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# Canadian Association of Gastroenterology Clinical Practice Guideline for the Endoscopic Management of Nonvariceal Nonpeptic Ulcer Upper Gastrointestinal Bleeding

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**BACKGROUND & AIMS:** Nonvariceal, nonpeptic ulcer bleeding, arising from etiologies such as malignant tumors, Mallory-Weiss tears (MWTs), Dieulafoy's lesions, and gastric antral vascular ectasia, constitutes a significant and increasing proportion of upper gastrointestinal bleeding cases. These evidence-based guidelines, developed by the Canadian Association of Gastroenterology with international collaboration, are the first to specifically address the endoscopic management of these conditions, aiming to support patients, clinicians, and others in making informed decisions. **METHODS:** The Canadian Association of Gastroenterology formed a guideline panel with a balanced representation to minimize potential bias from conflicts of interest. The Cochrane Gut Group supported the guideline-development process, including conducting literature searches and performing systematic reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and adult patients. The Grading of Recommendations Assessment, Development and Evaluation approach was used, including developing the Grading of Recommendations Assessment, Development and Evaluation Evidence-to-Decision frameworks, which underwent public comment. **RESULTS:** The panel formulated 19 conditional recommendations for adult patients with nonvariceal, nonpeptic ulcer bleeding due to malignant tumors, MWTs, Dieulafoy's lesions, and gastric antral vascular ectasia. **CONCLUSIONS:** For patients with active bleeding from malignant tumors, the panel suggested topical hemostatic agents over conventional endoscopic hemostatic therapy; it also suggested the administration of oncologic therapy after the endoscopic intervention. In patients with active bleeding from MWTs (oozing and spurting), the panel suggested endoscopic band ligation or endoscopic through-the-scope clip over epinephrine injection alone. For nonbleeding MWTs with visible vessels, adherent clots, flat pigmented spots, or clean-based ulcers, the panel suggested against endoscopic hemostatic therapy. For Dieulafoy's lesions, the panel suggested mechanical modalities with endoscopic band ligation or through-the-scope clip, contact thermocoagulation, or injection of sclerosants over epinephrine injection alone. For patients with gastric antral vascular ectasia, the panel suggested endoscopic band ligation over argon plasma coagulation. **GUIDELINE ENDORSEMENT:** This guideline has been formally endorsed by leading international endoscopy societies: the American Society for Gastrointestinal Endoscopy, the European Society of Gastrointestinal Endoscopy, the Sociedad Interamericana de Endoscopía Digestiva, and the World Endoscopy Organization, as well as by the American Gastroenterological Association.

*Keywords:* Gastrointestinal Neoplasms; Mallory-Weiss Syndrome; Dieulafoy's Lesions; Gastric Antral Vascular Ectasia; Gastrointestinal Hemorrhage; Practice Guidelines; GRADE; Equity.

***Authors share co-first authorship.**

***Abbreviations used in this paper:*** **APC, argon plasma coagulation; ARR, absolute risk reduction; CAG, Canadian Association of Gastroenterology; DEP, Doppler endoscopic probe; DL, Dieulafoy's lesion; EBL, endoscopic band ligation; EtD, evidence to decision; GAVE, gastric antral vascular ectasia; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation; Hgb, hemoglobin; HR, hazard ratio; MD, mean difference; MWT, Mallory-Weiss tear; NVNPUB, nonvariceal nonpeptic ulcer bleeding; PICO, patient population, intervention, comparator, outcome; PUB, peptic ulcer bleeding; RCT, randomized controlled trial; RD, risk difference; RFA, radiofrequency ablation; RR, risk ratio; UGI, upper gastrointestinal; UGIB, upper gastrointestinal bleeding; THA, topical hemostatic agent; TTSC, through-the-scope clip.**



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Upper gastrointestinal bleeding (UGIB) accounts for more than 300,000 hospital admissions annually in the United States.[1] Although peptic ulcer disease causes 30%–50% of UGIB cases, there has been a notable rise in nonvariceal nonpeptic ulcer bleeding (NVNPUB), accounting for more than one-third to two-thirds of UGIB cases and, sometimes surpassing peptic ulcer bleeding (PUB).[2–7] NVNPUB can result from various causes, including malignant tumors, Mallory-Weiss tears (MWTs), Dieulafoy's lesions (DLs), gastric antral vascular ectasia (GAVE), esophagitis, gastritis, duodenitis, and other vascular lesions. Recent US data indicate a 30% decrease in hospitalizations for PUB, while hospitalizations for UGIB due to malignancy, DLs, and angiodysplasia increased by 50%, 33%, and 32%, respectively.[7]

Endoscopic hemostatic interventions play a crucial role in managing NVNPUB. Most previous guidelines on nonvariceal UGIB primarily focused on PUB, often overlooking or grouping other causes with peptic ulcers.[8–12] This guideline is the first to specifically address endoscopic management of NVNPUB, providing health care professionals with evidence-based strategies that address the distinct challenges posed by NVNPUB. This guideline was based on original systematic reviews of evidence and was conducted under the auspices of the Canadian Association of Gastroenterology (CAG) with international collaborators. The panel followed best practices for guideline development recommended by the Institute of Medicine and the Guidelines International Network.[13–16] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence and formulate recommendations.[17–23]

## Interpretation of Strong and Conditional Recommendations

The strength of a recommendation is categorized as either strong, indicated by the phrase "the guideline panel recommends . . . " or conditional, indicated by the phrase "the guideline panel suggests . . ." Table 1 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

## Recommendations

The list of recommendations is provided in Table 2.

## Values and Preferences

The guideline panel rated further bleeding as critical for decision making regarding malignant UGIB, MWTs, and DLs. This composite outcome includes the failure to achieve immediate hemostasis and any rebleeding. For GAVE, the panel rated the number of units of blood transfusions needed and changes in hemoglobin (Hgb) levels as critical for decision making, as this condition typically results in anemia related to chronic blood loss rather than acute bleeding. These outcomes are highly valued, and a strong emphasis is placed on interventions that can effectively address them.

## Explanations and Other Considerations

These recommendations also consider cost and cost-effectiveness, impact on health equity, acceptability, and feasibility.

**Table 1.** Interpretation of Strong and Conditional Recommendations

| Implications for | Strong recommendation | Conditional recommendation |
|---|---|---|
| Patients | Most individuals in this situation would want the recommended course of action, and only a small proportion would not. | The majority of individuals in this situation would want the suggested course of action, but many would not. |
| Clinicians | Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences. | Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences. |
| Policy makers | The recommendation can be adopted as policy in most situations. Adherence to this recommendation, according to the guideline, could be used as a quality criterion or performance indicator. | Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate. |
| Researchers | The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations. | This recommendation will likely be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional recommendation will help identify possible research gaps. |

**Table 2.** List of Recommendations With Strength of Recommendation and Certainty of Evidence

| Recommendation | Strength of recommendation and certainty of evidence |
|---|---|
| Malignant UGIB | |
| 1A | In patients with active bleeding from malignant UGI tumors, we suggest conventional endoscopic hemostatic therapy (eg, injection, thermal devices, mechanical devices, or a combination thereof) over no endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 1B | In patients with active bleeding from malignant UGI tumors, we suggest THAs over no endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 2 | In patients with active bleeding from malignant UGI tumors, we were unable to reach a recommendation for or against any specific type of conventional endoscopic hemostatic therapy over another. |
| 3 | In patients with active bleeding from malignant UGI tumors, we suggest THAs over conventional endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 4 | In patients with active bleeding from malignant UGI tumors, we suggest administering oncologic therapy after endoscopic hemostatic therapy rather than not providing oncologic therapy after endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| MWTs | |
| 5 | In patients with active bleeding from MWTs (spurting or oozing), we suggest endoscopic hemostatic therapy over no endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 6A | In patients with active bleeding from MWTs (spurting or oozing), we suggest EBL or endoscopic TTSC placement over epinephrine injection alone (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 6B | In patients with active bleeding from MWTs (spurting or oozing), we suggest EBL or endoscopic TTSC placement (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 7A | In patients with MWTs with nonbleeding visible vessels, we suggest against endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 7B | In patients with MWTs with nonbleeding adherent clots, we suggest against endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 7C | In patients with MWTs with nonbleeding clean-based ulcers or flat pigmented spots, we suggest against endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| DLs | |
| 8A | In patients with UGIB from DL, we suggest either EBL with or without epinephrine injection or endoscopic TTSC placement with or without epinephrine injection (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 8B | In patients with UGIB from DL, we suggest either mechanical devices (EBL or endoscopic TTSC placement) with or without epinephrine injection or contact thermal devices (heater probe and bipolar electrocoagulation) with or without epinephrine injection (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 8C | In patients with UGIB from DL, we cannot make a recommendation for or against the use of cap-mounted clips over conventional endoscopic hemostatic therapy. |
| 8D | In patients with UGIB from DL, we suggest either mechanical devices (EBL or endoscopic TTSC placement) with or without epinephrine injection or injection of sclerosants with or without epinephrine injection (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 9A | In patients with upper GI bleeding from DL, we suggest against epinephrine injection alone over mechanical devices (EBL or endoscopic TTSC placement) (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 9B | In patients with UGIB from DL, we suggest against epinephrine injection alone over thermal devices (heater probe, bipolar or multipolar electrocoagulation) (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| GAVE | |
| 10 | In patients with GAVE, we suggest against RFA over APC (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |
| 11 | In patients with GAVE, we suggest EBL over APC (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖). |

