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Timing of Endoscopy for Acute Upper Gastrointestinal Bleeding

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ABSTRACT

BACKGROUND

It is recommended that patients with acute upper gastrointestinal bleeding undergo endoscopy within 24 hours after gastroenterologic consultation. The role of endoscopy performed within time frames shorter than 24 hours has not been adequately defined.

METHODS

To evaluate whether urgent endoscopy improves outcomes in patients predicted to be at high risk for further bleeding or death, we randomly assigned patients with overt signs of acute upper gastrointestinal bleeding and a Glasgow–Blatchford score of 12 or higher (scores range from 0 to 23, with higher scores indicating a higher risk of further bleeding or death) to undergo endoscopy within 6 hours (urgent-endoscopy group) or between 6 and 24 hours (early-endoscopy group) after gastroenterologic consultation. The primary end point was death from any cause within 30 days after randomization.

RESULTS

A total of 516 patients were enrolled. The 30-day mortality was 8.9% (23 of 258 patients) in the urgent-endoscopy group and 6.6% (17 of 258) in the early-endoscopy group (difference, 2.3 percentage points; 95% confidence interval [CI], –2.3 to 6.9). Further bleeding within 30 days occurred in 28 patients (10.9%) in the urgent-endoscopy group and in 20 (7.8%) in the early-endoscopy group (difference, 3.1 percentage points; 95% CI, –1.9 to 8.1). Ulcers with active bleeding or visible vessels were found on initial endoscopy in 105 of the 158 patients (66.4%) with peptic ulcers in the urgent-endoscopy group and in 76 of 159 (47.8%) in the early-endoscopy group. Endoscopic hemostatic treatment was administered at initial endoscopy for 155 patients (60.1%) in the urgent-endoscopy group and for 125 (48.4%) in the early-endoscopy group.

CONCLUSIONS

In patients with acute upper gastrointestinal bleeding who were at high risk for further bleeding or death, endoscopy performed within 6 hours after gastroenterologic consultation was not associated with lower 30-day mortality than endoscopy performed between 6 and 24 hours after consultation. (Funded by the Health and Medical Fund of the Food and Health Bureau, Government of Hong Kong Special Administrative Region; ClinicalTrials.gov number, NCT01675856.)

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Acute upper gastrointestinal bleeding is one of the most common medical emergencies. A national audit from the United Kingdom estimated a crude overall in-hospital mortality of 10% after acute upper gastrointestinal bleeding.[1] Endoscopy allows identification of the source of bleeding, as well as hemostatic treatment for actively bleeding lesions. Endoscopic hemostatic treatment of high-risk lesions stops bleeding and reduces the risk of further bleeding and the need for surgery.[2] An international consensus group recommends endoscopy within 24 hours after presentation for patients with acute upper gastrointestinal bleeding.[3] For patients who are at high risk for further bleeding or death, the consensus group could not make a recommendation for or against performing endoscopy within 12 hours as opposed to performing endoscopy later. Many observational studies,[4-16] three randomized, controlled trials,[17-19] and two systematic reviews[20,21] have shown that urgent endoscopy (the definitions of which have varied among studies, ranging from within 2 hours to within 12 hours after presentation) in unselected patients with acute upper gastrointestinal bleeding did not decrease mortality. The three randomized trials were not designed to focus on patients at high risk for further bleeding or death and did not report an assessment of patients' risk.

The Glasgow–Blatchford score is a validated risk-assessment score for the prediction of clinical outcomes, including the need for interventions and the risk of death (scores range from 0 to 23, with higher scores indicating a higher risk of further bleeding or death). In an international multicenter prospective study involving 3012 patients, a threshold score of 7 or higher was shown to provide the most accurate prediction of whether a patient will be determined to need endoscopic treatment.[22] In our own validation study, a higher score was associated with a greater likelihood of undergoing endoscopic treatment, as well as with a higher risk of death.[23] Recently, two large cohort studies[16,24] provided conflicting results regarding the association between urgent endoscopy (within 6 hours after admission) and mortality. In a prospective cohort study involving 961 patients with Glasgow–Blatchford scores greater than 7, Cho et al.[24] found that endoscopy performed within 6 hours, as compared with between 6 and 24 hours, was an independent predictor of lower mortality (odds ratio for death, 0.36; 95% confidence interval [CI], 0.14 to 0.95). However, in the study by Laursen et al.,[16] involving 2944 patients, the time frame for endoscopy that was associated with the lowest mortality was between 6 and 24 hours after admission. Mortality was higher among patients with hemodynamic instability or severe coexisting illnesses, defined as an American Society of Anesthesiologists grade of 3 to 5. A risk-assessment score was not used in that study.

