

International Consensus Guidelines for Nonvariceal Gastrointestinal Bleeding: A Step Forward

Nonvariceal upper gastrointestinal bleeding (UGIB) is common, may be severe, and often requires urgent attention. In recent decades, worldwide rates of this disorder have decreased because of strategies to prevent gastrointestinal damage from nonsteroidal anti-inflammatory drugs and aspirin, therapies to eradicate *Helicobacter pylori*, and a lower prevalence of *H pylori* infection in the population (1). During the same period, new endoscopic and pharmacologic therapies improved the evidence-based care of patients with nonvariceal UGIB.

Recently, an international multidisciplinary group of experts (2) updated the International Consensus Recommendations on the Management of Patients With Nonvariceal Upper Gastrointestinal Bleeding published in 2010 (3). The European Society of Gastrointestinal Endoscopy (4) and Asia-Pacific Working Group (5) released guidelines focused on nonvariceal UGIB that were based on similar evidence in 2015 and 2018, respectively. Frequent updates on nonvariceal UGIB management are necessary because of rapidly emerging new evidence and the changing clinical profile of patients presenting with this condition. Similar to the previous international consensus guideline process (3), the panel used rigorous methods to arrive at its recommendations. These guidelines are a step forward, particularly with regard to new endoscopic therapies and the management of nonvariceal UGIB in patients receiving antiplatelet or anticoagulant drugs. The document also identifies unanswered questions that should prompt future research.

In updating the recommendations, the consensus group considered evidence on innovative endoscopic therapies, such as hemostatic powder (TC-325) and Doppler endoscopy. With regard to TC-325, the panel recommends its use as a temporizing intervention if standard therapy fails or cannot be applied; however, it clearly indicates that TC-325 should not replace current standard therapy. With regard to Doppler endoscopy, the panel has articulated a need for further investigation of its use in identifying patients eligible for endoscopic therapy.

Several recommendations focus on patients receiving anticoagulation or antiplatelet therapy, an important topic because of the increase in the use of these drugs. The panel recommends proton-pump inhibitor (PPI) therapy to prevent nonvariceal UGIB in patients with previous ulcer bleeding who are receiving single- or dual-antiplatelet or anticoagulant therapy. This recommendation, supported by clinical evidence (6, 7), helps to allay concerns regarding the potential interaction between PPIs and clopidogrel, as well as warnings issued by regulatory agencies. Yet, the recent COMPASS (Rivaroxaban for the Prevention of Major Cardiovascular Events in Cor-

onary or Peripheral Artery Disease) trial suggests that PPIs do not prevent gastrointestinal bleeding in patients receiving anticoagulant agents (8), casting some doubt on the effectiveness of this recommendation. However, data from COMPASS should be interpreted cautiously, because the main outcome was a composite end point combining upper and lower gastrointestinal complications. Post hoc subgroup analyses of the COMPASS data indicate that PPIs reduce only acid-related bleeding complications. Thus, the panel's recommendation should apply to patients with a history of peptic ulcer or acid-related lesions. Controversy exists regarding the timing of endoscopy in patients receiving anticoagulation therapy, and the recommendations indicate that future studies are needed to inform these decisions. Patient management should be facilitated by the increased use of direct oral anticoagulants, which have a more predictable loss of effect after drug interruption and a more rapid effect after drug initiation versus vitamin K antagonists (1); however, this also warrants further study.

Other unresolved questions noted by the consensus group relate to the type of fluids to be administered (crystalloids vs. colloids) and the rate and timing of resuscitation (aggressive vs. restrictive) during initial management of patients with nonvariceal UGIB. The updated guidelines also address the use of restrictive versus liberal blood transfusions and recommend a more conservative blood transfusion threshold (8 g/L vs. 7 g/L of hemoglobin) than other guidelines (4, 5), with a higher, but undefined, threshold for patients with known cardiovascular disease. Overall, the quality of evidence is still low, and new studies are needed to clarify these issues.

Despite a recent systematic review that challenges the practice (9), the consensus group maintains its previous recommendation for 3 days of treatment with high-dose intravenous PPIs for patients with high-risk stigmata who have had successful endoscopic therapy (2). The group now recommends twice-daily oral PPI therapy from day 3 to day 14, followed by once-daily treatment. Yet, we still lack good evidence regarding the use of oral therapy or high-dose bolus administration, which may be a good option in low-income countries. The update provides no new recommendations regarding the use of PPIs before endoscopy. Although the available evidence indicates that the potential advantage of preendoscopic PPI therapy is limited, this approach is used commonly in current clinical practice (10).

Prognostic scores to predict outcomes have been among the most active research topics in the field of gastrointestinal bleeding in recent years. The previous international consensus guidelines (3) did not specifically recommend any scale, but the new guidelines rec-

ommend using a score of 1 or less on the Glasgow Blatchford scale to identify patients who do not require hospitalization. However, prognostic scores are not commonly used in many emergency departments, where clinical judgment tends to guide decision making (10). Also, a Glasgow Blatchford score greater than 1 is very common among patients presenting to emergency departments with nonvariceal UGIB, so the use of this tool may have little impact on hospitalization rates. Studies comparing clinical judgment with prognostic scores would help refine future recommendations, and the use of artificial intelligence to improve prediction is currently being explored.

In summary, the updated international consensus guidelines provide a rigorous review of the available evidence on nonvariceal UGIB management. The recommendations for managing patients receiving antiplatelets or anticoagulants and for the appropriate use of new therapeutic endoscopic techniques should be particularly helpful to clinicians. In addition, the new guidelines refine previous recommendations concerning resuscitation; risk scores; and preendoscopic, endoscopic, and pharmacologic management. Researchers interested in nonvariceal UGIB should direct their efforts at studying the issues for which evidence is limited so that future recommendations may provide additional steps forward.

*Angel Lanas, MD
University Clinic Hospital, University of Zaragoza,
CIBERehd, IIS Aragón
Zaragoza, Spain*

Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-2789.

Corresponding Author: Angel Lanas, MD, Servicio de Aparato Digestivo, Hospital Clínico Universitario Lozano Blesa, c/San Juan Bosco 15, 50009 Zaragoza, Spain; e-mail, alanas@unizar.es.

Ann Intern Med. doi:10.7326/M19-2789

References

1. Lanas A, Dumonceau JM, Hunt RH, et al. Non-variceal upper gastrointestinal bleeding. *Nat Rev Dis Primers.* 2018;4:18020. [PMID: 29671413] doi:10.1038/nrdp.2018.20
2. Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the International Consensus Group. *Ann Intern Med.* 2019 October 22. [Epub ahead of print]. doi:10.7326/M19-1795
3. Barkun AN, Bardou M, Kuipers EJ, et al; International Consensus Upper Gastrointestinal Bleeding Conference Group. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2010;152:101-13. [PMID: 20083829] doi:10.7326/0003-4819-152-2-201001190-00009
4. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy.* 2015;47:a1-46. [PMID: 26417980] doi:10.1055/s-0034-1393172
5. Sung JJ, Chiu PW, Chan FKL, et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. *Gut.* 2018;67:1757-1768. [PMID: 29691276] doi:10.1136/gutjnl-2018-316276
6. Bhatt DL, Cryer BL, Contant CF, et al; COGET Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med.* 2010;363:1909-17. [PMID: 20925534] doi:10.1056/NEJMoa1007964
7. Goodman SG, Clare R, Pieper KS, et al; Platelet Inhibition and Patient Outcomes Trial Investigators. Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: insights from the Platelet Inhibition and Patient Outcomes Trial. *Circulation.* 2012;125:978-86. [PMID: 22261200] doi:10.1161/CIRCULATIONAHA.111.032912
8. Moayyedi P, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. *Gastroenterology.* 2019;157:403-412.e5. [PMID: 31054846] doi:10.1053/j.gastro.2019.04.041
9. 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;174:1755-62. [PMID: 25201154] doi:10.1001/jamainternmed.2014.4056
10. 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;29:1026-36. [PMID: 23225523] doi:10.1007/s12325-012-0069-x

Management of Nonvariceal Upper Gastrointestinal Bleeding: Guideline Recommendations From the International Consensus Group

Alan N. Barkun, MD; Majid Almadi, MD; Ernst J. Kuipers, MD; Loren Laine, MD; Joseph Sung, MD; Frances Tse, MD; Grigoris I. Leontiadis, MD; Neena S. Abraham, MD; Xavier Calvet, MD; Francis K.L. Chan, MD; James Douketis, MD; Robert Enns, MD; Ian M. Gralnek, MD; Vipul Jairath, MD; Dennis Jensen, MD; James Lau, MD; Gregory Y.H. Lip, MD; Romaric Loffroy, MD; Fauze Maluf-Filho, MD; Andrew C. Meltzer, MD; Nageshwar Reddy, MD; John R. Saltzman, MD; John K. Marshall, MD; and Marc Bardou, MD

Description: This update of the 2010 International Consensus Recommendations on the Management of Patients With Nonvariceal Upper Gastrointestinal Bleeding (UGIB) refines previous important statements and presents new clinically relevant recommendations.

Methods: An international multidisciplinary group of experts developed the recommendations. Data sources included evidence summarized in previous recommendations, as well as systematic reviews and trials identified from a series of literature searches of several electronic bibliographic databases from inception to April 2018. Using an iterative process, group members formulated key questions. Two methodologists prepared evidence profiles and assessed quality (certainty) of evidence relevant to the key questions according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Group members reviewed the evidence profiles and, using a consensus process, voted on recommendations and determined the strength of recommendations as strong or conditional.

Recommendations: *Preendoscopic management:* The group suggests using a Glasgow Blatchford score of 1 or less to identify patients at very low risk for rebleeding, who may not require hospitalization. In patients without cardiovascular disease, the

suggested hemoglobin threshold for blood transfusion is less than 80 g/L, with a higher threshold for those with cardiovascular disease. *Endoscopic management:* The group suggests that patients with acute UGIB undergo endoscopy within 24 hours of presentation. Thermocoagulation and sclerosant injection are recommended, and clips are suggested, for endoscopic therapy in patients with high-risk stigmata. Use of TC-325 (hemostatic powder) was suggested as temporizing therapy, but not as sole treatment, in patients with actively bleeding ulcers. *Pharmacologic management:* The group recommends that patients with bleeding ulcers with high-risk stigmata who have had successful endoscopic therapy receive high-dose proton-pump inhibitor (PPI) therapy (intravenous loading dose followed by continuous infusion) for 3 days. For these high-risk patients, continued oral PPI therapy is suggested twice daily through 14 days, then once daily for a total duration that depends on the nature of the bleeding lesion. *Secondary prophylaxis:* The group suggests PPI therapy for patients with previous ulcer bleeding who require antiplatelet or anticoagulant therapy for cardiovascular prophylaxis.

Ann Intern Med. doi:10.7326/M19-1795

Annals.org

For author affiliations, see end of text.

This article was published at Annals.org on 22 October 2019.

Acute upper gastrointestinal bleeding (UGIB) is common, but the annual incidence has been decreasing: from 78 to 61 cases in 100 000 persons from 2001 to 2009 in one survey (1). Nonetheless, 30-day mortality remains high, at up to 11% (2).

The most recent guidelines for managing UGIB were published primarily between 2010 and 2015, including those from our group (in 2003, with an update in 2010) (3, 4), the American College of Gastroenterology (in 2012) (5), the American Society for Gastrointestinal Endoscopy (in 2012) (6), the National Institute for Health and Care Excellence (NICE) (in 2012) (7), and the European Society of Gastrointestinal Endoscopy (in 2015) (8). More recently, guidelines from the Asia-Pacific Working Group were updated in 2018 (9).

The management of UGIB has advanced with new endoscopic techniques, and the pharmacologic landscape has changed. Anticoagulant or antiplatelet therapy, including combination therapy, is becoming more common, substantially increasing the risk for UGIB (10). Thus, the International Consensus Group agreed that an update to the 2010 recommendations for the management of UGIB (4) was warranted.

METHODS

Scope and Purpose

Similar to the 2003 (3) and 2010 (4) guidelines, this update focuses on resuscitation and risk assessment; preendoscopic, endoscopic, and pharmacologic management; and secondary prophylaxis for recurrent UGIB. Specific PICO (patient population, intervention, comparator, and outcome) questions were developed by the cochairs (A.N.B. and M.B.), steering committee (L.L., M.A., J.S., and E.J.K.), and GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodologists (F.T. and G.I.L.) and finalized through a consensus process of iterative discussions with all other voting participants.

See also:

Editorial

Web-Only

Supplement

CME/MOC activity

Sources, Literature Searches, and Systematic Reviews

Sources included the evidentiary base of previous guidelines (3, 4) and English-language literature searches of MEDLINE, EMBASE (Elsevier), the Cochrane Database of Systematic Reviews (Wiley), and the Cochrane Central Register of Controlled Trials (Wiley) done by the editorial office of the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group at McMaster University. Initial searches were conducted from database inception to 2 April 2018, with supplemental, focused searches to mid-May 2018. Key search terms and details of search strategies are shown in **Supplement Appendix 1** (available at Annals.org). Conference abstracts, case reports, and studies in animals were excluded.

Teams of reviewers (A.B., M.B., X.C., L.L., G.I.L., and F.T.) screened titles and abstracts in duplicate and independently, and obtained full texts of potentially relevant studies. Reviewers also scanned bibliographies of retrieved systematic reviews. The cochairs, steering committee, and methodologists then selected the studies relevant for each PICO question. Discrepancies regarding inclusion were resolved by consensus.

A modified version of AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) (11) was used as a decision tool to assess the methodological quality of existing systematic reviews. We selected the most recent of the well-conducted, relevant systematic reviews as our baseline source. Selected reviews were used wholly or partially (with only some of the following components: included studies, study characteristics, numerical data extractions, forest plots, or risk-of-bias tables) and were updated or improved as needed by adding new studies, removing inappropriate studies, or further assessing the quality of the included studies (**Supplement Appendix 2**, available at Annals.org).

Assessment of the Quality of Evidence

The methodologists (F.T. and G.I.L.) assessed risk of bias, indirectness, inconsistency, imprecision, and other limitations (including publication bias) of the evidence by using the GRADE approach (12). Overall quality of evidence (QoE) was graded as very low, low, moderate, or high for each recommendation.

Evidence profiles (GRADE tables) were prepared for each PICO question and contained clear descriptions of benefits and harms as well as a QoE rating for individual outcomes. The profiles, systematic reviews, and meta-analyses were made available to voting participants 1 week before the consensus meeting (**Supplement Appendix 2**).

One statement (A1) met the criteria for "good practice" (13). The consensus group agreed that this recommendation was clinically obvious and that collection and analysis of evidence were unnecessary.

Consensus Process

Participants in the multidisciplinary consensus group were from 11 countries and included gastroenterologists, a cardiologist, a hematologist, a radiologist, a surgeon, and an emergency medicine specialist. The

meeting included up to 20 voting participants for each statement (numbers varied, mainly because of travel difficulties), 2 nonvoting GRADE methodologists, and a nonvoting moderator (J.K.M).

The cochairs, other steering committee members, and methodologists generated a list of new and old statements that were presented to the group through an anonymous, Web-based consensus platform (ECD Solutions). Via teleconference, the steering committee members reached consensus on which statements warranted inclusion in the guideline by focusing on priority areas. Using a modified Delphi process (14), all voting participants modified and finalized the new statements. After reviewing the evidence profiles, the participants anonymously voted on their degree of agreement or disagreement with each statement and submitted comments. Votes were nonbinding and designed to gauge the extent of agreement and the pattern of evidence uncertainty to guide the allotment of time for discussion during the meeting. The Canadian Association of Gastroenterology (CAG) office tabulated the votes and comments and presented the results to the group. Although initially discussed in the form of declarative statements, these were edited into specific PICO questions by the methodologists before the consensus meeting.

