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

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

Main Recommendations

MR1. ESGE recommends immediate assessment of hemodynamic status in patients who present with acute upper gastrointestinal hemorrhage (UGIH), with prompt intravascular volume replacement initially using crystalloid fluids if hemodynamic instability exists (strong recommendation, moderate quality evidence).

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

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

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

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

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

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

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

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

MR10. In patients with peptic ulcers having a flat pigmented spot (Forrest classification IIc) or clean base (Forrest classification III), ESGE does not recommend endoscopic hemostasis as these stigmata present a low risk of recurrent bleeding. In selected clinical settings, these patients may be discharged to home on standard PPI therapy, e.g., oral PPI once-daily (strong recommendation, moderate quality evidence).

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

MR12. ESGE recommends PPI therapy for patients who receive endoscopic hemostasis and for patients with adherent clot not receiving endoscopic hemostasis. PPI therapy should be high dose

and administered as an intravenous bolus followed by continuous infusion (80mg then 8mg/hour) for 72 hours post endoscopy (strong recommendation, high quality evidence).

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

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

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

Abbreviations

APC: argon plasma coagulation
ASA: American Society of Anesthesiologists
DAPT: dual antiplatelet therapy
$CHADS_2$: congestive heart failure, hypertension, age≥75 years, diabetes mellitus, and previous stroke or transient ischemic attack [risk score]
CI: confidence interval
DOAC: direct oral anticoagulant
ESGE: European Society of Gastrointestinal Endoscopy
FFP: fresh frozen plasma
GBS: Glasgow-Blatchford Score
GI: gastrointestinal
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HR: hazard ratio

INR: international normalized ratio
NBVV: nonbleeding visible vessel
NNT: number needed to treat
NOAC: non-VKA oral anticoagulant
NVUGIH: nonvariceal upper gastrointestinal hemorrhage
PAR: protease-activated receptor
PCC: prothrombin complex concentrate
PICO: patients, interventions, controls, outcomes
PPI: proton pump inhibitor
OR: odds ratio
PUB: peptic ulcer bleeding
RBC: red blood cell
RCT: randomized controlled trial
RR: relative risk or risk ratio
TAE: transcatheter angiographic embolization
UGIH: upper gastrointestinal hemorrhage
VCE: videocapsule endoscopy
VKA: vitamin K antagonist

Introduction

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

Methods

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

Each task force subgroup performed a systematic literature search to identify the relevant literature that was subsequently used to prepare evidence-based, well-balanced statements on each of their assigned key questions. The Ovid MEDLINE, EMBASE, Google/Google Scholar, and the Cochrane Database of Systematic Reviews were searched for English-language articles including at a minimum the following key words: nonvariceal upper gastrointestinal (GI) hemorrhage/bleeding, peptic ulcer hemorrhage/bleeding, fluid resuscitation, fluid therapy, critical illness, crystalloid solutions, colloid solutions, plasma transfusions, red blood cell transfusion, platelet transfusion, hemoglobin, restrictive transfusion strategy, liberal transfusion strategy, risk stratification, mortality, rebleeding, anti-thrombotic agent, antiplatelet agent, aspirin, dual anti-platelet therapy (DAPT), anti-coagulation/anti-coagulant, direct/new oral anticoagulants (DOACs), coagulopathy, vitamin K inhibitor/antagonist, prokinetic agent, erythromycin, fresh frozen plasma, nasogastric tube, orogastric tube, proton pump inhibitor, prokinetic agent, erythromycin, endoscopic hemostasis, injection therapy, thermal therapy (contact, non-contact), mechanical therapy/endoscopic clipping, topical hemostasis therapy, second-look endoscopy, helicobacter pylori, H. pylori, transcatheter angiographic embolization (TAE), and surgery. The hierarchy of studies included as part of this evidence-based guideline was, in decreasing order of evidence level, published systematic reviews/meta-analyses, randomized controlled trials (RCTs), prospective and retrospective observational studies. All selected articles were graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [3] [4].

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

and ESGE individual members. After agreement on a final version, the manuscript was submitted to the journal Endoscopy for publication. All authors agreed on the final revised manuscript.
This NVUGIH guideline will be considered for review and updating in 2020, or sooner if new relevant evidence becomes available. Any updates to this guideline in the interim will be noted on the ESGE website: http://www.esge.com/esge-guidelines.html.

Statements and recommendations

See [Table1].
Table 1 Summary of Guideline statements and recommendations. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

Initial patient evaluation and hemodynamic resuscitation

ESGE recommends immediate assessment of hemodynamic status in patients who present with acute upper gastrointestinal hemorrhage (UGIH), with prompt intravascular volume replacement initially using crystalloid fluids if hemodynamic instability exists (strong recommendation, moderate quality evidence).
The goals of hemodynamic resuscitation are to correct intravascular hypovolemia, restore adequate tissue perfusion, and prevent multi-organ failure. Early intensive hemodynamic resuscitation of patients with acute UGIH has been shown to significantly decrease mortality [5]. In an observational study of patients with acute UGIH and hemodynamic instability, patients who received intensive hemodynamic resuscitation had significantly fewer myocardial infarctions and lower mortality compared with those in the “observation group” ($P = 0.04$ for both comparisons). However, there is no evidence from randomized controlled trials (RCTs), for or against early or large-volume intravenous fluid administration in uncontrolled hemorrhage [6] [7]. Moreover, the selection of resuscitation fluid type in critically ill patients requires careful consideration based on safety, effects on patient outcomes, and costs. To date, there is ongoing uncertainty regarding the ideal fluid administration strategy in this clinical setting [8] [9].
ESGE recommends a restrictive red blood cell transfusion strategy that aims for a target hemoglobin between 7g/dL and 9g/dL. A higher target hemoglobin should be considered in patients with significant co-morbidity (e.g., ischemic cardiovascular disease) (strong recommendation, moderate quality evidence).
The use of red blood cell (RBC) transfusions may be lifesaving following massive UGIH. However, the role of RBC transfusion in less torrential GI bleeding remains controversial, with uncertainty

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

Risk stratification

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

ESGE recommends the use of the Glasgow-Blatchford Score (GBS) for pre-endoscopy risk stratification. Outpatients determined to be at very low risk, based upon a GBS score of 0–1, do not require early endoscopy nor hospital admission. Discharged patients should be informed of the

risk of recurrent bleeding and be advised to maintain contact with the discharging hospital (strong recommendation, moderate quality evidence).

Risk stratification of patients presenting with acute UGIH can assist in identifying those who may require more urgent intervention and help triage patients to in-hospital vs. out-of-hospital management. A number of scoring tools have been created for predicting outcomes following acute UGIH, with the Glasgow-Blatchford Score (GBS) ([Table2]) and Rockall score being the most widely evaluated and adopted [17] [18] [19]. However, no single scoring tool has been shown to excel at predicting all relevant outcomes in acute UGIH (e.g., rebleeding, need for intervention, mortality) [19]. This is not surprising as the most validated risk scores were derived to assess a specific UGIH outcome: that for the Rockall score being mortality and for the GBS being the need for intervention [17] [18].

Table2

Glasgow-Blatchford Score (GBS).

