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Review

Role of the endoscopic Doppler probe in nonvariceal upper gastrointestinal bleeding: Systematic review and meta-analysis

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Objectives: The effectiveness of the Doppler endoscopic probe (DEP) remains unclear in nonvariceal upper gastrointestinal bleeding (NVUGIB). We thus performed a systematic review characterizing the effectiveness of DEP in patients with NVUGIB addressing this question.

Methods: A literature search was done until July 2021 using MEDLINE, EMBASE, and ISI Web of Science. A series of meta-analyses were performed assessing outcomes among observational and interventional studies for DEP signal positive and negative lesions as well as DEP-assisted versus standard endoscopies. The primary outcome was “overall rebleeding”; secondary outcomes included all-cause mortality, bleeding-related mortality, need for surgery, length of stay, intensive care unit stay, and angiography.

Results: Fourteen studies were included from 1911 citations identified. Observational studies compared bleeding lesions with DEP-positive versus DEP-negative signals (11 studies, $n = 800$ prehemostasis; five studies, $n = 148$ with posthemostasis

data). Three interventional studies ($n = 308$) compared DEP-assisted to standard endoscopy management. DEP signal positive versus negative lesions either prior to or following any possible hemostasis were at greater risk of overall rebleeding (odds ratio [OR] 6.54 [2.36, 18.11] and OR 25.96 [6.74, 100.0], respectively). The use of DEP during upper endoscopy significantly reduced overall rebleeding rates (OR 0.27 [0.14, 0.54]). When removing outcomes analysis for which only one study was available, all evaluable outcomes were improved with DEP characterization of management guidance except for all-cause mortality.

Conclusion: Although with low certainty evidence, DEP-related information improves on sole visual prediction of rebleeding in NVUGIB, with DEP-guided management yielding decreased overall rebleeding, bleeding-related mortality, and need for surgery.

Key words: Doppler endoscopic probe, endoscopy, peptic ulcer disease, upper gastrointestinal bleeding

INTRODUCTION

DESPITE A DECREASING incidence over the past decades, nonvariceal upper gastrointestinal bleeding (NVUGIB) remains one of the most common gastrointestinal emergencies. Its management and outcomes have improved but mortality remains significant.^{1,2} Adoption of the Forrest endoscopic risk stratification has successfully

guided the management of patients with NVUGIB (especially with bleeding ulcers) for almost 50 years.³ Attempts to improve on this endoscopic risk assessment included the development of a through-the-scope endoscopic Doppler probe or Doppler endoscopic probe (DEP) as early as 40 years ago.³ Indeed, such technology can detect arterial submucosal blood flow during endoscopy by passing a probe through the operating channel of the endoscope. The device and its use are further detailed elsewhere.^{4,5} It may be used prior to endoscopic treatment to estimate the intrinsic rebleeding risk of a lesion and the subsequent need for endoscopic hemostasis, and/or after treatment to assess its effectiveness. Of note, DEP use does not require advanced ultrasonographic or Doppler expertise and has been shown to be cost-effective, providing immediate and

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actionable objective information.⁶ Despite being US Food and Drug Administration-approved since April 2003, the DEP technology has never been widely adopted. Despite the recent publication of a randomized clinical trial, which has led to renewed interest in this technique,⁷ DEP use was not addressed by recent international and North American guidelines published in 2019⁸ or 2021.² Furthermore, its adoption was rejected by two other international guideline groups, but seemingly only when considering the small number of patients included in an observational study in one⁹ and a randomized controlled trial (RCT) in the other.¹⁰ The heterogeneity with which the assessment of DEP has been addressed across different authoritative guidelines emphasizes the need for a high-quality effort clearly characterizing the available certainty of evidence with regard to the effectiveness of this technology.

We thus conducted a systematic review and meta-analysis targeting the use of DEP in the management of patients with NVUGIB.

METHODS

THE SYSTEMATIC REVIEW was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹¹

Search strategy

A comprehensive literature search was performed, from the start of databases to July 2021 using OVID MEDLINE, EMBASE, and ISI Web of Science, with a combination of MeSH term and controlled vocabulary to identify fully published studies related to: (i) Doppler; and (ii) gastrointestinal bleeding (Appendix S1). Abstracts presented at major gastroenterology conferences (ACG, CDDW, DDW, and UEGW) in the past 5 years were also hand-searched. Additional relevant studies were identified from cross-referencing and hand-searches of references of the retrieved articles.

Study selection and patient population

We selected all single-arm studies to analyze and report incidences of DEP-positive or -negative signal in the acute management of patients with NVUGIB. We then included all RCTs as well as observational, comparative, and noncomparative studies that included a DEP technology used in the acute management of patients with NVUGIB. All case reports, and studies not published in French or English, or addressing pediatric or nonhuman populations were excluded.

Validity assessment and data abstraction

Citations were handled in EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA). Two reviewers (N.C. and M.M.) independently evaluated the eligibility of citations based on the title and abstract. Selected full-text articles were reviewed for final inclusion/exclusion assessment. A third reviewer (A.B.) resolved conflicts. Risk of bias was assessed using the Cochrane risk of bias tool for randomized trials,¹² and the Ottawa–Newcastle criteria for observational studies.¹³ We used the GRADE rating of evidence to characterize the certainty of evidence.¹⁴

Outcome measures

The primary outcome of the study was the overall rebleeding rate defined as any rebleeding noted in a given study following the index endoscopy. Secondary outcomes included mortality (overall and NVUGIB-related mortality), need for surgery or angiography, and hospital and intensive care unit (ICU) length of stay.

Sensitivity and subgroup analyses

Subgroup and sensitivity analyses were conducted for the primary outcome in all meta-analyses presented, except in the one on incidences, according to the following predetermined study characteristics. Sensitivity analyses were conducted for RCTs alone, inclusion of sole high-risk stigmata of recent hemorrhage (that is: Forrest I, Forrest IIa, and IIb lesions), the use of a fixed-effect model (when appropriate), and correction for double-zero events. Due to the improvements in the management of NVUGIB over the search period, we also performed sensitivity analysis according to the type of endoscopic hemostatic procedure performed, differentiating past from currently recommended endoscopic therapy, more specifically, injection of epinephrine and saline alone versus other approaches.¹ The use of proton pump inhibitors of any dosage postprocedure as currently recommended adequate medical therapy was also analyzed.²

Subgroup analyses were: year of publication and continent where the study was conducted.

