**PICO’S WITH ASSOCIATED EVIDENCE TABLES**

**Abbreviations**

APC: argon plasma coagulation; CI: confidence interval; DTA: Diagnostic test accuracy; GBS: Glasgow-Blatchford Score; GI: gastrointestinal; HR: hazard ratio; NNT: number needed to treat; OR: odds ratio; PICO: population, intervention, comparator, outcome; PPI: proton pump inhibitor; RCT: randomized controlled trial; RR: risk ratio; SRMA: systematic review and meta-analysis; UGIB: upper gastrointestinal bleeding

“Overall quality of evidence” column is based on the quality of evidence for the critical outcome, further bleeding, with the exception of PICO 1, in which it is based on composite outcome.

**Risk Stratification**

PICO 1

**1. Use of risk stratification scores to identify very low-risk patients for outpatient management**

P: Patients with upper gastrointestinal bleeding (UGIB) with very low risk (e.g., Glasgow-Blatchford Score (GBS) 0 or 0-1; other scores) at presentation (all patients presenting to emergency department (not selected patients: e.g., based on hospitalization, only those who had upper endoscopy))

I: Discharge from emergency department with outpatient management

C: Hospitalize

O: Further bleeding, mortality; additional outcomes: composite of hospital-based intervention or death, hospital stay, cost, patient satisfaction, sensitivity of risk assessment score

**1.1 Use of Risk Score to Guide Discharge of Very-Low-Risk Patients from Emergency Department**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| No of patients (among patients with GBS=0) | Effect (after vs. before) |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Prior to implementing the rule to not admit patients with GBS=0 | After implementing the rule to not admit patients with GBS=0 | Relative(95% CI) | Absolute (95% CI) |
| **Mortality a**  | ⊕⊝⊝⊝**VERY LOW** |  |
| Before-after study1  |  Serious b | Not applicable | Not serious | Very serious c | None | ⊕⊝⊝⊝**VERY LOWd** | 0/105 (all 4 centers) (0%)(0/53 in the 2 centers assessing outcomes after implementing rule)) | 0/84(0%) | ---- | 0% (-2 to 2%) | Prospective except for 1 of 4 centers in “before” portion of study |
| **Composite (blood transfusion, endoscopic treatment, surgery, or death)** |  |
| Before-after study1 |  Serious b | Not applicable | Not serious | Very serious c | None | ⊕⊝⊝⊝**VERY LOWd** | 0/105 (all 4 centers) (0%) (0/53 in the 2 centers assessing outcomes after implementing rule) | 0/84(0%) | ---- | 0% (-2 to 2%) | Prospective except for 1 of 4 centers in “before” portion of study |

**Footnotes:**

a Mortality was assessed as in-hospital mortality for the first phase of the study (prior to implementing the rule to discharge patients with GBS=0) in 4 centers. After implementing the rule to discharge patients with GBS=0, mortality was assessed at time of endoscopy in those who returned for endoscopy and for a minimum of 6 months in those who did not return for endoscopy, but only 2 of the original 4 centers participated in this portion of study. One patient in “after” group died 2 months after endoscopy due to unrelated non-GI malignancy.

b Downgraded for risk of bias because of lack of a concurrent comparator group that did not receive the intervention, and lack of blinding of participants and personnel.

c Downgraded by two levels for very small number of events (none).

d The quality of evidence for before-after studies starts as low.

**1.2 Diagnostic Test Accuracy (DTA) Cohort Studies Assessing Outcomes with Risk Scores a**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Pooled diagnostic accuracy** | Comments |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | **Overall** Quality of Evidence | Cut-off value  | Pooled sensitivity(95% CI) | Pooled specificity(95% CI) |
| **Glasgow-Blatchford**  |
| SRMA of 6 DTA studies2 | Not serious b | Serious c  | Very serious d  | Not serious  | None | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | 0 | 0.99 (0.98 - 1.00)(I2=63.3%) | 0.08(0.07 - 0.09)(I2=92.7%) | **Endpoint:** composite of death, recurrent UGIB (UGIB after clinically stable period of 24 hrs resulting in admission, transfusion, or intervention to stop hemorrhage), and need for intervention (transfusion; angiographic, surgical, or endoscopic intervention for hemorrhage). |
| SRMA of 4 DTA studies2 | Not serious b | Serious c  | Very serious d  | Not serious  | None | ⊕⊝⊝⊝**VERY LOW** | 2 | 0.98 (0.96-0.99) | 0.36 (0.34-0.38) |
| DTA study3 | Not serious | Not serious | Very serious d  | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | 0 | 0.997 (CI not reported) | 0.222 (CI not reported) | **Endpoint:** composite of blood transfusion, hemostatic intervention (endoscopic, surgical, IR), or death during index hospital stay. (**rebleeding without intervention was not included**) |
| 1 | 0.992 (CI not reported) | 0.398 (CI not reported) |
| 2 | 0.976 (CI not reported) | 0.489 (CI not reported) |
| DTA study4  | Not serious | Very serious d  | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | 1 | 0.986(CI not reported) | 0.346(CI not reported) | **Endpoint:** composite of death (30 day) or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |
| DTA study5 | Not serious | Very serious d | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | 0 | 1.00 (CI not reported) | 0.12(CI not reported) | **Endpoint:** composite of death (30 day) or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |
| 1 | 0.99(CI not reported) | 0.27(CI not reported) |
| **Pre-endoscopic Rockall**  |
| SRMA of 6 DTA studies2 | Not serious b | Serious c | Very serious d | Not serious | None | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | 0  |  0.93(0.91 – 0.94) | 0.19(0.18 – 0.20) | **Endpoint:** composite of death, recurrent UGIB (UGIB after clinically stable period of 24 hrs resulting in admission, transfusion, or intervention to stop hemorrhage), and need for intervention (transfusion; angiographic, surgical, or endoscopic intervention for hemorrhage). |
| SRMA of 2 DTA studies2 | 2 | 0.95(0.91 – 0.97) | 0.38(0.35 – 0.40) |
| DTA study4  | Not serious | Not serious | Very serious d  | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | 0 | 0.956(CI not reported) | 0.234(CI not reported) | **Endpoint:** composite of death or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |
| DTA study5 | Not serious | Very serious d | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | 0 | 0.96(CI not reported) | Not reported | **Endpoint:** composite of death (30 day) or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |
| **AIMS65** |
| SRMA of 3 DTA studies2  | Not serious  | Not serious | Very serious d  | Not serious  | None | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | 0(2 studies) |  0.78(0.73 – 0.83) | 0.49(0.45 – 0.53) | **Endpoint:** composite of death, recurrent UGIB (UGIB after clinically stable period of 24 hrs resulting in admission, transfusion, or intervention to stop hemorrhage), and need for intervention (transfusion; angiographic, surgical, or endoscopic intervention for hemorrhage). |
| 2(1 study) | 0.79(0.76 – 0.82) | 0.61(0.61 – 0.61) |
| DTA study4  | Not serious | Not serious | Very serious d  | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | 0 | 0.815(CI not reported) | 0.499(CI not reported) | **Endpoint:** composite of death or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |
| DTA study5 | Not serious | Very serious d | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | 0 | 0.74 (CI not reported) | Not reported | **Endpoint:** composite of death (30 day) or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |
| **Machine Learning Model** |
| DTA study5 | Not serious | Not serious | Very serious d | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | 100% sensitivity | 1.00 (CI not reported) | 0.26(CI not reported) | **Endpoint:** composite of death or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |
| DTA study5 | Not serious | Very serious d | Serious e | None | 99% sensitivity | 0.99 (CI not reported) | 0.35(CI not reported) | **Endpoint:** composite of death or hospital-based intervention(red blood cell transfusion, endoscopic treatment,interventional radiology, or surgery) (**rebleeding without intervention was not included**) |

**Footnotes:**

a Studies restricted to the most recent SRMA of pre-endoscopic risk assessment scores and subsequent well-conducted diagnostic test accuracy studies of pre-endoscopic risk assessment scores including >2000 unselected patients presenting with UGIB

b Not downrated for serious risk of bias. Only 2 of the 6 studies were reported as high risk of bias (for patient selection and index test domains, respectively)

c Downrated due to substantial heterogeneity

d Downrated by 2 levels for lack of clinical outcomes (only diagnostic accuracy outcomes are available)

e Downrated due uncertainty about precision (confidence intervals were not reported)

**References**

1. Stanley AJ, Ashley D, Dalton HR, et al. Outpatient management of patients with low-risk upper-gastrointestinal haemorrhage: multicentre validation and prospective evaluation. Lancet 2009;373:42-7.

2. Ramaekers R, Mukarram M, Smith CA, et al. The predictive value of preendoscopic risk scores to predict adverse outcomes in emergency department patients with upper gastrointestinal bleeding: a systematic review. Acad Emerg Med. 2016;23:1218-27

3 . Laursen SB, Dalton HR, Murray IA, et al. Upper gastrointestinal hemorrhage international consortium. Performance of new thresholds of the Glasgow Blatchford score in managing patients with upper gastrointestinal bleeding. Clin Gastroenterol Hepatol. 2015 Jan;13:115-21.

4 . Stanley AJ, Laine L, Dalton HR, et al. Comparison of risk scoring systems for patients presenting with upper gastrointestinal bleeding: international multicentre prospective study. BMJ. 2017;356:i6432.