At a 2-day consensus meeting in May 2018, the group applied the GRADE Evidence to Decision framework to move from evidence to recommendations by assessing 7 key criteria: the balance between desirable and undesirable effects, quality (certainty) of the evidence, variability in patients' values and preferences, resource requirements, cost-effectiveness, acceptability, and feasibility (**Supplement Appendix 2**) (15-17). Participants voted on the direction of the PICO question (for or against) as yes, uncertain, or no. Consensus for or against a specific strategy was reached if at least 75% of the participants voted yes or no, respectively. For PICO questions on which agreement was reached, the group then discussed the strength of the recommendation (strong vs. conditional) by considering the factors in the Evidence to Decision framework (18). In cases of low or very low QoE, unless at least 1 of the other 3 factors was overwhelmingly strong, the strength of the recommendation would default (without a vote) to "conditional" by using the phrase "we suggest." If the statement warranted a vote and at least 75% of the participants voted "strong," then the recommendation would be designated as strong with the phrase "we recommend."

Consensus was not reached on 4 PICO questions (no recommendation A to D), because fewer than 75% of the participants voted either yes or no. No corresponding statements were developed for these questions, but the pertinent evidence and discussions are summarized briefly in the text.

Oversight and Review

The guideline process was overseen by the CAG clinical affairs committee to ensure methodological quality and a transparent, nonbiased, evidence-based

decision-making process. Recommendations are based on evidence from the literature and consensus discussion and may not fully reflect the product labeling for a given country.

The manuscript was initially drafted by the cochairs (A.N.B. and M.B.) and the GRADE experts (F.T. and G.I.L.). It was reviewed and revised by the steering committee members (E.J.K., J.S., L.L., and M.A.) before dissemination to the full consensus group for feedback. Finally, the manuscript was posted on the CAG Web site, and members were invited via e-mail to submit comments over a 2-week period.

In accordance with CAG policy, written conflict-of-interest disclosures for the 24 months preceding the consensus meeting were provided by all participants and made available to the group.

Role of the Funding Source

Funding for the consensus meeting was provided by unrestricted, arms-length grants to the CAG from the Institute of Nutrition, Metabolism and Diabetes of the Canadian Institutes of Health Research and the Saudi Gastroenterology Association. The CAG administered all aspects of the meeting; the funding sources had no involvement in, nor were they made aware of, any part of the process, from the development of search strings and statements to drafting and approving these guidelines.

RECOMMENDATION STATEMENTS FOR UGIB

Each statement is followed by the strength of evidence based on GRADE analyses and a discussion of the evidence. The voting results are shown in Table 1, along with summaries of the new recommendations established from this consensus, recommendations that were revised from the 2003 and 2010 guidelines (3, 4), and recommendations that were unchanged because most of the group believed that they currently did not require revision (3, 4).

Section A: Resuscitation, Risk Assessment, and Preendoscopy Management

Statement A1

For patients with acute UGIB and hemodynamic instability, resuscitation should be initiated.

(Designated a good practice statement.)

Discussion. Fluid resuscitation should be initiated in patients with UGIB and hemodynamic instability, because hemorrhagic shock may lead to multiorgan failure and death. The goals of fluid resuscitation are to restore end-organ perfusion and tissue oxygenation while steps are taken to control bleeding.

Uncertainty remains regarding the type of fluid (colloid vs. crystalloid) and the rate and timing of resuscitation (aggressive vs. restrictive). A Cochrane systematic review including 70 randomized controlled trials found no difference in mortality between critically ill patients who received colloids (albumin or plasma protein fraction, hydroxyethyl starch, modified gelatin, dextran, colloids in hypertonic crystalloid, or colloids in isotonic crystalloid) and those who received crystalloids

(normal saline, Ringer lactate, or hypertonic saline) for fluid resuscitation (19). One small randomized trial conducted in patients with UGIB who had hemorrhagic shock found no statistically significant difference in mortality between hypertonic saline dextran and Ringer lactate (relative risk [RR], 0.18 [95% CI, 0.02 to 1.41]) (20). A large trial, published after the systematic review, that included 2857 critically ill patients showed no difference in 28-day mortality between those given colloids and those who received crystalloids (21). The trial found an unexpected borderline reduction in 90-day mortality among patients receiving colloids (RR, 0.92 [CI, 0.86 to 0.99])—a finding that was considered hypothesis generating (21). Because current evidence does not show that colloids increase survival rates compared with crystalloids and because colloids are more expensive, the consensus group agreed that routine use in clinical practice is not justified (19).

Uncertainty also exists regarding the type of crystalloid for use in fluid resuscitation. A recent randomized trial in 15 802 critically ill patients found a small reduction in acute kidney injury (odds ratio [OR], 0.91 [CI, 0.84 to 0.99]) and a possible small reduction in in-hospital mortality (10.3% vs. 11.1%; $P = 0.08$) with balanced crystalloids (such as Ringer lactate) vs. saline (22).

Animal models have shown that early aggressive fluid resuscitation to increase blood pressure to normal values may exacerbate blood loss, disrupt coagulation, and increase mortality (23, 24). The alternative is restrictive or hypotensive resuscitation, in which fluid is given but the target end point is less than normotension. A Cochrane systematic review included 6 randomized trials that examined timing and volume of fluid administration in 2128 patients with bleeding. Trials were heterogeneous regarding patient types, clinical settings, types of fluids, and resuscitation protocols (25). None found restrictive fluid resuscitation (with a delayed or smaller volume of fluid) to be inferior to more aggressive fluid resuscitation (with an early or a larger volume of fluid) with regard to mortality (25). Two randomized trials published since the review also found no differences in mortality between restrictive and aggressive resuscitation in patients with trauma and hemorrhagic shock (26, 27). The consensus group agreed that the evidence was insufficient to make a recommendation regarding restrictive fluid resuscitation. The important issue in patients with hemorrhagic shock due to trauma or UGIB is to stop the bleeding while minimizing hemodynamic compromise.

Statement A2a

For patients with acute UGIB, we suggest using a Glasgow Blatchford score of 1 or less to identify patients who are at very low risk for rebleeding or mortality and thus may not require hospitalization or in-patient endoscopy.

(GRADE: conditional recommendation, low-quality evidence)

Table 1. Summary of Consensus Recommendations for the Management of UGIB***A. Resuscitation, risk assessment, and preendoscopy management**

- A1. For patients with acute UGIB and hemodynamic instability, resuscitation should be initiated.
Designated a good practice statement (see PICO question 1 in **Supplement Appendix 2**, available at Annals.org)
- A2a. For patients with acute UGIB, we suggest using a Glasgow Blatchford score of ≤1 to identify patients who are at very low risk for rebleeding or mortality and thus may not require hospitalization or inpatient endoscopy.
GRADE: conditional recommendation, low-quality evidence. Vote on PICO question: yes, 76%; uncertain/neutral, 18%; no, 6% (see PICO question 2 in **Supplement Appendix 2**)
- A2b. For patients with acute UGIB, we suggest *against* using the AIMS65 prognostic score to identify patients who are at very low risk for rebleeding or mortality and thus may not require hospitalization or inpatient endoscopy.
GRADE: conditional recommendation, low-quality evidence. Vote on PICO question: no, 100% (see PICO question 2 in **Supplement Appendix 2**)
- A3. Consider placement of a nasogastric tube in selected patients because the findings may have prognostic value.†
- A4. In patients with acute UGIB without underlying cardiovascular disease, we suggest giving blood transfusions for those with a hemoglobin level <80 g/L.
GRADE: conditional recommendation, low-quality evidence. Vote on PICO question: yes, 75%; uncertain/neutral, 15%; no, 10% (see PICO question 3a in **Supplement Appendix 2**)
- A5. In patients with acute UGIB with underlying cardiovascular disease, we suggest giving blood transfusions at a higher hemoglobin threshold than for those without cardiovascular disease.
GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 80%; uncertain/neutral, 5%; no, 15% (see PICO question 3b in **Supplement Appendix 2**)
- A6. In patients with acute UGIB receiving anticoagulants (vitamin K antagonists, DOACs), we suggest not delaying endoscopy (with or without endoscopic hemostatic therapy).
GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 100% (see PICO question 4 in **Supplement Appendix 2**)
- A7. Promotility agents should not be used routinely before endoscopy to increase the diagnostic yield.‡
- A8. Selected patients with acute ulcer bleeding who are at low risk for rebleeding on the basis of clinical and endoscopic criteria may be discharged promptly after endoscopy.‡
- A9. Pre-endoscopic PPI therapy may be considered to downstage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy.‡

B. Endoscopic management

- B1. Develop institution-specific protocols for multidisciplinary management. Include access to an endoscopist trained in endoscopic hemostasis.†
- B2. Have support staff trained to assist in endoscopy available on an urgent basis.†
- B3: For patients admitted with acute UGIB, we suggest performing early endoscopy (within 24 hours of presentation).
GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 100% (see PICO question 5a in **Appendix 2**)
- B4. Endoscopic hemostatic therapy is not indicated for patients with low-risk stigmata (a clean-based ulcer or a nonprotuberant pigmented dot in an ulcer bed).†
- B5. A finding of a clot in an ulcer bed warrants targeted irrigation in an attempt at dislodgement, with appropriate treatment of the underlying lesion.‡
- B6. The role of endoscopic therapy for ulcers with adherent clots is controversial. Endoscopic therapy may be considered, although intensive PPI therapy alone may be sufficient.‡
- B7. Endoscopic hemostatic therapy is indicated for patients with high-risk stigmata (active bleeding or a visible vessel in an ulcer bed).†
- B8. Epinephrine injection alone provides suboptimal efficacy and should be used in combination with another method.‡
- B9. No single method of endoscopic thermal coaptive therapy is superior to another.†
- B10a. For patients with acutely bleeding ulcers with high-risk stigmata, we recommend endoscopic therapy with thermocoagulation or sclerosant injection.
GRADE: strong recommendation, low-quality evidence. Vote on PICO question: yes, 94%; uncertain/neutral, 6% (see PICO question 6a1 in **Supplement Appendix 2**)
- B10b. For patients with acutely bleeding ulcers with high-risk stigmata, we suggest endoscopic therapy with (through-the-scope) clips.
GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 94%; uncertain/neutral, 6% (see PICO question 6a2 in **Supplement Appendix 2**)
- B11a. In patients with actively bleeding ulcers, we suggest using TC-325 as a temporizing therapy to stop bleeding when conventional endoscopic therapies are not available or fail.
GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 82%; uncertain/neutral, 18% (see PICO question 6b2 in **Supplement Appendix 2**)
- B11b. In patients with actively bleeding ulcers, we suggest *against* using TC-325 as a single therapeutic strategy vs. conventional endoscopic therapy (clips alone, thermocoagulation alone, or combination therapy).
GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 12%; uncertain/neutral, 12%; no, 76% (see PICO question 6b1 in **Supplement Appendix 2**)
- B12. Routine second-look endoscopy is not recommended.‡
- B13. A second attempt at endoscopic therapy is generally recommended in cases of rebleeding.†

C. Pharmacologic management

- C1. H₂RAs are not recommended for patients with acute ulcer bleeding.†
- C2. Somatostatin and octreotide are not routinely recommended for patients with acute ulcer bleeding.†
- C3. For patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy, we recommend using PPI therapy via intravenous loading dose followed by continuous intravenous infusion (as opposed to no treatment or H₂RAs).
GRADE: strong recommendation, moderate-quality evidence. Vote on PICO question: yes, 100% (see PICO question 8a in **Supplement Appendix 2**)
- C4. For patients who present with ulcer bleeding at high risk for rebleeding (that is, an ulcer requiring endoscopic therapy followed by 3 days of high-dose PPI therapy), we suggest using twice-daily oral PPIs (vs. once-daily) through 14 days, followed by once daily.
GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 95%; uncertain/neutral, 5% (see PICO question 10 in **Supplement Appendix 2**)
- C5. Patients should be discharged with a prescription for a single daily-dose oral PPI for a duration as dictated by the underlying cause.‡

Continued on following page

Table 1—Continued**D. Nonendoscopic and nonpharmacologic in-hospital management**

- D1. Patients at low risk after endoscopy can be fed within 24 hours.[†]
- D2. Most patients who have undergone endoscopic hemostasis for high-risk stigmata should be hospitalized for at least 72 hours thereafter.[‡]
- D3. Seek surgical consultation for patients for whom endoscopic therapy has failed.[†]
- D4. Where available, percutaneous embolization can be considered as an alternative to surgery for patients for whom endoscopic therapy has failed.[‡]
- D5. Patients with bleeding peptic ulcers should be tested for *Helicobacter pylori* and receive eradication therapy if it is present, with confirmation of eradication.[‡]
- D6. Negative *H pylori* diagnostic tests obtained in the acute setting should be repeated.[‡]

E. Secondary prophylaxis[§]

- E1. In patients with previous ulcer bleeding who require an NSAID, it should be recognized that treatment with a traditional NSAID plus a PPI or COX-2 inhibitor alone is still associated with a clinically important risk for recurrent ulcer bleeding.[‡]
 - E2. In patients with previous ulcer bleeding who require an NSAID, the combination of a PPI and a COX-2 inhibitor is recommended to reduce the risk for recurrent bleeding from that of COX-2 inhibitors alone.[‡]
 - E3. In patients who receive low-dose ASA and develop acute ulcer bleeding, ASA therapy should be restarted as soon as the risk for cardiovascular complication is thought to outweigh the risk for bleeding.[‡]
 - E4. In patients with previous ulcer bleeding receiving cardiovascular prophylaxis with single- or dual-antiplatelet therapy, we suggest using PPI therapy vs. no PPI therapy.
- GRADE: conditional recommendation, low-quality evidence. Vote on PICO question (single): yes, 95%; uncertain/neutral: 5%. Vote on PICO question (double): yes, 100% (see PICO questions 9a and 9c in Supplement Appendix 2)
- E5. In patients with previous ulcer bleeding requiring continued cardiovascular prophylaxis with anticoagulant therapy (vitamin K antagonists, DOACs), we suggest using PPI therapy vs. no PPI therapy.
- GRADE: conditional recommendation, very low-quality evidence. Vote on PICO question: yes, 85%; uncertain/neutral, 15% (see PICO question 9b in Supplement Appendix 2)

No recommendation statements||

No recommendation A: For patients with acute UGIB, the consensus group could not make a recommendation for or against using the preendoscopic Rockall prognostic scale to identify patients who are at very low risk for rebleeding or mortality and thus may not require hospitalization or inpatient endoscopy.

GRADE: no recommendation, very low-quality evidence. Vote on PICO question: yes, 12%; uncertain/neutral, 18%; no, 71% (see PICO question 2 in Supplement Appendix 2)

No recommendation B: For patients with acute UGIB at high risk for rebleeding or mortality, the consensus group could not make a recommendation for or against performing endoscopy within 12 hours vs. performing endoscopy later.

