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International Consensus Recommendations on the Management of Patients With Nonvariceal Upper Gastrointestinal Bleeding

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Description: A multidisciplinary group of 34 experts from 15 countries developed this update and expansion of the recommendations on the management of acute nonvariceal upper gastrointestinal bleeding (UGIB) from 2003.

Methods: The Appraisal of Guidelines for Research and Evaluation (AGREE) process and independent ethics protocols were used. Sources of data included original and published systematic reviews; randomized, controlled trials; and abstracts up to October 2008. Quality of evidence and strength of recommendations have been rated by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.

Recommendations: Recommendations emphasize early risk stratification, by using validated prognostic scales, and early endoscopy (within 24 hours). Endoscopic hemostasis remains indicated for high-risk lesions, whereas data support attempts to dislodge clots with hemostatic, pharmacologic, or combination treatment of the underlying stigmata. Clips or thermocoagulation, alone or with epinephrine injection, are effective methods; epinephrine injection alone is not recommended. Second-look endoscopy may be useful in selected high-risk patients but is not routinely recommended. Preendoscopy proton-pump inhibitor (PPI) therapy may downstage the lesion; intravenous high-dose PPI therapy after successful endoscopic hemostasis decreases both rebleeding and mortality in patients with high-risk stigmata. Although selected patients can be discharged promptly after endoscopy, high-risk patients should be hospitalized for at least 72 hours after endoscopic hemostasis. For patients with UGIB who require a nonsteroidal anti-inflammatory drug, a PPI with a cyclooxygenase-2 inhibitor is preferred to reduce rebleeding. Patients with UGIB who require secondary cardiovascular prophylaxis should start receiving acetylsalicylic acid (ASA) again as soon as cardiovascular risks outweigh gastrointestinal risks (usually within 7 days); ASA plus PPI therapy is preferred over clopidogrel alone to reduce rebleeding.

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* For a list of voting participants, see **Appendix 1**, available at www.annals.org.

Upper gastrointestinal bleeding (UGIB) represents a substantial clinical and economic burden, with reported incidence ranging from 48 to 160 cases per 100 000 adults per year (1–5), and mortality generally from 10% to 14% (5, 6). For patients with and without complications of nonvariceal UGIB in the United States, mean lengths of stay were 4.4 and 2.7 days and hospitalization costs were $5632 and $3402 (2004 US dollars), respectively (7).

Some data (2, 4, 5) suggest a decreasing annual incidence of UGIB amid an unchanging (3, 5) or decreasing (8) incidence of peptic ulcer bleeding, which is increasingly related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or low-dose acetylsalicylic acid (ASA). Mortality from UGIB has decreased by 23% in the United States (1998 to 2006) (4) and by 40% in the United Kingdom (1993 to 2007) (6), but has remained unchanged in Canada (1993 to 2003) (2) and the Netherlands (1993 to 2003) (5).

Recent national data suggest that previous recommendations, although still not optimally adhered to, may result in improved patient outcomes (9–13). Furthermore, new data have become available since the 2002 British Society of Gastroenterology guidelines (14) and the 2003 consensus guidelines (15) that warrant an update of the previous recommendations. A multidisciplinary group developed international guidelines to help clinicians make informed decisions regarding the management of patients who present with nonvariceal UGIB, which reflect the 2009 state of the art.

Methods

The participants developed these recommendations according to the Appraisal of Guidelines for Research and Evaluation (AGREE) process for the development of clinical practice guidelines (16, 17).

Scope and Purpose

These guidelines provide an international update to the 2003 consensus recommendations for the management of patients with nonvariceal UGIB. The participants determined issues to be covered by consensus, on the basis of a review of the 2003 guidelines (15) and subsequent published literature.

Stakeholder Involvement

A national survey of needs and barriers to the implementation of guidelines on UGIB identified target users

See also:

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Summary for Patients I-48

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(18). As a result, an organizing committee (Drs. Bardou, Kuipers, Sung, and Barkun [*Chair*]) selected an international, multidisciplinary group of 34 voting participants from 15 countries for their expertise in the areas of acute nonvariceal UGIB, evidence-based medicine, and continuing medical education (**Appendix 1**, available at www.annals.org). The group included community-based and academic family physicians, emergency department physicians, intensive care physicians, pharmacologists, hospital pharmacists, gastroenterologists, surgeons, radiologists, epidemiologists, and ethicists. The committee initially also consulted nurses and hospital administrators (18).

Sources and Searches

Literature searches included MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and ISI Web of Knowledge, with manual searches of bibliographies of key articles and proceedings of abstracts of major gastroenterology meetings held in the last 5 years (from the American College of Gastroenterology, Digestive Disease Week, and United European Gastroenterology Week). Researchers retrieved data up to October 2008 by searching for updated topics from 2002 and new topics from 1966. Researchers prioritized data from randomized, clinical trials, when available, and performed meta-analyses (when applicable) before the meeting. They derived search terms from previous Cochrane meta-analyses on nonvariceal UGIB and through discussions with the methodologists in the group, and the terms were then approved by the entire group. An independent research assistant performed the searches and summarized them by using standardized report forms. These were in turn reviewed by both methodological and content experts and approved by the entire group. Search strings and Quality of Reporting of Meta-analyses (QUOROM) diagrams for each of the statements are available on request.

Review and Grading of Evidence

Initially, 3 members of the group (Drs. Rostom, Malfertheiner, and Barkun) rated the level of evidence available and the strength of each recommendation by using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process (19, 20) (**Appendix Table 1**, available at www.annals.org). The entire group subsequently revised and approved the ratings after further review. The group considered health benefits, side effects, and risks, as well as cost data (when available). Seven new or updated meta-analyses were performed for the meeting, relating to statements A6, A8, B3, B11, C3, D6, and E4 (**Appendix Tables 2** and **3**, available at www.annals.org), by using a similar process as that for obtaining search string results. Most of these (for statements A6 [21], A8 [22], B11 [23], C3 [24], and D6 [25]) were presented at Digestive Disease Week 2009. All are available on request.

Group Processes

All participants identified statements to be modified, gaps in the previous recommendations, and the need for any new statements. Using a modified Delphi process, an organizing committee (chaired by Dr. Barkun) generated a list of new and old statements and circulated it electronically to all participants through 2 iterations before the meeting (26, 27). Participants anonymously voted on which statements they felt warranted discussion at the meeting, and provided comments on the wording of the statements, which were progressively finalized through 2 separate iterations and ultimately at the consensus meeting. All participants reviewed evidence packages before the meeting, which included both summary analyses, individual trial descriptions, and an electronic copy of the individual studies selected. The group analyzed further summary data and discussed individual studies at participants' request.

The group held a 2-day consensus conference in October 2008, chaired by a nonvoting member (Dr. Hunt), where data were presented and the grade attributed to the evidence was modified as needed and voted on by each participant. A statement was accepted if more than 75% of participants voted a, b, or c (agree strongly, agree moderately, or just agree) on a 6-point scale (with d, e, and f, being just disagree, disagree moderately, and disagree strongly, respectively). A working group drafted the manuscript, which was then reviewed and approved by all participants.

Applicability

The participants discussed cost implications and international availability and feasibility, as well as population-based ethnic variations, where applicable (such as for proton-pump inhibitor [PPI] pharmacokinetics). Initiatives on dissemination and economics are ongoing, including an analysis of needs and barriers identified by nurses, pharmacists, and physicians in applying guidelines and a systematic review of health economic aspects of UGIB. Separate papers will describe the criteria for monitoring and audit purposes (quality indicators).