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

Table2

Glasgow-Blatchford Score (GBS).

	Points
Pulse≥100	1
Melena	1
Syncope	2
Hepatic disease	2
Cardiac failure	2

TOTAL GBS _____

GBS restricted for use only in nonhospitalized, ambulatory patients

Risk variables measured at time of patient presentation

GBS=0–1 denotes “low-risk”

A recent systematic review evaluating the accuracy of the available UGIH risk stratification tools demonstrated substantial heterogeneity in predicted outcomes and highlighted that methodological quality of the prediction scores was less than optimal [19]. Regarding the need for intervention, retrospective and prospective studies have assessed the prognostic value of the GBS vs. the Rockall score. These studies showed that the GBS correctly identified 98% (95%CI 89%–100%) of those patients who did not require any subsequent intervention while 83% (95%CI 71%–91%) of those patients were identified using the Rockall score. Randomized controlled trials and observational studies consistently indicate that clinical, endoscopic, and social factors may identify patients who may be safely discharged for outpatient management [20] [21] [22] [23] [24] [25] [26] [27] [28]. The most frequent adverse event reported is rebleeding ranging between 0.5% and 4%, with no deaths or hospital readmissions for surgery reported. Moreover, studies consistently indicate that outpatient management of appropriately selected patients with acute UGIH reduces resource utilization [20] [21] [27]. Emergency department discharge without inpatient endoscopy (i.e., outpatient management) should be considered for patients if: systolic blood pressure ≥110mmHg, pulse <100 beats/minute, hemoglobin ≥13.0g/dL for men or ≥12.0g/dL for women, blood urea nitrogen<18.2mg/dL, along with the absence of melena, syncope, hepatic disease, and cardiac failure [18]. (See Appendix e2, online-only.)

Pre-endoscopy management

Initial management of antithrombotic agents (anticoagulants and antiplatelet agents)

For patients taking vitamin K antagonists (VKAs), ESGE recommends withholding the VKA and correcting coagulopathy while taking into account the patient's cardiovascular risk in consultation with a cardiologist. In patients with hemodynamic instability, administration of vitamin K, supplemented with intravenous prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) if PCC is unavailable, is recommended (strong recommendation, low quality evidence).
If the clinical situation allows, ESGE suggests an international normalized ratio (INR) value<2.5 before performing endoscopy with or without endoscopic hemostasis (weak recommendation, moderate quality evidence).
GI bleeding represents a serious complication of VKA therapy, with an incidence of 1%–4% per year [29] [30]. Discontinuation of anticoagulants and correction of coagulopathy before endoscopy is the "standard of practice" in patients with clinically significant GI bleeding [31] [32] [33]. Because data are limited, specific strategies to reverse VKAs in a patient with acute overt UGIH vary [34]. Practice guidelines recommend urgent reversal in all patients presenting with serious, life-threatening bleeding (i.e., hemodynamic instability or shock), either in the case of therapeutic or supratherapeutic INR elevations [32] [35]. For patients who are not actively bleeding and are hemodynamically stable, intravenous vitamin K administration may be an option. When more urgent reversal is required, administration of prothrombin complex concentrates (PCCs) or fresh frozen plasma (FFP) is necessary, with concomitant intravenous administration of 5–10mg vitamin K to prevent "rebound coagulopathy" once the transfused factors have been cleared. Prothrombin complex concentrates contain clotting factors prepared from pooled and concentrated human plasma and are preferred over FFP because of several advantages, including no need to check the patient's blood group, less risk for volume overload because of smaller transfusion volume, faster onset of action, similar thrombotic risk profile, and minimal risk of infectious transmission, albeit at a higher cost [36] [37] [38] [39] [40]. A recent prospective, nonrandomized, comparative study of 40 warfarin users who presented with UGIH and an INR>2.1 reported that patients who received PCC had a near normalized INR at 2 hours following infusion (INR=1.5) while those who received FFP had an INR of 2.4at 6 hours following infusion [38]. No patient in the PCC group had active bleeding at endoscopy compared with 7 in the FFP group (0 vs. 35%, P<0.01). The risk of thrombosis following PCC administration approximates 1%, and is similar to that reported with FFP [39] [40].
ESGE recommends temporarily withholding new direct oral anticoagulants (DOACs) in patients with suspected acute NVUGIH in coordination/consultation with the local hematologist/cardiologist (strong recommendation, very low quality evidence).
As an alternative to heparin and VKAs, the new non-VKA oral anticoagulants (NOACs; also referred to as direct oral anticoagulants [DOACs]) are being rapidly adopted worldwide, primarily for thromboembolic prevention in patients with nonvalvular atrial fibrillation and for prophylaxis or treatment of venous thromboembolism [41]. These pharmacological agents do however, present a

risk of significant GI bleeding similar to or greater than that reported with warfarin [42] [43]. Moreover, DOACs differ in comparison with heparin and VKA. Specifically, in the absence of renal or hepatic failure, DOAC clearance and the subsequent loss of anticoagulation effect is rapid and predictable (occurring gradually over 12–24 hours), routine laboratory tests are not sensitive for the quantitative assessment of their anticoagulant activity, and there is currently no specific reversal agent/antidote for emergency use with any DOAC, although potential agents are in development and may be commercially available in the next 1–2 years [44] [45] [46]. As there are no published clinical trials addressing the management of GI bleeding in patients using DOAC, current recommendations are based on expert opinion or laboratory end-points [47] [48] [49].