GRADE: no recommendation, very low-quality evidence. Vote on PICO question: yes, 41%; uncertain/neutral, 47%; no, 12% (see PICO question 5b in Supplement Appendix 2)

No recommendation C: In patients with acutely bleeding ulcers who have undergone endoscopic therapy, the consensus group could not make a recommendation for or against using DEP vs. no DEP to assess the need for further endoscopic therapy.

GRADE: no recommendation, very low-quality evidence. Vote on PICO question: yes, 47%; uncertain/neutral, 41%; no, 12% (see PICO question 7 in Supplement Appendix 2)

No recommendation D: For patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy, the consensus group could not make a recommendation for or against using non-high-dose PPI therapy (as opposed to no treatment or H₂RAs).

GRADE: no recommendation, very low-quality evidence. Vote on PICO question: yes, 24%; uncertain/neutral, 47%; no, 29% (see PICO question 8b in Supplement Appendix 2)

ASA = acetylsalicylic acid; COX-2 = cyclooxygenase-2; DEP = Doppler endoscopic probe; DOAC = direct oral anticoagulant; GRADE = Grading of Recommendations Assessment, Development and Evaluation; H₂RA = H₂-receptor antagonist; NSAID = nonsteroidal anti-inflammatory drug; PICO = patient population, intervention, comparator, and outcome; PPI = proton-pump inhibitor; UGIB = upper gastrointestinal bleeding.

* The strength of each recommendation was assigned by the consensus group, according to the GRADE system, as strong ("we recommend...") or conditional ("we suggest...") on the basis of 4 components: QoE, benefit-harm balance, patients' values and preferences, and resource requirements (18). However, when quality of evidence was low or very low, the strength of the recommendation would typically default (without a vote) to conditional, unless at least 1 of the other 3 factors was overwhelmingly strong.

[†] Recommendation unchanged from the 2003 guidelines. See reference 3 for supporting evidence and discussions.

[‡] Recommendation unchanged from the 2010 guidelines. See reference 4 for supporting evidence and discussions.

[§] Section was titled "Postdischarge, ASA, and NSAIDs" in the 2010 consensus recommendations (4).

|| Voting threshold of ≥75 for either yes or no was not reached.

No Recommendation A

For patients with acute UGIB, the consensus group could not make a recommendation for or against using the preendoscopic Rockall prognostic scale to identify patients who are at very low risk for rebleeding or mortality and thus may not require hospitalization or inpatient endoscopy.

(GRADE for PICO: very low-quality evidence)

Statement A2b

For patients with acute UGIB, we suggest against using the AIMS65 prognostic score to identify patients who are at very low risk for rebleeding or mortality and thus may not require hospitalization or inpatient endoscopy.

(GRADE: conditional recommendation, low-quality evidence)

Key Evidence. Evidence profiles for the 3 best-studied prognostic scores (Glasgow Blatchford [GBS], preendoscopic Rockall, and AIMS65) were considered separately. The QoE review focused on studies that assessed the use of preendoscopic scoring systems to identify patients at very low risk for undesirable outcomes. No randomized trials that directly assessed the clinical impact of using versus not using prognostic scales were identified. Therefore, the evidence was derived from "before-after" studies (28) and studies of diagnostic test accuracy that assessed the surrogate outcome of diagnostic (prognostic) accuracy of the scales.

A before–after study by Stanley and colleagues (28) assessed a strategy of not admitting emergency

department patients with UGIB who were predicted to be at very low risk for undesirable outcomes (GBS of 0). This reduced the number of hospitalization, and no difference was demonstrated in safety outcomes, although the study was not powered for safety outcomes.

The relevant evidence included 2 high-quality systematic reviews and meta-analyses of studies of diagnostic test accuracy (7, 29) as well as 2 additional studies notable for their quality and sample sizes (30, 31). The sensitivity of low cutoff values for detecting patients at high risk for undesirable clinical outcomes was very good for the GBS (0.99) and preendoscopic Rockall score (range, 0.93 to 0.96, but with more heterogeneity), and lower for AIMS65 (range, 0.78 to 0.82) (**Appendix Table 1**, available at Annals.org) (7, 29–31).

For the GBS and AIMS65, the QoE was low, with the evidence being downgraded for indirectness, imprecision, and inconsistency. For the preendoscopic Rockall score, QoE was very low, with the evidence being downgraded for the same reasons plus risk of bias.

Discussion. Use of prognostic scales and early discharge of patients at low risk have the potential to reduce the need for endoscopy, hospital stays, and associated costs without increasing harms. Sensitivity for detecting high-risk patients is a critical outcome, because it is important to avoid incorrectly classifying high risk as low risk when making decisions about early discharge. Specificity is less crucial, because low specificity results in more low-risk patients being hospitalized but not in high-risk patients being discharged. Patient preferences also should be considered; some patients may prefer diagnostic certainty, whereas others may prefer not to be hospitalized. Other factors when considering early discharge include urban versus rural environment, access to hospital or ambulance services, access to out-of-hours endoscopy, and reimbursement issues.

Whether using a prognostic scale results in better patient outcomes than using clinical judgment alone is not known. Because clinical judgment cannot be standardized, the consensus group agreed that use of a prognostic scoring system would help ensure consistent risk assessment and communication. Education is now needed to embed a scoring tool into clinical practice (such as in electronic medical records).

The consensus group suggests the GBS as the preferred prognostic tool because of its high sensitivity (misclassifying $\leq 1\%$ of high-risk patients as low risk). The preendoscopic Rockall scale has good sensitivity, but it may misclassify 4% to 7% of high-risk patients. Given differing views regarding the threshold sensitivity for discharge, the consensus group could not make a recommendation for or against use of the preendoscopic Rockall score.

The AIMS65 was designed to be used with high cutoff values to identify patients at high risk for death (32) rather than those at low risk for safe discharge. The consensus group suggested not using AIMS65 in this setting, because even at low cutoff values approximately 20% of high-risk patients may be misclassified as low risk.

Statement A4

In patients with acute UGIB without underlying cardiovascular disease, we suggest giving blood transfusions for those with a hemoglobin level less than 80 g/L.

(GRADE: conditional recommendation, low-quality evidence)

Key Evidence. Evidence for a hemoglobin threshold for the effectiveness and safety of red blood cell transfusions was available from a summary of studies comparing restrictive (70 to 80 g/L) versus liberal (90 to 100 g/L) transfusion thresholds for patients with acute UGIB (33).

In the systematic review of 5 randomized controlled trials in patients with UGIB ($n = 1965$), restrictive transfusion was associated with a lower risk for all-cause mortality (RR, 0.65 [CI, 0.45 to 0.97]) and further bleeding (RR, 0.58 [CI, 0.40 to 0.84]) (33) (**Appendix Table 2**, available at Annals.org). No subgroup differences were found with regard to risks for myocardial infarction, stroke or transient ischemic attack, or acute kidney injury (33), or to the rate of surgical or radiologic intervention between the 2 strategies (34, 35). These data were downgraded for serious risk of bias and serious indirectness. However, the QoE for the superiority of the restrictive transfusion strategy is higher (less indirectness) than the QoE for specific thresholds of transfusion.

Two other systematic reviews and meta-analyses that provided supportive data on patients in various clinical settings (cardiac surgery, orthopedic surgery, vascular surgery, acute blood loss or trauma, critical care, acute myocardial infarction, and hematologic cancer) including UGIB, found no difference in 30-day mortality, rebleeding, cardiac events, myocardial infarction, or stroke between the 2 strategies in the combined patient groups (36, 37).

Discussion. The data suggest that a restrictive transfusion strategy is beneficial in patients with UGIB (33) and is not associated with adverse events (36, 37). The restrictive threshold led to a decrease in the proportion of patients exposed to transfusions (36, 37) and in the mean number of units transfused (33). A study assessing direct and indirect costs reported that the total cost per red blood cell unit in 2008 was approximately \$760 (38). Although cost per unit may vary greatly across institutions, a restrictive strategy is probably the least expensive.

Only 3 randomized trials provided mortality data in the UGIB-specific review, with 2 high-quality trials providing 98.2% of the weight in the meta-analysis (33). A single-center study found reductions in mortality and rebleeding with a hemoglobin threshold of 70 g/L versus 90 g/L (35), whereas a cluster randomized trial found no reduction in mortality or rebleeding with a threshold of 80 g/L versus 100 g/L (34). Although it did not look at hemoglobin thresholds, 1 trial in UGIB patients with hemodynamic instability found no difference in mortality between early versus delayed blood transfusion; however, the study was underpowered (RR, 5.4 [CI, 0.3 to 107.1]) (39).

Factors that may affect the timing of transfusions include the availability of venipuncture staff, capacity for frequent assessments, timing of blood typing, avail-

ability of units, hemodilution factors, and degree of hemodynamic stability. In addition, some patients may have underlying, undiagnosed cardiovascular disease, potentially placing them at higher risk for negative outcomes. Therefore, the consensus group suggested that a more conservative hemoglobin threshold of 80 g/L is prudent, with a target of greater than 80 g/L. The threshold recommendation does not apply to patients with exsanguinating bleeding. In the setting of acute blood loss, hemoglobin values may initially remain unchanged from baseline because of plasma equilibrium times. In such situations, transfusion should not be dictated by current hemoglobin level alone but should take into account the predicted drop in hemoglobin and the patient's clinical status.

Statement A5

In patients with acute UGIB and underlying cardiovascular disease, we suggest giving blood transfusions at a higher hemoglobin threshold than for those without cardiovascular disease.

(GRADE: conditional recommendation, very low-quality evidence)

Key Evidence. Two meta-analyses, 1 in patients with UGIB (33) and 1 in patients with cardiovascular disease in various clinical settings (40), included an analysis of 1 randomized trial (34) that provided subgroup data on patients with and without cardiovascular disease. This small, underpowered trial (34) found no significant difference between liberal (hemoglobin threshold, 100 g/L) and restrictive (hemoglobin threshold, 80 g/L) transfusion with regard to mortality (RR, 4.10 [CI, 0.86 to 19.47]) (40) or further bleeding in adults with or without ischemic heart disease (RR, 0.50 [CI, 0.23 to 1.12], and RR, 0.69 [CI, 0.13 to 3.77]) (33). This study was downgraded for serious risk of bias (lack of blinding, possible selection bias) and very serious imprecision (very small sample size).

Reanalysis of the overall data from the meta-analysis of 11 trials in patients with cardiovascular disease (40) found no significant differences between the liberal (90 to 113 g/L) and restrictive (70 to 97 g/L) strategies with regard to 30-day mortality (RR, 0.87 [CI, 0.67 to 1.13]) or acute pulmonary edema (RR, 1.58 [CI, 0.55 to 4.53]) but did find a reduced risk for cardiovascular events with the liberal transfusion strategy (RR, 0.56 [CI, 0.37 to 0.85]). This analysis was downgraded for serious risk of bias, very serious indirectness, and serious imprecision. Because of the variation in outcomes included in the trials as well as in the meta-analyses, several sensitivity analyses were conducted. Although the results became more imprecise, the direction of effect did not change.

Discussion. The data suggest that a more liberal hemoglobin threshold for transfusion may be associated with a lower risk for cardiovascular events in patients with cardiovascular disease. This is based on data from studies in various clinical settings with heterogeneous patient subgroups (such as those with coronary syndromes, ischemic heart disease, congestive heart failure, peripheral vascular disease, or stroke or those with only cardiovascular risk factors, such as hypertension and diabetes). The effects of liberal versus restrictive transfusion strategies may differ among various subgroups. In addition, various definitions were used for the restrictive and liberal groups, including hemoglobin levels and the presence of anemia, and hemoglobin cutoff values varied.

On the basis of these limited data, the consensus group suggested that a higher hemoglobin threshold be considered in patients with cardiovascular disease than in those without it (<80 g/L; statement A4). The group did not recommend a specific cutoff, stating that a cutoff would depend on other factors, including the patient's clinical status, the type and severity of cardiovascular disease, and the severity of bleeding. Guidelines from NICE recommend a higher transfusion level for patients with cardiovascular disease than for those without it, whereas the AABB (formerly known as the American Association of Blood Banks) (41) recommends a hemoglobin threshold of 80 g/L for patients with cardiovascular disease, compared with 70 g/L for those without it. Again, this statement does not apply to patients with exsanguinating bleeding, who may require more liberal transfusion.

Statement A6

In patients with acute UGIB receiving anticoagulants (vitamin K antagonists, direct oral anticoagulants), we suggest not delaying endoscopy (with or without endoscopic hemostatic therapy).

(GRADE: conditional recommendation, very low-quality evidence)

Key Evidence. No systematic reviews, randomized trials, or observational studies that specifically addressed the timing of endoscopy as a primary outcome in patients receiving anticoagulants were found. A retrospective cohort study in patients with acute UGIB (47%) or lower gastrointestinal bleeding compared 157 patients using anticoagulants with 157 matched control participants (42). An international normalized ratio (INR) greater than 2.5 was seen in 22.9% of the patients receiving anticoagulants versus 6.4% of the control participants. No statistically significant differences were observed in rates of rebleeding (13.4% vs. 15.9%; $P = 0.52$) or thromboembolism (5.7% vs. 3.2%; $P = 0.68$) between the anticoagulant and control groups. Among the patients receiving anticoagulants, early endoscopy (<24 hours after onset) was not associated with rebleeding (OR, 0.7 [CI, 0.3 to 1.8]), thromboembolic events (OR, 0.5 [CI, 0.1 to 2.1]), or endoscopy-related adverse events (0%). Rebleeding also was not associated with an INR of 2.5 or greater (OR, 0.7 [CI, 0.2 to 2.3]). In contrast, probably because of rapid correction of INR periendoscopically (43, 44), thromboembolism was associated with an INR of 2.5 or greater (OR, 7.3 [CI, 1.5 to 35.3]) and the use of a reversal agent (OR, 4.1 [CI, 1.0 to 16.5]) (42).

No differences were found in rebleeding or thromboembolism risks between patients receiving direct oral anticoagulants (DOACs) and those receiving warfarin. However, patients using warfarin had a greater need for transfusion (4.3 ± 5.9 units vs. 2.2 ± 3.1 units; $P = 0.046$). Periendoscopic use of a reversal agent (vitamin K) was associated with a higher risk for thrombo-

embolism but not rebleeding, whereas anticoagulant interruption did not affect the risk for either outcome. The results of anticoagulant use in patients with UGIB were not reported separately, but UGIB was associated with a higher rate of endoscopic therapy and transfusions compared with lower gastrointestinal bleeding, suggesting that the combined results may not be entirely generalizable to patients with UGIB (42). This study was downgraded for serious indirectness and imprecision.

Discussion. For patients receiving anticoagulants, the 2010 UGIB guidelines suggested that coagulopathy be corrected but that endoscopy not be delayed (4). This recommendation was made on the basis of cohort studies suggesting that early endoscopy (≤ 24 hours) may be performed safely in patients using anticoagulants after partial correction of the INR, without an increase in rebleeding rates versus persons not using anticoagulants (45, 46). In the study by Nagata and colleagues (42), anticoagulant interruption did not affect risks and no increased risk was found in patients with an INR of 2.5 or greater. The consensus group cannot specify an INR cutoff level that should prompt correction of the INR.

Although available new data were limited, the introduction of DOACs prompted the update to this recommendation. Nagata and colleagues (42) found that patients receiving DOACs had less need for transfusion than those receiving warfarin. The DOACs have a short half-life—8 to 12 hours—and their anticoagulant effect resolves more rapidly than that of warfarin. Reversal agents are now available, although criteria for their use in patients with UGIB are not yet defined and availability may be limited in some areas. Whether the type or extent of anticoagulation would affect the type of endoscopic hemostatic therapy was not addressed.