5. Shung DL, Au B, Taylor RA, et al. Validation of a machine learning model that outperforms clinical risk scoring systems for upper gastrointestinal bleeding. Gastroenterology 2020;158:160-7

**Red Blood Cell Transfusion**

PICO 2

**2. Red blood cell transfusion: restrictive vs. liberal strategy.**

P: Patients with UGIB

I: Restrictive transfusion (e.g., hemoglobin 7, 8, or 7-8 g/dL)

C: Liberal transfusion (e.g., hemoglobin 9, 10 g/dL)

O: Further bleeding, mortality; additional outcomes: transfusion-related adverse events, cardiovascular events

**2.1 Restrictive vs. Liberal Transfusion Strategy**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcomes | Effect |
| Studies a | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Restrictive transfusion strategy (threshold 7-8g/dL) | Liberal transfusion strategy (threshold 9-10g/dL) | Relative(95%CI) | Absolute(95%CI) |
| **Further bleeding**  | ⊕⊕⊝⊝**LOW**  |  |
| RCT1 | Seriousb | Not serious | Not serious | Seriousc |  | ⊕⊕⊝⊝**LOW** | 45/444 (10.1%) | 71/445 (16.0%) | Adjusted HR=0.68 (0.47-0.98) | -6%(-10 to -1%) | Hemoglobin thresholds were <7 and <9 g/dL |
| RCT2 | Very seriousd | Not serious | Very serious e |  | ⊕⊝⊝⊝**VERY LOW** | Day 28: 13/257 (5.1%) | Day 28: 31/383 (8.1%) | RR=0.62 (0.33-1.17) | -3% (-7 to 1%) | Hemoglobin thresholds were <8 and <10 g/dL |
| **Mortality**  |  |
| RCT1 | Seriousb | Not serious | Not serious | Serious c |  | ⊕⊕⊝⊝**LOW** | 23/444 (5.2%) | 41/445 (9.2%) | Adjusted HR=0.55(0.33-0.92) | -4% (-7 to -1%) | Hemoglobin thresholds were <7 and <9 g/dL |
| RCT2 | Very seriousd | Not serious | Very serious e |  | ⊕⊝⊝⊝**VERY LOW** | 14/257 (5.4%) | 25/383 (6.5%) | RR=0.83 (0.44-1.57) | -1% (-5 to 3%) | Hemoglobin thresholds were <8 and <10 g/dL |

**Footnotes:**

a Three other small studies were excluded: an abstract (N=63 patients) from >5 years earlier without publication in full form3; a study (N=27 patients) with no deaths or rebleeding episodes4; and a study (N=50 patients) in which all patients in the liberal transfusion arm received transfusion regardless of hemoglobin and randomized assignment was only maintained for 24 hours5.

b Serious given lack of blinding: detection bias low risk for primary outcome of mortality (but not further bleeding outcome), but performance bias (e.g., management) still an issue.

c Serious given number of events and upper bound of 95% CI confidence interval crosses the clinical decision threshold between recommending and not recommending a strategy (i.e., clinical action may differ if the upper versus the lower boundary of the CI represented the truth).

d Very serious bias given cluster randomization, differences in numbers of patients in 2 treatment arms, likely selection bias, differences in adherence to protocol, lack of complete reporting, not powered for clinical outcome (but for Rockall score difference)

e Small number of events and wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

**References**

1. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013;368:11-21.

2. Jairath V, Kahan BC, Gray A, et al. Restrictive versus liberal blood transfusion for acute upper gastrointestinal bleeding (TRIGGER): a pragmatic, open-label, cluster randomised feasibility trial. Lancet. 2015;386:137-44.

3. Lee JM, Chun HJ, Lee JS. Target level hemoglobin correction in patients with acute non-variceal upper gastrointestinal bleeding. Gastroenterology 2014;146:S-321.

4. Villarejo F, Rizzolo M, Lópéz E, et al. Acute anemia in high digestive hemorrhage. Margins of security for their handling without transfusion of red globules. Acta Gastroenterol Latinoam. 1999;29:261-70

5. Blair SD, Janvrin SB, McCollum CN, et al. Effect of early blood transfusion on gastrointestinal haemorrhage. Br J Surg. 1986;73:783-5.

**Pre-Endoscopic Medical Therapy**

 **Prokinetic Therapy with Erythromycin**

PICO 3

**3. Use of prokinetic therapy**

P: Patients with UGIB

I: Erythromycin (also metoclopramide, other prokinetics)

C: Placebo/no treatment

O: Further bleeding, mortality; additional outcomes: length of hospitalization, repeat endoscopy in hospital

**3.1 Erythromycin vs. Placebo/No Treatment**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcome | Effect |
| Studies | Study limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall certainty of evidence | Erythromycin | Placebo/no treatment | Relative(95% CI) | Absolute(95% CI) |  |
| **Further bleeding** |  |
| RCT1 | Serious a | Not applicable | Not serious | Very serious b | None | **⊕⊝⊝⊝VERY LOW** |  **⊕⊝⊝⊝VERY LOW**  | 1/14 (7.1%) | 2/15 (13.3%) | RR=0.54 (0.05-5.28) | -6%, (-28 to 16%) | Comparator: gastric lavage |
| **Mortality**  |  |
| SRMA of 3 RCTs2-4  | Serious c | Not serious  | Not serious | Very serious b | None | **⊕⊝⊝⊝****VERY LOW** | ---- | ---- | RR=0.81 (0.41-1.60) | -2%(-9 to 5%) |  |
| **Repeat endoscopy**  |  |
| SRMA of 8 RCTs5 | Serious c | Not serious | Not serious | Not serious | Inclusion criteria d | **⊕⊕⊕⊝MODERATE** | ---- | ---- | OR=0.51(0.34-0.77) | ---- | 122 repeat endoscopies |
| **Days of hospitalization** |  |
| SRMA of 5 RCTs5 | Serious c | Not serious | Not serious | Not serious |  | **⊕⊕⊕⊝MODERATE** | ---- | ---- | ---- | Mean difference= -1.75(-2.43 to -1.06) |  |

**Footnotes:**

a Sequence allocation method and concealment not specified; lack of blinding

b Wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm, and very small total number of events

c Some studies had risks of bias including sequence allocation method and concealment not specified or lack of blinding

d Inclusion criteria in the English-language RCTs included hematemesis in 4 studies; hematemesis or melena in 2; hematemesis, melena, or acute anemia in 1; and blood on gastric lavage in 1; most studies required recent UGIB symptoms (e.g., within 12 hours before presentation, presenting within 12 hours of initial symptoms) and hemodynamic stability at the time of endoscopy. Based on these enrollment criteria the panel did not believe this recommendation should be restricted to a subgroup of patients with acute UGIB.

**References**

1. Na HK, Jung HY, Seo DW, et al. Erythromycin infusion prior to endoscopy for acute nonvariceal upper gastrointestinal bleeding: a pilot randomized controlled trial. Korean J Intern Med. 2017;32:1002-9.

2. Altraif I, Handoo FA, Aljumah A, et al. Effect of erythromycin before endoscopy in patients presenting with variceal bleeding: a prospective, randomized, double-blind, placebo-controlled trial. Gastrointest Endosc 2011;73:245-250.

3. Pateron D, Vicaut E, Debuc E, et al. Erythromycin infusion or gastric lavage for upper gastrointestinal bleeding: a multicenter randomized controlled trial. Ann Emerg Med 2011;57:582-589.

4. Javad Ehsani Ardakani M, Zare E, Basiri M, et al. Erythromycin decreases the time and improves the quality of EGD in patients with acute upper GI bleeding.

Gastroenterol Hepatol Bed Bench 2013;6:195-201.

5. Rahman R, Nguyen DL, Soahil U, et al. Pre-endoscopic erythromycin administration in upper gastrointestinal bleeding: an updated meta-analysis and systematic review. Ann Gastroenterol 2016;29:312-7

**Proton Pump Inhibitor Therapy**

PICO 4

**4. Proton pump inhibitor therapy**

P: Patients with UGIB prior to endoscopy

I: Proton pump inhibitor

C: Placebo/no treatment

O: Further bleeding, mortality; additional outcomes: length of stay, repeat endoscopy, endoscopic therapy, cost

**4.1 Pre-Endoscopic PPI vs. Placebo**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcome | Effect |
| Studies a | Study limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall certainty of evidence | PPI | Placebo | Relative(95% CI) | Absolute(95% CI) |  |
| **Further bleeding** |  |
| RCT1 | Not serious | Not applicable b | Not serious | Very serious c | None | **⊕⊕⊝⊝LOW** | **⊕⊕⊝⊝LOW**  | 11/314 (3.5%) | 8/317 (2.5%) | RR=1.39 (0.57- 3.40) | 1%(-2 to 4%) |  |
| SRMA of 2 other RCTs2,3  | Not serious d | Not serious | Very serious e | Serious f | None | **⊕⊝⊝⊝VERY LOW** |  |  | RR=0.85 (0.66- 1.10) | -2%(-6 to 1%) |  |
| **Mortality**  |  |
| RCT1 | Not serious | Not applicable b | Not serious | Very serious c | None  | **⊕⊕⊝⊝LOW** | 8/314 (2.5%) | 7/317 (2.2%) | RR=1.15 (0.42- 3.14) | 0 (-2 to 3%) |  |
| SRMA of 2 other RCTs2,3  | Not serious d | Not serious  | Very serious e | Serious f | None | **⊕⊝⊝⊝****VERY LOW** |  |  | RR=1.18 (0.77- 1.83) | -3%(-8 to 2%) |  |
| **Endoscopic hemostatic therapy** |  |  |  |  |  |
| SRMA of 3 RCTs1-3 | Not serious d | Not serious | Not serious | Serious g  | None | **⊕⊕⊕⊝MODERATE**  |  |  | RR=0.73 (0.57- 0.94) | -3%(-6 to -1%) |  |