In this trial, we hypothesized that for patients with acute gastrointestinal bleeding who were predicted to be at high risk for further bleeding or death, endoscopy performed within 6 hours after gastroenterologic consultation would forestall further bleeding and improve outcomes as compared with endoscopy performed between 6 and 24 hours after consultation.

METHODS

TRIAL DESIGN AND OVERSIGHT

The Joint Chinese University of Hong Kong–New Territories East Cluster Hospital Ethics Committee approved the protocol. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. We reported all serious adverse events, within 24 hours after their occurrence, to the Clinical Research and Ethics Committee at the Chinese University of Hong Kong. Serious adverse events were defined as events that were life-threatening, that led to prolongation of existing hospitalization, or that led to persistent or substantial disability or incapacitation. The committee provided ethics oversight and scientific oversight during the period of the trial. Senior physicians and biostatisticians on the committee adjudicated outcomes and monitored the progress of the trial.

PATIENTS

Our gastrointestinal bleeding team screened patients for eligibility and performed randomization either in the emergency department or after admission to a medical ward. Patients who had overt signs of acute upper gastrointestinal bleeding (hematemesis, melena, or both) and who were predicted to be at high risk for further bleeding or death on the basis of a Glasgow–Blatchford score of 12 or higher were eligible for

enrollment. The Glasgow–Blatchford score is based on the systolic blood pressure, pulse rate, hemoglobin and serum urea levels at admission, whether the patient presented with melena or syncope, and the presence or absence of hepatic disease or cardiac failure. Eligible inpatients in whom gastrointestinal bleeding developed while they were hospitalized for other medical illnesses also underwent randomization at the first gastrointestinal consultation. We calculated the Glasgow–Blatchford score on the basis of the lowest systolic blood pressure and highest pulse rate recorded and the hemoglobin and urea levels on admission to the emergency department (or, for patients already hospitalized, recent values obtained before gastrointestinal consultation). All patients provided written informed consent.

We excluded patients who were younger than 18 years of age, unable to provide written informed consent, pregnant, or moribund from terminal illness. We also excluded patients who were in hypotensive shock or whose condition did not stabilize after initial resuscitation, since they required urgent intervention.

RANDOMIZATION, INTERVENTIONS, AND DATA COLLECTION

We randomly assigned patients in a 1:1 ratio using a computer-generated sequence. After obtaining written informed consent from the patient, the admitting resident then logged on to a Web-based randomization program, which generated the randomization number and assigned treatment. We randomly assigned patients to undergo either urgent endoscopy within 6 hours after gastroenterologic consultation (urgent-endoscopy group) or early endoscopy the next morning and within 24 hours (early-endoscopy group). Patients in the early-endoscopy group whose gastroenterologic consultation took place between midnight and 8 a.m. underwent endoscopy in the morning endoscopy session of the same day of their admission and were scheduled for a time of endoscopy that was a minimum of 6 hours after consultation. Patients in the early-endoscopy group whose gastroenterologic consultation took place between 8 a.m. and 11:59 p.m. underwent endoscopy the next morning. We monitored these patients closely and offered emergency endoscopy if there were signs of further bleeding (i.e., fresh hematemesis or hematochezia, hypotensive shock, or both). The hospitals offer 24-hour endoscopy service with a fellow and a consultant on the team. All after-hours endoscopy procedures were supported by endoscopy nurses with skills in assisting with therapeutic endoscopy.