Other guidelines recommend administration of vitamin K supplemented with intravenous prothrombin complex concentrate (PCC), with use of fresh frozen plasma only if PCC is unavailable (8, 9, 47). Four-factor PCC has demonstrated efficacy in correcting INR (43, 44), as have specifically targeted anticoagulant reversal agents (48, 49). Some data suggest a higher risk for thrombosis with rapid reversal of anticoagulation (42, 48), but this is beyond the scope of these guidelines.

The consensus group agreed that the degree of coagulopathy should be assessed objectively before therapeutic decisions are made. The anticoagulant agent, patient physiology, and patient compliance with therapy may affect anticoagulation. Because of the recognized benefits of early endoscopy (statement B3), coagulopathy should be treated as necessary but endoscopy should not be delayed.

Section B: Endoscopic Management

Statement B3

For patients admitted with acute UGIB, we suggest performing early endoscopy (within 24 hours of presentation).

(GRADE: conditional recommendation, very low-quality evidence)

Key Evidence. Evidence for early endoscopy was assessed separately for patients at low and high risk for unfavorable outcomes (death, rebleeding) (Supplement Appendix 2).

Low-risk patients: Two systematic reviews (4, 50) including 3 randomized trials (51–53) assessed the timing of endoscopy in patients with UGIB. Two of the trials included low-risk patients randomly assigned to early versus later endoscopy (within 1 to 2 hours vs. 1 to 2 days [52], or within 6 hours vs. 48 hours [53]). No differences in mortality or rebleeding were found between groups in either trial (52, 53), but 1 study found that early endoscopy reduced length of stay and cost of care (52). The QoE was downgraded for serious risk of bias, indirectness, and very serious imprecision.

Observational studies were seriously confounded by severity of bleeding and comorbidity, which may bias the results in favor or against early endoscopy. Three retrospective cohort studies included exclusively or separately reported data on low-risk patients and adjusted for confounders (54–56). In 1 study, urgent endoscopy was a predictor of negative outcomes (composite of death; rebleeding; and surgical, radiologic, or endoscopic intervention) among low-risk patients with UGIB (adjusted OR, 0.71 per 6 hours [CI, 0.55 to 0.91]) (54). The definition of low risk in this study was a GBS less than 12, instead of the more common GBS of 2 or less. In another study using the same criterion, time to endoscopy was not associated with in-hospital mortality (55). In the largest study, among low-risk patients endoscopy within 24 hours was associated with lower in-hospital mortality (OR, 0.48 [CI, 0.24 to 0.97]), but not rebleeding, compared with later endoscopy (56). The QoE was downgraded for serious risk of bias and indirectness.

High-risk patients: See text under "No Recommendation B."

Discussion. Safety concerns regarding early endoscopy, including the potential for inadequate resuscitation before the procedure and the need to perform endoscopy during off-hours when fewer endoscopy resources are available, must be weighed against the potential for worse outcomes due to ongoing bleeding. Because such concerns are less of an issue in low-risk patients than in high-risk ones, the decision to perform early endoscopy in those at low risk is driven mainly by cost and length of stay.

The 2010 UGIB guidelines recommended early endoscopy (within 24 hours of presentation) for most patients with acute UGIB (4). This recommendation was based on data suggesting that early endoscopy allowed for safe discharge of low-risk patients, improved outcomes for high-risk patients, and reduced resource use (4).

Although the data were very low quality, they support the conclusion that for low-risk patients, early endoscopy may be performed safely and can reduce resource use. To reduce hospitalization and costs, the endoscopist's recommendations for early discharge of low-risk patients must be embraced by the attending physician. In the trial in which early endoscopy did not reduce resource use, only 21% of eligible patients were discharged early (53). Early endoscopy may also yield

more high-risk endoscopic stigmata that would have resolved spontaneously (52, 53), which may offset benefits in terms of hospitalization.

Availability of endoscopy resources is an important consideration. A meta-analysis of 20 cohort studies found that patients with UGIB hospitalized during off-hours were less likely to undergo endoscopy within 24 hours and had higher mortality rates (57). This was not the case in hospitals with formal out-of-hours endoscopy services.

On the basis of the available data, the consensus group suggested that endoscopy be performed within 24 hours of presentation, both for low- and high-risk patients.

For high-risk patients, see the discussion under "No Recommendation B."

No Recommendation B

For patients with acute UGIB at high risk for rebleeding or mortality, the consensus group could not make a recommendation for or against performing endoscopy within 12 hours versus performing endoscopy later.

(GRADE for PICO: very low-quality evidence)

Key Evidence. No randomized trial assessed the timing of endoscopy specifically in high-risk patients with UGIB. One trial in patients with peptic ulcer bleeding, including a high proportion of high-risk patients (44% with shock), found no difference in mortality with endoscopy before or after 12 hours (Appendix Table 3, available at Annals.org) (51). The QoE was downgraded for serious risk of bias and indirectness, and very serious imprecision.

Seven observational studies in high-risk patients with UGIB were assessed (54–56, 58–61); however, only 2 provided adjusted results for mortality (Appendix Table 3) (56, 58). One study found a reduction in mortality with very early endoscopy (<6 hours) compared with later endoscopy (>6 to ≤48 hours) (58). A large cohort study suggested that among hemodynamically unstable patients, very early endoscopy (≤6 hours) may increase mortality risk, whereas early endoscopy between 6 and 24 hours may reduce mortality risk compared with endoscopy outside that time frame (56). These data were downgraded for serious risk of bias, inconsistency, and imprecision.

Unadjusted results from observational studies were not considered for this guideline. Such results conflict and are difficult to interpret, because the effects of the confounders are bidirectional. More severe bleeding or comorbid conditions are associated with worse outcomes and present a clear bias toward more rapid endoscopy; however, if the severity is too great, then endoscopy might be delayed.

Discussion. Statement B3 recommends endoscopy within 24 hours for patients with UGIB. Whether high-risk patients would benefit from very early endoscopy (within 12 hours) remains unanswered. Although active bleeding is associated with a poor prognosis, patients who are hemodynamically unstable may have more ad-

verse outcomes during endoscopy. Therefore, very early endoscopy may be associated with a paradoxical negative effect in high-risk patients (56).

Because of conflicting data, widely variable patient populations (such as those differing in age, bleeding severity, comorbid conditions, or hemodynamic instability), and the potential for harm, the consensus group concluded that insufficient data exist to recommend for or against endoscopy more urgently than the 24-hour window in high-risk patients. Practitioners are reminded that for patients with suspected variceal bleeding, existing recommendations suggest endoscopy within 12 hours of presentation (62, 63).

Statement B10a

For patients with acutely bleeding ulcers with high-risk stigmata, we recommend endoscopic therapy with thermocoagulation or sclerosant injection.

(GRADE: strong recommendation, low-quality evidence)

Statement B10b

For patients with acutely bleeding ulcers with high-risk stigmata, we suggest endoscopic therapy with (through-the-scope) clips.

(GRADE: conditional recommendation, very low-quality evidence)

Key Evidence. Systematic reviews and meta-analyses have assessed the role of endoscopic therapy in patients with UGIB (64–67). One review looked only at epinephrine injection alone and in combination (66), whereas another was suboptimally reported (67). For this guideline, the evidence was derived mainly from the 2009 reviews by Laine and McQuaid (64) and Barkun and colleagues (65), which were updated via new literature searches from 2006 to 2018. For the comparison of endoscopic treatment with no endoscopic treatment, no new randomized trials were found; therefore, these analyses remain unchanged (64, 65).

Compared with pharmacotherapy or no treatment, thermocoagulation (heater probe or bipolar electrocoagulation) or sclerosant injection reduced mortality and rebleeding (64, 65). No randomized trials were found comparing hemoclips with no treatment.

The QoE was downgraded for risk of bias (mainly lack of blinding). The QoE for efficacy was moderate for all therapies combined and for sclerosant injection; QoE was low for thermocoagulation and was downgraded further for imprecision.

For comparisons of various active treatments, the meta-analysis by Barkun and colleagues (65) was updated with 3 new trials (68–70) (Supplement Appendix 2). No differences were found for mortality or rebleeding in comparisons of thermocoagulation, sclerosant injection, hemoclips, and combination therapies (64, 65). Meta-analysis of data from 2 trials showed that hemoclips were superior to epinephrine injection alone with regard to rebleeding (RR, 0.17 [CI, 0.05 to 0.55]) but not mortality (RR, 2.15 [CI, 0.59 to 7.78]) (68, 71).

Discussion. Endoscopic hemostatic therapy has been well documented to improve outcomes. The con-

sensus group agreed with the prior statements that endoscopic therapy is indicated in patients with high-risk stigmata (active bleeding, visible vessel) and may be considered in patients with an adherent clot (statements B6 and B7). Debate continues with regard to the optimal method. Sclerosant therapy is used less commonly in clinical practice but remains a viable option. Lack of routine PPI therapy and the constantly changing prevalence of *Helicobacter pylori* may affect the results of older studies. The group chose not to address other endoscopic mechanical techniques, such as over-the-scope clips.

On the basis of the available data, a strong recommendation was made for thermocoagulation or sclerosant injections, whereas hemoclips were suggested (conditional recommendation). However, the data generally have failed to show superiority of any one method, and each may be useful depending on location of the bleeding source and patient characteristics.

Statement B11a

In patients with actively bleeding ulcers, we suggest using TC-325 as a temporizing therapy to stop bleeding when conventional endoscopic therapies are not available or fail.

(GRADE: conditional recommendation, very low-quality evidence)

Statement B11b

In patients with actively bleeding ulcers, we suggest against using TC-325 as a single therapeutic strategy versus conventional endoscopic therapy (clips alone, thermocoagulation alone, or combination therapy).

(GRADE: conditional recommendation, very low-quality evidence)

Key Evidence. Evidence for the efficacy of TC-325 (hemostatic powder spray) was available from 1 small underpowered trial (72) and from observational studies (73, 74). The trial randomly assigned 20 patients and found no statistically significant differences in initial hemostasis (90% vs. 100%) or rebleeding (33% vs. 10%) with TC-325 monotherapy versus a conventional combination endoscopic technique (epinephrine injection with either hemoclip or heater probe application) (72). Among 8 patients with actively bleeding (spurting or oozing) ulcers, 4 of 5 in the TC-325 group had successful initial hemostasis, but 3 had rebleeding. In contrast, all 3 in the conventional treatment group achieved initial hemostasis and none had rebleeding.

A systematic review of observational data found an immediate hemostasis rate of 90% but very high rebleeding rates (72-hour, 19%; 7-day, 22%) among 86 patients with ulcer bleeds treated with TC-325 (73). Rebleeding rates (72-hour and 7-day) were highest among patients with active bleeding (spurting, 40% and 60%; oozing, 13% and 16%). Another large prospective cohort study included 202 patients with bleeding treated with TC-325; the rate of initial hemostasis was 97%, with day 8 and day 30 rebleeding rates of 27% and 34%, respectively (74).

Evidence was downgraded for serious risk of bias (lack of blinding) and very serious imprecision (small sample sizes and low total number of events).

Discussion. The success of TC-325 hemostatic powder spray seems to depend on the cause of bleeding and whether the powder is used alone or in combination with other hemostatic therapy. The powder adheres only to actively bleeding lesions (73), its residency time is 24 hours or less (75), and it does not induce tissue healing (73).

TC-325 use in UGIB is associated with a low complication rate, although rare cases of perforation and transient biliary obstruction have been reported (73, 76). Additional experience is needed to define the safety profile more clearly.

Decision modeling suggests that a strategy of conventional therapy followed by TC-325 improved the effectiveness and was less costly compared with conventional therapy alone or TC-325 alone in most patient populations with nonvariceal UGIB (77). TC-325 followed by conventional therapy was the most effective strategy for nonulcer high-risk bleeding lesions at low risk for delayed rebleeding.

On the basis of TC-325's mechanism of action and the clinical evidence, the consensus group concluded that TC-325 monotherapy may not adequately treat ulcers with high-risk stigmata, but may be useful as a temporary measure to stop bleeding, and that second-look endoscopy or a second hemostatic technique should be used.

No Recommendation C

In patients with acutely bleeding ulcers who have undergone endoscopic therapy, the consensus group could not make a recommendation for or against Doppler endoscopic probe (DEP) versus no DEP to assess the need for further endoscopic therapy.

(GRADE for PICO: very low-quality evidence)

Key Evidence. Two randomized trials compared DEP-guided versus conventional endoscopic treatment in patients with acute UGIB (78, 79). In a 1997 study by Kohler and colleagues (78), all patients had peptic ulcer bleeding, but actively bleeding lesions were excluded. Endoscopic treatment was directed by Doppler findings, injection therapy alone was used, and second-look endoscopy was performed for all patients. In a 2017 study by Jensen and colleagues (79), most of the 148 patients with severe nonvariceal UGIB (85%) had peptic ulcer bleeding (active bleeding, visible vessel, adherent clot, or flat spot). A meta-analysis of these 2 studies (78, 79) was performed for this guideline (Supplement Appendix 2). However, at the face-to-face meeting, it was decided to focus the evidence profiles on the trial by Jensen and colleagues, which reported data for patients with high-risk lesions (active bleeding, visible vessel) or adherent clot. Data for patients with low-risk lesions (flat spot) were considered indirect, because these lesions are not routinely subjected to endoscopic therapy. In Jensen and colleagues' study (79), DEP reduced rebleeding for all lesions (RR, 0.42 [CI, 0.20 to 0.90]) but not for high-risk lesions (RR, 0.50 [CI, 0.24 to 1.08]).

Overall, the QoE was downgraded for risk of bias, indirectness (population and intervention), and imprecision (moderate sample size).

Discussion. More studies are needed to determine whether DEP would be useful to guide endoscopic treatment decisions before or after initial therapy or in both settings. One study found only 58% agreement between DEP and findings at index endoscopy (78). Used to determine the need for additional therapy, DEP would be an add-on test with conventional endoscopic treatment for high-risk lesions, which would add cost related to the DEP technology. A cost-minimization analysis found that DEP-directed combination endoscopic therapy was cost-effective compared with combination therapy only for the management of high-risk patients (80).

The consensus group concluded that data suggesting efficacy for DEP is very limited and that lack of availability and expertise in many centers affects feasibility. The group generally agreed that although making a recommendation for or against DEP to manage UGIB is premature, it has the potential to alter the usual approach to visually assessing bleeding lesion risk when evaluating the need for, and adequacy of, endoscopic hemostasis.

Section C: Pharmacologic Management

Statement C3

For patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy, we recommend using PPI therapy via intravenous loading dose followed by continuous intravenous infusion (as opposed to no treatment or H₂-receptor antagonists).

(GRADE: strong recommendation, moderate-quality evidence)

No Recommendation D

For patients with bleeding ulcers with high-risk stigmata who have undergone successful endoscopic therapy, the consensus group could not make a recommendation for or against non-high-dose PPI therapy (as opposed to no treatment or H₂-receptor antagonists).

