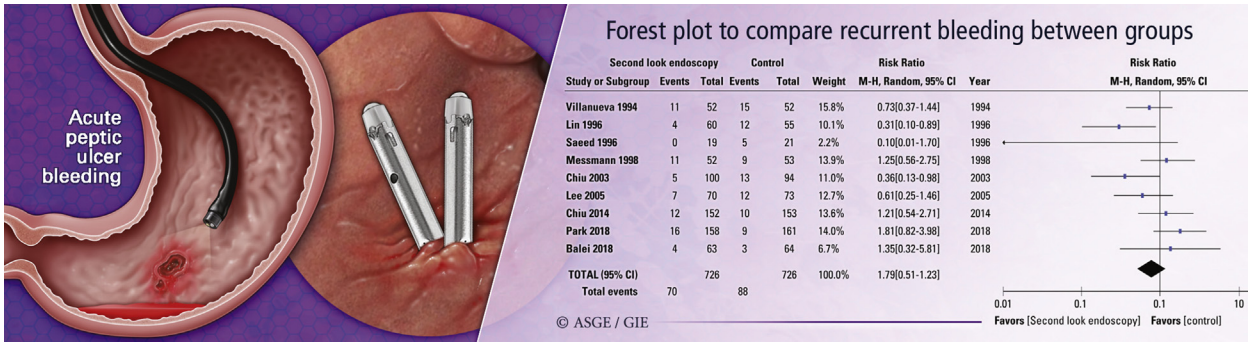
Role of routine second-look endoscopy in patients with acute peptic ulcer bleeding: meta-analysis of randomized controlled trials CME

Faisal Kamal, MD,[1] Muhammad Ali Khan, MD,[2,3] Wade Lee-Smith, MSL,[4] Sachit Sharma, MD,[5] Zaid Imam, MD,[6] Collin Henry, MD,[7] Dawit Jowhar, MD,[7] Zubair Khan, MD,[8] Ellen Petryna, MD,[7] Umair Iqbal, MD,[9] Claudio Tombazzi, MD,[1] Mohammad K. Ismail, MD,[1] Colin W. Howden, MD[1]

Memphis, Tennessee; Birmingham, Alabama; Houston, Texas; Toledo, Ohio; Royal Oak, Michigan; Danville, Pennsylvania, USA

GRAPHICAL ABSTRACT



Background and Aims: Studies evaluating the role of routine second-look endoscopy in patients with acute upper GI bleed because of peptic ulcer disease (PUD) have reported conflicting results. This meta-analysis evaluates the usefulness of routine second-look endoscopy in these patients.

Methods: We reviewed several databases from inception to September 15, 2020 to identify randomized controlled trials (RCTs) that compared routine second-look endoscopy with no planned second-look endoscopy in patients with acute upper GI bleed because of PUD. Our outcomes of interest were recurrent bleeding, mortality, need for surgery, and mean number of units of blood transfused. For categorical variables, we calculated pooled risk ratios (RRs) with 95% confidence intervals (CIs); for continuous variables, we calculated standardized mean difference with 95% CIs. Data were analyzed using a random effects model. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to ascertain the quality of evidence.

Results: We included 9 RTCs comprising 1452 patients; 726 patients underwent planned/routine second-look endoscopy and 726 did not. We found no significant difference in recurrent bleeding (RR, .79; 95% CI, .51-1.23), need for surgery (RR, .58; 95% CI, .29-1.15), mortality (RR, .69; 95% CI, .33-1.45), or mean number of units of blood transfused (standardized mean difference, –.06; 95% CI, –.19 to .07). Quality of evidence ranged from low to moderate based on the GRADE framework.

Conclusions: Single endoscopy with complete endoscopic hemostasis is not inferior to routine second-look endoscopy in reducing the risk of recurrent bleeding, mortality, or need for surgery in patients with acute upper GI bleed because of PUD. (Gastrointest Endosc 2021;93:1228-37.)

(footnotes appear on last page of article)

Peptic ulcer disease (PUD) is the most common cause of acute upper GI bleeding and is associated with substantial morbidity and mortality.[1,2] Endoscopic treatment is effective in achieving initial hemostasis, although recurrent bleeding can occur in 13% to 17% of patients.[1,3-5] Some risk factors for recurrent bleeding include large ulcer size, nonsteroidal anti-inflammatory drug (NSAID) use, hemodynamic instability, comorbidities, active bleeding at initial endoscopy, and certain ulcer locations such as the posterior duodenal bulb and the lesser curve of the stomach.[4-7]

Recurrent bleeding is associated with a substantial increased risk of mortality.[2] In a randomized controlled trial (RCT) in 40 patients with peptic ulcer bleeding, Saeed et al found that planned second-look endoscopy was associated with a decreased risk of recurrent bleeding. Since then, RCTs comparing planned or routine second-look endoscopy with no routine second-look endoscopy in patients with PUD bleeding have reported conflicting results. Routine second-look endoscopy in patients with PUD bleeding would increase overall costs of care and would predispose patients to the small risk of adverse events from the additional procedure and associated anesthesia or sedation. Therefore, high-quality evidence would be required to justify routine second-look endoscopy.

Previous meta-analyses and guidelines have not made consistent recommendations regarding the use of routine second-look endoscopy. Therefore, an updated meta-analysis is justified to re-evaluate this issue. We conducted this updated systematic review and meta-analysis including all available RCTs published to date to evaluate the usefulness of routine second-look endoscopy in patients with a bleeding peptic ulcer in whom hemostasis was successfully achieved at the initial endoscopy.

METHODS

Data sources and search strategy

We followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-Analysis. An experienced medical librarian (W.L.-S.) performed a comprehensive search of PubMed and MEDLINE, Embase, Web of Science Core Collection, and the Cochrane Central Register of Controlled Trials from inception to September 15, 2020. There was no restriction of language in conducting the search. The search included truncation-expanded key words and database-specific subject headings for second-look endoscopy combined with GI bleed or GI hemorrhage or peptic ulcer bleeding. Full search strategies from all databases are provided in Appendix 1 (available online at www.giejournal.org). Two authors (F.K. and S.S.) independently reviewed the titles and abstracts of the retrieved articles and excluded those that did not provide data on our outcomes of interest. Full texts of remaining articles were reviewed. We also reviewed the references of these articles to maximize the yield of the search. The screening results are shown in Figure 1.

Inclusion and exclusion criteria

Two authors (F.K. and M.A.K.) independently searched for original studies based on pre-established inclusion criteria detailed below. We included only RCTs that compared the usefulness of routine second-look endoscopy with no planned second-look endoscopy in patients with acute upper GI bleeding because of PUD. Only those patients who successfully achieved hemostasis on initial endoscopy were included in the analysis. Patients in whom bleeding could not be controlled at the initial endoscopy or in whom the source of bleeding was other than PUD were excluded. We excluded nonrandomized trials and review articles. All articles were downloaded into Endnote X9 (Clarivate, Philadelphia, Penn, USA), a bibliographic database manager. Duplicate citations were removed.