Both groups of patients received an intravenous high-dose infusion of a proton-pump inhibitor (80-mg bolus followed by 8 mg per hour) on admission, as well as at the first sign of bleeding during the hospital stay. Patients with suspected variceal bleeding (known liver disease, stigmata of liver cirrhosis, or a history of bleeding esophagogastric varices) received a vasoactive drug as well as intravenous antibiotic agents.

At endoscopy, gastroduodenal ulcers with active bleeding or with nonbleeding visible vessels were treated with either hemoclips or contact thermocoagulation, with or without preinjection of diluted epinephrine. Bleeding esophageal and gastric varices were treated with band ligation and injection of cyanoacrylate (a tissue adhesive), respectively. After endoscopic hemostatic treatment of the bleeding ulcers in these patients, a high-dose intravenous infusion of a proton-pump inhibitor was continued for 72 hours. We defined further bleeding as a composite of persistent bleeding (i.e., bleeding that was not successfully controlled at the first endoscopy) or recurrent bleeding (i.e., bleeding that recurred after hemostatic treatment). We generally adopted criteria from international guidelines on definitions of recurrent bleeding.[25] Endoscopy together with further hemostatic treatment was performed for patients with overt signs of recurrent bleeding after initial endoscopic control.

END POINTS

The primary end point was death from any cause within 30 days after randomization. Secondary end points included receipt of endoscopic therapy at first endoscopy, further bleeding (defined as persistent or recurrent bleeding),[25] duration of stay in the hospital and intensive care unit, receipt of further endoscopic treatment, emergency surgery or angiographic embolization to achieve hemostasis, blood transfusions, and adverse events within 30 days after randomization.

STATISTICAL ANALYSIS

We determined that a sample of 258 patients per group would provide 80% power to detect an 8-percentage-point difference (i.e., 16% vs. 8%)

in 30-day mortality, with a two-sided α level of 5%. We considered a 50% relative difference in mortality to be clinically significant. In our validation study of the Glasgow–Blatchford score,[23] 21% of patients had a score of 12 or higher, and the 30-day mortality in that group was 16.1%.

Our analysis was performed on an intention-to-treat basis. We did not have any data missing from our data set. We used the log-rank test to compare the time from randomization to the end points of death and further bleeding and a Cox proportional-hazards model to estimate the hazard ratio and 95% confidence intervals. We used the Schoenfeld residual test to verify the assumption of proportional hazards in the Cox analysis, which was fulfilled for the end points of death from any cause and further bleeding. Secondary end points were compared between the groups with a chi-square test for difference in proportions and with Student's t-test and a Mann–Whitney U test for parametric and nonparametric data, respectively. All tests of significance were two-tailed, and a P value of 0.025 or less was considered to indicate statistical significance for the primary end point, since we reported one unplanned interim analysis in 2015.[26] There was no prespecified plan to adjust for multiple comparisons of the secondary end points; the results for secondary end points are reported with 95% confidence intervals and without P values. Confidence intervals have not been adjusted for multiple comparisons and should not be used to infer treatment effects.

RESULTS

PATIENTS

From July 2012 through October 2018, a total of 4715 patients with acute upper gastrointestinal bleeding underwent screening; 598 had a Glasgow–Blatchford score of 12 or higher, and 516 were enrolled in the trial and underwent randomization (258 assigned to each group) (Fig. S1 in the Supplementary Appendix, available at NEJM.org). The baseline demographic and clinical characteristics and the endoscopic findings are shown in Table 1. Peptic ulcers were the source of bleeding in 158 patients (61.2%) in the urgent-endoscopy group and 159 patients (61.6%) in the early-endoscopy group, and esophagogastric varices were the cause in 25 (9.7%) and 19 (7.3%), respectively.