(GRADE for PICO: very low-quality evidence)

Key Evidence. Two Cochrane reviews on PPIs in UGIB were updated for this guideline (81, 82). The first

(81), which included 24 trials comparing PPIs with placebo or H₂-receptor antagonists (H₂RAs), was updated with an additional 14 randomized trials. Of these, 12 included data on patients with high-risk stigmata (active bleeding, visible vessel) or adherent clot who had undergone appropriate endoscopic therapy. There was moderate QoE that PPI therapy versus no PPIs or H₂RAs reduced mortality risk (OR, 0.56 [CI, 0.34 to 0.94]) and high QoE that it reduced rebleeding risk (OR, 0.43 [CI, 0.29 to 0.63]) (Table 2). The evidence for mortality was downgraded because of serious risk of bias (mainly lack of blinding in some trials).

The second meta-analysis (82), which included 22 trials comparing various PPI regimens, was updated with an additional 18 trials. Of these, 25 compared high-dose PPIs (defined as an 80-mg intravenous bolus followed by 72 hours of an 8-mg/h continuous intravenous infusion) with non-high-dose PPIs, and 17 included data on patients with high-risk stigmata or adherent clots who had undergone endoscopic treatment. No differences were found in the risk for mortality or rebleeding between high-dose and non-high-dose PPIs (low and moderate QoE) or between high-dose and oral PPIs (very low and low QoE) (Table 2). Indirect comparisons between high-dose PPIs and no treatment or H₂RAs and between non-high-dose PPIs and no treatment or H₂RAs yielded very low QoE for the superiority of high-dose PPI therapy (update of [81]). Moderate QoE supported the superiority of non-high-dose PPIs versus no PPIs for the outcome of rebleeding, but the QoE for mortality was low. The evidence was downgraded, mainly because of imprecision and risk of bias for some comparisons.

Adverse effects were poorly reported in most of the studies. Overall, no consistent signal of a difference was found between PPI therapy and placebo or H₂RAs, between high-dose and non-high-dose PPIs, or between intravenous and oral PPI therapy. The exception was an increased risk for thrombophlebitis with PPIs administered intravenously versus orally.

Discussion. High-dose PPI therapy (that is, an 80-mg intravenous bolus followed by 72 hours of 8-mg/h continuous intravenous infusion) reduces rebleeding and mortality. Because non-high-dose therapy has been associated with a reduction in rebleeding

Table 2. Pooled ORs and Absolute Risks of Unfavorable Outcomes, According to PPI Regimen, in Patients with High-Risk Stigmata Who Had Endoscopic Therapy

Studies	Active Treatment, n/N (%)	Control, n/N (%)	OR (95% CI)*	Absolute Effect, per 1000 Persons (95% CI)
PPIs vs. placebo or H₂RAs				
Deaths: 1 SR and MA (update of reference 81); 10 RCTs Rebleeds: 1 SR and MA (update of reference 81); 12 RCTs	24/1202 (2.0) 88/1269 (6.9)	43/1220 (3.5) 169/1277 (13.2)	0.56 (0.34 to 0.94) 0.43 (0.29 to 0.63)	-15 (-23 to -2) -71 (-90 to -45)
High-dose vs. non-high-dose PPIs				
Deaths: 1 SR and MA (update of reference 82); 15 RCTs Rebleeds: 1 SR and MA (update of reference 82); 17 RCTs	28/1042 (2.7) 126/1175 (10.7)	27/1027 (2.6) 107/1191 (9.0)	1.02 (0.59 to 1.76) 1.25 (0.93 to 1.66)	1 (-11 to +20) 20 (-6 to +51)
High-dose vs. oral PPIs				
Deaths: 1 SR and MA (update of reference 81); 3 RCTs Rebleeds: 1 SR and MA (update of reference 81); 4 RCTs	0/117 (0) 16/235 (6.8)	2/116 (1.7) 15/242 (6.2)	0.31 (0.04 to 2.93) 1.09 (0.54 to 2.17)	-12 (-17 to +33) 6 (-29 to +72)

OR = odds ratio; H₂RA = H₂-receptor antagonist; MA = meta-analysis; PPI = proton-pump inhibitor; RCT = randomized controlled trial; SR = systematic review.

* Boldface signifies statistically significant results.

but not mortality compared with no PPI therapy, a majority of the consensus group did not vote to recommend non-high-dose PPI therapy. The consensus group is not confident that the precision of the estimates of absolute differences between high- and non-high-dose PPI therapy regarding mortality and rebleeding is sufficient to consider the 2 therapies equivalent. Studies of non-high-dose PPI therapy are complicated by different dosing regimens and methods of administration, including continuous intravenous infusion, intravenous bolus, and oral regimens.

Cost-effectiveness studies have suggested that high-dose intravenous PPIs after successful endoscopic hemostasis improve outcomes at a modest cost increase relative to non-high-dose intravenous or oral PPI strategies (83–86). In addition, the incremental costs of different PPI regimens (continuous or intermittent, before or after endoscopic therapy) are modest compared with total per-patient costs.

The consensus group concluded that the evidence supports a strong recommendation for high-dose PPIs for patients with bleeding ulcers with high-risk stigmata (active bleeding or visible vessel) who have had successful endoscopic therapy. The recommendation for patients with adherent clots remains unchanged (statement B6) and includes endoscopic therapy or consideration of PPI therapy alone (Table 1). Given the demonstrated benefits on rebleeding outcomes and that the costs and availability of intravenous formulations may be issues in some areas, the consensus group also did not make a recommendation against using lower PPI doses.

Statement C4

For patients who present with ulcer bleeding at high risk for rebleeding (that is, an ulcer requiring endoscopic therapy followed by 3 days of high-dose PPI therapy), we suggest using twice-daily oral PPIs (vs. once daily) through 14 days, followed by once daily.

(GRADE: conditional recommendation, very low-quality evidence)

Key Evidence. One trial enrolled patients at high-risk for rebleeding (Rockall scores ≥6) who had undergone successful endoscopic therapy and received 3 days of high-dose PPI therapy (intravenous esomeprazole, 80-mg loading dose followed by 8-mg/h continuous infusion) (87). Patients were randomly assigned to receive oral esomeprazole, 40 mg, either once or twice daily for 11 days (days 3 to 14). All patients received an additional 2 weeks of once-daily PPI therapy. A reduction was found in rebleeding (RR, 0.37 [CI, 0.19 to 0.73]) but not mortality rates (RR, 0.38 [CI, 0.10 to 1.38]) with twice- versus once-daily PPIs. The QoE was downgraded for risk of bias and imprecision.

Discussion. Based on the data suggesting superiority over the standard dosage for rebleeding, the consensus group suggested the use of twice-daily PPIs to complete 2 weeks of PPI therapy, after 3 days of high-dose therapy.

Section D: Nonendoscopic and Nonpharmacologic In-Hospital Management

No updates to the 2010 international UGIB guidelines (4).

Section E: Secondary Prophylaxis

Statement E4

In patients with previous ulcer bleeding receiving cardiovascular prophylaxis with single- or dual-antiplatelet therapy, we suggest using PPI therapy versus no PPI therapy.

(GRADE: conditional recommendation, low-quality evidence)

Key Evidence. *Single-antiplatelet therapy:* Evidence for the role of PPI therapy in patients receiving single-agent antiplatelet therapy was available from 5 randomized trials (88–92) comparing PPIs versus no PPIs in patients requiring continued antiplatelet therapy. Because of heterogeneity in study designs and comparison groups, a meta-analysis of all 5 studies was not done. All 5 trials were conducted in Hong Kong. A history of *H pylori* infection and eradication treatment was common.

One trial found PPIs to be more effective than placebo in reducing recurrent complications (bleeding, perforation, and obstruction) (RR, 0.11 [CI, 0.01 to 0.84]) in patients with previous ulcer complications who had successful *H pylori* eradication and required continued antiplatelet therapy (acetylsalicylic acid [ASA]) (88). A meta-analysis of 2 trials showed that PPIs plus ASA reduced rebleeding rates versus clopidogrel alone (RR, 0.07 [CI, 0.01 to 0.34]) in patients with previous ASA-associated ulcer bleeding who did not have *H pylori* infection or who had it successfully eradicated (90, 91). In patients with previous ASA-associated ulcer bleeding, trials found no difference between PPIs and eradication treatment in those with *H pylori* infection (89), or between PPIs and H₂RAs in patients without *H pylori* infection or those in whom *H pylori* infection was eradicated (92). Two trials found no differences in mortality rates between PPI and placebo groups (88) or between PPIs plus ASA versus clopidogrel (89).

The evidence was downgraded, primarily for very serious imprecision (small studies, very low number of events).

Dual-antiplatelet therapy (DAPT): No randomized trials were found assessing the use of PPIs in patients receiving DAPT who had a history of ulcer bleeding. Two systematic reviews were found in patients receiving DAPT after percutaneous coronary intervention or in the presence of coronary artery disease (93, 94). The reporting and methodological quality of both reviews were suboptimal, with inclusion of studies that were not eligible (for example, because of patients not receiving DAPT, incorrect comparisons, or double counting). A meta-analysis conducted for this guideline included 4 randomized trials ($n = 4805$) comparing PPI versus no PPI therapy in patients receiving prophylactic DAPT (ASA and clopidogrel). The largest study was international (95), whereas the other 3 were conducted in China (96–98). The meta-analysis showed a reduction in gastrointestinal bleeding risk with PPI therapy versus placebo ($n = 4$ studies; RR, 0.25 [CI, 0.14 to 0.45]) and

no effects on mortality ($n = 3$ studies; RR, 1.02 [CI, 0.68 to 1.54]) or myocardial infarction risk ($n = 2$ studies; RR, 0.96 [CI, 0.51 to 1.81]).

No studies were found that assessed ASA in combination with other antiplatelet drugs, such as prasugrel or ticagrelor. The evidence was downgraded for high or unclear risk of bias in the Chinese studies and for serious indirectness in all 4 trials (most patients did not have a history of ulcer bleeding).

Discussion. The evidence consistently supports a benefit with PPI therapy in patients with previous ulcer bleeding who continue single- or dual-antiplatelet therapy and suggest that PPI therapy is superior to clopidogrel alone in patients receiving ASA.

Most patients in these studies had *H pylori* infection before PPI therapy, and in 1 study eradication treatment alone was as effective as PPI therapy (89). Observational data suggest that ulcer rebleeding risk in patients receiving low-dose ASA may be reduced among those who had *H pylori* infection eradicated compared with those who were never infected (99). It is anticipated that PPI therapy should be beneficial in populations with lower rates of *H pylori* infection, although the magnitude of effect may be decreased. The consensus group suggested that eradication therapy alone may be sufficient to reduce bleeding risk for some patients with *H pylori* infection, with only incremental benefits associated with additional PPI therapy.

Although various adverse events have been reported with PPI therapy (statement E5), the systematic review and meta-analysis conducted for this guideline found no increased risk for myocardial infarction in patients receiving DAPT.

On the basis of the evidence, the consensus group suggests PPI therapy to prevent rebleeding in most patients who require single- or dual-antiplatelet therapy for a duration consistent with the ongoing need for antiplatelet therapy.

Statement E5

In patients with previous ulcer bleeding requiring continued cardiovascular prophylaxis with anticoagulant therapy (vitamin K antagonists, DOACs), we suggest using PPI therapy versus no PPI therapy.

(GRADE: conditional recommendation, very low-quality evidence)

Key Evidence. Compared with no PPI therapy, the use of PPIs in patients receiving anticoagulant therapy was associated with a reduced risk for rebleeding in 2 large cohort studies (100, 101) but not in 3 case-control studies (102-104). Most patients included in these studies did not have a history of ulcer bleeding. In 1 small case-control study in patients with a history of UGIB, rebleeding risk was not significantly reduced in patients receiving warfarin plus PPIs (RR, 1.93 [CI, 0.23 to 16.28]) compared with those not receiving warfarin (103). In contrast, in 1 of the cohort studies the greatest risk reduction with PPI therapy versus no PPI therapy was seen in patients with a history of peptic

ulcers or gastrointestinal bleeding (adjusted incidence rate ratio, 0.14 [CI, 0.06 to 0.30]) (101). None of the included studies assessed mortality.

The evidence was downgraded for indirectness (most patients did not have previous ulcer bleeding).

Discussion. A history of ulcer bleeding is associated with an increased risk for bleeding, and although anticoagulants do not cause ulcer bleeding, they increase the risk for bleeding from sites that have mucosal breaks.

Meta-analyses of primarily observational studies have suggested potential associations between PPI therapy and adverse effects, including community-acquired pneumonia, hip fracture, colorectal cancer, chronic kidney disease, community-acquired enteric infection, and *Clostridium difficile* infection (105-109). An analysis of factors, such as consistency, specificity, temporality, and biological plausibility, as well as confounding factors, showed that the evidence for causality is very weak (110). The consensus group concluded that for high-risk patients with an ongoing need for anticoagulants, the evidence suggests that the benefits of secondary prophylaxis outweigh the risks. The unproven potential and rare safety concerns should not prevent treatment for patients at risk for life-threatening consequences.

ONGOING AND RESEARCH RECOMMENDATIONS

Although UGIB management has improved substantially during the past 2 decades, areas remain in which more data are needed (Appendix Table 4, available at Annals.org). In particular, more studies are needed to define the benefits of specific prognostic scales, the role of a restrictive versus liberal transfusion practice in patients with UGIB and cardiovascular disease, optimal PPI regimens, optimal endoscopic hemostatic therapies, and the role of PPIs in patients receiving antithrombotic therapy. Planned analyses from the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial may clarify the efficacy and safety of PPIs versus no PPIs in patients receiving anticoagulant therapy (111).

Several pertinent articles that were not available at the time of this consensus have been published since the literature searches were completed (as of May 2018). These include a large randomized trial in patients with cardiovascular disease that compared the efficacy and safety of DOACs or ASA with or without PPI therapy (112, 113). Randomized trials have assessed PPIs versus H₂RAs for recurrent UGIB (114), as well as endoscopic therapy with hemostatic powder and hemoclips (115, 116). In addition, the use of DEP to guide hemostasis has been studied further (117). Although a discussion of over-the-scope clips for recurrent peptic ulcer bleeding is beyond the scope of the statements addressed in this guideline, data are emerging (118). These are just some examples of new or ongoing studies that have the potential to affect clinical practice, but they may not do so. The consensus group cannot comment on the results of these trials, because a systematic

literature search was not performed and the GRADE approach was not applied.

APPLICABILITY AND IMPLEMENTATION ISSUES

Plans are under way to develop a user-friendly clinical algorithm for UGIB management, slide presentations, short videos, and CAG podcasts. The guidelines and supporting materials will be disseminated to all participating societies and regions through such venues as symposia sessions or workshops at society meetings. Major recommendations will be posted on society and government health Web sites. Finally, we anticipate that these guidelines will continue to be updated as new data become available.

From McGill University, Montreal, Quebec, Canada (A.N.B.); McGill University, Montreal, Quebec, Canada, and King Saud University, Riyadh, Saudi Arabia (M.A.); Erasmus University Medical Center, Rotterdam, the Netherlands (E.J.K.); Yale School of Medicine, New Haven, Connecticut, and VA Connecticut Healthcare System, West Haven, Connecticut (L.L.); Chinese University of Hong Kong, Hong Kong SAR (J.S., F.K.C., J.L.); McMaster University, Hamilton, Ontario, Canada (F.T., G.I.L., J.D., J.K.M.); Mayo Clinic, Scottsdale, Arizona (N.S.A.); Hospital Parc Taulí de Sabadell, University of Barcelona, Sabadell, Spain, and CiberEHD (Instituto de Salud Carlos III), Madrid, Spain (X.C.); St. Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada (R.E.); Technion-Israel Institute of Technology, Emek Medical Center, Afula, Israel (I.M.G.); Western University, London, Ontario, Canada (V.J.); University of California, Los Angeles, Los Angeles, California (D.J.); University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom, and Aalborg University, Aalborg, Denmark (G.Y.L.); Dijon-Bourgogne University Hospital, Dijon, France (R.L., M.B.); University of São Paulo, São Paulo, Brazil (F.M.); George Washington University, Washington, DC (A.C.M.); Asian Institute of Gastroenterology, Hyderabad, India (N.R.); and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (J.R.S.).