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

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

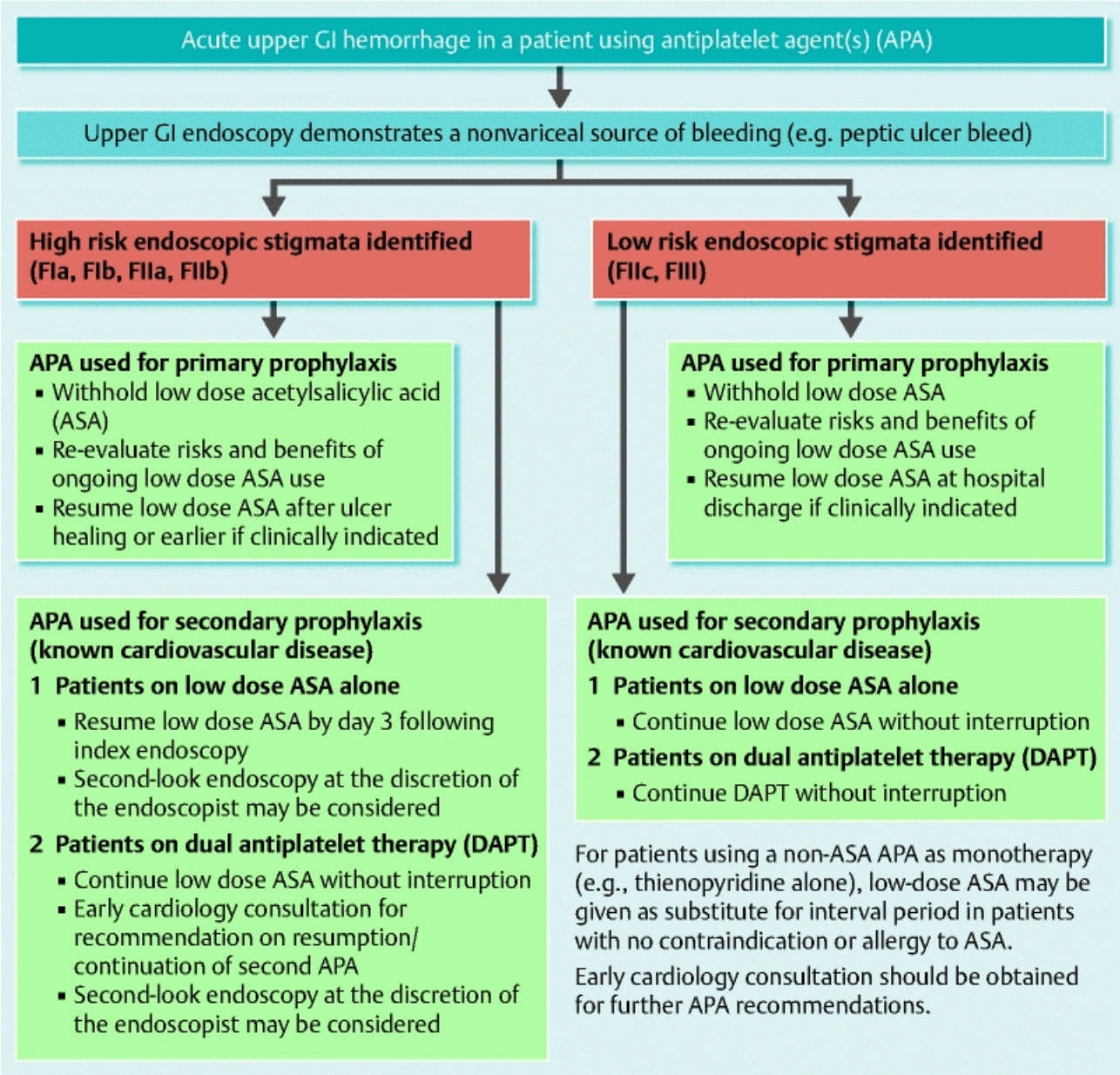

Fig.1 Algorithm for the management of patients with acute upper gastrointestinal hemorrhage who are using antiplatelet agent(s): European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

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

Studies have shown that in patients taking low dose aspirin for secondary cardiovascular prophylaxis, all-cause mortality was lower if aspirin was not discontinued following peptic ulcer bleeding [53] [54]. In an RCT, 156 recipients of low dose aspirin for secondary prophylaxis who

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

Pharmacological therapy

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

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

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

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

Tranexamic acid reduces clot breakdown by inhibiting the fibrinolytic action of plasmin. A recent RCT demonstrated that tranexamic acid significantly reduces bleeding-related and all-cause mortality in trauma patients with significant hemorrhage [60]. A Cochrane meta-analysis evaluating the use of tranexamic acid in 1654 UGIH patients showed a beneficial effect of tranexamic acid on mortality when compared with placebo (relative risk [RR] 0.61, 95%CI 0.42–0.89), but not on other patient outcomes including bleeding, surgery, or transfusion requirements [61]. However, the

beneficial effect on mortality did not persist in subgroup analysis. The studies included in this meta-analysis have important limitations that affect their generalizability including their methodological quality and the fact that the majority were conducted before the widespread use of therapeutic endoscopy and PPIs. To date, no controlled trial assessing the role of alternative antifibrinolytic agents (e.g., aminocaproic acid, aprotinin) in patients with acute UGIH has been reported. (See Appendix e4, online-only.)

ESGE does not recommend the use of somatostatin, or its analogue octreotide, in patients with NVUGIH (strong recommendation, low quality evidence).

Somatostatin, and its analogue octreotide, inhibit both acid and pepsin secretion while also reducing gastroduodenal mucosal blood flow [62]. However, they are not routinely recommended in NVUGIH (e.g., peptic ulcer bleeding), either pre-endoscopy or as an adjunctive therapy post endoscopy, since published data show little or no benefit attributable to these pharmacological agents. (See Appendix e5, online-only.)

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

It has been reported that in 3% to 19% of UGIH cases, no obvious cause of bleeding is identified [63] [64]. This may in part be related to the presence of blood and clots impairing endoscopic visualization. There are four published meta-analyses evaluating the role of prokinetic agent infusion prior to upper GI endoscopy in patients presenting with acute UGIH [65] [66] [67] [68]. The most recently published meta-analysis (n=558 patients) showed that erythromycin infusion prior to endoscopy significantly improved gastric mucosa visualization (OR 3.43, 95%CI 1.81–6.50; P<0.01), and decreased the need for second-look endoscopy (OR 0.47, 95%CI 0.26–0.83, P=0.01), RBC units transfused (weighted mean difference −0.41, 95%CI −0.82 to −0.01, P=0.04), and duration of hospital stay (weighted mean difference −1.51 days, 95%CI −2.45 to −0.56, P<0.01) [68].

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

second-look endoscopies [69]. Contraindications to erythromycin administration include sensitivity to macrolide antibiotics and prolonged QT interval.
Metoclopramide has been less studied, it has been assigned a “black box warning” by the United States Food and Drug Administration because of the risk of neurologic side effects, and caution should therefore be advised with the use of this prokinetic agent.

Role of gastric lavage and prophylactic endotracheal intubation

ESGE does not recommend the routine use of nasogastric or orogastric aspiration/lavage in patients presenting with acute UGIH (strong recommendation, moderate quality evidence).
A number of studies, including a meta-analysis, have evaluated the role of nasogastric aspiration/lavage in patients presenting with acute UGIH [70] [71] [72] [73]. In distinguishing upper from lower GI bleeding, nasogastric aspiration has low sensitivity 44% (95%CI 39%–48%) yet high specificity 95% (95%CI 90%–98%). In identifying severe UGIH, its sensitivity and specificity are 77% (95%CI 57%–90%) and 76% (95%CI 32%–95%), respectively [70]. This meta-analysis also found that as compared to nasogastric aspiration/lavage, clinical signs and laboratory findings (e.g., hemodynamic shock and hemoglobin <8g/dL) had similar ability to identify severe UGIH [70]. Others have reported that nasogastric aspiration/lavage failed to assist clinicians in correctly predicting the need for endoscopic hemostasis, did not improve visualization of the stomach at endoscopy, or improve clinically relevant outcomes such as rebleeding, need for second-look endoscopy, or blood transfusion requirements [71] [72] [73]. It also should be noted that nasogastric aspiration/lavage is a very uncomfortable procedure that is not well tolerated or desired by patients [74].
In an effort to protect the patient’s airway from potential aspiration of gastric contents, ESGE suggests endotracheal intubation prior to endoscopy in patients with ongoing active hematemesis, encephalopathy, or agitation (weak recommendation, low quality evidence).
It has been hypothesized that pre-endoscopic endotracheal intubation may prevent cardiorespiratory adverse events in patients with acute UGIH. However, between those patients who were prophylactically intubated prior to upper GI endoscopy as compared to those patients not intubated, published data show no significant difference in patient outcomes (e.g., pulmonary aspiration, in-hospital mortality) [75] [76] [77]. One study suggested that aspiration was actually more frequent in those patients who had undergone endotracheal intubation prior to upper GI endoscopy [75]. At this time, endotracheal intubation prior to upper GI endoscopy in patients with UGIH does not seem to make a difference in patient outcome but published data are limited with small numbers of subjects and low methodological quality.