Data extraction

Two authors (F.K. and M.A.K.) independently assessed the eligibility of included studies and collected data using predesigned data extraction forms. The data extracted by individual authors were compared for any discrepancies. Any discrepancy was resolved by a repeat review of data and discussion with a third reviewer (C.W.H.). Extracted data included year of publication, patient demographics, endoscopic treatments performed during first and second endoscopy, any other treatment interventions given to both groups in addition to endoscopy, and number of patients with active bleeding during initial endoscopy and, for each group, total numbers of patients and those with recurrent bleeding, mortality, and need for surgery and the mean number of units of blood transfused, size of ulcers, and length of stay. We also extracted data regarding some possible predictors of outcomes such as patient demographics, Forrest classification, ulcer location, size of ulcer, use of NSAIDs, comorbidity indices, and hemodynamic instability. These data are summarized in Supplementary Table 1 (available online at www.giejournal.org).

Risk of bias assessment

We used the Cochrane tool for assessing risk of bias for RCTs to assess the quality of included studies. The Cochrane tool assesses the presence of selection bias by evaluating the methods of randomization and allocation concealment; performance and detection biases by checking for blinding of personnel and outcome assessment, respectively; and attrition and reporting bias by evaluating for incomplete and selective reporting of data, respectively. Two authors (D.J. and Z.I.) independently performed risk of bias assessment and any disagreement was discussed with a third reviewer (C.W.H.). The risk of bias

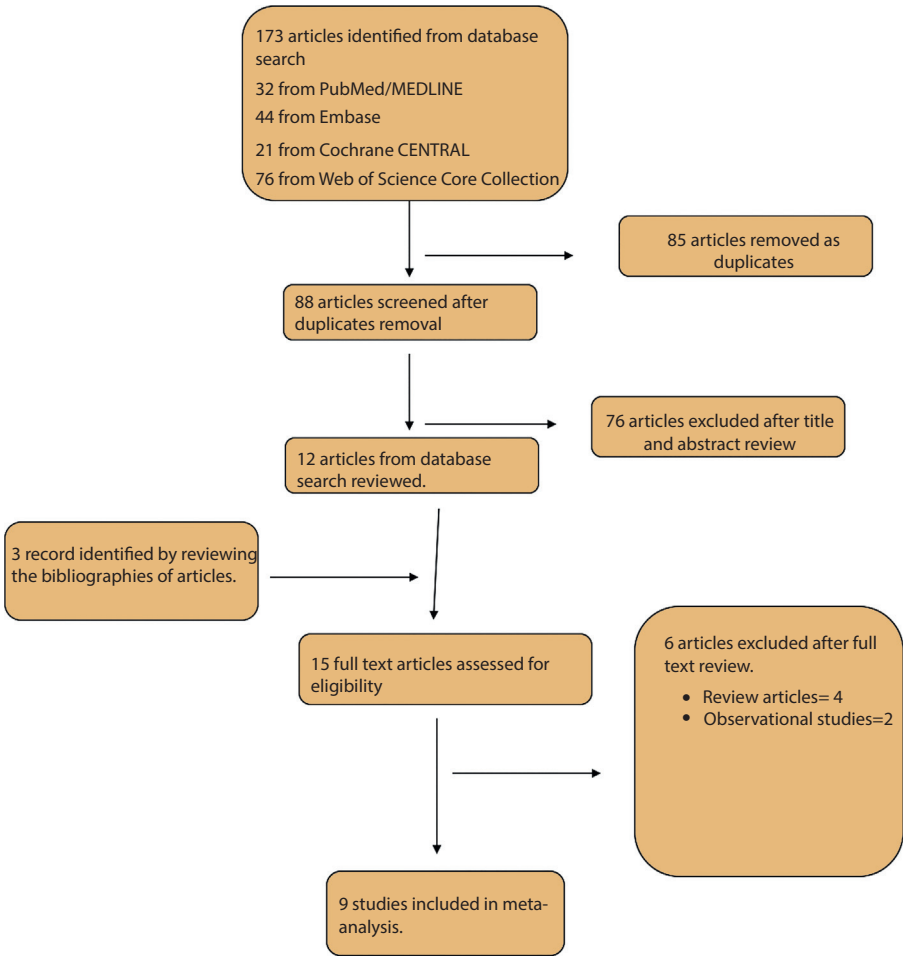


Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart.

assessment of RCTs is summarized in Supplementary Table 2 (available online at www.giejournal.org).

Data synthesis and statistical analysis

Our outcomes of interest were recurrent bleeding, mortality, need for surgery, and mean number of units of blood transfused. We performed subgroup analyses including full publications only. In 2 included studies,[8,9] the single endoscopy group received high-dose proton pump inhibitor (PPI) treatment as an intravenous (IV) bolus followed by continuous IV infusion for 72 hours, whereas the second-look endoscopy group received IV PPI by bolus injection twice a day for 72 hours. We performed a sensitivity analysis by excluding these 2 studies.

We performed a subgroup analysis including only those studies in which endoscopic combination therapy was used in conjunction with IV PPI twice daily. Combining the studies (using endoscopic combination therapy plus IV PPI twice daily) with those in which a single endoscopic treatment modality, IV ranitidine, or high-dose PPI infusion was used could have led to erroneous results. For recurrent bleeding analysis, we performed a sensitivity analysis by excluding 2 studies[10,11] in which a single endoscopic treatment method was used.

We calculated pooled risk ratios (RRs) with 95% confidence intervals (CIs) to compare recurrent bleeding, mortality, and need for surgery between groups. We calculated standardized mean difference with 95% CI to compare mean number of units of blood transfused between 2 groups. Some trials included in our meta-analysis had zero events in 1 arm.

We used Review Manager (RevMan, version 5.4 for Windows; The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark, 2014) for statistical analyses. When RR or odds ratio (OR) is used for analysis, RevMan automatically includes trials with zero events in 1 arm by adding .5 to each arm, but trials with zero events in both arms are omitted.[12,13] When studies included zero events in both arms, continuity correction of .5 was applied to both arms to include the zero-event study in pooled estimate.

We used a random effects model for our analyses. A $P <$ .1 for Cochran Q test or an I^2 value >50% indicated significant heterogeneity. We assessed publication bias graphically by using funnel plots. We did not use statistical tests

to assess for publication bias because the total number of studies we included was below 10.

Assessment of quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework to assess the certainty of evidence. For systematic reviews, the GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. It classifies the quality of evidence as high, moderate, low, or very low. For RCTs, the quality of evidence starts with high confidence; for observational studies, it starts with low confidence. It is further rated based on methodologic quality (risk of bias), directness of evidence, heterogeneity, precision of effect estimates, and publication bias. Details of quality of evidence based on GRADE are summarized in Supplementary Table 3 (available online at www.giejournal.org).

RESULTS

Search strategy yield

The search strategy produced 173 articles, 85 of which were removed as duplicates (Fig. 1). From the remaining 88 articles, 76 were removed after title and abstract review. Three additional studies were identified from review of bibliographies. The full texts of 15 articles were reviewed and included 9 in the final analysis.[8-11,14-18] Characteristics of studies are summarized in Table 1. Data on outcomes of interest are summarized in Table 2.

