the cost-effectiveness of high dose intravenous PPI.<br>Pre-emptive PPI use should not replace the performance of early endoscopy. |

**Appendix e3** (Continuation)

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitations | Conclusions |
|---|---|---|---|---|---|---|
| Rácz, 2012 [243] | Single-center, retrospective, comparative cohort study | 240 PUB patients, pantoprazole bolus 80 mg intravenous + 8 mg/h pantoprazole infusion before endoscopy<br>Control group: 93 PUB patients received saline infusion until endoscopy | Active ulcer bleeding at the first endoscopy<br>Need for endoscopic hemostasis at the first endoscopy<br>Need for urgent endoscopy<br>All outcomes were analyzed in subgroups of patients with different durations of intravenous pantoprazole before endoscopy.<br>Rebleeding rates<br>Separate analyses in duodenal ulcer and gastric ulcer patients | Mean duration of infusion before endoscopy:<br>5.4 ± 12.9 h in the saline group vs. 6.9 ± 13.2 h in the pantoprazole group ($P$ = 0.29).<br>Active bleeding at first endoscopy:<br>19.2 % in the pantoprazole group vs. 24.7 % in the saline infusion group ($P$ = 0.26).<br>Endoscopic treatment requirement at first endoscopy:<br>61.3 % in the pantoprazole group vs. 56.9 % in the saline group ($P$ = 0.82) | Retrospective study<br>Aspirin, NSAIDs, and anticoagulants were discontinued at time of hospital admission.<br>Only data from patients admitted during evening hours (6pm to 8am) were analyzed | Pre-emptive infusion of high dose pantoprazole longer than 4 h before endoscopy decreased the ratio of active bleeding only in gastric and not in duodenal ulcer patients. |
| Lanas, 2013 [244] | Summary of main studies | NA | – | – | – | It has been reported that the administration of a PPI prior to endoscopy or the early performance of endoscopy within 6 h of admission in patients with UGIB does not improve the prognosis of the event. |
| Sung, 2011 [245] | Consensus report | NA | NA | – | – | A pre-endoscopy proton pump inhibitor (PPI) is recommended as a stopgap treatment when endoscopy within 24 h is not available. |
| Al-Sabah, 2008 [246] | Decision model compared high dose PPI initiated while awaiting endoscopy with administration on the basis of endoscopic findings | | Cost-effectiveness | – | – | Intravenous PPIs given before endoscopy are slightly more effective than no administration. |
| Ghassemi. 2009 [247] | Overview | NA | NA | NA | – | Intravenous PPI therapy before endoscopy seems reasonable in patients presenting with severe upper gastrointestinal bleeding suspected from a peptic ulcer, if a delay is anticipated in urgent endoscopy. |
| Laursen, 2012 [248] | Guideline approved by the Society of Danish Society for Gastroenterology | NA | NA | NA | – | Treatment with PPI prior to endoscopy cannot be recommended and must not delay the timing of upper endoscopy. |
| Lin, 2010 [249] | Overview | NA | NA | NA | – | There was no evidence that PPI before endoscopy improves clinical outcomes. |

ESGE, European Society of Gastrointestinal Endoscopy; H2RA, histamine-2 receptor antagonist; trial; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUB, peptic ulcer bleeding; RCT, randomized controlled trial; UGIB, upper gastrointestinal bleeding.

**Appendix e4** Role of tranexamic acid (TXA) in upper gastrointestinal hemorrhage.

| First author, year [ref.] | Study type | Study population, Interventions | Key outcomes | Key results | Limitations | Conclusion |
|---|---|---|---|---|---|---|
| Gluud, 2012 [250] | Cochrane meta-analysis of<br>7 RCTs vs. placebo<br>1 RCT included also a treatment arm with cimetidine (Ref. 5)<br>1 RCT included also a treatment arm with lansoprazole and lansoprazole + TXA | Patients admitted with suspected upper gastrointestinal bleeding confirmed by gastric lavage, hematemesis or melena<br>Interventions:<br>– Oral TXA administration (3 studies;<br>– Intravenous TXA administration (4 studies.<br>Treatment duration (range): 2 – 7 days<br>Total daily TXA dose, range: 4 – 8 g (divided in four to six daily doses)<br>1 RCT offered endoscopic treatment to all randomized patients | – Mortality (1654 patients, 7 studies)<br>– Rebleeding or continued bleeding (1604 patients, 6 studies)<br>– Surgery (1504 patients, 6 studies)<br>– Need for transfusion (1504 patients, 6 studies)<br>– Any thromboembolic event (1048 patients, 3 studies | TXA versus placebo:<br>Significant difference in mortality: 5 % vs. 8.2 %; RR 0.61 (95 %CI 0.42 – 0.89)<br>No significant difference in a subgroup analysis stratified for quality of bias control (trials with adequate allocation sequence generation or allocation concealment included): RR 0.78, 95 %CI 0.58 – 1.05)<br>No significant difference in:<br>– Rebleeding: RR 0.73, 95 %CI 0.5 – 1.07<br>– Surgery: RR 0.62, 95 %CI 0.35 – 1.09<br>– Need for transfusion: 1.02, 95 %CI 0.93 – 1.11<br>– Any thromboembolic event: RR 1.86, 95 %CI 0.66 – 5.24<br>TXA versus cimetidine or lansoprazole:<br>No significant difference in all outcome variables | Methodological quality of studies included (unclear or high risk of bias of selection bias in many of them)<br>Scarce applicability of evidence (most trials do not include the currently recommended intervention for management of NVUGIB) | TXA cannot be recommended for routine use.<br>Additional trials in which TXA is used in combination with the currently recommended interventions are required. |

CI, confidence interval; NVUGIB, nonvariceal upper gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.

