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Doppler Endoscopic Probe Monitoring of Blood Flow Improves Risk Stratification and Outcomes of Patients With Severe Nonvariceal Upper Gastrointestinal Hemorrhage

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e16. Learning Objective: Upon completion of this CME activity successful learners will be able to explain how monitoring of blood flow, under stigmata of recent hemorrhage (in nonvariceal upper gastrointestinal bleeding), can improve risk stratification for rebleeding, successful endoscopic hemostasis, and clinical outcomes in patients.

See editorial on page 1280.

BACKGROUND & AIMS: For 4 decades, stigmata of recent hemorrhage in patients with nonvariceal lesions have been used for risk stratification and endoscopic hemostasis. The arterial blood flow that underlies the stigmata rarely is monitored, but can be used to determine risk for rebleeding. We performed a randomized controlled trial to determine whether Doppler endoscopic probe monitoring of blood flow improves risk stratification and outcomes in patients with severe nonvariceal upper gastrointestinal hemorrhage. **METHODS:** In a single-blind study performed at 2 referral centers we assigned 148 patients with severe nonvariceal upper gastrointestinal bleeding (125 with ulcers, 19 with Dieulafoy's lesions, and 4 with Mallory Weiss tears) to groups that underwent standard, visually guided endoscopic hemostasis (control, n = 76), or endoscopic hemostasis assisted by Doppler monitoring of blood flow under the stigmata (n = 72). The primary outcome was the rate of rebleeding after 30 days; secondary outcomes were complications, death, and need for transfusions, surgery, or angiography. **RESULTS:** There was a significant difference in the rates of lesion rebleeding within 30 days of endoscopic hemostasis in the control group (26.3%) vs the Doppler group (11.1%) (P = .0214). The odds ratio for rebleeding with Doppler monitoring was 0.35 (95% confidence interval, 0.143–0.8565) and the number needed to treat was 7. **CONCLUSIONS:** In a randomized controlled trial of patients with severe upper gastrointestinal hemorrhage from ulcers or other lesions, Doppler probe guided endoscopic hemostasis significantly reduced 30-day rates of rebleeding compared with standard, visually guided hemostasis. Guidelines for nonvariceal gastrointestinal bleeding should incorporate these results. ClinicalTrials.gov no: NCT00732212 (CLIN-013-07F).

Keywords: Endoscopy; UGI Bleeding; Stigmata of Hemorrhage; Clinical Trial.

For more than 40 years, stigmata of recent hemorrhage (SRH) have been used to guide decisions about endoscopic treatment for peptic ulcer and other types of nonvariceal upper gastrointestinal (UGI) bleeding.[1–5] Current guidelines rely on endoscopic SRH to estimate risks of rebleeding, describe visual guides to endoscopic hemostasis, and provide recommendations based on systematic review of published study results about nonvariceal UGI bleeding.[6–9] Although residual arterial blood flow has been reported to be an independent predictor of rebleeding for nonvariceal UGI lesions, arterial flow at endoscopy infrequently has been studied or used to guide treatment.[10–12]

Our hypothesis was that arterial blood flow monitoring with a Doppler endoscopic probe during endoscopy and endoscopic treatment of severe nonvariceal hemorrhage would improve patient care outcomes significantly compared with standard treatment based on SRH alone without blood flow monitoring. Our primary outcome was clinically defined severe rebleeding from the index lesion within 30 days and secondary outcomes were rates of surgery, major complications, deaths, and blood product transfusions within 30 days of the index bleed. The association between residual arterial blood flow after endoscopic treatment and rebleeding also was assessed.

Abbreviations used in this paper: **ASA, American Society for Anesthesia; DEP, Doppler endoscopic probe; EGD, esophagogastroduodenoscopy; MPEC, multipolar electrocoagulation; NVUGI, nonvariceal upper gastrointestinal; PPI, proton pump inhibitor; RBC, red blood cell; RCT, randomized controlled trial; SRH, stigmata of recent hemorrhage; UGI, upper gastrointestinal; VA, Veterans' Administration.**

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Stigmata of ulcer hemorrhage have been used for decades for risk stratification and endoscopic hemostasis, but arterial blood flow underlying stigmata actually determines rebleed risk, and monitoring it may improve outcomes.

NEW FINDINGS

In a blinded, randomized controlled study, outcomes of patients with severe non-variceal UGI bleeding treated with endoscopic Doppler monitoring had significantly lower rates of rebleeding than those treated by standard hemostasis.

LIMITATIONS

A two center, new, moderate sized study without a similar large confirmatory study yet reported.

IMPACT

Endoscopic Doppler probe monitoring of blood flow is a safe and effective way to improve clinical outcomes of patients with severe non-variceal UGI hemorrhage.

Materials and Methods

This randomized controlled trial (RCT) was designed to compare the clinical outcomes of standard visually guided hemostasis of severe hemorrhage from nonvariceal UGI lesions (ulcers, Dieulafoy's lesions, or Mallory Weiss tears without portal hypertension) with Doppler probe–assisted treatment with blood flow monitoring. The treatment allocation was 1:1 in a parallel treatment design.