Ethics

The conference was guided by existing ethics standards of medical institutions (28–30) and supplemented by additional procedures. An unconflicted ethics consultant (Dr. Jones) and an ad hoc advisory committee (Drs. Jones, Enns, and Barkun) developed and implemented a framework to manage declared conflicts of interest before the consensus meeting. Mandatory written disclosures of financial declared conflicts of interest within the 24 months before the meeting were obtained a priori from all voting participants and included in conference materials. The ad hoc advisory committee identified one third of the statements (7 of 21) as having the potential for conflict of interest. Before discussion of the identified statements, participants were asked openly to vol-

untarily recuse themselves from the discussion if they had a conflict of interest. The participants voted anonymously by using touchpad technology after completing scientific discussions for each statement (**Appendix 2**, available at www.annals.org). Substantial numbers of participants with declared conflicts of interests (≥24%) recused themselves from the discussions for 6 statements (A8, C3, C4, E1, E2, E3, and E4) (**Appendix 2**). However, vote tallies with and without those of participants with declared conflicts of interest revealed no differences in the final outcomes of the "agree" decisions.

Additional Domains Addressed by the Consensus Meeting

Knowledge gaps requiring further research were identified, and dissemination of the guidelines was discussed. A large, Canadian, randomized, controlled trial (RCT) (ClinicalTrials.gov registration number: NCT00840008) is assessing whether adherence to existing consensus recommendations on UGIB is improved with a multifaceted, tailored implementation strategy. In addition, subcommittees are developing manuscripts on methodology of RCTs in UGIB, quality indicators, the effect of the adopted ethical process, and endoscopic classification of ulcer bleeding stigmata.

Role of the Funding Source

The conference was underwritten by unrestricted, pooled funds contributed to the supporting societies. Funding or in-kind support was provided by the Canadian Association of Gastroenterology (CAG); European Association for Gastroenterology and Endoscopy; Asian Pacific Society of Digestive Endoscopy; and Institute of Diabetes, Metabolism, and Nutrition (of the Canadian Institutes of Health Research) and from at-arms-length contributions from AstraZeneca Mölndal (Sweden), Abbott Canada, and Olympus Canada provided to the CAG. The CAG administered all aspects of the meeting. The funding sources had no role in identifying statements, abstracting data, synthesizing results, grading evidence, or preparing the manuscript or in the decision to submit the manuscript for publication.

Recommendation Statements

Each statement is followed by the grade of supporting evidence, the result of the vote, and a discussion of the evidence.

The **Table** summarizes the recommendations that are new from this consensus and those that are revised from the 2003 guidelines (15), as well as those that are unchanged because the majority of the group felt that they did not require revision at this time. (These are not discussed within the text [15].)

Section A: Resuscitation, Risk Assessment, and Preendoscopy Management

Statement A2

Prognostic scales are recommended for early stratification of patients into low- and high-risk categories for rebleeding and mortality.

(Agree, 97% [Vote: a, 56%; b, 35%; c, 6%; d, 3%]. Grade: Low, 1c, "do it")

As stated in the 2003 guidelines (15), patients should be stratified into low and high risk by using prognostic scales, on the basis of clinical, laboratory, and endoscopic criteria. Early identification of high-risk patients allows appropriate intervention, which minimizes morbidity and mortality.

Clinical predictors of increased risk for rebleeding or mortality include age greater than 65 years; shock; poor overall health status; comorbid illnesses; low initial hemoglobin levels; melena; transfusion requirement; fresh red blood on rectal examination, in the emesis, or in the nasogastric aspirate; sepsis; and elevated urea, creatinine, or serum aminotransferase levels (15). Other factors predictive of outcomes include chronic alcoholism, active cancer, or unsuitable sociofamily conditions (31), and an Acute Physiology and Chronic Health Evaluation (APACHE) II score of 11 or greater (32).

The Blatchford and preendoscopic Rockall scores (33) use only clinical and laboratory data (before endoscopy) to identify patients who require intervention, whereas the complete Rockall score (34) also use endoscopic variables to predict rebleeding or mortality.

The Blatchford score includes hemoglobin level, blood urea level, pulse, systolic blood pressure, the presence of syncope or melena, and evidence of hepatic disease or cardiac failure and accurately identifies patients at low risk for clinical intervention (35–37), even without inclusion of urea level or syncope (38). Selected patients can be safely managed as outpatients without early endoscopy by using the Blatchford score (36, 37). This scale also compares favorably with the preendoscopic and complete Rockall scores (37–39).

Endoscopic predictors of increased risk for rebleeding and mortality include active bleeding (especially arterial bleeding rather than oozing), nonbleeding visible vessel (NBVV) or adherent clot, ulcer size (generally >2 cm) (40–43), ulcer location (posterior lesser gastric curvature or posterior duodenal wall), and lesion type (for example, ulcer, varices, or cancer) (15). A comparison of the Baylor College, Rockall, and Cedars–Sinai Medical Center predictive indexes found that the Rockall score best identified patients at low risk (44). This score has been validated in multiple countries (44–47) but has better discriminative ability for mortality than for rebleeding (38, 44, 46, 47). Use of the Rockall score has been shown to yield a more accurate diagnosis (significantly fewer undefined causes and increased identification of peptic ulcer) and shorter duration of hospitalization (48).

Table. **Summary of Consensus Recommendations for the Management of Patients With Nonvariceal Upper Gastrointestinal Bleeding**

A. Resuscitation, risk assessment, and preendoscopy management
- A1. Immediately evaluate and initiate appropriate resuscitation.*
- A2. Prognostic scales are recommended for early stratification of patients into low- and high-risk categories for rebleeding and mortality.†
- A3. Consider placement of a nasogastric tube in selected patients because the findings may have prognostic value.*
- A4. Blood transfusions should be administered to a patient with a hemoglobin level ≤70 g/L.
- A5. In patients receiving anticoagulants, correction of coagulopathy is recommended but should not delay endoscopy.
- A6. Promotility agents should not be used routinely before endoscopy to increase the diagnostic yield.
- A7. 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.†
- A8. Preendoscopic 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 available on an urgent basis support staff trained to assist in endoscopy.*
- B3. Early endoscopy (within 24 hours of presentation) is recommended for most patients with acute upper gastrointestinal bleeding.†
- 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.*
- B10. Clips, thermocoagulation, or sclerosant injection should be used in patients with high-risk lesions, alone or in combination with epinephrine injection.†
- B11. Routine second-look endoscopy is not recommended.†
- B12. A second attempt at endoscopic therapy is generally recommended in cases of rebleeding.*

C. Pharmacologic management
- C1. Histamine-2 receptor antagonists are not recommended for patients with acute ulcer bleeding.*
- C2. Somatostatin and octreotide are not routinely recommended for patients with acute ulcer bleeding.*
- C3. An intravenous bolus followed by continuous-infusion PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy.†
- C4. Patients should be discharged with a prescription for a single daily-dose oral PPI for a duration as dictated by the underlying etiology.

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 *H. 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. Postdischarge, ASA, and NSAIDs
- E1. In patients with previous ulcer bleeding who require an NSAID, it should be recognized that treatment with a traditional NSAID plus PPI or a 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 who require cardiovascular prophylaxis, it should be recognized that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI.

ASA = acetylsalicylic acid; COX-2 = cyclooxygenase-2; *H. pylori* = *Helicobacter pylori*; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor.
* Recommendation unchanged from 2003 guidelines. See reference 15 for supporting evidence and discussions.
† Recommendation revised from 2003 guidelines.

Statement A4

Blood transfusions should be administered to a patient with a hemoglobin level of 70 g/L or less.

(Agree, 100% [Vote: a, 59%; b, 35%; c, 6%]. Grade: Low, 1c, "do it")

The threshold for transfusion for each patient should be based on his or her underlying condition, hemodynamic status, and markers of tissue hypoxia in acute situations. The American Society of Anesthesiologists concluded (49) that preoperative blood transfusion should be based on the patient's risk for complications from inadequate oxygenation rather than by a fixed hemoglobin level. Red blood cell transfusion is rarely indicated when hemoglobin level is greater than 100 g/L and is almost always indicated when the level is less than 60 g/L.

The risk for adverse outcomes associated with anemia must be weighed individually against the potential side effects of blood transfusions. A meta-analysis of observational studies, including studies in trauma, surgery, and intensive care (50), found that transfusion was associated with a higher risk for death, nosocomial infection, multiorgan dysfunction, and acute respiratory distress syndromes than no exposure in multivariate analyses, although

confounding by need for transfusion could not be excluded.