Statistical analysis and possible sources of statistical heterogeneity

A series of meta-analyses were performed assessing outcomes among observational and interventional studies for DEP signal positive (pre- of postendoscopic therapy) and negative lesions as well as DEP-assisted versus standard endoscopies.

A meta-analysis of proportions to determine incidences was conducted, and the results are reported as weighted pooled proportions with 95% confidence intervals (CIs). For studies in which comparisons were performed, the effect size was calculated with mean differences (MDs) for continuous variables; medians were used if means were not available and standard deviations (SDs) were calculated or imputed when possible.¹⁵ Odds ratios (ORs) were calculated for categorical variables. The DerSimonian and Laird method¹⁶ for random effect models was applied to all outcomes to determine corresponding overall effect sizes and their CI. Sensitivity analyses were performed using the Mantel–Haenszel method with fixed-effects models when no statistical heterogeneity was noted. MDs were handled as continuous variables using the inverse variance approach. The presence of heterogeneity across studies was defined using a χ^2 -test of homogeneity with a 0.10 significance level.¹⁵ The Higgins I^2 statistic⁸ was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity, with values of 0–40%, 30–60%, 50–90%, and 75–100% that might represent not being important, moderate, substantial, or considerable heterogeneity, respectively.¹⁷ Publication bias was evaluated using the Egger regression asymmetry test and Begg adjusted rank correlation,^{18,19} if at least three citations were identified. In order to ensure that zero event trials did not significantly affect the heterogeneity or *P*-values, sensitivity analyses were performed where a continuity correction was added to each trial with zero events using the reciprocal of the opposite treatment arm size.²⁰ All statistical analyses were performed using Revman 5.4 and Meta package in R version 2.13.0, (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Presentation of results

TO COMPLETELY CAPTURE the range of possible benefits provided by the DEP technology, multiple analyses are presented. First, a meta-analysis of proportions alone defines the frequency of outcomes (incidence) as captured in single and pertinent multiple-arm studies. Single arms of comparative studies were also used, when possible, for this analysis. Most of the results pertaining to this aspect of the work are presented in [Appendices S1–S10](#). Next, a meta-analysis of studies reporting comparative predictive data contrasts the information obtained when characterizing a bleeding lesion using the DEP technology or not (i.e., in this latter case, using Forrest classification and visual assessment only). This analysis examines application of the ultrasound probe either in assessing the eligibility of the

bleeding lesion prior to possible endoscopic therapy, referred to as “prehemostasis,” or alternatively following its completion, then referred to as “posthemostasis.” Finally, a meta-analysis assesses comparative interventional studies in which the information obtained from DEP is taken into consideration and affects the subsequent management of patients or not. In this analysis, we thus compare DEP-assisted endoscopy versus performance of a traditional gastroscopy alone.

A “DEP-positive lesion” refers to one in which a Doppler signal identifying a patent vessel in the base of the targeted bleeding lesion is detected, and a “DEP-negative lesion” implies its absence.

Study selection and interventions

The structured literature search initially identified 1911 citations. After review, a total of 1897 studies were excluded. The PRISMA diagram is shown in [Figure 1](#). We finally selected a total of 14 studies; all studies were fully published.

The analysis of proportions, defining the incidence of outcomes across all single-¹² and multi-arm studies^{3–5,21–27} included 12 studies (in the prehemostasis analysis for DEP-positive $n = 466$ and DEP-negative $n = 368$, and in the posthemostasis DEP-positive $n = 42$ and DEP-negative $n = 106$).

A total of 11 studies (10 cohorts,^{3–5,12,21,22,24–27} one RCT²³) included patients with lesions that had Doppler-positive and -negative signals prior to any possible hemostasis, thus guiding decisions on whether to perform endoscopic hemostasis or not (DEP-positive $n = 431$, and DEP-negative $n = 369$). Additionally, five studies including three cohort studies^{5,26,27} and two RCTs^{7,23} looked at applying the ultrasound probe to the lesion once it had been treated, that is, posthemostasis, thus addressing the need for DEP-guided additional hemostasis (DEP-positive $n = 42$, and DEP-negative $n = 106$).

Three studies compared DEP-assisted to standard endoscopy,^{7,23,28} with DEP used prospectively to identify/confirm the need for a hemostatic procedure, its adequacy,^{7,28} or both.²³ Of these, one was a prospective cohort study²⁸ and two were RCTs^{7,23} (DEP-assisted endoscopy $n = 157$, and standard endoscopy $n = 151$).

Study quality assessment, risk of publication bias, and heterogeneity

In the two included RCTs^{7,23} across all comparisons, performance blinding was at high risk of bias for one trial²³ due to lack of blinding, whereas the study by Jensen *et al.*⁷