This study was approved by the Institutional Review Boards of the West Los Angeles Veterans Administration and the Ronald Reagan University of California Los Angeles Medical Centers. Before starting this study, it was registered with ClinicalTrials.gov as NCT00732212 (CLIN-013-07F). The clinical trials registration of the Veterans' Affairs (VA) research proposal included 2 separate RCTs, one on nonvariceal UGI bleeding and the other on variceal–portal hypertensive lesions. The nonvariceal lesion study reported here was conducted between February 2009 and January 2015 at both medical centers. The study was suspended for 9 months because of slow enrollment. The study was resumed after the following changes were made: Institutional Review Board approval of surrogate consenting and inclusion of sicker patients (eg, American Society for Anesthesia [ASA] grades III and IV).

Before study initiation, all treating physicians were trained in the use of the Doppler endoscopic probe, as previously reported by us.[12] Also, the same training methods used for SRH and endoscopic treatments were used in this RCT as described in the recent Doppler endoscopic probe (DEP) cohort study.[12] The same endoscopists treated all patients in each arm of the study. They were all skilled endoscopists who had been trained previously by the principal investigator (D.M.J.) in endoscopic hemostasis. There were 8 endoscopists who assessed, screened, and randomized patients for this RCT. These were all general gastroenterologists who are experienced in managing patients with UGI hemorrhage similar to other large referral centers.

Severe GI bleeding was defined clinically as the presence of hematemesis, melena, or hematochezia; signs or symptoms of hypovolemia (hypotension, tachycardia, orthostatic change in pulse and blood pressure, dizziness, or syncope); with a hemoglobin concentration decrease from baseline of 2 g/dL or more (from previous outpatient hemoglobin or after intravenous resuscitation before red blood cell [RBC] transfusion); and transfusion of 1 or more units of packed RBCs for hypovolemia, resuscitation, and acute blood loss anemia. Patients with less severe bleeding or patients who were not hospitalized were excluded. Patients were screened for inclusion if either bleeding started before presentation to the hospital or while they were hospitalized for other causes (eg, inpatient bleeding). Endoscopic inclusion criteria were as follows: (1) benign-appearing peptic ulcers that were at least 5 mm in size and had some SRH. SRH were divided into 2 categories: major SRH was defined as spurting or pulsatile bleeding, nonbleeding visible vessel, or adherent clot, and lesser SRH were defined as a flat spot or oozing bleeding without a clot or visible vessel; (2) a Dieulafoy's lesion with major SRH; or (3) a Mallory Weiss tear with pulsatile arterial bleeding. Other inclusion criteria were written informed consent (from the patient or a surrogate), ASA grade of I–IV before urgent endoscopy, and life expectancy of 30 days or longer. Exclusion criteria were severe coagulopathy not correctable by blood product transfusions (eg, platelet count $<$20,000, international normalized ratio of $>$2.5, or partial thromboplastin time that was twice normal), uncooperative or noncompliant patients including those unwilling to continue hospitalization as directed by the managing physicians or to return for follow-up evaluation, active UGI malignancy, ASA grade of V, hypotension necessitating intravenous drugs to maintain blood pressure, and a malignant-appearing ulcer. Consent for study inclusion was obtained before urgent endoscopy for patients who met clinical and laboratory inclusion criteria. Patients then were randomized at the bedside during urgent endoscopy if they met endoscopic criteria. Therapeutic panendoscopes (Olympus [Central Valley, PA] or Pentax [Montvale, NJ]) with a 3.8-mm suction channel and target jet irrigation were used.

A card inside the sealed envelope designated which treatment to use: either standard endoscopic treatment or Doppler-assisted hemostasis. Cards and notebooks had been prepared before the study started by the statistician using permuted blocks of 4 for randomization.

For patients randomized to the standard visually guided endoscopic treatment group, either endoscopic hemoclip (11-mm size opened; Boston Scientific Corporation, Marlborough, MA) or multipolar electrocoagulation (multipolar electrocoagulation [MPEC] 10F size, 8- to 10-s pulses/tamponade station, firm pressure on and next to SRH) was used with or without dilute epinephrine pre-injection (1:20,000 concentration mixed with normal saline), as previously described.[12–15] End points of endoscopic treatment were control of active bleeding and flattening the visible vessel, either through hemoclip use or coaptive coagulation with firm tamponade on the SRH.[12–16] For either treatment group, lesions with adherent clots first were injected with dilute epinephrine, shaved down with cold guillotining, and the residual pedicle or visible vessel was treated with hemoclips or MPEC probe, as previously described.[13,15] For patients randomized to the Doppler probe group, the probe was used to detect arterial blood flow before

epinephrine injection or visually guided endoscopic hemostasis, and, after this treatment, on the stigmata and out from it as previously described.[12] The probe is Food and Drug Administration–approved and is composed of a control unit and 1-time use, disposable Doppler probe (Vascular Technology, Inc, Nashua, NH).

The following was the treatment algorithm used by the investigators for chronic ulcers with active arterial bleeding, nonbleeding visible vessel, or adherent clot (after baseline DEP assessment before epinephrine injection and guillotining off the clot or shaving it down): epinephrine injection followed by MPEC until hemostasis or concerns about complications. If there was more bleeding or persistence of arterial signal in the DEP group, application of hemoclips (resulting in triple therapy) was used. If there were acute, small (<10 mm), or less fibrotic ulcers with nonbleeding visible vessel or adherent clots, or Dieulafoy's lesions and Mallory Weiss tears, injection of epinephrine and hemoclips were used.