## Aim of This Guideline and Specific Objectives

This guideline aims to provide evidence-based recommendations for the endoscopic management of adults with NVNPUB, with a focus on malignant UGIB, MWTs, DLs, and GAVE. Other causes of NVNPUB have been excluded from this iteration. The target audience includes health care providers managing UGIB, patients, and decision makers. Policy makers involved in developing local, national, or international programs for optimizing the management of NVNPUB will also find these guidelines valuable. This document can also serve as a basis for adaptation by local, regional, or national guideline panels.

## Description of the Health Problems

Malignant UGIB is associated with high morbidity and mortality.[3,24,25] It can arise from primary tumors, locally invasive tumors from adjacent structures, or metastases. GI malignancies account for up to 5% of UGIB cases, with gastric cancer being the most common.[26–28] Bleeding can vary from occult to overt and may be the first sign of a malignancy.[26,27] Unfortunately, by the time bleeding is evident, metastatic disease is often already present, which significantly limits treatment options.[26,27,29] Endoscopic treatment presents unique challenges due to factors such as tumor friability and diffuse bleeding, which lack a clear therapeutic target. In addition, the patient's overall health status is often complicated by multiple comorbidities.

MWTs, often caused by forceful retching or vomiting, account for approximately 5%–15% of UGIB cases.[30,31] Although most bleeding from MWTs resolves spontaneously and has a relatively low death rate of 1%–3%, certain factors, such as active bleeding; advanced age; and significant comorbidities, can increase mortality risk.[3,7,32]

DL is characterized by an abnormally large submucosal artery eroding through a small mucosal defect.[33] Although most commonly located in the proximal stomach, DL can also occur anywhere in the GI tract.[34,35] Despite accounting for only 1%–2% of UGIB cases, DL is likely underrecognized due to its small size, subtle appearance, and intermittent bleeding.[36,37] Nevertheless, it can cause significant and recurrent bleeding, posing serious risks of morbidity, prolonged hospitalization, and mortality if not treated promptly.[37] Mortality rates have decreased from 80% to 4%–10% in recent years, likely due to advances in endoscopic management and reduced need for surgical intervention.[35,38,39]

GAVE is characterized by vascular dilation in the muscularis mucosa, predominantly in the antrum with a striped pattern, but it can also appear in other parts of the stomach with nodular or diffuse punctate patterns.[40] GAVE accounts for approximately 4% of nonvariceal UGIB cases and 6% of GIB in patients with cirrhosis.[41–43] Clinical presentations range from occult to overt bleeding, with up to 60% of patients remaining transfusion-dependent.[44,45] This condition is associated with various conditions, including liver disease and portal hypertension, chronic kidney disease, and connective tissue disorders.[41,42] Despite its impact, large population-based epidemiologic studies are lacking, and its prevalence remains unknown. A screening study in cirrhotic patients estimated a prevalence of 12%.[46] Furthermore, misdiagnosis of GAVE as portal hypertensive gastropathy, gastritis, or other conditions is common.[47,48] In the United States, hospitalizations for GAVE have increased by 75% over 11 years, particularly in cases without active bleeding.[41]

## Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the evidence following the GRADE approach.[21,49] The overall guideline-development process, including funding, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by CAG policies and procedures derived from the Guidelines International Network–McMaster Guideline Development Checklist and was intended to meet recommendations for trustworthy guidelines by Institute of Medicine and the Guidelines International Network.[13–16]

### *Organization, Panel Composition, Planning, and Coordination*

The CAG coordinated the work of this panel, with project oversight managed by a steering committee (A.B., L.L., G.L., F.T.) reporting to the CAG Guideline Committee. The CAG was also responsible for selecting and appointing members to the guideline panel and vetting and retaining methodologists (F.T., N.F., M.C., N.C.) to conduct systematic reviews and coordinate the guideline development process using the GRADE approach. Details on panel membership are provided in Appendix 1.

The international panel included gastroenterologists and a surgeon with clinical and research expertise on the guideline topic from Canada, the United States, Hong Kong, Thailand, Israel, Egypt, and Kuwait. It also included methodologists with expertise in evidence appraisal and guideline development. One of the panel co-chairs (A.B.) was a content expert and the other (F.T.) was an expert in guideline-development methodology. The panel also incorporated input from 2 patient representatives who reviewed and provided feedback on the patient population, intervention, comparator, outcome (PICO) questions and the recommendations. The panel's activities were facilitated through a combination of web-based tools (https://www.slido.com and www.gradepro.org) and online meetings.

### *Guideline Funding and Management of Conflicts of Interest*

The development of these guidelines was funded by the CAG, a nonprofit medical specialty society representing gastroenterologists. CAG staff members facilitated panel appointments and meetings, but did not participate in selecting guideline questions or formulating recommendations. The panelists volunteered their expertise and the methodologists received funding support from the CAG. Conflicts of interests for all participants were managed according to CAG policies, following the recommendations of the Institute of Medicine and the Guidelines International Network.[50,51] Before appointment to the panel, individuals disclosed financial and nonfinancial interests, which were reviewed by the CAG Guideline Committee to identify and manage potential conflicts, as detailed in Appendix 1.

**Table 3.** Clinical Questions Formulated and Prioritized

| Question no. | Question |
|---|---|
| Malignant UGIB | |
| 1 | Should patients with active bleeding from malignant UGI tumors receive endoscopic hemostatic therapy vs no endoscopic hemostatic therapy? |
| 2 | Should patients with active bleeding from malignant UGI tumors receive one conventional endoscopic hemostatic therapy vs another conventional endoscopic hemostatic therapy? |
| 3 | Should patients with active bleeding from malignant UGI tumors receive THAs vs conventional endoscopic hemostatic therapies? |
| 4 | Should patients with active bleeding from malignant UGI tumors receive oncologic therapy after endoscopic hemostatic therapy vs no oncologic therapy after endoscopic hemostatic therapy? |
| MWTs | |
| 5 | Should patients with active bleeding from MWTs (spurting or oozing) receive endoscopic hemostatic therapy vs no endoscopic hemostatic therapy? |
| 6 | Should patients with active bleeding from MWTs (spurting or oozing) receive one endoscopic hemostatic therapy vs another endoscopic hemostatic therapy? |
| 7 | Should patients with no active bleeding from MWTs (nonbleeding visible vessels, adherent clots, flat pigmented spots, clean-based ulcers) receive endoscopic hemostatic therapy vs no endoscopic hemostatic therapy? |
| DLs | |
| 8 | Should patients with UGIB from DL receive one endoscopic hemostatic therapy vs another endoscopic hemostatic therapy? |
| 9 | Should patients with UGIB from DL receive injection of epinephrine alone vs other endoscopic hemostatic therapies? |
| GAVE | |
| 10 | Should patients with GAVE receive one endoscopic hemostatic therapy vs another endoscopic hemostatic therapy? |
| 11 | Should patients with GAVE receive EBL vs other endoscopic hemostatic therapies? |

Recusal was used to manage conflicts of interest. Panel members with a current direct financial interest in commercial entities that could be impacted by the guidelines were recused from making judgments about relevant recommendations. The evidence-to-decision (EtD) framework for each recommendation specifies which individuals were recused. Methodologists with material interest in commercial entities potentially impacted by the guidelines were recused from performing systematic reviews or rating the certainty of evidence related to those products.