Meta-analysis

Recurrent bleeding. Nine studies with 1452 patients were included in this analysis; 726 patients each were randomized to the routine second-look endoscopy and control groups. Rates of recurrent bleeding were 9.6% and 12%, respectively (RR, .79; 95% CI, .51-1.23), with moderate heterogeneity (I^2 = 46%) (Fig. 2). The funnel plot appeared to be symmetric (Supplementary Fig. 1, available online at www.giejournal.org). Subgroup analysis including only full publications showed similar results (RR, .94; 95% CI, .58-1.51) with low heterogeneity (I^2 = 42%). Sensitivity analysis excluding the studies in which the 2 groups received different PPI regimens[8,9] did not change the results materially (RR, .69; 95% CI, .40-1.18; I^2 = 55%). A subgroup analysis that only included those studies in which endoscopic combination therapy was used in conjunction with IV PPI twice daily also showed similar results (RR, .98; 95% CI, .40-2.37; I^2 = 69%). Sensitivity analysis excluding studies in which a single endoscopic treatment method was used also showed similar results (RR, .91; 95% CI, .55-1.52; I^2 = 44%). Certainty of evidence was low based on the GRADE framework (Supplementary Table 3).

Need for surgery. This analysis included 7 full publications with 1194 patients. Rates of surgery in second-look endoscopy and control groups were 2.2% and 4%, respectively. There was no significant difference between groups (RR, .58; 95% CI, .29-1.15; I^2 = 0%) (Fig. 3). One study included in this analysis had zero events in both arms. We repeated analysis by applying continuity correction of .5 to both arms in this study, but results did not change (RR, .59; 95% CI, .30-1.16; I^2 = 0%). No abstracts were included in this analysis. Sensitivity analysis excluding the studies in which the groups received different PPI regimens[8,9] also showed similar results (RR, .48; 95% CI, .22-1.06; I^2 = 0%). A subgroup analysis that only included the studies in which endoscopic combination therapy was used in conjunction with IV PPI twice daily did not change the results (RR, .51; 95% CI, .11-2.35; I^2 = 30%). Certainty of evidence was moderate based on the GRADE framework (Supplementary Table 3).

Mortality. This analysis included 6 full publications with 1067 patients. Rates of mortality in second-look endoscopy and control groups were 2.3% and 3.4%, respectively. There was no significant difference between groups (RR, .69; 95% CI, .33-1.45; I^2 = 0%) (Fig. 4). No abstracts were included in this analysis. Sensitivity analysis excluding the studies in which groups received different PPI regimens[8,9] also showed similar results (RR, .91; 95% CI, .38-2.21; I^2 = 0%). A subgroup analysis that only included the studies in which endoscopic combination therapy was used in conjunction with IV PPI twice daily did not change the results (RR, 1.16; 95% CI, .39-3.42; I^2 = 0%). Certainty of evidence was moderate based on the GRADE framework (Supplementary Table 3).

Blood transfusion. This analysis included 4 studies with 922 patients. We found no significant difference in mean number of units of blood transfused between groups (standardized mean difference, –.06; 95% CI, –.19 to .07; I^2 = 43%) (Fig. 5).

DISCUSSION

Routine second-look endoscopy does not improve outcomes in patients with acute upper GI bleeding because of PUD in whom hemostasis was successfully achieved at the initial endoscopy. Recommendations from an international consensus group,[19] the American College of Gastroenterology,[20] and the European Society of Gastrointestinal Endoscopy[21] do not recommend routine second-look endoscopy in patients with nonvariceal upper GI bleeding. Instead, they recommend its use only for recurrent bleeding. In the United Kingdom, the National Institute for Health and Care Excellence guidelines recommend considering a repeat endoscopy with treatment as appropriate for all patients at high risk of recurrent bleeding, particularly if there is doubt whether adequate hemostasis was achieved at the first endoscopy.

TABLE 1. Study characteristics

Study, year	No. of patients	Active bleeding at initial endoscopy n (%)	Endoscopic treatment during first and second endoscopy	Other treatments in both groups	Inclusion criteria	Exclusion criteria	Follow-up
Park et al, 2018[14]	319	130 (40.7)	Hemoclip or thermal coagulation and/or epinephrine or fibrin glue injection therapy.	IV PPI q 12 h	Patients aged 18 y who underwent successful endoscopic hemostasis for bleeding peptic ulcers within 24 h after the admission.	Bleeding not controlled at initial endoscopy, no informed consent, bleeding started while already hospitalized with another illness, bleeding from known carcinoma of the stomach or nonulcerative lesions such as Dieulafoy's lesion.	30 days
Belei et al, 2018[9]	127	52 (41)	Epinephrine injection followed by hemoclips	In second-look endoscopy group, esomeprazole .5 mg/kg q 12 h. In control group, 1 mg/kg IV bolus followed by .1 mg/kg/h continuous infusion. In children $\geq$40 kg and age $\geq$12 y, standard adult PPI dose was used.	Patients aged between 2 and 18 y who had undergone successful endoscopic hemostasis for bleeding peptic ulcers. Patients with bleeding peptic ulcers with endoscopic stigmata of active bleeding, nonbleeding visible vessels, or adherent clots were recruited.	If the bleeding could not be controlled during the first endoscopy, no informed consent, known allergy to PPI, bleeding from nonulcer lesions, ASA grade V or VI, patients weighing < 10 kg.	30 days
Chiu et al, 2016[8]	305	135 (42)	Epinephrine injection followed by heat probe or hemoclips	In second-look endoscopy group IV omeprazole q 12 h for 72 h. In single endoscopy group, IV omeprazole 80-mg bolus followed by continuous infusion of 8 mg omeprazole per hour for 72 h.	Patients aged 15-90 y who underwent successful endoscopic hemostasis for bleeding peptic ulcers. Patients with bleeding peptic ulcers with endoscopic stigmata of active bleeding, nonbleeding visible vessels, or adherent clots were recruited to the study.	Bleeding could not be controlled during the first endoscopy, no informed consent, pregnant, known allergy to PPIs, bleeding from carcinoma of the stomach or other nonulcer lesions including Dieulafoy's lesions or angiodysplasia, ASA grade V or VI.	30 days
Lee et al, 2005[15]	143	NA	Epinephrine injection followed by hemoclips	NA	Patients with bleeding gastric or duodenal ulcers admitted to Kyungpook National University Hospital.	NA	30 days

(*continued on the next page*)

TABLE 1. Continued

Study, year	No. of patients	Active bleeding at initial endoscopy n (%)	Endoscopic treatment during first and second endoscopy	Other treatments in both groups	Inclusion criteria	Exclusion criteria	Follow-up
Chiu et al, 2003[16]	194	89 (45.8)	Epinephrine injection followed by heater probe	IV PPI q 12 h	Patients aged 15-90 y who underwent successful endoscopic hemostasis for bleeding peptic ulcers within 24 h after admission.	Bleeding not controlled at primary endoscopy, no informed consent, bleeding from carcinoma of the stomach or other nonulcer lesions such as Dieulafoy lesions, patients with ASA grade V.	30 days
Messmann et al, 1998[17]	105	46 (43.8)	Epinephrine injection followed by fibrin glue injection	IV PPI q 12 h for 48 h	Patients who presented with upper GI bleed and endoscopy showed peptic ulcer with active bleeding or signs of recent bleeding.	Failed initial endoscopy treatment, malignant disease, severe coagulopathy, age <18 y, no informed consent.	4 weeks
Saeed et al, 1996[18]	40	27 (67.5)	Heat probe ± epinephrine injection	IV ranitidine	High-risk patients (Baylor bleeding score >5) in whom endoscopic hemostasis was achieved.	Low-risk patients (Baylor bleeding score <5), high-risk patients in whom endoscopic therapy was not indicated, and if initial endoscopic hemostasis was not successful.	Until discharge
Lin et al 1996[11]	115	NA	Epinephrine injection	Ranitidine. Route and dose not available	Patients with bleeding ulcer of upper GI tract were enrolled after endoscopic injection therapy with .01% epinephrine.	Patients with terminal cancer or multiple-organ failure.	NA
Villanueva et al, 1994[10]	104	40 (38.4)	Epinephrine injection	IV ranitidine	Patients presenting with upper GI bleed in whom endoscopy revealed a peptic ulcer with active bleeding or nonbleeding visible vessel.	Patients age <18 y, no informed consent.	

