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






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## MAIN RECOMMENDATIONS

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

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

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

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

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

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

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

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

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

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

## SOURCE AND SCOPE

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

## Introduction

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


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**ABBREVIATIONS**

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

## Methods

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

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

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

## Evidence statements and Recommendations

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

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

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

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

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

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

## Pre-endoscopy management

### Initial patient evaluation and hemodynamic resuscitation

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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

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

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## Red blood cell (RBC) transfusion strategy

**RECOMMENDATION**

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

Strong recommendation, moderate quality evidence.

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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

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

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

## Patient risk stratification

**RECOMMENDATION**

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

Strong recommendation, moderate quality evidence.

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

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



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

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

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

**RECOMMENDATION**

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

Strong recommendation, moderate quality evidence.

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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

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

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



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

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

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

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

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

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

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

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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

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

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

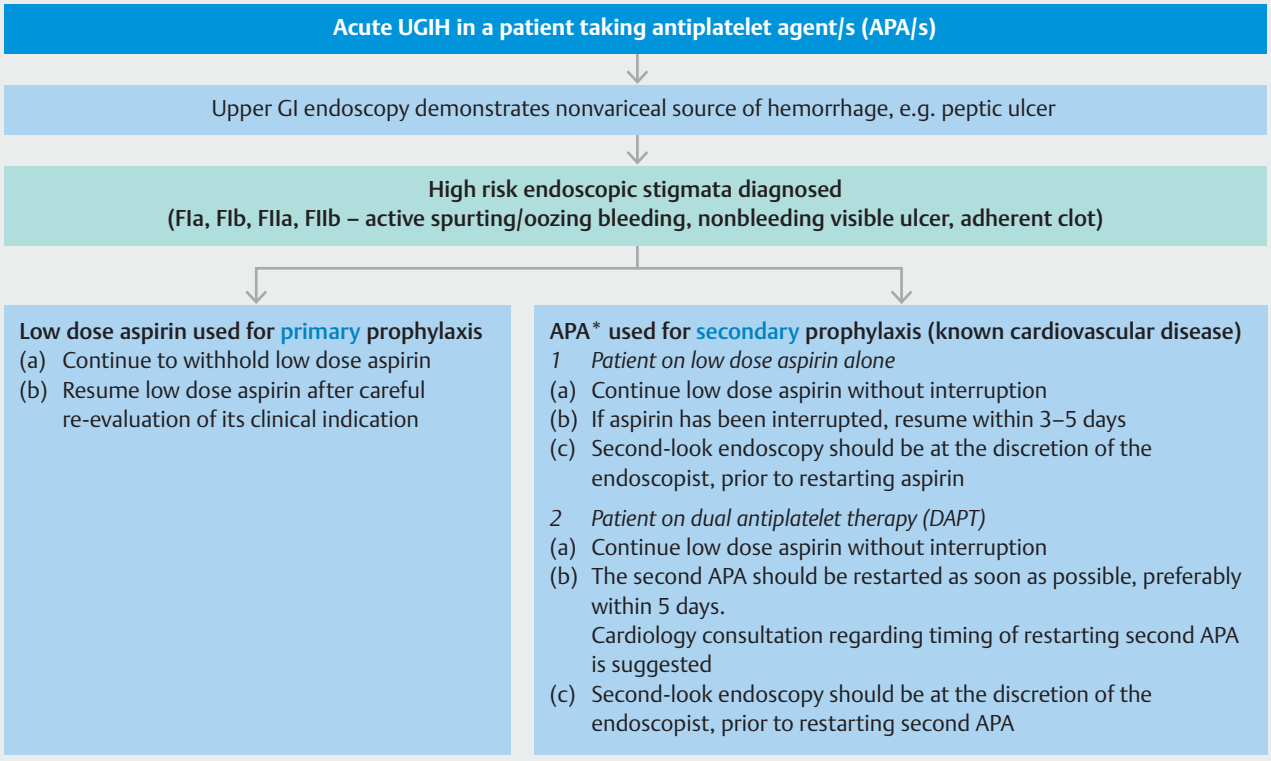
Patients who develop acute UGIH while taking DOACs must follow a similar protocol of early endoscopy and reversal of anticoagulation in cases of hemodynamic instability or life-threatening bleeding. However, there are particular considerations because of DOAC's specific pharmacodynamics and the availability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