**Appendix e5** Role of somatostatin in acute nonvariceal upper gastrointestinal hemorrhage (NVUGIH).

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitation | Conclusion |
|---|---|---|---|---|---|---|
| Magnusson, 1985 [251] | Randomized, double-blind | 95 patients with acute nonvariceal GI bleeds with "massive" bleeding (clinical signs of shock or preshock)<br>– 46 patients: 72 h somatostatin infusion<br>– 49 patients: placebo | Need for surgical treatment (indication: > 6 units PRBC needed to keep hemodynamically stable<br>Evidence of active bleeding 1 day after treatment | Patients who needed surgery ($P$ < 0.04):<br>– 14 placebo<br>– 5 somatostatin<br>$P$ < 0.04<br>Rebleeding:<br>– 5 placebo<br>– 6 somatostatin | Only included patients with signs of shock<br>Endoscopic treatment was not standardized | Somatostatin infusion was superior to placebo regarding surgical need in patients with nonvariceal upper gastrointestinal bleeding. |
| Choi, 2011 [252] | Retrospective analysis of a prospective database | 101 patients with acute ulcer bleeding, high risk stigmata (FIa,Ib, IIa)<br>Endoscopic therapy in all patients<br>– 52 patients: pantoprazole 80-mg bolus + continuous infusion 8 mg/h for 72 h<br>– 49 patients: pantoprazole as above, and also somatostatin as 250-µg bolus + continuous infusion 250 µg/h for 72 h | Clinically significant early rebleeding<br>Loss of endoscopic high risk stigmata at second-look endoscopy | Rebleeding rates:<br>– PPI: 12.2 %<br>– 14.3 % PPI + somatostatin<br>$P$ = 0.766<br>Loss of stigmata:<br>– 94.2 % PPI<br>– 95.9 % PPI + somatostatin<br>$P$ = 0.696 | Not randomized study | Adjunctive somatostatin for management of nonvariceal upper gastrointestinal bleeding did not show an additive effect in reducing early rebleeding. |
| Avgerinos, 2005 [253] | Randomized, double-blind | Adult patients admitted within 24 h of bleeding<br>Endoscopic stage IIc and III peptic ulcer bleeding<br>Not on PPI or H2 blockers in the previous week<br>No hypovolemia<br>Normal platelets, no coagulopathy<br>14 somatostatin<br>14 PPI<br>15 placebo | Gastric pH compared with patient baseline gastric pH during drug infusion<br>Intragastric pH > 4 in the fundus during the 24-h infusion period | Successful maintenance of pH > 4.0 in patients having somatostatin ($P$ < 0.0001) and PPI ($P$ < 0.0001)<br>During first half of treatment, time with above pH 4.0 and 5.4, respectively, was higher with somatostatin than PPI ($P$ < 0.005) and ($P$ < 0.02) | 186 patients screened; 143 excluded<br>Patients with stigmata of recent hemorrhage were excluded<br>Evaluation of rebleeding was only a secondary end point | During the first 12 h of the infusion somatostatin was more effective than pantoprazole maintaining high intragastric pH. |
| Archimandritis, 2000 [254] | Prospective, randomized, open | 84 patients with acute nonvariceal upper GI bleed<br>– 44 ranitidine<br>– 40 ranitidine + octreotide | Need for surgical intervention<br>Hospital stay length<br>Blood units transfused | No difference between groups for:<br>– Hospital stay length ($P$ = 0.25)<br>– Amount of blood units ($P$ = 0.16)<br>Need for emergency surgery did not differ ($P$ = 1.0) | Small numbers<br>Not blinded | |

**Appendix e5** (Continuation)

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitation | Conclusion |
|---|---|---|---|---|---|---|
| Lin, 1995 [255] | Randomized, open | Patients with active peptic ulcer bleeding, or Nonbleeding visible vessel at ulcer bases<br>– 42 octreotide<br>– 42 ranitidine | Hemostasis<br>Blood units transfused | Hemostasis achieved in 35/42 (83.3 %) octreotide group vs. 23/42 (54.8 %) in ranitidine group; ($P<0.01$)<br>Octreotide group had:<br>– Lower volume of blood ($P<0.05$)<br>– Fewer patients needing endoscopic hemostasis/surgery ($P<0.05$)<br>– Fewer days in hospital ($P<0.001$) | Not blinded | |
| Kim, 2008 [256] | Retrospective analysis | Patients with peptic ulcer bleeding, Forrest Ia, b, II a,b<br>Group A: 45 patients; 48 h pantoprazole infusion<br>Group B: 45 patients; 48 h pantoprazole + 250 µg/h infusion of somatostatin | Rebleeding in:<br>– 72 h, and<br>– 30 days | 72 h rebleeding:<br>– PPI alone: 11 %<br>– PPI + somatostatin: 13 %<br>Not significant<br>30-day rebleeding:<br>– 13 % vs. 16 %<br>Not significant | Not randomized<br>Endoscopic treatment was not standardized | Combined therapy with PPI and somatostatin did not result in better outcomes than PPI alone. |
| Antonioli, 1986 [257] | Multicenter, randomized, prospective, controlled trial | 56 PUB patients<br>Group A: 250 µg/h infusion somatostatin for 48 h<br>Group B: 1600 µg/24 h cimetidine for 48 h after endoscopy | Secondary hemostasis<br>Transfusion requirement | Hemostasis:<br>– Somatostatin group: 93.3 %<br>– Cimetidine group: 61.5 %<br>$P<0.01$<br>Blood requirement:<br>– Somatostatin: 1.14 PRBC<br>– Cimetidine: 2.46 PRBC<br>$P<0.05$ | Small patient numbers<br>Rebleeding rate was not defined | Somatostatin infusion for 48 h is superior to cimetidine infusion regarding definitive hemostasis. |
| Tisbouris, 2007 [258] | Randomized, double-blind, controlled trial | Patients with peptic ulcer bleeding, Forrest Ia, Ib, Iia<br>Group P: 82 patients, 8 mg/h pantoprazole infusion for 48 h<br>Group S: 82 patients, 250 µg somatostatin infusion for 48 h | Rebleeding 3 days after initial hemostasis<br>Need for endoscopic re-treatment | Rebleeding and need for endoscopic re-treatment:<br>– Group P: 5 % vs.<br>– Group S: 17 %<br>($P=0.046$)<br>Achieved pH > 6 for more than 85 % of the time:<br>– Group P: 56.7 % vs.<br>– Group S: 46.7 %<br>($P=0.44$) | Endoscopic treatment was not standardized<br>Not placebo-controlled | Infusion of pantoprazole after initial hemostasis was superior to somatostatin infusion to prevent bleeding recurrence<br>No difference in the need for surgery and in mortality. |