ASA, American Society of Anesthesiologists; *IV*, intravenous; *PPI*, proton pump inhibitor; *NA*, not available.

A previous meta-analysis by Ouali et al[22] included 8 RCTs and showed that routine second-look endoscopy was associated with a significant reduction in recurrent bleeding (pooled odds ratio, .55; 95% CI, .37-.81) and need for surgery (pooled odds ratio, .43; 95% CI, .19-.96). The authors concluded that routine second-look endoscopy was effective in the absence of high-dose PPI and in selected patients who were at high risk such as those with active bleeding at the initial endoscopy. However, we did not find any significant difference in the rates of recurrent bleeding or surgery between groups. Additionally, our findings also challenge the results of the previous

TABLE 2. Outcomes of interest

Study, year	Groups	No. of patients in each group	Recurrent bleeding	Need for surgery	Mortality	Units of blood transfused	Size of ulcer	Length of stay
Park et al, 2018[14]	Second-look EGD	158	16	0	2	2.4 ± 1.7	NA	6 (0-57)
	Single EGD	161	9	1	2	2.2 ± 1.6		5 (0-62)
Belei et al, 2018[9]	Second-look EGD	63	4	2	NA	NA	.8 ± .6	NA
	Single EGD	64	3	1			1 ± .5	
Chiu et al, 2016[8]	Second-look EGD	152	12	3	3	1.9 ± 2.4	1 ± .6	3 (1-49)
	Single EGD	153	10	6	8	2.2 ± 2.7	1.2 ± .8	2 (2-35)
Lee et al, 2005[15]	Second-look EGD	70	7	NA	NA	NA	NA	5
	Single EGD	73	12					7
Chiu et al, 2003[16]	Second-look EGD	100	5	1	2	1.9 ± 1.7	1 ± .5	4 (2-24)
	Single EGD	94	13	6	2	2.1 ± 2.3	.9 ± .5	4 (2-24)
Messmann et al, 1998[17]	Second-look EGD	52	11	3	3	3.5	1.3 ± .4	14
	Single EGD	53	9	2	2	3.1	1.1 ± .3	12
Saeed et al, 1996[18]	Second-look EGD	19	0	0	1	3	NA	NA
	Single EGD	21	5	0	2	2		
Lin et al, 1996[11]	Second-look EGD	60	4	NA	NA	NA	NA	NA
	Single EGD	55	12					
Villanueva et al, 1994[10]	Second-look EGD	52	11	4	1	1.7 ± 1.9	NA	9.3 ± 8.6
	Single EGD	52	15	8	2	2.5 ± 2.5		11.8 ± 10.8

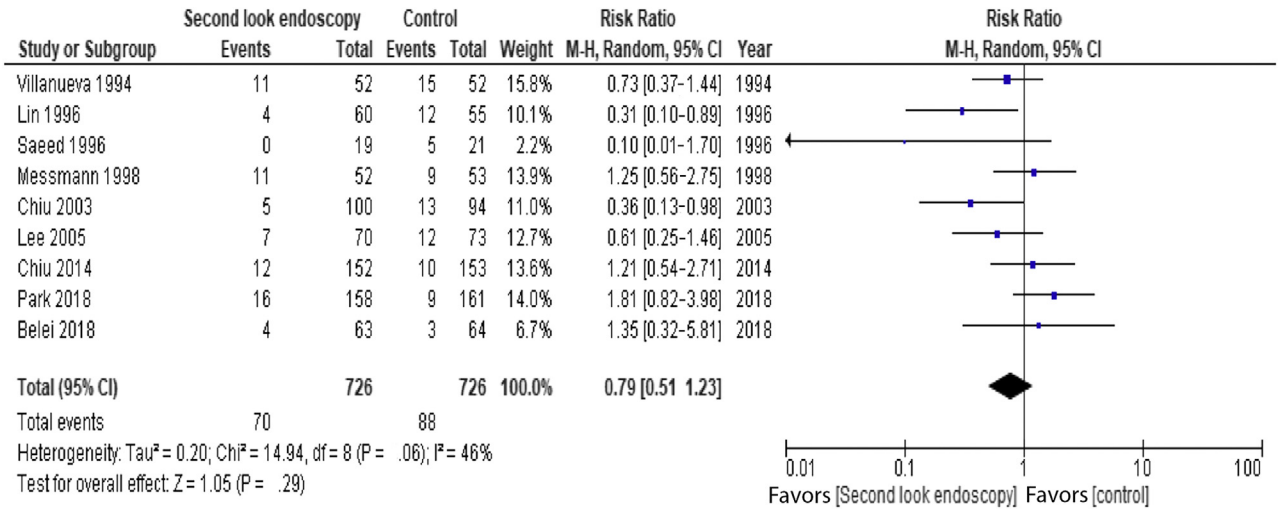


Figure 2. Forest plot to compare recurrent bleeding between groups. *CI*, Confidence interval.

meta-analysis about the role of second-look endoscopy in the absence of high-dose PPI and in selected patients who were at high risk.

In a meta-analysis including 13 RCTs, Sachar et al[23] found that intermittent PPI treatment was comparable with a regimen of IV bolus plus continuous infusion in patients with endoscopically treated high-risk bleeding ulcers. We performed a sensitivity analysis excluding 2 studies where the groups received different PPI regimens and found no difference in the rates of recurrent bleeding or surgery among groups. These findings are in line with those of Sachar et al and do not support the routine use of second-look endoscopy in the absence of high-dose IV PPI treatment.