In the urgent-endoscopy group, 3 patients did not undergo endoscopy (1 had undergone recent endovascular repair for an abdominal aneurysm and had cardiac arrest before endoscopy could be performed, 1 had acute pulmonary edema, and 1 declined), and 6 had endoscopy performed more than 6 hours after gastroenterologic consultation. In the early-endoscopy group, 5 patients did not undergo endoscopy (4 died before endoscopy [2 from ongoing bleeding, 1 from acute coronary syndrome, and 1 from a ruptured thoracic aortic aneurysm], and 1 declined). Emergency endoscopy was performed in 20 patients (7.8%) in the early-endoscopy group because of new-onset signs of bleeding: hypotension in 11 patients, fresh hematemesis in 6, fresh melena in 2, and a substantial decrease in hemoglobin level in 1. Three patients in the early-endoscopy group underwent endoscopy more than 24 hours after gastroenterologic consultation (Table 2).

TIMING OF ENDOSCOPY

The mean (±SD) time from presentation to gastroenterologic consultation was 7.4±6.2 hours in the urgent-endoscopy group and 8.0±7.1 hours in the early-endoscopy group (Table 2), and the mean time from gastroenterologic consultation to endoscopy was 2.5±1.7 hours and 16.8±6.8 hours, respectively. Therefore, the mean time from presentation to endoscopy was 9.9±6.1 hours in the urgent-endoscopy group and 24.7±9.0 hours in the early-endoscopy group. In the urgent-endoscopy group, 72 patients (27.9%) underwent endoscopy within 6 hours after presentation, and 124 patients (48.1%) underwent endoscopy within 12 hours (Fig. S3B). The time of day that patients had their gastroenterologic consultation was similar in the two groups. Endoscopy was performed between 6 p.m. and 5:59 a.m. in 96 of 255 patients (37.6%) in the urgent-endoscopy group and 17 of 253 patients (6.7%) in the early-endoscopy group. Additional details about the timing of endoscopy in each group are provided in Table 2 and Figure S3.

30-DAY MORTALITY

All-cause mortality at 30 days after randomization did not differ significantly between the two groups. A total of 23 patients (8.9%) in the urgent-endoscopy group and 17 (6.6%) in the early-endoscopy group died (hazard ratio, 1.35; 95% CI, 0.72 to 2.54; P=0.34). (Fig. 1A and Table 3).

Table 1. Baseline Characteristics of the Patients.*

Characteristics	Urgent-Endoscopy Group (N=258)	Early-Endoscopy Group (N=258)
Age — yr	69.6±16.0	71.4±14.9
Male sex — no. (%)	157 (60.9)	168 (65.1)
Hemoglobin level on admission — g/dl	7.4±1.8	7.2±1.6
Systolic blood pressure — mm Hg	109.6±22.1	107.8±20.8
Systolic blood pressure <90 mm Hg — no. (%)	46 (17.8)	37 (14.3)
Heart rate >100 beats/min — no. (%)	85 (32.9)	92 (35.7)
Glasgow–Blatchford score†	13.7±1.5	13.7±1.6
Glasgow–Blatchford score category — no. (%)		
12 to 14	193 (74.8)	183 (70.9)
15 to 23	65 (25.2)	75 (29.1)
Bleeding during hospitalization — no. (%)‡	22 (8.5)	20 (7.8)
Coexisting diseases — no. (%)		
Ischemic heart disease	33 (12.8)	29 (11.2)
Cancer	31 (12.0)	25 (9.7)
Renal disease	25 (9.7)	21 (8.1)
Liver cirrhosis	11 (4.3)	10 (3.9)
History of bleeding peptic ulcers — no. (%)	49 (19.0)	41 (15.9)
Risk factors for peptic ulcer disease — no. (%)		
NSAID use	42 (16.3)	45 (17.4)
Aspirin use	77 (29.8)	65 (25.2)
Clopidogrel use	3 (1.2)	4 (1.6)
Warfarin or direct oral anticoagulant use	7 (2.7)	10 (3.9)
Endoscopic findings		
Peptic ulcer — no. (%)	158 (61.2)	159 (61.6)
Gastric ulcer	69	77
Duodenal ulcer	81	74
Anastomotic ulcer or jejunal ulcer	4	4
Esophageal ulcer	4	4
Esophageal or gastric varices — no. (%)	25 (9.7)	19 (7.4)
Other findings on endoscopy — no. (%)§	72 (27.9)	75 (29.1)
No abnormality detected — no.	3	12