**Appendix e5** (Continuation)

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitation | Conclusion |
|---|---|---|---|---|---|---|
| Okan, 2000 [259] | Prospective, randomized, double-blind controlled study | Total of 48 patients with upper gastrointestinal bleeding<br>Group I: 15 Forrest Ib patients<br>Group II: 30 Forrest II patients<br>Randomly administered:<br>– Somatostatin 250 µg bolus + continuous infusion 6 mg/day for 72 h, or<br>– Ranitidine 300 mg/day continuous infusion for 72 h | Blood transfusion requirement<br>Time to bleeding cessation<br>Rebleeding rate | Transfusion requirement: no sign. difference<br>In group I (Forrest Ib patients), time to bleeding cessation was significantly shorter in those receiving somatostatin vs. those receiving ranitidine (3.24 vs. 11.25 h, $P = 0.038$)<br>No differences in rebleeding rate or mortality | Low patient numbers | Somatostatin is more effective than ranitidine in controlling acute nonvariceal upper gastrointestinal bleeding in patients with Forrest Ib bleeding activity. No additional benefit with Forrest II bleeding activity. |
| Rutgeerts, 2006 [260] | Double-blind randomized controlled trial | 369 PUB patients<br>Before endoscopy, randomized for intravenous treatment:<br>– S group: 250 µg bolus + 12 mg/day somatostatin for 72 h<br>– P group: placebo infusion for 72 h<br>Diagnostic endoscopy within 8 h of randomization | Failure rate (Forrest Ia or Ib at diagnostic endoscopy, clinical signs of active bleeding ≥ 1 h after the start of infusion<br>Use of rescue therapy (endoscopic treatment, surgery, vasoactive drugs) to stop bleeding | Failure rates in S and P groups:<br>– No statistically significant difference, 34 % vs. 36 %<br>Stigmata of bleeding:<br>– Statistically significant effect in favor of somatostatin<br>– $P = 0.034$<br>Rescue treatment:<br>– Significantly less in S vs. P group<br>$P = 0.012$ | Unusual presentation of results<br>“Failure rate” is not an established measure of results in studies | The results of this multicenter large trial were published only in abstract form. However, the results appear to support the use of intravenous somatostatin administered early and prior to diagnostic endoscopy and endotherapy to control bleeding in patients with suspected acute and severe PUB. |

PPI, proton pump inhibitor; PRBC, packed red blood cells; PUB, peptic ulcer bleeding.

**Appendix e6** Role of prokinetic agents in acute overt upper gastrointestinal hemorrhage.

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitation | Conclusion |
|---|---|---|---|---|---|---|
| Carbonell, 2006, [261] | Prospective, randomized, double-blind | Upper gastrointestinal bleeding patients, all with nasogastric tube<br>– 49 patients, 250 mg erythromycin prior to endoscopy<br>– 50 patients, placebo prior to endoscopy | Improvement of gastric cleansing prior to endoscopy<br>Identification of bleeding point<br>Effectiveness of hemostasis treatment | – Better visualization of entire gastric mucosa in erythromycin patients: 65 % vs. 44 %<br>$P<0.05$<br>– Clots in the stomach: 30 % erythromycin vs. 52 % placebo<br>$P<0.05$<br>– Hemostatic treatment: 67 % erythromycin vs. 62 % placebo<br>$P=0.67$ | Low patient numbers<br>Subjective criteria based on the endoscopist's judgment | Intravenous erythromycin before endoscopy improves stomach cleansing and the quality of endoscopic examination.<br>Limited clinical benefit. |
| Coffin, 2002 [262] | Prospective, randomized, endoscopist-blinded, controlled trial | Acute upper gastrointestinal bleeding within 12 h requiring esophagogastro-duodenoscopy (EGD)<br>Before EGD patients were given:<br>– 3 mg/kg erythromycin in 125 mL saline as a 30-minute infusion, or<br>– Observation without motility agent<br>EGD within 60 – 120 min following erythromycin infusion<br>Erythromycin group:<br>19 patients<br>Control group: 22 patients | Quality of EGD examination evaluated using a score<br>Need for second EGD<br>Effectiveness of endoscopy therapy | Significantly better visualization during EGD in the erythromycin group ($P=0.02$)<br>No interference with the hemostatic procedure<br>Need for second endoscopy: erythromycin:15.8 % vs. control:45.4 % ($P=0.089$) | Low patient numbers<br>Qualitative evaluation of results (by scoring system) | Erythromycin infusion before endoscopy significantly improved the quality of EGD.<br>Tendency to reduce the need for second-look endoscopy. |
| Frossard, 2002 [263] | Prospective, randomized, double-blind, monocentric | – Erythromycin intravenous 250 mg: 51 patients<br>– Placebo: 54 patients<br>20 minutes before endoscopy<br>Within 12 h after hematemesis | Effect of intravenous erythromycin on endoscopic yield<br>Need for second-look endoscopy<br>Transfusion requirement | Clear stomach found more often in erythromycin group: 82 % vs. 33 %, $P<0.001$<br>Erythromycin shortened the endoscopy duration and the need for second-look endoscopy | Low patient number with non-variceal upper gastrointestinal bleeding | Erythromycin infusion before endoscopy in patients with recent hematemesis makes endoscopy shorter and easier, and reduces the need for second-look endoscopy. |
| Theivanayagam, 2013 [264] | Meta-analysis of 6 studies | 558 patients with upper gastrointestinal bleeding (patients with variceal bleeds were also included) | Visualization of gastric mucosa<br>Need for second endoscopy | Erythromycin infusion before endoscopy significantly improved visualization vs. no erythromycin:<br>OR 3.43, 95 %CI 1.81 – 6.50<br>Significant decrease in the need for second endoscopy ($P=0.01$) | Inclusion of variceal bleedings | Erythromycin infusion before endoscopy in patients with upper gastrointestinal bleeding significantly improves visualization of gastric mucosa and decreases the need for a second endoscopy. |





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**Appendix e6** (Continuation)

