

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

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

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1526175> since 2015-10-07T09:12:32Z

Published version:

DOI:10.1055/s-0034-1393172

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Questa è la versione dell'autore dell'opera:

Endoscopy, 47(10):1-46, 2015, DOI: 10.1055/s-0034-1393172

The definitive version is available at:

La versione definitiva è disponibile alla URL:

<https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0034-1393172.pdf>

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

Ian M. Gralnek^{1,2}, Jean-Marc Dumonceau³, Ernst J. Kuipers⁴, Angel Lanas⁵, David S. Sanders⁶, Matthew Kurien⁶, Gianluca Rotondano⁷, Tomas Hucl⁸, Mario Dinis-Ribeiro⁹, Riccardo Marmo¹⁰, Istvan Racz¹¹, Alberto Arezzo¹², Ralf-Thorsten Hoffmann¹³, Gilles Lesur¹⁴, Roberto de Franchis¹⁵, Lars Aabakken¹⁶, Andrew Veitch¹⁷, Franco Radaelli¹⁸, Paulo Salgueiro¹⁹, Ricardo Cardoso²⁰, Luís Maia¹⁹, Angelo Zullo²¹, Livio Cipolletta²², Cesare Hassan²³

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

- ²⁰Department of Gastroenterology, Centro Hospitalar e Universitário de Coimbra, Portugal
- ²¹Endoscopy Unit, Nuovo Regina Margherita Hospital, Rome, Italy
- ²²Gastroenterology and Endoscopy Department, Antonio Cardarelli Hospital, Naples, Italy
- ²³Digestive Endoscopy Unit, Catholic University, Rome, Italy

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 (≤ 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

CHADS₂ : congestive heart failure, hypertension, age \geq 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 [Table 1].

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 $50 \times 10^9/L$ has been proposed for most patients, with a target of $10 \times 10^9/L$ 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 | |

Table 2

Glasgow-Blatchford Score (GBS).

| | Points |
|------------------|--------|
| Pulse \geq 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 \geq 110mmHg, pulse $<$ 100 beats/minute, hemoglobin \geq 13.0g/dL for men or \geq 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 2.4 at 6 hours following infusion [38]. No patient in the PCC group had active bleeding at endoscopy compared with 7 in the FFP group (0 vs. 35%, $P<0.01$). The risk of thrombosis following PCC administration approximates 1%, and is similar to that reported with FFP [39] [40].

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

As an alternative to heparin and VKAs, the new non-VKA oral anticoagulants (NOACs; also referred to as direct oral anticoagulants [DOACs]) are being rapidly adopted worldwide, primarily for thromboembolic prevention in patients with nonvalvular atrial fibrillation and for prophylaxis or treatment of venous thromboembolism [41]. These pharmacological agents do however, present a

risk of significant GI bleeding similar to or greater than that reported with warfarin [42] [43]. Moreover, DOACs differ in comparison with heparin and VKA. Specifically, in the absence of renal or hepatic failure, DOAC clearance and the subsequent 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).

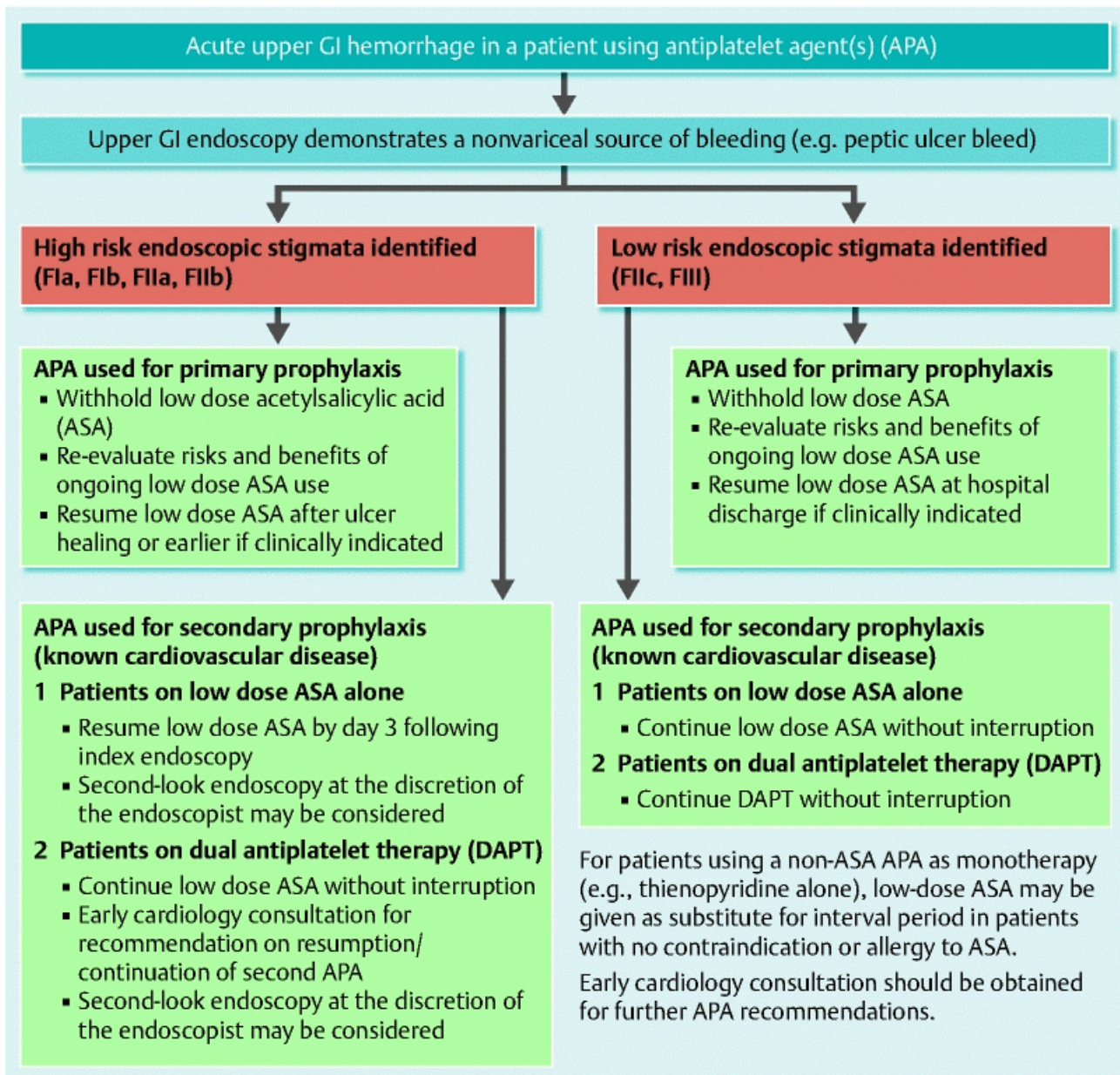


Fig.1 Algorithm for the management of patients with acute upper gastrointestinal hemorrhage who are using antiplatelet agent(s): European Society of Gastrointestinal Endoscopy (ESGE) Guideline.

Antiplatelet agents include low dose aspirin and thienopyridines (e.g., clopidogrel, prasugrel, ticlopidine) that irreversibly inhibit platelet aggregation, ticagrelor a reversible P2Y₁₂ 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 \leq 24 hours, and delayed >24 hours (strong recommendation, moderate quality evidence).

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).

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 \geq 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.

