American Journal of Gastroenterology
© 2004 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing
ISSN 0002-9270

# The Canadian Registry on Nonvariceal Upper Gastrointestinal Bleeding and Endoscopy (RUGBE): Endoscopic Hemostasis and Proton Pump Inhibition are Associated with Improved Outcomes in a Real-Life Setting

Alan Barkun, M.D.,C.M., M.Sc., Sandrine Sabbah, M.D., Robert Enns, M.D., David Armstrong, M.D., Jamie Gregor, M.D., Richard N.N. Fedorak, M.D., Elham Rahme, Ph.D., Youssef Toubouti, M.Sc., Myriam Martel, B.Sc., Naoki Chiba, M.D., Carlo A. Fallone, M.D., and the RUGBE investigators*
*Department of Medicine, Division of Gastroenterology, McGill University, Montreal, Canada; Division of Gastroenterology, University of British Columbia, Vancouver, Canada; Division of Gastroenterology, McMaster University Medical Centre, Hamilton, Canada; Division of Gastroenterology, University of Western Ontario, London, Canada; Division of Gastroenterology, University of Alberta, Edmonton, Canada; and Division of Clinical Epidemiology, McGill University Health Center, Montreal, Canada*

**OBJECTIVES:** From the Canadian Registry of patients with Upper Gastrointestinal Bleeding and Endoscopy (RUGBE), we determined clinical outcomes and explored the roles of endoscopic and pharmacologic therapies in a contemporary real-life setting.

**METHODS:** Analysis of randomly selected patients endoscoped for nonvariceal upper gastrointestinal bleeding at 18 community and tertiary care institutions between 1999 and 2002. Covariates and outcomes were defined *a priori* and 30-day follow-up obtained. Logistic regression models identified predictors of outcomes.

**RESULTS:** One thousand eight-hundred and sixty-nine patients were included (66 ± 17 yr, 38% female, 2.5 ± 1.6 comorbid conditions, hemoglobin, 96 ± 27 g/L, 54% received a mean of 2.9 ± 1.7 units of blood). Endoscopy was performed within 24 h in 76%, with ulcers (55%) most commonly noted. High-risk endoscopic stigmata and endoscopic therapy were reported in 37%. Rebleeding, surgery, and mortality rates were 14.1%, 6.5%, and 5.4%, respectively. Decreased rebleeding was significantly and independently associated with PPI use (85% of patients, mean daily dose 56 ± 53 mg) in all patients regardless of endoscopic stigmata, (odds ratio (OR):0.53, 95% confidence interval, 95% CI:0.37–0.77) and endoscopic hemostasis in patients with high-risk stigmata (OR:0.39, 95% CI:0.25–0.61). PPI use (OR:0.18, 95% CI:0.04–0.80) and endoscopic therapy (OR:0.31, 95% CI:0.11–0.91) were also each independently associated with decreased mortality in patients with high-risk stigmata.

**CONCLUSIONS:** These results appear to confirm the protective role of endoscopic therapy in patients with high-risk stigmata, and suggest that acute use of PPIs may be associated with a reduction of rebleeding in all patients, and lower mortality in patients with high-risk stigmata. Independent prospective validation of these observational findings is now required.

## INTRODUCTION

Despite the advent of endoscopic hemostatic techniques that have been shown to be efficacious in randomized trial settings, the mortality associated with nonvariceal upper GI bleeding has changed little over the past 30 yr (1–3). This observation has been attributed to a sicker population, and the underutilization of these endoscopic therapies (4). The acute administration of high-dose intravenous (IV) proton pump inhibitors (PPI) has recently been shown, also in randomized trial settings, to provide additional benefit and further decrease rebleeding in patients undergoing endoscopic hemostasis for high-risk ulcer lesions (5–8). The main aim of this study was to describe the outcomes of patients with acute nonvariceal upper GI bleeding in a contemporary, broadly generalizable "real-life" setting. Additional analyses assessed predictors of outcome, including, as part of exploratory analyses, a determination of the impact of modern endoscopic and pharmacologic therapies. Our corresponding

*The list of all the RUGBE investigators is available in the Appendix.

additional hypotheses were that both PPI use and endoscopic therapy would be associated with improved outcomes.

## METHODS

### *The RUGBE Initiative and Data Collection*

Specialized software including a commercially available generic endoscopic reporting system (GI-Trac™, AD/MediTrac, Las Vegas, NV) linked to a project-specific research database was developed. This software was distributed to 18 participating sites across Canada, establishing a network of centers from which source data were collected—the Registry in patients with Upper Gastrointestinal Bleeding undergoing an Endoscopy (RUGBE) study group. In an effort to increase the generalizability of the findings, 6 community and 12 tertiary care institutions were included. Specially trained research assistants collected and entered the data retrospectively from hospital records into the specialized electronic databases. Missing data were minimized since only data that were commonly recorded after initial presentation were collected. All data were denominalized, entered electronically, and downloaded into a central repository on a monthly basis. They were reviewed at a single national location for internal logic of patient flow and biological plausibility. All data queries were resolved within the month following original data entry. Ten percent of all records were audited on a quarterly basis by comparing them to the source data recorded in the hospital charts, thus further validating the abstracted information. Additional chart audits were performed to ensure the completeness of follow-up information as discussed below. Personnel from a clinical research organization, who also performed quarterly audits of all sites, trained all research nurses in a standardized fashion at a common start-up meeting and at each initial on-site visit prior to the first patient entry. All participating research staff and monitors used a glossary that included definitions of all variables entered in the registry to facilitate and standardize abstracted information.