* Plus–minus values are means ±SD. NSAID denotes nonsteroidal antiinflammatory drug.
† The Glasgow–Blatchford score ranges from 0 to 23, with higher scores indicating a higher risk of further bleeding or death.
‡ This category includes patients who had been admitted with other medical illnesses and in whom symptoms of acute upper gastrointestinal bleeding subsequently developed during hospitalization.
§ Other findings included esophagitis, gastritis, duodenitis or erosions, gastrointestinal cancers and submucosal tumors, Dieulafoy's lesions, angiodysplasia, Mallory–Weiss tears, antral vascular ectasia, gastric polyps, duodenal diverticulum, bleeding varices at anastomosis, papilloma, hiatal hernia, submucosal hematoma, post-sphincterotomy bleeding, hemobilia, and diffuse gastric hemorrhage.

The difference in mortality between the groups was 2.3 percentage points (95% CI, –2.3 to 6.9). Deaths from gastrointestinal bleeding accounted for 5 of the 23 deaths in the urgent-endoscopy group and 2 of the 17 deaths in the early-endoscopy group. Advanced cancer was present in 11 of 23 and 8 of 17 patients who died, respectively. The causes of deaths are listed in Table S2.

Table 2. Timing of Endoscopy.*

Measure	Urgent-Endoscopy Group (N=258)	Early-Endoscopy Group (N=258)
Time from presentation to gastroenterologic consultation — hr†	7.4±6.2	8.0±7.1
Time from gastroenterologic consultation to endoscopy — hr	2.5±1.7	16.8±6.8
Time from presentation to endoscopy — hr‡	9.9±6.1	24.7±9.0
Distribution of time from gastroenterologic consultation to endoscopy — no./total no. (%)‡		
≤6 hr	249/255 (97.6)	15/253 (5.9)
>6–12 hr	5/255 (2.0)	44/253 (17.4)
>12–18 hr	0/255	60/253 (23.7)
>18–24 hr	0/255	131/253 (51.8)
>24 hr	1/255 (0.4)	3/253 (1.2)
Time of gastroenterologic consultation — no. (%)		
6 a.m. to 11:59 a.m.	70 (27.1)	49 (19.0)
Noon to 5:59 p.m.	140 (54.3)	135 (52.3)
6 p.m. to 11:59 p.m.	35 (13.6)	48 (18.6)
Midnight to 5:59 a.m.	13 (5.0)	26 (10.1)
Time of endoscopy — no. (%)‡		
6 a.m. to 11:59 a.m.	31/255 (12.2)	152/253 (60.1)
Noon to 5:59 p.m.	128/255 (50.2)	84/253 (33.2)
6 p.m. to 11:59 p.m.	83/255 (32.5)	13/253 (5.1)
Midnight to 5:59 a.m.	13/255 (5.1)	4/253 (1.6)
Endoscopy not performed — no. (%)	3/255 (1.2)	5/253 (2.0)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Symptoms of acute upper gastrointestinal bleeding developed during hospitalization in 8.5% of patients in the urgent-endoscopy group and in 7.8% of patients in the early-endoscopy group.
‡ In the urgent-endoscopy group, 3 patients did not undergo endoscopy; the reasons were death on the day of enrollment (1), acute pulmonary edema (1), and the patient declining to undergo endoscopy (1). In the early-endoscopy group, 5 patients did not undergo endoscopy; the reasons were death on the day of or the day after enrollment (4) and the patient declining to undergo endoscopy (1).

FURTHER BLEEDING, ENDOSCOPIC TREATMENT, AND OTHER END POINTS

Further bleeding within 30 days occurred in 28 patients (10.9%) in the urgent-endoscopy group and 20 patients (7.8%) in the early-endoscopy group (hazard ratio, 1.46; 95% CI, 0.83 to 2.58). The between-group difference in the percentage of patients with further bleeding was 3.1 percentage points (95% CI, –1.9 to 8.1) (Fig. 1B and Table 3). Persistent bleeding at endoscopy occurred in 2 patients in the urgent-endoscopy group (one of whom had gastric varices and bled again on day 3 but was counted only once in the analysis of the composite end point of further bleeding) and in 1 patient in the early-endoscopy group. Recurrent bleeding occurred in 27 patients (10.5%) in the urgent-endoscopy group and in 19 patients (7.4%) in the early-endoscopy group.