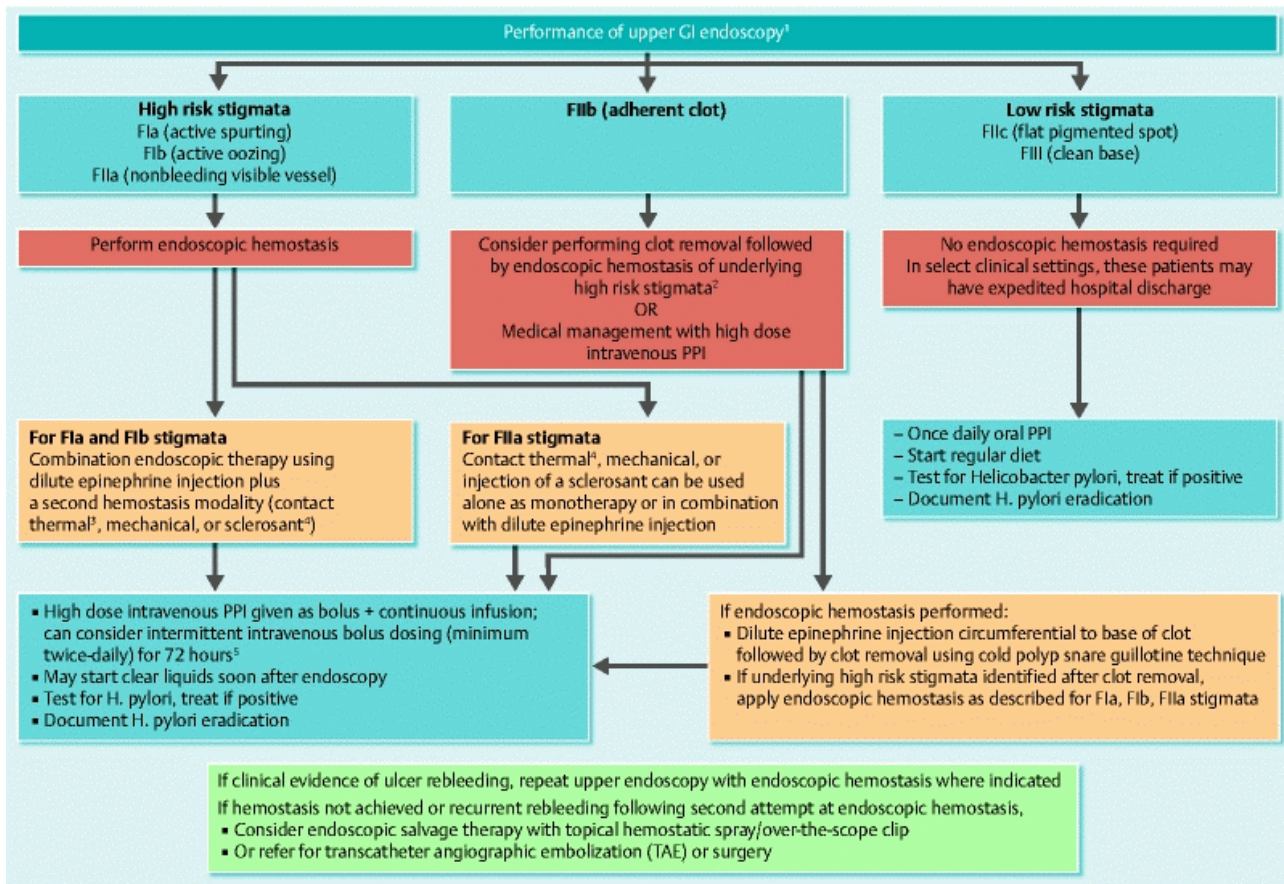


Fig.2 Algorithm for the endoscopic management of patients with nonvariceal upper gastrointestinal hemorrhage (NVUGIH) secondary to peptic ulcer, stratified by endoscopic stigmata: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. GI, gastrointestinal; PPI, proton pump inhibitor.

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

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

³ Large size 10-Fr probe recommended.

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

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

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-bleed 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 patients 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 comorbidities, 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, CHADS₂ 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 P2Y₁₂ 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 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 [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 (≤ 24 h) 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

References

- 1 van Leerdam ME. Epidemiology of acute upper gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol* 2008; 22: 209-224
- 2 Hearnshaw SA, Logan RF, Lowe D et al. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. *Gut* 2011; 60: 1327-1335
- 3 Guyatt GH, Oxman AD, Vist GE et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924-926
- 4 Dumonceau JM, Hassan C, Riphaut A et al. European Society of Gastrointestinal Endoscopy (ESGE) guideline development policy. *Endoscopy* 2012; 44: 626-629
- 5 Baradarian R, Ramdhaney S, Chapalamadugu R et al. Early intensive resuscitation of patients with upper gastrointestinal bleeding decreases mortality. *Am J Gastroenterol* 2004; 99: 619-622
- 6 Kwan I, Bunn F, Chinnock P et al. Timing and volume of fluid administration for patients with bleeding. *Cochrane Database Syst Rev* 2014; 3: CD002245
- 7 Spahn DR, Bouillon B, Cerny V et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit Care* 2013; 17: R76
- 8 Roberts I, Alderson P, Bunn F et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev* 2004; 4: CD000567
- 9 Myburgh JA, Finfer S, Bellomo R et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901-1911
- 10 Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med* 2008; 36: 2667-2674
- 11 Restellini S, Kherad O, Jairath V et al. Red blood cell transfusion is associated with increased rebleeding in patients with nonvariceal upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2013; 37: 316-322
- 12 Villanueva C, Colomo A, Bosch A et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013; 368: 11-21

- **13** Jairath V, Kahan BC, Stanworth SJ et al. Prevalence, management, and outcomes of patients with coagulopathy after acute nonvariceal upper gastrointestinal bleeding in the United Kingdom. *Transfusion* 2013; 53: 1069-1076
- **14** Shingina A, Barkun AN, Razzaghi A et al. Systematic review: the presenting international normalized ratio (INR) as a predictor of outcome in patients with upper nonvariceal gastrointestinal bleeding. *Aliment Pharmacol Ther* 2011; 33: 1010-1018
- **15** Karam O, Tucci M, Combescure C et al. Plasma transfusion strategies for critically ill patients. *Cochrane Database Syst Rev* 2013; 12: CD010654
- **16** Razzaghi A, Barkun AN. Platelet transfusion threshold in patients with upper gastrointestinal bleeding: a systematic review. *J Clin Gastroenterol* 2012; 46: 482-486
- **17** Rockall TA, Logan RF, Devlin HB et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut* 1996; 38: 316-321
- **18** Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. *Lancet* 2000; 356: 1318-1321
- **19** de Groot NL, Bosman JH, Siersema PD et al. Prediction scores in gastrointestinal bleeding: a systematic review and quantitative appraisal. *Endoscopy* 2012; 44: 731-739
- **20** Lee JG, Turnipseed S, Romano PS et al. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 1999; 50: 755-761
- **21** Cipolletta L, Bianco MA, Rotondano G et al. Outpatient management for low-risk nonvariceal upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 2002; 55: 1-5
- **22** Brullet E, Campo R, Calvet X et al. A randomized study of the safety of outpatient care for patients with bleeding peptic ulcer treated by endoscopic injection. *Gastrointest Endosc* 2004; 60: 15-21
- **23** Longstreth GF, Feitelberg SP. Outpatient care of selected patients with acute non-variceal upper gastrointestinal haemorrhage. *Lancet* 1995; 345: 108-111
- **24** Longstreth GF, Feitelberg SP. Successful outpatient management of acute upper gastrointestinal hemorrhage: use of practice guidelines in a large patient series. *Gastrointest Endosc* 1998; 47: 219-222
- **25** Rockall TA, Logan RF, Devlin HB et al. Selection of patients for early discharge or outpatient care after acute upper gastrointestinal haemorrhage. national audit of acute upper gastrointestinal haemorrhage. *Lancet* 1996; 347: 1138-1140
- **26** Lai KC, Hui WM, Wong BC et al. A retrospective and prospective study on the safety of discharging selected patients with duodenal ulcer bleeding on the same day as endoscopy. *Gastrointest Endosc* 1997; 45: 26-30

- **27** Cebollero-Santamaria F, Smith J, Gioe S et al. Selective outpatient management of upper gastrointestinal bleeding in the elderly. *Am J Gastroenterol* 1999; 94: 1242-1247
- **28** Gralnek IM, Dulai GS. Incremental value of upper endoscopy for triage of patients with acute non-variceal upper GI hemorrhage. *Gastrointest Endosc* 2004; 60: 9-14
- **29** Guerrouij M, Uppal CS, Alklabi A et al. The clinical impact of bleeding during oral anticoagulant therapy: assessment of morbidity, mortality and post-bleed anticoagulant management. *J Thromb Thrombolysis* 2011; 31: 419-423
- **30** Holbrook A, Schulman S, Witt DM et al. Evidence-based management of anticoagulant therapy: Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e152S-184S DOI: 10.1378/chest.11-2295
- **31** Irwin ST, Ferguson R, Weilert F et al. Supratherapeutic anticoagulation at presentation is associated with reduced mortality in nonvariceal upper gastrointestinal hemorrhage. *Endosc Int Open* 2014; 2: E148-E152 DOI: 10.1055/s-0034-1377287 [Epub 2014 Jul 10]
- **32** Tran HA, Chunilal SD, Harper PL et al. An update of consensus guidelines for warfarin reversal. *Med J Aust* 2013; 198: 198-199
- **33** Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal hemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. *Gut* 1994; 35: 464-466
- **34** Radaelli F, Paggi S, Terruzzi V et al. Management of warfarin-associated coagulopathy in patients with acute gastrointestinal bleeding: a cross-sectional physician survey of current practice. *Dig Liver Dis* 2011; 43: 444-447
- **35** Patriquin C, Crowther M. Treatment of warfarin-associated coagulopathy with vitamin K. *Expert Rev Hematol* 2011; 4: 657-665
- **36** Baron TH, Kamath PS, McBane RD. New anticoagulant and antiplatelet agents: a primer for the gastroenterologist. *Clin Gastroenterol Hepatol* 2014; 12: 187-195
- **37** Leissinger CA, Blatt PM, Hoots WK et al. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. *Am J Hematol* 2008; 83: 137-143
- **38** Karaca MA, Erbil B, Ozmen MM. Use and effectiveness of prothrombin complex concentrates vs. fresh frozen plasma in gastrointestinal hemorrhage due to warfarin usage in the ED. *Am J Emerg Med* 2014; 32: 660-664
- **39** Dentali F, Marchesi C, Pierfranceschi MG et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost* 2011; 106: 429-438