International guidelines (51) recommend initiating red blood cell transfusions for most critically ill patients when hemoglobin levels decrease to less than 70 g/L, with a target level of 70 to 90 g/L, in the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage. The Transfusion Requirements in Critical Care trial (52) in 838 critically ill patients suggested lower mortality with hemoglobin levels of 70 to 90 g/L than with levels of 100 to 120 g/L (52). Unfortunately, these data excluded patients with UGIB. The actual transfusion requirement and threshold hemoglobin for transfusion in patients with acute UGIB (assuming a value after equilibration) may be higher because of hemodynamic instability, inaccurate hemoglobin measures, or the presence of continued or recurrent bleeding that leads to a rapid decrease to dangerously low hemoglobin levels. In a prospective cohort study (53), hemoglobin levels less than 82 g/L in patients with UGIB predicted elevated cardiac troponin I levels.

Because patients with UGIB are often elderly or have comorbid cardiovascular conditions, they may have poor tolerance for anemia. Threshold hemoglobin levels of 60 to 100 g/L may warrant transfusion in patients with underlying cardiac disease (ischemic heart disease, peripheral vascular surgery, or heart failure) (49). However, a prospective study (54) found no difference in postoperative morbidity and mortality between transfusion threshold levels less than 80 g/L and less than 90 g/L in patients undergoing coronary artery bypass graft surgery.

Statement A5

In patients receiving anticoagulants, correction of coagulopathy is recommended but should not delay endoscopy.

(Agree, 97% [Vote: a, 38%; b, 44%; c, 15%; d, 3%]. Grade: Low, 2c, "probably do it")

Data on correction of coagulopathy are few and conflicting, as identified by a systematic review done for the conference (55). A retrospective cohort study (56) that included 233 patients with nonvariceal UGIB found that 95% of the patients who received anticoagulants had an international normalized ratio (INR) between 1.3 and 2.7 (56). A baseline INR less than 1.3 versus 1.3 or greater did not predict rebleeding, transfusion requirement, surgery, length of stay, or mortality. Therefore, data suggest that it may not be necessary to delay endoscopic therapy in patients with mild to moderate coagulation defects. Furthermore, an exploratory analysis of 1869 patients in the RUGBE (Registry on Non-variceal Upper Gastrointestinal Bleeding and Endoscopy) Canadian cohort study (9) found that neither INR nor platelet count predicted rebleeding. Although platelet count did not significantly predict mortality, a presentation INR of 1.5 or greater was a significant predictor of mortality in patients with UGIB (55), which may reflect its greater importance as a comorbid index.

Another study in patients with any UGIB (57) found that intensive measures to correct INR can reduce mortality. Baradarian and colleagues (57), who used a historical cohort comparison, suggested that correcting an INR to less than 1.8 as part of intensive resuscitation led to lower mortality and fewer myocardial infarctions in the intervention group. The groups did not differ in length of stay, units of blood transfused, or time to endoscopy. Other data suggest that endoscopic treatment with injection or heater probe may be safely performed in patients with an INR less than 2.5 (58). A cohort study in patients who underwent endoscopic treatment (58) found no differences in rebleeding, surgery, mortality, or complication rates between patients receiving warfarin (baseline INR, 1.5 to 6.0), whose INRs were corrected to 1.5 to 2.5 by using fresh frozen plasma, and a control group who did not receive anticoagulants.

Considering the paucity of data on INR correction and the recognized benefits of early endoscopy (see statement B3), the participants felt that treating coagulopathy was necessary in patients who received anticoagulants but that endoscopy should not be delayed while doing so unless the INR (or prothrombin time where INR is unavailable) is supratherapeutic, because correction in these patients may facilitate endoscopic treatment. This approach should not be generalized to patients with cirrhosis because the prothrombin time does not seem to predict bleeding risk in this setting (59). Correction of coagulopathy from other causes may be necessary on a case-by-case basis.

Statement A6

Promotility agents should not be used routinely before endoscopy to increase the diagnostic yield.

(Agree, 82% [Vote: a, 35%; b, 35%; c, 12%; d, 6%; e, 3%; f, 9%]. Grade: Moderate, 2b, "probably don't do it")

Although the use of preendoscopy promotility agents may improve diagnostic yield in selected patients with suspected blood in the stomach, they are not warranted for routine use in all patients who present with UGIB.

A meta-analysis (21) of 3 trials that evaluated erythromycin (60–62), comprising 316 patients, and 2 abstracts that evaluated metoclopramide (63, 64) found that use of a prokinetic agent significantly reduced the need for repeated endoscopy (odds ratio [OR], 0.51 [95% CI, 0.30 to 0.88]) in patients suspected of having blood in their stomach, compared with placebo or no treatment (**Appendix Table 2**). The groups did not differ in length of stay, units of blood transfused, or need for surgery. An analysis of data from the 3 erythromycin trials (65) found that preendoscopic erythromycin resulted in a cost-effective outcome in most of the trials.

Because adequate visualization allows proper treatment in most patients and on the basis of the characteristics of patients selected for inclusion in the aforementioned trials, participants felt that promotility agents were not warranted for routine use but may be useful in patients who are suspected to have substantial amounts of blood or clot in their upper gastrointestinal tract or those who have recently eaten.

Statement A7

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.

(Agree, 97% [Vote: a, 53%; b, 35%; c, 9%; d, 3%]. Grade: High, 1a, "do it")

Although some highly selected patients may be discharged before undergoing endoscopy (see statement A2), most patients will require risk stratification by endoscopic as well as clinical criteria. Those classified as being at low risk for rebleeding can be discharged promptly after endoscopy (15).

An RCT in 95 low-risk patients (66) prospectively assessed the role of early discharge and found no differences in rates of recurrent bleeding but that early discharge significantly reduced costs compared with admission (median costs, $340 and $3940, respectively; $P = 0.001$). Criteria for early discharge included a clean ulcer base or flat pigmented spot, hemodynamic stability, no serious concurrent medical illness, easy accessibility to hospital, and adequate sociofamily support at home. No patient who was discharged early had any serious adverse event, underwent surgery, or died during the 30-day follow-up.

Substantial observational data (67–71) also support early discharge of low-risk patients after endoscopy. Patients stratified as low risk who were discharged early did not differ in complications (for example, rebleeding, surgery, mortality), health status, or satisfaction from those who were admitted (72–74). Unfortunately, recommendations for early discharge based on endoscopic findings are often not followed (75).

Patients are not suitable for early discharge if they have serious comorbid conditions (heart failure, recent cardiovascular or cerebrovascular event, chronic alcoholism, or active cancer), are hemodynamically unstable, have an endoscopic finding of high-risk stigmata (active bleeding, NBVV, or adherent clot), or have unsuitable sociofamily conditions (31, 76). Patient location (distance to nearest emergency care center), local legal regulations, and social support should also be considered (76).

Statement A8

Preendoscopic PPI therapy may be considered to downstage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy.

(Agree, 94% [Vote: a, 32%; b, 38%; c, 24%; d, 3%; e, 3%]. Grade: Moderate, 1b, "do it")

Although preendoscopic PPI therapy has not been shown to affect rebleeding, surgery, or mortality, the beneficial effects on the need for intervention, supportive cost-effectiveness analyses, and excellent safety profile suggest that these agents may be useful, particularly in those suspected of having high-risk stigmata.

A Cochrane meta-analysis through February 2006 that included 5 RCTs (77) was updated with an additional trial (78) and the full publication (79) of an abstract (22) (**Appendix Table 2**). The updated meta-analysis in 2223 patients included 1 study that assessed oral PPI strategies and 5 studies that assessed intravenous strategies, only 1 of which used a high-dose regimen (79). The investigators found no statistically significant differences in rates of mortality, rebleeding, or surgery between the PPI therapy and control groups. However, preendoscopic PPI treatment significantly reduced the proportion of patients with high-risk stigmata (OR, 0.67 [CI, 0.54 to 0.84]) and the need for endoscopic therapy (OR, 0.68 [CI, 0.50 to 0.93]) compared with patients in the control group who received placebo or a histamine-2 receptor antagonist (22).