**Footnotes**

a An abstract comparing PPI vs. no treatment4 from >5 years earlier but not published in full form was excluded

b Not applicable because only Lau et al1 (and not the other 2 RCTs) was relied on for further bleeding and mortality outcomes

c Wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm, and very small total number of events

d Not rated down for study limitations, although the 2 RCTs (other than Lau) had unclear risk of bias (unclear risk of selection bias due to unclear allocation concealment).

e Rated down by two levels for very serious indirectness: the protocol for endoscopic hemostatic treatment was different from contemporary standards (treatment was provided only to a small minority of lesions that would have been treated currently; the modalities that were used are considered suboptimal at present); and study design did not directly address the underlying clinical question of the guideline (in these studies, after endoscopy, all patients remained in their assigned treatment arm for a pre-determined period regardless of the timing of endoscopy, the endoscopic findings or the application of endoscopic treatment)

f Wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

g Upper bound of 95% CI confidence interval crosses the clinical decision threshold between recommending and not recommending a strategy (i.e. clinical action may differ if the upper versus the lower boundary of the CI represented the truth).

**References**

1. Lau JY, Leung WK, Wu JCY, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. N Engl J Med 2007;356:1631-40.

2. Daneshmend TK, Hawkey CJ, Langman MJ, et al. Omeprazole versus placebo for acute upper gastrointestinal bleeding: Randomised double blind controlled trial. BMJ 1992;304:143-7.

3. Hawkey GM, Cole AT, McIntyre AS, et al. Drug Treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points. Gut 2001;49:372-9.

4. Naumovski-Mihalic S, Katicic M, Colic-Cvlje V, et al. Intravenous proton pump inhibitor in ulcer bleeding in patients admitted to an intensive care unit. Gastroenterology 2005;128(suppl 4):W1578.

**Endoscopy for Upper Gastrointestinal Bleeding**

 **Timing of Endoscopy**

PICO 5, 6, 7

**5. Timing of endoscopy in all patients admitted to or under observation in hospital**

P: Patients with UGIB admitted or under observation in hospital

I: Upper endoscopy within 24 hours of presentation

C: Upper endoscopy beyond 24 hours

O: Further bleeding, mortality; additional outcomes: surgery, length of hospitalization, cost

**6. Timing of endoscopy in patients with lower-risk clinical features—i.e., hemodynamically stable without serious comorbidities**

P: Patients with UGIB admitted or under observation in hospital, hemodynamically stable, no serious comorbidities

I: Early upper endoscopy (e.g., <24 hours)

C: Delayed upper endoscopy (e.g., >24 hours)

O: Further bleeding, mortality; additional outcomes: need for hospitalization, length of hospitalization, cost, low-risk endoscopic findings

**7. Timing of endoscopy in patients with higher-risk clinical features—i.e., hemodynamic instability, serious comorbidity.**

P: Patients with UGIB plus hemodynamic instability (hypotension and/or tachycardia) and/or serious comorbidity.

I: “Urgent” upper endoscopy (e.g., <6 hours, <12 hours)

C: “Later” upper endoscopy (e.g., >6 hours, >12 hours)

O: Further bleeding, mortality; additional outcomes: length of hospitalization, cost, endoscopic therapy.

**5.1 Timing of Endoscopy: Overall Population of Patients Admitted/Under Observation with UGIB**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcomes | Effect |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Early endoscopy | Later endoscopy | Relative(95% CI) | Absolute(95% CI) |
| **Further bleeding** |  |  |
| RCT1 | Serious a | Not applicable | Serious b | Serious c | None | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | 6/162 (4%) | 8/163 (5%) | RR=0.75 (0.27-2.13) | -1% (-6 to 3%) | Early endoscopy: ≤12 hrs |
| Cohort study2 | Serious d | Not applicable | Not serious | Serious e | None | ⊕⊝⊝⊝**VERY LOW** |  |  | OR=0.70 (0.44-1.13) |  | Outcome was rebleeding or surgery. adjusted for several potential confounding factors, including admission severity of illness, source of hemorrhage (4 indicator variables for duodenal ulcer, gastric ulcer, varices, and gastritis/duodenitis); and the presence of endoscopic stigmata of recent hemorrhage (indicator variables for “high risk” and “intermediate risk” stigmata) |
| **Mortality** |  |
| RCT1 | Serious a | Not applicable | Serious b  | Very serious c | None | ⊕⊝⊝⊝**VERY LOW** | 1/162(0.6 %) | 1/163(0.6 %) | RR=1.01(0.06-15.95) | 0 (-2 to 2%) | Early endoscopy : ≤ 12 h |
| Cohort study3 | Serious d | Serious f | Not serious | Serious e | Uncertain if within 1 day of admission is truly <24 hrs. | ⊕⊝⊝⊝**VERY LOW** |  |  | Nested multivariate : OR=1.12 (0.72-1.72)bivariate analysis stratified by quintile of propensity : OR=1.18 (0.80-1.73) |  | Early : within 1 day of admission |
| Cohort study2 | Serious d | Not serious | Serious e | None | ⊕⊝⊝⊝**VERY LOW** |  |  | Multivariable OR=0.70 (0.29-1.67) |  | Early : within 24 hrs of admissionadjusted for several potential confounding factors, including admission severity of illness, source of hemorrhage (4 indicator variables for duodenal ulcer, gastric ulcer, varices, and gastritis/duodenitis); and the presence of endoscopic stigmata of recent hemorrhage (indicator variables for “high risk” and “intermediate risk” stigmata) |
| Cohort study4 | Serious d | Serious g | Serious e | Uncertain if within 1 day of admission is truly <24 hrs. | ⊕⊝⊝⊝**VERY LOW** |  |  | Multivariable OR=0.88 (0.62-1.23) |  | Early : within 1 day of episode of care.Multivariable models adjusted for demographic factors, comorbidity, and the use of outpatient management.  |
| Cohort Study5 | Serious d | Not serious | Not serious | Uncertain if within 1 day of admission is truly <24 hrs. | ⊕⊝⊝⊝**VERY LOW** |  |  | Multivariable analysis: endoscopy within 1 day of admission no vs. yes: nonvariceal: OR=1.32 (1.26-1.38) Variceal: OR=1.18,(1.08-1.31) |  |  |
| **Days of hospitalization** |  |
| Cohort study3 | Serious d | Not serious | Not serious | Not serious | Uncertain if within 1 day of admission is truly <24 hrs. | ⊕⊝⊝⊝**VERY LOW** |  |  |  | Nested multivariate : -30% (-32 to -26%) |  |
| Cohort study2 | Serious d | Not serious | Not serious | None | ⊕⊝⊝⊝**VERY LOW** |  |  |  | 31% (24 to 37%) lower in early endoscopy | Adjusted for several potential confounding factors, including admission severity of illness, source of hemorrhage (4 indicator variables for duodenal ulcer, gastric ulcer, varices, and gastritis/duodenitis); and the presence of endoscopic stigmata of recent hemorrhage (indicator variables for “high risk” and “intermediate risk” stigmata) |
| Cohort study4 | Serious d | Serious g | Not serious | Uncertain if within 1 day of admission is truly <24 hrs. | ⊕⊝⊝⊝**VERY LOW** |  |  |  | Multivariable –1.95 days (–2.60 to –1.29 days) | Early : within 1 day of episode of care.Multivariable models adjusted for demographic factors, comorbidity, and the use of outpatient management.  |
| Surgery |  |
| RCT1 | Serious a | Not applicable | Serious b | Very serious b | None | ⊕⊝⊝⊝**VERY LOW** | 3/162(1.9 %) | 5/163(3.1 %) | RR=0.60(0.15 to 2.48) | -1% (-5 to 2%) | Early endoscopy: ≤ 12 h |
| Cohort study3 | Serious d | Not serious  | Not serious | Not serious | Uncertain if within 1 day of admission is truly <24 hrs. | ⊕⊝⊝⊝**VERY LOW** |  |  | Nested multivariate : OR=0.34 (0.28-0.49) |  |  |
| Cohort study4 | Serious d | Serious g | Not serious | Uncertain if within 1 day of admission is truly <24 hrs. | ⊕⊝⊝⊝**VERY LOW** |  |  | Multivariable OR=0.37 (0.21-0.66) |  | Early : within 1 day of episode of care.Multivariable models adjusted for demographic factors, comorbidity, and the use of outpatient management.  |

**Footnotes:**

a Lack of blinding; also unclear allocation sequence generation

b Randomized all UGIB, but reported only on patients with confirmed ulcer bleeding

c Very few events (N=2) and wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm.

d Adjustment was performed but it would have been impossible to fully adjust for factors such as severity of bleeding and comorbidities

e Wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm.