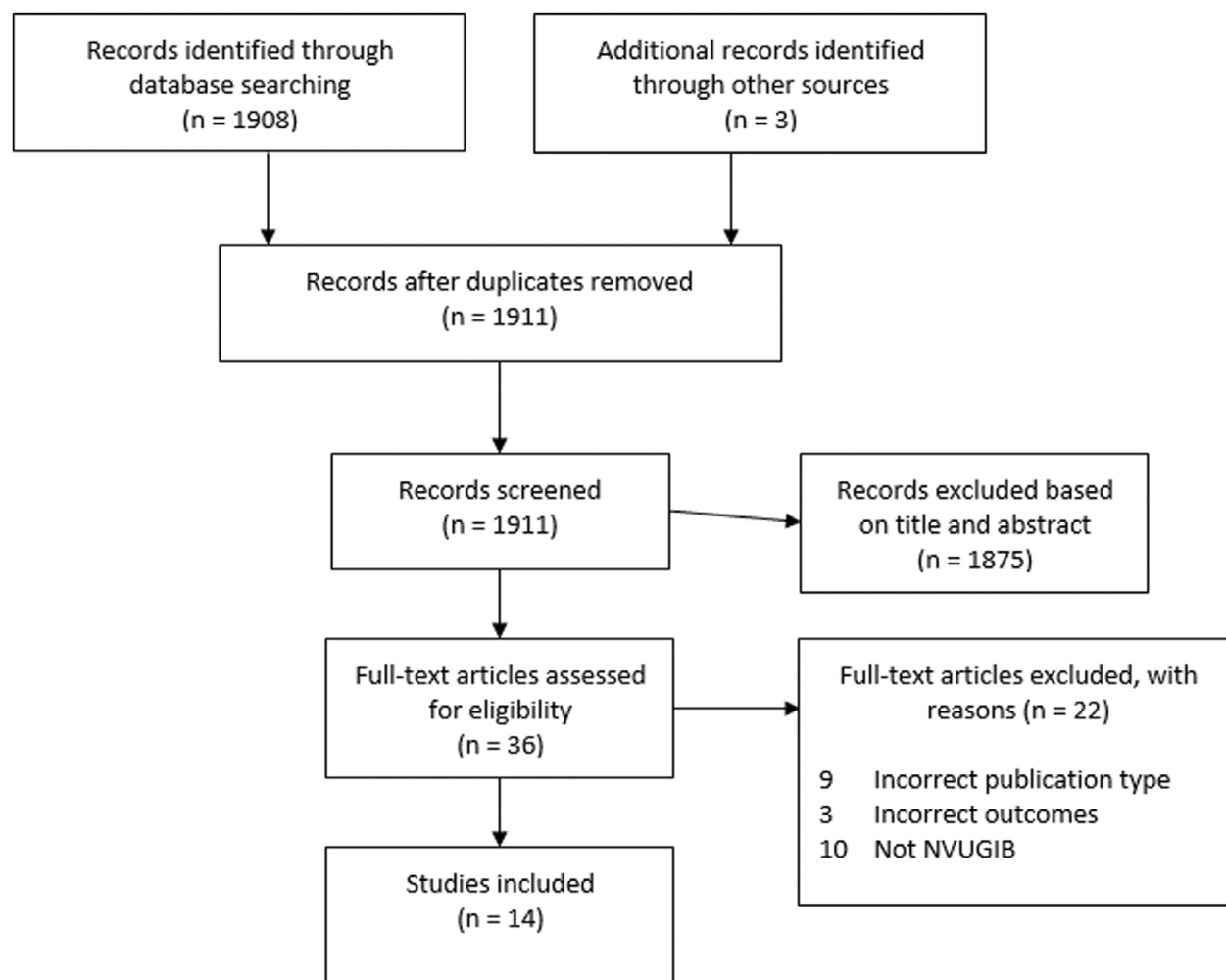


Figure 1 PRISMA diagram.

was single-blinded, with only the managing physicians being blinded to the endoscopic treatment (Appendix S3). The Newcastle–Ottawa scale yielded an average score of 6.2 ± 0.7 (range 5–7 stars) (Appendix S4). No publication bias was noted for the studies comparing DEP-positive versus DEP-negative lesions, or those comparing DEP-assisted to standard endoscopy (Egger *P*-values 0.09 and 0.20, respectively). Heterogeneity was moderate for the meta-analysis comparing DEP-positive to DEP-negative groups for overall rebleeding ($I^2 = 46\%$, $P < 0.05$). No heterogeneity was noted in any of the other comparisons.

Patient and study characteristics

The overall mean patient age was 65.1 ± 2.7 and 36.5% of patients were women. Details of the nature of included

lesions and details pertaining to the overall management of the NVUGIB are listed in Table 1.

Primary outcome: overall rebleeding

When considering all 12 single-arm¹² and two-arm studies,^{3–5,21–27} in the meta-analysis of proportions, the overall rebleeding rate was 16% (9%, 27%) for patients with DEP-positive, and 5% (3%, 9%) in patients with DEP-negative lesions. The results pertaining to the meta-analysis of proportions are presented in Appendix S2.

Analysis of 11 studies^{3–5,21–27} ($n = 800$) comparing the outcomes of patients with DEP-positive versus DEP-negative lesions, when assessing solely the lesion prior to any possible endoscopic hemostasis, showed overall rebleeding to be significantly greater when the lesion was

Table 1 Characteristics of patients, lesions, and management in the included studies

Study (country), type of study, quality score	Patient cohort, lesions, <i>N</i> , routine look endoscopy	Intervention	Control	Rebleeding definition	Endoscopic therapy, medical therapy, type of Doppler probe
Doppler positive compared to standard endoscopy					
Kohler <i>et al.</i> 1997 ²³ (Germany) RCT	Acute ulcer bleeding Included: Forrest II and III <i>N</i> = 100 (male: 65%; female: 35%) Cohort age: N/A Second look endoscopy at 24 h and before discharge	Doppler prehemostasis Doppler posthemostasis Doppler and additional hemostasis at second look Treatment was based exclusively on the findings of the Doppler examination irrespective of the endoscopic appearance	According to known Forrest classification	Suspected clinically when there was: blood in the gastric aspirate and/or melena accompanied by changes in cardiovascular parameters, or bloody vomit, or insufficient increase in hemoglobin, or a renewed drop in hemoglobin despite appropriate red blood cell replacement	Inj (Epi 1:10,000) 3 × 40 mg IV PPI (omeprazole) first 2–3 days then 40 mg PO PPI for the next 3 weeks Pulsed high frequency Doppler (EME, Überlingen, Germany) and Microdop (DWL, Söppingen, Germany)
Jensen <i>et al.</i> 2017 ⁷ (USA) RCT	Acute ulcer bleeding Included: ulcers, Dieulafoy's lesions, or Mallory–Weiss tears without portal hypertension <i>N</i> = 148 (male: 82.6%; female: 17.4%) Cohort age: N/A No mention of second look	Doppler prehemostasis Doppler posthemostasis	Standard	Clinically significant rebleeding episodes were defined as recurrent hematemesis or melena, with a minimum decrease of 2 g of hemoglobin, and/or the need for transfusions of red blood cells, as detailed in the previous report	Inj (Epi 1:10,000) + (clips or thermal) Ulcers and Dieulafoy's lesions: IV PPI (pantoprazole 80 mg bolus + 8 mg/h) for 72 h, then twice-daily oral PPI for 30 days (omeprazole 20 mg, pantoprazole 40 mg, or lansoprazole 30 mg) Mallory–Weiss tear: anti-emetics initially and a PPI twice daily for 7 days Disposable Doppler endoscopic probe (Vascular Technology, Inc, Nashua, NH, USA)