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



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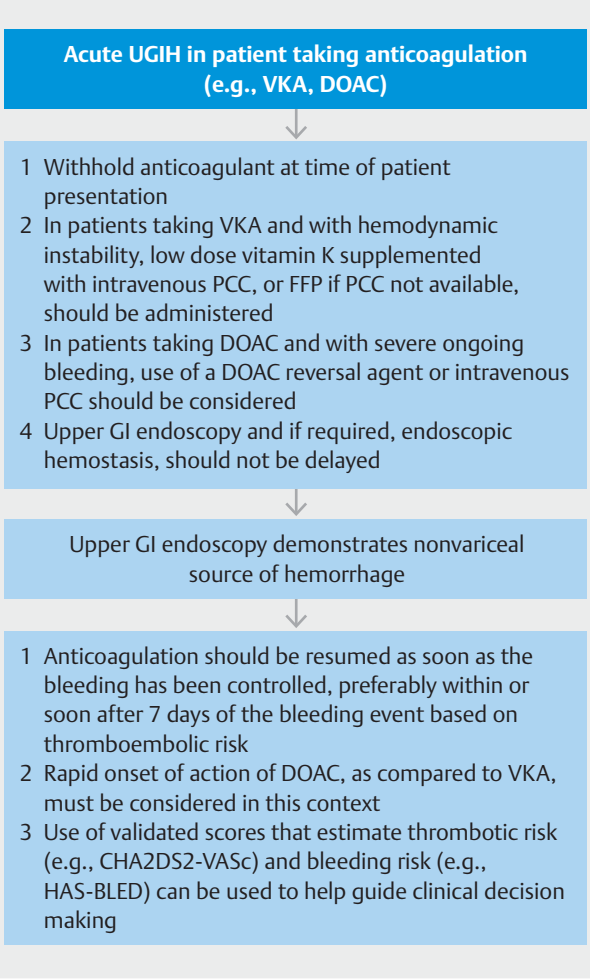



▶ **Fig. 1** Management of antiplatelet therapy in patients with acute nonvariceal upper gastrointestinal hemorrhage (NVUGIH) with **a** high risk, and **b** low risk stigmata, diagnosed at endoscopy. *In patients using a nonaspirin antiplatelet agent (APA) as monotherapy (e. g. thienopyridine alone),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

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

## Pre-endoscopy proton pump inhibitor (PPI) therapy

**RECOMMENDATION**

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

Weak recommendation, high quality evidence.

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

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

## Somatostatin and somatostatin analogues

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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



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

## Nasogastric/orogastric tube aspiration and lavage

**RECOMMENDATION**

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

Strong recommendation, moderate quality evidence.

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

## Endotracheal intubation

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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

## Prokinetic medications

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

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

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

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



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

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

## Endoscopic management

### Timing of upper GI endoscopy

**RECOMMENDATION**

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

Strong recommendation, moderate quality evidence.

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

**RECOMMENDATION**

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

Strong recommendation, moderate quality evidence.

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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

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

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



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

## On-call GI endoscopy resources

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

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

## Endoscopic diagnosis

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

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

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

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

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

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

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

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


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

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

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

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

## Endoscopic therapy for peptic ulcer hemorrhage

**RECOMMENDATION**

*FIa, FIb (active bleeding)*

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

Strong recommendation, high quality evidence.

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

Weak recommendation, low quality evidence.

**RECOMMENDATION**

*FIIa (nonbleeding visible vessel)*

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

Strong recommendation, high quality evidence.



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**RECOMMENDATION**

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

**RECOMMENDATION**

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

**RECOMMENDATION**

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

**RECOMMENDATION**

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

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

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

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

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

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

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


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**Performance of upper GI endoscopy[1]**

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

Perform endoscopic hemostasis

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

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

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

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

a

**Performance of upper GI endoscopy[1]**

FIIb (adherent clot)

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

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

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

b

**Performance of upper GI endoscopy[1]**

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

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

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

c

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

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

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

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


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

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

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

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

**RECOMMENDATION**

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

Weak recommendation, moderate quality evidence.

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

**Box 1** presents a description of the endoscopic hemostatic modalities.

## Post-endoscopy management

### Proton pump inhibitor therapy

**RECOMMENDATION**

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

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

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

Strong recommendation, high quality evidence.

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



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**BOX 1 ENDOSCOPIC HEMOSTASIS TOOLBOX**

*Injection therapy*

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

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

*Thermal therapy*

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

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

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

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

*Mechanical therapy*

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



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

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

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

*Topical therapy*

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

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

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

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

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

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

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

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

## Management of recurrent bleeding

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

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

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

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

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


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

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

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

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

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

## Helicobacter pylori

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

**RECOMMENDATION**

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

Strong recommendation, high quality evidence.

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

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



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

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

## Dual antiplatelet therapy and PPI co-therapy

**RECOMMENDATION**

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

Strong recommendation, moderate quality evidence.

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

## Restarting anticoagulation therapy (VKAs, DOACs)

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

**RECOMMENDATION**

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

Strong recommendation, low quality evidence.

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



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

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

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

### Use of PPI in patients taking anticoagulants

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

## Disclaimer

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

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### Competing interests

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

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