In the Doppler group, patients with flat spots in ulcers were treated at endoscopy only if arterial flow was detected. Neither patients with a negative Doppler signal nor patients with flat spots in the standard treatment group received endoscopic therapy, in accordance with current treatment guidelines.[7–9]

If residual arterial blood flow was detected after initial treatment in the Doppler group, more hemoclips were placed over the site of the positive Doppler signal. In cases of firm or fibrotic ulcer bases in which hemoclips would not adhere, more MPEC was applied if that was deemed safe by the investigator.

Patients, their families, and the managing medical–surgical teams were blinded as to whether a Doppler endoscopic probe was used or not. Decisions about transfusion of red blood cells and other blood products and the medical–surgical (or angiographic) management after randomization were made by the blinded medical–surgical physicians caring for the study patients during the hospitalization and after hospital discharge.

Medical treatment after endoscopy was as follows: patients with ulcers and Dieulafoy's lesions received high-dose proton pump inhibitor (PPI) (pantoprazole) infusion (80-mg bolus and 8 mg/h) for 72 hours, followed by twice-daily oral PPI for 30 days (omeprazole 20 mg, pantoprazole 40 mg, or lansoprazole 30 mg). Patients with a Mallory Weiss tear were treated with anti-emetics initially and a PPI twice daily for 7 days.

Helicobacter pylori infection was considered present if any of the following was positive for the ulcer patients: IgG serology, stool antigen, or gastric biopsy. For ulcer patients with *H pylori* infection, treatment with 3 or 4 drug therapies was started within 5–7 days of the index bleed. In patients requiring secondary prophylaxis to prevent heart or cardiovascular events, aspirin, anticoagulants, or dual antiplatelet agents were resumed within 4–5 days of the randomization.

The clinical criteria for rebleeding after randomization were clinical signs of rebleeding (recurrent hematemesis, melena, and/or hematochezia), acute signs of hypovolemia, a 2 g/dL or more decrease (from baseline after initial endoscopy and resuscitation) in hemoglobin concentration, and transfusion of 1 or more units of RBCs. A diagnosis of rebleeding required all 3 of these. These criteria were chosen to be more stringent than most of the RCTs of severe ulcer or nonvariceal upper gastrointestinal (NVUGI) bleeding including those studies forming the basis for recent guidelines of NVUGI bleeding,[6–9] Doppler studies,[17–20] and for a recent large international RCT of ulcer hemorrhage.[21] At the discretion of the managing physicians (who were blinded to the endoscopic treatment) either repeat endoscopy, angiography, or surgery were performed for severe rebleeding unless a severe complication or death precluded these. Angiography with embolization or surgery was performed when hemorrhage could not be controlled initially, was within 12 hours of randomization, or for rebleeding from the same lesion despite repeat upper endoscopy and hemostasis.

All patients who lived were followed up for up to 30 days after randomization. Some patients died before 30 days but were followed up until time of death. Each patient was followed up prospectively each day and had hemoglobin levels checked daily until hospital discharge. After discharge (if it was <30 days), they were contacted by telephone and/or had clinic follow-up visits at 30 days. Patients also were instructed to return to the same hospital for any signs of GI bleeding.

The primary clinical outcome was index lesion rebleeding within 30 days after randomization. This was ascertained prospectively using the clinical algorithm for rebleeding as detailed earlier. Secondary outcomes were rates of surgery, angiography, major complications, death, and blood product transfusions within 30 days after randomization, as well as length of hospital stay.

All authors had access to the study data and reviewed and approved the final manuscript.

Sample Size Calculation

Based on prior prospective studies by our group,[12–15] we estimated that the 30-day rebleeding rate in the standard treatment group would be 20% and for the endoscopic Doppler group would be 5%. To achieve an 80% power with a 2-tailed α of .05, the sample size was 75 patients per group. With an estimated 5% drop-out rate, we planned to randomize 79 patients per group. However, as the trial proceeded, there were no drop-outs, so the goal for randomization was reduced to 150 patients.

Statistical Methods

Data were collected prospectively, de-identified, and entered into electronic data files. SAS 9.4 (SAS, Inc, Cary, NC) was used for data management and statistical analyses. Data analysis compared the background characteristics, endoscopic findings, and 30-day outcomes according to the 2 treatments. The cut-off *P* value for statistical significance was .05 in 2-sided testing. Proportions were compared using the Fisher exact test and means were compared using the Wilcoxon rank-sum test (Mann–Whitney *U* test), because most continuous data such as hospital days did not follow the normal distribution. Computations were performed using StatXact 8.0 (Cytel, Inc, Cambridge MA) and SAS 9.4. All data analyses were performed according to an intention-to-treat basis and included all 148 patients who were randomized. Time to lesion rebleeding also was determined and compared by log-rank test.