Table 1 (Continued)

Study (country), type of study, quality score	Patient cohort, lesions, N, routine look endoscopy	Intervention	Control	Rebleeding definition	Endoscopic therapy, medical therapy, type of Doppler probe
Kantowski et al. 2018 ²⁸ (Germany) Prospective cohort	Acute ulcer bleeding Included: Forrest I–IIa and a Rockall score of 5 or higher (high rebleeding risk lesions) N = 60 (male: 65%; female: 35%) Cohort age: N/A No mention of second look	Doppler prehemostasis Doppler posthemostasis with additional if required	Standard	New occurrence of hematemesis, persistence of melan for more than 2 days or decrease in hemoglobin of 2 mg/dL and signs of recent hemorrhage upon endoscopic examination	(Epi 1:10,000+ glue) ± clips PPI (no dosage or duration reported) Endo-DopVR system (Com-pumedics DWL, Singen, Ger-many)
Doppler positive compared to Doppler negative					
Jensen et al. 2016 ⁴ (USA) Prospective cohort	Severe peptic ulcer bleeding Included: Forrest I–III N = 163 (male: 79.8%; female: 20.2%) Cohort mean age: 65.7 ± 19.9 years No mention of second look	Doppler positive Doppler prehemostasis Doppler hemostasis (not to apply more endoscopic treatment. Medical RX was done according to guidelines)	Doppler negative Doppler prehemostasis Doppler posthemostasis (not to apply additional hemostasis. Medical RX was done according to guidelines)	Clinical evidence of upper GI bleeding (hematemesis, melena, hematochezia, or red blood via nasogastric tube) with a hemoglobin drop of 2 g or transfusion of 2 or more units of red blood cells, 6 h after the index endoscopy and treatment	(Thermal or clips) ± Inj (Epi 1:20,000 and/or saline) Major SRH: IV PPI (80 mg bolus and 8 mg/h) for 72 h then twice daily oral PPI for 30 days FB to FII: PPI in standard doses orally (or IV if not eating) twice daily and not high-dose IV PPI infusion Disposable Doppler endoscopic probe (Vascular Technology, Inc, Nashua, NH, USA)
Jaspersen et al. 1992 ²² (clin Inv) (Germany) Prospective cohort Short communication	Acute ulcer bleeding Included: Forrest II N = 41 (male: 58.5%; female: 41.5%) Cohort mean age: 59 years (range: 24–79) Second look was done the next day and 14 days after	Doppler positive Doppler prehemostasis Doppler posthemostasis	Doppler negative Doppler prehemostasis Doppler posthemostasis not explicit	Not defined precisely ("Disappearance of the endoscopically detected arterial signal and lack of recurrent bleeding was regarded as signs of a successful therapy")	Inj (Epi 1:10,000 + Polydo 1%) No mention on medical therapy Pulsed microvascular Doppler (MF 20, Eden Medizinische Elektronik, Ubertingen, Germany)

Table 1 (Continued)

Study (country), type of study, quality score	Patient cohort, lesions, <i>N</i> , routine look endoscopy	Intervention	Control	Rebleeding definition	Endoscopic therapy, medical therapy, type of Doppler probe
van Leerdam <i>et al.</i> 2003 ⁵ (The Netherlands) Prospective cohort	Acute ulcer bleeding Included: Forrest Ib-Ib; IIc, III ¹ (results for high rebleeding risk lesions provided) <i>N</i> = 50 (male: 61%; female: 39%) Cohort mean age: N/A No mention of second look	Doppler positive Doppler prehemostasis Doppler posthemostasis when rebleeding was suspected, management at the discretion of the endoscopist	Doppler negative Doppler prehemostasis Doppler posthemostasis when rebleeding was suspected, management at the discretion of the endoscopist	Not defined precisely ("followed clinically for evidence of recurrent bleeding, HB level was determined daily")	Inj (Epi 1:10,000 ± Polydo 1%) IV PPI (80 mg bolus followed by 8 mg/h continuous infusion) for at least 24 h Then 40 mg per se PPI for 4 weeks Endo-Dop (DWL; Neurosoft, Siplingen, Germany)
Jaspersen <i>et al.</i> 1993 ²¹ (Germany) Prospective cohort	Acute ulcer bleeding Included: Forrest Ia, b, c, and Forrest III with no sign but with a history of bleeding <i>N</i> = 147 (male: 62.6%; female: 37.4%) Cohort mean age: 63 years (range: 20–89) Second look with Doppler at 24 h, day 5, and day 28	Doppler positive Doppler prehemostasis Doppler posthemostasis	Doppler negative Doppler prehemostasis	Not defined	Inj (Epi 1:10,000 ± Polydo 1%) IV PPI (day 1: 1 × 80 mg, 2 × 40 mg; day 2–5: 3 × 40 mg), then 20 mg per se PPI days 6–28 MF20 (EME, Ueberlingen, Germany)
Kohler <i>et al.</i> 1993 ²⁶ (Germany) Prospective cohort	Acute ulcer bleeding Included: Forrest II and III <i>N</i> = 114 Gender: N/A Cohort mean age: 65 years (range: 18–97) Second look in patients treated endoscopically, within 48 h, and in all patients before discharge	Doppler positive Doppler prehemostasis Doppler posthemostasis with additional after 48 h if required	Doppler negative Doppler prehemostasis	Not defined	Inj (Epi 1:10,000 ± Polydo) H ₂ RA was given (unknown dosage and duration) 20 MHz high-frequency Doppler probe