Endoscopic hemostatic treatment was performed during the first endoscopy in 155 patients (60.1%) in the urgent-endoscopy group and in 125 patients (48.4%) in the early-endoscopy group (difference, 11.6 percentage points; 95% CI, 0.3 to 20.0) (Table 3). Endoscopic hemostatic treatment for bleeding peptic ulcers was performed in 109 of the 158 patients with ulcers (68.9%) in the urgent-endoscopy group and in 81 of the 159 patients with ulcers (50.9%) in the early-endoscopy group. (The endoscopic stigmata of bleeding observed in peptic ulcers are shown in Fig. S2.) Among the patients who had peptic ulcers, ulcers with active bleeding or visible vessels

were found in 105 patients (66.4%) in the urgent-endoscopy group and in 76 (47.8) in the early-endoscopy group. The two groups did not differ substantially in the number of patients who underwent surgery (2 in the urgent-endoscopy group and 1 in the early-endoscopy group) or angiographic treatment (3 and 2, respectively).

The duration of hospitalization did not differ between the urgent-endoscopy group and the early-endoscopy group (median of 5 days in both groups), and the two groups were similar in the number of patients who were admitted to the intensive care unit (4 and 3, respectively), the percentage of patients who received a transfusion (89.5% and 90.7%), and the mean number of units of packed red cells received by transfusion (2.4 units in both groups).

TIMING OF ENDOSCOPY AND CLINICAL END POINTS

We performed a post hoc analysis to investigate the association between the time of day during which patients underwent endoscopy and the end points of further bleeding and death (Table S1). We analyzed end points in the urgent-endoscopy group after endoscopy performed during office hours (6 a.m. to 5:59 p.m.) and after endoscopy performed after hours (6 p.m. to 5:59 a.m.). The percentage of patients with further bleeding and the percentage of patients who died did not differ significantly according to the time of day of endoscopy (further bleeding, 10.7% [17 of 159] for endoscopy performed during office hours and 10.4% [10 of 96] for endoscopy performed after hours; death, 7.5% [12 of 159] and 10.4% [10 of 96], respectively). In the early-endoscopy group, 4 of 15 patients (26.7%) who underwent endoscopy within 6 hours after randomization and 3 of 44 (6.8%) of those who underwent endoscopy between 6 and 12 hours after randomization died within 30 days; among the 194 patients who underwent endoscopy more than 12 hours after randomization, 6 (3.1%) died. Additional details regarding nonfatal and fatal serious adverse events are provided in Table S3.