In a sensitivity analysis excluding 2 studies,[8,18] Ouali et al[22] found that second-look endoscopy was not effective in reducing recurrent bleeding (odds ratio, .65; 95%

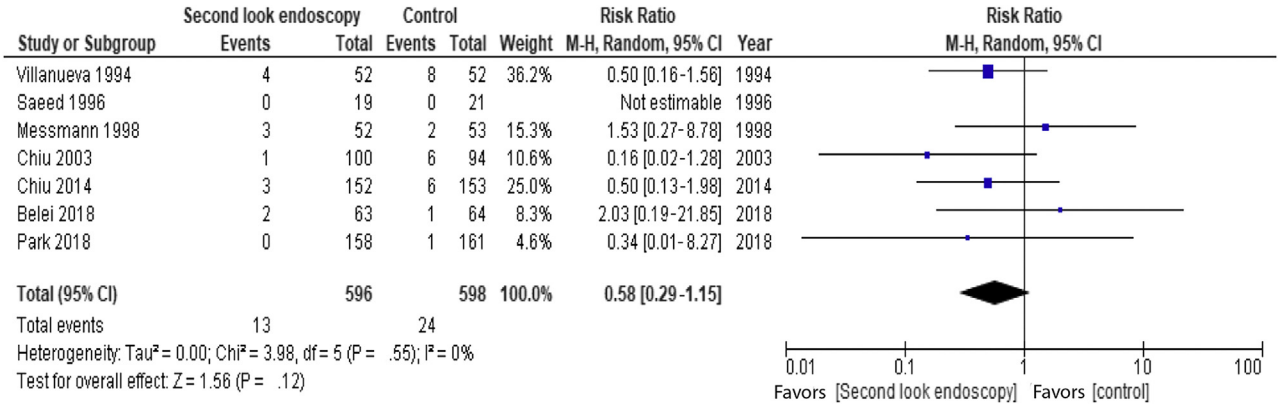


Figure 3. Forest plot to compare need for surgery between groups. *CI*, Confidence interval.

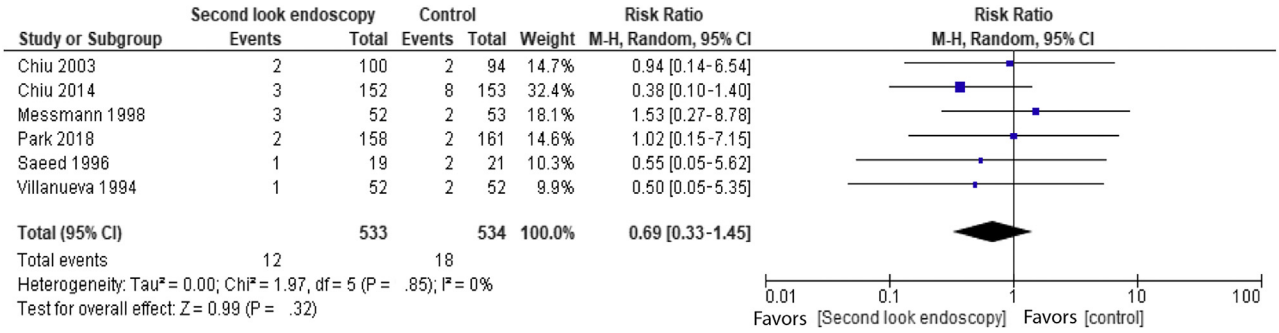


Figure 4. Forest plot to compare mortality between groups. *CI*, Confidence interval.

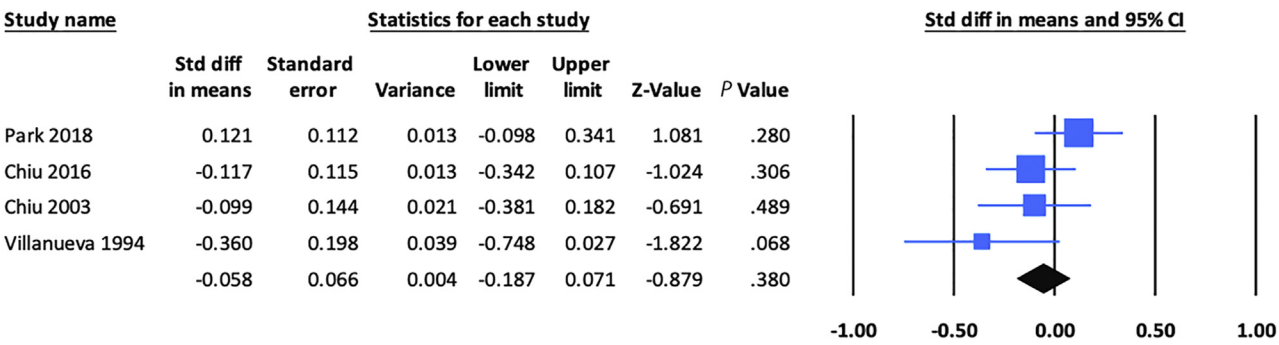


Figure 5. Forest plot to compare mean number of units of blood transfused. *CI*, Confidence interval.

CI, .42-1.00). These studies included patients at high risk of recurrent bleeding. Chiu et al[16] included 47% who were in shock and 41% who had active bleeding. Saeed et al[18] included high-risk patients based on the Baylor bleeding score. We did not find any significant difference in rate of recurrent bleeding after exclusion of these 2 studies.

The role of second-look endoscopy in patients at high risk of recurrent bleeding has been controversial. Initial recommendations from an Asia Pacific group in 2011[24] recommended that second-look endoscopy should be reserved for selected patients at high risk of recurrent bleeding. However, this statement was rejected in updated guidelines in 2018[25] because of a lack of evidence to suggest that any risk stratification method is effective in selecting patients at high risk who would benefit from second-look endoscopy.

One of the strengths of our meta-analysis is its restriction to RCTs only. RCTs are considered the criterion standard for clinical research and represent the highest level of

evidence. Our findings remained robust in several predetermined subgroup and sensitivity analyses. Our work also has some limitations. We included 2 studies that were only available as abstracts[11,15] in which some important data were missing. A Cochrane systematic review has found that over half of abstracts (including a third of RCTs that were initially presented as abstracts) are not subsequently published in full.[26] However, subgroup analyses excluding the studies available only as abstracts found no substantive change in results. There was moderate heterogeneity (I^2 = 46%) in the analysis of recurrent bleeding but low heterogeneity (I^2 = 42%) on subgroup analysis excluding the abstracts. The definitions of recurrent bleeding and the type of endoscopic treatments varied across studies. PPI treatment is considered standard of care in patients with acute upper GI bleeding from a peptic ulcer. However, ranitidine was used in 2 studies instead of a PPI.[10,11] One study[15] did not provide information about whether any acid-suppressing medicine was used.

We also found evidence of clinical heterogeneity among studies. As is evident from Supplementary Table 1, some predictors of outcomes we assessed were not standardized across studies. Studies did not report comorbidity indices consistently: Different studies reported these in different ways, and some did not report them at all. NSAID use and hemodynamic instability have been identified as risk factors for recurrent bleeding,[4,6] and proportions of patients with NSAID use and hemodynamic instability varied across studies. The Rockall score is an important tool that is often used in patients with acute upper GI bleeding to estimate the risk of recurrent bleeding and mortality.[27] However, it was reported by only 1 study.[14] Proportions of patients with distribution of ulcers based on location varied across studies. There were no substantial differences in the proportions of patients based on Forrest classification or patients with active bleeding across studies, except 1 study[18] that included a higher proportion of patients with active bleeding. Although all studies only included patients in whom successful hemostasis had been achieved on initial endoscopy and excluded those in whom it had not, a formal assessment of endoscopists' consideration of successful hemostasis was only performed in 1 study.[14] Park et al[14] performed assessment of endoscopists' estimation of success of initial endoscopic hemostasis using a 5-point Likert scale ranging from 0 (absolutely satisfactory) to 4 (absolutely unsatisfactory) and also compared it between groups and found no significant differences. This assessment was not performed in any other studies, which can raise concerns about observer bias because assessment of achievement of hemostasis is subjective.