Timing of endoscopy

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

Following hemodynamic resuscitation, ESGE recommends early (≤24 hours) upper GI endoscopy.

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

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

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

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

With respect to very early upper GI endoscopy, an RCT that included 325 patients with peptic ulcer bleeding showed that upper GI endoscopy performed within 12 hours of admission (as compared with 12–24 hours) resulted in a significant reduction in transfusion requirements in patients with bloody nasogastric lavage (P<0.001). No such reduction was observed in patients with “coffee grounds” or clear lavage [83]. A retrospective analysis that included 934 UGIH patients showed that in the subset of patients having a GBS≥12 (n=97, 10.4%), the time lapse between

presentation to endoscopy was the lone independent risk factor associated with all-cause in-hospital mortality [84]. In this study, a cutoff time of 13 hours in delay to endoscopy best discriminated between patient survival and nonsurvival.

In patients who are hemodynamically stable and without serious co-morbidities, RCTs have shown that performing endoscopy without hospital admission facilitates discharge in up to 46% of patients and reduces costs/resource utilization [20] [85]. Discharging low risk suspected NVUGIH patients (GBS=0) directly from the emergency department without undergoing upper GI endoscopy has been proposed as a safe and cost-saving option in multiple studies in various clinical settings [18] [86] [87] [88] [89]. Some investigators have suggested that using a GBS$\leq$1 (see [Table2]) could double the number of patients eligible for ambulatory management while maintaining safety [89].

There are four published studies, one RCT and three prospective case series, that have evaluated the test characteristics and accuracy parameters of video capsule endoscopy (VCE) in risk stratification of patients presenting with acute UGIH [90] [91] [92] [93]. The overall sensitivity, specificity, positive predictive value, and negative predictive value of VCE for detecting blood in the upper GI tract in patients suspected of acute UGIH are 75%, 76%, 67%, and 82% respectively. Because the data are limited, at this time there is no role for VCE in the emergency department setting in evaluating acute upper GIH. However, additional studies are needed to further assess VCE in this patient population since, for low to moderate risk UGIH patients, VCE may be a cost-effective modality if post-VCE low risk patients are discharged directly home from the emergency department and hospital admission is avoided [94] [95].

Endoscopic management

Endoscopic diagnosis

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

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

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

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

The Forrest (F) classification was developed more than 40 years ago in an attempt to standardize the characterization of peptic ulcers [96]. The Forrest classification is defined as follows: FIa spurting hemorrhage, FIb oozing hemorrhage, FIIa nonbleeding visible vessel, FIIb an adherent clot, FIIc flat pigmented spot, and FIII clean base ulcer [97] [98] [99]. This classification has been used in numerous studies that aimed to identify patients at risk of persistent ulcer bleeding, rebleeding and mortality. Most of these studies have shown that the presence of an ulcer endoscopically classified as FIa or FIb is an independent risk factor for persistent bleeding or rebleeding [100] [101] [102] [103] [104] [105] [106] [107]. A potential limitation of the Forrest classification is that stigmata recognition and identification, as well as interobserver agreement, may be less than optimal, although the data are conflicting [108] [109].

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

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

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

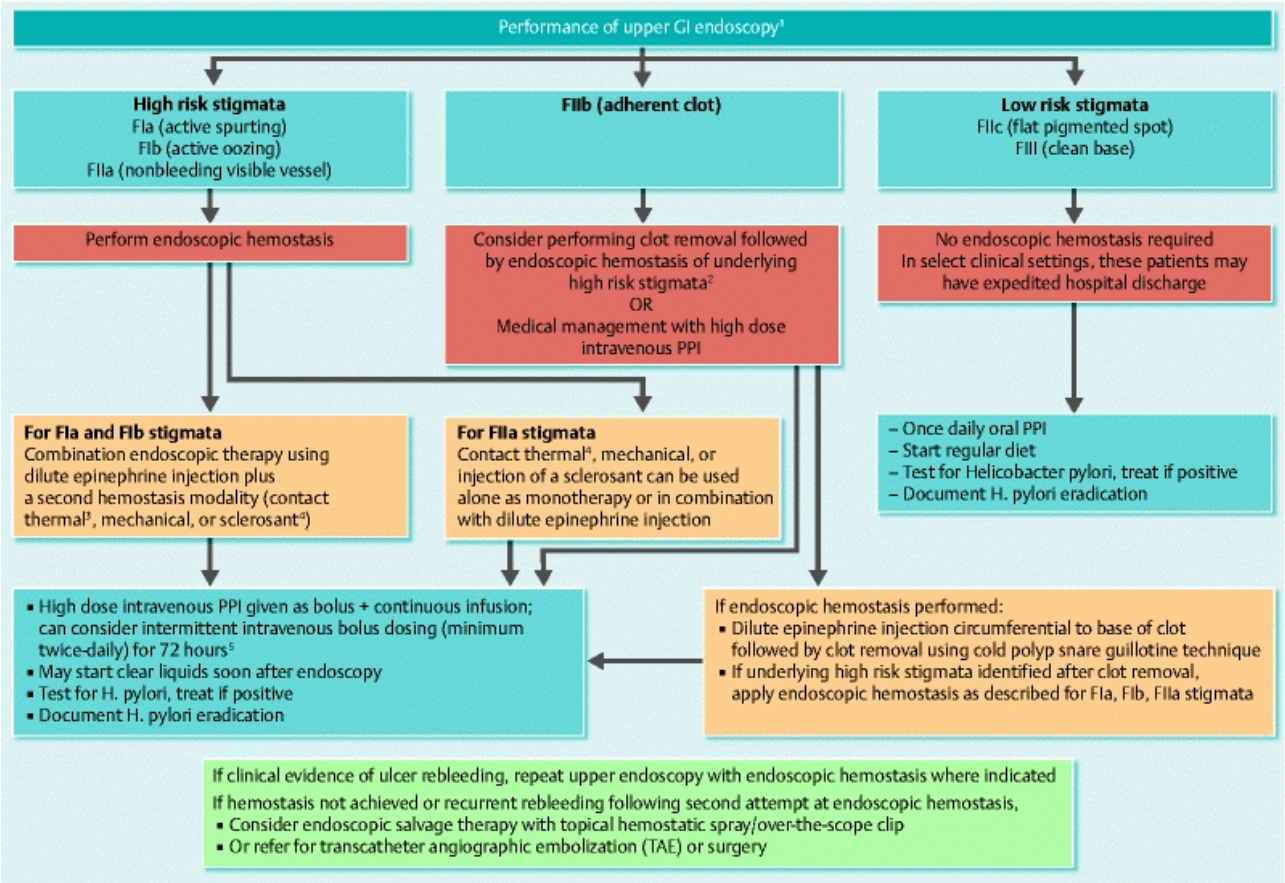

Fig.2Algorithm for the endoscopic management of patients with nonvariceal upper gastrointestinal hemorrhage (NVUGIH) secondary to peptic ulcer, stratified by endoscopic stigmata: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. GI, gastrointestinal; PPI, proton pump inhibitor.