- **40** Hickey M, Gatién M, Taljaard M et al. Outcomes of urgent warfarin reversal with frozen plasma versus prothrombin complex concentrate in the emergency department. *Circulation* 2013; 128: 360-364
- **41** Chai-Adisaksopha C, Crowther M, Isayama T et al. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. *Blood* 2014; 124: 2450-2458
- **42** Holster IL, Valkhoff VE, Kuipers EJ et al. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013; 145: 105-112
- **43** Ruff CT, Guigliano RP, Braunwald E et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomized trials. *Lancet* 2014; 383: 955-962
- **44** Lu G, DeGuzman FR, Hollenbach SJ et al. A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa. *Nat Med* 2013; 19: 446-451
- **45** Ansell JE, Bakhrú SH, Laulicht BE et al. Use of PER977 to reverse the anticoagulant effect of edoxaban. *N Engl J Med* 2014; 371: 2141-2142
- **46** Pollack Jr CV, Reilly PA, Eikelboob J et al. Idarucizumab for dabigatran reversal. *N Engl J Med* 2015; 373: 511-520
- **47** Abraham NS, Castillo DL. Novel anticoagulants: bleeding risk and management strategies. *Curr Opin Gastroenterol* 2013; 29: 676-683
- **48** Desai J, Kolb JM, Weitz JI et al. Gastrointestinal bleeding with the new oral anticoagulants – defining the issues and the management strategies. *Thromb Haemost* 2013; 110: 205-212
- **49** Makris M, Van Veen JJ, Tait CR et al. British Committee for Standards in Haematology. Guideline on the management of bleeding in patients on antithrombotic agents. *Br J Haematol* 2013; 160: 35-46
- **50** Siegal DM, Cuker A. Reversal of novel oral anticoagulants in patients with major bleeding. *J Thromb Thrombolysis* 2013; 35: 391-398
- **51** Fawole A, Daw HA, Crowther MA. Practical management of bleeding due to the anticoagulants dabigatran, rivaroxaban, and apixaban. *Clev Clin J Med* 2013; 80: 443-451
- **52** Boustiere C, Veitch A, Vanbiervliet G et al. Endoscopy and antiplatelet agents. European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2011; 43: 445-461
- **53** Sung JJY, Lau JYW, Ching JYL et al. Continuation of low dose aspirin therapy in peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2010; 152: 1-9

- **54** Derogar M, Sandblom G, Lundell L et al. Discontinuation of low dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events. *Clin Gastroenterol Hepatol* 2013; 11: 38-42
- **55** Liu C-P, Chen W-C, Lai K-H et al. Esomeprazole alone compared with esomeprazole plus aspirin for the treatment of aspirin-related peptic ulcers. *Am J Gastroenterol* 2012; 107: 1022-1029
- **56** Ng FH, Wong BCY, Wong SY et al. Clopidogrel plus omeprazole compared with aspirin plus omeprazole for aspirin-induced symptomatic peptic ulcers/erosions with low to moderate bleeding/re-bleeding risk – a single-blind, randomized controlled study. *Aliment Pharmacol Ther* 2004; 19: 359-365
- **57** Sreedharan A, Martin J, Leontiadis GI et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010; 7: CD005415
- **58** Sabah AIS, Barkun AN, Herba K et al. Cost-effectiveness of proton-pump inhibition before endoscopy in upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2008; 6: 418-425
- **59** Tsoi KKF, Lau JYW, Sung JJY. Cost-effectiveness analysis of high-dose omeprazole infusion before endoscopy for patients with upper-GI bleeding. *Gastrointest Endosc* 2008; 67: 1056-1063
- **60** Shakur H, Roberts I. CRASH-2 trial collaborators et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. *Lancet* 2010; 376: 23-32
- **61** Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2012; 1: CD006640
- **62** Raptis S, Dollinger HC, von Berger L et al. Effects of somatostatin on gastric secretion and gastrin release in man. *Digestion* 1975; 13: 15-26
- **63** Hearnshaw SA, Logan RF, Lowe D et al. Use of endoscopy for management of acute upper gastrointestinal bleeding in the UK: results of a nationwide audit. *Gut* 2010; 59: 1022-1029
- **64** Enestvedt BK, Gralnek IM, Mattek N et al. An evaluation of endoscopic indications and findings related to non-variceal upper-GI hemorrhage in a large multicenter consortium. *Gastrointest Endosc* 2008; 67: 422-429
- **65** Barkun AN, Bardou M, Martel M et al. Prokinetics in acute upper GI bleeding: a meta-analysis. *Gastrointest Endosc* 2010; 72: 1138-1145
- **66** Szary NM, Gupta R, Choudhary A et al. Erythromycin prior to endoscopy in acute upper gastrointestinal bleeding: a meta-analysis. *Scand J Gastroenterol* 2011; 46: 920-924

- **67** Bai Y, Guo JF, Li ZS. Meta-analysis: erythromycin before endoscopy for acute upper gastrointestinal bleeding. *Aliment Pharmacol Ther* 2011; 34: 166-171
- **68** Theivanayagam S, Lim RG, Cobell WJ et al. Administration of erythromycin before endoscopy in upper gastrointestinal bleeding: a meta-analysis of randomized controlled trials. *Saudi J Gastroenterol* 2013; 19: 205-210
- **69** Winstead NS, Wilcox CM. Erythromycin prior to endoscopy for acute upper gastrointestinal haemorrhage: a cost-effectiveness analysis. *Aliment Pharmacol Ther* 2007; 26: 1371-1377
- **70** Srygley FD, Gerardo CJ, Tran T et al. Does this patient have a severe upper gastrointestinal bleed?. *JAMA* 2012; 307: 1072-1079
- **71** Aljebreen AM, Fallone CA, Barkun AN. Nasogastric aspirate predicts high-risk endoscopic lesions in patients with acute upper GI bleeding. *Gastrointest Endosc* 2004; 59: 172-178
- **72** Pateron D, Vicaut E, Debuc E et al. Erythromycin infusion or gastric lavage for upper gastrointestinal bleeding: a multicenter randomized controlled trial. *Ann Emerg Med* 2011; 57: 582-589
- **73** Huang ES, Karsan S, Kanwal F et al. Impact of nasogastric lavage on outcomes in acute GI bleeding. *Gastrointest Endosc* 2011; 74: 971-980
- **74** Singer AJ, Richman PB, Kowalska A et al. Comparison of patient and practitioner assessments of pain from commonly performed emergency department procedures. *Ann Emerg Med* 1999; 33: 652-658
- **75** Koch DG, Arguedas MR, Fallon MB. Risk of aspiration pneumonia in suspected variceal hemorrhage: the value of prophylactic endotracheal intubation prior to endoscopy. *Dig Dis Sci* 2007; 52: 2225-2228
- **76** Rehman A, Iscimen R, Yilmaz M et al. Prophylactic endotracheal intubation in critically ill patients undergoing endoscopy for upper GI hemorrhage. *Gastrointest Endosc* 2009; 69: 55-59
- **77** Rudolph SJ, Landsverk BK, Freeman ML. Endotracheal intubation for airway protection during endoscopy for severe upper GI hemorrhage. *Gastrointest Endosc* 2003; 57: 58-61
- **78** Kanwal F, Barkun A, Gralnek IM et al. Measuring quality of care in patients with nonvariceal upper gastrointestinal hemorrhage: development of an explicit quality indicator set. *Am J Gastroenterol* 2010; 105: 1710-1718
- **79** Lanas A, Aabakken L, Fonseca J et al. Variability in the management of nonvariceal upper gastrointestinal bleeding in Europe: an observational study. *Adv Ther* 2012; 29: 1026-1036

- **80** Spiegel BM, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: is sooner better? A systematic review. *Arch Intern Med* 2001; 161: 1393-1404
- **81** Tsoi KKF, Ma TKW, Sung JJY. Endoscopy for upper gastrointestinal bleeding: how urgent is it?. *Nat Rev Gastroenterol Hepatol* 2009; 6: 463-469
- **82** Wysocki JD, Srivastav S, Winstead NS. A nationwide analysis of risk factors for mortality and time to endoscopy in upper gastrointestinal haemorrhage. *Aliment Pharmacol Ther* 2012; 36: 30-36
- **83** Lin HJ, Wang K, Perng CL et al. Early or delayed endoscopy for patients with peptic ulcer bleeding. A prospective randomized study. *J Clin Gastroenterol* 1996; 22: 267-271
- **84** Lim L, Ho K, Chan Y et al. Urgent endoscopy is associated with lower mortality in high-risk but not low-risk nonvariceal upper gastrointestinal bleeding. *Endoscopy* 2011; 43: 300-306
- **85** Bjorkman DJ, Zaman A, Fennerty MB et al. Urgent vs. elective endoscopy for acute non-variceal upper-GI bleeding: an effectiveness study. *Gastrointest Endosc* 2004; 60: 1-8
- **86** Stanley AJ, Ashley D, Dalton HR et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. *Lancet* 2009; 373: 42-47
- **87** McLaughlin C, Vine L, Chapman L et al. The management of low-risk primary upper gastrointestinal haemorrhage in the community. *Eur J Gastroenterol Hepatol* 2012; 24: 288-293
- **88** Girardin M, Bertolini D, Ditisheim S et al. Use of Glasgow-Blatchford bleeding score reduces hospital stay duration and costs for patients with low-risk upper GI bleeding. *Endosc Int Open* 2014; 2: E74-E79 DOI: 10.1055/s-0034-1365542 Epub 2014 May 7
- **89** Laursen SB, Dalton HR, Murray IA et al. Performance of new thresholds of the Glasgow Blatchford score in managing patients with upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2015; 13: 115-121
- **90** Rubin M, Hussain SA, Shalomov A et al. Live view video capsule endoscopy enables risk stratification of patients with acute upper GI bleeding in the emergency room: a pilot study. *Dig Dis Sci* 2011; 56: 786-791
- **91** Chandran S, Testro A, Urquhart P et al. Risk stratification of upper GI bleeding with an esophageal capsule. *Gastrointest Endosc* 2013; 77: 891-898
- **92** Gralnek IM, Ching JYL, Maza I et al. Capsule endoscopy in acute upper gastrointestinal hemorrhage: a prospective cohort study. *Endoscopy* 2013; 45: 12-19
- **93** Meltzer AC, Ali MA, Kresiberg RB et al. Video capsule endoscopy in the emergency department: a prospective study of acute upper gastrointestinal hemorrhage. *Ann Emerg Med* 2013; 61: 438-443