f Results of cohort studies by Cooper et al2-4 conflicting with results of cohort study by Wysocki et al5

g  Restricted to elderly (66 or older) and peptic ulcer bleeding

**6.1 Timing of Endoscopy: Patients with Lower-Risk Clinical Features (hemodynamically stable with no severe comorbidities)**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcomes | Effect |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Early endoscopy  | Later endoscopy  | Relative(95% CI) | Absolute(95% CI) |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| RCT6  | Serious a | Not applicable | Not serious | Very serious b | None | ⊕⊝⊝⊝**VERY LOW** | 2/56 (3.6%) | 3/54 (5.6%) | RR=0.64 (0.11- 3.70) | -2%(-10 to 6%) | Early : In 1-2 hrs in emergency department.Later : within 1-2 days of admission |
| **Mortality** |  |
| RCT6 | Serious a | Not serious | Not serious | Very serious b | None | ⊕⊝⊝⊝**VERY LOW** | 0/56 | 2/54 (3.7%) | RR=0.19, (0.01-3.93) | -4%(-10 to 2%) | Early : In 1-2 hrs in emergency department.Later : within 1-2 days of admission |
| RCT7 | Serious a | Not serious | Very serious b | None | ⊕⊝⊝⊝**VERY LOW** | 0/47 | 0/46 | ---- | 0%(-4 to 4%) | Early : within 6 hrs of initial evaluation in emergency department |
| Cohort study8 | Serious c | Not applicable | Serious d | Not serious | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ----  | Endoscopy 0-24 hrs from admission vs. > 24 hrs :In-hospital mortality OR=0.59 (0.33-1.05); 30-day mortality OR=1.02 (0.50-2.09)  | ---- | 5415 hemodynamically stable patients (systolic blood pressure ≥100mm Hg and heart rate ≤100 beats/min) with American Society of Anesthesiologists score 1-2 |
| **Days of hospitalization** |  |
|  RCT6 | Serious a | Serious e | Not serious | Serious f | None | ⊕⊝⊝⊝**VERY LOW** | Median 1 days | Median 2 days | ---- | ---- | P=0.0001 |
| RCT7 | Serious a | Not serious | Very serious g | None | ⊕⊝⊝⊝**VERY LOW** | Median 3 days | Median 3 days | ---- | ---- | P=0.45 |
| **Cost** |  |
| RCT6 | Serious a | Not applicable | Serious h | Serious f | None | ⊕⊝⊝⊝**VERY LOW** | $2068 (interquartile range: $928 to $3960) | $3662 (interquartile range: $2473 to $7280) | ---- | ----- | p=0.00006 |

**Footnotes:**

a Lack of blinding and unclear allocation sequence generation.

b Very few events and wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

c Adjustment for confounders was performed but it would have been impossible to fully adjust for factors such as severity of bleeding and comorbidities

d Only included patients with ulcer bleeding rather than all patients with UGIB.

e Difference in days of hospitalization in the 2 RCTs was markedly different

f Small sample size (N=110)

g Small sample size (N=93) and hospital stay similar in 2 groups allowing broad range of possible outcomes from shorter to longer hospital stay.

h Cost is at a single Sacramento hospital in the years 1998 or earlier

**7.1 Timing of Endoscopy: Patients with Higher-Risk Clinical Features**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcomes | Effect |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Very early endoscopy | Later endoscopy | Relative(95% CI) | Absolute(95% CI) |
| **Further bleeding** |  |  |
| RCT9 | Serious a | Not applicable | Not serious | Serious | None | ⊕⊕⊝⊝**LOW** | ⊕⊕⊝⊝**LOW** | 28/258 (10.9%) | 20/258 (7.8%) | RR=1.40 (0.81-2.42) | 3% (-2 to 8%) | High risk=GBS≥12;Very early endoscopy : within 6 hrs of GI consultEarly endoscopy : within 6-24 hrs of GI consult |
| **Mortality**  |  |
| RCT9 | Serious a | Not applicable | Not serious | Serious | None | ⊕⊕⊝⊝**LOW** | 23/258 (8.9%) | 17/258 (6.6%) | RR=1.35 (0.74-2.47) | 2%(-2 to 7%) | High risk=GBS≥12;Very early endoscopy : within 6 hrs of GI consultEarly endoscopy : within 6-24 hrs of GI consult |
| Cohort study10 | Serious b | Serious c | Not serious  | Serious d | None | ⊕⊝⊝⊝**VERY LOW** | Unadjusted9/571(1.6 %) | Unadjusted 15/390(3.8%) | Adjusted OR=0.36 (0.14–0.95) | ---- | High risk=GBS≥8;Very early endoscopy : ≤ 6 hrs after presentationElective endoscopy: 6-48 hrs after presentation |
| Cohort Study8 | Serious b | Serious e | Serious f | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | 0-12 hrs after admission vs. >12 hrs: adjusted OR=1.53 (1.07-2.19);6-24 hrs vs. other timeframe: adjusted OR=0.73 (0.54-0.98) | ---- | 2933 patients with hemodynamic instability (systolic blood pressure<100 mm Hg and heart rate>100 beats/min) |
| Cohort Study8 | Serious b | Serious e | Not serious | None | ⊕⊝⊝⊝**VERY LOW** |  |  | 0-12 hrs after admission vs. >12 hrs: adjusted OR=1,65 (1.22-2.22); 12-36 hrs vs other timeframe: adjusted OR=0.48 (0.34-0.67) |  | 3941 hemodynamically stable patients (systolic blood pressure ≥100mm Hg and heart rate ≤100 beats/min) with American Society of Anesthesiologists score 3-5 |
| **Days of hospitalization** |  |
| RCT9 | Serious | Not applicable | Not serious | Serious | None | ⊕⊕⊝⊝**LOW** | Median: 5 days | Median: 5 days | --- | --- | High risk=GBS≥12;Very early endoscopy : within 6 hrs of GI consultEarly endoscopy : within 6-24 hrs of GI consult |

**Footnotes:**

a Not blinded

b Adjustment was performed but it would have been impossible to fully adjust for factors such as severity of bleeding and comorbidities

c The cohort study by Laursen et al8 included 2 separate comparisons which are shown separately in table. The results of the two cohort studies8,10 reported conflicting results.

d Very few events (N=24)

e Only included patients with ulcer bleeding rather than all patients with UGIB.

f Bounds of 95% CI confidence interval (lower bound 1.07 for 0-12 vs. >12 hrs; upper bound 0.98 for 6-24 hrs vs. other timeframe) crosses the clinical decision threshold between recommending and not recommending a strategy (i.e. clinical action may differ if the upper versus the lower boundary of the CI represented the truth).

**References**

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**Need for Endoscopic Hemostatic Therapy for Ulcers with Active Bleeding or Non-Bleeding Visible Vessel**

PICO 8

**8. Endoscopic therapy in patients with active spurting or oozing bleeding or a non-bleeding visible vessel**

P: Patients with UGIB, due to ulcers with active spurting or oozing bleeding or a non-bleeding visible vessel

I: Endoscopic therapy (all types)

C: No endoscopic therapy

O: Further bleeding, mortality

**8.1 Endoscopic Therapy vs. No Endoscopic Therapy for Active Bleeding or Non-Bleeding Visible Vessel**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Effect****(Endoscopic therapy vs. no endoscopic therapy)** | **Comments** |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Relative(95%CI) | Absolute(95%CI) |
| **Further bleeding** | ⊕⊕⊕⊝**MODERATE** |
| SRMA of 19 RCTs1 | Seriousa | Not serious | Not serious | Not serious |  | ⊕⊕⊕⊝**MODERATE** | Active bleeding: RR=0.29 (0.20-0.43)Non-bleeding visible vessel: RR=0.49 (0.40-0.59) | Active bleeding: NNT=2 (2-2)Non-bleeding visible vessel: NNT=5 (4-6) |  |
| **Mortality** |  |
| SRMA of 15 RCTs1 | Seriousa | Not serious | Not serious | Seriousb |  | ⊕⊕⊝⊝**LOW** | Active bleeding: RR=1.28 (0.26-6.21)Non-bleedingvisible vessel:RR=0.62 (0.36-1.06) | ----- |  |

**Footnotes:**

a Lack of blinding, allocation not detailed in a number of studies

b Active bleeding would be very serious (very broad CIs and very few events (2)) while non-bleeding visible vessel serious; most of patients are in non-bleeding visible vessel group (e.g., control sample size of 579 in non-bleeding visible vessel group and 95 in active bleeding group) so assigned “serious” designation

**References**

1. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence based approach based on meta-analyses of randomized controlled trials. Clin Gastroenterol Hepatol. 2009;7:33-47

 **Need for Endoscopic Hemostatic Therapy for Ulcers with Adherent Clot**

PICO 9

**9. Endoscopic therapy in patients with an adherent clot resistant to vigorous irrigation.**

P: Patients with UGIB, due to ulcers with adherent clot (resistant to targeted vigorous irrigation)

I: Endoscopic therapy (all types)

C: No endoscopic therapy

O: Further bleeding, mortality

**9.1 Endoscopic Therapy vs. No Endoscopic Therapy for Adherent Clot**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Effect** **(Endoscopic therapy vs. no endoscopic therapy)** | Comments |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Relative(95%CI) | Absolute(95%CI) |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| SRMA of 5 RCTs1 | Seriousa | Very serious | Not serious | Very seriousb | The 2 positive studies were terminated prematurely, didn’t use high-dose PPI | ⊕⊝⊝⊝**VERY LOW** | RR=0.31 (0.06-1.77) |  | Heterogeneity (p=0.03) |
| **Mortality** |  |
| SRMA of 2 RCTs1 | Seriousa | Not serious | Not serious | Very seriousb | The 2 positive studies were terminated prematurely, didn’t use high-dose PPI | ⊕⊝⊝⊝**VERY LOW** | RR=0.90, (0.23-3.58) |  |  |