## Selection of Questions and Outcomes of Interest

The steering committee brainstormed the questions, which the panel prioritized, as outlined in Table 3. The questions address all types of endoscopic therapies with published studies relevant to the conditions in question, including randomized controlled trials (RCTs) and observational studies. Some questions have been divided into sub-questions to compare different modalities.

The panel selected outcomes of interest for each question *a priori*, following the GRADE approach.[52] For malignant UGIB, MWTs, and DLs, the panel rated further bleeding as critical for decision making. This composite outcome includes the failure to achieve immediate hemostasis and any rebleeding. An International Consensus Panel has emphasized the importance of using further bleeding as the primary end point for RCTs on UGIB management, highlighting its vital role as the primary clinical goal for patients with UGIB.[53] For GAVE, which commonly presents as chronic GIB leading to anemia,[54–56] the panel rated the number of units of blood transfusion and changes in Hgb levels as critical for decision making. Table 4 outlines the critical and important outcomes for all questions.

## Evidence Review and Development of Recommendations

The Cochrane Gut Group at McMaster University conducted systematic searches of the published English-language literature, including MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials from inception through March 6, 2024. Search strategies and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[57] flow diagram are included in Appendix 2. The search aimed to identify studies assessing any endoscopic hemostatic therapy for NVNPUB, including malignant UGIB, MWTs, DLs, and GAVE.

Methodologists performed duplicate screening, data extraction, and risk of bias assessment. RCTs, meta-analyses, and observational studies were sought to address the guideline questions. RCTs that included patients with nonvariceal UGIB were considered, provided they offered subgroup data specifically for the conditions. Observational studies with fewer than 10 patients for any specific type of endoscopic therapy were excluded to ensure the reliability and robustness of the evidence being synthesized. Evidence on values, preferences, and costs was also sought.

We performed our systematic reviews and assessed the risk of bias following the Cochrane Handbook for Systematic Reviews of Interventions.[58] The risk of bias was assessed at the outcome level using the Cochrane Collaboration's risk of bias tool for randomized trials or the modified Newcastle-Ottawa Scale for nonrandomized studies.[58,59] The certainty ("quality") of evidence was assessed for each outcome based on GRADE domains: risk of bias, imprecision, inconsistency, indirectness, risk of publication bias, presence of large effects, dose-response, and residual confounding. The certainty of the evidence was categorized as very low, low, moderate, or high.[19,20]

For each question, the methodologists prepared evidence profiles and Etd frameworks, summarizing the systematic review results (Appendices 3–6).[17,18,23] The EtD table addressed the magnitude of the effects of interventions, patients' values and preferences, the balance between desirable and undesirable effects, resource utilization, health equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables for accuracy and completeness.

During a 2-day online meeting, the panel developed recommendations based on the evidence summarized in the EtD frameworks. For each recommendation, the panel took an

**Table 4.** Critical or Important Outcomes for Decision Making

| Variable | Outcomes |
|---|---|
| Malignant UGIB | |
| 1–3 | Further bleeding (30-d): critical<br>Overall mortality (6-mo): important<br>Failure to achieve immediate hemostasis: important<br>Rebleeding (30-d): important<br>No. of units of blood transfusions needed: important<br>Length of hospitalization: important<br>Readmissions: important<br>Adverse effects – important |
| 4 | Further bleeding (30-d, 6-mo): critical (only 6-month)<br>Overall mortality (6-mo): critical<br>Failure to achieve immediate hemostasis: important<br>Rebleeding (30-d): important<br>No. of units of blood transfusions needed: important<br>Length of hospitalization: important<br>Readmissions: important<br>Adverse effects: important |
| MWTs | |
| 5–7 | Further bleeding (7-d, 30-d): critical (only 7-d)<br>Overall mortality: important<br>Failure to achieve immediate hemostasis: important<br>Rebleeding (7-d, 30-d): important<br>No. of units of blood transfusions needed: important<br>Length of hospitalization: important<br>Adverse effects: important |
| DL | |
| 8–9 | Further bleeding (7-d, 30-d): critical (only 7-d)<br>Failure to achieve immediate hemostasis: important<br>Overall mortality: important<br>Rebleeding (7-d, 30-d): important<br>Adverse effects: important<br>Additional hemostatic therapy (eg repeat endoscopic hemostatic therapy, radiologic embolization, surgery): important |
| GAVE | |
| 10–11 | Change in units of blood transfusions needed: critical<br>Change in Hgb level: critical<br>Overall mortality: important<br>Number of endoscopic sessions required for obliteration of lesions: important<br>Adverse effects: important |

individual patient perspective and reached a consensus on every domain of the EtD table.

Recommendations were agreed upon by consensus, with at least 75% voting agreement. The manuscript was prepared following the McMaster GRADE guidance for transparent and complete reporting of guidelines.[60] All panel members reviewed and approved the final guideline manuscript.

### *Interpretation of Strong and Conditional Recommendations*

According to the GRADE approach, recommendations are categorized as "strong" or "conditional." For strong recommendations, the words "the guideline panel recommends. . . " are used, and for conditional recommendations, "the guideline panel suggests . . ." Table 1 provides GRADE's interpretation of strong and conditional recommendations.

### *Document Review*

All panel members reviewed and revised the draft recommendations before making them available online on February 3, 2025, for external review by stakeholders, including allied organizations, medical professionals, patients, and the public. Comments were received, and although relevant feedback was addressed, the recommendations remain unchanged. On February 20, 2025, the CAG Guideline Committee confirmed adherence to the guideline-development process, and on February 25, 2025, the CAG Executive Board approved the submission of the guidelines for publication under the imprimatur of CAG. The guidelines were then subjected to the peer review process of *Gastroenterology*.

### *How to Use This Guideline*

This guideline is intended to aid clinicians in selecting endoscopic treatment options, while also supporting policy making, education, advocacy, and identifying future research needs. Patients may find them useful as well. It is not intended to define a standard of care. Clinicians should make decisions based on each patient's clinical presentation, ideally through a shared decision-making process that considers the patient's values and preferences. Decision making may be influenced by specific clinical settings and available resources. This guideline may not cover all suitable care methods, and recommendations may become outdated as new evidence emerges. Each recommendation includes statements about its underlying values and preferences, along with qualifying remarks that are essential for accurate interpretation and should be included when the guideline is quoted or translated. The guideline is further supported by EtD frameworks and summary-of-findings tables, enhancing their usability.

## Recommendations

### *Malignant Upper Gastrointestinal Bleeding*

**Question 1:** Should patients with active bleeding from malignant UGI tumors receive endoscopic hemostatic therapy vs no endoscopic hemostatic therapy?

**Recommendation 1A: In patients with active bleeding from malignant UGI tumors, we suggest conventional endoscopic hemostatic therapy (eg, injection, thermal devices, mechanical devices, or a combination thereof) over no endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Recommendation 1B: In patients with active bleeding from malignant UGI tumors, we suggest topical hemostatic agents (THAs) over no endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 1A. Conventional Endoscopy Hemostatic Therapy vs No Endoscopic Hemostatic Therapy*

**Evidence summary.** We found no RCTs or observational studies that directly addressed this question. Six

comparative cohort studies were excluded due to seriously biased comparisons between patients treated for active bleeding and those untreated due to inactive bleeding.[24–26,29,61,62] Twelve cohort studies provided data on the outcomes of treating malignant UGIB with various conventional endoscopic therapies, including injection therapy (ie, epinephrine, saline, sclerosant, ethanol, and fibrin glue), thermocoagulation (ie, argon plasma coagulation [APC], heater probe, bipolar devices, coagulation forceps, and Nd-YAG laser), and mechanical devices (through-the-scope clips [TTSCs]), either alone or in combination.[24–26,29,61–68] The majority of patients (62%) received APC in these studies.[24–26,29,61–68] Yet, most studies did not provide subgroup data for each intervention. The validity of subgroup comparisons was further compromised by the small sample sizes and selection bias present in these nonrandomized studies. Due to significant heterogeneity in populations, interventions, outcomes, duration of follow-up, and study designs, a proportional meta-analysis of these studies was deemed inappropriate and potentially misleading. Instead, we summarized the results as ranges and presented them in forest plots without pooled estimates following the recommendations of the Cochrane Non-Randomized Studies Methods Group.[58] These details, along with the EtD framework, are provided in Appendix 3.