One interim analysis was performed when 60% of the patients were randomized and followed up for 30 days. This was used by the VA Data and Safety Monitoring Committee to monitor accrual, drop-outs, complications, and safety, but not to assess efficacy. This was not used as a means to stop this study early, which was the responsibility of the VA Data and Monitoring Committee. This gave us the opportunity to reassess

Table 1. Patient Characteristics

	Standard	Doppler	*P* value
Patients	76	72	
Age[a]	66.34 ± 16.1	65.18 ± 15.6	.505
Female/male	14/62	15/57	.836
Inpatient bleed	14 (18.4%)	15 (20.8%)	.836
Ulcers ≥ 20 mm	12 (15.8%)	12 (16.7%)	.999
CURE prognosis score, 1–6[a]	2.95 ± 0.99	2.94 ± 1.17	.622
ASA grade			.899
I	5 (6.6%)	5 (6.9%)	
II	21 (27.6%)	24 (33.3%)	
III	43 (56.6%)	37 (51.4%)	
IV	7 (9.2%)	6 (8.3%)	
Cirrhosis	12 (15.8%)	10 (14.0%)	.820
Child–Pugh score[a]	9.5 ± 2.9	8.0 ± 2.6	.258
Hypotension	35 (46.1%)	34 (47.2%)	.755
H pylori–positive ulcers	23 (35.9%)	23 (37.8%)	.986
UCLA/VA	44/32	39/33	.648
Smoking, yes/no	3/73	2/70	.694
Drinking, yes/no	14/62	15/57	.836
Aspirin	28 (36.8%)	39 (54.2%)	.034
Other antiplatelet drugs	9 (11.8%)	8 (11.1%)	.889
Nonsteroidal anti-inflammatory drugs	19 (25%)	20 (27.8%)	.701
Warfarin	13 (17.1%)	8 (11.1%)	.296
Other anticoagulant	4 (5.3%)	7 (9.7%)	.359
Both antiplatelet and anticoagulant drugs	6 (7.9%)	5 (6.9%)	.826
Endoscopic diagnosis			.258
DUs	32 (42%)	30 (41.7%)	
Posterior DUs	12 (37.5%)	8 (26.7%)	
GUs	24 (31.6%)	20 (27.8%)	
Lesser-curve GUs	12 (50%)	9 (45%)	
EU/HH ulcers	2 (2.6%)	5 (6.9%)	
Anastomotic ulcers	4 (5.3%)	7 (9.7%)	
Dieulafoy lesion	13 (17.1%)	6 (8.3%)	
Mallory Weiss tears	1 (1.3%)	3 (4.2%)	
Baseline hemoglobin[a]	7.6 ± 1.5	7.9 ± 1.7	.348
Baseline red cell transfusions[a]	3.1 ± 2.3	3.4 ± 2.9	.657
Baseline fresh-frozen plasma transfusions[a]	0.95 ± 2.3	0.6 ± 1.5	.406
Baseline platelet transfusions[a]	0.92 ± 6.7	0.14 ± 0.5	.661

CURE, Center for Ulcer Research and Education; DU, duodenal ulcer; EU, esophageal ulcer; GU, gastric ulcer; HH, ulcer in a hiatal hernia; UCLA, University of California Los Angeles.
[a]Means ± SD.

drop-out rates (which were 0%), and therefore to reduce the sample size estimate for enrollment by 5%.

The interactions between treatment group (standard vs Doppler) and enrollment date also were analyzed in 2 ways: early vs late period and year of enrollment. In the first analysis, the early period was on or before June 23, 2012, which was the median date of entry. Late was after that date. For the second analysis, year of enrollment was used. All the patient characteristics and risk factors (Table 1) and the primary outcome (rebleed with 30 days) were analyzed. Each specified variable and 30-day lesion rebleeding were compared between the 2 treatment groups separately by time period using the chi-square or Fisher exact tests (for categoric variables) or the Wilcoxon rank-sum test (for continuous variables). In addition, we assessed whether the relationship between treatment group and the specific variable or rebleeding varied significantly according to time period, using the logistic or linear regression module, as appropriate.

Results

By the completion of this study of nonvariceal UGI bleeding, 968 patients with severe UGI hemorrhage were assessed for potential enrollment. Because of clinical and/or laboratory exclusion criteria, 445 patients were excluded at screening before endoscopy (Supplementary Figure 1). Another 375 patients who met clinical inclusion criteria were excluded after an upper endoscopy showed that they failed to meet endoscopic criteria (Supplementary Figure 1). A total of 148 patients meeting clinical and endoscopic criteria were randomized. Each endoscopist randomized 4–20 patients (of the total 148 nonvariceal patients), and helped manage another 40–150 patients with UGI hemorrhage who were screened but excluded on clinical or laboratory criteria, or excluded at esophagogastroduodenoscopy (EGD) after meeting clinical and laboratory entry criteria (of a total of 820 patients from this nonvariceal UGI RCT).

There was no statistically significant difference between the intervention (Doppler) and the standard (control) group as far as demographic characteristics, laboratory values, distribution of bleeding lesions (Table 1), or distribution of the stigmata of recent hemorrhage (Table 2). The only difference was a higher proportion of patients using aspirin in the intervention (Doppler) group (54.2% vs 36.8%; $P = .034$) (Table 1). In this study, 84.5% of the patients had peptic ulcers (63 duodenal ulcers, 44 gastric ulcers, 7 esophageal or hiatal hernia ulcers, and 11 anastomotic ulcers), 12.8% had Dieulafoy's lesions, and 2.7% had bleeding Mallory Weiss tears (Table 1).

