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

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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.

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

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

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Abstract

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.

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.

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-ofinterest 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 inpatient endoscopy.

(GRADE: conditional recommendation, low-quality evidence)

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 beststudied 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 ≤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 allcause 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, availability 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 thromboembolism 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 adverse 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 consensus 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 H_2receptor antagonists).

(GRADE:strongrecommendation,moderate-qualityevidence)

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 H_2-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 H_2-receptor antagonists (H_2RAs), 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 H_2RAs 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 H_2RAs and between non–high-dose PPIs and no treatment or H_2RAs 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 H_2RAs, 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 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 H_2RAs 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 H_2RAs 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 superiorto 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. H_2RAs 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 H_2RAs).

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.‡

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 H_2RAs).

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; H_2RA = H_2-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.

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 H_2RAs				
Deaths: 1 SR and MA (update of reference 81); 10 RCTs	24/1202 (2.0)	43/1220 (3.5)	0.56 (0.34 to 0.94)	−15 (−23 to −2)
Rebleeds: 1 SR and MA (update of reference 81); 12 RCTs	88/1269 (6.9)	169/1277 (13.2)	0.43 (0.29 to 0.63)	−71 (−90 to −45)
High-dose vs. non-high-dose PPIs				
Deaths: 1 SR and MA (update of reference 82); 15 RCTs	28/1042 (2.7)	27/1027 (2.6)	1.02 (0.59 to 1.76)	1 (−11 to +20)
Rebleeds: 1 SR and MA (update of reference 82); 17 RCTs	126/1175 (10.7)	107/1191 (9.0)	1.25 (0.93 to 1.66)	20 (−6 to +51)
High-dose vs. oral PPIs				
Deaths: 1 SR and MA (update of reference 81); 3 RCTs	0/117 (0)	2/116 (1.7)	0.31 (0.04 to 2.93)	−12 (−17 to +33)
Rebleeds: 1 SR and MA (update of reference 81); 4 RCTs	16/235 (6.8)	15/242 (6.2)	1.09 (0.54 to 2.17)	6 (−29 to +72)

OR = odds ratio; H_2RA = H_2-receptor antagonist; MA = meta-analysis; PPI = proton-pump inhibitor; RCT = randomized controlled trial; SR = systematic review.

*Boldface signifies statistically significant results.