### *Patient Population*

All patients presenting for medical attention because of overt upper GI bleeding or a history of hematemesis/coffee ground vomiting, melena, hematochezia, or a combination of any of the above within 24 h preceding admission were considered for the study (6, 9, 10). Furthermore, upper GI bleeding was confirmed only if a member of the medical or nursing staff documented and witnessed either hematemesis, melena, or the recovery of bloody nasal gastric aspirate, or if they noted black tarry material on rectal examination (6, 9, 10). Patients were entered in the registry only if an upper GI endoscopy was performed. Patients in whom esophageal, gastric, or duodenal varices were noted to be the source of bleeding were excluded from the registry. The volume of patients who fulfilled these criteria treated across all sites would not allow a complete inclusion of cases, particularly as we wanted to study over a 2-yr period the introduction of IV PPIs onto the Canadian practice setting. We purposefully thus only included a sampling of eligible patients. This sampling was carried out at regular intervals using randomly varying sequential time series to avoid any systematic bias in patient selection. The proportion of cases enrolled at each center from all possible candidate patients was related to the assignment of a part-time or full-time research nurse to that particular participating institution. An audit of all patients presenting over a fixed time period, at each participating institution, was carried out to better identify the possibility of any selection bias in the way in which the study population was sampled. Patients initially assessed at another institution for the episode of bleeding and subsequently transferred to one of the participating sites were tracked separately. The reference time was the onset of initial presentation to the emergency room or when bleeding started if the patient was already in hospital for other reasons.

### *Study Variables*

INDEPENDENT VARIABLES. Recorded information included the following independent variables: demographic information (age, sex, site, date of endoscopy); historical data (presenting symptoms, comorbid illnesses, the patient's health status on presentation using the American Society of Anesthesiologists (ASA) classification (11), relevant past medical history, medication intake, thorough evaluation of the time elapsed from the onset of the bleeding); physical examination findings (hemodynamic data, rectal exam, nasogastric tube use, and findings); initial laboratory data (CBC, INR, platelets); and resuscitative efforts (type and quantity of fluids, timing of administration). The endoscopic components of the database were created to be compatible with Minimal Standard Terminology (12) and included identification of the bleeding lesion, description of stigmata of bleeding, method of endoscopic hemostasis if any, number of therapeutic attempts, timing, and conditions in which the endoscopy was performed. The performance of other therapies (surgery, angiography), administration of pharmacologic therapy for bleeding (types and method of administration), and relevant *Helicobacter pylori*-related information obtained during the initial bleeding event were also recorded.

OUTCOMES. The outcomes included the frequency of continued bleeding and rebleeding, surgical therapy, transfusions, hospital stay, and mortality. *A priori* definitions for all outcomes were adopted according to adaptations of established definitions in the literature (6, 9, 10). Continued bleeding was defined as (a) spurting arising from an artery on the initial endoscopic examination that did not respond to endoscopic therapy, or the persistence following initial endoscopy of; (b) the presence of a bloody nasogastric aspirate; (c) shock with a pulse greater than 100 beats/min, a systolic blood pressure of under 100 mmHg, or both; and/or (d) the need for substantial replacement of blood and fluid volume (transfusion of greater than 3 units of blood within 4 h)

following endoscopic therapy (6, 9, 10). Persistent bleeding in many cases was confirmed during surgery, which was performed within a few hours of admission. Rebleeding was defined by recurrent vomiting of fresh blood, melena, or both with either shock or a decrease in hemoglobin concentration of at least 2 g/L following initial successful treatment including resuscitation and endoscopic therapy, if indicated (modified from Daneshmend *et al*. (10)). The outcomes of continued bleeding and rebleeding likely formed a spectrum in this retrospective data collection, and an *a priori* decision was taken to group them together for the purposes of all analyses even though this conservative decision may subsequently lead to an underestimation of protective effects attributable to some therapies. Additional information regarding patient transfer to and from other institutions and any readmission was also noted. All data were recorded for the full duration of the initial medical encounter. The data abstraction of charts for all patients included a subsequent medical records chart review, after RUGBE had been completed, which assessed all charts of included patients for a full 30 days following the initial emergency room visit, admission, or onset of bleeding while in hospital. This audit also ensured capture of possible readmissions or admissions following an initial emergency room discharge.

### *Data Analysis*

DESCRIPTIVE. Owing to the nature of the study design, principally descriptive data were generated for the independent and dependent variables listed above. All categorical data were expressed as proportions. All continuous data were expressed as means $\pm$ standard deviations. Where appropriate, alternate descriptive statistics such as quartile ranges, and medians with ranges for categorical and continuous data respectively are reported.

MODELING. We generated predictors of outcome, based on clinical considerations that related to baseline patient characteristics or therapies administered. We determined independent predictors of mortality and rebleeding in patients with low- and high-risk endoscopic stigmata, since the recommended management of patients differs according to endoscopic findings both with regard to endoscopic hemostasis and the use of high-dose IV PPI (3). Patients with rebleeding/continued bleeding and those going on to surgery were grouped together with regard to predictive modeling. Standard step-wise logistic regression analysis techniques were used for model creation and selection (SAS, Cary, NC). Independent variables were tested for multicollinearity, and only included in the model if none was noted. Levels of significance for the independent predictors were considered based on whether or not the 95% confidence intervals (95% CI) for the corresponding odds ratios crossed 1 or not. For all predictive models presented below, we excluded patients transferred from other institutions as the historical, physical exam, initial laboratory, and in some cases, endoscopic findings would be misleading since they were only captured following admission to the referred participating institution.

EXPLORATORY ANALYSES. Since the registry is a "natural" experiment (with utilization of a multitude of PPI doses), we sought a threshold PPI dose that may be associated with improved outcomes. Standard calculation of a daily dose of medication would not be meaningful because of confounding by indication, as both patients at high risk for rebleeding as well as those who did rebleed, may have been started on a specific medication at a specific dose. To resolve these issues statistically, we used a well-recognized statistical methodology termed propensity scores (13, 14), which was defined as a patient's probability of being prescribed an IV PPI, given all available covariates. Patients with similar propensity scores have similar characteristics, and exhibit similar baseline risks. Calculated using a logistic regression model and used as categorical or continuous covariates in multivariate analyses, propensity scores effectively remove 90% or more of possible selection bias (13, 14) and create a quasi-randomization among patients within similar scores with regard to measurement of outcomes. Patients were stratified into quintiles according to their propensity scores, from the least likely to receive IV PPIs (propensity scores $<20\%$) to the most likely (propensity scores $\geq 80\%$). The PPI daily dose was categorized into 0, 1–50, 51–100, 101–150, and $>150$ mg/day. Separate logistic regression models were used to compare mortality and rebleeding between PPI daily dose categories adjusting for propensity scores. In these analyses, we decided *a priori* to include adjustment for all possible confounders that would be identified in our predictive models of outcome.