A North American analysis found that preendoscopic PPI therapy was more effective and more costly in the United States, whereas in Canada it became more effective and less costly as the duration of hospitalization for high-risk patients increased or that of low-risk patients decreased (80). Identifying patients with a greater likelihood of having a high-risk lesion, such as those who present with red blood in the emesis or nasogastric aspirate, may optimize the cost-effectiveness of this approach (81). Other cost-effectiveness analyses have suggested either the economic dominance of preendoscopic high-dose intravenous PPI therapy (82) or the cost-effectiveness of oral PPI in this setting (83), but certain model assumptions limit these conclusions.

The observed lesion downstaging attributable to PPI therapy before endoscopy may be even more beneficial in situations in which early endoscopy may be delayed or when available endoscopic expertise may be suboptimal.

Section B: Endoscopic Management

Statement B3

Early endoscopy (within 24 hours of presentation) is recommended for most patients with acute upper gastrointestinal bleeding.

(Agree, 100% [Vote: a, 85%; b, 12%; c, 3%]. Grade: Moderate, 1b, "do it")

The definition of early endoscopy ranges from 2 to 24 hours after initial presentation (71, 75, 84, 85). Among the 1869 patients of the RUGBE cohort, 76% received their first endoscopy within 24 hours of presentation (mean, 23 hours [SD, 38]) (9). In contrast, in a United Kingdom survey of 6750 patients (13), only 50% received endoscopy within 24 hours. Early endoscopy (within the first 24

hours), with risk classification by clinical and endoscopic criteria, allows for safe and prompt discharge of patients classified as low risk, improves patient outcomes for patients classified as high risk, and reduces use of resources for patients classified as either low or high risk (15).

Although early endoscopy is encouraged for most patients, endoscopy may need to be delayed or deferred in selected high-risk patients, such as those with active acute coronary syndrome or suspected perforation. Also, a very low Blatchford score can identify very low-risk patients who are unlikely to have high-risk stigmata or benefit from endoscopic therapy (38) or who can be safely managed as outpatients (36, 37) without the need for early endoscopy; however, this remains controversial (see statement A2).

Data suggest that early endoscopy is safe and effective for all risk groups. A systematic review (71) found no major complications in patients triaged to outpatient care after early endoscopy. Early endoscopy is associated with significant reductions in length of hospital stay in patients at low risk (66, 72, 85), high risk (84), and combined patient groups (71, 86, 87), compared with delayed endoscopy. Recent administrative data found that the performance of early endoscopy was associated with a decreased need for surgery in elderly patients (88) and that patients with nonvariceal UGIB who were admitted on weekends had higher adjusted in-hospital mortality and were less likely to undergo early endoscopy within 1 day of hospitalization (87). A large United Kingdom cohort analysis (13) has also shown a strong trend in risk-adjusted mortality ratio that just failed to show a statistically significant link between decreased mortality and the practice of after-hours endoscopy.

Further analysis found no additional benefit from very early or urgent (<12 hours) endoscopy over early (>12 hours) endoscopy. A meta-analysis of 3 trials (75, 84, 85), comprising 528 patients, found no significant reduction in rebleeding (OR, 0.71 [CI, 0.28 to 1.81]), surgery (OR, 1.16 [CI, 0.39 to 3.51]), or mortality (OR, 0.70 [CI, 0.14 to 3.57]) with urgent (1 to 12 hours) endoscopy compared with later (>12 hours) endoscopy (**Appendix Table 2**). One study (85) reported significantly shorter hospital stays and lower costs with very early (1 to 2 hours) versus elective (1 to 2 days) endoscopy. In a subgroup of patients with a bloody gastric aspirate, blood transfusions and hospital stay were significantly reduced with urgent (<12 hours vs. >12 hours) endoscopy (84). Retrospective analyses that assessed urgent (0 to 8 hours) versus early (6 or 8 to 24 hours) endoscopy (89–91) reported no between-group differences in clinical outcomes; however, these studies did not control for other endoscopist-related factors, type of therapeutic interventions, or co-interventions. A study identified 4 independent predictors ($P < 0.050$) of active bleeding and the need for very early endoscopy (<12 hours): fresh blood in the nasogastric tube, hemodynamic instability, a hemoglobin level less than 80 g/L, and a leukocyte count greater than 12×10^9 cells/L (92). Of note, indirect findings from recent administrative data (87) suggest that early endoscopy may be associated with lower mortality.

On the basis of available data, the participants recommended a target time to endoscopy of within 24 hours of presentation.

Statement 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.

(Agree, 97% [Vote: a, 59%; b, 29%; c, 9%; d, 0%; f, 3%]. Grade: Moderate, 2b, "probably do it")

Statement 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.

(Agree, 86% [Vote: a, 24%; b, 50%; c, 12%; d, 9%; e, 3%; f, 3%]. Grade: Moderate, 2b, "probably do it")

Vigorous irrigation (for example, water pump) of a clot in an ulcer bed has successfully exposed the underlying stigmata in 26% to 43% of cases (93, 94), and the revealed stigmata were high risk in 70% of those cases (94). The endoscopic findings present after clot removal should be appropriately managed.

The risk for rebleeding with clots that remain adherent after washing without endoscopic therapy (with or without PPI therapy) has been reported to be as low as 0% to 8% (94, 95) but also as high as 25% to 35% (93, 96–98) in clinically high-risk patients. The disparity of these data has led to controversy as to the optimal management of adherent clots (99).

For the most part, endoscopic therapy for adherent clots refers to preinjecting them with epinephrine before shaving them down with a cold guillotining snare technique—without disrupting the pedicle of the clot—and then applying combination treatment to the residual stigmata of hemorrhage (97, 98).

One meta-analysis of 5 RCTs (99), comprising 189 patients with adherent clots, found no significant benefits for endoscopic versus no endoscopic therapy (relative risk [RR], 0.31 [CI, 0.06 to 1.77]). Similarly, another meta-analysis that included 6 RCTs (100), comprising 240 patients, also found that endoscopic therapy did not significantly reduce rebleeding (RR, 0.48 [CI, 0.18 to 1.30]) compared with medical therapy. A patient-level analysis of data from 4 fully published trials (100) did find a significant benefit for rebleeding (RR, 0.30 [CI, 0.10 to 0.77]). These discrepant results fuel the controversy and may be attributed to both varying patient populations and statistical heterogeneity not fully accounted for in the meta-analytic methods (101). No data suggest excess risk; a systematic review (102) found a low incidence of complications resulting from endoscopic therapy.

The 1 RCT that compared endoscopic therapy plus high-dose intravenous PPI therapy with high-dose intravenous PPI therapy alone found no rebleeding among 24 Asian patients with clots resistant to vigorous irrigation (95). Therefore, among patients with adherent clots resistant to vigorous irrigation, endoscopic therapy may be beneficial in patients at high risk for rebleeding (such as those with serious concurrent illness), whereas intensive PPI therapy without endoscopic treatment may be sufficient in patients at low risk (particularly those who are Asian or *Helicobacter pylori*–positive) (99).

Statement B8

Epinephrine injection alone provides suboptimal efficacy and should be used in combination with another method.

(Agree, 100% [Vote: a, 71%; b, 24%; c, 6%]. Grade: Moderate, 1b, "don't do it")

Statement B10

Clips, thermocoagulation, or sclerosant injection should be used in patients with high-risk lesions, alone or in combination with epinephrine injection.

(Agree, 97% [Vote: a, 50%; b, 35%; c, 12%; d, 3%]. Grade: High, 1a, "do it")

Several recent meta-analyses have better quantified the efficacy of endoscopic therapies (99, 102–107). Although monotherapy with epinephrine injection is more effective than medical therapy in patients with high-risk stigmata, it is inferior to other monotherapies or to combination therapy that uses 2 or more methods (99, 102–107). Numerous meta-analyses indicate that adding a second procedure, such as a second injectate (for example, alcohol, thrombin, or fibrin glue), thermal contact, or clips, is superior to epinephrine injection alone (99, 102, 103, 105, 107). Epinephrine plus a second method for treating high-risk stigmata significantly reduced rebleeding (OR, 0.51 [CI, 0.39 to 0.66]), surgery (OR, 0.63 [CI, 0.45 to 0.89]), and mortality compared with epinephrine monotherapy (OR, 0.50 [CI, 0.30 to 0.82]) (105).