[1] Use of a large single-channel or double-channel therapeutic upper GI endoscope is recommended.

[2] The benefit of endoscopic hemostasis may be greater in patients at higher risk for rebleeding, e.g., older age, co-morbidities, in-hospital UGIH.

[3] Large size 10-Fr probe recommended.

[4] Absolute alcohol, polidocanol, or ethanolamine injected in limited volumes.

[5] High dose oral PPI may be an option in those able to tolerate oral medications.

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

The indication for endoscopic treatment of FIIb ulcers (adherent clot) remains controversial because of conflicting data. In evaluation of the natural history of FIIb ulcers (that did not receive

endoscopic hemostasis), it was found that 25% of patients re-bled within 30 days of follow-up [115]. In patients with FIIb ulcers, RCTs and a meta-analysis comparing medical therapy alone with endoscopic hemostasis demonstrated a significant advantage for endoscopic hemostasis in reducing ulcer rebleeding (8.2% vs. 24.7%, P<0.01, yet there was no difference in need for surgery or mortality [116] [117] [118]. In contrast, in a separate RCT, Sung and colleagues reported no ulcer rebleeding in those patients with adherent clots who received medical therapy alone; however the numbers of such patients in the trial were quite limited (n=24) [113]. Moreover, a meta-analysis restricted only to RCTs showed no benefit for endoscopic hemostasis in patients with an adherent clot (RR 0.31, 95%CI 0.06–1.77) [112].

In patients with peptic ulcers having a flat pigmented spot (FIIc) or clean base (FIII), rebleeding is rare and therefore endoscopic hemostasis does not provide a significant advantage [97] [98] [99].

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

The persistence of a positive Doppler signal following endoscopic hemostasis has been shown to predict recurrent bleeding [119]. The results of available studies have been disparate and limited by their methodology, older endoscopic treatments applied, and small numbers of subjects included; thus there is currently no consensus as to the advantage for the routine use of Doppler ultrasound in patents with NVUGIH [120] [121] [122] [123]. A cost-minimization analysis did however demonstrate per-patient cost savings with use of Doppler ultrasound in patients with peptic ulcer bleeding [124].

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

Endoscopic therapy

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

For patients with nonbleeding visible vessel (FIIa), ESGE recommends mechanical therapy, thermal therapy, or injection of a sclerosing agent as monotherapy or in combination with

epinephrine injection. ESGE recommends that epinephrine injection therapy not be used as endoscopic monotherapy (strong recommendation, high quality evidence).

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

Endoscopic hemostasis can be achieved using injection, thermal, and mechanical modalities (see Box 1), and any endoscopic therapy is superior to pharmacotherapy in patients with FIa, FIb and FIIa ulcers [112] [126]. Meta-analyses show that thermal devices (contact and noncontact), injectable agents other than epinephrine (i.e., sclerosing agents, thrombin/fibrin glue), and clips are all effective methods for achieving hemostasis, with no single modality being superior [112] [126] [137] [138] [139] [140] [141].

Box 1 Endoscopic hemostasis modalities: a primer

Injection therapy

The primary mechanism of action of injection therapy is local tamponade resulting from a volume effect. Diluted epinephrine (1:10 000 or 1:20 000 with normal saline injected in 0.5–2-ml aliquots in and around the ulcer base) may also have a secondary effect that produces local vasoconstriction [126]. Sclerosing agents such as absolute ethanol, ethanolamine, and polidocanol produce hemostasis by causing direct tissue injury and thrombosis. It should be noted that when using a sclerosing agent in nonvariceal upper gastrointestinal hemorrhage (NVUGIH), the volume injected should be limited because of concerns about tissue necrosis, perforation, or pancreatitis. Another class of injectable agents is tissue adhesives including thrombin, fibrin, and cyanoacrylate glues, which are used to create a primary seal at the site of bleeding.

Endoscopic injection is performed using needles which consist of an outer sheath and an inner hollow-core needle (19–25 gauge). The endoscopist or nursing assistant can retract the needle into the sheath for safe passage through the working channel of the endoscope. When the catheter is passed out of the working channel and placed near the site of bleeding, the needle is extended out of the sheath and the solution injected into the submucosa using a syringe attached to the catheter handle [126].

Thermal therapy

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

Contact thermal probes use local tamponade (mechanical pressure of the probe tip directly onto the bleeding site) combined with heat or electrical current to coagulate blood vessels, a process known as “coaptive coagulation.” Heater probes (available in 7-Fr and 10-Fr sizes) consist of a Teflon-coated hollow aluminum cylinder with an inner heating coil combined with a thermocoupling device at the tip of the probe to maintain a constant energy output (measured in joules, commonly 15–30 joules of thermal energy are delivered). An endoscopist-controlled foot pedal activates the heater probe and provides waterjet irrigation. Multipolar/bipolar electrocautery contact probes (7-Fr and 10-Fr sizes) deliver thermal energy by completion of an electrical local circuit (no grounding pad required) between two electrodes on the tip of the probe as current flows through nondesiccated tissue. As the targeted tissue desiccates, there is a decrease in electrical conductivity, limiting the maximum temperature, depth, and area of tissue injury. An endoscopist-controlled foot pedal controls the delivery of the energy [127]. The standard setting for use in achieving hemostasis in peptic ulcer bleeding is 15–20 watts, which is delivered in 8–10-second applications (commonly referred to as tamponade stations) [96].

APC, a noncontact thermal modality, uses high frequency, monopolar alternating current conducted to the target tissue through a stream of ionized gas, without mechanical contact, resulting in coagulation of superficial tissue [128]. As the tissue surface loses its electrical conductivity, the argon plasma stream shifts to adjacent nondesiccated (conductive) tissue, which again limits the depth of tissue injury [126]. If the APC catheter is not near the target tissue, there is no ignition of the gas and depression of the foot pedal results only in flow of inert argon gas (flow rates of 0.5–0.7L/min). Coagulation depth is dependent on the generator power setting, duration of application, and distance from the probe tip to the target tissue (optimal distance, 2–8mm) [129] [130].

Mechanical therapy

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

Clips are available in a variety of jaw lengths and opening widths. The delivery catheter consists of a metal cable within a sheath enclosed within a Teflon catheter. After insertion of the catheter through the working channel of the endoscope, the clip is extended out of the sheath, positioned over the target area and opened with the plunger handle. A rotation mechanism on the handle is available on some commercially available clips and this allows the endoscopist to change the orientation of the clip at the site of bleeding. The jaws of the clip are applied with pressure and closed onto the target tissue by using the device handle. Some clips may be opened, closed, and repositioned, whereas others are permanently deployed and released upon clip closure. Some clips are provided with a reusable delivery sheath, greatly reducing costs. Similarly, some clips are

automatically released on deployment, while others require repositioning of the plunger handle to release the deployed clip from the catheter [131].