- **94** Meltzer AC, Pinchbeck C, Burnett S et al. Emergency physicians accurately interpret video capsule endoscopy findings in suspected upper gastrointestinal hemorrhage: a video survey. *Acad Emerg Med* 2013; 20: 711-715
- **95** Meltzer AC, Ward MJ, Gralnek IM et al. The cost-effectiveness analysis of video capsule endoscopy compared to other strategies to manage acute upper gastrointestinal hemorrhage in the ED. *Am J Emerg Med* 2014; 32: 823-832
- **96** Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. *Lancet* 1974; 2: 394-397
- **97** Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med* 2008; 359: 928-937
- **98** Barkun AN, Bardou M, Kuipers EJ et al. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med* 2010; 152: 101-113
- **99** Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol* 2012; 107: 345-360
- **100** Chung IK, Kim EJ, Lee MS et al. Endoscopic factors predisposing to rebleeding following endoscopic hemostasis in bleeding peptic ulcers. *Endoscopy* 2001; 33: 969-975
- **101** Guglielmi A, Ruzzenente A, Sandri M et al. Risk assessment and prediction of rebleeding in bleeding gastroduodenal ulcer. *Endoscopy* 2002; 34: 778-786
- **102** Zaragoza AM, Tenías JM, Llorente MJ et al. Prognostic factors in gastrointestinal bleeding due to peptic ulcer: construction of a predictive model. *J Clin Gastroenterol* 2008; 42: 786-790
- **103** Elmunzer BJ, Young SD, Inadomi JM et al. Systematic review of the predictors of recurrent hemorrhage after endoscopic hemostatic therapy for bleeding peptic ulcers. *Am J Gastroenterol* 2008; 103: 2625-2632
- **104** Marmo R, Del Piano M, Rotondano G et al. Mortality from nonulcer bleeding is similar to that of ulcer bleeding in high-risk patients with nonvariceal hemorrhage: a prospective database study in Italy. *Gastrointest Endosc* 2012; 75: 263-272
- **105** Bratanic A, Puljiz Z, Ljubicic N et al. Predictive factors of rebleeding and mortality following endoscopic hemostasis in bleeding peptic ulcers. *Hepatogastroenterology* 2013; 60: 112-117
- **106** Sung JJ, Barkun A, Kuipers EJ et al. Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding: a randomized trial. *Ann Intern Med* 2009; 50: 455-464
- **107** de Groot NL, van Oijen MG, Kessels K et al. Reassessment of the predictive value of the Forrest classification for peptic ulcer rebleeding and mortality: can classification be simplified?. *Endoscopy* 2014; 46: 46-52

- **108** Lau JY, Sung JJ, Chan AC et al. Stigmata of hemorrhage in bleeding peptic ulcers: an interobserver agreement study among international experts. *Gastrointest Endosc* 1997; 46: 33-36
- **109** Mondardini A, Barletti C, Rocca G et al. Non-variceal upper gastrointestinal bleeding and Forrest's classification: diagnostic agreement between endoscopists from the same area. *Endoscopy* 1998; 30: 508-512
- **110** Lin HJ, Perng CL, Lee FY et al. Clinical courses and predictors for rebleeding in patients with peptic ulcers and non-bleeding visible vessels: a prospective study. *Gut* 1994; 35: 1389-1393
- **111** Cheng CL, Lin CH, Kuo CJ et al. Predictors of rebleeding and mortality in patients with high-risk bleeding peptic ulcers. *Dig Dis Sci* 2010; 55: 2577-2583
- **112** Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. *Clin Gastroenterol Hepatol* 2009; 7: 33-47
- **113** Sung J, Chan F, Lau J et al. The effect of endoscopic therapy in patients receiving omeprazole for bleeding ulcers with nonbleeding visible vessels or adherent clots: a randomized comparison. *Ann Intern Med* 2003; 139: 237-243
- **114** Andriulli A, Annese V, Caruso N et al. Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: a series of meta-analyses. *Am J Gastroenterol* 2005; 100: 207-219
- **115** Lin JH, Wang K, Perng CL et al. Natural history of bleeding peptic ulcers with a tightly adherent blood clot: a prospective observation. *Gastrointest Endosc* 1996; 43: 470-473
- **116** Jensen DM, Kovacs TO, Jutabha R et al. Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. *Gastroenterology* 2002; 123: 407-413
- **117** Bleau BL, Gostout CJ, Sherman KE et al. Recurrent bleeding from peptic ulcer associated with adherent clot: a randomized study comparing endoscopic treatment with medical therapy. *Gastrointest Endosc* 2002; 56: 1-6
- **118** Kahi CJ, Jensen DM, Sung JJY et al. Endoscopic therapy versus medical therapy for bleeding peptic ulcer with adherent clot: a meta-analysis. *Gastroenterology* 2005; 129: 855-862
- **119** Wong RC, Chak A, Kobayashi K et al. Role of Doppler US in acute peptic ulcer hemorrhage: can it predict failure of endoscopic therapy?. *Gastrointest Endosc* 2000; 52: 315-321
- **120** Kohler B, Maier M, Benz C et al. Acute ulcer bleeding. A prospective randomized trial to compare Doppler and Forrest classifications in endoscopic diagnosis and therapy. *Dig Dis Sci* 1997; 42: 1370-1374

- **121** Fullarton GM, Murray WR. Prediction of rebleeding in peptic ulcers by visual stigmata and endoscopic Doppler ultrasound criteria. *Endoscopy* 1990; 22: 68-71
- **122** Kohler B, Riemann JF. Endoscopic injection therapy of Forrest II and III gastroduodenal ulcers guided by endoscopic Doppler ultrasound. *Endoscopy* 1993; 25: 219-223
- **123** van Leerdam ME, Rauws EA, Geraedts AA et al. The role of endoscopic Doppler US in patients with peptic ulcer bleeding. *Gastrointest Endosc* 2003; 58: 677-684
- **124** Chen VK, Wong RC. Endoscopic doppler ultrasound versus endoscopic stigmata-directed management of acute peptic ulcer hemorrhage: a multimodel cost analysis. *Dig Dis Sci* 2007; 52: 149-160
- **125** Cipolletta L, Bianco MA, Salerno R et al. Improved characterization of visible vessels in bleeding ulcers by using magnification endoscopy: results of a pilot study. *Gastrointest Endosc* 2010; 72: 413-418
- **126** Barkun AN, Martel M, Toubouti Y et al. Endoscopic hemostasis in peptic ulcer bleeding for patients with high-risk lesions: a series of meta-analyses. *Gastrointest Endosc* 2009; 69: 786-799
- **127** ASGE Technology Committee. Conway JD, Adler DG et al. Endoscopic hemostatic devices. *Gastrointest Endosc* 2009; 69: 987-996
- **128** Laine L. Therapeutic endoscopy and bleeding ulcers. Bipolar/multipolar electrocoagulation. *Gastrointest Endosc* 1990; 36: S38-S41
- **129** Ginsberg GG, Barkun AN, Bosco JJ et al. The argon plasma coagulator. *Gastrointest Endosc* 2002; 55: 807-810
- **130** Watson JP, Bennett MK, Griffin SM et al. The tissue effect of argon plasma coagulation on esophageal and gastric mucosa. *Gastrointest Endosc* 2000; 52: 342-345
- **131** Raju GS, Gajula L. Endoclips for GI endoscopy. *Gastrointest Endosc* 2004; 59: 267-279
- **132** Chuttani R, Barkun A, Carpenter S et al. Endoscopic clip application devices. *Gastrointest Endosc* 2006; 63: 746-750
- **133** Kirschniak A, Kratt T, Stüker D et al. A new endoscopic over-the-scope clip system for treatment of lesions and bleeding in the GI tract: first clinical experiences. *Gastrointest Endosc* 2007; 66: 162-167
- **134** Kirschniak A, Subotova N, Zieker D et al. The over-the-scope clip (OTSC) for the treatment of gastrointestinal bleeding, perforations, and fistulas. *Surg Endosc* 2011; 25: 2901-2905
- **135** Gottlieb KT, Banerjee S, Barth BA. ASGE Technology Committee et al. Endoscopic closure devices. *Gastrointest Endosc* 2012; 76: 244-251