Monotherapy with thermal devices, sclerosants, clips, thrombin, or fibrin glue provides more effective endoscopic hemostasis than epinephrine alone (99) or pharmacotherapy alone (106). Clips were superior to injection monotherapy in 4 (99, 102, 103, 106) of 5 meta-analyses (99, 102–104, 106). Clips with injection were superior to injection alone but not to clips alone (103, 106). Combination therapy (injection plus second injectate, thermal, or clips) was superior to injection therapy alone, but not to clips or thermal therapy alone (102, 106). The participants felt that the data were insufficient to show superiority or equivalence of the recommended treatments but that the data were strongest for the use of thermal devices, clips, or combination treatments.

Complications with dual versus single endoscopic therapy included induction of bleeding (1.7% in each group) and perforation (0.6% vs. 0%; $P = 0.003$) (102); however, perforation has also been reported with monotherapy in some RCTs (108, 109).

Statement B11

Routine second-look endoscopy is not recommended.

(Agree, 91% [Vote: a, 50%; b, 21%; c, 21%; d, 3%; e, 3%; f, 3%]. Grade: Moderate, 2b, "probably don't do it")

A routine second-look endoscopy is generally defined as a preplanned systematic second endoscopy performed 16 to 24 hours after the initial endoscopy, with appropriate therapy in patients with evidence of active bleeding or NBVV.

Although data support some benefits associated with second-look endoscopy, they are generally older data and do not include the use of PPI therapy or optimal hemostatic strategies. The findings are therefore not generalizable to current clinical practice. In addition, cost-effectiveness data do not seem to support the routine use of second-look endoscopy.

Five published studies (110–114) and 4 abstracts of randomized trials (115–118) have assessed a second-look approach, with only 1 in each group demonstrating statistically significant benefits. The conclusions of 2 previous meta-analyses of these trials (119, 120), which suggest benefits in rebleeding, are hampered by methodological limitations. In 1 case (119), the investigators noted analytical shortcomings in data abstraction from 2 trials (111, 113), whereas selection bias may have resulted in the other case (120) from the inclusion of a decade-old abstract of a positive study (117), not yet fully published, but not of another abstract from the same era (118) that failed to show efficacy.

A more recent meta-analysis of 6 trials (121) found that routine second-look endoscopy, with heater probe therapy when appropriate, significantly reduced the risk for rebleeding (RR, 0.29 [CI, 0.11 to 0.73]) compared with single endoscopy; however, performing second-look endoscopy with injection monotherapy conferred no advantage. A meta-analysis performed for the meeting (23) included 6 trials comprising 750 patients. It excluded 2 older abstracts (117, 118), which have not been fully published, and Rutgeerts and colleagues' study (114), which included second-look endoscopy in both study groups. In the meta-analysis, routine second-look endoscopy significantly decreased rebleeding (OR, 0.59 [CI, 0.38 to 0.91]) and surgery (OR, 0.43 [CI, 0.19 to 0.96]) but not mortality (OR, 0.65 [CI, 0.26 to 1.62]) (**Appendix Table 2**). These findings must be interpreted in light of differences across trials with regard to patient selection, adopted methodologies, and both intervention and control treatments, as well as sensitivity analyses that show poor robustness of the results. The most favorable results were from studies with the greatest proportions of high-risk patients (110, 113). Indeed, Chiu and colleagues (110) included 47% of patients who pre-

sented with shock and more than 40% with active bleeding. Similarly, Saeed and colleagues (113) assessed patients with a very high risk for rebleeding (on the basis of Forrest high-risk stigmata, as well as additional clinical and endoscopic criteria), of whom 70% had active bleeding. Although the investigators reported the noted decrease in rebleeding (OR, 0.08 [CI, 0.00 to 1.50]) as statistically significant in the final results of the latter trial, it did not remain so when conventional 2-sided inferential testing, adapted to the small sample size, was applied.

Of note, the most recently published trial—and the only one with a control group that received high-dose intravenous PPI therapy (115)—found no benefit with second-look endoscopy. High-dose intravenous PPI therapy is the current standard in many health care systems, which suggests that second-look endoscopy may not provide additional benefits when PPI therapy is available.

A U.S. cost-effectiveness analysis (122) found that a strategy of selective (not routine) second-look endoscopy at 24 hours only in patients at high risk for rebleeding was more effective and less expensive than repeated endoscopy in patients with rebleeding (with or without intravenous PPIs) or routine repeated endoscopy in all patients, although extrapolations were made from trials that did not actually use high-dose intravenous PPI therapy. Intravenous PPI therapy became the dominant strategy if the rebleeding rate was 9% (closer to real-life outcomes) or if the cost of PPI dropped below $10 per day. When considering baseline assumptions in the model and how they relate to current practice, PPI therapy seemed to be the most cost-effective alternative.

In the only study that fully reported risks (110), no complications directly attributable to the second-look endoscopy were reported.

In conclusion, although older data supported a second-look approach, these trials did not use contemporary management strategies associated with decreased rebleeding, such as initial endoscopic hemostasis with hemoclips or combination therapy (123), or post–endoscopic hemostasis high-dose PPI therapy (24). Furthermore, the few existing contemporary data do not favor the use of routine second-look endoscopy at this time. A subgroup of patients with particularly high-risk presentations may benefit, but this requires further study. In light of these considerations, the participants did not recommend the routine use of second-look endoscopy.

Section C: Pharmacologic Management

Statement C3

An intravenous bolus followed by continuous-infusion PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy.

(Agree, 94% [Vote: a, 65%; b, 24%; c, 6%; d, 3%; e, 0%; f, 3%]. Grade: High, 1a, "do it")

A 2006 Cochrane meta-analysis of data as of November 2004 (124) included 24 RCTs and was updated (24) with 7 additional trials (125–131) (**Appendix Table 2**). The updated meta-analysis included 5792 patients. Overall, PPI therapy with or without endoscopic therapy reduced rebleeding (OR, 0.45 [CI, 0.36 to 0.57]) and surgery (OR, 0.56 [CI, 0.45 to 0.70]) but not mortality (OR, 0.90 [CI, 0.67 to 1.19]) compared with placebo or histamine-2 receptor agonist. Proton-pump inhibitor therapy reduced mortality among patients with active bleeding or NBVV and in trials conducted in Asia. Further analysis showed that in patients with active bleeding or NBVV who received endoscopic hemostatic therapy, high-dose intravenous PPI therapy (80 mg bolus plus 8 mg/h continuous infusion) reduced rebleeding (OR, 0.43 [CI, 0.27 to 0.67]), surgery (OR, 0.60 [CI, 0.37 to 0.96]), and mortality (OR, 0.57 [CI, 0.34 to 0.96]). Lower doses of PPI (either intravenous or oral) reduced rebleeding but no evidence was found of an effect on mortality.

Similarly, the meta-analysis by Laine and McQuaid (99) found significant benefit in rebleeding (RR, 0.40 [CI, 0.28 to 0.59]), surgery (RR, 0.43 [CI, 0.24 to 0.58]), and mortality (RR, 0.41 [CI, 0.20 to 0.84]) with high-dose intravenous PPI therapy after endoscopic therapy, whereas lower doses were associated with significant benefits in rebleeding (RR, 0.53 [CI, 0.35 to 0.78]) but not surgery or mortality compared with placebo or no treatment.

Strong evidence demonstrates the efficacy of high-dose intravenous PPI therapy after successful endoscopy, but it is not possible to make conclusions regarding the efficacy of either lower intravenous doses or high-dose oral therapy. Indeed, head-to-head comparisons and subgroup analyses of high versus lower intravenous doses are underpowered, and no direct comparisons of high-dose intravenous therapy and high-dose oral therapy have been made. However, lower intravenous doses or high-dose oral PPI therapy (at doses equivalent to at least 4 times the standard daily oral dose) are also effective (especially in Asian populations) and can be considered when high-dose intravenous therapy is not available or feasible.

