Consensus Recommendations for Managing Patients with Nonvariceal Upper Gastrointestinal Bleeding

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Background: **The management of patients with acute nonvariceal upper gastrointestinal bleeding has evolved substantially over the past 10 years amid a paucity of published consensus guidelines.**

Purpose: **To provide evidence-based management recommendations that address clinically relevant issues.**

Review and Consensus Processes: **A multidisciplinary consensus group of 25 voting participants representing 11 national societies used a 7-step approach to develop recommendation statements according to accepted standards. Sources of data included narrative and systematic reviews as well as published and new meta-analyses. The quality of the evidence, the strength of the recommendation, and the level of consensus were graded according to recognized classifications.**

Main Findings: **Recommendations emphasize appropriate initial resuscitation of the patient and a multidisciplinary approach to clinical risk stratification that determines the need for early endoscopy. Early endoscopy allows safe and prompt discharge of selected patients classified as low risk. Endoscopic hemostasis is reserved for patients with high-risk endoscopic lesions. Although monotherapy with injection or thermal coagulation is effective, the combination is superior to either treatment alone. The placement of endoscopic clips for endoscopic hemostasis appears promising. High-dose intravenous proton-pump inhibition is recommended in patients who have undergone successful endoscopic therapy. Routine second-look endoscopy is not recommended. Patients with upper gastrointestinal bleeding should be tested for *Helicobacter pylori* infection and receive eradication therapy if infection is present.**

Future Directions: **The efficacy of newer endoscopic therapeutic technologies, the optimal regimen of proton-pump inhibition, and the roles of other pharmacologic agents require further research.**

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* For a list of the voting participants in the Nonvariceal Upper GI Bleeding Consensus Conference Group, see the Appendix, available at www.annals.org.

Upper gastrointestinal (GI) bleeding represents a substantial clinical and economic burden. It has a prevalence of approximately 170 cases per 100 000 adults per year (1), at an estimated total cost of $750 million in U.S. dollars (2). Peptic ulcer disease accounts for 50% to 70% of cases of acute nonvariceal upper GI bleeding (3, 4). Despite recent advances in therapy, mortality rates have remained essentially unchanged at 6% to 8% (1, 2, 5). This could be explained by the fact that patients are older and have more concurrent illnesses; it may also be due to underuse of endoscopic hemostatic techniques. The Canadian Registry in Upper Gastrointestinal Bleeding and Endoscopy (RUGBE) initiative and international data have demonstrated wide variations in the utilization and timing of different diagnostic and therapeutic technologies, as well as disparate management approaches (4–10).

In this context, it is surprising that, except for the recent British Society of Gastroenterology guidelines (9), the last widely disseminated consensus conference and publication of practice guidelines occurred more than 10 years ago (11, 12). Since publication of the British Society of Gastroenterology guidelines, new data have become available and are strengthened by a series of evidence-based systematic reviews and meta-analyses performed for this consensus (13, 14). The current guidelines are a consensus paper with multisociety representation.

METHODS

The recommendation statements were developed according to generally accepted standards (15, 16). A 7-step approach addressing most of 37 pertinent criteria of validity was followed (16–20). The process of guideline development is described in the **Figure**.

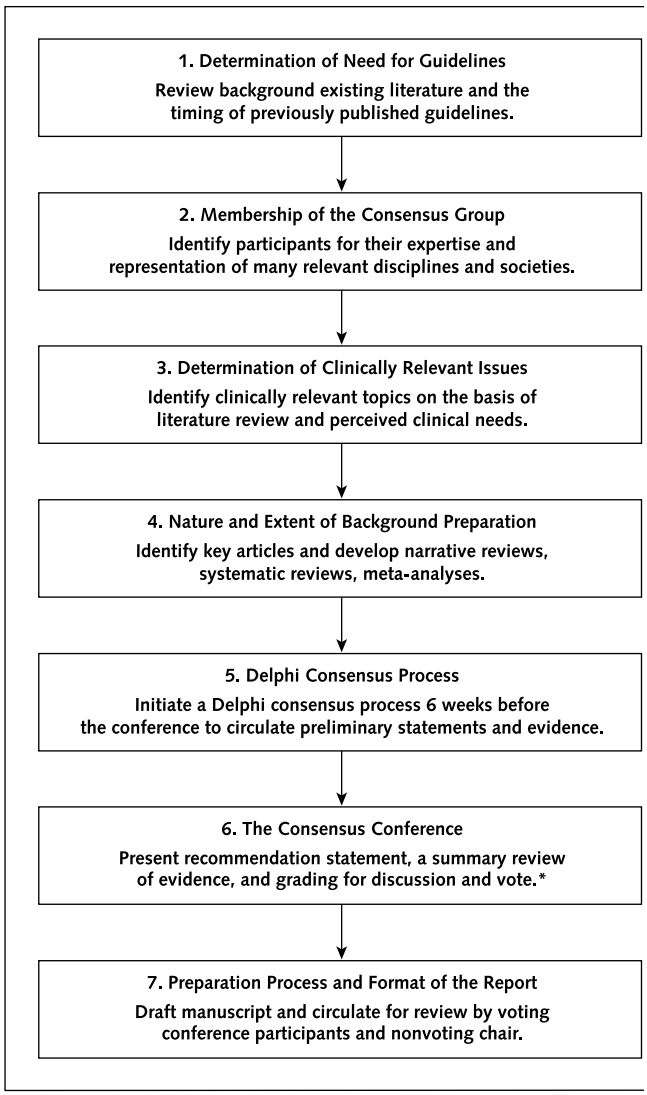
Determination of Need for Guidelines

The need for clinical practice guidelines on the management of patients with nonvariceal upper GI bleeding was identified by an initial review of the existing literature, current recommendations, and the timing of previously published guidelines. Recommendations are directed primarily to the management of nonvariceal bleeding largely due to peptic ulcers.

Membership of the Consensus Group

An organizing committee selected a multidisciplinary group of 25 voting participants for their expertise in the management of patients with acute nonvariceal upper GI bleeding, evidence-based medicine, and continuing medical education. The group included Canadian and international gastroenterologists, endoscopists, surgeons, family physicians, emergency medicine physicians, pharmacologists, epidemiologists (with methodologic and health economic expertise), and a hospital pharmacist. The attendees represented 11 national societies (Appendix, available at www.annals.org). A representative from the Canadian Association of General Surgeons reviewed the consensus guidelines a posteriori. Nonvoting observers included representatives from government (Health Canada), the pharmaceutical industry, and distributors and manufacturers of endoscopic equipment (Appendix, available at www.annals.org).