Table 1 (Continued)

Study (country), type of study, quality score	Patient cohort, lesions, N, routine look endoscopy	Intervention	Control	Rebleeding definition	Endoscopic therapy, medical therapy, type of Doppler probe
Kohler <i>et al.</i> 1994 ²⁴ (Germany) Prospective cohort	Acute ulcer bleeding Included: Forrest II and III N = 150 Gender: N/A Cohort mean age: N/A Second look in patients treated endoscopically, within 48 h	Doppler positive Doppler posthemostasis with additional within 48 h if required	Doppler negative	Not defined	Inj (Epi 1:10,000 ± Polydo 1%) H ₂ RA or IV PPI was given (unknown dosage and duration) 20 MHz high-frequency Doppler probe
Kohler <i>et al.</i> 1991 ²⁵ (Germany) Prospective cohort	Acute ulcer bleeding Included: Forrest II and III N = 80 (male: 58.8%; female: 41.2%) Cohort mean age: 66 years (range: 18–97) Second look (lunk time)	Doppler positive Doppler prehemostasis Doppler posthemostasis with additional in the following days if required	Doppler negative Doppler prehemostasis Doppler posthemostasis with additional in the following days if required	Not defined	Inj (Epi 1:10,000 ± Polydo) No mention on medical therapy 20 MHz high-frequency Doppler probe (EME, Überlingen, Germany)
Wong <i>et al.</i> 2000 (USA) ³³ Prospective cohort	Acute ulcer bleeding Included: all peptic gastric or duodenal ulcer N = 52 (male: 59.6%; female: 40.4%) Cohort mean age: 65 years No mention of second look	Doppler positive Doppler prehemostasis Doppler posthemostasis Endoscopist was blinded to the results of Doppler pre and post	Doppler negative Doppler prehemostasis Doppler posthemostasis Endoscopist was blinded to the results of Doppler pre and post	Recurrence of melena, hematochezia, or hematemesis coupled with unstable vital signs or a decrease in hematocrit after stabilization of ≥4% in 24 h or active bleeding documented at repeat endoscopy	Inj (Epi 1:10,000) ± thermal No mention on medical therapy 16 MHz pulsed-wave, linear scanning, Doppler US probe (DWL, Sipplingen, Germany)
Beckly <i>et al.</i> 1986 (USA) ³⁴ Prospective cohort	Acute ulcer bleeding Included: Forrest II N = 49 Gender: N/A Cohort mean age: 68 years No mention of second look	Doppler positive Doppler prehemostasis No Doppler posthemostasis mentioned Endoscopist was blinded to the results of Doppler pre and post	Doppler negative Doppler prehemostasis No Doppler posthemostasis mentioned Endoscopist was blinded to the results of Doppler pre and posthemostasis	Only those cases in whom surgery was carried out solely to stop hemorrhage or who bled to death were classified as “rebleeds”	No mention of type of endoscopic hemostasis No mention of medical therapy 8 MHz system derived from Sonicaid BV 102 vascular flow detector

Table 1 (Continued)

Study (country), type of study, quality score	Patient cohort, lesions, <i>N</i> , routine look endoscopy	Intervention	Control	Rebleeding definition	Endoscopic therapy, medical therapy, type of Doppler probe
Fullarton <i>et al.</i> 1990 ³⁵ (Scotland) Prospective cohort	Acute ulcer bleeding Included: active nonarterial bleeding (oozing) and/or visible vessel and confirmed accessibility of the ulcer site to the TVD probe (high risk lesions) <i>N</i> = 22 Gender: N/A Cohort mean age: 65.9 ± 4.8 years No mention of second look	Doppler positive Doppler prehemostasis No Doppler posthemostasis Endoscopist was blinded to the results of Doppler pre and post	Doppler negative Doppler prehemostasis No Doppler posthemostasis Endoscopist was blinded to the results of Doppler pre and posthemostasis	a) Fresh blood in the upper gastrointestinal tract at re-endoscopy or surgery b) Vomiting fresh blood at any time other than immediately after endoscopy where fresh blood had been noted in the UGIT c) Fresh melena plus one of the following 1. Hemodynamic and clinical evidence of hypovolemic shock (systolic BP <100, pulse rate >100) 2. Falling Hb despite blood transfusion (failure to raise Hb by more than 0.5 g/dl per unit of blood transfused)	No mention of type of endoscopic therapy No mention of medical therapy Transendoscopy Vascular Detector, TVD01 (KeyMed, Southend-on-Sea, UK)
Jakobs <i>et al.</i> 2004 ³⁶ (Germany) Prospective cohort	Acute ulcer bleeding Active bleeding ulcer bleeding at endoscopy (Doppler classification according to Kohler or Forrest Ia or Ib) (high rebleeding risk lesions) <i>N</i> = 20 (male: 45%; female: 55%) Cohort mean age: 68 years (range: 33–91) Second look 24 h after	Doppler positive Doppler posthemostasis until Doppler negative	No comparisons	Not defined precisely (a follow-up endoscopy including a Doppler ultrasound scan was routinely performed on the next day and if rebleeding was suspected clinically)	Inj (adrenaline 1:10,000) IV PPI 40 mg BID for 2 days Endo-Dop (DWL, Sipplingen, Germany)

BP, blood pressure; CI, confidence interval; GI, gastrointestinal; Hb, hemoglobin; ICU, intensive care unit; Inj, injection; IV, intravenous; N/A, not available; PPI, proton pump inhibitor; SRH, stigmata of recent hemorrhage; US, ultrasound.