In patients with UGIB who have undergone successful endoscopic hemostasis, administering high-dose intravenous PPI therapy for 3 days is both more effective and less costly than not doing so, as demonstrated by cost analyses (132–134)—or can become so, as demonstrated by sensitivity analyses (83, 122). The intervention group usually receives high-dose intravenous PPI therapy, and the comparator group usually receives placebo; few trials have included low-dose intravenous or oral PPI as comparators. High-dose intravenous PPI therapy is a dominant strategy mainly because the cost of the medications is relatively lower than the incremental expenses of 1 additional rebleeding episode. Comparisons of intravenous and oral PPI use remain theoretical, because only a few underpowered RCTs (135–137) have assessed this comparison.

Although recent data have linked PPI use to in-hospital *Clostridium difficile* infection (138, 139), the participants felt that the benefits outweighed the risks in patients who have acute UGIB that requires PPI therapy.

Statement C4

Patients should be discharged with a prescription for a single daily-dose oral PPI for a duration as dictated by the underlying etiology.

(Agree, 94% [Vote: a, 56%; b, 32%; c, 6%; d, 3%; e, 3%]. Grade: Low, 1c, "do it")

Because rebleeding episodes may occur more than 3 days after endoscopy (125, 140, 141), most RCTs that assess the role of postendoscopic PPI therapy have also included a prescription for once-daily PPI therapy that starts 72 hours after endoscopic hemostasis (125, 129, 140–142). In the nonacute setting, once-daily PPI therapy has demonstrated effective ulcer healing for patients with peptic ulcer disease (143), and inadequate evidence supports the need for twice-daily therapy in the maintenance setting. In the absence of direct comparative trial data of single versus daily PPI administration, this recommendation is supported by observational results in studies that used a standard once-daily dosage (125, 129, 140–142). However, the duration and dose of the PPI will be determined by the underlying etiology; for example, healing rates for complicated or severe esophagitis are relatively low in some studies, and twice-daily doses may be warranted in the context of UGIB (144). In addition, patients who require ASA or NSAID therapy may require long-term secondary prophylaxis, as discussed in statements E1 to E4.

In community-based population studies, the use of PPIs has been associated with potential side effects, including *C. difficile* infection (145), pneumonia (146), and osteoporosis-related fractures (147). These findings remain controversial, and the benefits of PPI administration for acute ulcer healing outweigh these potential risks in the acute treatment setting; however, caution may be warranted during long-term use.

Section D: Nonendoscopic and Nonpharmacologic In-Hospital Management

Statement D2

Most patients who have undergone endoscopic hemostasis for high-risk stigmata should be hospitalized for at least 72 hours thereafter.

(Agree, 100% [Vote: a, 68%; b, 24%; c, 9%]. Grade: Low, 1c, "do it")

Studies of the natural history of ulcer lesions show that it takes 72 hours for most high-risk lesions to become low-risk lesions after endoscopic therapy (96, 148). In many contemporary trials (125, 140, 141), 60% to 76% of patients who had rebleeding within 30 days after endoscopic hemostasis plus high-dose PPI therapy did so within the first 72 hours. Thus, patients identified as being at high risk for rebleeding, such as those with high-risk endoscopic stigmata, should be admitted to a hospital for at least 72 hours.

However, 1 RCT showed that selected patients at higher risk might be safely managed as outpatients after endoscopic therapy without an increased risk for complications (149). The study in 82 patients with NBVV, ulcer size less than 1.5 cm, no hypovolemia, no associated severe disease, and appropriate family support found no differences in rebleeding, morbidity, or mortality at the 30-day follow-up among patients randomly assigned to outpatient or hospital care (149). Mean cost of care per patient was significantly lower for the outpatient group than for the hospital group ($970 vs. $1595; $P < 0.001$). However, the study was underpowered to be able to confidently recommend early discharge of patients at higher risk at this time. The consensus participants felt that further research was needed, especially in light of recent data that suggest some patients may be discharged too early (150).

Patients should be admitted to a monitored setting for at least the first 24 hours on the basis of risk (hemodynamic instability, increasing age, severe comorbidity, active bleeding at endoscopy, or large ulcer size [for example, >2 cm]) (5, 32, 40, 151, 152) or clinical condition.

One study (153) showed that use of a checklist with specific recommendations on diet, PPI therapy, *H. pylori* eradication therapy, NSAID use, discharge, and follow-up can significantly reduce the length of hospital stay for patients with UGIB.

Statement D4

Where available, percutaneous embolization can be considered as an alternative to surgery for patients for whom endoscopic therapy has failed.

(Agree, 100% [Vote: a, 62%; b, 32%; c, 6%]. Grade: Low, 2c, "probably do it")

Percutaneous or transcatheter arterial embolization has been investigated as an alternative to surgery in patients for whom endoscopic therapy has failed, especially those who are high-risk candidates for surgery. Gelatin sponges, polyvinyl alcohol, cyanoacrylic glues, and coils have been used to embolize the vessels feeding bleeding lesions (154).

In uncontrolled trials, primary rates of technical success range from 52% to 98%, with recurrent bleeding occurring in about 10% to 20% of patients (155–159). A retrospective, single-center study (160) showed no significant differences between embolization therapy and surgery for rates of rebleeding, surgery, or mortality, despite patients in the embolization group being older and having a higher prevalence of heart disease.

Although uncommon with modern, highly selective techniques, complications include bowel ischemia; secondary duodenal stenosis; and gastric, hepatic, and splenic infarction (154, 155, 159, 161). The high periprocedural mortality of 25% to 30% is largely attributed to patients being selected for this procedure because they are at high

surgical risk because of advanced age and underlying conditions (156, 158–160).

For patients who had rebleeding after initial successful, endoscopic hemostasis, a second attempt at endoscopic therapy remains the preferred strategy (15, 162). When persistent or recurrent bleeding cannot be controlled by endoscopic therapy, percutaneous embolization can be considered as an alternative to surgery, if such expertise is available.

Statement D5

Patients with bleeding peptic ulcers should be tested for H. pylori *and receive eradication therapy if it is present, with confirmation of eradication.*

(Agree, 94% [Vote: a, 82%; b, 12%; c, 0%; d, 3%; e, 3%]. Grade: High, 1a, "do it")

Statement D6

Negative H. pylori *diagnostic tests obtained in the acute setting should be repeated.*

(Agree, 94% [Vote: a, 68%; b, 21%; c, 6%; d, 3%; e, 3%]. Grade: Moderate, 1b, "do it")

As recommended in the previous consensus (15), patients with UGIB should be tested for *H. pylori* and receive eradication therapy if infection is present. A meta-analysis (163) demonstrated that eradication of *H. pylori* was significantly more effective than PPI therapy alone in preventing rebleeding from peptic ulcer disease. The rebleeding rate was even lower among the subgroup of patients with successful eradication, which emphasizes the importance of confirming eradication.

Tests for *H. pylori* may show increased false-negative rates in the context of acute bleeding, although the data vary. Although the biological mechanisms involved are poorly understood—and may indeed vary depending on the test—one suggestion is the pH buffering effect of the blood, because more alkaline settings are known to be associated with more false-negative results (164). A systematic review of 23 studies (165–187), done for the consensus meeting, found that diagnostic tests for *H. pylori* infection (including serology, histology, urea breath test, rapid urease test, stool antigen, and culture) demonstrate high positive predictive value (0.85 to 0.99) but low negative predictive value (0.45 to 0.75) in the setting of acute UGIB, with 25% to 55% of *H. pylori*–infected patients yielding false-negative results (**Appendix Table 3**) (25). This suggests caution in the interpretation of initially negative results and the need for repeated testing at follow-up.

Section E: Postdischarge, ASA, and NSAIDs

The following statements are similar to those included in the NSAID guidelines developed by a Canadian consensus group, which included 8 of the participants present at this consensus (188). Statements E1 and E2 were included in the NSAID guidelines and are here in condensed format. We also refer the reader to consensus publications from U.S. and international groups on the reduction of gastrointestinal risks associated with NSAID and antiplatelet therapy (189, 190).