**Benefits, harms, and burden.** Based on data from 12 single-arm cohort studies, outcomes for patients treated with conventional endoscopic therapies were variable: 30-day further bleeding occurred in 22%–87% of patients (approximately 50% for most studies), failure to achieve immediate hemostasis in 0%–69% (approximately 20% for most studies), 30-day rebleeding in 17%–53% (approximately 30% for most studies), and mortality in 13%–93%, with most studies reporting 30-day mortality.[24–26,29,61–68] Two studies reported 0% adverse effects in 81 patients treated with APC.[25,68]

Without comparative data, estimating the effects of conventional endoscopic therapies compared with no therapy was impossible. To address this, an expert evidence survey was conducted using the GRADE expert evidence approach.[69] The panel estimated that patients with active bleeding from malignant UGI tumors who do not receive endoscopic therapy have a risk of further bleeding of at least 85%, failure to achieve immediate hemostasis of at least 50%, and 30-day rebleeding of at least 35% for those who stopped bleeding spontaneously. The panel judged that conventional endoscopic hemostatic therapies likely have variable magnitudes of desirable and undesirable effects.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias, serious inconsistency, and serious imprecision.

**Other evidence-to-decision criteria and considerations.** There was no research evidence on patients' values and preferences in the context of malignant UGIB. The panel agreed, based on their experience, that patients place a high value on reducing further bleeding (critical outcome) to avoid prolonged or repeated hospitalizations, additional interventions, and decreased quality of life. However, the panel recognized possible variability and uncertainty in patients' values and preferences regarding blood transfusions and 6-month mortality, influenced by their overall prognosis and care goals. Patients may prefer less invasive procedures if their goal is comfort care, and those aiming for extended survival might choose more aggressive treatments. Costs may vary depending on the intervention. There was no research evidence on cost-effectiveness. The panel judged conventional endoscopic therapies as probably acceptable and feasible with no adverse impact on equity-deserving groups.

**Conclusions and research needs.** The panel judged that the balance of effects likely favors conventional endoscopic hemostatic therapy in patients with active bleeding from malignant UGI tumors. As a result, the panel issued a conditional recommendation for conventional endoscopic hemostatic therapies over no endoscopic hemostatic therapy, recognizing that the certainty of the evidence was very low. This conditional recommendation would be more applicable to tumors with spurting bleeding rather than those with diffuse oozing. When tumors are diffusely oozing over a large area, conventional endoscopic therapies can be challenging to apply, and some (eg, thermocoagulation and sclerosants) may lead to further tissue injury. Therefore, some patients with diffusely oozing tumors may not be suitable for conventional endoscopic hemostatic intervention. Future research should focus on well-designed RCTs or observational studies comparing conventional endoscopic therapy with no endoscopic therapy, potentially in combination with other hemostatic interventions, such as radiation, embolization, or surgery. In addition, research on patient values and preferences would enhance shared decision making.

### *Recommendation 1B. Topical Hemostatic Agents vs No Endoscopic Hemostatic Therapy*

**Evidence summary.** We found no RCTs that directly addressed this question.

Nineteen studies provided single-arm cohort-type data that addressed this question, including 4 RCTs and 15 observational studies.[70–83] Fourteen studies exclusively used TC-325 (588 patients),[70–83] and others involved Endoclot (15 patients),[84–86] Ankaferd Blood Stopper (10 patients),[87] and UI-EWD (41 patients).[88] Despite the differences in composition, all of these agents function as mechanical barriers to control bleeding, justifying their inclusion in pooled proportional meta-analyses. These results, along with the EtD framework, are detailed in Appendix 3.

**Benefits.** A comparative cohort study suggested that THAs, compared with no endoscopic therapy, may reduce 30-day rebleeding (risk ratio [RR], 0.67; 95% CI, 0.14–3.17; absolute risk reduction [ARR], 99 fewer per 1000; 95% CI, 258 fewer to 651 more) and 6-month mortality (RR, 0.33; 95% CI, 0.04–2.69; ARR, 201 fewer per 1000; 95% CI, 288 fewer to 507 more), but these estimates were very imprecise.[80]

Thirty-day further bleeding with THA was reported in 18 studies, with a pooled proportion of 26% (95% CI, 20% to 32%).[63,70–85,88] Failure to achieve immediate hemostasis was reported by 19 studies, with a pooled proportion of 5% (95% CI, 3%–7%).[63,70–85,87,88] Thirty-day rebleeding was reported by 18 studies, with a pooled proportion of 23% (95% CI, 18%–28%).[63,70–85,88] Mortality was reported by 13 studies, with a pooled proportion of 29% (95% CI, 20%–39%).[63,70,72,73,75,77–82,84,88] Most studies reported 30-day mortality, and 5 reported 6-month mortality.[70,73,79,81,88] Most deaths were not related to GIB. Estimating the effects of THA vs no endoscopic therapy was challenging due to limited comparative data. To address this, expert survey results from PICO question 1A were applied, and the panel concluded that THA likely has large desirable effects over no endoscopic therapy.

**Harms and burden.** A comparative cohort study suggested THA, compared with no endoscopic therapy, may increase blood transfusions (MD, 5.60 units; 95% CI, 4.59 fewer to 15.79 more units) and length of hospitalization (MD, 4.40 days; 95% CI, 10.85 fewer to 19.65 more days).[80] However, the data were skewed, and these outcomes can be subjective, influenced by factors such as the health system's structure, institutional protocols, clinical judgment, and patient-specific factors.[80] Few studies reported adverse effects related to THA, but a systematic review of THAs in UGIB, including patients with malignant UGIB, found a pooled adverse event rate of 2% (95% CI, 1%–3%), with abdominal distention and bleeding being observed most frequently.[89] Serious complications like perforation were uncommon, occurring in only 3 of 2111 patients (0.14%).[89] The panel judged that THA likely has moderate undesirable effects over no endoscopic therapy.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and serious imprecision.

**Other evidence-to-decision criteria and considerations.** No research evidence was available on patients' values and preferences, but the panel assumed that avoiding further bleeding is critical to patients. The panel considered the cost of THA to be high. There was no research evidence on the cost-effectiveness of THA compared with no endoscopic therapy. The panel judged THA probably acceptable with no adverse impact on equity-deserving groups, but its feasibility may vary due to access challenges in some countries.

**Conclusions and research needs.** The panel judged that the balance of effects likely favors THA in patients with active bleeding from malignant UGI tumors (oozing or spurting). Thus, the panel issued a conditional recommendation for THA over no endoscopic hemostatic therapy, recognizing the very low certainty of the evidence, which was based predominantly on TC-325. If TC-325 is chosen as a THA, it is crucial that TC-325 be applied to actively bleeding lesions only. The panel highlighted the need for more comparative studies, potentially in combination with other hemostatic interventions, such as radiation, embolization, or surgery. Because most evidence was derived from TC-325, further research on other THAs is needed.

**Question 2:** Should patients with active bleeding from malignant UGI tumors receive one conventional endoscopic hemostatic therapy vs another conventional endoscopic hemostatic therapy?

**Recommendation 2: In patients with active bleeding from malignant UGI tumors, we were unable to reach a recommendation for or against any specific type of conventional endoscopic hemostatic therapy over another.**

### *Recommendation 2. Specific Type of Conventional Endoscopic Therapy vs Another Type of Conventional Endoscopic Therapy*

**Evidence summary.** We did not find any studies that directly compared various conventional endoscopic hemostatic therapies with each other.