- **136** Barkun AN, Moosavi S, Martel M. Topical hemostatic agents: a systematic review with particular emphasis on endoscopic application in GI bleeding. *Gastrointest Endosc* 2013; 77: 692-700
- **137** Sung JJ, Tsoi KK, Lai LH et al. Endoscopic clipping versus injection and thermo-coagulation in the treatment of non-variceal upper gastrointestinal bleeding: a meta-analysis. *Gut* 2007; 56: 1364-1373
- **138** Calvet X, Vergara M, Brullet E et al. Addition of a second endoscopic treatment following epinephrine injection improves outcome in high-risk bleeding ulcers. *Gastroenterology* 2004; 126: 441-450
- **139** Marmo R, Rotondano G, Piscopo R et al. Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials. *Am J Gastroenterol* 2007; 102: 279-289
- **140** Vergara M, Bennett C, Calvet X et al. Epinephrine injection versus epinephrine injection and a second endoscopic method in high risk bleeding ulcers. *Cochrane Database Syst Rev* 2014; 10: CD005584
- **141** Hwang JH, Fisher DA, Ben-Menachem T et al. Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy. The role of endoscopy in the management of acute non-variceal upper GI bleeding. *Gastrointest Endosc* 2012; 75: 1132-1138
- **142** Yuan Y, Wang C, Hunt RH. Endoscopic clipping for acute nonvariceal upper-GI bleeding: a meta-analysis and critical appraisal of randomized controlled trials. *Gastrointest Endosc* 2008; 68: 339-351
- **143** Arima S, Sakata Y, Ogata S et al. Evaluation of hemostasis with soft coagulation using endoscopic hemostatic forceps in comparison with metallic hemoclips for bleeding gastric ulcers: a prospective, randomized trial. *J Gastroenterol* 2010; 45: 501-505
- **144** Kataoka M, Kawai T, Hayama Y et al. Comparison of hemostasis using bipolar hemostatic forceps with hemostasis by endoscopic hemoclippping for nonvariceal upper gastrointestinal bleeding in a prospective non-randomized trial. *Surg Endosc* 2013; 27: 3035-3038
- **145** Sung JJ, Chan FK, Chen M et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. *Gut* 2011; 60: 1170-1177
- **146** Wong Kee Song LM, Banerjee S, Barth BA et al. Emerging technologies for endoscopic hemostasis. *Gastrointest Endosc* 2012; 75: 933-937
- **147** Manta R, Galloro G, Mangiavillano B et al. Over-the-scope clip (OTSC) represents an effective endoscopic treatment for acute GI bleeding after failure of conventional techniques. *Surg Endosc* 2013; 27: 3162-3164

- **148** Giday SA, Kim Y, Krishnamurty DM et al. Long-term randomized controlled trial of a novel nanopowder hemostatic agent (TC-325) for control of severe arterial upper gastrointestinal bleeding in a porcine model. *Endoscopy* 2011; 43: 296-269
- **149** Chen YI, Barkun AN, Soulellis C et al. Use of the endoscopically applied hemostatic powder TC-325 in cancer-related upper GI hemorrhage: preliminary experience. *Gastrointest Endosc* 2012; 75: 1278-1281
- **150** Leblanc S, Vienne A, Dhooge M et al. Early experience with a novel hemostatic powder used to treat upper GI bleeding related to malignancies or after therapeutic interventions. *Gastrointest Endosc* 2013; 78: 169-175
- **151** Holster IL, Kuipers EJ, Tjwa ET. Hemospray in the treatment of upper gastrointestinal hemorrhage in patients on antithrombotic therapy. *Endoscopy* 2013; 45: 63-66
- **152** Yau AH, Ou G, Galorport C et al. Safety and efficacy of Hemospray in upper gastrointestinal bleeding. *Can J Gastroenterol Hepatol* 2014; 28: 72-76
- **153** Sung JJ, Luo D, Wu JC et al. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. *Endoscopy* 2011; 43: 291-295
- **154** Smith LA, Stanley AJ, Bergman JJ et al. Hemospray application in nonvariceal upper gastrointestinal bleeding: results of the survey to evaluate the application of hemospray in the luminal tract. *J Clin Gastroenterol* 2014; 48: 89-92
- **155** Barkun A, Sabbah S, Enns R et al. The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. *Am J Gastroenterol* 2004; 99: 1238-1246
- **156** Nahon S, Nouel O, Hagège H et al. Favorable prognosis of upper-gastrointestinal bleeding in 1041 older patients: results of a prospective multicenter study. *Clin Gastroenterol Hepatol* 2008; 6: 886-892
- **157** Loperfido S, Baldo V, Piovesana E et al. Changing trends in acute upper-GI bleeding: a population-based study. *Gastrointest Endosc* 2009; 70: 212-224
- **158** Guntipalli P, Chason R, Elliott A et al. Upper gastrointestinal bleeding caused by severe esophagitis: a unique clinical syndrome. *Dig Dis Sci* 2014; 59: 2997-3003
- **159** Wang WH, Huang JQ, Zheng GF et al. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: A meta-analysis. *World J Gastroenterol* 2005; 11: 4067-4077
- **160** Gralnek IM, Dulai GS, Fennerty MB et al. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: a meta-analysis of randomized clinical trials. *Clin Gastroenterol Hepatol* 2006; 4: 1452-1458

- **161** Ljubičić N, Budimir I, Pavić T et al. Mortality in high-risk patients with bleeding Mallory–Weiss syndrome is similar to that of peptic ulcer bleeding. Results of a prospective database study. *Scand J Gastroenterol* 2014; 49: 458-464
- **162** Bharucha AE, Gostout CJ, Balm RK. Clinical and endoscopic risk factors in the Mallory-Weiss syndrome. *Am J Gastroenterol* 1997; 92: 805-808
- **163** Kortas DY, Haas LS, Simpson WG et al. Mallory–Weiss tear: predisposing factors and predictors of a complicated course. *Am J Gastroenterol* 2001; 96: 2863-2865
- **164** Chung IK, Kim EJ, Hwang KY et al. Evaluation of endoscopic hemostasis in upper gastrointestinal bleeding related to Mallory–Weiss syndrome. *Endoscopy* 2002; 34: 474-479
- **165** Kim JW, Kim HS, Byun JW et al. Predictive factors of recurrent bleeding in Mallory–Weiss syndrome. *Korean J Gastroenterol* 2005; 46: 447-454
- **166** Fujisawa N, Inamori M, Sekino Y et al. Risk factors for mortality in patients with Mallory–Weiss syndrome. *Hepatogastroenterology* 2011; 58: 417-420
- **167** Huang SP, Wang HP, Lee YC et al. Endoscopic hemoclip placement and epinephrine injection for Mallory-Weiss syndrome with active bleeding. *Gastrointest Endosc* 2002; 55: 842-846
- **168** Park CH, Min SW, Sohn YH et al. A prospective, randomized trial of endoscopic band ligation vs. epinephrine injection for actively bleeding Mallory–Weiss syndrome. *Gastrointest Endosc* 2004; 60: 22-27
- **169** Cho YS, Chae HS, Kim HK et al. Endoscopic band ligation and endoscopic hemoclip placement for patients with Mallory–Weiss syndrome and active bleeding. *World J Gastroenterol* 2008; 14: 2080-2084
- **170** Leclaire S, Antonietti M, Iwanicki-Caron I et al. Endoscopic band ligation could decrease recurrent bleeding in Mallory–Weiss syndrome as compared to haemostasis by hemoclips plus epinephrine. *Aliment Pharmacol Ther* 2009; 30: 399-405
- **171** Lara LF, Sreenarasimhaiah J, Tang SJ et al. Dieulafoy lesions of the GI tract: localization and therapeutic outcomes. *Dig Dis Sci* 2010; 55: 3436-3441
- **172** Chung IK, Kim EJ, Lee MS et al. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. *Gastrointest Endosc* 2000; 52: 721-724
- **173** Kasapidis P, Georgopoulos P, Delis V et al. Endoscopic management and long-term follow-up of Dieulafoy's lesions in the upper GI tract. *Gastrointest Endosc* 2002; 55: 527-531
- **174** Cheng CL, Liu NJ, Lee CS et al. Endoscopic management of Dieulafoy lesions in acute nonvariceal upper gastrointestinal bleeding. *Dig Dis Sci* 2004; 49: 1139-1144
- **175** Park CH, Sohn YH, Lee WS et al. The usefulness of endoscopic hemoclippping for bleeding Dieulafoy lesions. *Endoscopy* 2003; 35: 388-392

- **176** Katsinelos P, Paroutoglou G, Mimidis K et al. Endoscopic treatment and follow-up of gastrointestinal Dieulafoy's lesions. *World J Gastroenterol* 2005; 11: 6022-6026
- **177** Iacopini F, Petruzzello L, Marchese M et al. Hemostasis of Dieulafoy's lesions by argon plasma coagulation (with video). *Gastrointest Endosc* 2007; 66: 20-26
- **178** Alis H, Oner OZ, Kalayci MU et al. Is endoscopic band ligation superior to injection therapy for Dieulafoy lesion?. *Surg Endosc* 2009; 23: 1465-1469
- **179** Sone Y, Kumada T, Toyoda H et al. Endoscopic management and follow up of Dieulafoy's lesion in the upper gastrointestinal tract. *Endoscopy* 2005; 37: 449-453
- **180** Lim W, Kim TO, Park SB et al. Endoscopic treatment of Dieulafoy lesions and risk factors for rebleeding. *Korean J Intern Med* 2009; 24: 318-322
- **181** Durham JD, Kumpe DA, Rothbarth LJ et al. Dieulafoy disease: arteriographic findings and treatment. *Radiology* 1990; 174: 937-941
- **182** Alshumrani G, Almuaikael M. Angiographic findings and endovascular embolization in Dieulafoy disease: a case report and literature review. *Diagn Interv Radiol* 2006; 12: 151-154
- **183** Jackson CS, Gerson LB. Management of gastrointestinal angiodysplastic lesions (GIADs): a systematic review and meta-analysis. *Am J Gastroenterol* 2014; 109: 474-483
- **184** Swanson E, Mahgoub A, MacDonald R et al. Medical and endoscopic therapies for angiodysplasia and gastric antral vascular ectasia: a systematic review. *Clin Gastroenterol Hepatol* 2014; 12: 571-582
- **185** Heller SJ, Tokar JL, Nguyen MT et al. Management of bleeding GI tumors. *Gastrointest Endosc* 2010; 72: 817-824
- **186** Sheibani S, Kim JJ, Chen B et al. Natural history of acute upper GI bleeding due to tumours: short-term success and long-term recurrence with or without endoscopic therapy. *Aliment Pharmacol Ther* 2013; 38: 144-150
- **187** Kim YI, Choi IJ, Cho SJ et al. Outcome of endoscopic therapy for cancer bleeding in patients with unresectable gastric cancer. *J Gastroenterol Hepatol* 2013; 28: 1489-1495
- **188** Koh KH, Kim K, Kwon DH et al. The successful endoscopic hemostasis factors in bleeding from advanced gastric cancer. *Gastric Cancer* 2013; 16: 397-403
- **189** Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2006; 1: CD002094
- **190** Leontiadis G, Martin J, Sharma V et al. T1942 Proton pump inhibitor (PPI) treatment for peptic ulcer (PU) bleeding: an updated Cochrane meta-analysis of randomized controlled trials (RCTs) [abstract]. *Gastroenterology* 2009; DOI: [http://dx.doi.org/10.1016/S0016-5085\(09\)62789-X](http://dx.doi.org/10.1016/S0016-5085(09)62789-X)