In conclusion, we found that a single endoscopy with complete endoscopic hemostasis is not inferior to scheduled second-look endoscopy in reducing the risk of recurrent bleeding, mortality, or need for surgery. Our findings lend further support to current guidelines from the American College of Gastroenterology, European Society of Gastrointestinal Endoscopy, and an international consensus group[17-19] and would support a change in National Institute for Health and Care Excellence guidelines. Based on our analysis, we recommend reserving second-look endoscopy for patients with evidence of recurrent bleeding or those in whom there was concern about the adequacy of hemostasis at the initial endoscopy.

REFERENCES

1. Lau JY, Sung J, Hill C, et al. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. Digestion 2011;84:102-13.
2. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717-27.
3. Han YJ, Cha JM, Park JH, et al. Successful endoscopic hemostasis is a protective factor for rebleeding and mortality in patients with nonvariceal upper gastrointestinal bleeding. Dig Dis Sci 2016;61:2011-8.
4. Hong MJ, Lee SY, Kim JH, et al. Rebleeding after initial endoscopic hemostasis in peptic ulcer disease. J Korean Med Sci 2014;29:1411-5.
5. Elmunzer BJ, Young SD, Inadomi JM, et al. Systematic review of the predictors of recurrent hemorrhage after endoscopic hemostatic therapy for bleeding peptic ulcers. Am J Gastroenterol 2008;103:2625-32; quiz 33.
6. Garcia-Iglesias P, Villoria A, Suarez D, et al. Meta-analysis: predictors of rebleeding after endoscopic treatment for bleeding peptic ulcer. Aliment Pharmacol Ther 2011;34:888-900.
7. Nam JH, Jeon TJ, Cho JH, et al. Risk factors of the rebleeding according to the patterns of nonvariceal upper gastrointestinal bleeding. Turk J Gastroenterol 2017;28:266-71.
8. Chiu PW, Joeng HK, Choi CL, et al. High-dose omeprazole infusion compared with scheduled second-look endoscopy for prevention of peptic ulcer rebleeding: a randomized controlled trial. Endoscopy 2016;48:717-22.
9. Belei O, Olariu L, Puiu M, et al. Continuous esomeprazole infusion versus bolus administration and second look endoscopy for the prevention of rebleeding in children with a peptic ulcer. Rev Esp Enferm Dig 2018;110:352-7.
10. Villanueva C, Balanzó J, Torras X, et al. Value of second-look endoscopy after injection therapy for bleeding peptic ulcer: a prospective and randomized trial. Gastrointest Endosc 1994;40:34-9.
11. Lin CKLK, Lo GH, Cheng JS, et al. The value of second-look endoscopy after endoscopic injection therapy for bleeding peptic ulcer [abstract]. Gastroenterology 1996;110:A177.
12. Keus F, Wetterslev J, Gluud C, et al. Robustness assessments are needed to reduce bias in meta-analyses that include zero-event randomized trials. Am J Gastroenterol 2009;104:546-51.
13. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. BMC Med Res Methodol 2007;7:5.
14. Park SJ, Park H, Lee YC, et al. Effect of scheduled second-look endoscopy on peptic ulcer bleeding: a prospective randomized multicenter trial. Gastrointest Endosc 2018;87:457-65.
15. Lee SYLM, Cho CM, Tak WY, et al. The effect of second look endoscopy in patients with bleeding peptic ulcers [abstract]. Gastroenterology 2005;128:A639.
16. Chiu PWY, Lam CYW, Lee SW, et al. Effect of scheduled second therapeutic endoscopy on peptic ulcer rebleeding: a prospective randomised trial. Gut 2003;52:1403-7.

17. Messmann H, Schaller P, Andus T, et al. Effect of programmed endoscopic follow-up examinations on the rebleeding rate of gastric or duodenal peptic ulcers treated by injection therapy: a prospective, randomized controlled trial. Endoscopy 1998;30:583-9.
18. Saeed ZA, Cole RA, Ramirez FC, et al. Endoscopic retreatment after successful initial hemostasis prevents ulcer rebleeding: a prospective randomized trial. Endoscopy 1996;28:288-94.
19. Barkun AN, Almadi M, Kuipers EJ, et al. Management of nonvariceal upper gastrointestinal bleeding: guideline recommendations from the international consensus group. Ann Intern Med 2019;171:805-22.
20. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012;107:345-60; quiz 61.
21. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2015;47:a1-46.
22. Ouali SE, Barkun AN, Wyse J, et al. Is routine second-look endoscopy effective after endoscopic hemostasis in acute peptic ulcer bleeding? A meta-analysis. Gastrointest Endosc 2012;76:283-92.
23. Sachar H, Vaidya K, Laine L. Intermittent vs continuous proton pump inhibitor therapy for high-risk bleeding ulcers: a systematic review and meta-analysis. JAMA Intern Med 2014;174:1755-62.
24. Sung JJ, Chan FK, Chen M, et al. Asia-Pacific Working Group consensus on non-variceal upper gastrointestinal bleeding. Gut 2011;60:1170-7.
25. Sung JJ, Chiu PW, Chan FKL, et al. Asia-Pacific working group consensus on non-variceal upper gastrointestinal bleeding: an update 2018. Gut 2018;67:1757-68.
26. Scherer RW, Meerpohl JJ, Pfeifer N, et al. Full publication of results initially presented in abstracts. Cochrane Database Syst Rev 2018;11:MR000005.
27. Rockall TA, Logan RF, Devlin HB, et al. Risk assessment after acute upper gastrointestinal haemorrhage. Gut 1996;38:316-21.

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUD, peptic ulcer disease; RCT, randomized controlled trial; RR, risk ratio.

DISCLOSURE: *All authors disclosed no financial relationships.*

See CME section, p. 1421.

Use your mobile device to scan this QR code and watch the author interview. Download a free QR code scanner by searching "QR Scanner" in your mobile device's app store.

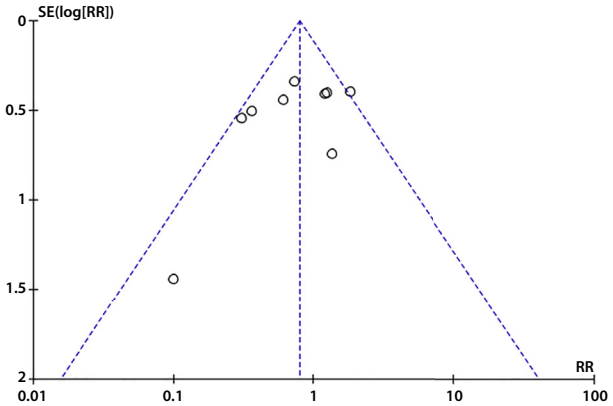
0016-5107/$36.00
https://doi.org/10.1016/j.gie.2020.12.039

Received October 9, 2020. Accepted December 18, 2020.

Current affiliations: Division of Gastroenterology (1), Department of Medicine (7), University of Tennessee Health Science Center, Memphis, Tennessee, USA; Division of Gastroenterology, University of Alabama at Birmingham, Birmingham, Alabama, USA (2), Department of Gastroenterology, Hepatology and Nutrition, University of Texas MD Anderson Cancer Center, Houston, Texas, USA (3), Mulford Health Sciences Library (4), Department of Medicine (5), University of Toledo, Toledo, Ohio, USA; Division of Gastroenterology, William Beaumont Hospital, Royal Oak, Michigan, USA (6), Division of Gastroenterology, University of Texas at Houston, Houston, Texas, USA (8), Division of Gastroenterology, Geisinger Medical Center, Danville, Pennsylvania (9).