### *Ethics*

The registry was approved by the Institutional Ethics Review Boards of all participating centers. The approval by the Director of Professional or Hospital Services was also obtained at all sites. In addition, patient consent was obtained where required by local regulations.

## RESULTS

### *Study Population*

A total of 1,878 patients were entered in the RUGBE registry between September 1999 and December 2001 (with data queries collected until January 2002). Nine of these patients were subsequently excluded because of bleeding secondary to esophageal varices. The mean enrollment per site was 104 $\pm$ 80 patients. The medical record audit designed to ensure an adequate, nonbiased sampling of patients was carried out in 14 sites, and revealed that 56% of all patients seen in these institutions were entered in RUGBE over a mean 11.5 $\pm$ 4.9 study-months. Furthermore, the 1,163 cases (62% of all RUGBE population) enrolled by the top six recruiting centers represented 82% of all patients with upper GI bleeding seen

**Table 1.** Study Population Characteristics

| | Low Risk (n = 1177) | | High Risk[α] (n = 692) | | Total (n = 1869) | |
|---|---|---|---|---|---|---|
| Population (n = 1869) | Mean (median, IQR**) | $CI_{95}$/SD* | Mean (median, IQR**) | $CI_{95}$/SD* | Mean (median, IQR**) | $CI_{95}$/SD* |
| Male | 61 | 58.8–63.4 | 64 | 60.6–67.7 | 62 | 59.7–64.1 |
| Age (yr) | 67(70; 56–79) yrs | ± 17 yr | 66 yrs (69; 54–78) | ± 16 yr | 66 yrs (70; 55–79) | ± 17 yrs |
| Number of comorbid conditions | 2.5(2.0; 1.0–3.0) | ± 1.6 | 2.6(2.0; 1.0–4.0) | ± 1.7 | 2.5(2.0; 1.0–3.0) | ± 1.6 |
| ASA Score[†] | | | | | | |
| 1–2 | 48% | 45.0–50.7 | 28% | 24.5–31.2 | 40% | 37.8–42.3 |
| 3 | 42% | 38.7–44.4 | 51% | 47.4–54.9 | 45% | 42.7–47.3 |
| 4–5 | 11% | 8.9–12.4 | 21% | 17.9–24.0 | 14% | 12.4–15.6 |
| Inpatient at the time of onset bleed | 25% | 22.4–27.3 | 26% | 22.4–29.0 | 25% | 23–27 |
| Transferred patients | 6% | 4.6–7.3 | 11% | 8.7–13.5 | 8% | 6.5–9.1 |
| Past history of upper GI bleed | 18.4% | 16.1–20.7 | 21.0% | 17.8–24.2 | 19.5% | 17.1–20.9 |
| Past history of PUD | 25% | 22.8–28.1 | 28% | 24.5–31.6 | 27% | 23.9–28.1 |
| Symptoms on presentation | | | | | | |
| Melena | 66% | 63.3–68.7 | 75% | 71.7–78.2 | 69% | 67.2–71.4 |
| Hematemesis | 28% | 25.6–30.7 | 32% | 28.5–35.5 | 30% | 27.5–31.6 |
| Coffee ground vomiting | 30% | 27.4–32.6 | 24% | 20.9–27.3 | 28% | 25.8–29.8 |
| Hematochezia | 13% | 10.9–14.8 | 19% | 16.4–22.3 | 15% | 13.6–16.9 |
| Medications at presentation | | | | | | |
| Aspirin[‡] | 41% | 38.5–44.2 | 38% | 34.6–41.8 | 40% | 38.0–42.4 |
| NSAIDs | 19% | 16.7–21.2 | 20% | 17.5–23.6 | 20% | 17.7–21.4 |
| COX–2 | 3.8% | 2.7–4.8 | 2.5% | 1.3–3.5 | 3.3% | 2.5–4.1 |
| Coumadin | 11% | 8.9–12.4 | 11% | 8.3–12.8 | 11% | 9.2–12.0 |
| Heparin | 10% | 7.9–11.3 | 13% | 10.5–15.5 | 11% | 9.5–12.3 |
| Steroids | 6.3% | 4.9–7.7 | 7.2% | 5.3–9.2 | 6.7% | 5.5–7.8 |
| Rectal exam yield | | | | | | |
| Melena | 23% | 21.0–25.9 | 27% | 23.4–30.0 | 25% | 22.7–26.6 |
| Bright red blood | 5% | 3.6–6.0 | 6% | 4.4–8.1 | 5% | 4.3–6.4 |
| Occult blood positive | 25% | 22.1–27.1 | 26% | 22.7–29.2 | 25% | 23.1–27.1 |
| Not documented | 35.1% | 32.3–37.8 | 33.1% | 29.6–36.6 | 34.5% | 32.2–36.5 |
| Naso-gastric aspirates yield | | | | | | |
| Coffee ground material | 13% | 10.7–14.5 | 9% | 7.1–11.4 | 11% | 9.9–12.8 |
| Bright red blood | 6% | 5.1–7.9 | 12% | 9.9–18.4 | 9% | 7.4–9.9 |
| Tube not placed/documented | 71% | 68.0–73.2 | 72% | 68.4–75.1 | 71% | 69.0–73.1 |
| Initial hemodynamic instability | 29% | 26.2–31.7 | 37% | 33.2–40.8 | 32% | 29.7–34.2 |
| Lab results | | | | | | |
| Initial mean hemoglobin (g/L) | 99(97; 81–117) | ± 30 SD | 91(89; 75–106) | ± 25 SD | 96(94; 78–113) | ± 27 SD |
| Hematocrit | 0.30(0.29; 0.24–0.35) | ± 0.08 SD | 0.27(0.27; 0.22–0.32) | ± 0.07 SD | 0.29(0.28; 0.23–0.34) | ± 0.08 SD |
| Platelet count | 255(237; 184–310) × $10^9$/L | ± 123 × $10^9$ SD | 245(228; 172–296) × $10^9$/L | ± 119 × $10^9$ SD | 251(234; 180–306) × $10^9$/L | ± 121 × $10^9$ SD |
| INR | 1.5(1.1; 1.0–1.3) | ± 1.8 SD | 1.6(1.2; 1.1–1.4) | ± 1.6 SD | 1.5 (1.2, 1.0–1.3) | ± 1.7 SD |

*SD = standard deviation; $CI_{95}$ = 95% confidence interval.
**IQR = Interquartile range.
[†]ASA score refers to the American Society of Anesthesiologists classification of a patient's severity and acuity of disease index (11).
[α]High-risk stigmata includes active bleeding(spurting and oozing), visible vessels, visible vessels with clots.
[‡]Mean daily dose of aspirin was 342 ± 517 mg.

in those institutions during the study period. Patient characteristics are listed in Table 1.