**Conclusions and research needs.** Due to the lack of evidence, the panel was unable to reach a recommendation for or against any specific type of conventional endoscopic therapy over another in patients with active bleeding from malignant UGI tumors. Because current evidence suggests that THA may be more effective than conventional hemostatic therapies for malignant UGIB, the panel did not consider clinical trials comparing conventional endoscopic therapies a high research priority.

**Question 3:** Should patients with active bleeding from malignant UGI tumors receive THAs vs conventional endoscopic hemostatic therapies?

**Recommendation 3: In patients with active bleeding from malignant UGI tumors, we suggest THAs over conventional endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 3. Topical Hemostatic Agents vs Conventional Endoscopic Hemostatic Therapy*

**Evidence summary.** We identified 2 systematic reviews that indirectly addressed this question.[89,90] One review performed proportional meta-analyses of 16 studies that provided single-arm cohort-type data on THA in malignant GIB.[90] The other review assessed THA in UGIB of any etiology but provided subgroup analyses for malignancy-related bleeding, including data from 2 RCTs.[89] An individual patient data meta-analysis, published after our search period, included 3 RCTs and found TC-325 more effective than conventional endoscopic therapy in malignant GIB.[91]

We conducted a systematic review that included 4 RCTs.[73,76,77,79] Three RCTs compared TC-325 with

conventional endoscopic hemostatic therapies for malignancy-related GIB, while the fourth RCT focused on acute nonvariceal UGIB and provided subgroup data for malignancy-related cases.[73,76,77,79] Two RCTs included both upper and lower GI tumors.[73,79] Most (81.1%) patients in the 4 RCTs had UGI tumors. All RCTs evaluated TC-325, with none examining other THAs. The conventional endoscopic hemostatic therapies for comparison included injection techniques, contact and noncontact thermal coagulation methods, and mechanical devices. However, no subgroup data were provided for these interventions.

We found 1 retrospective comparative cohort study that compared THA (ie, TC-325 or Endoclot) with conventional endoscopic hemostatic therapy (ie, epinephrine injection combined with APC and/or TTSCs) in patients with GIB and reported subgroup data on malignant bleeding.[84]

The EtD framework is available in Appendix 3.

**Benefits.** Meta-analyses of 4 RCTs suggested that TC-325, when compared with conventional endoscopic hemostatic therapies, may reduce 30-day further bleeding (RR, 0.31; 95% CI, 0.08 to 1.23; ARR, 296 fewer per 1000; 95% CI, 394 fewer to 99 more), failure to achieve immediate hemostasis (RR, 0.10; 95% CI, 0.03 to 0.37; ARR, 231 fewer per 1000; 95% CI, 249 fewer to 162 fewer), 30-day rebleeding (RR, 0.50; 95% CI, 0.14 to 1.77; ARR, 119 fewer per 1000; 95% CI, 205 fewer to 183 more), and blood transfusions (MD, –0.09 units; 95% CI, –0.93 to 0.74 units), but these estimates were very imprecise.[73,76,77,79] THA appeared to have little or no impact on 6-month mortality (RR, 0.94; 95% CI, 0.69 to 1.29, ARR, 23 fewer per 1000; 95% CI, 118 fewer to 110 more).[73,76,77,79]

One comparative cohort study also showed that THA may reduce 30-day further bleeding (RR, 0.82; 95% CI, 0.42–1.60; ARR, 120 fewer per 1000; 95% CI, 387 fewer to 400 more) and failure to achieve immediate hemostasis (RR, 0.07; 95% CI, 0.0046–1.13; ARR, 543 fewer per 1000; 95% CI, 581 fewer to 76 more), but these estimates were very imprecise.[84]

The panel judged that THA likely has large desirable effects compared with conventional endoscopic hemostatic therapy.

**Harms and burden.** Compared with conventional endoscopic hemostatic therapies, THA may increase the length of hospitalization (MD, 4.28 days; 95% CI, –0.27 to 8.82 days).[73,76,79] Two RCTs reported more adverse effects associated with THA (RR, 1.27; 95% CI, 0.83 to 1.94; ARR, 53 more per 1000; 95% CI, 33 fewer to 183 more).[76,77] However, these estimated effects were very imprecise. A systematic review of THAs in UGIB, including patients with malignant GIB, found a pooled adverse event rate of 2% (95% CI, 1% to 3%).[89]

A comparative cohort study suggested that THA may increase 30-day rebleeding (RR, 6.55; 95% CI, 0.93–46.12; ARR, 462 more per 1000; 95% CI, 6 fewer to 1000 more), but the estimate was very imprecise.[84] Notably, the 30-day rebleeding outcome may be affected by other hemostatic therapies, such as embolization, radiation, and surgery. Due to inherent selection bias in this observational study, the panel prioritized the effect estimates from the systematic review of 4 RCTs.[73,76,77,79]

The panel judged that THA likely has moderate undesirable effects compared with conventional endoscopic hemostatic therapy.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias, serious inconsistency, and very serious imprecision. The evidence was not downgraded for indirectness because most patients had bleeding from UGI tumors, as opposed to lower GI tumors.

**Other evidence-to-decision criteria and considerations.** No research evidence existed on patients' values and preferences, but the panel assumed that avoiding further bleeding was critical for decision making for patients. A cost minimization study published after our search period found that using THA compared with standard endoscopic therapy resulted in a cost-saving of US$1613 for malignant UGIB, considering device-related costs, incremental facility costs, and additional physician and staff member time.[92] In addition, a cost-utility analysis published later also found that using TC-325 as first-line treatment for malignant GIB in the United Kingdom resulted in a cost savings of £245.88 compared with standard endoscopic therapy.[93] The panel judged THA likely to be acceptable, with no adverse impact on equity-deserving groups, although its feasibility may vary due to access challenges in some countries. Conclusions and research needs. The panel judged that the balance of effects likely favors THA in patients with active bleeding (oozing or spurting) from malignant UGI tumors. The data on hospitalization length were skewed and may not be generalizable to all settings. As a result, the panel prioritized the potential benefits of reducing further bleeding over the potential burden and costs. Therefore, the panel issued a conditional recommendation for THA over conventional endoscopic hemostatic therapy, recognizing the very low certainty of the evidence, which was predominantly based on TC-325. The panel emphasized the need for more comparative studies to increase the certainty of the evidence. In addition, RCTs should compare the efficacy and safety of THAs with other nonendoscopic hemostatic therapies.

**Question 4:** Should patients with active bleeding from malignant UGI tumors receive oncologic therapy after endoscopic hemostatic therapy vs no oncologic therapy after endoscopic hemostatic therapy?

**Recommendation 4: In patients with active bleeding from malignant UGI tumors, we suggest administering oncologic therapy after endoscopic hemostatic therapy rather than not providing oncologic therapy after endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 4. Oncologic Therapy vs No Oncologic Therapy After Endoscopic Hemostatic Therapy*

**Evidence summary.** We defined oncologic therapies as surgery, chemotherapy, and radiation therapy. The goals of these therapies can vary based on cancer type, stage, and the patient's overall health, but generally include curative intent, disease control, symptom management, palliative care, prolongation of survival, and prevention of complications, such as bleeding. Although radiologic embolization is not typically considered a primary oncologic therapy for UGI cancers, it can play a crucial role in a multimodal approach.

We did not find any RCTs addressing this question directly. However, there were observational data from an RCT and a multicenter retrospective cohort study.[79,81] In the RCT, patients with malignant GI bleeding were randomized to receive TC-325 or standard endoscopic treatment.[79] The proportion of patients undergoing additional nonendoscopic hemostatic or oncologic treatments, such as surgery, chemotherapy, radiation, embolization, or a combination thereof, within 1 month after the initial endoscopy was similar in the 2 arms (50.9% in the TC-325 arm vs 62.7% in the standard endoscopic treatment arm).[79] The high rate of additional treatment was likely due to the good performance status of the included patients (Eastern Cooperative Oncology Group score 0–2).[79] Both studies reported on 6-month overall mortality (critical outcome) and 30-day rebleeding, but not on 6-month further bleeding (critical outcome).[79,81] No studies provided direct evidence of adverse effects from oncologic therapy after endoscopic hemostatic therapy compared to without it. Three systematic reviews of noncomparative cohort studies provided indirect evidenfce on the toxicity of palliative radiotherapy for symptomatic locally advanced gastric cancer, chemotherapy in advanced gastric cancer, and complications after surgical resection in patients with gastric cancer.[94–96]

The EtD framework is available in Appendix 3.