**Footnotes:**

a Lack of blinding, allocation not detailed in a number of studies

b Small sample sizes with few events (31 further bleeding outcome in 5 RCTs; 8 mortality outcomes in 3 RCTs (1 RCT had no deaths so mortality meta-analysis result based on 2 RCTs)), and wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

**References**

1. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence based approach based on meta-analyses of randomized controlled trials. Clin Gastroenterol Hepatol. 2009;7:33-47

**Choice of Endoscopic Hemostatic Therapy for Bleeding Ulcers**

PICO 10

**10 Endoscopic hemostatic therapy**

**10a. Endoscopic therapies vs. no endoscopic therapy**

P: UGIB due to ulcers with active bleeding (spurting or oozing), non-bleeding visible vessels, or clots

I: Specific endoscopic therapies

C: No endoscopic therapy

O: Further bleeding, mortality

**10b. Comparisons of different endoscopic therapies**

P: UGIB due to ulcers with active bleeding (spurting or oozing), non-bleeding visible vessels, or clots

I: Specific endoscopic therapies

C: Other specific endoscopic therapies

O: Further bleeding, mortality

**10.1 Endoscopic Therapies vs. No Endoscopic Therapy or Other Endoscopic Therapies**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcomes | Effect |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Endoscopic treatment | No endoscopic treatment or other endoscopic treatment | Relative(95% CI) | Absolute(95% CI) |
| **Epinephrine monotherapy vs. other monotherapy** |
| **Further bleeding** |  |  |
| SRMA of 4 RCTs1-4 | Serious a | Serious b  | Not serious | Serious c  | None | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=2.20(1.04-4.64) | 15% (9 to 22%) | Comparators : biploar electrocoagulation, clips x 2; fibrin glue; Heterogeneity, I2=56% |
| **Mortality** |  |
| SRMA of 4 RCTs1-4 | Serious a | Not serious  | Not serious | Very serious d,e  | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.98 (0.56-1.73) | 0 (-3 to 3%) | Comparators : bipolar electrocoagulation, clips x 2; fibrin glue |
| **Epinephrine + second modality vs. epinephrine monotherapy**  |
| **Further bleeding** | ⊕⊕⊕⊝**MODERATE** |  |
| SRMA of 7 RCTs5 | Serious a | Not serious | Not serious | Not serious | None | ⊕⊕⊕⊝**MODERATE** | ---- | ---- | RR=0.34 (0.23-0.50) | NNT=5 (5-7) | 2nd modalities: bipolar, sclerosant, clips, thrombin |
| **Mortality** |  |
| SRMA of 6 RCTs5 | Serious a | Not serious | Not serious | Serious e | None | ⊕⊕⊝⊝**LOW** | ---- | ---- | RR=0.52(0.23-1.16) | ---- | 2nd modalities: bipolar, sclerosant, clips, thrombin |
| **Clips vs. epinephrine monotherapy** |
| **Further bleeding** | ⊕⊕⊝⊝**LOW** |  |
| SRMA of 2 RCTs1,2 | Serious a | Not serious  | Not serious | Serious d | None | ⊕⊕⊝⊝**LOW** |  |  | RR=0.20, (0.07-0.56) | -17% (-25 to -9%) |  |
| **Mortality** |  |
| SRMA of 2 RCTs1,2 | Serious a | Not serious  | Not serious | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | **----** | **----** | RR=2.11 (0.60-7.44) | 3% (-3 to 9%) |  |
| **Thermal contact with bipolar electrocoagulation or heater probe vs. no endoscopic treatment** |
| **Further bleeding** | ⊕⊕⊕⊝**MODERATE** |  |
| SRMA of 15 RCTs5 | Serious a | Not serious  | Not serious | Not serious  | None | ⊕⊕⊕⊝**MODERATE** | ----  | ----  | RR=0.44 (0.36-0.54) | NNT=4 (3 to 5) |  |
| **Mortality** |  |
| SRMA of 13 RCTs5 | Serious a | Not serious  | Not serious | Serious c | None | ⊕⊕⊝⊝**LOW** | ----  | ----  | RR=0.58 (0.34-0.98) | NNT=33 (21 to 1000) |  |
| **Epinephrine + bipolar electrocoagulation vs. bipolar electrocoagulation monotherapoy** |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |  |  |  |  |
| SRMA of 2 RCTs5 | Serious a | Serious | Not serious | Serious d  | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.35(0.18-0.71) | ---- | Bipolar monotherapy had unusually high rates of further bleeding (25,% 34%) |
| **Mortality** |  |
| SRMA of 2 RCTs5 | Serious a | Not serious | Not serious | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.49 (0.09-2.60) | ---- |  |
| **Absolute ethanol injection vs. no endoscopic treatment**  |
| **Further bleeding**  | ⊕⊕⊕⊝**MODERATE** |  |
| SRMA of 3 RCTs5 | Serious a | Not serious  | Not serious | Not serious | None | ⊕⊕⊕⊝**MODERATE** | ----  | ---- | RR=0.56 (0.38-0.83) | NNT=5 (4 to 13) |  |
| **Mortality** |  |
| SRMA of 3 RCTs 5 | Serious a | Not serious  | Not serious | Not serious | None | ⊕⊕⊕⊝**MODERATE** | ---- | ---- | RR=0.18 (0.05-0.68) | NNT=9 (8 to 24) |  |
| **Epinephrine/polidocanol injection vs. no endoscopic treatment** |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| SRMA of 6 RCTs 5 | Serious a | Serious b | Not serious | Serious c | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.60(0.36-1.00) | ---- | Heterogeneity, I2=58% |
| **Mortality** |  |
| SRMA of 6 RCTs 5 | Serious a | Not serious | Not serious | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.80(0.40-1.61) | ---- |  |
| **Thermal contact with bipolar electroagulation or heater probe vs. absolute ethanol injection** |
| **Further bleeding** | ⊕⊕⊝⊝**LOW** |  |
| SRMA of 5 RCTs 5 | Serious a | Not serious | Not serious | Serious c | None | ⊕⊕⊝⊝**LOW** | ---- | ---- | RR=0.69(0.47-1.01) | ---- |  |
| **Mortality** |  |
| SRMA of 4 RCTs 5 | Serious a | Not serious | Not serious | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=1.60 (0.57-4.52) | ---- |  |
| **Clips + Epinephrine vs. clips alone** |
| **Further bleeding**  | ⊕⊝⊝⊝**VERY LOW** |  |
| SRMA of 2 RCTs2,6 | Serious a | Not serious | Serious f | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=1.10, (0.42-2.88) | 1% (-8 to 10%) | Epinephrine injected after clips placed |
| **Mortality** |  |
| SRMA of 2 RCTs2,6 | Serious a | Not serious | Serious f | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.63, 0.10-3.87 | -1% (-7 to 4%) | Epinephrine injected after clips place |
| **Clips vs. thermal contact with bipolar electrocoagulation or heater probe**  |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| SRMA of 4 RCTs5 | Serious a | Serious b  | Serious g | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=1.31 (0.36-4.75) | ---- | Comparators: heater probe (3 studies); epinephrine + bipolar electrocoagulation (1 study) |
| **Mortality** |  |
| SRMA of 4 RCTs5 | Serious a | Not serious  | Serious g | Serious e | None | ⊕⊝⊝⊝**VERY LOW** | ----  | ---- | RR=1.16 (0.38-3.52) | ----  | Comparators: heater probe (3 studies); epinephrine + bipolar electrocoagulation (1 study)  |
| **Argon plasma coagulation vs. sub-standard therapy (distilled water injection followed by argon plasma coagulation vs. distilled water injection alone)** |
| **Further bleeding** |  |  |
| RCT7 | Serious a | Not applicable | Serious h | Very serious c,d | None | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | 4/58 | 12/58 | RR=0.33(0.11-0.97) | -14%(-27 to -1% ) |  |
| **Mortality** |  |
| RCT7 | Serious a | Not applicable | Serious h | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | 2/58 | 2/58 | RR=1.00(0.15-6.86) | 0 (-8 to 8%) |  |
| **Argon plasma coagulation vs. other therapy** |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| SRMA of 3 RCTs8-10 | Serious a | Serious b | Serious i | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.82(0.21-3.19) | -3% (-17 to 11%) | Comparisons : APC vs. epinephrine/polidocanol, epinephrine + APC vs. epinephrine + heater probe, epinephrine + APC vs. epinephrine + clip |
| **Mortality** |  |
| SRMA of 3 RCTs8-10 | Serious a | Not serious | Serious i | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.85(0.30-2.33) | 0(-3 to 3%) | Comparisons : APC vs. epinephrine/polidocanol, epinephrine + APC vs. epinephrine + heater probe, epinephrine + APC vs. epinephrine + clip |
| **Soft monopolar electrocoagulation vs. other therapy** |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| RCT11 | Serious a | Not applicable | Serious j | Serious d | None | ⊕⊝⊝⊝**VERY LOW** | 3/56 (5.4%) | 19/56 (33.9%) | RR=0.16(0.05-0.50) | -33%(-54 to -13%) | Comparator : clips Initial epinephrine injection in both groups for actively bleeding ulcers |
| **Mortality** |  |
| RCT11 | Serious a | Not applicable | Serious j | Very serious d,e | None | ⊕⊝⊝⊝**VERY LOW** | 0/56 | 0/56 | ---- | ---- | Comparator : clips Initial epinephrine injection in both groups for actively bleeding ulcers |
| **Persistent bleeding** |  |
| SRMA of 4 RCTs11-14 | Serious a | Serious b | Not serious | Serious c | None | ⊕⊝⊝⊝**VERY LOW** | ---- | ---- | RR=0.35(0.12-1.03) | -12%(-27 to 2%) | Comparators : clips, heater probe |
| **Over-the-scope clips vs. other therapy for recurrent ulcer bleeding after prior successful endoscopic hemostasis** |
| **Further bleeding** | ⊕⊕⊝⊝**LOW** |  |
| RCT15 | Serious a | Not applicable | Not serious | Serious d | Only relevant to rebleeding after prior successful endoscopic hemostasis | ⊕⊕⊝⊝**LOW** | 5/33 (15.2%) | 19/33 (57.6%) | RR=0.26(0.11-0.62) | -42% (-63 to -22%) | >75% had standard clips as initial unsuccessful therapy; standard clips were standard comparator therapy in 31/33 |
| **Mortality** |  |
| RCT15 | Serious a | Not applicable | Not serious | Very serious d,e | Only relevant to rebleeding after prior successful endoscopic hemostasis | ⊕⊝⊝⊝**VERY LOW** | 4/33 (12.1%) | 2/33 (6.1%) | RR=2.00(0.39-10.18) | 6%(-8 to 20%) | >75% had standard clips as initial unsuccessful therapy; standard clips were standard comparator therapy in 31/33 |
| **Over-the-scope clips vs. other therapy for initial treatment** |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| RCT16 | Very serious k | Not applicable | Serious l | Very serious m | None | ⊕⊝⊝⊝**VERY LOW** | 1/23 (4.3%) | 7/25 (28.0%) | RR=0.16 (0.02-1.17) | -24%(-43 to -4%) | Comparator: epinephrine plus bipolar or clips |
| **Mortality** |  |
| RCT16 | Very serious k | Not applicable | Serious l | Very serious m | None | ⊕⊝⊝⊝**VERY LOW** | 0/23 | 0/25 | Not estimable | 0(-8 to 8%) | Comparator : epinephrine plus bipolar or clips |
| **Hemostatic powder TC-325 vs. other therapy n** |
| **Further bleeding** | ⊕⊝⊝⊝**VERY LOW** |  |
| 1 RCT17 | Serious a | Not applicable | Not serious | Very serious d,e | Non-inferiority trial | ⊕⊝⊝⊝**VERY LOW** | 8/65 (12.3%) | 10/65 (15.4%) | RR=0.80(0.34-1.90) | -3%(-15 to 9%) | Comparator : clipping or contact thermocoagulation ± prior epinephrine |