### *Initial Management and Endoscopic Data*

IV fluids were administered to 78% of patients within 3.4 ± 6.9 h of admission or bleeding onset in hospitalized patients. Both crystalloid solutions (74%) and frozen plasma (15%) were used, with a mean of 2.9 ± 1.7 (median: 2, interquartile range (IQR 2.0–4.0): 2) units of blood given to 54% of patients.

Overall, 2,484 endoscopic procedures were performed with a median of one procedure per patient (range 1–6). An endoscopy was first performed in 76% of patients within 24 h of presentation to the emergency room or of the onset of bleeding in patients already hospitalized (Fig. 1). Repeat endoscopy was performed in 25% of patients. Findings on endoscopy included ulcers (56%) (gastric (47%), duodenal (42%), esophageal (11%)) duodenal and gastric erosions (10%), and esophagitis (9%), with other lesions, including Mallory–Weiss tear, Dieulafoy lesions, vascular lesions, tumors, and polyps being less prevalent. Blood without a specific associated lesion was noted in 1%, and endoscopy was normal in 3.6%. Actively bleeding lesions were found in 27% of patients (3% spurting, 22% oozing, and 2% unspecified). Among patients with high-risk endoscopic stigmata, 74% had an endoscopic treatment. No active bleeding was reported in 69% (47% clean base, 10% visible vessel, 7% clot, 5.2% pigmented material). Of the 37% of patients receiving endoscopic therapy, injection therapy alone was performed in 38%, isolated thermal therapy in 23%, combination thermal and injection therapy in 34%, and hemoclips (alone or in combination) in 3%, and other 2%. Detailed results on the endoscopic findings are reported elsewhere (15).

### *Pharmacotherapy*

The first dose of medication was administered within 10.7 ± 16.7 h following presentation to hospital or onset of bleeding in patients already hospitalized. A PPI (oral and/or IV) was given during hospitalization or emergency room visit to 85% of patients. Overall, 66% received at least one dose of an oral PPI, while 56% of patients received at least one dose of an IV PPI. The mean daily dose of PPI was 56 ± 53 mg, and included 92 ± 65 mg of an IV and 33 ± 30 mg of an oral preparation. In Canada, the only approved IV PPI available during the study period was IV pantoprazole, although in 1% of cases, IV omeprazole was administered through a special access plan. Among patients with high-risk endoscopic lesions, the mean daily doses of IV and oral PPI were 105 ±

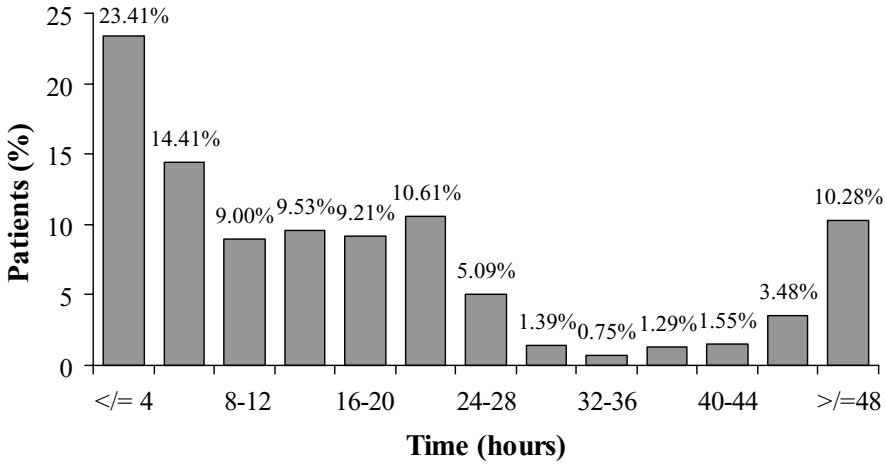


**Figure 1.** Timing of endoscopy following initial presentation with bleeding.

61 mg and 39 ± 30 mg, respectively. Overall, 24% received an oral and/or IV $H_2$ receptor antagonist (ranitidine 51%, famotidine 48%). Nineteen percent of patients received both a PPI and a $H_2$ receptor antagonist, and 7.1% received either octreotide (6.3%) or somatostatin (0.8%). These percentages are not mutually exclusive.

Endoscopic and PPI therapy were used together in 34% of all patients (with IV PPI in 27.4%, and oral PPI in 26.3%). Among patients receiving a PPI, 11% underwent endoscopic therapy, while 94% of patients undergoing endoscopic hemostasis also received a PPI (with a mean daily dose over 100 mg in 42%). Of the 1,177 patients with low-risk stigmata, 66.1% received PPI therapy without endoscopic treatment, 45.0% received at least one dose of IV PPI, and 64.0% received at least one dose of oral PPI.

### *Management of H. Pylori*

Testing for *H. pylori* was performed during the hospital stay in 47% of patients (77% histology, 9% rapid urease testing, 6% serology, and 8% others). Among patients with gastroduodenal ulcers who were tested, *H. pylori* was found in 45% of patients overall (43.1% for gastric and 53.5% for duodenal ulcers), and 0.6% of whom had used NSAIDs. Eradication therapy was initiated during hospitalization in only 10% of cases within a mean of 70.6 ± 12 h.

### *Outcomes*

Continued and/or rebleeding during the same hospitalization or a subsequent admission within 30 days occurred in 14.1% of patients, with 6.5% requiring surgery, and 5.4% dying. The mean age of patients who died was 72 ± 12.6 yr. Among these patients, 38% (37/98) had continued bleeding (70.5 ± 14 yr), and 13.3% (13/98) had rebleeding (67.9 ± 16 yr). Mean length of stay was 5.6 ± 6.1 days (median: 2.0, IQR: 2.0–7.0), and included a mean of 0.89 days in the intensive care unit. Overall, 11.7% of patients were discharged directly from the emergency room. Full 30-day follow-up information was available for 1,758 (94.1%) patients; readmissions or admissions following an initial discharge from the emergency room were noted in only14 (0.8%) patients.