Figure. **The adopted process of guideline development (16).**



* See **Table 1**.

Determination of Clinically Relevant Issues

The issues were determined according to perceived clinical importance, likelihood of being resolved with the existing knowledge base, applicability to current practice, and perceived need for change (16). The RUGBE data were critical to this process (4). The conference organizer and a small working group generated a list of topics and circulated it electronically in advance (21, 22). For each topic, a statement was proposed to the consensus conference participants for discussion, revision, and voting.

Nature and Extent of Background Preparation

Literature review methods for relevant articles included MEDLINE searches and manual searches of bibliographies of key articles published in English between 1966 and June 2002. Search terms included *upper GI bleeding*, *non-variceal*, *guidelines*, *meta-analysis*, *naso-gastric tube*, *risk stratification*, *re-bleeding*, *mortality*, *surgery*, *endoscopy*, *second-look*, *clot*, *stigmata*, *injection*, *thermal coaptive*, *laser*, *hemostatic clips*, *proton pump inhibitor*, *histamine-receptor antagonist*, *somatostatin*, and *octreotide*. We referred to past reviews, meta-analyses, and published consensus conferences to summarize data up to 1992. New systematic reviews were conducted on data from the past 10 years on the prevalence and natural history of nonvariceal GI bleeding, risk stratification, and various management strategies. Economic considerations were recognized, but the country-specific nature of most cost data limited the review. Data were formally reviewed, including previous consensus opinions (for recommendations 1, 2, 3, and 18), narrative reviews (for recommendations 4, 11, 12, 13, 14, and 19), systematic reviews (for recommendations 5.1, 5.2, 6, and 20), and meta-analyses (for recommendations 7, 8, 9, 10, 15, 16, and 17).

Data available only in abstract form were not considered, with the exception of results from 2 meta-analyses by Bardou and colleagues from McGill University (13, 14) and the RUGBE initiative (4), which had been submitted for publication at the time of writing of this manuscript. In addition, for recommendations 7 and 10, data from pivotal abstracts were discussed in detail and were published within 3 months following the conference (23, 24). Consequently, a postconference Delphi process was carried out and results from this final vote were included.

More than 875 articles were initially reviewed, and the Delphi process identified 20 issues for discussion. A series of original meta-analyses, including 71 articles and nearly 9000 patients, were performed (13, 14). The key results of specific meta-analyses follow individual statements when appropriate, and full methods and results are available in separate publications (13, 14).

Delphi Consensus Process

Each statement was graded to indicate the level of evidence available and the strength of the recommendation by using the classification system of the Canadian Task Force on the Periodic Health Examination (**Table 1**) (25). This scheme was developed to assess therapeutic literature, not literature addressing prognosis (25).

General Organization

A 2-day consensus conference was held in June 2002 under the auspices of the Canadian Association of Gastroenterology. The conference was conducted according to generally accepted standards for the development of clinical practice guidelines (15, 16). At the consensus conference, data were presented and the statements and the grades attributed to evidence were discussed, modified if necessary, and voted on by each participant according to the recognized criteria shown in **Table 1** (26).

The Canadian Association of Gastroenterology, which administered all aspects of the meeting, secured multipartner funding from industry sponsors. Additional funds were obtained through a peer-review grant received by the Canadian Institutes of Health Research and an internal award

Table 1. **Categorization of Evidence, Classification of Recommendations, and Voting Schema**

Category and Grade	Description
Quality of evidence	
I	Evidence obtained from at least 1 properly randomized, controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than 1 center or research group.
II-3	Evidence obtained from comparisons between times or places with or without the intervention, or dramatic results in uncontrolled experiments.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
Classification of recommendations	
A	There is good evidence to support the procedure or treatment.
B	There is fair evidence to support the procedure or treatment.
C	There is poor evidence to support the procedure or treatment, but recommendations may be made on other grounds.
D	There is fair evidence that the procedure or treatment should not be used.
E	There is good evidence that the procedure or treatment should not be used.
Voting on the recommendations*	
a	Accept completely.
b	Accept with some reservation.
c	Accept with major reservation.
d	Reject with reservation.
e	Reject completely.

* Statements for which more than 50% of participants voted a, b, or c were accepted.

from the Research Institute of the McGill University Health Centre. Statements of conflicts of interest were obtained from all voting participants, and additional ethical information was collected (27).

Preparation Process and Format of the Report

A working group drafted the manuscript, which was then reviewed by all voting conference participants and the nonvoting chair, who approved the final draft. A brief narrative summary regarding the pediatric patient was prepared and can be accessed at www.cag-acg.org/cag_at_glance/positions.htm. An algorithm specifically designed for use in Canada is also under development.

Role of the Funding Sources

The funding sources had no role in the design, conduct, and reporting of the study or in the decision to submit the results for publication.

RECOMMENDATION STATEMENTS

A summary of all of the recommendations is provided in **Table 2**.

Initial Management

Recommendation 1: Hospitals should develop institution-specific protocols for multidisciplinary management, which should include access to an endoscopist with training in endoscopic hemostasis. Recommendation: C (vote: a, 100%); Evidence: III

Previous consensus groups have recommended a multidisciplinary approach with early involvement of a gastroenterologist and surgeon (9, 11, 12, 28). Hospitals with endoscopy services should have a multidisciplinary team in place with a prespecified chain of notification. Not all institutions have immediate access to these specialists, and not all patients require urgent endoscopy; thus, institution-specific protocols should be developed and updated. Endoscopy privileges should be reserved for practitioners who are properly trained according to established credentialing recommendations (29, 30).

Recommendation 2: Support staff trained to assist in endoscopy should be available for urgent endoscopy. Recommendation: C (vote: a, 92%; b, 8%); Evidence: III

Support staff, including appropriately trained endoscopy assistants, should be available to assist with urgent endoscopies. Any patient identified as high risk for rebleeding ideally should be admitted to a monitored setting for at least the first 24 hours (9). If intensive care beds are unavailable, wards with more intensive monitoring than standard units can be considered.

Recommendation 3: Immediate evaluation and appropriate resuscitation are critical to proper management. Recommendation: C (vote: a, 96%; b, 4%); Evidence: III

Patients with acute bleeding should be evaluated immediately on presentation. Resuscitation, including stabilization of blood pressure and restoration of intravascular volume (9, 11, 12, 28), should precede further diagnostic and therapeutic measures.