**Benefits.** In a post-hoc observational analysis of an RCT, multivariable analysis identified the Charlson comorbidity index (hazard ratio [HR], 1.17; 95% CI, 1.05–1.32) and the receipt of additional nonendoscopic hemostatic treatments or oncologic treatments, such as surgery, chemotherapy, radiation, embolization, or a combination of these (HR, 0.16; 95% CI, 0.06–0.43), as independent predictors of 6-month survival, after adjustment for Eastern Cooperative Oncology Group score, Glasgow-Blatchford score, and upper GI lesions; TC-325 application was not an independent predictor.[79] Receiving additional nonendoscopic hemostatic treatments or oncologic treatments did not predict 30-day rebleeding (HR, 1.1; 95% CI, 0.24–5.06).[79]

In the retrospective cohort study, factors associated with 6-month survival included low Eastern Cooperative Oncology Group scores 0–2 (HR, 0.14; 95% CI, 0.04–0.47); cancer stage I–III (HR, 0.31; 95% CI, 0.01–0.96); and receipt of definitive hemostatic treatments, including surgery, chemotherapy, radiotherapy, or radiologic embolization (HR, 0.24; 95% CI, 0.09–0.59), after adjusting for comorbidity, type of cancer bleeding, and coagulopathy.[81]

However, these observational analyses are prone to residual confounding, as the comparison was not randomized. The association between oncologic treatments after endoscopic hemostatic therapy and improved 6-month survival may be confounded by baseline health and cancer stage. Nevertheless, the panel judged that oncologic therapies likely have large desirable effects over no oncologic therapies.

**Harms and burden.** A systematic review of 7 cohort studies involving 161 patients with symptomatic locally advanced gastric cancer found grade 3 to 4 toxicities in up to 15% of those treated with radiotherapy alone and up to 25% with chemoradiotherapy.[95] Another systematic review of 60 RCTs involving 11,698 patients receiving systemic chemotherapy for advanced gastric cancer reported treatment discontinuation due to toxicity ranging from 8% to 21%.[96] In addition, a systematic review of single-arm cohort studies including 32,067 patients who underwent gastrectomy for gastric cancer reported postoperative complication rates between 12.5% and 51.0%, with infectious complications, anastomotic leakage, and pneumonia being the most common.[94] The panel judged that oncologic therapies likely have moderate undesirable effects over no oncologic therapies.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias, serious indirectness from different types and early stages of GI cancers, and the inclusion of both oncologic treatments and radiologic embolization as the intervention, as well as very serious imprecision.

**Other evidence-to-decision criteria and considerations.** There was no research evidence on patients' values and preferences regarding oncologic therapies, but the panel assumed patients might have variable views on adverse effects from these therapies, particularly when considering improving quality of life vs increasing survival.[97,98] In the context of malignant GI bleeding, patients may choose interventions that align with their personal goals—opting for less invasive procedures if prioritizing quality of life or more aggressive treatments for prolonged survival. Therefore, engaging patients in shared decision making is crucial. The cost of oncologic therapies can vary widely due to factors such as tumor location, specific treatments, and individual patient circumstances (eg, staging and comorbidities). No data existed on the cost-effectiveness of oncologic therapies after endoscopic hemostatic therapies. Although the panel judged that oncologic therapies were probably acceptable and feasible, they could increase inequity due to cancer health disparities. Factors such as race, gender, age, geography, socioeconomic status, cultural beliefs, social support, and health literacy could impact equitable access to these treatments.[99] To address cancer health disparities, it is crucial to ensure equitable access to treatment for all populations. This involves culturally sensitive community outreach, policy changes to reduce socioeconomic barriers, and investment in research focused on underserved groups.[99]

**Conclusions and research needs.** Although endoscopic therapies may reduce further bleeding from malignant UGI tumors in the short term, they appear to have little or no benefit by themselves on long-term mortality. For patients with active bleeding from malignant UGI tumors, the panel determined that oncologic therapies after endoscopic hemostatic therapy likely offer a net benefit, despite the very low certainty of the evidence. As a result, the panel issued a conditional recommendation in favor of administering oncologic therapy after endoscopic hemostatic therapy, as opposed to not providing it. This conditional recommendation placed a higher value on the potential reduction in 6-month mortality (critical outcome) over the potential burdens, harms, costs, and negative impact on equity. The panel emphasized a patient-centered, multidisciplinary approach to decision making, as optimal oncologic care requires collaboration among gastroenterologists, oncologists, surgeons, radiologists, and palliative care specialists. Patients should be involved in discussions about personalized treatment risks and benefits. Given the ethical and practical challenges of conducting an RCT on this topic, the panel emphasized the need for well-designed observational studies to determine optimal timing for oncologic therapy and called for more comparative studies to strengthen the evidence.

## *Mallory Weiss Tears*

**Question 5:** Should patients with active bleeding from MWTs (spurting or oozing) receive endoscopic hemostatic therapy vs no endoscopic hemostatic therapy?

**Recommendation 5: In patients with active bleeding from MWTs (spurting or oozing), we suggest endoscopic hemostatic therapy over no endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 5. Endoscopic Hemostatic Therapy vs No Endoscopic Hemostatic Therapy*

**Evidence summary.** We identified 2 RCTs that addressed this question. One included patients with UGIB from MWTs with "active bleeding" or nonbleeding visible vessels, comparing epinephrine and polidocanol injections with no endoscopic hemostatic therapy.[100] Only the "active bleeding" subgroup was included in our systematic review.[100] Another RCT included patients with UGIB and provided data on a subgroup of patients with MWTs with spurting or oozing bleeding, comparing multipolar electrocoagulation with no endoscopic hemostatic therapy.[101] No study provided data for further bleeding (critical outcome). One study reported failure to achieve immediate hemostasis,[101] and the other provided data for rebleeding.[100] All rebleeding occurred within 7 days. To avoid double-counting 7-day and 30-day outcomes, we included the rebleeding outcomes as 7-day results only. This approach was based on our *a priori* decision that 7-day further bleeding was the critical outcome. One study provided data for the length of hospitalization.[100] Both studies provided data on adverse effects.[100,101] Only 2 outcomes—blood transfusions and 30-day mortality—could be pooled for meta-analyses.

Four comparative cohort studies evaluated endoscopic hemostatic therapy vs no endoscopic hemostatic therapy in patients with UGIB due to MWT.[102–105] Meta-analyses of these studies were deemed inappropriate as they compared patients with active bleeding who received endoscopic therapy to those without active bleeding who did not receive endoscopic treatment.

The EtD framework is available in Appendix 4.

**Benefits.** Meta-analyses of 2 RCTs suggested that endoscopic hemostatic therapy, compared with no endoscopic hemostatic therapy, may reduce failure to achieve immediate hemostasis (RR, 0.06; 95% CI, 0.004 to 0.91; ARR, 823 fewer per 1000; 95% CI, 871 fewer to 79 fewer), 7-day rebleeding (RR, 0.20; 95% CI, 0.03 to 1.58; ARR, 174 fewer per 1000; 95% CI, 211 fewer to 126 more), blood transfusions (MD, –2.20 units; 95% CI, –5.23 to 0.84 units), and length of hospitalization (MD, –2.10 days; 95% CI, –2.20 to 2.00 days), but these effects were very imprecise.[100,101] Endoscopic hemostatic therapy may have little or no impact on 30-day mortality (RR, 0.24; 95% CI, 0.03 to 2.05; ARR, 58 fewer per 1000; 95% CI, 75 fewer to 81 more), but the effect was very imprecise.[100,101] Given the natural history of MWT with relatively low rebleeding rates, the panel prioritized failure to achieve immediate hemostasis over 7-day rebleeding and judged that endoscopic hemostatic therapy likely has large desirable effects compared with no endoscopic hemostatic therapy.