### *Predictive Models*

Predictors of rebleeding/continued bleeding/surgery included the patient's health status, rectal examination findings, nasogastric tube aspirate, and the presence of high-risk endoscopic stigmata (Table 2). Protective therapies included the acute use of a PPI (initiated before the outcome) in patients with or without high-risk endoscopic lesions, and the performance of endoscopic therapy in patients with high-risk endoscopic stigmata (Table 2, Fig. 2A). Institution, type of institution (tertiary *vs* nontertiary setting), geographic location (by province), and the timing of endoscopy were all assessed in the overall patient analyses and none was found to be a significant predictor of outcome.

**Table 2.** Logistic Regression Model to Determine Significant Predictors of Rebleeding*

| Predictors (n = 1677) | Odds Ratio Estimates | |
|---|---|---|
| | Point Estimate | $CI_{95}$ |
| Health status | 1.94 | 1.44–2.62 |
| Rectal exam 1 | 3.76 | 2.26–6.26 |
| NGT aspirate 1 | 2.55 | 1.70–3.82 |
| Endoscopic high-risk stigmata | 4.81 | 3.26–7.1 |
| PPI use | 0.53 | 0.37–0.77 |
| Endoscopic treatment† | 0.39 | 0.25–0.61 |

*For the purposes of predictive modeling, patients who experienced rebleeding, continued bleeding or surgery were grouped together.
†Values are for all patients, except for endoscopic treatment, which applies only to patients with endoscopic high-risk stigmata for rebleeding, including active bleeding (spurting and oozing), visible vessels, and clots.
Health status = class 1 or 2 versus others as determined by the ASA score (11); (severely stable, severely unstable or moribund *vs* healthy or moderately healthy).
NGT aspirate 1 = a nasogastric tube aspirate showing bright blood *versus* other findings
PPI use = use of a PPI prior to the episode of rebleeding.
Rectal exam 1 = a rectal examination showing bright blood *versus* other findings.

Significant baseline predictors of increased mortality included increasing age (per decade, OR: 1.36, 95% CI: 1.13–1.61), decreasing systolic blood pressure at initial assessment (per 10 mm–Hg, OR: 1.18, 95% CI: 1.08–1.30), increasing number of comorbidities (1 or none *vs* more, OR: 1.19, 95% CI: 1.04–1.35), worsening health status (severely stable, severely unstable or moribund *vs* healthy or moderately healthy, OR = 9.52, 95% CI: 3.37; 26.31), bright blood on rectal examination (OR: 2.95, 95% CI: 1.29–6.76), bright red blood in nasogastric tube aspirate (OR: 2.14, 95% CI: 1.11–4.10), inpatient status at onset of bleeding (OR: 2.77, 95% CI: 1.64–4.66), and rebleeding (OR: 5.29, 95% CI: 3.23–8.65). Among patients who were outpatients at onset of bleeding, significant predictors in those with high-risk endoscopic stigmata included comorbidities and low systolic blood pressure (Table 3). Protective therapies in these patients included the acute use of a PPI, and the performance of endoscopic therapy (Table 3, Fig. 2B). Additional analyses showed that further adjustment for setting of care (community *vs* tertiary) did not alter the results, and that a survivor bias (or in this case early mortality bias) did not play a role in the noted significant association between decreased mortality and PPI use.

### *Exploratory PPI Dose Threshold Analysis*

In this set of analyses, adjustment was initially carried out according to the following possible confounders of outcome: age, sex, comorbidity, health status, rectal exam findings, nasogastric tube aspirate findings, blood pressure, inpatient status at the time of bleed, the initial hemoglobin level, the nature and risk of the endoscopic lesion, the number of transfused units of blood, the time of the endoscopy, and the performance of endoscopic therapy. Higher compared to lower propensity scores (20–40%, 40–60%, 60–80%, and 80–100% likelihood of receiving an IV PPI *vs* a comparator group of 0–20%) were associated with a higher risk for rebleeding, even after adjusting for known possible confounders. The search for a dose threshold did not yield a significant cut-off but suggested a trend for a daily dose of 100 mg or more as being more strongly protective (OR: 0.44, 95% CI: 0.27–0.71).

**Table 3.** Predictors of Mortality in Patients with High-Risk Stigmata Who Were not in Hospital When the Bleeding Started

| Effects (n = 432) | Odds Ratio Estimates | |
|---|---|---|
| | Point Estimate | $CI_{95}$ |
| Age by decade* | 1.50 | 1.03–2.16 |
| Comorbidity >2 *vs* ≤2* | 2.92 | 1.02–8.4 |
| Low systolic blood pressure (per 10 mmHg)* | 1.46 | 1.16–1.87 |
| PPI use* | 0.18 | 0.04–0.80 |
| Endoscopic treatment* | 0.31 | 0.11–0.91 |

*Significant predictors (odds ratio does not cross 1).
Comorbidity = patients with 2 or fewer comorbid conditions *versus* patients with 3 or more.
Systolic blood pressure = systolic blood pressure at the initial assessment.
Baseline hemoglobin = hemoglobin at the initial assessment.
PPI use = use of a PPI during the patient's hospitalization.