Recommendation 4: In selected patients, the placement of a nasogastric tube can be considered because the findings may have prognostic value. Recommendation: B (vote: a, 40%; b, 36%; c, 24%); Evidence: II-3

The presence of blood in nasogastric aspirate confirms an upper GI source. Although some data do not support the placement of a nasogastric tube (31), the detection of red blood with an in-and-out nasogastric tube has been shown to predict poor outcome and the need for emergency endoscopy (4, 5, 32–37). In RUGBE, the presence

Table 2. **Summary of Consensus Recommendations for the Management of Patients with Nonvariceal Upper Gastrointestinal Bleeding***

Hospital Preparation	At Patient Presentation	At Endoscopy
Develop institution-specific protocols for multidisciplinary management. Include access to an endoscopist trained in endoscopic hemostasis [1].	Immediately evaluate and initiate appropriate resuscitation [3].	Stratify patients into low- and high-risk categories for rebleeding and death on the basis of clinical and endoscopic criteria. Use available prognostic scales to assist in decision making [5.2].
Have available on an urgent basis support staff trained to assist in endoscopy [2].	Consider placement of a nasogastric tube in selected patients because the findings may have prognostic value [4].	Perform early diagnostic endoscopy (≤24 hours) with risk classification by clinical and endoscopic criteria to assist in 1) safe and prompt discharge of patients at low risk, 2) improvement of outcomes for patients at high risk, 3) reduction of resource utilization for patients at either low or high risk [6].
	Stratify patients into low- and high-risk categories for rebleeding and death on the basis of clinical criteria. Use available prognostic scales to assist in decision making [5.1].	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) [7].
		Endoscopic hemostatic therapy is indicated for a patient with a clot in an ulcer bed, including targeted irrigation in an attempt at dislodgment, with appropriate treatment of the underlying lesion [7].
		Endoscopic hemostatic therapy is indicated for patients with high-risk stigmata (active bleeding or a visible vessel in an ulcer bed) [7].

* Numbers in square brackets are numbers of recommendations. For precise wording of the statements and scientific rationale, see text.

of bright blood in the aspirate was an independent predictor of rebleeding (**Appendix Table 1**, available at www.annals.org) (4). Although the consensus panel felt that diagnostic nasogastric aspiration is redundant, if very early endoscopy is to be performed orogastric or nasogastric lavage may be helpful to clear the stomach of blood and clots before endoscopy.

Risk Stratification

Recommendation 5.1: Clinical (nonendoscopic) stratification of patients into low- and high-risk categories for rebleeding and mortality is important for proper management. Available prognostic scales may be used to assist in decision making. Recommendation: B (vote: a, 76%; b, 24%); Evidence: II-2

Approximately 80% of patients will stop bleeding spontaneously without recurrence (10). Most morbidity and mortality occur among the remaining 20% who have continued or recurrent bleeding (10). Thus, the main goal of management is to identify patients at high risk for an adverse outcome on the basis of clinical (4, 11, 38–40), laboratory (4, 32), and endoscopic variables (4, 10, 39, 41).

Many risk stratification schemes use both clinical and endoscopic criteria. However, patients must often be triaged before endoscopy (4, 42), and reports disagree on the additional prognostic power provided by endoscopic findings (32, 43, 44). There is a large body of evidence on risk stratification using clinical criteria, with variations in patient samples, standards of care, and analytic approaches. Older studies predated modern resuscitation and endoscopy, many included univariate but not multivariate analyses, and few provided prospective validation (45).

We reviewed studies from the past 10 years that used multivariate analyses (1, 4, 32–34, 37, 41, 44, 46–59). The evidence on which such stratification is based stems principally from cohort studies and not cohort-type analyses of actual trials. Clinical predictors of increased risk for rebleeding included age older than 65 years; shock; poor overall health status; comorbid illnesses; low initial hemoglobin level; melena; transfusion requirement; and fresh red blood on rectal examination, in the emesis, or in the nasogastric aspirate (**Appendix Table 1**, available at www.annals.org) (4, 37, 41, 46–48, 51–59). An increased risk for death was associated with age older than 60 years; shock; poor overall health status; comorbid illnesses; continued bleeding or rebleeding; fresh red blood on rectal examination, in the emesis, or in the nasogastric aspirate; onset of bleeding while hospitalized for another reason; sepsis; or elevated urea, creatinine, or serum aminotransferase levels (**Appendix Table 2**, available at www.annals.org) (1, 4, 32–34, 49, 56, 58). The setting in which care is provided and the specialty of the attending physician may also influence patient outcomes (60–62).

The nonendoscopic-based risk score determined by Blatchford and colleagues (63) is calculated from patients' admission hemoglobin level, blood urea level, pulse, sys-

Table 2—**Continued**

Endoscopic Hemostatic Therapy	Follow-up	Pharmacotherapy
No single solution for endoscopic injection therapy is superior to another [8].	Routine second-look endoscopy is not recommended [12].	H_2-receptor antagonists are not recommended for patients with acute ulcer bleeding [15].
No single method of endoscopic thermal coaptive therapy is superior to another [9].	A second attempt at endoscopic therapy is generally recommended in cases of rebleeding [13].	Somatostatin and octreotide are not routinely recommended for patients with acute ulcer bleeding [16].
Monotherapy, with injection or thermal coagulation, is effective for high-risk stigmata; however, the combination is superior to either treatment alone [10].	Seek surgical consultation for patients in whom endoscopic therapy has failed [14].	Intravenous bolus followed by continuous-infusion proton-pump inhibitor can effectively decrease rebleeding in patients who have had successful endoscopic therapy [17].
The placement of clips is promising for high-risk stigmata [11].	Patients at low risk after endoscopy can be fed within 24 hours [19].	Consider high-dose proton-pump inhibition for patients awaiting endoscopy [18].
	Test patients for *Helicobacter pylori* infection; eradicate infection if present [20].	

tolic blood pressure, presence of syncope or melena, and evidence of hepatic disease or cardiac failure. Cameron and associates (64) have also identified a preendoscopic stratification scheme (64). Concerns about generalizability and validation in different patient populations remain.