Table 2 Primary and secondary outcome for comparative studies (Doppler endoscopic probe [DEP]-positive vs. DEP-negative) pre-endoscopic therapy

	<i>N</i> studies	<i>N</i> patients	Odds ratio (95% CI)	<i>P</i> -value for heterogeneity	<i>I</i> ²
Primary outcome					
Overall rebleeding	11	800	6.54 (2.36, 18.11)	0.05	46%
Secondary outcome					
Surgery	7	657	4.22 (1.64, 10.90)	0.97	0%
All-cause mortality	5	455	1.80 (0.50, 6.47)	0.16	39%
Bleeding-related mortality	4 [†]	375	31.71 (1.49, 672.74)	N/A	N/A
Length of stay	1 [‡]	80	N/A	N/A	N/A
ICU stay	0	0	N/A	N/A	N/A
Angiography	0	0	N/A	N/A	N/A

[†]All double-zero event except one.

[‡]Data not analyzable.

CI, confidence interval; ICU, intensive care unit; N/A, not available.

DEP-positive (OR 6.54 [2.36, 18.1]) (Table 2, Fig. 2a). Five studies^{5,7,23,26,27} (*n* = 148) assessed the clinical impact of DEP assessment posthemostasis. Overall rebleeding was significantly greater in patients whose treated lesions exhibited a persistent positive DEP signal (OR 26 [6.74, 100]), as compared to those for which the DEP signal became negative after endoscopic treatment (Table 3, Fig. 2a,b).

Pooled analysis of the three studies^{7,23,28} (*n* = 308) comparing DEP-assisted to standard endoscopy found that the use of DEP was associated with a significantly lower overall rebleeding rate (OR 0.27 [0.14, 0.54]) (Table 4, Fig. 2a,c).

Secondary outcomes

In the seven studies^{3,5,21,24–27} (*n* = 657) comparing patients with DEP-positive versus DEP-negative lesions prehemostasis, all-cause mortality (five studies,^{3,5,24–26} *n* = 455) was not significantly different between the two groups (OR 1.80 [0.50, 6.47]) in contradistinction to the need for surgery (seven studies,^{3,5,21,24–27} *n* = 657) (OR 4.22 [1.64, 10.90]) and bleeding-related mortality (four studies,^{3,24–26} *n* = 375) (OR 31.71 [1.49, 672.74]) that were significantly greater in the DEP-positive group (Table 2). Lack of data prevented analyses of other outcomes.

In the single study²⁶ assessing DEP-positive versus DEP-negative lesions posthemostasis, all-cause mortality was significantly increased in the DEP-positive patients (OR 25.26 [1.22, 525.09]) (Table 3). Lack of data prevented the analyses of the other outcomes.

In the three studies^{7,23,28} comparing DEP-assisted to standard endoscopy, bleeding-related mortality (OR 0.12

[0.02, 0.71]) and surgery (OR 0.09 [0.02, 0.42]) were both significantly lower in the DEP-assisted group. However all-cause mortality was not statistically reduced (OR 0.40 [0.15, 1.06]), as was also the case for the need for angiography, duration of hospital, and ICU stays, even if the last three outcomes were assessed in only one study⁷ (Table 4).

Sensitivity and subgroup analyses

These were only performed when more than one study was available for analysis. Overall rebleeding was greater among patients with DEP-positive versus DEP-negative lesions in all subgroups and sensitivity analyses performed (including contemporary studies and studies in which endoscopists were blinded, Appendices S5–S7). In general, posthemostasis predictions presented markedly greater effect sizes when contrasted with prehemostasis results. Similar findings favoring DEP-assisted versus standard endoscopies were noted. Across all analyses, effect sizes and corresponding confidence intervals varied predictably according to the patient numbers available for the different comparisons (Appendices S5–S7).

Grading of the evidence

Grading of the evidence was found to be “very low” in all outcomes when comparing DEP-positive and negative lesions pre- and posthemostasis (Appendices S8, S9). This was also the case when assessing DEP-assisted versus standard endoscopy except for the outcomes of length of stay, ICU stay, and angiography for which the grade was “low” (Appendix S10).