Note: This clinical practice guideline (CPG) on UGIB was developed under the direction of Drs. Alan N. Barkun and Marc Bardou, in accordance with the policies and procedures of the CAG and under the direction of CAG Clinical Affairs. It has been reviewed by the CAG Clinical Affairs Committee and the CAG Board of Directors. The CPG was developed after a thorough consideration of the medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian and international panel comprising experts on this topic. The CPG aims to provide a reasonable and practical approach to care for specialists and allied health professionals who are charged with providing optimal care to patients and their families, and it may be subject to change as scientific knowledge and technology advance and as practice patterns evolve.

Disclaimer: The CPG is not intended as a substitute for physicians using their individual judgment in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, the diagnostic and treatment options available, and the available re-

sources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

Acknowledgment: The CAG thanks the Canadian Institutes of Health Research (CIHR) Institute of Nutrition, Metabolism and Diabetes and the Saudi Gastroenterology Association for their generous support of the guideline process. The consensus group thanks Dr. Waleed Alhazzani (McMaster University) for participation in the development of PICO questions and in preliminary discussions and voting; Paul Sinclair, Cindy Roll, and Lesley Marshall (CAG representatives) for administrative and technical support and logistical assistance; and Pauline Lavigne and Steven Portelance for editorial assistance and medical writing services (supported by funds from the CAG).

Financial Support: By an unrestricted grant to the CAG by the CIHR Institute of Nutrition, Metabolism and Diabetes and the Saudi Gastroenterology Association.

Disclosures: Dr. Barkun reports grants and consulting fees from and advisory board membership at Pendopharm and At-Gen, and advisory membership at Olympus and Cook, outside the submitted work. Dr. Chan reports grants from the Research Grant Council of Hong Kong during the conduct of the study and advisory board membership at Pfizer, AstraZeneca, the Rome Foundation, Antibe Therapeutics, and the AGA Council; personal fees and honoraria from Pfizer, AstraZeneca, Eisai, Takeda Pharmaceuticals, EA Pharma, Japan Gastroenterological Endoscopy Society, Takeda (China) Holdings, Ministry of Health of Singapore, Olympus Hong Kong and China, Medical Association of Guangdong Province, and Associação Dos Medicos Hospitalares Da Funcao Publica De Macau; personal fees and royalties from Wiley; grants from Pfizer, AstraZeneca, Triangle Pharmaceuticals, Given Imaging, Osaka City University, and Olympus Hong Kong and China; and commentary for American College of Physicians Journal Club, Nature Review: Gastroenterology and Hepatology, Evidence-based Medicine and Ministry of Health P.R. China, and Ministry of Health of Singapore, outside the submitted work. Dr. Douketis reports personal fees from Boehringer Ingelheim, Janssen, Pfizer, Bayer, Bristol-Myers Squibb, Sanofi, and Daiichi Sankyo outside the submitted work. Dr. Gralnek reports personal fees from Boston Scientific and Taro Pharmaceuticals outside the submitted work. Dr. Jairath reports personal fees from AbbVie, Takeda, Pfizer, Sandoz, Janssen, Arena Pharma, GSK, Eli Lilly, Ferring, Shire, Robarts Clinical Trials, Genentech, Merck, Topivert, Celltrion, Sublimity Therapeutics, F. Hoffman-La Roche, and Sigmatic Limited outside the submitted work. Dr. Jensen reports grants from the National Institute of Diabetes and Digestive and Kidney Diseases; U.S. Veterans Affairs Clinical Merit Review, and American Society for Gastrointestinal Endoscopy Research Foundation; grants and personal fees from Vascular Technology; and personal fees from Boston Scientific outside the submitted work. Dr. Lip reports consulting and speakers fees from Bayer, Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi Sankyo outside the submitted work. Dr. Meltzer reports an active research grant from Medtronic to study gastrointestinal bleeding and serves on an advisory board for AnX Robotics. Dr. Saltzman reports personal fees from Cook Endoscopy outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-1795.

Corresponding Author: Alan N. Barkun, MD, Division of Gastroenterology, McGill University and the McGill University Health Centre, 1650 Cedar Avenue, Room D7.346, Montreal, Quebec H3G 1A4, Canada; e-mail, alan.barkun@muhc.mcgill.ca.

Current author addresses and author contributions are available at Annals.org.

References

1. Laine L, Yang H, Chang SC, et al. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol.* 2012;107:1190-5; quiz 1196. [PMID: 22688850] doi:10.1038/ajg.2012.168
2. Rosenstock SJ, Møller MH, Larsson H, et al. Improving quality of care in peptic ulcer bleeding: nationwide cohort study of 13,498 consecutive patients in the Danish Clinical Register of Emergency Surgery. *Am J Gastroenterol.* 2013;108:1449-57. [PMID: 23732464] doi:10.1038/ajg.2013.162
3. Barkun A, Bardou M, Marshall JK; Nonvariceal Upper GI Bleeding Consensus Conference Group. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2003;139:843-57. [PMID: 14623622]
4. Barkun AN, Bardou M, Kuipers EJ, et al; International Consensus Upper Gastrointestinal Bleeding Conference Group. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2010; 152:101-13. [PMID: 20083829] doi:10.7326/0003-4819-152-2-201001190-00009
5. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol.* 2012;107:345-60; quiz 361. [PMID: 22310222] doi:10.1038/ajg.2011.480
6. 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;75:1132-8. [PMID: 22624808] doi:10.1016/j.gie.2012.02.033
7. National Institute for Health and Care Excellence. Acute upper gastrointestinal bleeding: management (NICE clinical guideline 141), 2012. Last update: November 2018. Accessed at www.nice.org.uk/guidance/cg141 on 12 August 2019.
8. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy.* 2015;47:a1-46. [PMID: 26417980] doi:10.1055/s-0034-1393172
9. Sung JJ, Chiu PW, Chan FKL, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. *Gut.* 2018;67:1757-1768. [PMID: 29691276] doi:10.1136/gutjnl-2018-316276
10. Abraham NS, Hartman C, Richardson P, et al. Risk of lower and upper gastrointestinal bleeding, transfusions, and hospitalizations with complex antithrombotic therapy in elderly patients. *Circulation.* 2013;128:1869-77. [PMID: 24025594] doi:10.1161/CIRCULATIONAHA.113.004747
11. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017; 358:j4008. [PMID: 28935701] doi:10.1136/bmj.j4008
12. Guyatt GH, Oxman AD, Vist GE, et al; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ.* 2008;336:924-6. [PMID: 18436948] doi:10.1136/bmj.39489.470347.AD
13. Guyatt GH, Schünemann HJ, Djulbegovic B, et al. Guideline panels should not GRADE good practice statements. *J Clin Epidemiol.* 2015;68:597-600. [PMID: 25660962] doi:10.1016/j.jclinepi.2014.12.011
14. Dalkey N. An experimental study of group opinion: the Delphi method. *Futures.* 1969;1:408-26.
15. Schünemann HJ, Mustafa R, Brozek J, et al; GRADE Working Group. GRADE Guidelines: 16. GRADE evidence to decision frameworks for tests in clinical practice and public health. *J Clin Epidemiol.* 2016;76:89-98. [PMID: 26931285] doi:10.1016/j.jclinepi.2016.01.032
16. Alonso-Coello P, Oxman AD, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ.* 2016;353:i2089. [PMID: 27365494] doi:10.1136/bmj.i2089
17. Alonso-Coello P, Schünemann HJ, Moberg J, et al; GRADE Working Group. GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction. *BMJ.* 2016;353:i2016. [PMID: 27353417] doi:10.1136/bmj.i2016
18. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. Going from evidence to recommendations. *BMJ.* 2008;336:1049-51. [PMID: 18467413] doi:10.1136/bmj.39493.646875.AE
19. Perel P, Roberts I, Ker K. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev.* 2013;CD000567. [PMID: 23450531] doi:10.1002/14651858.CD000567.pub6
20. Chávez-Negrete A, Majluf Cruz S, Frati Munari A, et al. Treatment of hemorrhagic shock with intraosseous or intravenous infusion of hypertonic saline dextran solution. *Eur Surg Res.* 1991;23:123-9. [PMID: 1718756]
21. Annane D, Siami S, Jaber S, et al; CRISTAL Investigators. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA.* 2013;310:1809-17. [PMID: 24108515] doi:10.1001/jama.2013.280502
22. Semler MW, Self WH, Wanderer JP, et al; SMART Investigators and the Pragmatic Critical Care Research Group. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med.* 2018;378:829-839. [PMID: 29485925] doi:10.1056/NEJMoa1711584
23. Kowalenko T, Stern S, Dronen S, et al. Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. *J Trauma.* 1992;33:349-53; discussion 361-2. [PMID: 1404501]
24. Stern SA, Dronen SC, Birrer P, et al. Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. *Ann Emerg Med.* 1993;22:155-63. [PMID: 8427424]
25. Kwan I, Bunn F, Chinnock P, et al. Timing and volume of fluid administration for patients with bleeding. *Cochrane Database Syst Rev.* 2014;CD002245. [PMID: 24599652] doi:10.1002/14651858.CD002245.pub2
26. Schreiber MA, Meier EN, Tisherman SA, et al; ROC Investigators. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. *J Trauma Acute Care Surg.* 2015;78:687-95; discussion 695-7. [PMID: 25807399] doi:10.1097/TA.0000000000000600
27. Carrick MM, Morrison CA, Tapia NM, et al. Intraoperative hypotensive resuscitation for patients undergoing laparotomy or thoracotomy for trauma: early termination of a randomized prospective clinical trial. *J Trauma Acute Care Surg.* 2016;80:886-96. [PMID: 27015578] doi:10.1097/TA.0000000000001044
28. Stanley AJ, Ashley D, Dalton HR, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multi-centre validation and prospective evaluation. *Lancet.* 2009;373:42-7. [PMID: 19091393] doi:10.1016/S0140-6736(08)61769-9
29. Ramaekers R, Mukarram M, Smith CA, et al. The predictive value of preendoscopic risk scores to predict adverse outcomes in emergency department patients with upper gastrointestinal bleeding: a systematic review. *Acad Emerg Med.* 2016;23:1218-1227. [PMID: 27640399] doi:10.1111/acem.13101
30. Laursen SB, Dalton HR, Murray IA, et al; Upper Gastrointestinal Hemorrhage International Consortium. Performance of new thresholds of the Glasgow Blatchford score in managing patients with up-