- **191** Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA Intern Med* 2014; 174: 1755-1762
- **192** Javid G, Zargar SA, U-Saif R et al. Comparison of p. o. or i.v. proton pump inhibitors on 72-h intragastric pH in bleeding peptic ulcer. *J Gastroenterol Hepatol* 2009; 24: 1236-1243
- **193** Sung JJ, Suen BY, Wu JC et al. Effects of intravenous and oral esomeprazole in the prevention of recurrent bleeding from peptic ulcers after endoscopic therapy. *Am J Gastroenterol* 2014; 109: 1005-1010
- **194** Lau JYW, Sung JJY, Lam YH et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcer. *N Engl J Med* 1999; 340: 751-756
- **195** Wong TCF, Wong TT, Chiu PWY et al. A comparison of angiographic embolization with surgery after failed endoscopic hemostasis to bleeding peptic ulcers. *Gastrointest Endosc* 2011; 73: 900-908
- **196** Kyaw M, Tse Y, Ang D et al. Embolization versus surgery for peptic ulcer bleeding after failed endoscopic hemostasis: a meta-analysis. *Endos Int Open* 2014; 2: E6-E14
- **197** Beggs AD, Dilworth MP, Powell SL et al. A systematic review of transarterial embolization versus emergency surgery in treatment of major nonvariceal upper gastrointestinal bleeding. *Clin Exp Gastroenterol* 2014; 7: 93-104
- **198** Sulz M, Frei R, Meyenberger C et al. Routine use of Hemospray for gastrointestinal bleeding: prospective two-center experience in Switzerland. *Endoscopy* 2014; 46: 619-624
- **199** El Ouali S, Barkun AN, Wyse J et al. Is routine second-look endoscopy effective after endoscopic hemostasis in acute peptic ulcer bleeding? A meta-analysis. *Gastrointest Endosc* 2012; 76: 283-292
- **200** Imperiale TF, Kong N. Second look endoscopy for bleeding peptic ulcer disease: a decision and cost-effectiveness analysis. *J Clin Gastroenterol* 2012; 46: e71-e75
- **201** Holster IL, Kuipers EJ. Management of acute nonvariceal upper gastrointestinal bleeding: current policies and future perspectives. *World J Gastroenterol* 2012; 18: 1202-1207
- **202** Sbrozzi-Vanni A, Zullo A, Di Giulio E et al. Low prevalence of idiopathic peptic ulcer disease: an Italian endoscopic survey. *Dig Liver Dis* 2010; 42: 773-776
- **203** Gisbert JP, Khorrani S, Carballo F et al. Meta-analysis: Helicobacter pylori eradication therapy vs. anti-secretory non-eradication therapy for the prevention of recurrent bleeding from peptic ulcer. *Aliment Pharmacol Ther* 2004; 19: 617-629
- **204** Gisbert JP, Calvet X, Cosme A et al. Long-term follow-up of 1,000 patients cured of Helicobacter pylori infection following an episode of peptic ulcer bleeding. *Am J Gastroenterol* 2012; 107: 1197-1204

- **205** Gisbert JP, Abraira V. Accuracy of Helicobacter pylori diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. *Am J Gastroenterol* 2006; 101: 848-863
- **206** Sánchez-Delgado J, Gené E, Suárez D et al. Has H. pylori prevalence in bleeding peptic ulcer been underestimated? A meta-regression. *Am J Gastroenterol* 2011; 106: 398-405
- **207** Witt DM, Delate T, Garcia DA et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med* 2012; 172: 1484-1491
- **208** Lee JK, Kang HW, Kim SG et al. Risks related with withholding and resuming anticoagulation in patients with non-variceal upper gastrointestinal bleeding while on warfarin therapy. *Int J Clin Pract* 2012; 66: 64-68
- **209** Qureshi W, Mittal C, Patsias I et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. *Am J Cardiol* 2014; 113: 662-668
- **210** Douketis JD, Spyropoulos AC, Spencer FA et al. Perioperative management of antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; 141 Suppl e326S-e350S
- **211** Sibon I, Orgogozo JM. Antiplatelet drug discontinuation is a risk factor for ischemic stroke. *Neurology* 2004; 62: 1187-1189
- **212** Biondi-Zoccai GG, Lotrionte M, Agostoni P et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006; 27: 2667-2674
- **213** Garcia-Rodriguez LA, Cea-Soriano L, Martin-Merino E et al. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011; 343: d4094 DOI: 10.1136/bmj.d4094
- **214** Cea Soriano L, Bueno H, Lanás A et al. Cardiovascular and upper gastrointestinal bleeding consequences of low dose acetylsalicylic acid discontinuation. *Thromb Haemost* 2013; 110: 1298-1304
- **215** King III SB, Smith Jr SC, Hirshfeld Jr JW et al. 2007 focused update of the ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *J Am Coll Cardiol* 2008; 51: 172-209
- **216** Anderson JL, Adams CD, Antman EM et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of

Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013; 61: 179-347

- **217** Garcia-Rodriguez LA, Lin KJ, Hernandez-Diaz S et al. Risk of upper gastrointestinal bleeding with low dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. *Circulation* 2011; 123: 1108-1115
- **218** Lanas A, Garcia-Rodriguez LA, Arroyo MT et al. Effect of anti-secretory drugs and nitrates on the risk of ulcer bleeding associated with non-steroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *Am J Gastroenterol* 2007; 102: 507-515
- **219** Bhatt DL, Scheiman J, Abraham NS et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *Circulation* 2008; 118: 1894-1909
- **220** Kwok CS, Nijar RS, Loke YK. Effects of proton pump inhibitors on adverse gastrointestinal events in patients receiving clopidogrel: a systematic review and meta-analysis. *Drug Saf* 2011; 34: 47-57
- **221** Gilard M, Arnaud B, Cornily JC et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study. *J Am Coll Cardiol* 2008; 51: 256-260
- **222** Cuisset T, Frere C, Quilici J et al. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose: the PACA (Proton Pump Inhibitors And Clopidogrel Association) prospective randomized study. *J Am Coll Cardiol* 2009; 54: 1149-1153
- **223** Siller-Matula JM, Spiel AO, Lang IM et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2009; 157: 148-145
- **224** O'Donoghue ML, Braunwald E, Antman EM et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009; 374: 989-997
- **225** Chen J, Chen SY, Lian JJ et al. Pharmacodynamic impacts of proton pump inhibitors on the efficacy of clopidogrel in vivo – a systematic review. *Clin Cardiol* 2013; 36: 184-189
- **226** Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther* 2010; 31: 810-823
- **227** Siller-Matula JM, Jilma B, Schror K et al. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost* 2010; 8: 2624-2641
- **228** Cardoso RN, Benjo AM, DiNicolantonio JJ et al. Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump

inhibitors: an updated meta-analysis. *Open Heart* 2015; 2: e000248 DOI: 10.1136/openhrt-2015-000248