Recommendation 5.2: Early stratification of patients into low- and high-risk categories for rebleeding and mortality, based on clinical and endoscopic criteria, is important for proper management. Available prognostic scales may be used to assist in decision making. Recommendation: A (vote: a, 96%; b, 4%); Evidence: I

Previous consensus guidelines and several cohort studies have demonstrated that the risk for rebleeding or continued bleeding is strongly associated with the hemorrhagic stigmata seen at endoscopy (10, 11, 41, 44, 53, 56). In an analysis of data from 37 prospective trials in which patients did not receive endoscopic therapy, Laine and Peterson (10) found that the rate of further bleeding was less than 5% in patients with a clean ulcer base and increased to 10% in patients with a flat spot, 22% in those with an adherent clot, 43% in those with a nonbleeding visible vessel, and 55% in those with active bleeding (oozing and spurting). More recent studies that included multivariate analyses confirmed the increased risk for rebleeding associated with active bleeding and high-risk endoscopic stigmata (**Appendix Table 2**, available at www.annals.org) (4, 41, 44, 46, 56, 57). Other such endoscopic features included ulcer size (>1 or 2 cm) (52–54, 57, 58) and the site of bleeding (the posterior lesser gastric curvature and posterior duodenal wall) (53, 57).

Several validated scoring systems based on combinations of clinical and endoscopic characteristics can accurately predict the risk for rebleeding or death and permit early discharge and outpatient management of patients at low risk without an increased rate of negative sequelae (see recommendation 6) (37, 48, 49, 51, 63, 65–68). Here, too, the evidence stems principally from cohort studies and not cohort-type analyses of comparative trials. Widely referenced systems include the Rockall risk score, which includes age, presence of shock, comorbid conditions, diagnosis, and endoscopic stigmata of recent hemorrhage (69), and the Baylor bleeding score, generated only from patients who underwent therapeutic endoscopy (51). The Rockall risk score has been validated in most but not all studies for predicting rebleeding; death; and, consequently, health care resource utilization (70–72).

Endoscopic Therapy

Recommendation 6: 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 (Recommendation: A [vote: a, 92%; b, 8%]; Evidence: I)*; improves patient outcomes for patients classified as high risk* (Recommendation: C [vote: a, 64%; b, 36%]; Evidence: II-2)*; and reduces resource utilization for patients*

classified as either low or high risk (Recommendation: A [vote: a, 88%; b, 12%]; Evidence: I).

The definition of *early endoscopy* varies widely among studies, from 2 to 24 hours after presentation to the emergency department (41, 73–77). In the RUGBE cohort, first endoscopy in "real life" was performed within 24 hours of presentation in 76% of patients (mean [±SD], 23 ± 38 hours) (4). This was similar to the rate of 78% reported in a survey in the Amsterdam area (42). The consensus panel agreed to define *early* as within the first 24 hours.

Several observational studies (65, 67, 76, 78–80) and a systematic review (81) support the use of early endoscopic stratification for all risk groups. Studies in low-risk patients have shown no major complications in those triaged to outpatient care with early endoscopy (65, 67, 73, 75, 78, 79, 82, 83). A retrospective cohort trial found reductions in both length of hospital stay and need for surgery with early endoscopy in unselected patients (76).

In a randomized, controlled trial, early endoscopy and endoscopic therapy reduced transfusion requirements and length of hospital stay in patients with bloody nasogastric tube aspirate but not in those with clear or "coffee-grounds" aspirate (74). Studies in patients at low risk (66, 73, 75), patients at high risk (74), and unselected patients (69, 76, 82) have demonstrated statistically significant reductions in length of hospital stay. In patients at low risk, 2 randomized, controlled trials have demonstrated cost reductions of 43% to 91% with the use of early endoscopy (73, 75).

Recommendation 7: A finding of low-risk endoscopic stigmata (a clean-based ulcer or a nonprotuberant pigmented dot in an ulcer bed) is not an indication for endoscopic hemostatic therapy (Recommendation: A [vote: a, 100%]; Evidence: I). *A finding of a clot in an ulcer bed warrants targeted irrigation in an attempt at dislodgment, with appropriate treatment of the underlying lesion* (Recommendation: A [vote: a, 72%; b, 28%]; Evidence: I). *A finding of high-risk endoscopic stigmata (active bleeding or a visible vessel in an ulcer bed) is an indication for immediate endoscopic hemostatic therapy* (Recommendation: A [vote: a, 100%]; Evidence: I).

On the basis of the favorable natural history discussed in recommendation 5, the 1989 National Institutes of Health Consensus Conference did not recommend any endoscopic treatment for patients with low-risk endoscopic stigmata (a clean-based ulcer or a nonprotuberant pigmented spot in an ulcer bed) (11). Furthermore, the 2 meta-analyses that have demonstrated the benefits of endoscopic therapy mainly examined patients with high-risk rather than low-risk stigmata, with resultant statistically significant decreases in rates of further bleeding, surgery, and mortality (84, 85). Modern endoscopic hemostasis techniques were reviewed more recently in meta-analyses of 56 studies. Bardou and colleagues (13, 14) showed that, compared with drug or placebo treatment, endoscopic treatment was associated with statistically significant absolute decreases in rates of rebleeding, surgery, and mortality.

The optimal management of adherent clots has long been controversial, since this finding obscures underlying stigmata that may be at high or low risk for rebleeding. The risk for rebleeding with clots that remained adherent after washing has been reported as only 8% in 1 study (86) but as high as 25% to 29% in others (47, 87). Two recent studies found that endoscopic therapy for adherent clots statistically significantly reduced the rate of rebleeding compared with medical therapy alone (23, 24).

Recommendation 8: No single solution for endoscopic injection therapy is superior to another for hemostasis. Recommendation: A (vote: a, 92%; b, 8%); Evidence: I

The meta-analyses by Bardou and colleagues (13, 14), which included 38 relevant studies (52, 88–124), demonstrated no statistically significant benefits of 1 solution over another for endoscopic injection. In individual trials, no statistically significant differences were seen for epinephrine alone versus distilled water (52), cyanoacrylate (107), epinephrine in combination with ethanolamine or polidocanol (94, 123), thrombin (89, 104), sodium tetradecyl sulfate (96), or ethanol (97, 109). Ethanol injection was superior to sprayed epinephrine plus thrombin (103) and epinephrine plus polidocanol (121). In 1 study, no statistically significant differences were seen in treatment with normal saline, hypertonic saline (3% NaCl), 50% glucose–water solution, or pure alcohol (108). Some data suggested that injection of fibrin glue was the same as or better than polidocanol (90, 120).