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitation | Conclusion |
|---|---|---|---|---|---|---|
| Sussman, 2008 [265] | Single-center, prospective, randomized, controlled study<br>Intravenous metoclopramide bolus (10 mg intravenous) | Patients with overt hematemesis or melena<br>A total of 26 patients | Mucosal visualization during EGD (Avgerinos score)<br>Duration of EGD<br>Rebleeding rate | Better visualization after metoclopramide, *P* = not significant<br>No significant difference regarding blood transfusion, repeat EGD | Low patient numbers<br>Subjective quality score | Intravenous metoclopramide may increase visualization of the proximal stomach during EGD, but not significantly.<br>No translation into better clinical outcome. |
| Barkun, 2010 [266] | Meta-analysis<br>3 fully published articles, 2 abstracts | 3 erythromycin studies<br>2 metoclopramide studies<br>316 patients | Primary:<br>– Need for repeat EGD<br>Secondary:<br>– Blood transfusion<br>– Need for surgery | A prokinetic agent significantly reduced the need for repeat EGD:<br>OR 0.55, 95 %CI 0.32 – 0.94<br>No significant alterations:<br>– Blood transfusion, and<br>– Need for surgery: | Small numbers of patients | Intravenous erythromycin or metoclopramide immediately before EGD in patients with acute upper gastrointestinal bleeding decreases the need for repeat EGD, but does not improve clinical outcomes. |
| Habashi, 2007 [267] | Prospective, randomized, controlled trial | 54 patients with hematemesis (42 % PUB patients)<br>– Intravenous erythromycin: 15 patients<br>– Intravenous metoclopramide: 15 patients<br>– Placebo: 15 patients | Visualization of the mucosa<br>Quality of the EGD | Gastric mucosa entirely visualized:<br>– erythromycin group: 86 %, vs.<br>– metoclopramide group: 66 %<br>Quality of EGD significantly better in erythromycin group vs. metoclopramide and placebo groups | Small sample sizes<br>Subjective scores<br>Dosage of prokinetics not reported | No significant difference between placebo and either medication regarding key outcomes. |
| Winstead, 2007 [268] | Cost-effectiveness analysis | 3 RCTs were analyzed with a total of 126 patients<br>(Frossard, Coffin and Carbonell studies) | Quality-adjusted life-years (QALYs)<br>Need for second-look endoscopy | Intravenous erythromycin before endoscopy was cost-effective when the rate of second-look endoscopy was less than 0.29<br>Intravenous erythromycin was cost-effective when the charges for uncomplicated peptic ulcer disease PUD were less than 8000 US dollars | The estimates need for repeat endoscopy.<br>The complex model may fail to capture all the slight variations in patterns of care among different hospitals. | Intravenous erythromycin before endoscopy in acute upper gastrointestinal hemorrhage (UGIH) is cost-saving and increases QALYs.<br>Erythromycin is recommended prior to EGD in UGIH. |

CI, confidence interval; EGD, esophagogastroduodenoscopy; PUB, peptic ulcer bleeding; OR, odds ratio; RCT, randomized controlled trial.

**Appendix e7** Summary of the evidence regarding impact of early endoscopy (≤ 24 h) on the outcome of patients with nonvariceal upper gastrointestinal hemorrhage (NVUGIH).

| First author, year [ref.] | Country | Study type, Study period | Patients, n | Major findings |
|---|---|---|---|---|
| Spiegel, 2001 [269] | – | Systematic review<br>1980 – 2000<br>23 studies<br>– 6 controlled in low risk patients<br>– 7 uncontrolled in low risk patients<br>– 6 controlled in high risk patients<br>– 4 comparing resource utilization | 12 625 | Early endoscopy ( ≤ 24 h) safe and effective in all risk groups.<br>Low risk: allows safe and prompt discharge.<br>High risk: significantly reduces recurrent bleeding, transfusion requirements, need for surgery and length of hospital stay. |
| Tsoi, 2009 [270] | – | Systematic review<br>1996 – 2007<br>8 studies<br>– 3 RCT<br>– 5 retrospective | 5 677 | Early endoscopy aids risk stratification and reduces the need for hospitalization; however it may increase the use of unnecessary therapeutic procedures.<br>Endoscopy performed ≤ 8 h of presentation has no advantage over endoscopy performed within 12 – 24 h of presentation in reducing recurrent bleeding or improving survival. |
| Sarin, 2009 [271] | Canada | Retrospective<br>2004 – 2006 | 502 | No advantage for early endoscopy (< 6 h) compared with endoscopy within 24 h in terms of mortality, need for surgery, or transfusion requirements. |
| Lim, 2011 [272] | Singapore | Retrospective | 837 low risk<br>97 high risk | Endoscopy within 13 h of presentation is associated with lower mortality in high risk but not low-risk patients with NVUGIH. |
| Marmo, 2011 [273] | Italy | Multicenter, prospective cohort studies (3 databases)<br>2004 – 2009 | 3 207 | Significant increase of mortality in high risk patients when endoscopy is performed ≤ 12 h compared with endoscopy performed 13 – 24 h after presentation (14.3 % – 16.6 % vs. 5.2 %, $P = 0.001$). |
| Wysocki, 2012 [274] | US | Retrospective<br>Administrative data<br>NIS 2002 – 2007 | 435 765 | Increased mortality risk in patients who do not receive endoscopy within 1 day of admission: OR 1.32, 95 %CI 1.26 – 1.38. |
| Jairath, 2012 [275] | UK | Multicenter, prospective cohort study<br>2007 | 4 478 | Compared with later endoscopy (> 24 to 48 h), endoscopy performed ≤ 12 h did not affect mortality (OR 0.98, 95 %CI 0.88 – 1.09), but led to a decreased risk-adjusted length of hospital stay (1.7 days, 95 %CI 1.39 – 1.99). |

CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial.