The overall rebleeding rate was significantly lower for the Doppler group than for the standard group (20 of 76 [26.3%] vs 8 of 72 [11.1%]; $P = .0214$). The 30-day lesion rebleeding rates according to each stigmata of recent hemorrhage (on index endoscopy) are reported in Table 2. For all stigmata combined by treatment, there was a significant difference in the primary outcome of 30-day rebleed rates for the Doppler treatment group compared with standard treatment (odds ratio, 0.35; 95% confidence interval, 0.143–0.8565). However, for each individual SRH, there were no significant differences in rebleed rates.

The time to lesion rebleeding for Doppler and standard treatments is shown in Figure 1. The difference also was significant ($P = .0174$). The median times (and ranges) to rebleeding were similar for the standard treatment (2 days; range, 1–30 days) and Doppler groups (3 days; range, 1–12 days).

Secondary outcomes are presented in Table 3. The 2 treatment groups did not differ for any other outcome (angiography for rebleeding; length of hospital or intensive care unit stay; transfusion of red cells, fresh-frozen plasma, or platelets; other GI bleeds; or mortality). There was 1 perforation in the standard group and none in the Doppler group. Other major complications in the standard group

Table 2. Differences in Rebleeding by Stigmata of Recent Hemorrhage and Use of Doppler Probe

Stigmata	Standard	Doppler	*P* value	Difference (standard Doppler), %	95% CI, %
Active arterial bleed	5/10 (50.0%)	4/14 (28.6%)	.403	21.4	-17.6 to 60.4
Nonbleeding visible vessel	7/27 (25.9%)	4/26 (15.4%)	.501	10.5	-11.0 to 32.1
Adherent clot	4/16 (25%)	0/12 (0%)	.113	25.0	-1.1 to 49.9
Flat spots	3/16 (18.8%)	0/16 (0%)	.226	18.8	0.4–37.9
Oozing bleeding	1/7 (14.3%)	0/4 (0%)	.428	14.3	-11.6 to 40.2
Totals	20/76 (26.3%)	8/72 (11.1%)[a]	.0214	15.2	2.9–27.5

NOTE. Shown are patients (and percentages) with lesion rebleeding for individual stigmata and for all patients (totals) according to endoscopic treatment.
CI, confidence interval.
[a]*P* values by Fisher exact test.

were 2 cerebral vascular accidents related to rebleeding and 1 pneumoperitoneum after endoscopic retreatment for rebleeding that was managed medically.

For the standard group with rebleeds (20 of 76): 9 had a repeat EGD, 4 had EGDs scheduled but 3 died beforehand, 1 had to cancel the EGD because of a severe cerebral vascular accident, 4 had surgery, and 1 underwent an angiography. For the Doppler group with rebleeds (8 of 72): 7 had a repeat EGD (and 2 of these later had angiography also) and 1 had neither EGD, angiography, nor surgery.

The other 3 GI bleeds in the standard group consisted of the following: 1 esophageal varices, 1 Crohn's disease (terminal ileal ulcers), and 1 intraperitoneal bleed. For the Doppler group, the 4 other bleeds were as follows: 1 esophageal varices, 1 gastric angioma, 1 antral erosion (after anticoagulation), and 1 postbulbar ulcer (whose index lesion was a bulbar ulcer with a visible vessel).

These was a strong association between residual blood flow after endoscopic hemostasis and rebleeding rates. During the index endoscopy, 23.6% (17 of 72) of patients randomized to the Doppler group had residual blood flow detected after the initial visually guided endoscopic treatment and 76.5% (13 of 17) of those patients received further endoscopic hemostatic treatment until less (only a faint Doppler signal [5 of 13], and 4 of the 5 later rebled) or no more residual blood flow was detected (8 of 13, and none rebled). The other 4 patients did not receive further treatment because of the concern for complications and all 4 rebled. Therefore, 8 of 9 (88.9%) patients in the Doppler group with residual blood flow that was not obliterated later rebled, compared with 0 of 8 (0%) in patients whose residual blood flow was obliterated with additional hemostasis ($P = .0004$, Fisher exact test).

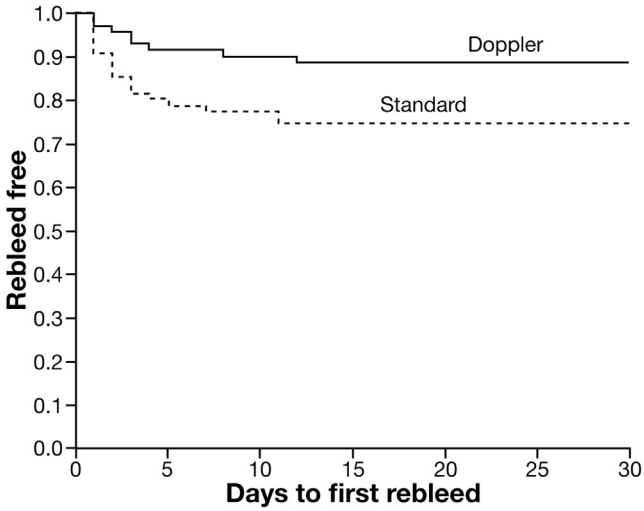

Figure 1. Proportion of patients without rebleeding (rebleed free) during the 30 days after randomization. *Top curve*: Doppler patients, *lower curve*: standard treated patients. Product limit plots, compared by log-rank test: $P = .0174$.