Statement E1

In patients with previous ulcer bleeding who require an NSAID, it should be recognized that treatment with a traditional NSAID plus PPI or a cyclooxygenase-2 (COX-2) inhibitor alone is still associated with a clinically important risk for recurrent ulcer bleeding.

(Agree, 97% [Vote: a, 73%; b, 21%; c, 3%; d, 3%]. Grade: Moderate, 1b)

Statement 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.

(Agree, 94% [Vote: a, 52%; b, 33%; c, 9%; d, 0%; e, 6%]. Grade: Moderate, 1b, "do it")

Two small RCTs conducted in Asia (191–193) found no significant difference in the rate of recurrent bleeding or ulcer complications (about 4% to 6%) at 6 months with COX-2 inhibitor therapy alone versus therapy with a traditional NSAID plus PPI. The relatively small numbers of patients in these studies do not exclude a benefit of one strategy over the other. These studies did not assess traditional NSAID therapy alone or complete withdrawal of NSAID therapy, and although a strategy of COX-2 inhibitor therapy alone or therapy with a traditional NSAID plus PPI may have lowered the rates of recurrent bleeding compared with historical rates from therapy with traditional NSAIDs alone, the risk was not eliminated (191–193).

Population-based studies (194, 195) also support adding a PPI to traditional NSAID therapy or administering a COX-2 inhibitor to reduce the risk for upper gastrointestinal complications; however, the combination of a COX-2 inhibitor with a PPI was associated with the greatest risk reduction.

One RCT (196) demonstrated a significantly lower rate of recurrent UGIB with a COX-2 inhibitor plus a PPI (0%) compared with a COX-2 inhibitor alone (8.9%) over 1 year (difference, 8.9 percentage points [CI, 4.1 to 13.7 percentage points). A subgroup analysis (197) of pooled data from 3 RCTs with similar study designs, comprising 34 701 patients, suggested a lower incidence of clinical gastrointestinal events with a COX-2 inhibitor plus a PPI compared with a COX-2 inhibitor alone; however, no statistical analysis was performed. Several studies (198, 199) have also shown lower risks for endoscopic ulcers in patients who receive a COX-2 inhibitor plus a PPI compared with those who receive a COX-2 inhibitor alone.

Two meta-analyses (200, 201) have demonstrated an excess risk for serious cardiovascular events associated with COX-2 inhibitors compared with placebo. Optimal man-

agement of patients who require long-term NSAID therapy should consider both gastrointestinal and cardiovascular risks (188). No evidence has been found of a further increased risk for renal, cardiovascular, or dermatologic adverse events with COX-2 inhibitor plus PPI therapy compared with COX-2 inhibitor therapy alone (196).

Several cost-effectiveness analyses (202–204) in patients at high risk for gastrointestinal events found that a COX-2 inhibitor was more cost-effective than a traditional NSAID plus PPI, and a traditional NSAID plus PPI was more cost-effective than a traditional NSAID alone; however, these analyses did not include a strategy of therapy with a COX-2 inhibitor plus PPI.

In summary, patients with previous ulcer bleeding require more careful follow-up and alternative strategies, including discontinuation of NSAID therapy when possible or therapy with a COX-2 inhibitor plus PPI. Statement C4 discusses the potential side effects associated with long-term PPI use.

Statement 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.

(Agree, 100% [Vote: a, 70%; b, 30%]. Grade: Moderate, 1b, "do it")

Patients receiving low-dose ASA who develop UGIB are often advised to discontinue ASA therapy until the ulcers have healed. However, prolonged discontinuation of ASA therapy increases thrombotic risk in patients who require cardioprotective ASA therapy (205, 206). In a meta-analysis (206), ASA nonadherence or withdrawal was associated with a 3-fold higher risk for major adverse cardiac events. The delay to a thrombotic event is generally reported as between 7 and 30 days, and usually between 7 and 10 days (205, 207, 208). This temporal pattern has biological plausibility because the inhibited platelets circulate in the blood for about 10 days (205). The American Heart Association recommends (189) that the decision to discontinue ASA therapy in the setting of acute ulcer bleeding be made on an individual basis, on the basis of cardiac and gastrointestinal risks.

Data from RCTs (209, 210) suggest that the cardiovascular benefits of early reintroduction of ASA or clopidogrel may outweigh the gastrointestinal risks. An RCT in 156 patients with ASA-induced ulcer bleeding who underwent endoscopic therapy (209) found that immediate reintroduction of ASA in the presence of intravenous and oral PPI therapy was associated with a 2-fold (but statistically insignificant) increase in the risk for recurrent bleeding from peptic ulcers, but discontinuation of ASA therapy was associated with a significantly increased 8-week mortality rate. Another RCT (210) found no cases of rebleeding in patients with ASA-associated endoscopic ulcers who were treated with a PPI and randomly assigned to restart antiplatelet therapy with ASA or clopidogrel within 1 day of endoscopy. Therefore, the participants agreed that no ASA-free period should be mandated; instead, patients who require ASA for cardiovascular protection should restart ASA therapy as soon as the risks for cardiovascular complication are thought to outweigh the risks for bleeding.

Statement E4

In patients with previous ulcer bleeding who require cardiovascular prophylaxis, it should be recognized that clopidogrel alone has a higher risk for rebleeding than ASA combined with a PPI.

(Agree, 100% [Vote: a, 70%; b, 24%; c, 6%]. Grade: Moderate, 1b, "do it" [adding PPI to ASA])

Clopidogrel is often perceived as relatively safe in terms of gastrointestinal adverse events, but data show that even as monotherapy, clopidogrel is associated with a high risk for rebleeding (9% to 14%) (211, 212).

Pooled results of 2 RCTs (211, 212) showed a significant reduction in rebleeding with ASA plus a PPI compared with clopidogrel therapy alone (OR, 0.06 [CI, 0.01 to 0.32]) but no significant effect on mortality (OR, 0.63 [CI, 0.24 to 1.64]) (**Appendix Table 2**). The 2 groups did not differ in the development or relapse of cardiovascular or cerebrovascular events.

Physicians should be aware that PPIs may decrease the platelet inhibitory effect of clopidogrel (213–215). The PPI and clopidogrel may compete for the cytochrome P450 isoenzyme CYP2C19, which is required to convert the prodrug clopidogrel to its active metabolite (216–218). Some observational studies in clopidogrel recipients (218–220) show a small but significant association between PPI use and cardiovascular events, whereas others (215, 221, 222) do not. No randomized trials addressing this issue are available.

The American College of Cardiology, American Heart Association, and American College of Gastroenterology currently recommend that patients receiving these medications not change their treatment regimen unless advised by their health care provider (223). The U.S. Food and Drug Administration found sufficient evidence of an interaction to require the inclusion of a statement on the clopidogrel product label that concomitant administration of drugs that inhibit CYP2C19 (such as omeprazole) should be discouraged (224). On the basis of pharmacologic profiles, some experts suggest a staggered schedule of intake for clopidogrel and the PPI (216, 225), but further research in this area is needed.

With regard to the potential side effects associated with long-term PPI use, we refer the reader to statement C4.

Future Directions

Although considerable advances have been made in both endoscopic and pharmacologic therapies for UGIB, more data are needed in many areas (**Appendix Table 4**, available at www.annals.org).

We plan to facilitate the application of these guidelines by disseminating them to all participating societies and regions through such venues as symposia sessions or workshops at society meetings. Other scheduled application initiatives include preparation of an algorithm, a standardized slide presentation, and additional relevant peer-reviewed publications (including ethics; dissemination of guidelines; methodology of randomized, controlled trials in UGIB; quality indicators; endoscopic classification of ulcer bleeding stigmata; and health economics of UGIB); posting of major recommendations on society and government health Web sites; and translation of the guidelines in society or regional journals. Finally, we anticipate that these guidelines will be updated periodically as new data become available, as was the case for this update of the 2003 guidelines.