- per gastrointestinal bleeding. *Clin Gastroenterol Hepatol.* 2015;13:115-21.e2. [PMID: 25058843] doi:10.1016/j.cgh.2014.07.023
31. Stanley AJ, Laine L, Dalton HR, et al; International Gastrointestinal Bleeding Consortium. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. *BMJ.* 2017;356:i6432. [PMID: 28053181] doi:10.1136/bmj.i6432
32. Saltzman JR, Tabak YP, Hyett BH, et al. A simple risk score accurately predicts in-hospital mortality, length of stay, and cost in acute upper GI bleeding. *Gastrointest Endosc.* 2011;74:1215-24. [PMID: 21907980] doi:10.1016/j.gie.2011.06.024
33. Odutayo A, Desborough MJ, Trivella M, et al. Restrictive versus liberal blood transfusion for gastrointestinal bleeding: a systematic review and meta-analysis of randomised controlled trials. *Lancet Gastroenterol Hepatol.* 2017;2:354-360. [PMID: 28397699] doi:10.1016/S2468-1253(17)30054-7
34. Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. *Lancet.* 2015;386:137-44. [PMID: 25956718] doi:10.1016/S0140-6736(14)61999-1
35. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013;368:11-21. [PMID: 23281973] doi:10.1056/NEJMoa1211801
36. Carson JL, Stanworth SJ, Roubinian N, et al. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev.* 2016;10:CD002042. [PMID: 27731885]
37. Holst LB, Petersen MW, Haase N, et al. Restrictive versus liberal transfusion strategy for red blood cell transfusion: systematic review of randomised trials with meta-analysis and trial sequential analysis. *BMJ.* 2015;350:h1354. [PMID: 25805204] doi:10.1136/bmj.h1354
38. Shander A, Hofmann A, Ozawa S, et al. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion.* 2010;50:753-65. [PMID: 20003061] doi:10.1111/j.1537-2995.2009.02518.x
39. Blair SD, Janvrin SB, McCollum CN, et al. Effect of early blood transfusion on gastrointestinal haemorrhage. *Br J Surg.* 1986;73:783-5. [PMID: 3533203]
40. Docherty AB, O'Donnell R, Brunskill S, et al. Effect of restrictive versus liberal transfusion strategies on outcomes in patients with cardiovascular disease in a non-cardiac surgery setting: systematic review and meta-analysis. *BMJ.* 2016;352:i1351. [PMID: 27026510] doi:10.1136/bmj.i1351
41. Carson JL, Guyatt G, Heddle NM, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. *JAMA.* 2016;316:2025-2035. [PMID: 27732721] doi:10.1001/jama.2016.9185
42. Nagata N, Sakurai T, Moriyasu S, et al. Impact of INR monitoring, reversal agent use, heparin bridging, and anticoagulant interruption on rebleeding and thromboembolism in acute gastrointestinal bleeding. *PLoS One.* 2017;12:e0183423. [PMID: 28863196] doi:10.1371/journal.pone.0183423
43. Goldstein JN, Refaai MA, Milling TJ Jr, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *Lancet.* 2015;385:2077-87. [PMID: 25728933] doi:10.1016/S0140-6736(14)61685-8
44. Sarode R, Milling TJ Jr, Refaai MA, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation.* 2013;128:1234-43. [PMID: 23935011] doi:10.1161/CIRCULATIONAHA.113.002283
45. Choudari CP, Rajgopal C, Palmer KR. Acute gastrointestinal haemorrhage in anticoagulated patients: diagnoses and response to endoscopic treatment. *Gut.* 1994;35:464-6. [PMID: 8174982]
46. Thomopoulos KC, Mimidis KP, Theocharis GJ, et al. Acute upper gastrointestinal bleeding in patients on long-term oral anticoagula-
- tion therapy: endoscopic findings, clinical management and outcome. *World J Gastroenterol.* 2005;11:1365-8. [PMID: 15761977]
47. National Institute for Health and Care Excellence. Blood transfusion (NICE clinical guideline 24), 2015. Last update: November 2015. Accessed at www.nice.org.uk/guidance/ng24 on 12 August 2019.
48. Connolly SJ, Milling TJ Jr, Eikelboom JW, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med.* 2016;375:1131-41. [PMID: 27573206] doi:10.1056/NEJMoa1607887
49. Pollack CV Jr, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal - full cohort analysis. *N Engl J Med.* 2017;377:431-441. [PMID: 28693366] doi:10.1056/NEJMoa1707278
50. Spiegel BM, Vakil NB, Ofman JJ. Endoscopy for acute non-variceal upper gastrointestinal tract hemorrhage: is sooner better? A systematic review. *Arch Intern Med.* 2001;161:1393-404. [PMID: 11386888]
51. 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;22:267-71. [PMID: 8771420]
52. 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;50:755-61. [PMID: 10570332]
53. 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. [PMID: 15229417]
54. Kumar NL, Cohen AJ, Naylor J, et al. Timing of upper endoscopy influences outcomes in patients with acute nonvariceal upper GI bleeding. *Gastrointest Endosc.* 2017;85:945-952.e1. [PMID: 27693643] doi:10.1016/j.gie.2016.09.029
55. Lim LG, Ho KY, Chan YH, et al. Urgent endoscopy is associated with lower mortality in high-risk but not low-risk non-variceal upper gastrointestinal bleeding. *Endoscopy.* 2011;43:300-6. [PMID: 21360421] doi:10.1055/s-0030-1256110
56. Laursen SB, Leontiadis GI, Stanley AJ, et al. Relationship between timing of endoscopy and mortality in patients with peptic ulcer bleeding: a nationwide cohort study. *Gastrointest Endosc.* 2017;85:936-944.e3. [PMID: 27623102] doi:10.1016/j.gie.2016.08.049
57. Xia XF, Chiu PWY, Tsui KKF, et al. The effect of off-hours hospital admission on mortality and clinical outcomes for patients with upper gastrointestinal hemorrhage: a systematic review and meta-analysis of 20 cohorts. *United European Gastroenterol J.* 2018;6:367-381. [PMID: 29774150] doi:10.1177/2050640617732651
58. Cho SH, Lee YS, Kim YJ, et al. Outcomes and role of urgent endoscopy in high-risk patients with acute nonvariceal gastrointestinal bleeding. *Clin Gastroenterol Hepatol.* 2018;16:370-377. [PMID: 28634135] doi:10.1016/j.cgh.2017.06.029
59. Ahn DW, Park YS, Lee SH, et al. Clinical outcome of acute non-variceal upper gastrointestinal bleeding after hours: the role of urgent endoscopy. *Korean J Intern Med.* 2016;31:470-8. [PMID: 27048253] doi:10.3904/kjim.2014.099
60. Targownik LE, Murthy S, Keyvani L, et al. The role of rapid endoscopy for high-risk patients with acute nonvariceal upper gastrointestinal bleeding. *Can J Gastroenterol.* 2007;21:425-9. [PMID: 17637943]
61. Tai CM, Huang SP, Wang HP, et al. High-risk ED patients with nonvariceal upper gastrointestinal hemorrhage undergoing emergency or urgent endoscopy: a retrospective analysis. *Am J Emerg Med.* 2007;25:273-8. [PMID: 17349900]
62. Garcia-Tsao G, Sanyal AJ, Grace ND, et al; Practice Guidelines Committee of American Association for Study of Liver Diseases. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Am J Gastroenterol.* 2007;102:2086-102. [PMID: 17727436]
63. de Franchis R; Baveno V Faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol.* 2010;53:762-8. [PMID: 20638742] doi:10.1016/j.jhep.2010.06.004
64. 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; quiz 1-2. [PMID: 18986845] doi:10.1016/j.cgh.2008.08.016
65. 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;69:786-99. [PMID: 19152905] doi:10.1016/j.gie.2008.05.031
 66. 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;CD005584. [PMID: 25308912] doi:10.1002/14651858.CD005584.pub3
 67. Baracat F, Moura E, Bernardo W, et al. Endoscopic hemostasis for peptic ulcer bleeding: systematic review and meta-analyses of randomized controlled trials. *Surg Endosc.* 2016;30:2155-68. [PMID: 26487199] doi:10.1007/s00464-015-4542-x
 68. Ljubicic N, Budimir I, Biscanin A, et al. Endoclips vs large or small-volume epinephrine in peptic ulcer recurrent bleeding. *World J Gastroenterol.* 2012;18:2219-24. [PMID: 22611315] doi:10.3748/wjg.v18.i18.2219
 69. Cui J, Huang LY, Liu YX, et al. Efficacy of endoscopic therapy for gastrointestinal bleeding from Dieulafoy's lesion. *World J Gastroenterol.* 2011;17:1368-72. [PMID: 21455339] doi:10.3748/wjg.v17.i10.1368
 70. Grgov S, Radovanovic-Dinic B, Tasic T. Could application of epinephrine improve hemostatic efficacy of hemoclips for bleeding peptic ulcers? A prospective randomized study. *Vojnosanit Pregl.* 2013;70:824-9. [PMID: 24266309]
 71. Chung IK, Ham JS, Kim HS, et al. Comparison of the hemostatic efficacy of the endoscopic hemoclip method with hypertonic saline-epinephrine injection and a combination of the two for the management of bleeding peptic ulcers. *Gastrointest Endosc.* 1999;49:13-8. [PMID: 9869717]
 72. Kwek BEA, Ang TL, Ong PLJ, et al. TC-325 versus the conventional combined technique for endoscopic treatment of peptic ulcers with high-risk bleeding stigmata: A randomized pilot study. *J Dig Dis.* 2017;18:323-329. [PMID: 28485544] doi:10.1111/1751-2980.12481
 73. Chen YI, Barkun AN. Hemostatic powders in gastrointestinal bleeding: a systematic review. *Gastrointest Endosc Clin N Am.* 2015;25:535-52. [PMID: 26142037] doi:10.1016/j.giec.2015.02.008
 74. Haddara S, Jacques J, Leclaire S, et al. A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the "GRAPHE" registry). *Endoscopy.* 2016;48:1084-1095. [PMID: 27760437]
 75. Chen YI, Barkun A, Nolan S. Hemostatic powder TC-325 in the management of upper and lower gastrointestinal bleeding: a two-year experience at a single institution. *Endoscopy.* 2015;47:167-71. [PMID: 25264762] doi:10.1055/s-0034-1378098
 76. Hagel AF, Albrecht H, Nägel A, et al. The application of hemospray in gastrointestinal bleeding during emergency endoscopy. *Gastroenterol Res Pract.* 2017;2017:3083481. [PMID: 28232848] doi:10.1155/2017/3083481
 77. Barkun AN, Adam V, Lu Y, et al. Using hemospray improves the cost-effectiveness ratio in the management of upper gastrointestinal nonvariceal bleeding. *J Clin Gastroenterol.* 2018;52:36-44. [PMID: 27749635] doi:10.1097/MCG.0000000000000709
 78. 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;42:1370-4. [PMID: 9246030]
 79. Jensen DM, Kovacs TOG, Ohning GV, et al. Doppler endoscopic probe monitoring of blood flow improves risk stratification and outcomes of patients with severe nonvariceal upper gastrointestinal hemorrhage. *Gastroenterology.* 2017;152:1310-1318.e1. [PMID: 28167214] doi:10.1053/j.gastro.2017.01.042
 80. 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;52:149-60. [PMID: 17109216]
 81. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev.* 2006;CD002094. [PMID: 16437441]
 82. Neumann I, Letelier LM, Rada G, et al. Comparison of different regimens of proton pump inhibitors for acute peptic ulcer bleeding. *Cochrane Database Syst Rev.* 2013;CD007999. [PMID: 23760821] doi:10.1002/14651858.CD007999.pub2
 83. Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. *Health Technol Assess.* 2007;11:iii-iv, 1-164. [PMID: 18021578]
 84. Barkun AN, Adam V, Sung JJ, et al. Cost effectiveness of high-dose intravenous esomeprazole for peptic ulcer bleeding. *Pharmacoeconomics.* 2010;28:217-30. [PMID: 20151726] doi:10.2165/11531480-00000000-00000
 85. 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;6:418-25. [PMID: 18304891] doi:10.1016/j.cgh.2007.12.037
 86. Lu Y, Adam V, Teich V, et al. Timing or dosing of intravenous proton pump inhibitors in acute upper gastrointestinal bleeding has low impact on costs. *Am J Gastroenterol.* 2016;111:1389-1398. [PMID: 27140030] doi:10.1038/ajg.2016.157
 87. Cheng HC, Wu CT, Chang WL, et al. Double oral esomeprazole after a 3-day intravenous esomeprazole infusion reduces recurrent peptic ulcer bleeding in high-risk patients: a randomised controlled study. *Gut.* 2014;63:1864-72. [PMID: 24658598] doi:10.1136/gutjnl-2013-306531
 88. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. *N Engl J Med.* 2002;346:2033-8. [PMID: 12087138]
 89. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. *N Engl J Med.* 2001;344:967-73. [PMID: 11274623]
 90. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *N Engl J Med.* 2005;352:238-44. [PMID: 15659723]
 91. Lai KC, Chu KM, Hui WM, et al. Esomeprazole with aspirin versus clopidogrel for prevention of recurrent gastrointestinal ulcer complications. *Clin Gastroenterol Hepatol.* 2006;4:860-5. [PMID: 16797240]
 92. Chan FK, Kyaw M, Tanigawa T, et al. Similar efficacy of proton-pump inhibitors vs H2-receptor antagonists in reducing risk of upper gastrointestinal bleeding or ulcers in high-risk users of low-dose aspirin. *Gastroenterology.* 2017;152:105-110.e1. [PMID: 27641510] doi:10.1053/j.gastro.2016.09.006
 93. Khan MY, Siddiqui WJ, Alvarez C, et al. Reduction in postpercutaneous coronary intervention angina in addition to gastrointestinal events in patients on combined proton pump inhibitors and dual antiplatelet therapy: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2018;30:847-853. [PMID: 29596078] doi:10.1097/MEG.0000000000001125
 94. Hu W, Tong J, Kuang X, et al. Influence of proton pump inhibitors on clinical outcomes in coronary heart disease patients receiving aspirin and clopidogrel: a meta-analysis. *Medicine (Baltimore).* 2018;97:e9638. [PMID: 29504996] doi:10.1097/MD.0000000000009638
 95. Bhatt DL, Cryer BL, Contant CF, et al; COGET Investigators. Clopidogrel with or without omeprazole in coronary artery disease. *N Engl J Med.* 2010;363:1909-17. [PMID: 20925534] doi:10.1056/NEJMoa1007964
 96. Wei P, Zhang YG, Ling L, et al. Effects of the short-term application of pantoprazole combined with aspirin and clopidogrel in the treatment of acute STEMI. *Exp Ther Med.* 2016;12:2861-2864. [PMID: 27882086]
 97. Ren YH, Zhao M, Chen YD, et al. Omeprazole affects clopidogrel efficacy but not ischemic events in patients with acute coronary syndrome undergoing elective percutaneous coronary intervention. *Chin Med J (Engl).* 2011;124:856-61. [PMID: 21518592]

98. Wu H, Jing Q, Wang J, et al. Pantoprazole for the prevention of gastrointestinal bleeding in high-risk patients with acute coronary syndromes. *J Crit Care.* 2011;26:434.e1-6. [PMID: 21273036] doi:10.1016/j.jcrc.2010.12.007
99. Chan FK, Ching JY, Suen BY, et al. Effects of Helicobacter pylori infection on long-term risk of peptic ulcer bleeding in low-dose aspirin users. *Gastroenterology.* 2013;144:528-35. [PMID: 23333655] doi:10.1053/j.gastro.2012.12.038
100. Ray WA, Chung CP, Murray KT, et al. Association of proton pump inhibitors with reduced risk of warfarin-related serious upper gastrointestinal bleeding. *Gastroenterology.* 2016;151:1105-1112.e10. [PMID: 27639805] doi:10.1053/j.gastro.2016.08.054
101. Chan EW, Lau WC, Leung WK, et al. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. *Gastroenterology.* 2015;149:586-95.e3. [PMID: 25960019] doi:10.1053/j.gastro.2015.05.002
102. Lin KJ, Hernández-Díaz S, García Rodríguez LA. Acid suppressants reduce risk of gastrointestinal bleeding in patients on anti-thrombotic or anti-inflammatory therapy. *Gastroenterology.* 2011;141:71-9. [PMID: 21458456] doi:10.1053/j.gastro.2011.03.049
103. Massó González EL, García Rodríguez LA. Proton pump inhibitors reduce the long-term risk of recurrent upper gastrointestinal bleeding: an observational study. *Aliment Pharmacol Ther.* 2008;28:629-37. [PMID: 18616644] doi:10.1111/j.1365-2036.2008.03780.x
104. Lanas A, García-Rodríguez LA, Arroyo MT, et al; Investigators of the Asociación Española de Gastroenterología (AEG). Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *Am J Gastroenterol.* 2007;102:507-15. [PMID: 17338735]
105. Islam MM, Poly TN, Walther BA, et al. Adverse outcomes of long-term use of proton pump inhibitors: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2018;30:1395-1405. [PMID: 30028775] doi:10.1097/MEG.0000000000001198
106. Hussain S, Siddiqui AN, Habib A, et al. Proton pump inhibitors' use and risk of hip fracture: a systematic review and meta-analysis. *Rheumatol Int.* 2018;38:1999-2014. [PMID: 30159775] doi:10.1007/s00296-018-4142-x
107. Nochaiwong S, Ruengorn C, Awiphan R, et al. The association between proton pump inhibitor use and the risk of adverse kidney outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant.* 2018;33:331-342. [PMID: 28339835] doi:10.1093/ndt/gfw470
108. Hafiz RA, Wong C, Paynter S, et al. The risk of community-acquired enteric infection in proton pump inhibitor therapy: systematic review and meta-analysis. *Ann Pharmacother.* 2018;52:613-622. [PMID: 29457492] doi:10.1177/1060028018760569
109. Cao F, Chen CX, Wang M, et al. Updated meta-analysis of controlled observational studies: proton-pump inhibitors and risk of Clostridium difficile infection. *J Hosp Infect.* 2018;98:4-13. [PMID: 28842261] doi:10.1016/j.jhin.2017.08.017
110. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology.* 2017;153:35-48. [PMID: 28528705] doi:10.1053/j.gastro.2017.04.047
111. Bosch J, Eikelboom JW, Connolly SJ, et al. Rationale, design and baseline characteristics of participants in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial. *Can J Cardiol.* 2017;33:1027-1035. [PMID: 28754388] doi:10.1016/j.cjca.2017.06.001
112. Moayyedi P, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Pantoprazole to prevent gastroduodenal events in patients receiving rivaroxaban and/or aspirin in a randomized, double-blind, placebo-controlled trial. *Gastroenterology.* 2019;157:403-412.e5. [PMID: 31054846] doi:10.1053/j.gastro.2019.04.041
113. Moayyedi P, Eikelboom JW, Bosch J, et al; COMPASS Investigators. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology.* 2019;157:682-691.e2. [PMID: 31152740] doi:10.1053/j.gastro.2019.05.056
114. Wong GLH, Lau LHS, Ching JYL, et al. Prevention of recurrent idiopathic gastroduodenal ulcer bleeding: a double-blind, randomised trial. *Gut.* 2019. [PMID: 31229990] doi:10.1136/gutjnl-2019-318715
115. Baracat FI, de Moura DTH, Brunaldi VO, et al. Randomized controlled trial of hemostatic powder versus endoscopic clipping for non-variceal upper gastrointestinal bleeding. *Surg Endosc.* 2019. [PMID: 30927124] doi:10.1007/s00464-019-06769-z
116. Toka B, Eminler AT, Karacaer C, et al. Comparison of monopolar hemostatic forceps with soft coagulation versus hemoclip for peptic ulcer bleeding: a randomized trial (with video). *Gastrointest Endosc.* 2019;89:792-802. [PMID: 30342026] doi:10.1016/j.gie.2018.10.011
117. Kantowski M, Schoepfer AM, Settmacher U, et al. Assessment of endoscopic Doppler to guide hemostasis in high risk peptic ulcer bleeding. *Scand J Gastroenterol.* 2018;53:1311-1318. [PMID: 30394134] doi:10.1080/00365521.2018.1509121
118. Schmidt A, Gölder S, Goetz M, et al. Over-the-scope clips are more effective than standard endoscopic therapy for patients with recurrent bleeding of peptic ulcers. *Gastroenterology.* 2018;155:674-686.e6. [PMID: 29803838] doi:10.1053/j.gastro.2018.05.037

Current Author Addresses: Dr. Barkun: Division of Gastroenterology, McGill University and the McGill University Health Centre, 1650 Cedar Avenue, Room D7.346, Montreal, Quebec H3G 1A4, Canada.