Recommendation 9: No single method of endoscopic thermal coaptive therapy is superior to another. Recommendation: A (vote: a, 100%); Evidence: I

The McGill University meta-analyses by Bardou and colleagues (13, 14) included 20 studies relevant to this question (93, 95, 100, 105, 106, 110–112, 116, 122, 124–133) and demonstrated no statistically significant benefit of one coaptive endoscopic technique over another. Most individual randomized studies have shown no differences in rates of rebleeding, surgery, and mortality among coaptive therapy with heater probe thermocoagulation, multipolar electrocoagulation, or neodymium yttrium–aluminium–garnet laser when compared with injection therapy, although some studies have shown differences in rates of hemostasis (93, 95, 110, 112, 116, 122, 132). Laser therapy is no longer commonly used for acute management of high-risk patients because of high costs and poor portability of the equipment (134).

Argon plasma coagulation is a noncoaptive method of electrocoagulation in which current is applied to tissues by means of ionized argon gas (plasma) (135). Early uncontrolled experience found it was safe, effective, and easy to perform, with advantages over standard electrocoagulation

(135). In a prospective study comparing argon plasma coagulation with heater probe in 41 patients with bleeding peptic ulcers, rates of hemostasis, recurrent bleeding, mortality, and surgery were comparable in both groups, with argon plasma coagulation providing faster hemostasis (126). However, the statistical power of the study was insufficient to conclude equivalence. A larger study, published since the consensus conference was held, suggested no difference between injection plus heater probe and injection plus argon plasma coagulation in 185 patients with high-risk lesions (136).

Recommendation 10: Monotherapy, with injection or thermal coagulation, is an effective endoscopic hemostatic technique for high-risk stigmata; however, the combination is superior to either treatment alone. Recommendation: B (vote: a, 48%; b, 48%; c, 4%); Evidence: I

Previous meta-analyses of injection or thermal endoscopic hemostatic therapies reported statistically significant relative decreases in rebleeding rates (odds ratio, 0.27 to 0.31) and mortality (odds ratio, 0.55 to 0.7) compared with standard therapy (84, 85). The more recent McGill University meta-analyses by Bardou and colleagues found statistically significant reductions in the absolute rates of rebleeding and mortality with endoscopic treatment compared with placebo or pharmacotherapy (see previously discussed recommendations) (13, 14). Combination therapy with both injection and coaptive therapy has shown superiority over medical therapy (23, 24, 137). How combination therapy compares with endoscopic monotherapy and whether combination therapy should be the initial approach remains controversial. Bardou and colleagues (13, 14) investigated combinations of 2 endoscopic methods in 8 studies: epinephrine injection plus thermal treatment in 5 studies (23, 24, 98, 111, 137), epinephrine injection plus laser treatment in 2 studies (102, 113), and epinephrine injection plus clips in 1 study (99). Combination treatment was associated with statistically significant reductions in absolute rates of rebleeding compared with injection alone, thermal treatment alone, or pharmacotherapy. Similar reductions in rebleeding were not observed when the combination was compared with hemoclip therapy alone, despite statistically significant reductions in surgery rates. In an analysis of the 5 studies combining thermal methods with injection (23, 24, 98, 111, 137), combination treatment was associated with statistically significant reductions in absolute rates of rebleeding compared with pharmacologic, injection, or thermal treatment alone. The absolute mortality rates were statistically significantly lower with combination therapy than with pharmacologic or injection therapy. Stratification by endoscopic stigmata yielded insufficient data to compare the combination of injection plus nonlaser thermal therapy with single treatment methods for lesions other than actively spurting lesions (98) and adherent clots (23, 24). Combined injection and laser therapy has shown no substantial advantage over use of injection alone (102, 113).

Recommendation 11: The placement of clips is a promising endoscopic hemostatic therapy for high-risk stigmata. Recommendation: B (vote: a, 44%; b, 52%; c, 4%); Evidence: I

Several randomized, controlled trials have investigated the use of endoscopic clips, alone (99, 127, 138) or in combination (99, 138, 139), for endoscopic hemostasis. Endoscopic clips have shown superiority over heater probe (127) or injection therapy (99) in 2 trials but higher failure rates compared with injection therapy (138) in another. Studies of the combination of injection plus endoscopic clips have demonstrated no statistically significant benefit over injection alone (138, 139) or clips alone (99). The finding of increased rebleeding with the combination of injection and clips compared with clips alone (99, 138) requires further study.

The variable success of endoscopic clips may reflect difficulty with their placement. Some studies report outcomes only of patients in whom clips were successfully placed, rather than performing an intention-to-treat analysis. It is likely that further improvement in the clips and their ease of placement will lead to more widespread use. It was suggested that as the choice of endoscopic therapeutic method evolves, it may, in the future, be tailored to the nature of the underlying high-risk lesion.

Recommendation 12: Routine second-look endoscopy is not recommended. Recommendation: E (vote: a, 92%; b, 8%); Evidence: I

Four randomized, controlled trials have specifically examined the utility of scheduled (programmed) repeated endoscopy after endoscopic hemostatic therapy. Messmann and coworkers (140) found that scheduled repeated endoscopies after initial successful treatment did not improve outcomes compared with second endoscopy performed only at recurrent hemorrhage. In a study of patients with high-risk stigmata, Villanueva and colleagues (141) noted a statistically nonsignificant trend toward better outcomes in the group that received routine second-look endoscopy within 24 hours. A study by Saeed and associates (142) in highly selected patients who had undergone initial endoscopic therapy for persistent high-risk lesions showed benefits for those randomly assigned to repeated hemostatic treatment compared with no retreatment. Rutgeerts and coworkers (120) did not find superiority of repeated sessions versus a single session of fibrin glue injection in patients with high-risk stigmata but did find that the former was superior to polidocanol injection. The variability in patient samples and interventions limits any attempt to pool these data quantitatively. Second-look endoscopy may therefore be of statistical benefit in select high-risk patients, but data are conflicting regarding its routine use. A second endoscopy is ultimately needed in patients whose initial

endoscopic examination is incomplete because of technical reasons (such as excessive blood).

Recommendation 13: In cases of rebleeding, a second attempt at endoscopic therapy is generally recommended. Recommendation: A (vote: a, 100%); Evidence: I

In the only randomized comparison, immediate endoscopic retreatment in patients with rebleeding after endoscopic hemostasis reduced the need for surgery without increasing the risk for death and was associated with fewer complications than surgery (143). However, these surgical procedures performed in Hong Kong were somewhat more complex and had greater attendant morbidity than those usually performed in North America. This limits the generalizability of the results. Endoscopic therapy should be tailored according to available expertise.