Reprint requests: Faisal Kamal, MD, The University of Tennessee Health Science Center, 956 Court Ave, Ste H314C, Memphis, TN 38163.

If you would like to chat with an author of this article, you may contact Dr Kamal at fkamal36@gmail.com.



Supplementary Figure 1. Funnel plot to assess publication bias for the analysis of recurrent bleeding. *SE*, Standard error; *RR*, risk ratio.

APPENDIX 1. Search strategies

Search number	PubMed search query	Results
1	(Esophagoduodenoscop* OR EGD OR esophagogastroduodenoscop* OR esophago-gastro-duodenoscop* OR oesophagogastroduodenoscop* OR endoscop* OR gastroscop* OR duodenoscop* OR esophagoscop*)OR "Endoscopy, Gastrointestinal"[Mesh])	296,129
2	(Upper-gastrointestinal-bleed* OR upper-GI-bleed* OR upper-Gastrointestinal-Hemorrhage OR upper-digestive-haemorrhage OR upper-digestive-hemorrhage OR upper-digestive-tract-haemorrhage OR upper-digestive-tract-hemorrhage OR Upper-gastrointestinal-tract-bleed* OR upper-GI-tract-bleed* OR esophagogastroduodenal-bleed* OR esophagogastroduodenal-hemorrhage* OR esophagogastroduodenal-haemorrhage* OR ("Gastrointestinal Hemorrhage"[Mesh] AND (gastric* OR gastro* OR stomach OR esophagi* OR duoden*)))	50,754
3	Second-look* OR "Second-Look Surgery"[Mesh]	5132
4	#1 AND #3	430
5	#2 AND #4	103
6	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh]))	4,220,476*
7	#5 AND #6	49
8	#7 NOT ("editorial"[Publication Type] OR "guideline"[Publication Type] OR "introductory journal article"[Publication Type] OR "review"[Publication Type] OR "meta analysis"[Publication Type] OR "systematic review"[Publication Type])	32
	*Search terms for randomized controlled trials from Cochrane: https://work.cochrane.org/pubmed (Sensitivity-maximizing version)	

No.	Embase query	Results
1	'second look*' OR 'second look surgery'/exp OR '2nd look*'	7982
2	esophagoduodenoscop* OR egd OR esophagogastroduodenoscop* OR 'esophago gastro duodenoscop*' OR oesophagogastroduodenoscop* OR endoscop* OR gastroscop* OR duodenoscop* OR esophagoscop* OR 'esophagogastroduodenoscopy'/exp	521,125

(*continued on the next page*)

APPENDIX 1. Continued

No.	Embase query	Results
3	#1 AND #2	964
4	'upper gastrointestinal bleed*' OR 'upper gi bleed*' OR 'upper gastrointestinal hemorrhage' OR 'upper digestive haemorrhage' OR 'upper digestive hemorrhage' OR 'upper digestive tract haemorrhage' OR 'upper digestive tract hemorrhage' OR 'upper gastrointestinal tract bleed*' OR 'upper gi tract bleed*' OR 'esophagogastroduodenal bleed*' OR 'esophagogastroduodenal hemorrhage*' OR 'esophagogastroduodenal haemorrhage*' OR 'upper gastrointestinal bleeding'/exp OR 'gastrointestinal hemorrhage'/exp OR 'peptic ulcer bleeding'/exp	117,602
5	#3 AND #4	243
6	random* OR factorial* OR crossover* OR 'cross over' OR placebo* OR (doubl* NEXT/2 blind*) OR (singl* NEXT/2 blind*) OR assign* OR allocat* OR volunteer* OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp	2,623,171
7	#5 AND #6	76
8	#7 NOT ('conference review'/it OR 'editorial'/it OR 'review'/it)	59
9	#8 NOT ('meta analysis'/de OR 'practice guideline'/de OR 'systematic review'/de)	44

Cochrane Central Register of Controlled Trials
Issue 9 of 12, September 2020
21 Trials matching Second-look* in Title Abstract Keyword AND (Esophagoduodenoscop* OR EGD OR esophagogastroduodenoscop* OR esophago-gastro-duodenoscop* OR oesophagogastroduodenoscop* OR endoscop* OR gastroscop* OR duodenoscop* OR esophagoscop*) in Title Abstract Keyword AND (Upper-gastrointestinal-bleed* OR upper-GI-bleed* OR upper-Gastrointestinal-Hemorrhage OR upper-digestive-haemorrhage OR upper-digestive-hemorrhage OR upper-digestive-tract-haemorrhage OR upper-digestive-tract-hemorrhage OR Upper-gastrointestinal-tract-bleed* OR upper-GI-tract-bleed* OR esophagogastroduodenal-bleed* OR esophagogastroduodenal-hemorrhage* OR esophagogastroduodenal-haemorrhage*) OR ((bleed* OR hemorrhag*) AND (gastric* OR gastro* OR stomach OR esophagi* OR duoden*)) in Title Abstract Keyword AND "randomized controlled trial" in Publication Type
Query from Web of Science Core Collection
You searched for: TOPIC: (Second-look* OR 2nd-look* OR second-therapeutic*) *AND* TOPIC: ((Esophagoduodenoscop* OR EGD OR esophagogastroduodenoscop* OR esophago-gastro-duodenoscop* OR oesophagogastroduodenoscop* OR endoscop* OR gastroscop* OR duodenoscop* OR esophagoscop*)) *AND* TOPIC: ((Upper-gastrointestinal-bleed* OR upper-GI-bleed* OR upper-Gastrointestinal-Hemorrhage OR upper-digestive-haemorrhage OR upper-digestive-hemorrhage OR upper-digestive-tract-haemorrhage OR upper-digestive-tract-hemorrhage OR Upper-gastrointestinal-tract-bleed* OR upper-GI-tract-bleed* OR esophagogastroduodenal-bleed* OR esophagogastroduodenal-hemorrhage* OR esophagogastroduodenal-haemorrhage*) OR ((bleed* OR hemorrhag*) AND (gastric* OR gastro* OR stomach OR esophagi* OR duoden*))) *AND* TOPIC: (random* OR factorial* OR crossover* OR cross-over OR placebo* OR (doubl* NEAR/2 blind*) OR (singl* NEAR/2 blind*) OR assign* OR allocat* OR volunteer* OR "crossover procedure" OR "double-blind procedure" OR "randomized controlled trial" OR "single-blind procedure")
Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.
Results: 76