**Appendix e8** Medical management following endoscopic hemostasis

| First author, year [ref.] | Study design | Intervention | Participants | Outcomes | Results | Level of evidence, conclusions |
|---|---|---|---|---|---|---|
| Barkun, 2010 [240] | International consensus guideline | After endoscopic therapy:<br>– Proton pump inhibitor (PPI) vs.<br>– Placebo or H2RA | Patients with endoscopic signs of high risk of rebleeding | Mortality<br>Rebleeding 3 – 7 days | Rebleeding: OR 0.45, CI 0.36 – 0.57<br>Surgery: OR 0.56, CI 0.45 – 0.70<br>Mortality: OR 0.90 CI 0.67 – 1.19 | Intravenous PPI 80 mg bolus + 8 mg/h for 72 h recommended.<br>Evidence: High |
| Sachar, 2014 [276] | Systematic review | After endoscopic therapy:<br>– PPI intravenous continuous infusion (80 mg + 8 mg/h for 72 h) vs.<br>– Intermittent PPI | Patients with endoscopic signs of high risk of rebleeding | Rebleeding 7 days<br>Mortality | Rebleeding: risk ratio (RR) 0.72 (upper boundary of 1-sided 95 %CI 0.97).<br>RRs for rebleeding 3 – 30 days, mortality, urgent interventions were less than 1. | No differences between intermittent high dose PPI (all routes) vs. intravenous PPI 80 mg bolus + 8 mg/h for 72 h.<br>Evidence: High |
| Sung, 2014 [277] | Randomized, controlled trial, double blind | After endoscopic therapy:<br>– Intravenous esomeprazole bolus 80 mg + 8 mg/h for 72 h vs.<br>– Oral esomeprazole 40 mg/12 h | Patients with endoscopic signs of high risk of rebleeding | Rebleeding at 30 days | Intravenous esomeprazole group: 118 patients<br>Oral esomeprazole group: 126 patients<br>Recurrent bleeding:<br>– Intravenous group: 7.7 %, vs.<br>– Oral group: 6.4 % | High dose oral esomeprazole may be considered as a useful alternative to intravenous therapy.<br>Evidence: Moderate |
| Mostaghni, 2011 [278] | Randomized, open-label | – Oral omeprazole (80 mg twice-daily for 3 days), or<br>– Intravenous pantoprazole (80 mg bolus and 8 mg/hour infusion for 3 days)<br>Followed in all patients by omeprazole (20 mg each day for 30 days). | Patients with endoscopic signs of high risk of rebleeding | Rebleeding (30 days?; timing not well-defined) | – Oral omeprazole: 44 patients<br>– Intravenous pantoprazole: 41 patients<br>Rebleeding:<br>– Oral omeprazole: 11.4 %, vs.<br>– Intravenous pantoprazole: 9.8 %<br>Mean hospital stay and blood transfusion were not different between the two groups. | Oral omeprazole and intravenous pantoprazole had equal effects on prevention of rebleeding after endoscopic therapy in patients with high risk bleeding peptic ulcers.<br>Evidence: Low |
| Yen, 2012 [279] | Randomized, open-label | Esomeprazole group: 40 mg continuous infusion of esomeprazole every 6 h for 3 days. Then oral esomeprazole 40 mg once-daily for 2 months.<br>Lansoprazole group: oral 30 mg four times daily for 3 days followed by once daily for 2 months. | Patients with endoscopic signs of high risk of rebleeding | Rebleeding rate within 14 days.<br>Secondary outcomes included:<br>– Hospital stay<br>– Volume of blood transfusion<br>– Surgical intervention, and<br>– Mortality within 1 month | 100 patients enrolled.<br>Rebleeding rates:<br>– esomeprazole intravenous group: 4 % (2/50), and<br>– Lansoprazole oral group: 4 % (2/50)<br>No difference between the two groups with regard to:<br>– Hospital stay<br>– Volume of blood transfusion<br>– Surgery, or<br>– Mortality rate | There is no evidence of a difference in clinical outcomes between oral and intravenous PPI treatment. (not powered to prove equivalence or noninferiority). Patients receiving oral PPI have a shorter hospital stay.<br>Evidence: Low |

**Appendix e8** (Continuation)

| First author, year [ref.] | Study design | Intervention | Participants | Outcomes | Results | Level of evidence, conclusions |
|---|---|---|---|---|---|---|
| Tsai, 2008 [280] | Randomized, open-label | – Oral rabeprazole (20 mg twice-daily for 3 days), or<br>– Intravenous omeprazole (40 mg intravenous infusion every 12 h for 3 days). | Patients with endoscopic signs of high risk of rebleeding | Bleeding up to 14 days.<br>Also compared:<br>– Hospital stay<br>– Volume of blood transfusion<br>– Surgery, and<br>– Mortality within 14 days | 156 patients with 78 in each group<br>Rebleeding:<br>– Omeprazole group: 12 patients (15.4 %)<br>– Rabeprazole group: 13 patients (16.7 %)<br>– 95 %CI of difference: 12.82 – 10.22<br>No differences in the other evaluated outcomes | Oral rabeprazole and intravenous regular-dose omeprazole are equally effective in preventing re-bleeding in patients with high risk bleeding peptic ulcers after successful endoscopic injection with epinephrine.<br>Evidence: Low |
| Wang, 2010 [281] | Systematic review | High dose PPIs (80 mg bolus + 8 mg/h for 3 days vs.<br>Non-high dose PPIs (40 mg160 mg/day for 3 days) | Patients with bleeding peptic ulcer | – Rebleeding<br>– Surgical intervention, and<br>– Mortality | 7 studies and 1157 patients<br>– Rebleeding: OR 1.30, 95 %CI 0.88 – 1.91<br>– Surgical intervention: OR 1.49, 0.66 – 3.37<br>– Mortality: OR 0.89, 0.37 – 2.13 | Compared with non – high dose PPIs, high dose PPIs do not further reduce the rates of rebleeding, surgical intervention, or mortality after endoscopic treatment.<br>Evidence: High |
| Masjedizadeh, 2014 [282] | Randomized, open-label | – High dose pantoprazole (80 mg bolus, 8 mg per hour) infused for 3 days vs.<br>– Low dose pantoprazole (40 mg bolus, 4 mg per hour) infused for 3 days | Patients with endoscopic signs of high risk of re-bleeding | Rebleeding at 30 days | 166 patients (83 patients per group)<br>Rebleeding observed in:<br>– High dose group: 27 patients (32.53 %)<br>– Low dose group: 21 patients (25.30 %)<br>$P = 0.30$ | For controlling peptic ulcer bleeding, there is no difference between high dose and low dose pantoprazole infusion.<br>Evidence: Low |

CI, confidence interval; H2RA, histamine-2 receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor; RR, risk ratio.