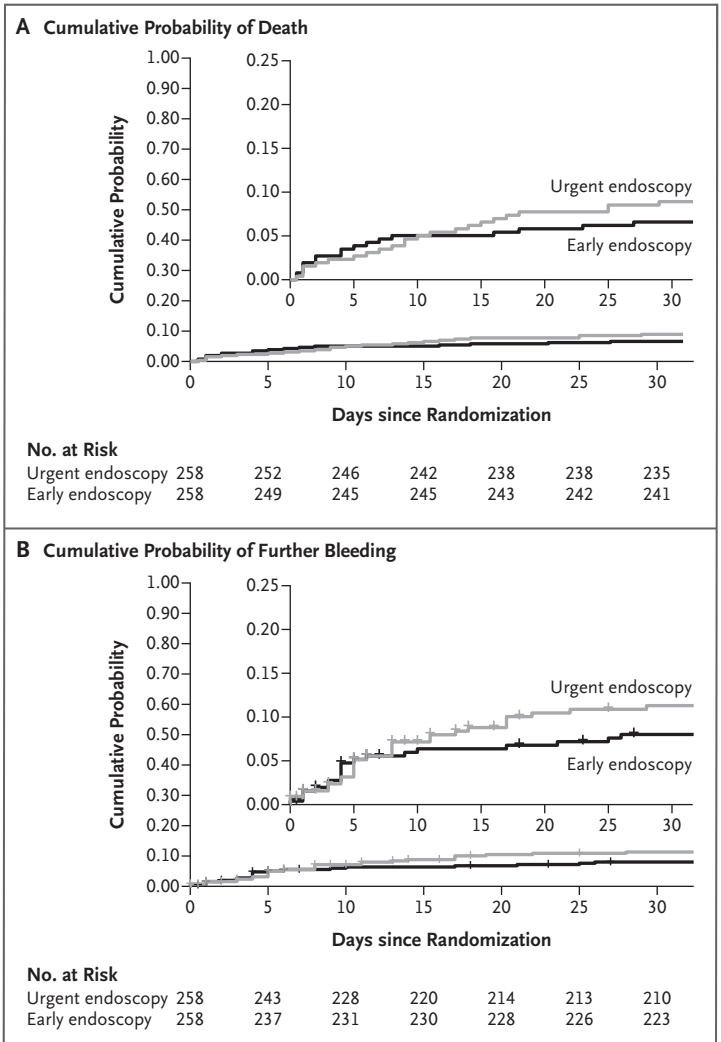

Figure 1. Kaplan–Meier Estimates of the Cumulative Incidences of Death and Further Bleeding.

Panel A shows the estimates of mortality during the 30 days after randomization, and Panel B shows the estimates of the incidence of further bleeding during the 30 days after randomization. The inset in each panel shows the same data on an enlarged y axis.

DISCUSSION

In this randomized trial involving patients with upper gastrointestinal bleeding who were predicted to be at high risk for further bleeding or death, we found that endoscopy performed within 6 hours after gastroenterologic consultation did not lead to lower mortality or a lower incidence of further bleeding than endoscopy performed within 24 hours after consultation. In this trial, randomization was performed at the time of gastroenterologic consultation and approximately 7 to 8 hours after patients presented with bleeding to the emergency department. Our trial, therefore, evaluated endoscopy performed at a mean of 9.9 hours as compared with 24.7 hours after initial presentation.

In the urgent-endoscopy group, we found more

Table 3. Primary and Secondary End Points.*

Outcome	Urgent-Endoscopy Group (N=258)	Early-Endoscopy Group (N=258)	Relative Risk or Hazard Ratio (95% CI)†	P Value
Primary end point				
Death from any cause within 30 days — no. (%)	23 (8.9)	17 (6.6)	1.35 (0.72–2.54)	0.34
Secondary end points				
Further bleeding — no. (%)‡				
Within 7 days	15 (5.8)	14 (5.4)	1.07 (0.53–2.17)	
Within 30 days	28 (10.9)	20 (7.8)	1.46 (0.83–2.58)	
Source of further bleeding — no.				
Bleeding peptic ulcers	19	12		
Bleeding esophagogastric varices	4	3		
Other	5	5		
Treatment for bleeding				
Endoscopic treatment administered during initial endoscopy — no. (%)	155 (60.1)	125 (48.4)	1.24 (1.06–1.46)	
Endoscopic treatment for bleeding ulcers — no. of patients/total no. with ulcers	109/158	81/159	1.35 (1.13–1.63)	
Endoscopic treatment for varices — no. of patients/total no. with varices	20/25	17/19	0.89 (0.70–1.15)	
Endoscopic treatment for other conditions — no. of patients/total no. of patients	26/72	27/75	1.02 (0.66–1.56)	
Surgical treatment — no. (%)	2 (0.8)	1 (0.4)	2.00 (0.18–21.92)	
Angiographic embolization — no. (%)	3 (1.2)	2 (0.8)	1.50 (0.25–8.90)	
Median duration of hospitalization after randomization (range) — days§	5 (4–9)	5 (3–8)		
ICU admission — no. (%)	4 (1.6)	3 (1.2)	1.33 (0.30–5.90)	
Red-cell transfusion — no. (%)	231 (89.5)	234 (90.7)	0.99 (0.93–1.05)	
Units of red cells received by transfusion	2.4±2.3	2.4±2.1		