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

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

Topical therapy

Topical hemostatic sprays have been used in acute NVUGIH with promising results, but thus far in a limited number of patients and without any comparative data regarding standard endoscopic hemostasis therapies [135] [136]. Advantages of noncontact, spray catheter delivery of hemostatic agents include ease of use, lack of need for precise lesion targeting, access to lesions in difficult locations, and the ability to treat a large surface area.

Topical hemostatic sprays include TC-325, (Hemospray, Cook Medical Inc, Winston-Salem, North Carolina, USA), which is a proprietary, inorganic, absorbent powder that rapidly concentrates clotting factors at the bleeding site, forming a coagulum. Hemospray comes in a hand-held device consisting of a pressurized CO2 canister, a through-the-scope delivery catheter, and a reservoir for the powder cartridge. The powder is delivered via pushbutton in 1–2-second bursts until hemostasis is achieved. The maximum amount of TC-325 that can be safely administered during a single treatment session has not yet been established [135] [136]. The coagulum typically sloughs within 3 days and is naturally eliminated. Hemospray has received regulatory clearance in some countries.

Additional topical hemostatic sprays include EndoClot and the Ankaferd Blood Stopper [135] [136]. EndoClot (EndoClot Plus Inc, Santa Clara, California, USA) is a starch-derived compound that rapidly absorbs water from serum and concentrates platelets, red blood cells, and coagulation proteins at the bleeding site to accelerate the clotting cascade. Hemostatic sprays derived from plant products/extracts have also been evaluated. Clinical experience with these agents for endoscopic hemostasis is currently limited to the off-label use of the Ankaferd Blood Stopper

(Ankaferd Health Products Ltd, Istanbul, Turkey). This topical agent promotes formation of a protein mesh that acts as an anchor for erythrocyte aggregation without significantly altering coagulation factors or platelets and is delivered onto the bleeding site via an endoscopic spray catheter until an adherent coagulum is formed. The particles are subsequently cleared from the bleeding site within hours to days later. The overall efficacy of these topical agents is unknown in brisk arterial bleeding and may be limited because of the rapid “wash-away” effect of the hemostatic agent by ongoing blood flow.

Epinephrine injection therapy is effective at achieving primary hemostasis, but inferior to other endoscopic hemostasis monotherapies or combination therapy in preventing ulcer rebleeding [112] [126] [139]. In the most recently published meta-analysis (19 RCTs, 2033 patients), epinephrine plus any second hemostasis modality significantly reduced rebleeding (OR 0.53, 95%CI 0.35–0.81) and emergency surgery (OR 0.68, 95%CI 0.50–0.93) but not mortality as compared with epinephrine injection monotherapy for high risk peptic ulcers [140]. Therefore, it is recommended that if epinephrine is used to treat peptic ulcer bleeding with high risk stigmata, it should only be used in combination with a second endoscopic hemostasis modality [97] [98] [99] [141].

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

Mechanical therapy using through-the-scope clips was found to be superior to injection monotherapy in four of five meta-analyses [112] [126] [137] [139] [142]. Mechanical therapy significantly reduced the risk of recurrent bleeding by 78% (RR 0.22, 95%CI 0.09–0.55) [112]. Compared with thermal coagulation, mechanical therapy provided no significant improvement in definitive hemostasis (RR 1.00, 95%CI 0.77–1.31) [137]. However, a separate meta-analysis [126] found through-the-scope clips to be significantly more effective than thermal therapy in reducing the risk of recurrent bleeding (OR 0.24, 95%CI 0.06–0.95). Two small studies from Japan compared the efficacy of clips versus hemostatic forceps [143] [144]. The first was an RCT conducted in 96 patients with high risk bleeding gastric ulcers and showed that use of monopolar, soft coagulation hemostatic forceps was as effective as clipping [143]. The second was an observational prospective cohort study on 50 patients in which use of bipolar hemostatic forceps was more effective than endoscopic clipping for both initial hemostasis (100% vs. 78.2%) and preventing recurrent bleeding (3.7% vs. 22.2%) [144]. Unlike thermal therapies and sclerosing agents, mechanical therapy using clips has the theoretical benefit of inducing only limited tissue

injury, and therefore may be preferred in patients on antithrombotic therapy and those patients undergoing repeat endoscopic hemostasis for rebleeding. A multidisciplinary expert panel developed an explicit set of evidence-based quality indicators for NVUGIH [78]. Among them, it was felt that patients with ulcer-related bleeding with high risk stigmata and elevated INR (>1.5–2.0), should receive endoscopic hemostasis using endoscopic clips or a combination of epinephrine injection plus clips.

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

New endoscopic hemostasis modalities (topical hemostatic sprays and over-the-scope clips) are emerging as possible alternative endotherapies for primary hemostasis when bleeding is refractory or not amenable to standard endoscopic hemostasis therapies [136] [146]. Moreover, several small retrospective studies have reported that an over-the-scope clip (OVESCO), may have a role as rescue hemostasis therapy for severe NVUGIH when conventional endoscopic treatment modalities fail [133] [134] [147]. An inert nanopowder (Hemospray) that causes immediate hemostasis when sprayed onto active bleeding [136] [148] has recently been used as a primary hemostasis agent or as a second-line salvage therapy. Several prospective uncontrolled studies, a large European registry [149] [150] [151] [152] [153] [154] and a systematic review of the current limited data suggests that Hemospray is safe and effective and may be best used in high risk cases as a temporizing measure or a bridge toward more definitive treatment [136]. Other topical agents, such as the starch-derived polysaccharide hemostatic system (EndoClot) and the Ankaferd blood stopper are also emerging [136]. However, RCTs directly comparing topical agents with traditional hemostasis methods are required to better define their optimal role and safety in the endoscopic management of NVUGIH.

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

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

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

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

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

Erosive esophagitis, gastritis and duodenitis are common causes of NVUGIH and generally have a benign course and excellent prognosis [2] [64] [155] [156] [157] [158]. Meta-analyses show that acid suppression therapy is effective, with high dose PPI therapy being significantly more effective than H2-receptor antagonists and no observed differences in effectiveness amongst PPIs [159] [160]. Endoscopic hemostasis is usually not required in this patient population and selected patients are candidates for early hospital discharge.

Although spontaneous resolution of bleeding is frequent, observational studies have demonstrated that acute UGIH secondary to Mallory–Weiss syndrome has a mortality similar to that of peptic ulcer bleeding [161] [162]. Risk factors for adverse outcomes include older age, medical co-morbidities, and active bleeding at the time of endoscopy. The latter supports early endoscopy to stratify risk and to perform endoscopic hemostasis if active bleeding is identified [162] [163] [164] [165] [166]. Despite suggestions that mechanical methods (clips and band ligation) are more effective than epinephrine injection, this has not been found in all studies [164] [167] [168]. Mechanical therapy appears to be safe, yet data are insufficient to make a clear recommendation of one hemostasis modality over another [164] [167] [169] [170].