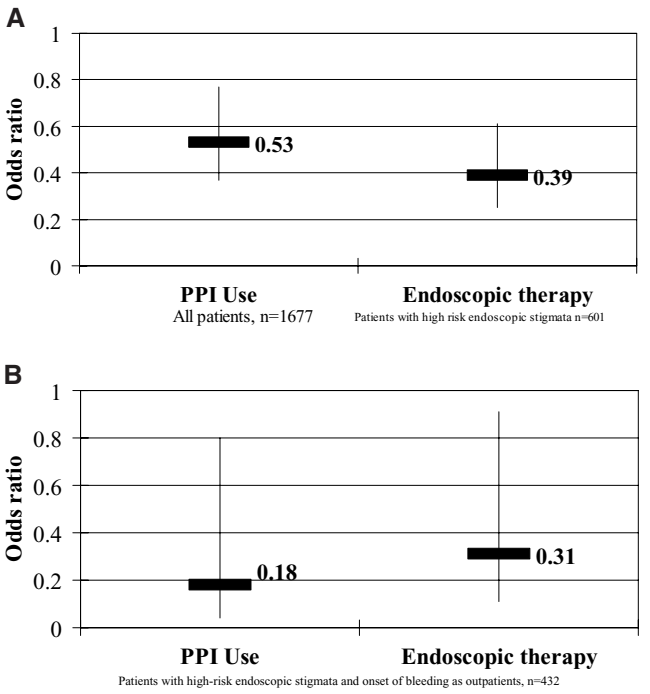


**Figure 2.** Treatments that have significant protective effects on (*A*) rebleeding or (*B*) mortality. For the purposes of predictive modeling, patients who experienced rebleeding, continued bleeding, or surgery, were grouped together. PPI use = use of PPI prior to rebleeding, for the outcome of rebleeding, or at any time during hospitalization for the outcome of mortality.

## DISCUSSION

Most descriptive results noted in RUGBE, such as patient demographics and endoscopic findings, including the prevalence of stigmata, were comparable to previously published large databases, excluding patients with varices (1, 16–22). The rebleeding rate of 14.6% is comparable to that reported in other recent large "real-life" databases (18, 23), and includes patients with continued bleeding. Access to endoscopy was also similar to that reported (18), as was the modest use of combination endoscopic therapy. The baseline clinical predictors of mortality and rebleeding that we identified are similar to those previously reported in the literature (24). In the analyses, the different obtainable components that make up the Rockall score were included individually in the model. We have assessed validation of the Rockall scoring scheme in a separate study (25).

Despite adopting a conservative approach by grouping rebleeding, continued bleeding, and surgery in the predictive modeling, endoscopic and pharmacological treatments were shown to be independent predictors of improved outcomes. No single clinical trial had, to date, been large enough to demonstrate a significant reduction in mortality attributable to endoscopy although it had been reported by metaanalyses (26–28). The RUGBE results also demonstrate a decrease in mortality attributable to PPI use in this subgroup—also a new finding, which is probably related to the large number of

patients included in the registry and is supported by observed trends from smaller randomized trials (8), and a preliminary metaanalysis report (29). Because of the nature of the study design, these findings need to be considered exploratory and require prospective confirmation, although it is unlikely that a prospective controlled trial will be initiated that can include a sufficient patient number to better define many of these observations.

RUGBE suggests confirmation that both endoscopic therapy and PPI use decrease rebleeding in patients with high-risk stigmata, as shown previously in randomized trials of patients with bleeding ulcers (5–8, 26–30). Perhaps the most interesting finding is the independent and significant decrease in rebleeding attributable to PPI use that was noted in patients without high-risk stigmata, most of whom did not undergo endoscopic therapy. The reasons for this may include adequate statistical power to demonstrate a small but significant benefit since the rebleeding rate in these patients is quite low (31). Alternatively, high-risk stigmata may have been incorrectly diagnosed as low risk, although a large number of incorrect diagnoses would have been necessary to provide the magnitude of observed protective effect, and the prevalence and distribution of the observed endoscopic stigmata, as stated before, was in keeping with those reported in similar registries (17, 21, 32, 33). In this regard, it is interesting to note that although wide interobserver variation exists in endoscopic diagnoses (34), a recent Canadian study demonstrated good agreement for bleeding lesions among 30 endoscopists, half of whom participated in the RUGBE registry (35).

The clinical significance of this possible, more generalized benefit attributable to PPI use remains unclear as the probability of rebleeding in this patient population is already quite low (31), particularly in patients with clean base ulcers who can be discharged home directly from the emergency room (36). However, the cost implications of this additional effect in patients with low-risk stigmata in any bleeding lesion are potentially significant and may, if confirmed, favor a policy of PPI administration to all patients prior to endoscopy, as has been suggested in recent decision modeling (37, 38).

Even though the protective effects associated with the use of endoscopic therapy and PPIs are statistically independent of each other, PPI use was administered in association with endoscopic therapy in 34% of the patients. Unfortunately, the data collected in the registry do not allow us to identify the magnitude of effect in relation to whether the PPI was given before or after endoscopic therapy.

An attempt to examine the effect of therapeutic combinations did not yield clinically useful information due to shrinking numbers; similarly, subgroup modeling attempting to isolate effects in patients bleeding from causes other than ulcers quickly lost the needed statistical power to allow for meaningful assessment (data not shown).

The respective contributions of oral *versus* IV PPI to improved outcomes cannot fully be evaluated, particularly as both high-dose IV and oral administration have been shown efficacious (5–8, 39–42). We attempted to better define an optimal threshold for decreased rebleeding, yet such an analysis must be considered only exploratory as we could not determine with precision a quantitative estimate of actual doses that were given prior to a rebleed, in contrast to the qualitative PPI use covariate.

The adopted study design is not an experimental one, and thus is not as rigorous as that of a randomized controlled trial (43). In this sense, again, the demonstrated associations should be seen as suggestive, especially since biologically plausible, but require prospective independent confirmation. However, it is recognized that observational databases can be useful adjuncts to randomized controlled trials to determine whether efficacy under the controlled conditions in specialist centers translates into effective treatment in routine practice (43). Furthermore, the common concept that observational trials overestimate treatment effect has recently been challenged by a number of investigators (44, 45).

Methodological limitations can nonetheless threaten the internal validity of registries. These include the completeness of follow-up, ascertainment of outcomes, possible patient selection bias, and inadequate adjustment for confounding when attempting to identify predictors of outcome and treatment effects (43). The external validity of the trial may also be questioned due to the method of patient selection. We attempted to address these possible shortcomings by establishing conservative and *a priori* definitions for all study variables including outcomes, by training all research personnel in a standardized fashion and providing them with a glossary, by enforcing strict data verification and validation protocols, and by completing an audit that ensured complete 30-day follow-up. We also attempted to optimize the random nature of subject selection by having the research nurses randomly select the charts to review; a separate audit confirmed the unlikelihood of patient selection bias. We increased recruitment as a proportion of all eligible patients at the sites where nurses were hired on a full-time, rather than a part-time basis. In this regard, the lack of confounding attributable to center, institution-type, or geographical area further validates the adequacy of the patient selection process. With regard to follow-up, although it is possible that some patients may have rebled and gone to another hospital at that time, such an event is unlikely in the manner in which patients were cared for in the participating institutions. In addition, when considering the usual timing of a rebleed (8), and the mean duration of hospital stay of patients included in RUGBE, we feel quite confident that the numbers of missed negative outcomes is very low.