**Appendix e9** Salvage therapy in failed endoscopic hemostasis.

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitations | Level of evidence, Conclusion |
|---|---|---|---|---|---|---|
| Lau, 1999 [283] | Prospective, randomized trial<br>Comparison between immediate endoscopic re-treatment vs. surgery | Endoscopic re-treatment with the same device (epinephrine injection + heater probe):<br>– n = 48 patients<br>Surgery:<br>– n = 44 | Definitive hemostasis<br>Complications<br>Surgery<br>Mortality | Definitive hemostasis: 35/48<br>Salvage surgery: 13<br>– Persistent bleeding: 11<br>– Perforation: 2<br>Complications:<br>7 patients in the endoscopy group (including 6 who underwent salvage surgery) had complications, as compared with 16 in the surgery group ($P = 0.03$)<br>7<br>Mortality: n.s.<br>Hypotension at randomization and ulcer > 2 cm were independent predictors of re-treatment failure | Very high expertise center<br>Not blinded<br>2 perforations related to re-treatment with heater probe | High quality<br>In patients with peptic ulcers and rebleeding after initial hemostatic success, endoscopic re-treatment reduces the need for surgery without increasing risk of death and is associated with fewer complications than surgery. |
| Wong, 2011 [284] | Retrospective | Transcatheterangiographic embolization (TAE): n = 23<br>Surgery: n = 56 | Definitive hemostasis<br>Complications<br>Mortality | Bleeding recurrence:<br>– TAE group 34.4 %<br>– Surgery group 12.5 %<br>$P = 0.1$<br>More complications after surgery: 67.9 % vs. 40.6 %, $P = 0.1$<br>No difference in mortality: 25 % vs. 30.4 % | Results of initial failure and rebleeding are mixed | Moderate quality<br>In patients with ulcer bleeding after failed endoscopic hemostasis, TAE reduces the need for surgery without increasing the overall mortality and is associated with fewer complications. |
| Kyaw, 2014 [285] | Meta-analysis<br>6 retrospective studies that involved 423 patients | TAE patients were older, mean age:<br>– TAE: 75 years vs.<br>– Surgery: 68 years | Definitive hemostasis<br>Complications<br>Mortality | Risk of rebleeding was significantly higher in TAE vs. surgery:<br>RR 1.82, 95 %CI 1.23 – 2.67<br>After age exclusion, the high risk of rebleeding remained in the TAE group:<br>RR 2.64, 95 %CI 1.48 – 4.71<br>No difference in:<br>– Mortality, or<br>– Requirement for additional interventions | Retrospective studies | High quality<br>A higher rebleeding rate was observed after TAE, suggesting surgery more definitively secured hemostasis, with no significant differences in mortality rate or requirement for additional interventions. |
| Beggs, 2014 [286] | Systematic review (with homogeneity) of cohort studies | TAE: n = 347<br>Surgery: n = 364 | Mortality<br>Rebleeding<br>Length of hospital stay<br>Adverse events | Deaths:<br>– TAE: 61<br>– Surgery: 101<br>Rebleeding:<br>– TAE: 78<br>– Surgery: 45<br>Length of hospital stay:<br>– Mean difference between TAE and surgery: 0.75 days<br>Complications:<br>– TAE: 92<br>– Surgery: 81 | | Moderate quality<br>When compared with surgery, TAE had a significantly increased risk of rebleeding. However, there were no differences in mortality. |

**Appendix e9** (Continuation)

| First author, year [ref.] | Study type | Patient group | Key outcomes | Key results | Limitations | Level of evidence, Conclusion |
|---|---|---|---|---|---|---|
| Smith, 2014 [287] | European register | Patients who otherwise might have required either surgery or TAE<br>n = 8 | Definitive hemostasis | Definitive hemostasis:<br>– n = 8 (100 %) | Small number of patients | Low quality<br>Hemospray may be useful as a rescue therapy. |
| Sulz, 2014 [288] | Prospective, case series | n = 16 | Definitive hemostasis | Initial hemostasis: 15/16<br>Salvage therapy: 13/14<br>Monotherapy: 2/2<br>Rebleeding: 12.5 % | Small number of patients | Low quality<br>Hemospray may be useful as a salvage therapy. |
| Skinner, 2014 [289] | Retrospective | Over-the-scope clip after failure of conventional endoscopic treatment | n = 12<br>Cause of bleed:<br>– Duodenal ulcer: 6<br>– Gastric ulcer: 2<br>– Dieulafoy lesion: 2<br>– Anastomotic ulceration: 1<br>– Mallory-Weiss: 1<br>– Prior endoscopies<br>– Mean of 2<br>– Shock present:<br>– n = 9 (75 %)<br>RBC:<br>– Mean 5.1 units (2 – 12) | Primary hemostasis: 11/12<br>Rebleeding n = 2 (day1, day7)<br>No complication | Retrospective<br>Small number of patients<br>Expertise needed | Low quality<br>Over-the-scope clip effective and safe for severe acute gastrointestinal bleeding when conventional endoscopic therapy fails. |
| Manta, 2013 [290] | Retrospective | Over-the-scope clipping after failure of conventional endoscopic treatment | n = 23<br>– Duodenal ulcer: 12<br>Forrest Ia n = 5<br>Forrest Ib n = 4<br>– Gastric ulcer 6<br>Forrest Ia: n = 2<br>Forrest Ib: n = 2<br>– Mallory-Weiss: n = 3<br>– Dieulafoy: n = 2<br>– Anastomosis: n = 1 | Primary hemostasis: 22 (96 %)<br>– Duodenal ulcer: 11 (1 rebleeding)<br>– Gastric ulcer: 6 (1 rebleeding)<br>– Mallory-Weiss: 2 (no rebleeding)<br>– Dieulafoy: 2 (no rebleeding)<br>– Anastomosis1: (no rebleeding) | Retrospective<br>Small number of patients<br>Expertise needed | Low quality<br>Over-the-scope clipping is effective and safe for severe acute gastrointestinal bleeding when conventional endoscopic therapy fails. |

CI, confidence interval; NA, not available; NVUGIB, nonvariceal upper gastrointestinal bleeding; OR, odds ratio; RUT, rapid urease test; UBT, urea breath test.

**Appendix e10** *Helicobacter pylori* and nonvariceal upper gastrointestinal hemorrhage (NVUGIH).

| First author, year [ref.] | Study design, study objective | Participants | Outcomes | Results | Level of evidence, conclusions |
|---|---|---|---|---|---|
| Sánchez-Delgado, 2011 [291] | Meta-regression analysis | NVUGIB patients | *H. pylori* infection rate after the event | Delayed testing for *H. pylori* increases the detection rate (OR 2.08, 95 %CI 1.10 – 3.93) | Moderate |
| Gisbert, 2006 [292] | Meta-analysis | NVUGIB patients | *H. pylori* infection rate after the event | Low sensitivity of histology, RUT, culture, UBT, and serology | Moderate |
| Barkun, 2010 [240] | International consensus re-commendations | NVUGIB patients | Re-bleeding | *H. pylori* therapy and eradication confirmation needed | High |
| Gisbert, 2012 [293] | Prospective study on 1000 patients | NVUGIB patients | Re-bleeding after *H. pylori* eradication | Rebleeding was 0.15 % per patient-year of follow-up and it was associated with either re-infection or NSAIDs use. | Moderate |
| Gisbert, 2004 [294] | Meta-analysis | NVUGIB patients | Re-bleeding after eradication | Rebleeding was significantly lower in the *H. pylori* eradication group than in antisecretory therapy group (1.6 % vs. 5.6 %) | High |
| Dixon, 1996 [295] | International workshop | Gastritis | NA | Presence of neutrophil histology strongly suggests *H. pylori* infection | Moderate |

CI, confidence interval; NA, not available; NVUGIB, nonvariceal upper gastrointestinal bleeding; OR, odds ratio; RUT, rapid urease test; UBT, urea breath test.