The proximal stomach and duodenum are the most common locations for Dieulafoy lesions [171]. Endoscopic hemostasis is warranted if technically feasible. Observational studies have reported the superiority of combined, thermal and mechanical methods over injection monotherapy, in achieving primary hemostasis, preventing rebleeding, and in reducing the need for rescue therapy, yet with no proven mortality benefit [172] [173] [174] [175] [176] [177] [178] [179] [180]. All

endoscopic hemostasis modalities (e.g., band ligation, through-the-scope clips, over-the-scope clips, contact thermal coagulation, and argon plasma coagulation) appear safe and have similar reported outcomes [171] [172] [173] [174] [175] [176] [177] [178] [179] [180]. Selective TAE has been described as an effective rescue therapy if endoscopic hemostasis fails or in patients who are poor surgical candidates [181] [182]. If both endoscopic and angiographic therapies fail, surgery should be considered.

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

There are limited published data on the role of endoscopic hemostasis in bleeding due to upper GI tract neoplasia and evidence to support a specific modality is scarce [185] [186] [187] [188]. Numerous endoscopic hemostasis modalities (e.g., injection, thermal, mechanical, topical spray/powder) have been reported, generally with limited impact on primary hemostasis, prevention of rebleeding, or mortality. However, endoscopic treatment may avert urgent surgery, reduce transfusion requirements, and may provide a temporary bridge to oncologic therapy and/or selective embolization [185] [186] [187] [188].

Management following endoscopy/endoscopic hemostasis

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

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

Based upon previously published meta-analytic data, evidence-based guidelines on NVUGIH have recommended that PPI therapy be given as an 80mg intravenous bolus followed by 8mg/hour continuous infusion to reduce rebleeding, surgery, and mortality in patients with high risk ulcers

that had undergone successful endoscopic hemostasis [98] [99] [189] [190]. More recently however, a meta-analysis of RCTs of high risk bleeding ulcers treated with endoscopic hemostasis compared intermittent PPI dosing (oral or intravenous) with the currently recommended post hemostasis PPI regimen of 80mg intravenous bolus followed by 8mg/hour continuous infusion [191]. In that meta-analysis, Sachar et al reported that the risk ratio of recurrent ulcer bleeding within 7 days for intermittent infusion of PPI vs. bolus plus continuous infusion of PPI was 0.72 (upper boundary of one-sided 95%CI 0.97), with an absolute risk difference of −2.64%. Risk ratios for other outcomes, including radiologic/surgical intervention and mortality, showed no differences between infusion regimens. These meta-analytic data indicate that intermittent PPI therapy appears comparable to the currently recommended regimen of intravenous bolus plus continuous PPI infusion post endoscopic hemostasis. It should be noted however, that intermittent PPI bolus dosing is associated with a somewhat higher risk of rebleeding that in general can be managed endoscopically. Given the pharmacodynamic profile of PPIs, consideration should be given to use of high dose PPI infusion given at least twice-daily, and using high dose oral PPIs in patients able to tolerate oral medications [191]. The concept of high dose PPI varies between the different studies used in the meta-analysis conducted by Sachar et al. However, it appears that an 80mg oral PPI dose followed by 40–80mg orally every 12 hours for 72 hours yields an intragastric pH similar to that reported with continuous intravenous PPI infusion following successful endoscopic hemostasis of high risk peptic ulcers [192]. This is but one study, and therefore we need more data to confirm these findings before drawing firm practical conclusions for the post-endoscopy management of patients with NVUGIH. These data are in agreement with an RCT that randomized patients to high dose continuous infusion of esomeprazole vs. 40mg of oral esomeprazole twice-daily for 72 hours (118 vs. 126 patients respectively) [193]. Recurrent bleeding at 30 days was reported in 7.7% and 6.4% of patients, respectively (difference −1.3 percentage points, 95%CI −7.7 to 5.1 percentage points). However, this study was conducted in an Asian population (e.g., PPI slow metabolizers) and its findings may not be generalizable to Western NVUGIH populations. Moreover, this study was stopped prematurely since it was not designed as an equivalency trial, and based on the preliminary data, thousands of patients would have been required in order to complete the study. (See Appendix e8, online-only.)

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

An RCT comparing endoscopic therapy with surgery for recurrent peptic ulcer bleeding after successful initial endoscopic control of bleeding showed that 35/48 (73%) of patients randomized to endoscopic re-treatment had long-term control of their peptic ulcer bleeding, avoided surgery, and had a lower rate of adverse events as compared to the surgery-treated patients [194]. The

remaining 13 patients underwent salvage surgery because of failed repeat endoscopic hemostasis (n=11) or perforation due to contact thermal therapy (n=2).

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

(See Appendix e9, online-only.)

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

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

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

Peptic ulcer remains the most frequent cause of acute NVUGIH with H. pylori infection remaining the primary cause of peptic ulcer disease [201] [202]. Indeed, when H. pylori is eradicated, the risk of ulcer rebleeding is reported to be extremely low [203] [204]. However, the false-negative rate of

H. pylori diagnostic testing is higher if the test is performed at the time of the acute bleeding episode as compared to later follow-up [205]. A meta-regression analysis including 8496 bleeding peptic ulcer patients found an H. pylori prevalence of 72%, with the infection rate being significantly higher when diagnostic testing was delayed until at least 4 weeks following the bleeding event (OR 2.08, 95%CI 1.10–3.93; P=0.024) [206]. Therefore, it is advisable to re-test at a later time those patients who had a negative H. pylori test in the acute setting.

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

ESGE recommends restarting anticoagulant therapy following NVUGIH in patients with an indication for long-term anticoagulation. The timing for resumption of anticoagulation should be assessed on a patient by patient basis. Resuming warfarin between 7 and 15 days following the bleeding event appears safe and effective in preventing thromboembolic complications for most patients. Earlier resumption, within the first 7 days, may be indicated for patients at high thrombotic risk (strong recommendation, moderate quality evidence).

Retrospective, observational data have shown that resuming anticoagulation in patients with GI bleeding is associated with a lower risk of thrombosis and death [207] [208] [209]. Restarting warfarin therapy within 7 days of the index bleeding event was associated with an approximately twofold increased risk of rebleeding [207] [209]. Conversely, as compared with resuming warfarin beyond 30 days, resuming warfarin between 7 and 30 days did not increase the risk of rebleeding, but did significantly decrease the risk of thromboembolism and improved survival [209]. These data appear to support that resumption of anticoagulation after 7 days of interruption is safe and effective in preventing thromboembolic complications for most patients. However, in patients at high thrombotic risk (e.g., chronic atrial fibrillation with previous embolic event, $CHADS_2$ score ≥ 3, mechanical prosthetic heart valve, recent [within past 3 months] deep venous thrombosis or pulmonary embolism, and patients with known severe hypercoagulable state), for whom early resumption of anticoagulation within the first week following an acute bleeding event might be appropriate, bridging therapy using unfractionated or low molecular weight heparin may be considered [210]. No data are currently available to guide the management of DOACs following NVUGIH. Yet caution in the early resumption of DOACs is required because of their rapid onset of action and the current lack of reversal agents. (See Appendix 11, online-only.)