Recommendation 14: Surgical consultation should be sought for patients who have failed endoscopic therapy. Recommendation: B (vote: a, 100%); Evidence: II-2

In the RUGBE cohort, continued bleeding or rebleeding was noted in 14.1% of patients, and 6.5% required surgery (4). Similar proportions, after differing patient population characteristics are taken into account, have been reported in other large cohorts (34, 42, 49, 56, 81, 144–147). In the study by Lau and colleagues of patients at high risk (143), 27% of those with rebleeding after endoscopic treatment required salvage surgery. Thus, early surgical consultation may be particularly beneficial in patients at high risk for failed endoscopic retreatment.

Pharmacotherapy

Recommendation 15: H_2-receptor antagonists are not recommended in the management of patients with acute upper GI bleeding. Recommendation: D (vote: a, 92%; b, 8%); Evidence: I

An initial 1985 meta-analysis by Collins and Langman (148), which included 27 randomized trials with more than 2500 patients, suggested that H_2-receptor antagonist treatment might reduce the rates of rebleeding, surgery, and death by approximately 10%, 20%, and 30%, respectively, compared with placebo or usual care. However, these results were statistically significant only for surgery and death, and it appeared that the benefit was confined to patients with bleeding gastric ulcers (**Appendix Table 3**, available at www.annals.org) (148). A 2000 meta-analysis by Selby and associates (149), which included 21 studies and 3566 patients treated with H_2-receptor antagonists or proton-pump inhibitors, demonstrated statistically significant reductions in rates of rebleeding and surgery but not mortality compared with placebo. Another recent meta-analysis by Levine and coworkers (150) concluded that intravenous H_2-receptor antagonists provided no additional benefit in bleeding duodenal ulcers but provided small but statistically significant absolute risk reductions in rebleeding (7.2%), surgery (6.7%), and death (3.2%) in patients with bleeding gastric ulcer compared with placebo.

In the McGill University meta-analyses by Bardou and colleagues (13, 14), which included 16 relevant studies assessing H_2-receptor antagonist therapy (100, 114, 119, 125, 129, 132, 137, 151–159), no statistically significant improvement in outcomes was noted compared with other pharmacotherapy or endoscopic therapy. However, the results were not stratified according to H_2-receptor antagonist dosing regimens or ulcer location.

Recent meta-analyses have found proton-pump inhibitors to be more effective than H_2-receptor antagonists (160) and H_2-receptor antagonists or placebo (161) in preventing persistent or recurrent bleeding (160, 161) and surgery (161) in selected patients. Given the proven benefit of proton-pump inhibitors (see recommendation 17) and the inconsistent and at best marginal benefits of H_2-receptor antagonists, the latter are not recommended for the management of acute upper GI bleeding.

Recommendation 16: Somatostatin and octreotide are not recommended in the routine management of patients with acute nonvariceal upper GI bleeding. Recommendation: C (vote: a, 96%; b, 4%); Evidence: I

A meta-analysis of 14 trials, including 1829 patients treated with somatostatin or octreotide compared with H_2-receptor antagonists or placebo, found a reduced risk for rebleeding (**Appendix Table 3**, available at www.annals.org) (162). The overall results suggested a decreased need for surgery in the somatostatin group, but this was not statistically significant in a subgroup analysis of investigator-blinded trials (162), and no adjustment for confounding or stratification by stigmata was made.

In the McGill University meta-analyses by Bardou and colleagues (13, 14), neither somatostatin nor octreotide improved outcomes compared with other pharmacotherapy or endoscopic therapy (132, 153, 157, 158, 163). Several studies have shown octreotide to be similar to or better than ranitidine in terms of rebleeding but statistically significantly less effective than endoscopic hemostatic therapy (132, 153, 157). In other studies, somatostatin was no more effective than ranitidine (158) but was superior to secretin (163).

The panel felt there was little evidence to support somatostatin or octreotide in the routine management of acute upper GI bleeding. However, this therapy might be useful for patients who are bleeding uncontrollably while awaiting endoscopy or for patients with nonvariceal bleeding who are awaiting surgery or for whom surgery is contraindicated. Although not part of the formal recommendation, this suggestion was made in light of the favorable safety profile of these medications in the acute setting.

Recommendation 17: An intravenous bolus followed by continuous-infusion proton-pump inhibitor is effective in decreasing rebleeding in patients who have undergone successful endoscopic therapy. Recommendation: A (vote: a, 100%); Evidence: I

Four randomized trials specifically assessing high-dose bolus and continuous-infusion proton-pump inhibitors, largely in patients with high-risk stigmata following endoscopic therapy, have shown decreased rebleeding and, in some cases, reduced need for surgery compared with H_2-receptor antagonists or placebo (151, 164–166). Two recent meta-analyses demonstrated that intravenous proton-pump inhibitors were more effective than H_2-receptor antagonists in preventing persistent or recurrent bleeding (160, 161). Only 1 showed a decrease in surgery rates (161), and neither demonstrated a decrease in mortality rates (**Appendix Table 3**, available at www.annals.org) (160, 161). The McGill University meta-analyses (13, 14) found that high-dose proton-pump inhibitor therapy after successful endoscopic therapy led to a statistically significant reduction in the absolute rate of rebleeding compared with H_2-receptor antagonists alone, H_2-receptor antagonists in combination with somatostatin, or placebo. Intravenous proton-pump inhibitors also statistically significantly reduced absolute mortality rates compared with placebo and surgery rates compared with placebo or a combination of H_2-receptor antagonists and somatostatin (13, 14). The only study of continuous proton-pump inhibitor infusion that did not show benefit over a regular intravenous omeprazole dosage of 20 mg/d (167) was not included in the meta-analysis; more than 25% of patients had low-risk endoscopic lesions, and the published data did not allow results in the high-risk group to be adequately analyzed separately. Among 156 patients with nonbleeding visible vessels and adherent clots, a recent randomized trial by Sung and colleagues (168) demonstrated the superiority of a combination of intravenous high-dose omeprazole infusion and endoscopic hemostasis over intravenous high-dose treatment alone.

Of interest, the RUGBE registry appeared to confirm that proton-pump inhibitor therapy reduces rates of rebleeding and mortality in high-risk patients and even suggested a trend toward decreased rebleeding in patients with low-risk stigmata after adjustment for confounders (4). These data require prospective confirmation from properly designed comparative trials.