**Footnotes:**

a Mainly due to lack of blinding.

b Statistical heterogeneity

c The confidence interval crosses the clinical decision threshold between recommending and not recommending a strategy (i.e. clinical action would differ if the upper versus the lower boundary of the CI represented the truth).

d Small number of events

e Wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm.

f Epinephrine injection after clips does not directly assess more clinically relevant question of epinephrine injection before clip placement

g The studies used older clips which may not be generalizable to more modern clips

h Distilled water injected before argon plasma coagulation, which prevents direct comparison of distilled water alone to argon plasma coagulation alone

I Epinephrine also used in 2 of the 3 trials confounding the direct comparison of argon plasma coagulation alone to other therapies

j Epinephrine also used in both treatment groups for actively bleeding ulcers confounding the direct comparison between soft monopolar electrocoagulation and clips

k Lack of blinding; increase in anticipated sample size from 45 to 55 at end of study without explanation (<https://clinicaltrials.gov/ct2/history/NCT03065465>); in overall study fewer patients with spurting bleeding (2 vs. 7) and more with flat spots (6 vs. 3) in over-the-scope clip group, which favors the over-the-scope clip group.

l Study population restricted to “severe UGIB” requiring hemoglobin ≤9 g/dl and ≥1 unit red-cell transfusion, and included ulcers with flat spots that had positive Doppler signal. All patients received epinephrine injection prior to clip placement preventing direct assessment of over-the-scope clips alone.

m Very few events (8 further bleeding and 0 deaths in ulcer population) and small sample size; upper bound of 95% CI confidence interval crosses the clinical decision threshold between recommending and not recommending a strategy (i.e. clinical action may differ if the upper versus the lower boundary of the CI represented the truth): if change in further bleeding outcome by 1 patient in either arm, difference not significant

n Two published RCTs were identified but not relied upon because both included routine second-look endoscopies. Furthermore, in the first RCT18 only 8 of the 20 patients enrolled had actively bleeding ulcers (initial hemostasis achieved in 4/5 treated with hemostatic powder and 3/3 treated with epinephrine plus clip or heater probe). The second RCT19 allowed use of epinephrine with TC-325, which confounds assessment of TC-325 in achieving hemostasis of active bleeding. Finally, the second RCT19 included a variety of different bleeding etiologies: ulcers represented only 44% and results for ulcers were not reported separately.

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**Anti-Secretory Therapy after Endoscopic Hemostatic Therapy for Bleeding Ulcers**

PICO 11

**11. High-dose PPI therapy after successful endoscopic hemostasis**

**11a. High-dose PPI therapy after successful endoscopic hemostasis (compared to no treatment)**

P: Patients with UGIB due to ulcers after successful endoscopic hemostasis.

I: High-dose PPI

C: Placebo/no treatment

O: Further bleeding, mortality; additional outcomes: interventional radiology/surgery

**11b. High-dose PPI therapy after successful endoscopic hemostasis (compared to H2-receptor antagonist)**

P: Patients with UGIB due to ulcers after successful endoscopic hemostasis.

I: High-dose PPI

C: H2-receptor antagonist

O: Further bleeding, mortality; additional outcomes: interventional radiology/surgery

**11c. High-dose PPI therapy after successful endoscopic hemostasis (characteristics of PPI administration)**

P: Patients with UGIB due to ulcers after successful endoscopic hemostasis.

I: High-dose bolus followed by continuous infusion of intravenous PPI

C: Different PPI regimen (dose, route, frequency)

O: Further bleeding, mortality; additional outcomes: interventional radiology/surgery

**11.1 High-Dose PPI Therapya vs. Placebo/No Treatment after Successful Endoscopic Hemostatic Therapy**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcome | Effect |
| Studies | Study limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall certainty of evidence | PPI | Placebo | Relative(95% CI) | Absolute(95% CI) |  |
| **Further bleeding** |  |
| SRMA of 8 randomized comparisons in 7 publications1-7 | Not serious b | Not serious | Not serious | Not serious | None | ⊕⊕⊕⊕**HIGH** | ⊕⊕⊕⊕**HIGH** |  |  | RR=0.43(0.33-0.56) | -10%(-13 to -7%) |  |
|  | Subgroup Analysis | Continuous PPI (intravenous bolus followed by continuous infusion) (4 comparisons1-4) |  |  | RR=0.43(0.31-0.61) | -9%(-12 to -5%) | Subgroup difference:p = 0.94; I2 = 0% |
| Intermittent PPI (intravenous or oral, mean 80-93mg daily)(4 comparisons2,5-7) |  |  | RR=0.42(0.27-0.67) | -13%(-19 to -7%) |
| **Mortality** |  |
| SRMA of 8 randomized comparisons in 7 publications1-7 | Not serious b | Not serious | Not serious | Not serious | None | ⊕⊕⊕⊕**HIGH** |  |  | RR=0.41(0.22-0.79) | -2%(-3 to -1%) |  |
|  | Subgroup Analysis | Continuous PPI (intravenous bolus followed by continuous infusion) (4 comparisons1-4) |  |  | RR=0.41(0.20-0.84) | -2%(-4 to -1%) | Subgroup difference:p = 0.99; I2 = 0% |
| Intermittent PPI (intravenous or oral)(4 comparisons2,5-7) |  |  | RR=0.42(0.08-2.13) | -1%(-3 to 1%) |
| **Surgery** |  |  |  |  |  |
| SRMA of 6 RCTs1, 3-7 | Not serious b | Not serious | Not serious | Not serious | None | ⊕⊕⊕⊕**HIGH** |  |  | RR=0.42(0.25-0.71) | -3%(-5 to -1%) |  |
|  | Subgroup Analysis | Continuous PPI (intravenous bolus followed by continuous infusion) (3 RCTs1,3,4) |  |  | RR=0.43 (0.24-0.76) | -5%(-6 to -1%) | Subgroup difference:p = 0.90; I2 = 0% |
|  | Intermittent PPI (intravenous or oral)(3 RCTs5-7) |  |  | RR=0.39(0.11-1.43) | -2%(-6 to 1%) |

**Footnotes**

a High-dose PPI therapy defined as ≥80mg daily for at least 3 days after endoscopic treatment

b Only 1 study was high risk of bias2 due to lack of blinding (no placebo) and concealed allocation not documented