- **References for Appendices**

- **229** Longstreth GF, Feitelberg SP. Outpatient care of selected patients with acute non-variceal upper gastrointestinal haemorrhage. *Lancet* 1995; 345: 108-111
- **230** Longstreth GF, Feitelberg SP. Successful outpatient management of acute upper gastrointestinal hemorrhage: use of practice guidelines in a large patient series. *Gastrointest Endosc* 1998; 47: 219-222
- **231** Cebollero-Santamaria F, Smith J, Gioe S et al. Selective outpatient management of upper gastrointestinal bleeding in the elderly. *Am J Gastroenterol* 1999; 94: 1242-1247
- **232** Brullet E, Campo R, Calvet X et al. A randomized study of the safety of outpatient care for patients with bleeding peptic ulcer treated by endoscopic injection. *Gastrointest Endosc* 2004; 60: 15-21
- **233** Lai KC, Hui WM, Wong BC et al. A retrospective and prospective study on the safety of discharging selected patients with duodenal ulcer bleeding on the same day as endoscopy. *Gastrointest Endosc* 1997; 45: 26-30
- **234** Lee JG, Turnipseed S, Romano PS et al. Endoscopy-based triage significantly reduces hospitalization rates and costs of treating upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 1999; 50: 755-761
- **235** Gralnek IM, Dulai GS. Incremental value of upper endoscopy for triage of patients with acute non-variceal upper GI hemorrhage. *Gastrointest Endosc* 2004; 60: 9-14
- **236** Cipolletta L, Bianco MA, Rotondano G et al. Outpatient management for low-risk nonvariceal upper GI bleeding: a randomized controlled trial. *Gastrointest Endosc* 2002; 55: 1-5
- **237** Sreedharan A, Martin J, Leontiadis GI et al. Proton pump inhibitor treatment initiated prior to endoscopic diagnosis in upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010; 7: CD005415
- **238** Lau JY, Leung WK, Wu JC et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med* 2007; 356: 1631-40
- **239** Liu N, Liu L, Zhang HH et al. Effect of intravenous proton pump inhibitor requirements and timing of endoscopy of peptic ulcer bleeding. *J Gastroenterol Hepatol* 2012; 27: 1473-79
- **240** Barkun AN, Bardou M, Kuipers EJ et al. International consensus recommendations on the management of patients with non-variceal upper gastrointestinal bleeding. *Ann Intern Med* 2010; 152: 101-113

- **241** Tsoi KKF, Lau JYW, Sung JJY. Cost-effectiveness analysis of high-dose omeprazole infusion before endoscopy for patients with upper GI bleeding. *Gastrointest Endosc* 2008; 67: 1056-1063
- **242** Barkun AN. Should every patient with suspected upper GI bleeding receive a proton pump inhibitor while awaiting endoscopy?. *Gastrointest Endosc* 2008; 67: 1064-1066
- **243** Rácz I, Szalai M, Dancs N et al. Pantoprazole before endoscopy in patients with gastroduodenal ulcer bleeding: Does the duration of infusion and ulcer location influence the effects?. *Gastroenterol Res Pract* 2012; Article ID561207
- **244** Lanas A. Update on non variceal gastrointestinal bleeding. *Gastroenterol Hepatol* 2013; 36: 57-65
- **245** Sung JJ, Chan FK, Chen M et al. Asia-Pacific Working consensus on non-variceal upper gastrointestinal bleeding. *Gut* 2011; 60: 1170-1177
- **246** Al-Sabah S, Barkun AN, Herba K et al. Cost-effectiveness of proton pump inhibition before endoscopy in upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2008; 6: 418-425
- **247** Ghassemi KA, Kovacs TOG, Jensen DM. Gastric acid inhibition in the treatment of peptic ulcer haemorrhage. *Curr Gastroenterol Rep* 2009; 11: 462-469
- **248** Laursen SB, Jorgensen HS, Schaffalitzky de Muckadell OB. Management of bleeding gastroduodenal ulcers. *Dan Med J* 2012; 59: C4473
- **249** Lin HJ. Role of proton pump inhibitors in the management of peptic ulcer bleeding. *World J Gastrointest Pharmacol Ther* 2010; 1: 51-53
- **250** Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2012; 1: CD006640
- **251** Magnusson I, Ihre T, Johansson C et al. Randomized double blind trial of somatostatin in the treatment of massive upper gastrointestinal hemorrhage. *Gut* 1985; 26: 221-226
- **252** Choi CW, Kang DH, Kim HW et al. Somatostatin adjunctive therapy for non-variceal upper gastrointestinal rebleeding after endoscopic therapy. *World J Gastroenterol* 2011; 17: 3441-3447
- **253** Avgerinos A, Sgouros S, Viazis N et al. Somatostatin inhibits gastric acid secretion more effectively than pantoprazole in patients with peptic ulcer bleeding: A prospective, randomized, placebo controlled trial. *Scan J Gastroenterol* 2005; 40: 515-522
- **254** Archimandritis A, Tsirantonaki M, Tryphonos M et al. Ranitidine versus ranitidine plus octreotide in the treatment of acute nonvariceal upper gastrointestinal bleeding: a prospective randomized study. *Curr Med Res Opin* 2000; 16: 178-183

- **255** Lin H, Perng C, Wang K et al. Octreotide for arrest of peptic ulcer hemorrhage – a prospective randomized controlled trial. *Hepatogastroenterology* 1995; 42: 856-860
- **256** Kim I, Lee YS, Koh BS et al. Does adding somatostatin to proton pump inhibitor improve the outcome of peptic ulcer bleeding?. *Korean J Crit Care Med* 2008; 23: 75-78
- **257** Antonioli A, Gandolfo M, Rigo GD et al. Somatostatin and cimetidine in the control of acute upper gastrointestinal bleeding. A controlled multicentre study. *Hepatogastroenterology* 1986; 33: 71-94
- **258** Tisbouris P, Zintzas E, Lappas C et al. High-dose pantoprazole infusion is superior to somatostatin after endoscopic hemostasis in patients with peptic ulcer bleeding. *Am J Gastroenterol* 2007; 102: 1192-1199
- **259** Okan A, Simsek I, Akpinar H et al. Somatostatin and ranitidine in the treatment of non-variceal upper gastrointestinal bleeding: a prospective randomized, double-blind, controlled study. *Hepatogastroenterology* 2000; 47: 1325-1327
- **260** Rutgeerts P, Avgerinos A et al. Early administration of somatostatin before endoscopy to non-cirrhotic patients with suspected peptic ulcer bleeding: The PUB double-blind, randomized, placebo-controlled trial. *Gut* 2006; 55: A47
- **261** Carbonell N, Pauwels A, Serfaty L et al. Erythromycin infusion prior to endoscopy for acute upper gastrointestinal bleeding: a randomized, controlled, double-blind trial. *Am J Gastroenterol* 2006; 101: 1211-1215
- **262** Coffin B, Pocard M, Panis Y et al. Erythromycin improves the quality of EGD in patients with acute upper GI bleeding: a randomized controlled study. *Gastrointest Endosc* 2002; 56: 174-179
- **263** Frossard JL, Spahr L, Queneau PE et al. Erythromycin intravenous bolus infusion in acute upper gastrointestinal bleeding: a randomized, controlled, double-blind trial. *Gastroenterology* 2002; 123: 17-23
- **264** Theivanayagam S, Lim RG, Cobell WJ et al. Administration of erythromycin before endoscopy in upper gastrointestinal bleeding: a meta-analysis of randomized controlled trials. *Saudi J Gastroenterol* 2013; 19: 205-210
- **265** Sussman DA, Deshpande AR, Parra JL et al. Intravenous metoclopramide to increase mucosal visualization during endoscopy in patients with acute upper gastrointestinal bleeding: a randomized, controlled study. *Gastrointest Endosc* 2008; 67: AB247
- **266** Barkun AN, Bardou M, Martel M et al. Prokinetics in acute upper GI bleeding: a meta-analysis. *Gastrointest Endosc* 2010; 72: 1138-1145

- **267** Habashi SL, Lambiase LR, Kottoor R. Prokinetics infusion prior endoscopy for acute upper gastrointestinal bleeding: A randomized, controlled, double-blind and placebo-controlled trial [abstract]. *Am J Gastroenterol* 2007; 102: S526
- **268** Winstead NS, Wilcox CM. Erythromycin prior to endoscopy for acute upper gastrointestinal haemorrhage: a cost-effectiveness analysis. *Aliment Pharmacol Ther* 2007; 26: 1371-1377
- **269** Spiegel BM, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: is sooner better? A systematic review. *Arch Intern Med* 2001; 161: 1393-1404
- **270** Tsoi KKF, Ma TKW, Sung JY. Endoscopy for upper gastrointestinal bleeding: how urgent is it?. *Nat Rev Gastroenterol Hepatol* 2009; 6: 463-469
- **271** Sarin N, Monga N, Adams PC. Time to endoscopy and outcomes in upper gastrointestinal bleeding. *Can J Gastroenterol* 2009; 23: 489-493
- **272** Lim L, Ho K, Chan Y et al. Urgent endoscopy is associated with lower mortality in high-risk but not low-risk nonvariceal upper gastrointestinal bleeding. *Endoscopy* 2011; 43: 300-306
- **273** Marmo R, Del Piano M, Rotondano G et al. Mortality from nonvariceal upper gastrointestinal bleeding: is it time to differentiate the timing of endoscopy?. *Gastrointest Endosc* 2011; 73: AB224
- **274** Wysocki JD, Srivastav S, Winstead NS. A nationwide analysis of risk factors for mortality and time to endoscopy in upper gastrointestinal haemorrhage. *Aliment Pharmacol Ther* 2012; 36: 30-36
- **275** Jairath V, Kakan BC, Logan RF et al. Outcomes following acute nonvariceal upper gastrointestinal bleeding in relation to time to endoscopy: results from a nationwide study. *Endoscopy* 2012; 44: 723-730
- **276** Sachar H, Vaidya K, Laine L. Intermittent vs. continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. *JAMA Intern Med* 2014; 174: 1755-1762
- **277** Sung JJ, Suen BY, Wu JC et al. Effects of intravenous and oral esomeprazole in the prevention of recurrent bleeding from peptic ulcers after endoscopic therapy. *Am J Gastroenterol* 2014; 109: 1005-1010
- **278** Mostaghni AA, Hashemi SA, Heydari ST. Comparison of oral and intravenous proton pump inhibitor on patients with high risk bleeding peptic ulcers: a prospective, randomized, controlled clinical trial. *Iran Red Crescent Med J* 2011; 13: 458-463