Both the rationale for the use of proton-pump inhibition and the existing data suggest that this is a class effect and that the improvement in rebleeding can be achieved by using either intravenous omeprazole or pantoprazole, 80-mg bolus followed by 8 mg/h for 72 hours after endoscopic therapy. It is unclear what the threshold, or lowest effective dose, would be and whether it would differ among proton-pump inhibitors.

Recommendation 18: In patients awaiting endoscopy, empirical therapy with a high-dose proton pump inhibitor should be considered. Recommendation: C (vote: a, 40%; b, 32%; c, 16%; d, 12%); Evidence: III

This recommendation is based primarily on consensus formed by consideration of biological plausibility of physiologic effect and best available evidence. One study of the use of intravenous proton-pump inhibitors before endoscopic therapy in unselected patients with upper GI bleeding found no difference compared with placebo, despite an improvement in endoscopic stigmata. However, doses of proton-pump inhibitors (omeprazole, 80-mg bolus plus 40 mg intravenously every 8 hours for 1 day, followed by 40 mg orally every 12 hours for 4 days) may have been suboptimal (169). Two studies in Asia compared oral omeprazole, 40 mg every 12 hours for 5 days, with either placebo (without endoscopic therapy) (170) or endoscopic injection of alcohol for high-risk lesions (171). A third study compared the same omeprazole dosage after endoscopic injection therapy with placebo (172). All showed decreased rebleeding with or without decreased rates of surgery. A study from Iran using oral omeprazole, 20 mg every 6 hours for 5 days, which was published after the consensus conference, also suggested decreased rebleeding compared with placebo after injection hemostasis (173). Western trials assessing high-dose oral proton-pump inhibition have included few patients or have adopted an unblinded assessment of outcomes (153, 155), have yielded disparate results, and do not allow definitive conclusions. Indeed, the applicability of the Asian results to a western population has been questioned because of possible differences in physiologic characteristics and proton-pump inhibitor metabolism (174–177). The RUGBE data have suggested some efficacy in patients with both low- and high-risk endoscopic lesions (4). Recent analyses suggest that preendoscopy administration of proton-pump inhibitors may be cost-effective in certain situations (178, 179).

This recommendation recognizes the excellent safety profile of proton-pump inhibitors. The panel did not explicitly endorse an optimal route of administration, although some advocated an intravenous route for patients at high risk and an oral route for those at low risk. Proton-pump inhibitor infusion is not a replacement for urgent endoscopy and hemostasis, where appropriate.

Recommendation 19: Patients considered at low risk for rebleeding after endoscopy can be fed within 24 hours. Recommendation: A (vote: a, 88%; b, 12%); Evidence: I

A randomized trial has shown that the time of refeeding does not influence the hospital course of patients at low risk (180). Patients with major hemorrhage and endoscopic findings of a Mallory–Weiss tear or an ulcer with a clean base, flat spot, or clot may be fed and discharged home immediately after stabilization. The decision is otherwise made on a case-by-case basis depending on the patient's clinical status and the likelihood of repeated endoscopy or surgery.

Recommendation 20: Patients with upper GI bleeding should be tested for Helicobacter pylori *and receive eradication therapy if infection is present.* Recommendation: A (vote: a, 96%; b, 4%); Evidence: I

Post-treatment *H. pylori* infection status has been shown to be an independent predictor of rebleeding (181). Eradication of *H. pylori* has been demonstrated, in a meta-analysis of selected patients with duodenal ulcers not associated with nonsteroidal anti-inflammatory medication intake (182) and in many randomized, controlled trials (183–187), to reduce the rate of ulcer recurrence and rebleeding in complicated ulcer disease.

Most tests of active infection may exhibit increased false-negative rates in the context of acute bleeding (188–192). Although the optimal diagnostic approach remains unclear, it may include acute testing for *H. pylori* infection, followed, if results are negative, by a confirmatory test outside the acute context of bleeding. There is no rationale for urgent intravenous eradication therapy; oral therapy can be initiated either immediately or during follow-up in patients found to have *H. pylori* infection.

Ulcers Associated with Nonsteroidal Anti-Inflammatory Drugs

All of the preceding recommendations also apply to patients who have ulcers associated with nonsteroidal anti-inflammatory drugs. The roles of cyclooxygenase-2 selective inhibitors, coprescription, or *H. pylori* eradication in patients with bleeding ulcers associated with nonsteroidal anti-inflammatory drugs were beyond the scope of the consensus conference, which focused principally on acute management.

FUTURE DIRECTIONS

Although considerable advances have been made in both endoscopic and pharmacologic therapy for upper GI bleeding, data are far from complete. More comparative data are needed on the efficacy of hemostatic clips, combination endoscopic therapy, and other newer techniques, as well as the cost-effectiveness of proton-pump inhibitors, the role of oral administration, the transition from intravenous to oral therapy, and the optimal dose and duration of therapy. Although the benefits of proton-pump inhibitors are probably a class effect, further prospective studies are also needed on intravenous pantoprazole. Current data primarily apply to intravenous omeprazole, which is not available in the United States. Questions remain about the role of other pharmacologic agents, such as somatostatin and octreotide; strategies for managing pediatric patients and those in the intensive care unit; and primary and secondary prophylaxis for patients taking aspirin or nonsteroidal anti-inflammatory drugs.

The conference did not address a formal blueprint for the application of these guidelines as planned. However, we hope that dissemination of the guidelines will result in their implementation and will ultimately improve patient care. Setting quality indicator benchmarks for main outcomes (for example, rebleeding and surgical and mortality rates, as well as duration of hospitalization) may assist the measurement of delivered care. Finally, it is anticipated that these guidelines will need to be updated as data become available for emerging diagnostic and therapeutic technologies.

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Appendix: List of Attendees

Voting Participants

Canada: John K. Marshall (*Non-Voting Chair*), David Armstrong, Marc Bardou, Alan Barkun, J. Decker Butzner, Naoki Chiba, Alan Cockeram, Brian Craig, Robert Enns, Carlo A. Fallone, Marty Fishman, Nigel Flook, Jamie Gregor, Jonathan Love, Norm Marcon, Janet Martin, Joseph Romagnuolo, Alaa Rostom, Sandrine Sabbah, Anthony Taylor, Alan Thomson, and Sander Veldhuyzen van Zanten.

International: Livio Cipolletta, Martin Freeman, James Lau, and Joseph Sung.

Robin McLeod reviewed the manuscript as representative for the Canadian Association of General Surgeons.