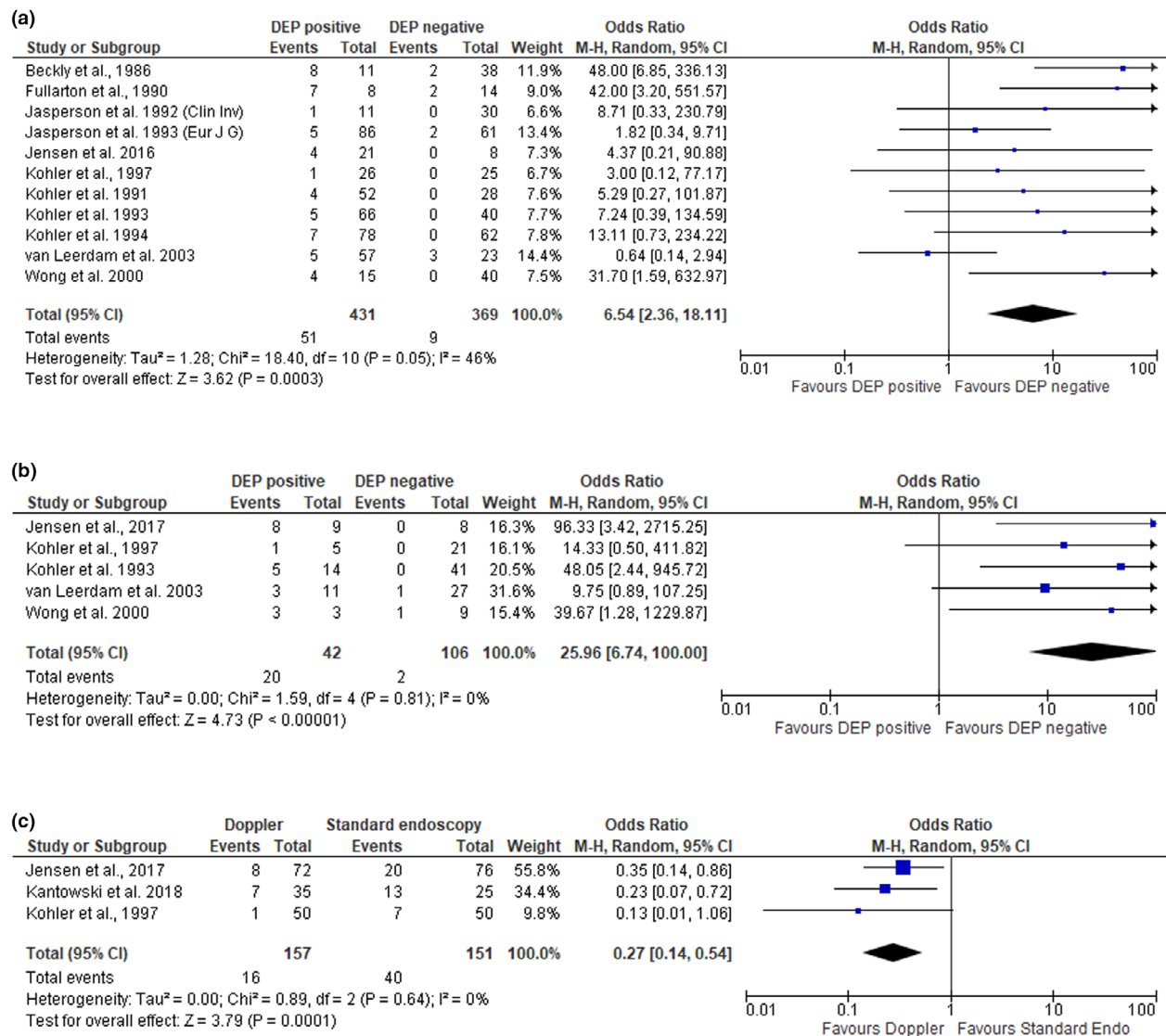


Figure 2 (a) Forrest plot for overall rebleeding (Doppler endoscopic probe [DEP]-positive vs. DEP-negative, DEP assessment before any endoscopic therapy). (b) Forrest plot for overall rebleeding after endoscopic therapy (DEP-positive vs. DEP-negative). (c) Forrest plot for overall rebleeding (DEP-assisted endoscopy vs. standard endoscopy). CI, confidence interval.

DISCUSSION

THE PRESENT SYSTEMATIC review with its series of meta-analyses provides a comprehensive and up-to-date summary of published data on the use of DEP in NVUGIB. Although DEP was first studied about 40 years ago, this device has been progressively and almost totally abandoned. Reasons for this may be that the Forrest classification was developed a little bit earlier, and enjoyed preferential widespread dissemination and quick adoption. Reasons

favoring this choice included the Forrest classification simplicity, robustness, and avoidance of additional equipment. However, in light of recent published cost-effectiveness and RCT, there has been renewed interest in this device. The meta-analysis of proportions provides a broad overview of adverse outcome incidences that are more prevalent in patients with DEP-positive lesions. Lesion assessment using DEP is associated with improved prediction of outcomes both pre- and postendoscopic hemostasis, leading to a significant reduction in overall rebleeding. DEP

Table 3 Primary and secondary outcome for comparative studies (Doppler endoscopic probe [DEP]-positive vs. DEP-negative) postendoscopic therapy

	N studies	N patients	Odds ratio (95% CI)	P-value for heterogeneity	I^2
Primary outcome					
Overall rebleeding	5	148	25.96 (6.74, 100.0)	0.81	0%
Secondary outcome					
Surgery	0	N/A	N/A	N/A	N/A
All-cause mortality	1	55	25.26 (1.22, 525.09)	N/A	N/A
Bleeding-related mortality	0	N/A	N/A	N/A	N/A
Length of stay	0	N/A	N/A	N/A	N/A
ICU stay	0	N/A	N/A	N/A	N/A
Angiography	0	N/A	N/A	N/A	N/A

CI, confidence interval; ICU, intensive care unit; N/A, not available.

Table 4 Primary and secondary outcome for comparative studies (Doppler endoscopic probe-assisted endoscopy vs. standard endoscopy)

	N studies	N patients	Odds ratio (95% CI)	P-value for heterogeneity	I^2
Primary outcome					
Overall rebleeding	3	308	0.27 (0.14, 0.54)	0.64	0%
Secondary outcome					
Surgery	3	308	0.09 (0.02, 0.42)	0.99	0%
All-cause mortality	3	308	0.40 (0.15, 1.06)	0.48	0%
Bleeding-related mortality	2	160	0.12 (0.02, 0.71)	0.71	0%
Length of stay	1	148	−0.35 (−3.13, 2.43)	N/A	N/A
ICU stay	1	148	−1.17 (−3.18, 0.84)	N/A	N/A
Angiography	1	148	4.41 (0.48, 40.45)	N/A	N/A

CI, confidence interval; ICU, intensive care unit; N/A, not available.

also assists in identifying lesions that will benefit from endoscopic hemostasis better than visual inspection (Forrest classification) alone and predicts the completeness of this hemostasis, better informing clinical care following the endoscopy. Importantly, a DEP-assisted endoscopy also results in subsequent decreased rates of bleeding-related mortality and the need for surgery when compared to a standard gastroscopy. Further studies are required to assess learning aspects required to achieve competence and inter-rater variability when using this technology.

These conclusions are robust, remaining true in subgroup analyses when including solely more contemporary studies for the posthemostasis lesion analysis and the DEP-assisted endoscopic interventional studies; it is also the case when limiting the analyses to studies in which managing endoscopists were blinded to the results of the DEP signal,^{3,27} leading to a markedly more accurate prediction of overall rebleeding for DEP-positive versus -negative signal lesions with an OR of 42.3 (10.7, 167.9) (Appendix S5). This is a remarkably high point estimate, challenging the current

practice gold standard, that is, the discriminative ability of the Forrest classification. This is even more a possibility when considering the latter's modest inter-rater agreement,²⁹ with DEP potentially allowing for a more objective measurement of endoscopic therapy efficiency.