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

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

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

Discontinuing low dose aspirin therapy in the setting of secondary cardiovascular prophylaxis significantly increases the risk of an adverse cardiovascular event, usually occurring within the first week of discontinuation [211] [212] [213] [214]. In a retrospective cohort study, patients with cardiovascular disease who discontinued low dose aspirin following peptic ulcer bleeding had an almost twofold increase in risk for death or an acute cardiovascular event in the first 6 months after hospital discharge, as compared with patients who continued aspirin therapy [54]. In an RCT evaluating continuous vs. interrupted aspirin treatment in patients with high risk peptic ulcers and at high cardiovascular risk, those receiving continuous aspirin had a twofold increased risk of early, nonfatal, recurrent bleeding (10.3% vs. 5.4% at 4 weeks; difference 4.9 percentage points, 95%CI −3.6 to 13.4 percentage points; HR 1.9, 95%CI 0.6–6.0), yet a 10-fold reduced risk of all-cause mortality at 8 weeks (1.3% vs. 12.9%; difference 11.6 percentage points, 95%CI 3.7–19.5 percentage points; HR 0.2 95%CI 0.06–0.60) and a lower mortality rate related to cardiovascular, cerebrovascular, or gastrointestinal events (1.3% vs. 10.3%; difference 9 percentage points, 95%CI 1.7–16.3 percentage points; HR 0.2, 95%CI 0.05–0.70), compared with those patients in whom aspirin was withheld [53]. Patients who required DAPT were excluded from this study. The antiplatelet effect of aspirin lasts for approximately 5 days (although new active platelets increase in number each day), and the risk of early recurrent bleeding is high in the first 3 days [53]. Therefore, restarting aspirin on day 3 in patients with high risk endoscopic stigmata is a reasonable trade-off between the risks of rebleeding and thrombosis. In patients with peptic ulcer bleeding with no high risk endoscopic stigmata, aspirin can be resumed immediately as RCTs have shown that neither aspirin nor clopidogrel use impede ulcer healing promoted by PPIs [53] [55] [56]. No high level evidence helps guide the timing for resumption of $P2Y_{12}$ platelet receptor inhibitors (e.g., clopidogrel) following NVUGIH. However, in view of its similar antiplatelet activity, it seems reasonable to apply a similar management strategy. Moreover, there is no evidence in the literature to help guide the management of patients receiving DAPT in the setting of NVUGIH. The overriding principle of balancing bleeding and thrombotic event risks requires close collaboration between the gastroenterology and cardiology teams.

In patients requiring dual antiplatelet therapy (DAPT) and who have had NVUGIH, ESGE recommends the use of a PPI as co-therapy (strong recommendation, moderate quality evidence. Dual antiplatelet therapy, combining low dose aspirin and a $P2Y_{12}$ platelet receptor inhibitor (e.g., clopidogrel), is the cornerstone of management of patients with acute coronary syndromes and following coronary stent placement, but is associated with an increased risk of GI bleeding [215] [216] [217]. Proton pump inhibitors substantially reduce this risk and their use is recommended in patients with a previous GI bleeding event [218] [219] [220]. Pharmacodynamic studies have shown that the co-administration of PPIs with clopidogrel reduces platelet inhibition, but the clinical significance of this interaction has been extensively debated [221] [222] [223] [224] [225]. Previous meta-analyses suggest that concomitant clopidogrel and PPI use may be associated with increased adverse cardiovascular events and myocardial infarction, but no effect on mortality [226] [227]. However, the presence of significant heterogeneity in the included studies indicates that this evidence is at best, inconsistent, and at worst, potentially biased or confounded. A recent meta-analysis included a subanalysis limited to RCTs and propensity-matched studies evaluating the interaction between PPI and clopidogrel; the subanalysis showed no significant differences between patients using clopidogrel alone and patients receiving the combination of clopidogrel and a PPI (n=11 770) for all-cause mortality (OR 0.91, 95%CI 0.58–1.40; P=0.66), acute coronary syndrome (OR 0.96, 95%CI 0.88–1.05; P=0.35), myocardial infarction (OR 1.05, 95%CI 0.86–1.28; P=0.65), and cerebrovascular accident (OR 1.47, 95%CI 0.660–3.25; P=0.34) [228]. The incidence of GI bleeding was significantly decreased in the group of patients who received a PPI (OR 0.24, 95%CI 0.09–0.62; P=0.003). Current evidence does not support a clinically relevant interaction between PPIs and clopidogrel. (See Appendices e12 and e13, online-only.)

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

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

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

GI, gastrointestinal; INR, international normalized ratio; RCT, randomized controlled trial.

[1] Only patients with peptic ulcer

[2] The hospital stay and the costs of care were significantly less for early endoscopy

Appendix e3 Role of proton pump inhibitors (PPIs) prior to upper endoscopy in acute upper gastrointestinal hemorrhage.
ESGE, European Society of Gastrointestinal Endoscopy; H2RA, histamine-2 receptor antagonist; trial; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUB, peptic ulcer bleeding; RCT, randomized controlled trial; UGIB, upper gastrointestinal bleeding.
Appendix e4 Role of tranexamic acid (TXA) in upper gastrointestinal hemorrhage.
CI, confidence interval; NVUGIB, nonvariceal upper gastrointestinal bleeding; RCT, randomized controlled trial; RR, relative risk.
Appendix e5 Role of somatostatin in acute nonvariceal upper gastrointestinal hemorrhage (NVUGIH).
PPI, proton pump inhibitor; PRBC, packed red blood cells; PUB, peptic ulcer bleeding.
Appendix e6 Role of prokinetic agents in acute overt upper gastrointestinal hemorrhage.
CI, confidence interval; EGD, esophagogastroduodenoscopy; PUB, peptic ulcer bleeding; OR, odds ratio; RCT, randomized controlled trial.
Appendix e7 Summary of the evidence regarding impact of early endoscopy ($\leq$24h) on the outcome of patients with nonvariceal upper gastrointestinal hemorrhage (NVUGIH).
CI, confidence interval; OR, odds ratio; RCT, randomized controlled trial.
Appendix e8 Medical management following endoscopic hemostasis
CI, confidence interval; H2RA, histamine-2 receptor antagonist; OR, odds ratio; PPI, proton pump inhibitor; RR, risk ratio.
Appendix e9 Salvage therapy in failed endoscopic hemostasis.
CI, confidence interval; NA, not available; NVUGIB, nonvariceal upper gastrointestinal bleeding; OR, odds ratio; RUT, rapid urease test; UBT, urea breath test.
Appendix e10 Helicobacter pylori and nonvariceal upper gastrointestinal hemorrhage (NVUGIH).
CI, confidence interval; NA, not available; NVUGIB, nonvariceal upper gastrointestinal bleeding; OR, odds ratio; RUT, rapid urease test; UBT, urea breath test.
Appendix e11 Risk of thromboembolism, recurrent gastrointestinal (GI) bleeding and death after warfarin therapy interruption for GI bleeding.
CI, confidence interval; HR, hazard ratio; NVUGIB, nonvariceal upper gastrointestinal bleeding.
Appendix e12 Observational studies assessing the effect of proton pump inhibitors (PPIs) on clinical cardiovascular outcomes in patients prescribed clopidogrel.

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

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

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

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