For analysis of interactions between treatment group (standard vs Doppler) and enrollment period (early vs late), there were no significant interactions with respect to any of the baseline variables. There was no significant interaction between treatment group vs time period for the primary outcome of lesion rebleeding. The probability of same rebleeding tended to be higher for the standard treatment group than the Doppler group, regardless of the time period in either the early vs late or the enrollment year analysis. For the early vs late analysis, the difference in rebleeding rates between the 2 treatment groups was approximately 14% for both periods with an interaction *P* value of .7638. Table 4 shows the details of the second analysis (by year of enrollment and treatment). The interaction *P* value of that logistic regression was .6531, which was similar to the analysis of early vs late enrollment.

Discussion

The important new findings of this RCT are that monitoring of arterial blood flow underneath the SRH in patients with severe nonvariceal UGI hemorrhage and using it as a guide to endoscopic hemostasis improved clinical outcomes. Specifically, those were significantly lower rates of rebleeding, surgery, and complications, and RBC transfusion for the Doppler group compared to the standard hemostasis group where endoscopic hemostasis was guided by stigmata of recent hemorrhage without Doppler. In the Doppler group, residual arterial blood flow after endoscopic hemostasis of SRH was highly associated with lesion rebleeding. Use of a Doppler endoscopic probe as a guide to risk

Table 3. Primary and Secondary Outcomes Within 30 days

	Standard	Doppler	Difference	95% CI lower	95% CI upper	*P* value
Patients	76	72				
Routine 30-day outcomes						
Index lesion rebleed	20 (26.3%)	8 (11.1%)	15.2%	2.7%	27.7%	.021
Surgery for rebleeds	4 (5.3%)	0 (0%)	5.3%	0.0%	12.8%	.12
Angiography for rebleeds	1 (1.3%)	4 (5.6%)	-4.2%	-12.3%	2.5%	.200
Death	3 (4.0%)	1 (1.4%)	2.6%	-3.9%	9.8%	.337
Major complications	4 (5.3%)	0 (0%)	5.3%	0.0%	12.8%	.12
CVA	2 (2.6%)	0 (0%)				
Perforation	1 (1.3%)	0 (0%)				
Pneumoperitoneum	1 (1.3%)	0 (0%)				
Other gastrointestinal bleeds	3 (4.0%)	4 (5.6%)	-1.6%	-10.1%	6.2%	.714
Transfusions and hospital days[a]						
More red cell units transfused	1.09 ± 2.94	0.56 ± 2.41	0.53	-0.34	1.40	.230
More units of fresh-frozen plasma transfused	0.12 ± 0.49	0.06 ± 0.29	0.06	-0.07	0.19	.502
More units of platelets transfused	0.03 ± 0.23	0.06 ± 0.33	-0.03	-0.12	0.06	.890
Hospital days						
Length of stay in the intensive care unit, days	4.21 ± 8.40	3.04 ± 3.04	1.17	-0.86	3.20	.220
Length of hospital stay, days	7.00 ± 8.79	6.65 ± 8.48	0.35	-2.46	3.16	.997

CVA, cerebral vascular accident.
[a]Means ± SD.

stratification and endoscopic hemostasis during emergency endoscopy was safe.

This was a large RCT that used a Doppler endoscopic probe as both a guide to risk stratification and for directing definitive endoscopic hemostasis of nonvariceal UGI hemorrhage. These results are highly clinically significant and relevant. This RCT also included both major stigmata of hemorrhage and lesser stigmata for nonvariceal UGI lesions with severe hemorrhage. We also combined currently recommended medical therapy with standard-of-care endoscopic hemostasis for different SRH. Two previously reported RCTs using a Doppler probe lacked one or more of these important features, or were negative, and used a much more complicated DEP unit.[17,18] Several other cohort studies using a Doppler probe for risk stratification reported encouraging early results for peptic ulcer hemorrhage but did not include other nonvariceal UGI lesions.[10,11,19,20]

Patients with severe NVUGI bleeding requiring hospitalization are the most likely to benefit from DEP for risk assessment and as a guide to endoscopic hemostasis. DEP may have been associated with improved outcomes in different ways in patients with NVUGI bleeding according to different SRH. First, patients with major stigmata (spurting, nonbleeding visible vessel, and adherent clot) benefited the most because approximately 24% had residual arterial blood flow after standard visually guided endoscopic hemostasis. Residual blood flow increased the risk of rebleeding and further endoscopic treatment with DEP guidance in the current RCT reduced the rebleeding rate and improved other outcomes compared with visually guided (standard) hemostasis (Tables 2 and 3). Second, patients with flat spots (Forrest IIC) could be risk stratified to endoscopic hemostasis if DEP positive at baseline, or no endoscopic hemostasis and medical treatment if DEP is negative. Third, oozing (Forrest IB) bleeding (without other SRH such as a clot or vessel) could be stratified into low risk (DEP negative) vs higher risk (DEP positive before endoscopic treatment). After endoscopic hemostasis in the oozing group, the rebleeding rate was low, so oozing patients benefited less from DEP; similar to our recent cohort study.[12]

The number needed to treat to prevent one episode of rebleeding was 7 patients with the Doppler probe. The number needed to treat varied according to the type of SRH.