Dr. Almadi: Division of Gastroenterology, Department of Medicine, College of Medicine, King Khalid University Hospital, King Saud University 12372, Riyadh, Saudi Arabia.

Dr. Kuipers: Erasmus MC University Medical Center, P.O. Box 2040, 3000CA Rotterdam, the Netherlands.

Dr. Laine: Section of Digestive Diseases, Yale School of Medicine, P.O. Box 208019, New Haven, CT 06520.

Dr. Sung: Department of Medicine and Therapeutics, Institute of Digestive Disease, The Chinese University of Hong Kong, Shatin, Hong Kong.

Dr. Tse: Division of Gastroenterology, Department of Medicine, McMaster University, Room 2F53, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada.

Dr. Leontiadis: Division of Gastroenterology, Department of Medicine, McMaster University, 1280 Main Street West, Health Sciences Centre, Suite 3V3, Hamilton, Ontario L8S 4K1, Canada.

Dr. Abraham: Mayo Clinic, 13400 East Shea Boulevard, Scottsdale, AZ 85259.

Dr. Calvet: Servei d'Aparell Digestiu, Corporació Sanitària Universitària Parc Taulí, Parc Taulí 1, 08208 Sabadell, Barcelona, Catalunya, Spain.

Dr. Chan: Institute of Digestive Disease, Chinese University of Hong Kong, Hong Kong SAR.

Dr. Douketis: Department of Medicine, McMaster University and St. Joseph's Healthcare, 50 Charlton Avenue East, Hamilton, Ontario L8N 4A6, Canada.

Dr. Enns: Division of Gastroenterology, University of British Columbia, Vancouver, British Columbia V6Z 2K5, Canada.

Dr. Gralnek: Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

Dr. Jairath: London Health Sciences Centre, Room A10-228, University Hospital, London, Ontario N6A 4V2, Canada.

Dr. Jensen: Ronald Reagan UCLA Medical Center, Digestive Diseases-Westwood, 200 MP, 200 UCLA Medical Plaza, Suite 365C, Los Angeles, CA 90024.

Dr. Lau: Department of Surgery, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong SAR.

Dr. Lip: Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, 6 West Derby Street, Liverpool L7 8TX, United Kingdom.

Dr. Loffroy: Department of Interventional Radiology, Image-Guided Therapy Centre, Dijon-Bourgogne University Hospital, 14 rue Gaffarel, 21000 Dijon, France.

Dr. Maluf-Filho: Cancer Institute of São Paulo-ICESP-USP, Av. Dr. Arnaldo, 251, CEP 01246-000, São Paulo-SP, Brazil.

Dr. Meltzer: Department of Emergency Medicine, GW Medical Faculty Associates, 2120 L Street Northwest, Washington, DC 20037.

Dr. Reddy: Asian Institute of Gastroenterology, 6-3-661, Somajiguda, Hyderabad-500 082, India.

Dr. Saltzman: Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

Dr. Marshall: Division of Gastroenterology, McMaster University, 1280 Main Street West, Room 2F59, Hamilton, Ontario L8S 4K1, Canada.

Dr. Bardou: Clinical Investigation Centre INSERM 1432, Hospitalisation Unit and Gastroenterology and Liver Department, CHU Dijon-Bourgogne, Hopital Francois Mitterrand, 14 rue Gaffarel, BP77908, 21079 Dijon Cedex, France.

Author Contributions: Conception and design: A.N. Barkun, M. Almadi, E.J. Kuipers, L. Laine, F. Tse, G.I. Leontiadis, I.M. Gralnek, A.C. Meltzer, J.K. Marshall, M. Bardou.

Analysis and interpretation of the data: A.N. Barkun, M. Almadi, E.J. Kuipers, L. Laine, J. Sung, F. Tse, G.I. Leontiadis, N.S. Abraham, X. Calvet, J. Douketis, R. Enns, I.M. Gralnek, V. Jairath, J. Lau, G.Y.H. Lip, R. Loffroy, F. Maluf-Filho, A.C. Meltzer, J.R. Saltzman, M. Bardou.

Drafting of the article: A.N. Barkun, M. Almadi, J. Sung, F. Tse, G.I. Leontiadis, N.S. Abraham, F.K.L. Chan, R. Enns, I.M. Gralnek, M. Bardou.

Critical revision for important intellectual content: A.N. Barkun, M. Almadi, E.J. Kuipers, L. Laine, J. Sung, F. Tse, G.I. Leontiadis, N.S. Abraham, X. Calvet, F.K.L. Chan, J. Douketis, I.M. Gralnek, V. Jairath, D. Jensen, G.Y.H. Lip, R. Loffroy, F. Maluf-Filho, A.C. Meltzer, N. Reddy, J.R. Saltzman, J.K. Marshall.

Final approval of the article: A.N. Barkun, M. Almadi, E.J. Kuipers, L. Laine, J. Sung, F. Tse, G.I. Leontiadis, N.S. Abraham, X. Calvet, F.K.L. Chan, J. Douketis, R. Enns, I.M. Gralnek, V. Jairath, D. Jensen, J. Lau, G.Y.H. Lip, R. Loffroy, F. Maluf-Filho, A.C. Meltzer, N. Reddy, J.R. Saltzman, J.K. Marshall, M. Bardou.

Statistical expertise: A.N. Barkun, M. Almadi, L. Laine, G.I. Leontiadis.

Obtaining of funding: A.N. Barkun, M. Almadi.

Administrative, technical, or logistic support: A.N. Barkun, G.I. Leontiadis, M. Bardou.

Collection and assembly of data: A.N. Barkun, F. Tse, G.I. Leontiadis, X. Calvet, R. Enns, I.M. Gralnek, F. Maluf-Filho, A.C. Meltzer, J.K. Marshall, M. Bardou.

Appendix Table 1. Pooled Sensitivity and Specificity of Pre-endoscopic Scoring Systems to Identify Patients at High Risk for Undesirable Clinical Outcomes

Study, Year (Reference)	Study Type	Cutoff Value	Pooled Sensitivity (95% CI)*	Pooled Specificity (95% CI)*
Glasgow Blatchford score				
NICE CPG, 2012 (7)	1 SR and MA of 7 DTA studies	0	0.99 (0.98–1.00)	0.20 (0.06–0.34)
Ramaekers et al, 2016 (29)	1 SR and MA of 6 DTA studies	0	0.99 (0.98–1.00)	0.08 (0.07–0.09)
Laursen et al, 2015 (30)	1 DTA study	0 1	0.997 (NR) 0.992 (NR)	0.222 (NR) 0.398 (NR)
Stanley et al, 2017 (31)	1 DTA study	1	0.986 (NR)	0.346 (NR)
Pre-endoscopic Rockall score				
NICE CPG, 2012 (7)	1 SR and MA of 7 DTA studies	Not specified	0.96 (0.84–1.00)	0.29 (0.17–0.41)
Ramaekers et al, 2016 (29)	1 SR and MA of 8 DTA studies	0 (6 studies) 2 (2 studies)	0.93 (0.91–0.94) 0.95 (0.91–0.97)	0.19 (0.18–0.20) 0.38 (0.35–0.40)
Stanley et al, 2017 (31)	1 DTA study	0	0.956 (NR)	0.234 (NR)
AIMS65 score				
Ramaekers et al, 2016 (29)	1 SR and MA of 3 DTA studies	0 (2 studies) 2 (1 study)	0.78 (0.73–0.83) 0.79 (0.76–0.82)	0.49 (0.45–0.53) 0.61 (0.61–0.61)
Stanley et al, 2017 (31)	1 DTA study	0	0.815 (NR)	0.499 (NR)

CPG = clinical practice guideline; DTA = diagnostic test accuracy; MA = meta-analysis; NICE = National Institute for Health and Care Excellence; NR = not reported; SR = systematic review.

* Boldface signifies statistically significant results.

Appendix Table 2. Pooled Relative and Absolute Risks for Adverse Outcomes, According to Restrictive or Liberal RBC Transfusion Thresholds in Patients With UGIB

Outcome	Studies (Reference)	Transfusion Strategy, n/N (%)		RR (95% CI)*	Absolute Risk, per 1000 (95% CI)
		Restrictive†	Liberal‡		
Death	1 SR and MA, 3 RCTs (33)§	37/727 (5.1)	68/851 (8.0)	0.65 (0.44 to 0.97)	-28 (-45 to -2)
Further bleeding (persistent or recurrent)	1 SR and MA, 5 RCTs (33)	64/765 (8.5)	117/877 (13.5)	0.58 (0.40 to 0.84)	-56 (-80 to -21)
Surgical or radiologic intervention	2 RCTs (34, 35)	14/485 (2.9)	23/592 (3.9)	0.73 (0.38 to 1.42)	-10 (-24 to +16)
Myocardial infarction	1 SR and MA, 2 RCTs (33)	10/684 (1.5)	15/787 (1.9)	0.79 (0.33 to 1.89)	-4 (-13 to +17)
Stroke or transient ischemic attack	1 SR and MA, 1 RCT (33)	3/444 (0.7)	6/445 (1.3)	0.49 (0.12 to 2.01)	-7 (-12 to +14)
Acute kidney injury	1 SR and MA, 2 RCTs (33)	83/685 (12.1)	110/792 (13.9)	0.77 (0.56 to 1.05)	-32 (-61 to +6)

MA = meta-analysis; RBC = red blood cell; RCT = randomized controlled trial; RR = relative risk; SR = systematic review; UGIB = upper gastrointestinal bleeding.

* Boldface signifies statistically significant results.

† Hemoglobin threshold, 70–80 g/L.

‡ Hemoglobin threshold, 90–100 g/L.

§ 2 RCTs provided 97% of all patients.

|| 2 RCTs provided 91% of all patients.

Appendix Table 3. Summary of Adjusted Results From Studies Assessing Timing of Endoscopy in Patients With UGIB at High Risk for Rebleeding or Death

Study, Year (Reference)	Type of Study	Definition of High Risk	Very Early Endoscopy, n/N (%)	Later Endoscopy, n/N (%)	Adjusted Risk*	Absolute Effect
Mortality						
Lin et al, 1996 (51)†	RCT	In-hospital mortality	≤12 h: 1/162 (0.6)	>12 h: 1/163 (0.6)	RR, 1.01 (95% CI, 0.06 to 16.0)	Comparator risk (later endoscopy): 6 deaths per 1000 Very early endoscopy: 0 fewer deaths per 1000 (CI, -1 to +96)
Cho et al, 2018 (58)	Cohort	GBS >7 at initial ED presentation, 28-d mortality	≤6 h, unadjusted: 9/571 (1.6)	>6 to ≤48 h, unadjusted: 15/390 (3.8)	OR, 0.36 (CI, 0.14 to 0.95)	Comparator risk (later endoscopy): 38 deaths per 1000 Very early endoscopy: 24 fewer deaths per 1000 (CI, -33 to -2)
Laursen et al, 2017 (56)	Cohort	Hemodynamically unstable patients, in-hospital mortality	≤6 h: 261/1808 (14)	>6 to ≤24 h: 85/908 (9.4) >24 h: 23/217 (11)	Early endoscopy (>6 to ≤24 h) vs. <6 or >24 h: OR, 0.73 (CI, 0.54 to 0.98) Very early endoscopy (≤6 h) vs. >6 to 24 h: higher mortality with very early endoscopy (≤6 h), but OR not reported and statistical significance not assessed‡	Comparator risk (endoscopy <6 or >24 h): 94 deaths per 1000 Early endoscopy (>6 to ≤24 h): 34 fewer deaths per 1000 (CI, -59 to -2) Very early endoscopy (≤6 h) vs. >6 to 24 h: not calculable
Rebleeding						
Lin et al, 1996 (51)†	RCT	—	≤12 h: 6/162 (4)	>12 h: 8/163 (5)	RR, 0.76 (CI, 0.27 to 2.15)	Comparator risk (later endoscopy): 50 rebleeds per 1000 Very early endoscopy: 12 fewer rebleeds per 1000 (CI, -37 to +57)

ED = emergency department; GBS = Glasgow Blatchford score; OR = odds ratio; RCT = randomized controlled trial; RR = relative risk; UGIB = upper gastrointestinal bleeding.

* Boldface signifies statistically significant results.

† Not all patients were high risk; 44% had shock at presentation.

‡ Similar results for hemodynamically stable patients with severe comorbid conditions. Endoscopy in <12 h was associated (adjusted results) with higher mortality than endoscopy at 12–36 h, but statistical significance was not assessed.

Appendix Table 4. Areas of Future Research

A. Resuscitation, risk assessment, and preendoscopy management

Optimal fluid resuscitation strategy (including timing and volume) for patients with UGIB and hemodynamic instability
Benefits of using vs. not using a prognostic scale, with outcomes of mortality, rebleeding, and cost-effectiveness
Low risk-of-bias DTA studies comparing existing prognostic scales
Patient preferences for early discharge based on prognostic scales vs. diagnostic certainty with early endoscopy
Optimal transfusion threshold and targets, and comparison of restrictive vs. liberal transfusion strategies in patients with UGIB and cardiovascular disease, with outcomes of mortality, rebleeding, and cost-effectiveness
Effectiveness of targeted reversal vs. nonreversal of anticoagulant therapy in patients with UGIB with access to early endoscopy
Optimal endoscopic hemostatic therapies in patients receiving anticoagulant therapy, with outcomes of mortality, rebleeding, and cost-effectiveness

B. Endoscopic management

Cost-effectiveness analysis of performing endoscopy at various time frames, earlier vs. later
Analysis of potential for poorer outcomes with very early endoscopy
Comparison of clips and thermal contact therapies, with blinded caregiver and outcome assessments
A greater characterization of the role of over-the-scope clips in UGIB
Effectiveness of TC-325 as a monotherapy for actively bleeding ulcers with high-risk stigmata (spurting or oozing), or as a temporizing measure in peptic ulcer or other causes of bleeding followed by endoscopy therapy, with outcomes of mortality and rebleeding
Effectiveness of DEP after endoscopic therapy to guide further treatment, or as a triage test to determine the need for endoscopic therapy

C. Pharmacologic management

Efficacy and safety of various PPI regimens (including timing, dose, and duration), with outcomes of mortality, rebleeding, and cost-effectiveness

E. Secondary prophylaxis

Efficacy, safety, and cost-effectiveness of PPI vs. no PPI therapy in patients receiving single-, dual-, or triple-antithrombotic therapy, particularly in populations who are *Helicobacter pylori* naive

DEP = Doppler endoscopic probe; DTA = diagnostic test accuracy;
PPI = proton-pump inhibitor; UGIB = upper gastrointestinal bleeding.