Regarding other adjustment of possible confounding, even though we cannot exclude unknown sources of bias, the predictive models that examined baseline clinical predictors and the exploratory propensity score analyses adjusted for all recognized possible confounders of outcome and these are very much in keeping with previously published results (24). Furthermore, the results we observed that identified protective effects attributable to PPI use and endoscopic therapy, have either been reported before, or if novel, are biologically

plausible findings if one considers the rationale for using profound acid suppression (26, 27, 30, 46, 47) coupled to sample size considerations.

In conclusion, results from the RUGBE registry data on patients with a variety of nonvariceal UGI bleeding lesions have shown that endoscopic therapy and the acute use of PPIs may both decrease rebleeding and mortality in selected patients exhibiting high-risk stigmata. This acute PPI use may also independently and significantly decrease rebleeding in patients with low-risk endoscopic lesions. Additional studies are now required to confirm these findings, determine the optimal method and dose of PPI administration, and assess the impact of newer endoscopic treatment methods.

## ACKNOWLEDGMENTS

The RUGBE initiative was a collaborative effort supported by the Canadian Association of Gastroenterology and an unrestricted grant from Altana Pharma Canada (formerly Byk Canada Inc.) The RUGBE group would particularly like to thank Douglas Elliot, Margaret Siguenza, Jennifer Bereziuk, and the RUGBE research nurses for their valuable help in completing the registry.

## APPENDIX

The RUGBE investigators' group includes Alan Barkun, Carlo Fallone, and Gad Friedman, The McGill University Health Centre; the Montreal General and Royal Victoria Hospital sites, and the Sir Mortimer B Davis–Jewish General Hospital, Montréal, Québec; Raymond Lahaie, Georges Ghattas, and Judith Dorais, le centre hospitalier de l'université de Montréal, les pavillons hôpitaux St-Luc, Notre Dame, et Hôtel-Dieu, Montréal, Québec; Naoki Chiba, Guelph General Hospital, Guelph & McMaster University, Hamilton, Ontario; David Armstrong and John Marshall, McMaster University & Hamilton Health Sciences, Hamilton, Ontario; Norman Marcon, St-Michael's Hospital, Toronto, Ontario; Jonathon Love, the Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; Alan Cockeram, Saint John Regional Hospital, St John, New Brunswick; Franzjoseph Schweiger, Moncton Hospital, Moncton, New Brunswick; Jamie Gregor and John McDonald, London Health Sciences Centre, the University Hospital and Victoria Campuses, London, Ontario; Rob Enns, St Paul's Hospital, Vancouver, British Columbia; Richard Fedorak, Bob Bailey, and Connie Switzer, the University of Alberta, Royal Alexander, and Grey Nuns Hospitals, Edmonton, Alberta.

**Reprint requests and correspondence:** Alan Barkun, M.D., Division of Gastroenterology, The McGill University Health Centre – the Montreal General Hospital Site, 1650 Cedar Avenue, Montréal, Québec, Canada, H3G 1A4.
*Received October 31, 2003; accepted February 24,2004.*

## REFERENCES

1. Rockall TA, Logan RF, Devlin HB, et al. Influencing the practice and outcome in acute upper gastrointestinal haemorrhage. Steering Committee of the National Audit of Acute Upper Gastrointestinal Haemorrhage. Gut 1997;41:606–11.
2. Silverstein FE, Gilbert DA, Tedesco FJ, et al. The national ASGE survey on upper gastrointestinal bleeding. II. Clinical prognostic factors. Gastrointest Endosc 1981;27:80–93.
3. British Society of Gastroenterology Endoscopy Committee. Non-variceal upper gastrointestinal haemorrhage: Guidelines. Gut 2002;51(Suppl IV):1–6.
4. Chung CS. Surgery and gastrointestinal bleeding. Gastrointest Endosc Clin N Am 1997;7:687–701.
5. Schaffalitzky de Muckadell OB, Havelund T, Harling H, et al. Effect of omeprazole on the outcome of endoscopically treated bleeding peptic ulcers. Randomized double-blind placebo-controlled multicentre study. Scand J Gastroenterol 1997;32:320–7.
6. Hasselgren G, Lind T, Lundell L, et al. Continuous intravenous infusion of omeprazole in elderly patients with peptic ulcer bleeding. Results of a placebo-controlled multicenter study. Scand J Gastroenterol 1997;32:328–33.
7. Lin HJ, Lo WC, Lee FY, et al. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. Arch Intern Med 1998;158:54–8.
8. Lau J, Sung J, Lee K, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000;343:310–6.
9. Cooper GS, Chak A, Lloyd LE, et al. The accuracy of diagnosis and procedural codes for patients with upper GI hemorrhage. Gastrointest Endosc 2000;51:423–6.
10. Daneshmend TK, Hawkey CJ, Langman MJ, et al. Omeprazole versus placebo for acute upper gastrointestinal bleeding: Randomised double blind controlled trial. Br Med J 1992;304:143–7.
11. Owens W, Felts J, Spitznagel E. ASA physical status classifications: A study of consistency of ratings. Anesthesiology 1978;49:239–43.
12. Minimal standard terminology in digestive endoscopy. Endoscopy 2000;32:162–88.
13. Rubin D. Estimating causal effects from large data sets using propensity scores. Ann Intern Med 1997;127:757–63.
14. Braitman L, Rosenbaum P. Rare outcomes, common treatments: Analytic strategies using propensity scores. Ann Intern Med 2002;137:693–5.
15. Barkun AN, Chiba N, Enns R, et al. A national endoscopic database to determine the adoption of pharmacological and endoscopic technologies in patients with non-variceal upper GI bleeding: The RUGBE initiative (abstract 111). Can J Gastroenterol 2002;16(Suppl A):87A.
16. Longstreth GF. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: A population-based study. Am J Gastroenterol 1995;90:206–10.
17. Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996;38:316–21.
18. Vreeburg E, Snel P, de Bruijne J, et al. Acute upper gastrointestinal bleeding in the Amsterdam area: Incidence, diagnosis, and clinical outcome. Am J Gastroenterol 1997;92:236–43.
19. Cooper GS, Chak A, Harper DL, et al. Care of patients with upper gastrointestinal hemorrhage in academic medical centers: A community-based comparison. Gastroenterology 1996;111:385–90.