* Plus–minus values are means ±SD.
† The relative risk is shown for all end points with the exception of death from any cause within 30 days and further bleeding within 30 days, for which the hazard ratio is shown.
‡ Further bleeding was defined as a composite of persistent bleeding or recurrent bleeding. Persistent bleeding occurred in 2 patients in the urgent-endoscopy group (1 had gastric varices and bled again on day 3 but was counted only once in the analysis of the composite end point of further bleeding) and in 1 patient in the early-endoscopy group, and recurrent bleeding occurred in 27 patients and 19 patients, respectively.
§ For patients in whom bleeding developed during hospitalization, the duration of the hospital stay was calculated from the day of randomization.

ulcers that were actively bleeding and that had major stigmata of bleeding, resulting in more frequent endoscopic treatment. The more frequent endoscopic treatment, however, did not translate into a lower incidence of further bleeding or fewer deaths. Patients in the early-endoscopy group, on the other hand, received overnight acid suppression. The longer period until endoscopy and longer duration of acid suppression reduced the number of ulcers with active bleeding and major stigmata of bleeding. This observation corroborates the findings from an earlier randomized, controlled trial[27] that evaluated the use of a high-dose proton-pump inhibitor before endoscopy. Acid suppression before endoscopy can reduce the need for endoscopic treatment.

In our trial, the observed mortality was lower than what was assumed in the sample-size calculation. There may be several explanations. First,

our earlier validation study was conducted over a 12-month period in 2006. Our management of these conditions may have improved over the past decade, resulting in better outcomes. Second, in this trial, we enrolled only patients whose condition could be stabilized after initial resuscitation. These patients probably belonged to a lower-risk group than we had assumed in our predictions of mortality. Third, patients are better monitored in the context of a clinical trial, and their outcomes are better in general than those in real-life contexts.

The observed higher incidences of further bleeding and death with urgent endoscopy than with early endoscopy contrast sharply with our hypothesis that urgent endoscopy would be associated with improved outcomes. With a between-group difference in mortality of 2.3 percentage points and a 95% confidence interval of −2 to 7 percentage points in favor of early endoscopy, our trial ruled out a mortality benefit of greater than 2 percentage points in association with urgent endoscopy. A substantially larger sample would have been required to rule out smaller benefits. We observed numerically more deaths in the urgent-endoscopy group. This raises the possibility that patients may benefit from treatment for coexisting medical illnesses and a period of acid suppression. In a post hoc analysis, outcomes after endoscopy performed during office hours and endoscopy performed after hours were similar, which suggests that the quality of after-hours endoscopy was not inferior.

To detect possible benefits of urgent endoscopy, we selected high-risk patients who presented with acute upper gastrointestinal bleeding. We used the Glasgow–Blatchford score as a measure of risk; the score has been shown to correlate with mortality.[22] In an observational study from Asia,[14] a delay of endoscopy in patients with a Glasgow–Blatchford score of 12 or higher was associated with a significant increase in mortality.

There were limitations of our trial. Although we enrolled patients who were predicted to be at high risk for further bleeding and death, we excluded patients who had persistent hypotensive shock despite undergoing resuscitation. Thus, our results are not generalizable to patients with ongoing bleeding and hypotensive shock, who require urgent intervention. In addition, our hospitals offered around-the-clock endoscopy service with a fellow and a senior endoscopist. Our results are not generalizable to hospitals that do not have such support. Finally, the proportion of patients with variceal bleeding in our cohort was small. Our trial findings may not be applicable in localities with a high prevalence of esophagogastric varices.

In this trial, endoscopy that was performed within 6 hours, rather than between 6 and 24 hours, after gastroenterologic consultation did not reduce mortality among patients in stable condition who were hospitalized with acute upper gastrointestinal bleeding and who were assessed as having a high risk of further bleeding and death.

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