Represented Societies

Canadian Association of Gastroenterology (CAG), CAG Practice Affairs Committee, CAG Endoscopy Committee, Canadian Association of General Surgeons, Canadian Association of Emergency Physicians, Canadian Society of Hospital Pharmacists, College of Family Physicians of Canada, Canadian Society of Primary Care Gastroenterology, CAG Pediatrics Committee, American Society for Gastrointestinal Endoscopy, and Health Canada.

Nonvoting Observers

Abdullah M. Hassen (Health Canada); Paul Sinclair (CAG); and representatives of the pharmaceutical industry from Abbott Laboratories Ltd., Altana Canada Inc., AstraZeneca Canada, Carsen Group Inc., Janssen-Ortho Inc., and Pentax Precision Instrument Corp.

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Appendix Table 1. **Summary of Statistically Significant Predictors of Persistent or Recurrent Bleeding as Assessed by Multivariate Analyses in Studies within the Past 10 Years***

Risk Factor (Reference)	Range of Odds Ratios for Increased Risk†
Clinical factors	
Age (46, 51)	
>65 y	1.3
≥70 y	2.30
Shock (systolic blood pressure <100 mm Hg) (37, 41, 46–48, 52, 56–58)	1.2–3.65
Health status (ASA class 1 vs. 2–5) (4, 51)	1.94–7.63
Comorbid illness (47, 48, 51, 53)	1.6–7.63
Erratic mental status (48)	3.21 [1.53–6.74]
Ongoing bleeding (48)	3.14 [2.40–4.12]
Transfusion requirement (59)	NA
Laboratory factors	
Initial hemoglobin ≤100 g/L or hematocrit <0.3 (37, 47, 55)	0.8–2.99
Coagulopathy (prolonged partial thromboplastin time) (48)	1.96 [1.46–2.64]
Presentation of bleeding	
Melena (56)	1.6 [1.1–2.4]
Red blood on rectal examination (4)	3.76 [2.26–6.26]
Blood in gastric aspirate or stomach (4, 37, 54, 56)	1.1–11.5
Hematemesis (37, 46, 55)	1.2–5.7
Endoscopic factors	
Active bleeding on endoscopy (44, 46, 56, 57)	2.5–6.48
Endoscopic high-risk stigmata (4, 41, 56)	1.91–4.81
Clot (41, 56)	1.72–1.9
Ulcer size ≥2 cm (52–54, 57, 58)	2.29–3.54
Diagnosis of gastric or duodenal ulcer (56)	2.7 [1.2–4.9]
Ulcer location (53, 57)	
High on lesser curvature	2.79
Superior wall	13.9
Posterior wall	9.2

* ASA = American Society of Anesthesiologists; NA = not available.
† Values in square brackets are 95% CIs.

Appendix Table 2. **Summary of Statistically Significant Predictors of Death as Assessed by Multivariate Analyses in Studies within the Past 10 Years***

Risk Factor (Reference)	Range of Odds Ratios for Increased Risk†
Clinical factors	
Age (1, 4, 32, 49, 56)	
60–69 y	3.5 [1.5–4.7]
≥75 y	4.5–12.7
>80 y	5.7 [2.9–10.2]
Shock or low blood pressure (1, 4, 32, 33, 49)	1.18–6.4
ASA classification (4, 58)	2.6–9.52
Comorbid conditions (0 vs. ≥1) (1, 4, 32, 49)	1.19–12.1
Continued bleeding or rebleeding (4, 32, 49, 56, 58)	5.29–76.23
Presentation of bleeding	
Blood in the gastric aspirate (4, 32, 34, 56)	0.43–18.9
Hematemesis (1)	2.0 [1.1–3.5]
Red blood on rectal examination (4)	2.95 [1.29–6.76]
Onset of bleeding while hospitalized for other causes (4)	2.77 [1.64–4.66]
Laboratory factors	
Elevated urea level (1)	5.5–18
Serum creatinine level >150 μmol/L (32)	14.8 [2.6–83.5]
Elevated serum aminotransferase levels (32, 33)	4.2–20.2
Sepsis (33)	5.4 [1.5–19.6]
Endoscopic factors	
Major stigmata of recent hemorrhage (49)	NA

* ASA = American Society of Anesthesiologists; NA = not available.
† Values in square brackets are 95% CIs.

Appendix Table 3. **Meta-Analyses of Pharmacotherapy for the Treatment of Upper Gastrointestinal Bleeding***

Study, Year (Reference)	Trials, *n*	Comparison Groups	Rebleeding	Surgery	Death
Collins and Langman, 1985 (148)	27	H_2-receptor antagonists vs. placebo	OR, 0.89 (NS)	OR, 0.78†	OR, 0.70‡
Selby et al., 2000 (149)	17 3 1	H_2-receptor antagonists PPI Antacid	OR, 0.727§	OR, 0.707§	OR, 1.14 (NS)
Levine et al., 2002 (150)‖	–	H_2-receptor antagonists vs. placebo	Absolute RR, −7.2% [−0.7% to −13.7%]	Absolute RR, −6.7% [−0.7% to −12.8%]	Absolute RR, −3.2% [0% to −6.3%]
Gisbert et al., 2001 (160)	11	PPI vs. H_2-receptor antagonists	OR, 0.4¶	OR, 0.7 (NS)	OR, 0.69 (NS)
Zed et al., 2001 (161)	9	PPI vs. H_2-receptor antagonists or placebo	OR, 0.50**	OR, 0.47††	OR, 0.92 (NS)
Imperiale and Birgisson, 1997 (162)	14	Somatostatin or octreotide vs. H_2-receptor antagonists or placebo	RR, 0.53¶	RR, 0.71¶	NA
Bardou et al., 2003 (13, 14)‡‡	25	PPI vs. placebo PPI vs. H_2-receptor antagonist PPI vs. H_2-receptor antagonist + somatostatin	Absolute RR, −15.6% Absolute RR, −20.2% Absolute RR, −11.1%	Absolute RR, −6.1% Absolute RR, −0.3% (NS) Absolute RR, −11.8%	Absolute RR, −2.8% Absolute RR, −1.9% (NS) Absolute RR, 5.3% (NS)

* NS = not significant; OR = odds ratio; PPI = proton-pump inhibitor; RR = relative risk.
† $P = 0.05$.
‡ $P = 0.02$.
§ $P < 0.001$.
‖ These results are for patients with gastric ulcer only; differences were not significant for patients with duodenal ulcers, or when all ulcer patients were pooled together.
¶ Significant.
** $P = 0.002$.
†† $P = 0.003$.
‡‡ 25 trials.