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**11.2 High-Dose PPI Therapya vs. H2-Receptor Antagonist (H2RA) after Successful Endoscopic Hemostatic Therapy**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcome | Effect |
| Studies | Study limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall certainty of evidence | PPI | H2RA | Relative(95% CI) | Absolute(95% CI) |  |
| **Further bleeding** |  |
| SRMA of 9 RCTs1-9 | Serious b | Not serious | Not serious | Not serious | None | **⊕⊕⊕⊝MODERATE** | **⊕⊕⊕⊝MODERATE** |  |  | RR=0.56(0.41-0.77) | -4%(-6 to -2%) |  |
|  | Subgroup Analysis | Continuous PPI (intravenous bolus followed by continuous infusion) (5 RCTs1-5) |  |  | RR=0.56(0.37-0.84) | -3%(-5 to -1%) | Subgroup difference:p = 0.92; I2 = 0% |
| Intermittent PPI (intravenous or oral, mean 80-133mg/daily)(4 RCTs6-9) |  |  | RR=0.57(0.35-0.94) | -8%(-16 to -1%) |
| **Mortality** |  |
| SRMA of 9 RCTs1-9 | Serious b | Not serious | Not serious | Serious c | None | **⊕⊕⊝⊝LOW**  |  |  | RR=0.66(0.27-1.64) | 0%(-1 to 0%) |  |
|  | Subgroup Analysis | Continuous PPI (intravenous bolus followed by continuous infusion) (5 RCTs1-5) |  |  | RR=0.67 (0.23-1.92) | 0%(-1 to 0%) | Subgroup difference:p = 0.97; I2 = 0% |
| Intermittent PPI (intravenous or oral)(4 RCTs,6-9) |  |  | RR=0.65(0.11-3.82) | -1%(-4 to 3%) |
| **Surgery** |  |  |  |  |  |
| SRMA of 7 RCTs2-8 | Serious b | Not serious | Not serious | Serious c | None | **⊕⊕⊝⊝LOW** |  |  | RR=0.82(0.49-1.36) | -1%(-2 to 1%) |  |
|  | Subgroup Analysis | Continuous PPI (intravenous bolus followed by continuous infusion) (4 RCTs 2-5) |  |  | RR=0.84 (0.42-1.66) | 0%(-2 to 1%) | Subgroup difference:p = 0.92; I2 = 0% |
| Intermittent PPI (intravenous or oral)(3 RCTs6-8) |  |  | RR=0.80(0.37-1.70) | -2%(-8 to 4%) |

**Footnotes**

a High-dose PPI therapy defined as ≥80mg daily for at least 3 days after endoscopic treatment

b Five studies at high risk of bias3,5-8 primarily related to lack of blinding. One study2 had routine 2nd-look endoscopy at day 3. Because this may impact outcomes beyond day 3, we used 3-day outcomes for this study and did not include bleeding identified only at 2nd-look endoscopy.

c Wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

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**11.3 High-Dose Bolus Followed by Continuous Infusion Intravenous PPI Therapya vs. Other PPI Regimens after Successful Endoscopic Hemostatic Therapy**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcome | Effect |
| Studies | Study limitations | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall certainty of evidence | Bolus/ contin-uous | Other regimen | Relative(95% CI) | Absolute(95% CI) |  |
| **Further bleeding** |  |
| SRMA of 12 RCTs1-12 | Serious b | Not serious | Not serious c | Serious d | None | **⊕⊕⊝⊝LOW** | **⊕⊕⊝⊝LOW** |  |  | RR=1.12(0.86-1.47) | 1%(-2 to 4 %) |  |
|  | Subgroup Analysis | Comparator regimen: cumulative dose ≤ 120mg/72 h 1-4 |  |  | RR=0.97(0.63-1.49) | 0%(-4 to 3%) | Subgroup difference: p=0.37; I2=0% |
| Comparator regimen: cumulative dose > 120mg/72 h 5-12 |  |  | RR=1.25(0.89-1.76) | 3% (-1 to 7%) |
|  | Subgroup Analysis | Comparator regimen: intravenous continuous infusion, 40mg bolus and 4mg/hr infusion 9 |  |  | RR=1.29(0.79-2.08) | 7%(-7 to 21%) | Subgroup difference: p=0.54; I2=0%(Only 1 RCT (with 24% of weight) had continuous-infusion comparator) |
| Comparator regimen: intermittent oral or intravenous doses, mean 40-173mg daily 1-8, 10-12 |  |  | RR=1.07(0.78-1.48) | 1%(-2 to 3%) |
|  | Subgroup Analysis | Comparator regimen: intermittent oral, mean 40-160mg daily 4,5,8,12 |  |  | RR=1.11(0.57-2.16) | 1%(-4 to 5%) | Subgroup difference: p=0.91; I2=0% |
| Comparator regimen: intermittent intravenous, mean 40-173mg daily 1-3,, 6, 7, 10, 11 |  |  | RR=1.06(0.78-1.48) | 1%(-3 to 4%) |
| **Mortality** |  |
| SRMA of 11 RCTs1-11 | Serious e | Not serious | Not serious f | Very serious g | None | **⊕⊝⊝⊝VERY LOW** |  |  | RR=0.94(0.46-1.90) | 0%(-2 to 1%) |  |
|  | Subgroup Analysis | Comparator regimen: cumulative dose ≤ 120mg/72 h 1-4 |  |  | RR=0.90(0.37-2.20) | 0%(-2 to 2%) | Subgroup difference: p=0.89, I2=0 |
| Comparator regimen: cumulative dose > 120mg/72 h 5-11 |  |  | RR=1.00(0.32-3.17) | 0%(-2 to 2%) |
|  | Subgroup Analysis  | Comparator regimen: intravenous continuous infusion 9 |  |  | RR=1.00(0.42-2.39) | -1%(-8 to 6%) | Subgroup difference: p=0.77; I2=0% (Only 1 RCT (with 11% of weight) had continuous-infusion comparator) |
| Comparator regimen: intermittent oral or intravenous doses 1-8, 10, 11 |  |  | RR=1.08(0.50-2.30) | 0%(-1 to 1%) |
|  | Subgroup Analysis | Comparator regimen: intermittent oral 4, 5, 8 |  |  | RR=0.35(0.01-8.30) | -1% (-5 to 3%) | Subgroup difference: p=0.49; I2=0%(Only 1 death in the 3 RCTs with oral PPI) |
| Comparator regimen: intermittent intravenous 1-3, 6, 7, 10, 11 |  |  | RR=1.11(0.45-2.70) | 0%(-1 to 2%) |
| **Surgery** |  |  |  |  |  |
| SRMA of 12 RCTs1-12 | Serious h | Not serious | Not serious i | Serious d | None | **⊕⊕⊝⊝LOW** |  |  | RR=1.07(0.61-1.85) | 0%(-1 to 2%) |  |
|  | Subgroup Analysis | Comparator regimen: cumulative dose ≤ 120mg/72 h 1-4 |  |  | RR=0.60(0.19-1.93) | -1%(-2 to 1%) | Subgroup difference: p=0.26; I2=21% |
| Comparator regimen: cumulative dose > 120mg/72 h 5-12 |  |  | RR=1.29(0.68-2.44) | 1%(-2 to 4%) |
|  | Subgroup Analysis  | Comparator regimen: intravenous continuous infusion 9 |  |  | RR=1.20(0.55-2.62) | 1%(-6 to 9%) | Subgroup difference: p=0.82; I2=0% (Only 1 RCT (with 9% of weight) had continuous-infusion comparator) |
| Comparator regimen: intermittent oral or intravenous doses 1-8, 10-12 |  |  | RR=1.03(0.55-1.92) | 0%(-1 to 1%) |
|  | Subgroup Analysis | Comparator regimen: intermittent oral 4, 5, 8, 12 |  |  | RR=1.10 (0.30-4.07) | 0%(-2 to 2%) | Subgroup difference: p=1.00; I2=0% |
| Comparator regimen: intermittent intravenous 1-3, 6, 7, 10, 11 |  |  | RR=1.11(0.50-2.48) | 0%(-1 to 1%) |

**Footnotes**

a Defined as 80mg bolus of intravenous PPI followed by 8 mg/hr continuous infusion for 72 hours

b Of the 12 RCTs, only one12 had low risk of bias. Six RCTs had unclear risk of bias and five had high risk of bias (mainly for lack of blinding). The low risk of bias studies provided 9% of the weight in this analysis.

c Two of the studies9,10 with 38% of the weight in the meta-analysis reported rates for further bleeding that were unexpectedly high compared to current clinical practice (further bleeding in those 2 studies was 29% and 32% respectively, while the remaining 10 studies had mean rate for further bleeding of 8%), without an obvious explanation. Although this raises concern for indirectness in the population, interventions, and/or definition of the outcome, no obvious substantive differences were noted in these characteristics for these 2 studies as compared to other studies.

d 95% CI crosses unity, with results consistent with at least no effect or less effect for bolus/continuous vs. other regimens.

e Of the 11 RCTs, none had low risk of bias. Six RCTs had unclear risk of bias and five had high risk of bias (mainly for lack of blinding).

f One of the studies9 with 49% of the weight in the meta-analysis reported mortality rates that were unexpectedly high compared to current clinical practice (mortality in this study was 10.8%, while the remaining 10 studies had mean mortality 1.5%). Half of the deaths in study of Masjedizadeh et al9 occurred post discharge (within 1 month from randomization), but an in-hospital mortality of 5.4% is still substantially higher than the mortality that was observed in the remaining studies. Although this raises concern for indirectness in the population, interventions, and/or definition of the outcome, no obvious substantive differences were noted in these characteristics for this study as compared to other studies.

g Small number of events (27 deaths); wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

h Of the 12 RCTs, only one12 had low risk of bias. Six RCTs had unclear risk of bias and five had high risk of bias (mainly for lack of blinding). The low risk of bias studies provided 2.6% of the weight in this analysis.