20. Mahadeva S, Linch M, Hull M. Variable use of endoscopic haemostasis in the management of bleeding peptic ulcers. Postgrad Med J 2002;78:347–51.
21. Guglielmi A, Ruzzenente A, Sandri M, et al. Risk assessment and prediction of rebleeding in bleeding gastroduodenal ulcer. Endoscopy 2002;34:778–86.
22. Blatchford O, Davidson L, Murray W, et al. Acute upper gastrointestinal haemorrhage in west of Scotland: Case ascertainment study. Br Med J 1997;315:510–4, 269–70.
23. Peura DA, Lanza FL, Gostout CJ, et al. The American College of Gastroenterology Bleeding Registry: Preliminary findings. Am J Gastroenterol 1997;92:924–8.
24. Barkun A, Bardou M, Marshall J. Non-variceal Upper GI Bleeding Consensus Conference Group. The Banff consensus conference on the management of patients with non-variceal upper gastrointestinal bleeding. Ann Intern Med 2003;139:843–57.
25. Enns R, Barkun A, Gregor J, et al. Validation of Rockall Scoring System for upper gastrointestinal bleeding (UGIB) in a Canadian endoscopic database (RUGBE). Gastrointest Endosc 2003;57:AB148.
26. Cook DJ, Guyatt GH, Salena BJ, et al. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: A meta-analysis. Gastroenterology 1992; 102:139–48.
27. Sacks HS, Chalmers TC, Blum AL, et al. Endoscopic hemostasis. An effective therapy for bleeding peptic ulcers. JAMA 1990;264:494–9.
28. Bardou M, Toubouti Y, Benhaberou-Brun D, et al. Newer endoscopic therapies decrease both re-bleeding and mortality in high risk patients with acute peptic ulcer bleeding: A series of meta-analyses (Abstract S1650). Gastroenterology 2003;123:A239.
29. Bardou M, Toubouti Y, Benhaberou-Brun D, et al. High dose proton pump inhibition decrease both re-bleeding and mortality in high-risk patients with acute peptic ulcer bleeding. A series of meta-analyses (Abstract W1078). Gastroenterology 2003;123:A625.
30. Barkun AN, Cockeram AW, Plourde V, et al. Review article: Acid suppression in non-variceal acute upper gastrointestinal bleeding. Aliment Pharmacol Ther 1999;13:1565–84.
31. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717–27.
32. Cooper G, Chak A, Way L, et al. Early endoscopy in upper gastrointestinal hemorrhage: Associations with recurrent bleeding, surgery, and length of hospital stay. Gastrointest Endosc 1999;49:145–52.
33. Podila PV, Ben-Menachem T, Batra SK, et al. Managing patients with acute, nonvariceal gastrointestinal hemorrhage: Development and effectiveness of a clinical care pathway. Am J Gastroenterol 2001;96:208–19.
34. Lau JY, Sung JJ, Chan AC, et al. Stigmata of hemorrhage in bleeding peptic ulcers: An interobserver agreement study among international experts. Gastrointest Endosc 1997;46:33–6.
35. Armstrong D, Barkun AN, Grace E, et al. "Do you see what I see?" Inter-observer agreement for upper GI Endoscopy (CADET-PE) (EGD) video clips in 30 endoscopists (Abstract T1516). Gastroenterology 2002;122:A471.
36. Spiegel BM, Vakil NB, Ofman JJ. Endoscopy for acute nonvariceal upper gastrointestinal tract hemorrhage: Is sooner better? A systematic review. Arch Intern Med 2001;161:1393–404.
37. Barkun A, Kennedy W, Herba K, et al. The cost effectiveness of proton pump inhibitor continuous infusion (IV PPI) administered prior to endoscopy in the treatment of patients with non-variceal upper GI bleeding (Abstract 332). Gastroenterology 2002;122:A67.
38. Enns R, Gagnon Y, Rioux K, et al. Cost-effectiveness in Canada of intravenous proton pump inhibitors for all patients presenting with acute upper gastrointestinal bleeding. Aliment Pharmacol Ther 2003;17:1–9.
39. Khuroo MS, Yattoo GN, Javid G, et al. A comparison of omeprazole and placebo for bleeding peptic ulcer. N Engl J Med 1997;336:1054–8.
40. Javid G, Masoodi I, Zargar SA, et al. Omeprazole as adjuvant therapy to endoscopic combination injection sclerotherapy for treating bleeding peptic ulcer. Am J Med 2001;111:280–4.
41. Jung H, Son H, Jung S, et al. Comparison of oral omeprazole and endoscopic ethanol injection therapy for prevention of recurrent bleeding from peptic ulcers with nonbleeding visible vessels or fresh adherent clots. Am J Gastroenterol 2002;97:1736–40.
42. Kaviani M, Hashemi M, Kazemifar A, et al. Effect of oral omeprazole in reducing re-bleeding in bleeding peptic ulcers: A prospective, double-blind, randomized, clinical trial. Aliment Pharmacol Ther 2003;17:211–6.
43. Pocock S, Elbourne D. Randomized trials or observational tribulations? N Engl J Med 2000;342:1907–9.
44. Benson K, Hartz A. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342:1878–86.
45. Concato J, Shah N, Horwitz R. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887–92.
46. Gisbert JP, Gonzalez L, Calvet X, et al. Proton pump inhibitors versus H2-antagonists: A meta-analysis of their efficacy in treating bleeding peptic ulcer. Aliment Pharmacol Ther 2001;15:917–26.
47. Zed PJ, Loewen PS, Slavik RS, et al. Meta-analysis of proton pump inhibitors in treatment of bleeding peptic ulcers. Ann Pharmacother 2001;35:1528–34.