**Harms and burden.** Both RCTs reported no adverse effects, with or without endoscopic hemostatic therapy, making relative and absolute effects nonestimable.[100,101] The panel judged that endoscopic hemostatic therapy likely has trivial undesirable effects. This assessment was also supported by indirect evidence from PUB.[8,11]

Certainty in the evidence of effects. Very low certainty of evidence due to serious risk of bias and very serious imprecision.

**Other evidence-to-decision criteria and considerations.** There was no research evidence on patients' values and preferences in the context of MWTs. However, the panel assumed there is probably no important uncertainty or variability in how much patients value the main outcomes, such as avoiding failure to achieve immediate hemostasis or rebleeding. The costs of endoscopic hemostatic therapy were considered moderate. Although cost-effectiveness studies were lacking, the panel considered endoscopic hemostatic therapy for actively bleeding MWTs as likely cost-effective by achieving immediate hemostasis, reducing rebleeding rates, and decreasing blood transfusions and length of hospitalization. The panel judged endoscopic hemostatic therapy as likely acceptable and feasible with no adverse impact on equity-deserving groups.

**Conclusions and research needs.** For patients with active bleeding (oozing or spurting) from MWTs, the panel judged that endoscopic hemostatic therapy likely offers a net benefit over no endoscopic hemostatic therapy, despite very low certainty of evidence. Therefore, the panel issued a conditional recommendation for endoscopic hemostatic therapy over no endoscopic hemostatic therapy. The panel highlighted the need for more comparative studies to increase the certainty of the evidence. In addition, future RCTs should compare the efficacy and safety of different endoscopic hemostatic therapies and stratify randomization based on stigmata.

**Question 6:** Should patients with active bleeding from MWTs (spurting or oozing) receive one endoscopic hemostatic therapy vs another endoscopic hemostatic therapy?

**Recommendation 6A: In patients with active bleeding from MWTs (spurting or oozing), we suggest EBL or endoscopic TTSC placement over epinephrine injection alone (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Recommendation 6B: In patients with active bleeding from MWTs (spurting or oozing), we suggest EBl or endoscopic TTSC placement (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 6A. Mechanical Modalities (Endoscopic Band Ligation/Endoscopic Through-the-Scope Clip Placement) vs Epinephrine Injection Alone*

**Evidence summary.** We identified 3 RCTs that addressed this question.[103,106,107] Two studies included only patients with active bleeding stigmata (spurting or oozing),[106,107] and 1 study included both active and nonactive bleeding stigmata, but provided subgroup data for active bleeding stigmata.[103] All 3 studies reported further bleeding, rebleeding, and overall mortality.[103,106,107] Two studies reported a follow-up period of 30 days, noting that all rebleeding occurred within 7 days.[106,107] One study did not specify a follow-up period or the timing of rebleeding.[103] To avoid double-counting 7-day and 30-day outcomes, we considered all rebleeding and further bleeding outcomes as 7-day outcomes. One study reported failure to achieve immediate hemostasis and length of hospitalization.[107] Two studies reported units of blood transfused and adverse effects.[106,107]

No comparative cohort studies addressing this question were identified.

We also conducted proportional meta-analyses of single-arm cohort-type data from 7 studies on EBL/TTSC and 4 studies on epinephrine injection alone.[103,105–111] The results of the proportional meta-analyses were provided as supplementary data in the Evidence Profile Table, but were not included in the EtD framework due to the absence of direct comparison. The EtD framework is in Appendix 4.

**Benefits.** Meta-analyses of 3 RCTs suggested that EBL/TTSC, compared with epinephrine injection alone, may reduce the risk of 7-day further bleeding (RR, 0.32; 95% CI, 0.06–1.64; ARR, 95 fewer per 1000; 95% CI, 131 fewer to 89 more) and 7-day rebleeding (RR, 0.31; 95% CI, 0.03–3.13; ARR, 80 fewer per 1000; 95% CI, 103 fewer to 248 more), with no significant subgroup differences among EBL, TTSC, or EBL/TTSC.[103,106,107] However, these estimates were very imprecise due to small sample sizes and very low event rates.[103,106,107] Due to zero events in the EBL/TTSC group for failure to achieve immediate hemostasis, calculating the RR and CI with continuity corrections introduced instability and potential bias.[107] However, when considering the opposite outcome (immediate hemostasis), EBL/TTSC appeared to have no impact compared with epinephrine injection alone (RR, 1.01; 95% CI, 0.94–1.09).[107] Thirty-day mortality was not estimable due to double-zero events.[103,106,107] Overall, the panel judged that EBL/TTSC likely has moderate desirable effects compared with epinephrine injection alone.

**Harms and burden.** Compared with epinephrine injection, EBL/TTSC may increase blood transfusions (MD, 0.85 units; 95% CI, −0.34 to 2.04 units) and length of hospitalization (MD, 0.80 days; 95% CI, 0.13 to 1.47 days).[106,107] These estimates were very imprecise and were not considered clinically meaningful by the panel. In addition, the outcomes related to blood transfusion requirements and length of hospitalization can be subjective and influenced by individual clinical practices. We were unable to assess the adverse effects of EBL/TTSC compared with epinephrine injection alone due to double-zero events.[106,107] The panel judged that EBL/TTSC likely has trivial undesirable effects compared with epinephrine injection alone.

Certainty in the evidence of effects. Very low certainty of evidence due to serious risk of bias and very serious imprecision.

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. Costs of EBL/TTSC were considered moderate, but no studies have assessed its cost-effectiveness compared with epinephrine injection alone in MWT. The panel judged EBL/TTSC as likely acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with active bleeding from MWT (oozing or spurting), the panel judged that EBL/TTSC likely offers a net benefit over epinephrine injection alone, despite the evidence being of very low certainty. This conditional recommendation placed a higher value on the potential benefits of reducing 7-day further bleeding than the potential burden and costs. The panel stressed the importance of conducting more comparative studies to increase the certainty of the evidence. In addition, future RCTs should investigate how different stigmata (oozing, spurting) and the size of MWT respond to each intervention. Cost-effectiveness analyses should also be performed to assess the economic impact of each treatment option.

### *Recommendation 6B. Endoscopic Band Ligation vs Endoscopic Through-the-Scope Clip Placement*

**Evidence summary.** We found 1 RCT and 1 comparative cohort study that addressed this question.[108,112] Both studies reported further bleeding and all of the important outcomes.[108,112] Because all rebleeding occurred within 7 days, we included all rebleeding and further bleeding outcomes as 7-day outcomes.

We also conducted proportional meta-analyses using single-arm cohort-type data from 5 studies on EBL and 5 studies on TTSC.[103,106–112] The results were provided as supplementary data in the Evidence Profile Table, but were not included in the EtD framework due to the lack of direct comparative data. The EtD framework is in Appendix 4.

**Benefits, harms, and burden.** Based on 1 RCT, the relative and absolute effects of EBL compared with TTSC on 7-day further bleeding and 7-day rebleeding were highly uncertain (RR, 2.10; 95% CI, 0.21 to 21.39; ARR, 52 more per 1000; 95% CI, 38 fewer to 971 more).[108] The relative effects for failure to achieve immediate hemostasis, overall mortality, and adverse effects were not estimable due to double-zero events.[107] For "immediate hemostasis," EBL appeared to have no impact compared with TTSC (RR, 1.00; 95% CI, 0.91 to 1.10).[108] The estimates for blood transfusions (MD, 1.30 units; 95% CI, –0.36 to 2.96 units) and length of hospitalization (MD, 0.60 days; 95% CI, –2.02 to 3.22 days) were very imprecise and were not deemed clinically meaningful by the panel.[108]

A comparative cohort study also found highly uncertain effects of EBL compared with TTSC on 7-day further bleeding and 7-day rebleeding (risk difference [RD], –0.19; 95% CI, –0.34 to 0.03; ARR, 190 fewer per 1000; 95% CI, 340 fewer to 30 more).[112] The relative effects for failure to achieve immediate hemostasis, overall mortality, and adverse effects were not estimable due to double-zero events.[112] EBL appeared to have no impact on "immediate hemostasis" compared with TTSC (1.00; 95% CI, 0.95 to 1.06).[112] For units of blood transfused, the MD was 0.00 (95% CI, –1.31 to 1.31)[112] and for the length of hospitalization, the MD was –0.10 (95% CI, –1.67 to 1.47).[112]

Due to the low event rates and the fragility of results in both the RCT and observational study, the panel judged that there was very serious imprecision, rendering the relative and absolute effects of EBL compared with TTSC for active bleeding MWT highly uncertain. Nevertheless, both EBL and TTSC appeared to be highly effective in achieving "immediate hemostasis" with low rates of failure to achieve immediate hemostasis, 7-day rebleeding and 7-day further bleeding (critical outcome).