The prehemostasis use of DEP did not yield significant benefits among more recent studies, but this body of evidence exhibits limitations independent of date of publication. Indeed, when assessing the results that address the use of DEP prior to any possible endoscopic hemostasis, one must consider two scenarios. First, DEP may identify lesions requiring endoscopic treatment that would not have been categorized as such based on the Forrest classification alone. In most of the older studies investigating such potential benefits, lesions with active bleeding (Forrest Ia, Ib) were excluded (as they would be treated regardless due to the presence of active bleeding). In this clinical scenario, the aim is thus to focus on rare cases of “low-risk” lesions (Forrest IIc or III) that could rebleed if not treated endoscopically, such as those exhibiting a transparent

pseudoanurysm.³⁰ Only one methodologically robust study tried to address this question, but could not be completed due to poor recruitment.⁵

DEP may also play a role in avoiding unnecessary treatment of lesions categorized as high risk using the Forrest classification, yet exhibit no DEP signal and thus do not require endoscopic treatment. Jensen *et al.* recently highlighted much lower rebleeding risks with Forrest Ib lesions compared to what was initially reported,³¹ possibly due to friable margins of an ulcer base without the presence of an actual vessel being the cause of active oozing.

With regard to actual interventional studies assessing patient outcomes, the pooled analysis of 308 patients from three studies^{7,23,28} comparing DEP-assisted to standard endoscopy found that its use was associated with a significantly lower overall rebleeding rate (OR 0.27 [0.14, 0.54]); this subgroup included two recently published works in 2017 and 2018.^{7,28} Importantly, the significant improvement in overall rebleeding persisted when limiting the analysis to the two RCTs^{7,23} (OR 0.30 [0.13, 0.69]).

Even though the results are limited by the low or very low quality of evidence, the robustness of results across the many study designs and outcomes studied, and the point estimates of treatment effects that are of great clinically significant magnitude, all contribute to the clinical relevance of the conclusions. The robustness of conclusions also is confirmed by extensive sensitivity and subgroup analyses of the primary outcome. This thorough and exhaustive up-to-date synthesis of available data addressing DEP use in NVUGIB from so many different perspectives is novel and adds to a previously published systematic review with methodological issues that was also limited in its scope that included fewer studies.¹⁵ Indeed, the present meta-analysis investigated more thoroughly all possible operational aspects of using the DEP technology, including the different clinical situations in which DEP may be of interest (both pre- and postendoscopic hemostasis). Our analysis also assessed several additional outcomes that confirm the biological plausibility of the overall results: critical additional information was required to properly grade the certainty of evidence.¹⁴ Society guidelines have chosen not to address DEP or did not assess the DEP body of data completely in making recommendations by limiting their evidence review to a few selected publications.^{2,8–10}

Several limitations of the available body of evidence are worth discussing. First, the overall number of studies included is modest, even though many comparisons of outcomes are significantly improved with DEP in a robust fashion. Improvements in bleeding-related mortality and

surgery, although robust, are arguably limited by their subjectivity in ascertainment and/or diminished use in contemporary management.

Additional secondary outcomes could not be assessed due to the paucity or absence of analyzable data (e.g., the need for angiography, length of stay, repeated endoscopy). Although no statistical heterogeneity was noted in the main analysis that addresses overall rebleeding, sources of clinical and technical heterogeneity across studies do exist (for example, different Doppler probes were used, with various wavelengths ranging from 8 MHz to 20 MHz), and are unavoidable, acknowledging the more than 30 years that have elapsed since the earliest included publications. Also, from a study design point of view, among the 11 observational studies, only five^{5,7,23,26,27} assessed DEP lesion prediction both pre- and posthemostasis, while measuring subsequent outcomes. All these limitations contributed to a grading of low to very low certainty of evidence.

Finally, cost-effectiveness analyses^{8,32} concluded that DEP use results in an increased effectiveness at a modest increase in cost with corresponding favorable cost-acceptability estimates across broad ranges of assumptions in sensitivity analyses, further strengthening arguments for its broader diffusion.

CONCLUSION

IN SUMMARY, DEP use in NVUGIB provides better prediction of high-risk bleeding lesions requiring hemostasis than sole visual assessment and a more accurate evaluation of the completeness of endoscopic treatment, with corresponding significant decreases in overall rebleeding, bleeding-related mortality, and surgical rates. Additional studies would be useful in confirming the generalizability of these conclusions, but this systematic review should at least motivate experts in the field to question whether we can improve on the existing gold standard that is sole visual assessment of NVUGIB lesions to guide endoscopic management.

CONFLICT OF INTEREST

AUTHORS DECLARE NO conflict of interest for this article.

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DATA AVAILABILITY STATEMENT

ALL DATA ARE available upon reasonable request.

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SUPPORTING INFORMATION

ADDITIONAL SUPPORTING INFORMATION may be found in the online version of this article at the publisher's web site.

Appendix S1 Search string.

Appendix S2 (a) Primary and secondary outcome for proportions prehemostasis endoscopic therapy. (b) Primary

and secondary outcome for proportions posthemostasis endoscopic therapy.

Appendix S3 Cochrane risk of bias.

Appendix S4 Ottawa–Newcastle scale for observational studies.

Appendix S5 Sensitivity analysis and subgroup analysis for primary outcome for comparative studies (Doppler endoscopic probe [DEP]-positive vs. DEP-negative) – pre-endoscopic hemostasis.

Appendix S6 Sensitivity analysis and subgroup analysis for primary outcome for comparative studies (Doppler endoscopic probe [DEP]-positive vs. DEP-negative) – postendoscopic hemostasis.

Appendix S7 Sensitivity analysis and subgroup analysis for primary outcome for comparative studies (Doppler endoscopic probe [DEP]-assisted endoscopy vs. standard endoscopy).

Appendix S8 Grading of the evidence for comparative studies (Doppler endoscopic probe [DEP]-positive vs. DEP-negative) pre-endoscopic hemostasis.

Appendix S9 Grading of the evidence for comparative studies (Doppler endoscopic probe [DEP]-positive vs. DEP-negative) postendoscopic hemostasis.

Appendix S10 Grading of the evidence for comparative studies (Doppler endoscopic probe-assisted endoscopy vs. standard endoscopy).