**Appendix e11** Risk of thromboembolism, recurrent gastrointestinal (GI) bleeding and death after warfarin therapy interruption for GI bleeding.

| First author, year [ref.] | Study type | Study population Intervention | Key outcomes | Key results | Limitations | Conclusion |
|---|---|---|---|---|---|---|
| Witt, (2012) [296] | Retrospective, cohort | 442 patients with warfarin-associated GI bleeding<br>Intervention:<br>Withhold warfarin (no-warfarin group): 182 (41.2 %)<br>Resumed warfarin (warfarin group): 260 (58.8 %) | Thromboembolic events<br>Recurrent GI bleeding<br>Death | 90-day thromboembolic event rate:<br>– 0.4 % (1/260) in warfarin group<br>– 5.5 % (10/182) in no-warfarin group<br>HR (95 %CI): 0.05 (0.001 – 0.58)<br>No thromboembolic events in patients who resumed therapy within 14 days<br>90-day recurrent GI bleeding rate:<br>– Warfarin group: 10 % (26/260)<br>– No-warfarin group: 5.5 % (10/182)<br>HR (95 %CI): 1.32 (0.50 – 3.57)<br>Higher risk of recurrent GI bleeding in patients who resumed warfarin within 7 days from index bleeding as compared with those who resumed warfarin later:<br>– 12.4 % vs. 6.2 %<br>*P* = 0.03<br>90-day mortality rate:<br>– Warfarin group: 5.8 % (15/260) in<br>– No-warfarin group: 20.3 % (37/182)<br>HR (95 %CI): 0.31 (0.15 – 0.62) | Retrospective study<br>Data from administrative databases<br>Selection bias (greater co-morbidity burdens in no-warfarin group, which may have contributed to their worse outcomes)<br>Detection and survivorship biases | The decision to not resume warfarin therapy in the 90 days following a GI bleeding event is associated with increased risk for thrombosis and death.<br>Resuming warfarin within 7 days is associated with a twofold higher risk of rebleeding. |
| Qureshi, 2014 [297] | Retrospective, cohort study | 1329 atrial fibrillation patients with warfarin-associated major GI bleeding<br>Intervention:<br>676 (50.9 %) withhold warfarin (no-warfarin group)<br>653 (49.1 %) resumed warfarin (warfarin group)<br>Time duration of interruption:<br>– <7 days: 62 patients<br>– 7 – 30 days: 162 patients<br>– 30 days: 429 patients | Thromboembolic events<br>Recurrent GI bleeding<br>Death | Warfarin group vs. no-warfarin group, adjusted HR (95 %CI):<br>– Thromboembolism: 0.71 (054 – 0.93)<br>– Recurrent GI bleeding; 1.20 (0.78 – 1.86)<br>– Mortality: 0.72 (0.60 – 0.86)<br>Incidence of adverse outcomes per 100 person-years in the warfarin group, stratified by the duration of warfarin interruption:<br>– <7 days (n = 62):<br>Thromboembolism: 11.6 (8.3 – 16.2)<br>Recurrent GI bleeding: 19.3 (14.6 – 25.5)<br>– 7 – 15 days (n = 51):<br>Thromboembolism: 12.0 (8.2 – 17.5)<br>Recurrent GI bleeding: 10.8 (7.2 – 16.3)<br>– 15 – 21 days (n = 58):<br>Thromboembolism: 18.1 (13.4 – 24.5)<br>Recurrent GI bleeding: 10.9 (7.2 – 16.4)<br>– 21 – 30 days (n = 53):<br>Thromboembolism 20.7 (15.5 – 27.7)<br>Recurrent GI bleeding 9.9 (6.3 – 15.5)<br>– >30 days (n = 429):<br>Thromboembolism 20.4 (17.8 – 23.5)<br>Recurrent GI bleeding 9.9 (8.0 – 12.3) | Retrospective study. Data from administrative database<br>Selection bias (greater co-morbidity burdens in no-warfarin group)<br>Detection and survivorship biases | The decision to not resume warfarin therapy after a GI bleeding event is associated with increased risk for thrombosis and death.<br>There is a trend toward reduced incidence of thromboembolic events the earlier the warfarin is introduced; this trend is more evident within the first 15 days.<br>Resuming warfarin within 7 days is associated with a twofold higher risk of rebleeding.<br>Decision to restart warfarin after 7 days of interruption is associated with improved survival and decreased thromboembolism without increased risk of recurrent GI bleeding. |

**Appendix e11** (Continuation)

| First author, year [ref.] | Study type | Study population<br>Intervention | Key outcomes | Key results | Limitations | Conclusion |
|---|---|---|---|---|---|---|
| Lee, 2011 [298] | Retrospective, case-control study | 58 patients with NVUGIB on warfarin for native valvular heart disease<br>Controls (aspirin group): 41 age- and gender-matched patients with NVUGIB on aspirin for ischemic heart disease presenting<br>Intervention<br>Cases:<br>– Discontinued warfarin (no-warfarin group): 36/58<br>– Restarted warfarin (warfarin group): 22/58<br>Controls:<br>– Discontinued aspirin: 41/41 | Recurrent GI bleeding<br>Thromboembolic events<br>Mean follow-up: 255 + 14 days (range 182 – 330) | Warfarin vs. no-warfarin group:<br>– Rebleeding rate: 7 % vs.0 %<br>– Thromboembolism rate: 0 % vs. 17 % (6 thromboembolic events occurred, at days 21, 27, 28, 31, 58, 75 from admission)Aspirin group:<br>– Rebleeding rate: 0 %<br>– Thromboembolic event rate: 2 % (1 myocardial infarction at day 95 from admission) | Retrospective design<br>Time of resuming anticoagulation not specified<br>Individual thromboembolic risk not specified | Anticoagulation is recommended to be resumed within 20 days from the cessation to prevent thromboembolic events. |

CI, confidence interval; HR, hazard ratio; NVUGIB, nonvariceal upper gastrointestinal bleeding.