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Note: This consensus conference, organized by the Canadian Association of Gastroenterology, was held in Vienna, Austria, on 23–24 October 2008. These consensus recommendations are endorsed by the Canadian Association of Gastroenterology, the Asian Pacific Society of Digestive Endoscopy, and the European Association for Gastroenterology and Endoscopy. Since the consensus conference, the following professional societies have reviewed and also endorsed the recommendations: European Society of Gastrointestinal Endoscopy, Hong Kong Society of Digestive Endoscopy, Italian Society of Digestive Endoscopy, Asociación Española de Gastroenterología, Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas y Digestivas, and Sociedad de Gastroenterologia del Uruguay.

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Appendix 1: List of Attendees, International Consensus Upper Gastrointestinal Bleeding Conference Group

Nonvoting chair: Richard Hunt, Canada.

Voting steering committee: Alan N. Barkun, Canada; Marc Bardou, France; Ernst J. Kuipers, the Netherlands; Joseph Sung, Hong Kong.

Voting participants: Lars Agreus, Sweden; David Armstrong, Canada; Xavier Calvet, Spain; Naoki Chiba, Canada; Livio Cipolletta, Italy; Henry Cohen, Uruguay; Robert Enns, Canada; Lars-Gunnar Ericsson, Sweden; Ian Gralnek, Israel; Dennis Jensen, United States; Michio Kaminishi, Japan; Fasiha Kanwal, United States; Loren Laine, United States; Angel Lanas, Spain; James Lau, Hong Kong; Grigoris Leontiadis, Greece; Lars Lundell, Sweden; Peter Malfertheiner, Germany; John Marshall, Canada; Janet Martin, Canada; David Metz, United States; Paul Moayyedi, Canada; Jean-Pierre Quenot, France; Erik Rauws, the Netherlands; Joseph Romagnuolo, United States; Alaa Rostom, Canada; Brennan Spiegel, United States; Frances Tse, Canada; Monique Van Leerdam, the Netherlands; and Christo Van Rensburg, South Africa.

Nonvoting ethics expert: Derek J. Jones, Canada.

Represented societies: Canadian Association of Gastroenterology, American Society for Gastrointestinal Endoscopy, Asian Pacific Society of Digestive Endoscopy, European Association for Gastroenterology and Endoscopy, European Society of Gastrointestinal Endoscopy, and Asociación Interamericana de Gastroenterología.

Nonvoting observers: Andres Gardeazabal, Canada; István Rácz, Hungary; Pauline Lavigne, United States; and Paul Sinclair, Canada.

Appendix 2

Statements Identified as Having Potential for Conflict of Interest and Participants Who Were Recused From the Discussions

Statement A8: David Armstrong, Lars Agreus, Angel Lanas, Xavier Calvet, Joseph Romagnuolo, Alan Barkun, Ernst Kuipers, Joseph Sung, Loren Laine, Rob Enns, Henry Cohen, Paul Moayyedi, and David Metz.

Statement B10: None.

Statement C3: David Armstrong, Lars Agreus, Angel Lanas, Xavier Calvet, Joseph Romagnuolo, Alan Barkun, Ernst Kuipers, Joseph Sung, Loren Laine, Rob Enns, Henry Cohen, Paul Moayyedi, and David Metz.

Statement C4: David Armstrong, Lars Agreus, Peter Malfertheiner, Michio Kaminishi, Dennis Jensen, Angel Lanas, Joseph Romagnuolo, Alan Barkun, Ernst Kuipers, Joseph Sung, Loren Laine, Rob Enns, Henry Cohen, Paul Moayyedi, and David Metz.

Statement E1: Lars Agreus, Angel Lanas, Alan Barkun, Loren Laine, Rob Enns, Brennan Spiegel, Paul Moayyedi, David Metz.

Statement E2: David Armstrong, Lars Agreus, Angel Lanas, Joseph Romagnuolo, Alan Barkun, Ernst Kuipers, Loren Laine, Rob Enns, Brennan Spiegel, Paul Moayyedi, and David Metz.

Statement E3: None.

Statement E4: David Armstrong, Lars Agreus, Angel Lanas, Joseph Romagnuolo, Alan Barkun, Ernst Kuipers, Loren Laine, Rob Enns, Brennan Spiegel, and Paul Moayyedi.

Declaration of Personal Interests

Marc Bardou, Naoki Chiba, Livio Cipolletta, Lars-Gunnar Ericsson, Ian Gralnek, Fasiha Kanwal, Lars Lundell, Myriam Martel, Janet Martin, Jean-Pierre Quenot, Erik Rauws, Frances Tse, Monique Van Leerdam, and Christo Van Rensburg have no personal interests to declare.

Lars Agreus has served as a speaker for AstraZeneca and a consultant for Orexo AB and has received research support from AstraZeneca.

David Armstrong has served as both a speaker and a consultant for AstraZeneca and Abbott and as a speaker for Nycomed and has received research support and funding for educational programs from AstraZeneca and Abbott.

Alan Barkun has served as both a speaker and a consultant and has received research support from AstraZeneca and Abbott.

Xavier Calvet has served as a speaker for AstraZeneca and Almirall-Prodesfarma and has received research support from AstraZeneca and Janssen-Cilag.

Henry Cohen has served as both a speaker and a consultant for AstraZeneca and Roemmers.

Rob Enns has served as both a speaker and a consultant for Abbot, AstraZeneca, Given Imaging, Nycomed, Olympus, Proctor & Gamble, Schering-Plough, and UCB Pharma.

Richard Hunt has served as a consultant for Alevium Pharmaceuticals, AstraZeneca, Nycomed, Santarus, Schering-Plough, Steba Biotech, and TAP Pharmaceuticals; has received research support from Steba Biotech; and is CEO of Strategic Consultants International.

Dennis Jensen has served as both a speaker and a consultant for AstraZeneca and Boston Scientific and has received research support from AstraZeneca, Boston Scientific, Ethicon Endosurgery, and Olympus.

Michio Kaminishi has served as a speaker for Taiho and Otsuka and has received research support from Esai, Otsuka, Taiho, Takeda, and Zeria.

Ernst Kuipers has served as both a speaker and a consultant for AstraZeneca and has received research support from AstraZeneca, Janssen-Cilag, and Nycomed.

Loren Laine has served as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Horizon, Merck, Novartis, Nicox, Pfizer, Pozen, and Santarus and has received research funding from GlaxoSmithKline and TAP Pharmaceuticals.

Angel Lanas has served as both a speaker and a consultant for AstraZeneca and Pfizer and has received research funding from AstraZeneca, Bayer, Cogentus, and Pfizer.

James Lau has served as a consultant for AstraZeneca.

Grigoris Leontiadis has served as a speaker for AstraZeneca and sanofi-aventis and a consultant for GlaxoSmithKline and Given Imaging.

Peter Malfertheiner has served as a speaker for Abbott, AstraZeneca, and Nycomed.

John Marshall has served as both a speaker and a consultant for Abbott, Axcan, Proctor & Gamble, Schering-Plough, Shire, Solvay Pharma, and UCB Pharma and has served as a consultant for Ferring Pharmaceuticals.

David Metz has served as a consultant for AstraZeneca, Nycomed, Wyeth, and TAP Pharmaceuticals and has served as a speaker for Santarus and TAP Pharmaceuticals.

Paul Moayyedi has served as both a speaker and a consultant for AstraZeneca and Janssen Ortho and as a speaker for Nycomed and Esai and has received research support from AstraZeneca.

Joseph Romagnuolo has served as a consultant for AstraZeneca and Olympus and has received research support from Lantheus Imaging and Ethicon Endosurgery.

Alaa Rostom has served as a speaker for AstraZeneca.

Paul Sinclair has served as a consultant for AstraZeneca.

Brennan Spiegel has served as a speaker for AstraZeneca, Prometheus Laboratories, and Sucampo Pharmaceuticals and a consultant for AstraZeneca, Johnson & Johnson, Novartis, and Phynova.

Joseph Sung has served as speaker for Nycomed and a consultant for AstraZeneca.