I Two of the studies9,10 with 60% of the weight in the meta-analysis reported rates for surgery that were unexpectedly high compared to current clinical practice (in those 2 studies 13% and 18% of patients respectively underwent surgery, while the proportion was 1.5% in the remaining 10 studies ), without an obvious explanation. Although this raises concern for indirectness in the population, interventions, and/or definition of the outcome, no obvious substantive differences were noted in these characteristics for these 2 studies as compared to other studies.

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11. Yüksel I, Ataseven H, Köklü S, et al. Intermittent versus continuous pantoprazole infusion in peptic ulcer bleeding: a prospective randomized study. Digestion 2008;78:39-43.

12. Sung JJ, Suen BY, Wu JC, et al. Effects of intravenous and oral esomeprazole in the prevention of recurrent bleeding from peptic ulcers after endoscopic therapy. Am J Gastroenterol 2014;109:1005-10

PICO 12

**12. PPI therapy after initial high-dose PPI therapy**

P: Patients with UGIB who received endoscopic hemostatic therapy and short-term (e.g., 3 day) high-dose PPI therapy

I: More than once-daily PPI

C: Once-daily PPI

O: Further bleeding, mortality

**12.1 Twice-Daily vs. Once-Daily PPI after Intensive PPI Therapy**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcomes | Effect |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Twice-daily PPI | Once-daily PPI | Relative(95% CI) | Difference (95% CI) |
| **Further bleeding** |  |  |
| RCT1 | Seriousa | Not applicable | Serious b | Not serious c | None | ⊕⊕⊝⊝**LOW** | **⊕⊕⊝⊝LOW** | 10/93 (10.8%) | 27/94 (28.7%) | RR=0.37(0.19-0.73) | -18%(-29 to -7%) |  |
| **Mortality** |  |
| RCT1 | Seriousa | Not applicable | Serious b | Very serious d | None | ⊕⊝⊝⊝**VERY LOW** | 3/93 (3.2%) | 8/94 (8.5%) | RR=0.38 (0.10-1.38) | -5%(-12 to 1%) |  |

**Footnotes:**

a High risk of bias due to lack of blinding and uncertain allocation concealment

b Only patients with Rockall score ≥6 were included, so not clearly generalizable to all patients in population defined in PICO

c Although modest number of events, not rated down because the optimal information size was only 154 (due to very large relative risk reduction of 63%).

d Small number of events and wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

**References**

1. Cheng HC, Wu CT, Chang WL, et al. Double oral esomeprazole after a 3-day intravenous esomeprazole infusion reduces recurrent peptic ulcer bleeding in high-risk patients: a randomised controlled study. Gut 2014;63:1864-72.

**Recurrent Ulcer Bleeding after Successful Endoscopic Hemostatic Therapy**

PICO 13

**13. Repeat endoscopy for recurrent bleeding after endoscopic therapy for bleeding ulcer**

P: Patients with recurrent ulcer bleeding in hospital after initial endoscopic therapy

I: Endoscopic therapy

C: Surgery or interventional radiology

O: Further bleeding, mortality; additional outcomes: adverse events, length of hospitalization

**13.1 Endoscopy vs. Surgery for Recurrent Bleeding after Endoscopic Therapy**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Summary of Findings** | **Comments** |
| Outcomes | Effect |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | Overall quality of evidence | Endoscopy | Surgery | Relative(95% CI) | Difference (95% CI) |
| **Further bleeding** |  |  |
| RCT1 | Serious a | Not applicable | No | Serious b | None | ⊕⊕⊝⊝**LOW** | **⊕⊕⊝⊝LOW** | 11/48 (22.9%) | 3/44 (6.8%) | RR=3.36 (1.00-11.26) | 16% (2 to 30%) |  |
| **Mortality** |  |
| RCT1 | Serious a | Not applicable | No | Very serious c | None | ⊕⊝⊝⊝**VERY LOW** | 5/48 (10.4%) | 8/44 (18.2%) | RR=0.57(0.20-1.62) | -8%, (-22 to 7%) |  |
| **Surgery for rebleeding or complication of assigned treatment** |  |
| RCT1 | Serious a | Not applicable | No | Serious b | None | ⊕⊕⊝⊝**LOW** | 13/48 (27.1%)  | 4/44 (9.1%) | RR=2.98(1.05-8.46) | 18%(3 to 33%) |  |
| **Days of hospitalization (median)** |  |
| RCT1 | Serious a | Not applicable | No | Serious d | None | ⊕⊕⊝⊝**LOW** | 10  | 11 |  |  | p = 0.59 |
| **Complications** |  |
| RCT1 | Serious a | Not applicable | No | Serious b | None | ⊕⊕⊝⊝**LOW** | 7/48 (14.6%)  | 16/44 (36.4%) | 0.40(0.18-0.88) | -22% (-39 to -4%) |  |

**Footnotes:**

a Lack of blinding and unclear sequence allocation generation; also choice of surgery left to surgeon so varied type of surgery.

b Small number of events and upper bound of 95% CI confidence interval crosses the clinical decision threshold between recommending and not recommending a strategy (i.e. clinical action may differ if the upper versus the lower boundary of the CI represented the truth).

c Small number of events and wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

d Results consistent with no effect as well as important increase or decrease in length of hospitalization

**References**

1. Lau JYW, Sung JJY, Lam YH, et al. Endoscopic retreatment compared with surgery in patients with recurrent bleeding after initial endoscopic control of bleeding ulcers. N Engl J Med 1999;340:751-6.

**Failure of Endoscopic Hemostatic Therapy for Bleeding Ulcers**

PICO 14

**14. Management of patients with bleeding ulcers with failure of endoscopic therapy.**

P: Patients with ulcer bleeding who have failure of endoscopic therapy (further (persistent or recurrent) bleeding)

I: Interventional radiology with transcatheter arterial embolization

C: Surgery

O: Further bleeding, mortality; additional outcomes: adverse events, length of hospitalization

**14.1 Transcatheter Arterial Embolization vs. Surgery after Failure of Endoscopic Therapy**

|  |  |  |
| --- | --- | --- |
| **Certainty Assessment** | **Effect (Embolization vs. Surgery)** | Comments |
| Studies | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Quality of Evidence | **Overall** Quality of Evidence | Relative (95% CI) |
| **Further bleeding** |
| SRMA of 11 studies1 | Very seriousa | Not seriousb | No | Not serious |  | ⊕⊝⊝⊝**VERY LOW** | ⊕⊝⊝⊝**VERY LOW** | OR=2.44 (1.77-3.36) | Rebleeding: N=209 |
| Cohort Study2 | Seriousc | Not applicable | No | Not serious |  | ⊕⊝⊝⊝**VERY LOW** | Adjusted HR=2.48 (1.33-4.62) |  |
| **Mortality** |  |
| SRMA of 13 studies1 | Very seriousa | Seriousb | No | Serious d |  | ⊕⊝⊝⊝**VERY LOW** | OR=0.77 (0.50-1.18) | Deaths: N=258 |
| Cohort Study2 | Seriousc | Not applicable | No | Serious d |  | ⊕⊝⊝⊝**VERY LOW** | Adjusted HR 30-day mortality = 0.70 (0.37-1.35) | Deaths: N=194 |
| **Further Intervention** |  |
| SRMA of 9 studies1 | Very seriousa | Seriousb | No | Not serious |  | ⊕⊝⊝⊝**VERY LOW** | OR=2.13 (1.21-3.77) | Further interventions: N=165 |
| Cohort Study2 | Seriousc | Not applicable | No | Not Serious |  | ⊕⊝⊝⊝**VERY LOW** | Adjusted HR=5.41 (2.49-11.76) |  |
| **Major complications** |  |
| SRMA of 6 studies1 | Very seriousa | Not seriousb | No | Not serious |  | ⊕⊝⊝⊝**VERY LOW** | OR=0.45 (0.30-0.67) | Complications: N=206 |
| Cohort Study2 | Seriousc | Not applicable | No | Serious e |  | ⊕⊝⊝⊝**VERY LOW** | 9/109 (8.3%) vs. 66/205 (32.2%)RR=0.26 (0.13-0.49) | Complications: N=75 |
| **Length of hospitalization** |  |
| Cohort Study2 | Seriousc | Not applicable | No | Not serious |  | ⊕⊝⊝⊝**VERY LOW** | Adjusted acceleration factor = 0.59 (0.45-0.77)[median days 8 vs. 16] |  |

**Footnotes:**

a Author assessment (Newcastle-Ottawa): all studies poor quality with high risk of bias

b Heterogeneity for mortality (p=0.05, I2=43%) and need for further intervention (P=0.02 I2=56%) but less so for further bleeding (p=0.41 I2=4%) and complications (P=0.24 I2=26%).

c Adjustment performed but impossible to fully adjust for important confounders

d Wide 95% CI that includes no effect as well as clinically important benefit and clinically important harm

e Small number of events

**References**

1. Tarasconi A, Baiocchi GL, Pattonieri V, et al. Transcatheter arterial embolization versus surgery for refractory non-variceal upper gastrointestinal bleeding: a meta-analysis. World J Emerg Surgery 2019;14:1-13.

2. Sverdén E, Mattsson F, Lindström D, et al. Transcatheter arterial embolization compared With surgery for uncontrolled peptic ulcer bleeding: A population-based cohort study. Ann Surg 2019;269:304-309