**Appendix e12** Observational studies assessing the effect of proton pump inhibitors (PPIs) on clinical cardiovascular outcomes in patients prescribed clopidogrel.

| First author, year [ref.] | Design | Population | Patients, n | | End point | Results |
|---|---|---|---|---|---|---|
| | | | PPI | No PPI | | |
| Studies with evidence of a clinically significant interaction | | | | | | |
| Goodman, 2012 [299] | Retrospective cohort within RCT (PLATO) | Acute coronary syndrome (ACS) | 3 255 | 6 021 | Cardiovascular death, myocardial infarction, cerebrovascular accident | Clopidogrel cohort: HR 1.20 (95 %CI 1.04 – 1.38) Ticagrelor cohort: HR 1.24 (95 %CI, 1.07 – 1.45) |
| Stockl, 2010 [300] | Retrospective Propensity matching | Post myocardial infarction or post percutaneous coronary intervention | 1 033 | 1 033 | Myocardial infarction Myocardial infarction or revascularization | HR 1.93 (95 %CI, 1.05 – 3.54) HR 1.91 (95 %CI 1.19 – 3.06) |
| Kreutz, 2010[301] | Retrospective cohort | Post percutaneous coronary intervention | 6 828 | 9 862 | Cardiovascular deaths, acute coronary syndrome, cerebrovascular accident revascularization | HR 1.51 (95 %CI, 1.39 – 1.64) |
| Ho, 2009 [302] | Retrospective cohort | Post myocardial infarction | 5 244 | 2 961 | Deaths, acute coronary syndrome | HR 1.25(95 %CI, 1.11 – 1.41) |
| Huang, 2010 [303] | Registry | Post percutaneous coronary intervention | 572 | 2 706 | Death | HR 1.65(95 % CI, 1.35 – 2.01) |
| Zou, 2014 [304] | Retrospective cohort | Post percutaneous coronary intervention | 61 288 | 1 465 | Myocardial infarction, stent thrombosis, cardiovascular deaths | HR 1.33 (95 % CI 1.12 – 1.57) |
| Van Boxel, 2010 [305] | Retrospective cohort | Clopidogrel users | 5 734 | 12 405 | Deaths, acute coronary syndrome, cerebrovascular accident | HR 1.75 (95 % CI, 1.58 – 1.94) |
| Munoz-Torrero, 2011 [306] | Registry | Vascular disease | 519 | 703 | Deaths, myocardial infarction, acute coronary syndrome, cerebrovascular accident, chronic limb ischemia | HR 1.8 (95 % CI, 1.1 – 2.7) |
| Studies without evidence of a clinically significant interaction | | | | | | |
| O'Donoghue, 2009 [307] | Retrospective cohort within RCT (TRITON-TIMI 38) | Acute coronary syndrome and post percutaneous coronary intervention | 2 257 | 4 538 | Cardiovascular death, myocardial infarction, cerebrovascular accident | No effect |
| Hsiao, 2011 [308] | Retrospective Propensity matching | Post myocardial infarction | 622 | 9 131 | Acute coronary syndrome | No effect |
| Banerjee, 2011 [309] | Retrospective Propensity matching | Post percutaneous coronary intervention | 867 | 3 678 | Death, myocardial infarction, revascularization | No effect |
| Harjai, 2011 [310] | Registry Propensity matching | Post percutaneous coronary intervention | 751 | 1 900 | Death, myocardial infarction, revascularization | No effect |
| Aihara, 2012 [311] | Registry Propensity matching | Post percutaneous coronary intervention | 819 | 1 068 | Death, myocardial infarction | No effect |
| Tentzeris, 2010 [312] | Registry Propensity matching | Post percutaneous coronary intervention | 691 | 519 | Death, acute coronary syndrome | No effect |
| Schmidt, 2012 [313] | Retrospective cohort | Post percutaneous coronary intervention | 2 742 | 10 259 | Cardiovascular deaths, acute coronary syndrome, cerebrovascular accident, revascularization | No effect |
| Rassen, 2009 [314] | Retrospective cohort | Post percutaneous coronary intervention or post acute coronary syndrome | 3 996 | 14 569 | Death, myocardial infarction, revascularization | No effect |
| Ray, 2010 [315] | Retrospective cohort | Post percutaneous coronary intervention or post acute coronary syndrome | 7 593 | 13 003 | Death, myocardial infarction, revascularization | No effect |

CI, confidence interval; HR, hazard ratio; PLATO, Platelet Inhibition and Patient Outcomes; RCT, randomized controlled trial.

**Appendix e13** Meta-analyses evaluating the effect of proton pump inhibitors (PPIs) on clinical outcomes in patients treated with clopidogrel.

| First author, year [ref.] | Included studies | Patients, n | End point | Results |
|---|---|---|---|---|
| Kwok, 2010 [316] | 1 nested case-control<br>20 retrospective<br>(3 studies used a propensity scoring method for the analysis)<br>3 post.hoc analyses of RCT<br>1 prospective RCT | 93 278 | Myocardial infarction or acute coronary syndrome (12 studies) | RR 1.43 (95 %CI 1.15 – 1.77)<br>RR 1.15 (0.89 – 1.48): analysis from propensity matched or trial participants |
| | | | Overall mortality (13 studies) | RR 1.09 (95 %CI 0.94 – 1.53)<br>RR 1.00 (0.66 – 1.48): analysis from propensity matched or trial participants |
| | | | Major adverse cardiovascular event (MACE)<br>(19 studies) | RR 1.25 (95 %CI 1.09 – 1.42)<br>RR 1.07 (0.90 – 1.48): analysis from propensity matched or trial participants |
| Siller-Matula, 2010 [317] | 2 nested case-control<br>20 retrospective cohort<br>(3 studies used a propensity scoring method for the analysis)<br>2 post.hoc analyses of RCT<br>1 prospective RCT | 159 138 | Myocardial infarction<br>(13 studies) | RR 1.31 (95 %CI 1.12 – 1.53) |
| | | | Death<br>(13 studies) | RR 1.04 (95 %CI 0.93 – 1.24) |
| | | | MACE<br>(19 studies) | RR 1.29 (95 %CI 1.15 – 1.44) |

CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio

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