- **279** Yen HH, Yang CW, Su WW et al. Oral versus intravenous proton pump inhibitors in preventing re-bleeding for patients with peptic ulcer bleeding after successful endoscopic therapy. *BMC Gastroenterology* 2012; 12: 66
- **280** Tsai JJ, Hsu YC, Perng CL et al. Oral or intravenous proton pump inhibitor in patients with peptic ulcer bleeding after successful endoscopic epinephrine injection. *Br J Clin Pharmacol* 2009; 67: 326-332
- **281** Wang CH, Ma MH, Chou HC et al. High-dose vs non-high-dose proton pump inhibitors after endoscopic treatment in patients with bleeding peptic ulcer: a systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2010; 170: 751-758
- **282** Mazjedizadeh AR, Hajiani E, Alavinejad P et al. High dose versus low dose intravenous pantoprazole in bleeding peptic ulcer: a randomized clinical trial. *Middle East J Dig Dis* 2014; 6: 137-143
- **283** Lau JYW, Sung JJY, Lam YH et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcer. *N Engl J Med* 1999; 340: 751-756
- **284** Wong TCF, Wong TT, Chiu PWY et al. A comparison of angiographic embolization with surgery after failed endoscopic hemostasis to bleeding peptic ulcers. *Gastrointest Endosc* 2011; 73: 900-908
- **285** Kyaw M, Tse Y, Ang D et al. Embolization versus surgery for peptic ulcer bleeding after failed endoscopic hemostasis: a meta-analysis. *Endosc Int Open* 2014; 2: E6-E14
- **286** Beggs AD, Dilworth MP, Powell SL et al. A systematic review of transarterial embolization versus emergency surgery in treatment of major nonvariceal upper gastrointestinal bleeding. *Clin Exp Gastroenterol* 2014; 7: 93-104
- **287** Smith LA, Stanley AJ, Bergman JJ et al. Hemospray application in nonvariceal upper gastrointestinal bleeding: results of the survey to evaluate the application of hemospray in the luminal tract. *J Clin Gastroenterol* 2014; 48: 89-92
- **288** Sulz M, Frei R, Meyenberger C et al. Routine use of Hemospray for gastrointestinal bleeding: prospective two-center experience in Switzerland. *Endoscopy* 2014; 46: 619-624
- **289** Skinner M, Gutteriez JP, Neumann H et al. Over-the-scope clip placement is effective rescue therapy for severe acute upper gastrointestinal bleeding. *Endosc Int Open* 2014; 02: E37-E40
- **290** Manta R, Galloro G, Mangiavillano B et al. Over-the-scope clip (OTSC) represents an effective endoscopic treatment for acute GI bleeding after failure of conventional techniques. *Surg Endosc* 2013; 27: 3162-3164

- **291** Sanchez-Delgado J, Gene E, Suarez D et al. Has H. pylori prevalence in bleeding peptic ulcer been underestimated? A meta-regression. *Am J Gastroenterol* 2011; 106: 398-405
- **292** Gisbert JP, Abaira V. Accuracy of [Helicobacter pylori](#) diagnostic tests in patients with bleeding peptic ulcer: a systematic review and meta-analysis. *Am J Gastroenterol* 2006; 101: 848-863
- **293** Gisbert JP, Calvet X, Cosme A et al. Long-term follow-up of 1,000 patients cured of [Helicobacter pylori](#) infection following an episode of peptic ulcer bleeding. *Am J Gastroenterol* 2012; 107: 1197-1204
- **294** Gisbert JP, Khorrani S, Carballo F et al. Meta-analysis: [Helicobacter pylori](#) eradication therapy vs. anti-secretory non-eradication therapy for the prevention of recurrent bleeding from peptic ulcer. *Aliment Pharmacol Ther* 2004; 19: 617-629
- **295** Dixon MF, Genta RM, Yardley JH et al. Classification and grading of gastritis. The updated Sydney System. *Am J Surg Pathol* 1996; 20: 1161-1181
- **296** Witt DM, Delate T, Garcia DA et al. Risk of thromboembolism, recurrent hemorrhage, and death after warfarin therapy interruption for gastrointestinal tract bleeding. *Arch Intern Med* 2012; 172: 1484-1491
- **297** Qureshi W, Mittal C, Patsias I et al. Restarting anticoagulation and outcomes after major gastrointestinal bleeding in atrial fibrillation. *Am J Cardiol* 2014; 113: 662-668
- **298** Lee JK, Kang HW, Kim SG et al. Risks related with withholding and resuming anticoagulation in patients with non-variceal upper gastrointestinal bleeding while on warfarin therapy. *Int J Clin Pract* 2012; 66: 64-68
- **299** Goodman SG, Clare R, Pieper KS et al. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the platelet inhibition and patient outcomes trial. *Circulation* 2012; 125: 978-986
- **300** Stockl KM, Le L, Zakharyan A et al. Risk of rehospitalization for patients using clopidogrel with a proton pump inhibitor. *Arch Intern Med* 2010; 170: 704-710
- **301** Kreutz RP, Stanek EJ, Aubert R et al. Impact of proton pump inhibitors on the effectiveness of clopidogrel after coronary stent placement: the clopidogrel Medco outcomes study. *Pharmacotherapy* 2010; 30: 787-796
- **302** Ho PM, Maddox TM, Wang L et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301: 937-944
- **303** Huang CC, Chen YC, Leu HB et al. Risk of adverse outcomes in Taiwan associated with concomitant use of clopidogrel and proton pump inhibitors in

patients who received percutaneous coronary intervention. *Am J Cardiol* 2010; 105: 1705-1709

- **304** Zou JJ, Chen SL, Tan J et al. Increased risk for developing major adverse cardiovascular events in stented Chinese patients treated with dual antiplatelet therapy after concomitant use of the proton pump inhibitor. *PLoS One* 2014; 9: e84985 DOI: 10.1371/journal.pone. 0084985
- **305** van Boxel OS, van Oijen MG, Hagens MP et al. Cardiovascular and gastrointestinal outcomes in clopidogrel users on proton pump inhibitors: results of a large Dutch cohort study. *Am J Gastroenterol* 2010; 105: 2430-2436
- **306** Munoz-Torrero JF, Escudero D, Suarez C et al. Concomitant use of proton pump inhibitors and clopidogrel in patients with coronary, cerebrovascular, or peripheral artery disease in the factores de Riesgo y ENfermedad Arterial (FRENA) registry. *J Cardiovasc Pharmacol* 2011; 57: 13-19
- **307** O'Donoghue ML, Braunwald E, Antman EM et al. Pharmacodynamic effect and clinical efficacy of clopidogrel and prasugrel with or without a proton-pump inhibitor: an analysis of two randomised trials. *Lancet* 2009; 374: 989-997
- **308** Hsiao FY, Mullins CD, Wen YW et al. Relationship between cardiovascular outcomes and proton pump inhibitor use in patients receiving dual antiplatelet therapy after acute coronary syndrome. *Pharmacoepidemiol Drug Saf* 2011; 20: 1043-1049
- **309** Banerjee S, Weideman RA, Weideman MW et al. Effect of concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention. *Am J Cardiol* 2011; 107: 871-878
- **310** Harjai KJ, Shenoy C, Orshaw P et al. Clinical outcomes in patients with the concomitant use of clopidogrel and proton pump inhibitors after percutaneous coronary intervention: an analysis from the Guthrie Health Off-Label Stent (GHOST) investigators. *Circ Cardiovasc Interv* 2011; 4: 162-170
- **311** Aihara H, Sato A, Takeyasu N et al. Effect of individual proton pump inhibitors on cardiovascular events in patients treated with clopidogrel following coronary stenting: results from the Ibaraki Cardiac Assessment Study Registry. *Catheter Cardiovasc Interv* 2012; 80: 556-563
- **312** Tentzeris I, Jarai R, Farhan S et al. Impact of concomitant treatment with proton pump inhibitors and clopidogrel on clinical outcome in patients after coronary stent implantation. *Thromb Haemost* 2010; 104: 1211-1218
- **313** Schmidt M, Johansen MB, Robertson DJ et al. Concomitant use of clopidogrel and proton pump inhibitors is not associated with major adverse cardiovascular

events following coronary stent implantation. *Aliment Pharmacol Ther* 2012; 35: 165-174

- **314** Rassen JA, Choudhry NK, Avorn J et al. Cardiovascular outcomes and mortality in patients using clopidogrel with proton pump inhibitors after percutaneous coronary intervention or acute coronary syndrome. *Circulation* 2009; 120: 2322-2329
- **315** Ray WA, Murray KT, Griffin MR et al. Outcomes with concurrent use of clopidogrel and proton-pump inhibitors: a cohort study. *Ann Intern Med* 2010; 152: 337-345
- **316** Kwok CS, Loke YK. Meta-analysis: the effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. *Aliment Pharmacol Ther* 2010; 31: 810-823
- **317** Siller-Matula JM, Jilma B, Schror K et al. Effect of proton pump inhibitors on clinical outcome in patients treated with clopidogrel: a systematic review and meta-analysis. *J Thromb Haemost* 2010; 8: 2624-2641