SUPPLEMENTARY TABLE 1. Data on possible predictors of outcomes

Study, year	Groups	No. of patients	No. (%) of male patients	Mean age	Forest classification Class, n (%)	Ulcer location n (%)
Park et al, 2018[14]	Second-look endoscopy	158	124 (78.5)	58.4 ± 16.6	Ia=17(10.7), Ib=49 (31), IIa=68 (43), IIb= 24 (15.1)	Gastric = 92 (58.2), Duodenal= 66 (41.8)
	Control	161	120 (74.5)	58.7 ± 18.3	Ia=15 (9.3), Ib=50 (31), IIa=75 (46.6), IIb= 21 (13)	Gastric= 101 (62.7) Duodenal= 60 (37.3)
Belei et al, 2018[9]	Second-look endoscopy	63	24 (38)	9.7 ± 1.5	Ia=5(7.9) , Ib=21(33.3), IIa=17(27) , IIb= 20 (31.2)	Gastric=15(23.8) duodenal= 48 (76.2)
	Control	64	23 (35.9)	10.5 ± 1.2	Ia=6(9.3), Ib=20(31.2), IIa=19(29.6), IIb= 19(29.6)	Gastric= 13 (20.3) Duodenal= 51 (79. 7)
Chiu et al, 2016[8]	Second-look endoscopy	152	114 (75)	67.4	Ia=14(9.2), Ib=51(33.5), IIa=42(27.6), IIb= 45(29.6)	Gastric= NA Duodenal= 91(59.8) Anastomotic =6 (3.9)
	Control	153	117 (76.4)	67.1	Ia=8 (5.2), Ib=62 (40.5), IIa=41 (26.8), IIb= 42 (27.4)	Gastric= NA Duodenal= 91(59.8) Anastomotic= 5 (3.3)
Lee et al, 2005[15]	Second-look endoscopy	70	NA	NA	NA	NA
	Control	73				
Chiu et al, 2003[16]	Second-look endoscopy	100	70 (70)	68.7 ± 13.9	Ia=10 (10), Ib=33 (33), IIa=37(37), IIb= 20 (20)	Gastric= 44 (44), Duodenal= 56 (56)
	Control	94	62 (66)	67.5 ± 12.6	Ia=14 (14.8), Ib=32 (34), IIa=27 (28.7), IIb= 21 (22.3)	Gastric= 40 (42.5) Duodenal= 54 (50.7)
Messmann et al, 1998[17]	Second-look endoscopy	52	29 (55.7)	63.1 ± 6.2	Ia=9 (17.3), Ib=16 (30.7), IIa=16(30.7),IIb= 11 (21)	Gastric=22 (42.3) Duodenal= 30 (57.7)
	Control	53	34 (64.2)	60.9 ± 5.9	Ia=7 (13.2), Ib=14 (26.4), IIa=17 (32), IIb= 15(28.3)	Gastric=24 (45.3) Duodenal= 29 (54.7)
Saeed et al, 1996[18]	Second-look endoscopy	19	NA	62 (23-75)	Ia and Ib= 13 (68), IIb= 3 (16)	Gastric= 6 (32) Duodenal= 11 (58) Esophageal= 2 (10)
	Control	21		70 (51-94)	Ia and Ib= 14 (67) IIb= 1 (5)	Gastric= 12 (57) Duodenal=9 (43) Esophageal= 0
Lin et al 1996[11]	Second-look endoscopy	60	NA	NA	NA	NA
	Control	55				
Villanueva et al, 1994[10]	Second-look endoscopy	52	39 (75)	62.4 ± 16.4	Ia=1 (2), Ib=16 (30.7), IIa=35 (67.3)	Gastric=15 (29), Duodenal= 34 (65) Stomal= 1 (2) Pyloric=2 (4)
	Control	52	33 (63.4)	66.5 ± 13.5	Ia=3 (5.7), Ib=20 (38.4), IIa=29 (55.7)	Gastric: 12 (23) Duodenal: 33 (63) Stomal: 4 (8) Pyloric: 3 (6)

NA, Not available; *ASA*, American Society of Anesthesiologists.
*Only aspirin use.

SUPPLEMENTARY TABLE 1. Continued

Mean size of ulcer (cm)	Hemodynamic instability n (%)	Mean hemoglobin at presentation	Use of nonsteroidal anti-inflammatory drugs n (%)	*Helicobacter pylori* infection n (%)	Comorbidity indices
NA	NA	9.5 ± 1.7	56 (35.4)	63 (39.9)	Rockall score = 5.3 ± 1.7 Charlson comorbidity index = 1.8 ± 1.4
		9.8 ± 1.8	57 (35.4)	52 (32.3)	Rockall score = 5.1 ± 1.8 Charlson comorbidity index = 1.6 ± 1.4
0.8 (.6)	7 (11.1)	9.5 ± 2.3	28 (44.4)	35 (55.5)	ASA = 2 (1-3)
1 (.5)	6 (9.3)	9.1 ± 2.4	25 (39)	32 (50)	ASA = 2 (1-3)
1 (.6)	17 (11.2)	9.6 (2.6)	54 (35.5)	67 (44.1)	ASA= 2 (1-3) Comorbidities, median= 2 (1-3)
1.2 (.8)	14 (9.2)	9.4 (2.8)	60 (39.2)	66 (43.1)	ASA = 2 (1-3) Comorbidities, median = 2 (0-7)
NA	NA	NA	NA	NA	NA
1 (.5)	48 (48)	8.9 (2.6)	12 (12) *	56 (56)	Coexisting illnesses= 65%, ASA I=44, ASA II=30, ASA III=23, ASA IV=3
.9 (.5)	44 (46.8)	9.4 (2.7)	6 (6.4)*	44 (46.8)	Coexisting illnesses= 69.1%, ASA I= 43, ASA II= 37, ASA III=15, ASA IV= 1
1.3 ± 0.4	31 (60)	10.3 ± 1.2	24 (47)	NA	NA
1.1 ± .3	29 (53)	9.8 ± 2.1	27 (53)		
NA	NA	NA	7 (39)	NA	NA
			9 (42)		
NA	NA	NA	NA	NA	NA
NA	NA	10 (2.6)	21 (44)	NA	Associated diseases: 23 (44)
		9.5 (2.3)	31 (59)		Associated diseases: 31 (59)

SUPPLEMENTARY TABLE 2. Risk of bias assessment of randomized controlled trials using the Cochrane Collaboration Tool

Study	Random sequence generation	Allocation concealment	Performance bias	Detection bias	Attrition bias	Reporting bias
Belei et al[9]	Low	Unclear	Low	Low	Low	Low
Lin et al[11]	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Chiu et al[16]	Low	Low	Low	Low	Low	Low
Chiu et al[8]	Low	Low	Low	Low	Low	Low
Lee et al[15]	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Messmann et al[17]	Low	Low	Low	Low	Low	Low
Park et al[14]	Low	Low	Low	Low	Low	Low
Saeed et al[18]	Low	Low	Low	Low	Low	Low
Villanueva et al[10]	Low	Low	Low	Low	Low	Low

SUPPLEMENTARY TABLE 3. Assessment of certainty of evidence by Grading of Recommendations Assessment, Development and Evaluation for outcomes of interest

Outcomes	Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	Quality of evidence
Rebleeding	Low	No serious indirectness	Moderate heterogeneity	Serious imprecision*	Not detected	Low (because of Inconsistency and imprecision)
Need for surgery	Low	No serious indirectness	Low heterogeneity	Serious imprecision*	Not detected	Moderate (because of imprecision)
Mortality	Low	No serious indirectness	Low heterogeneity	Serious imprecision*	Not detected	Moderate (because of imprecision)

*Serious imprecision because of confidence interval including benefit and harm.