Table 4. Enrollment Year × Treatment Interaction for 30-Day Rebleeding

Year enrolled	n	Standard rebleeds, n	Rebleed, %	n	Doppler rebleeds, n	Rebleed, %
2008–2009	9	0	0.0	10	0	0.0
2010	6	1	16.7	4	0	0.0
2011	12	3	25.0	14	2	14.3
2012	14	6	42.9	17	3	17.6
2013	20	9	45.0	18	1	5.6
2014–2015	15	1	6.7	9	2	22.2
Total	76	20	26.3	72	8	11.1

It was 4 for adherent clots, 5 for flat spots, 5 for spurting bleeding, 7 for oozing, and 10 with nonbleeding visible vessels. Although the confidence intervals are wide for rebleeding and the subgroups were too small to show statistically significant differences, these are clinically relevant (Table 3).

The high rebleeding rates of patients with major stigmata of hemorrhage were associated with incomplete initial hemostasis and high rates of residual arterial blood flow underneath the SRH, as we reported both in this RCT and in a recent prospective cohort study of severe ulcer hemorrhage.[12] The rates of residual blood flow after visually guided endoscopic hemostasis in the Doppler-treated patients varied by stigmata from 0% for oozing bleeding to 28% for major stigmata, consistent with our prior cohort study in which these rates were 0% for oozing and 27.4% for major stigmata.[12] Even after further endoscopic treatment for residual blood flow in the majority of the patients in the Doppler group, there still was a high rebleeding rate for the spurting bleeding and nonbleeding visible vessel subgroups (28.6% and 15.4%). This related to untreated patent arteries in some patients who did not receive further endoscopic hemostasis or others in which the signal was faint but not obliterated completely. Other possible reasons for the high rebleeding rates may be large artery size (perhaps too large to effectively treat with current through the endoscope hemoclips or with thermal coaptive coagulation), only transient interruption of arterial blood flow by treatment, incomplete coaptive coagulation or mechanical closure of the artery underlying the stigmata, fibrinolysis, coagulopathies, large ulcer size, and medications.

For clinically high-risk patients such as those enrolled in this study, there is the opportunity for significant improvements in both coaptive coagulation and mechanical closure of the underlying arteries of nonvariceal lesions. One potential candidate for further study is a large, over-the-endoscope hemoclip that may be able to close larger or deeper underlying arteries and obliterate blood flow more effectively than current transendoscopic hemoclips and potentially be safer than additional thermal coagulation for treatment of residual arterial blood flow.[22] Besides surgery, another option is selective angiographic embolization targeted to the artery under the endoscopically placed hemoclips, if blood flow persists or rebleeding occurs after what is judged by the endoscopist to be safe as maximum endoscopic treatment. Five of our patients with rebleeding had angiographic embolization, as shown in Table 3.

A discussion of potential limitations and weaknesses of this study will provide the reader with further perspective. These include use of a new technology that may be hard to learn; that this RCT was small and no other confirmatory studies have yet been reported; concerns about the small number of patients with some major SRH such as spurting bleeding or an adherent clot, which could make results of statistical comparisons inconclusive for individual SRH; higher rebleed rates than have been reported in other international RCTs of bleeding ulcers; and no inclusion of baseline Rockall or Glasgow–Blatchford scores so that an equal distribution of baseline risk could not be confirmed by those who use these scores. Other potential limitations and weaknesses may be the quality of the RCT and lack of comparability of the patients because of the long duration of the study and an early suspension that could limit the generalizability of results. Finally, there are concerns about increasing the cost of care by adding a new technology.

We address each of these for the readers to give them our perspective. First, this is relatively new technology and a new type of Doppler endoscopic probe. However, unlike the more technically complex endoscopic ultrasound endoscopies, the DEP unit does not produce a visual image but rather an auditory output that is gated by depth and much easier to apply and interpret than endoscopic ultrasound endoscopes or probes, which require much more training and experience.[12] Also, the DEP system used in this study with single-use endoscopic probes is Food and Drug Administration–approved, and is newer and much simpler than those more complex and cumbersome systems previously used in Europe and the United Kingdom 1 or 2 decades ago, which often had multiple depth settings, multichannel recorders, or oscilloscope outputs requiring technician support for recording and interpretation.[10,17–20] Second, in regard to confirmatory studies, there have been no other recent RCTs reported. Third, we agree that there were small numbers of patients with some major SRH, and conclusions about differences in rebleeding rates in Table 2 of individual SRH are inconclusive because of large confidence intervals. However, this study was not designed or powered to differentiate rebleeding rates of different individual SRH for the 2 treatments. Instead, our primary goal was to compare overall rebleeding rates according to treatment and those were significantly different (Table 2 and Figure 1). Fourth, concerning higher rebleeding rates in this RCT compared with other recent international bleeding ulcer studies, this was accounted for by the higher risk of our patients including high ASA scores (~60% in categories III or IV); high rates of inpatient start of bleeding (18%–21%); high prevalence of large ulcers (16%–17%); inclusion of cirrhotic patients (14%–16%); and frequent use of antiplatelet drugs or aspirin (48%–65%); or anticoagulants (21%–22%). We also included Dieulafoy lesions and Mallory Weiss tears in high-risk patients, whereas international trials focused on ulcers. Nevertheless, the gender, heterogeneous ethnicity, low prevalence of *H pylori*, and these other risk factors are representative of patients managed in referral centers in the United States such as ours.[12–15,23] Our patients differ from those commonly included in RCTs of ulcer hemorrhage from Asia or other countries that previously were reported and therefore included as evidence in current guidelines.[6–9] The latter patients typically are younger, have fewer comorbidities, and lower ASA scores, but have a higher prevalence of *H pylori* infection, which all improve their prognosis, their response to PPIs, and reduce their risk of rebleeding compared with the current RCT. It may be a limitation of this RCT that Rockall or Glasgow–Blatchford scores were not included. However, based on other scores that we have used in our prior interventional studies (ASA, Center for Ulcer Research and Education prognosis score, and

Child–Pugh) and detailing the known risk factors for rebleeding[23] that are compared in Table 1, the treatment groups were very similar at baseline and these did not explain the outcomes reported. Fifth, there were potential limitations of quality control and comparability of patients because our RCT took a long time to complete and was suspended once. It was monitored carefully by an independent VA Data and Safety Monitoring Committee, which stopped the study at one point because of slow enrollment (as detailed earlier) and approved all protocol changes such as surrogate consent and inclusion of sicker patients (ASA III and IV) for enrollment. Most similar interventional studies were not performed in the United States and excluded such sick patients. Our group has a track record of completing well-designed, clinically relevant, credible, and new RCTs in GI bleeding.[12–15] Some readers may think that a small number of patients were recruited, that the 2 centers were in the same city, and because patients were recruited over more than 4 years that time might have confounded the results. However, the study met recruitment goals (which was a relatively large size), included 148 patients, and reported clinically relevant outcome (rebleeding), which was improved significantly with the Doppler group. Furthermore, there was no evidence that enrollment date affected the distribution of baseline variables or the primary outcome (Table 4).

Regarding the potential limitation related to cost, an updated cost-effectiveness study using current techniques will be required to formally evaluate cost effectiveness. However, our current RCT results corroborate those of a prior cost minimization analysis about potential savings with Doppler endoscopic probe utilization for the treatment of severe peptic ulcer hemorrhage based on anticipated costs in health care management.[24]

Our conclusions are as follows. First, the use of a Doppler endoscopic probe as a guide to endoscopic risk stratification and hemostasis for patients with severe UGI hemorrhage from peptic ulcers, Dieulafoy's lesions, and Mallory Weiss tears reduced the 30-day rebleeding rate compared with standard visually guided endoscopic hemostasis. Second, Doppler-guided treatment during emergency endoscopy was safe. Third, residual arterial blood flow after endoscopic hemostasis was associated with a significantly higher rebleeding rate than successful obliteration of blood flow. We recommend that current guidelines for management of NVUGI bleeding incorporate these new findings.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2017.01.042.

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Conflicts of interest
This author discloses the following: Dennis Jensen is a consultant for Vascular Technology, Inc. The remaining authors disclose no conflicts.

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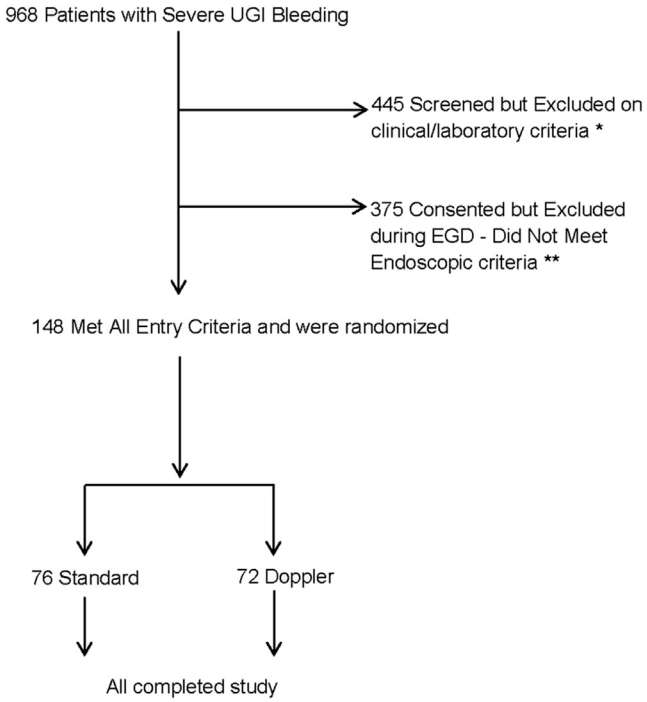

Supplementary Figure 1. CONSORT diagram of Doppler endoscopic probe randomized controlled trial. *The specific reasons were mesalamine or very poor prognosis: 30-day survival not expected including those without organ transplantation (176 patients); no consent for study including surrogate (110 patients); uncooperative, noncompliant, or unable to return for study follow-up evaluation (45 patients); refused to consent (32 patients); UGI malignancy (26 patients); hypotensive on pressors (17 patients); not severe enough hemorrhage (13 patients); or did not meet entry criteria. **These included esophageal varices or portal hypertensive lesions (87 patients) and no SRH or UGI lesions that did not meet endoscopic inclusion criteria (288 patients).