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and very serious imprecision.

**Other evidence-to-decision criteria and considerations.** The panel assumed there is no important uncertainty or variability in how patients value the critical outcome of avoiding further bleeding. The panel considered the relative costs negligible. No published cost-effectiveness analyses were available. The panel judged EBL compared with TTSC as probably acceptable and feasible and unlikely to negatively affect equity-deserving groups.

**Conclusions and research needs.** For patients with active bleeding from MWT (oozing or spurting), the panel could not determine whether the balance of effects favored EBL or TTSC due to the very low certainty of the evidence. Consequently, the panel made a conditional recommendation for either EBL or TTSC. The panel emphasized the need for more comparative studies to increase the certainty of the evidence.

**Question 7:** Should patients with no active bleeding from MWTs (nonbleeding visible vessels, adherent clots, flat pigmented spots, clean-based ulcers) receive endoscopic hemostatic therapy vs no endoscopic hemostatic therapy?

**Recommendation 7A: In patients with MWTs with nonbleeding visible vessels, we suggest against endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Recommendation 7B: In patients with MWTs with nonbleeding adherent clots, we suggest against endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Recommendation 7C: In patients with MWTs with nonbleeding clean-based ulcers or flat pigmented spots, we suggest against endoscopic hemostatic therapy (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 7A. Endoscopic Hemostatic Therapy vs No Endoscopic Hemostatic Therapy in Non-bleeding Visible Vessels; and Recommendation 7B. Endoscopic Hemostatic Therapy vs No Endoscopic Hemostatic Therapy in Adherent Clots*

**Evidence summary.** We found 1 RCT and 2 retrospective cohort studies that addressed the above 2 questions.[100,103,104] The RCT included patients with MWT with nonbleeding visible vessels and compared epinephrine and polidocanol injections against no endoscopic hemostatic therapy.[100] Both cohort studies included patients with various stigmata of MWT and compared endoscopic hemostatic therapies (eg, epinephrine injection, EBL, TTSC, or fibrin glue injection) with medical treatment for UGIB due to MWT, providing subgroup data on nonbleeding visible vessels or adherent clots.[103,104] Patients who received endoscopic treatment had more severe bleeding, as indicated by higher rates of transfusion.[104] Because these were nonrandomized studies, there may be inherent selection bias that could influence the results.

None of the studies provided data on the critical outcome of further bleeding or the important outcomes of mortality, units of blood transfusions, and length of hospitalization. However, all studies provided data on 7-day rebleeding. One RCT reported adverse effects.[100]

We also conducted a proportional meta-analysis of single-arm cohort-type data from 3 studies for 7-day rebleeding.[100,103,104] As indirect evidence of the adverse effects of endoscopic hemostatic therapy in patients with nonbleeding stigmata, we performed a proportional meta-analysis of 9 studies involving patients with bleeding MWT who received endoscopic hemostatic therapy.[100–102,106–109,111,113] In addition, to assess the adverse effects of no endoscopic hemostatic therapy, we performed a proportional meta-analysis using single-arm cohort-type data from 3 studies involving patients with flat-pigmented spot or clean-based ulcers who did not receive this therapy.[100–102] The results of the proportional meta-analyses were provided as supplementary data in the Evidence Profile Table.

The EtD framework is available in Appendix 4.

**Benefits, harms, and burden.** Based on 1 RCT, the relative and absolute effects of endoscopic hemostatic therapy compared with no endoscopic hemostatic therapy on 7-day rebleeding in patients with MWT and visible vessels were highly uncertain due to the small sample size and very low event rates (RR, 0.30; 95% CI, 0.04 to 2.31; ARR, 262 fewer per 1000; 95% CI, 360 fewer to 491 more).[100] A systematic review of 2 comparative cohort studies also found highly uncertain effects of endoscopic hemostatic therapy compared with no endoscopic hemostatic therapy on 7-day rebleeding in patients with nonbleeding visible vessels or adherent clots due to very low event rates with zero event in the group receiving no endoscopic hemostatic therapy (RD, 0.03; 95% CI, −0.06 to 0.11; ARR, 30 more per 1000; 95% CI, 60 less to 110 more).[103,104] In 1 study, none of the patients experienced rebleeding, regardless of whether they received endoscopic hemostatic therapy or medical treatment.[103] In the other study, there was 1 case of rebleeding in a patient with a nonbleeding visible vessel who had undergone endoscopic hemostatic therapy.[104] In contrast, no rebleeding cases occurred in patients with adherent clots.[103,104] Proportional meta-analyses of single-arm cohort-type data suggested that no endoscopic hemostatic therapy was associated with very low 7-day rebleeding rates (pooled rebleeding rates of 6% for nonbleeding visible vessels and 0% for adherent clots).[100,103,104]

Based on 1 RCT, adverse effects related to endoscopic hemostatic therapy were not estimable due to double-zero events.[100] Based on proportional meta-analyses of single-arm cohort-type data, the pooled rate of adverse effects with endoscopic hemostatic therapy was 5% (95% CI, 2%–12%),[100–102,106–109,111,113] and without endoscopic hemostatic therapy was 0% (95% CI, 0%–0.04%).[100–102]

The panel judged these effect estimates as highly uncertain due to low event rates and the fragility of the RCT and observational data. For nonbleeding visible vessels in MWT, the panel determined that the desirable and undesirable effects of endoscopic hemostatic therapy compared with no therapy were unclear. For adherent clots, the panel determined that both the desirable and undesirable effects of endoscopic hemostatic therapy were trivial.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and very serious imprecision.

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the main outcome of rebleeding. The costs of endoscopic hemostatic therapy were deemed moderate, yet no studies have assessed its cost-effectiveness compared with no endoscopic hemostatic therapy. The panel judged endoscopic hemostatic therapy likely to be acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with MWT with nonbleeding visible vessels, the panel could not determine whether the balance of effects favored endoscopic hemostatic therapy or no endoscopic hemostatic therapy due to very low certainty evidence and the fragility of results. For patients with MWT with adherent clots, the panel judged that the balance of effects does not favor either endoscopic hemostatic therapy or no endoscopic hemostatic therapy. Although the evidence comparing endoscopic and no endoscopic therapy for MWT with nonbleeding visible vessels was extremely limited, fragile, and of very low certainty, the rebleeding rates without endoscopic therapy were very low for both nonbleeding visible vessels and adherent clots—far lower than in ulcers with the same stigmata. Given these very low rebleeding rates, the panel would not anticipate meaningful ARRs to be demonstrated with endoscopic hemostatic therapy and expressed concerns about potentially inducing bleeding with such therapy.

Given the uncertainty surrounding the benefits and the potential harms of endoscopic hemostatic therapy and its moderate costs, the panel issued a conditional recommendation against endoscopic hemostatic therapy for MWT with nonbleeding vessels or adherent clots. This decision aligns with PUB guidelines concerning adherent clots, which advise against endoscopic intervention for lesions with similarly low rebleeding rates.[8,11] However, for nonbleeding visible vessels, this recommendation diverges from PUB guidelines, as the rebleeding risk in MWT appears to be much lower, thereby justifying the decision against endoscopic therapy. The panel highlighted the need for more comparative studies to increase the certainty of the evidence. In addition, understanding the natural history of visible vessels or adherent clots in the context of MWT, especially in the era of proton pump inhibitor treatment, is crucial.

### *Recommendation 7C. Endoscopic Hemostatic Therapy vs No Endoscopic Hemostatic Therapy in Clean-Based Ulcers or Pigmented Spots*

**Evidence summary.** We did not find any RCT that addressed this question. One comparative cohort study included 52 patients who did not receive endoscopic hemostatic therapy and only 2 who did, making comparative analysis unfeasible.[104] Proportional meta-analyses of single-arm cohort-type data were conducted on 2 studies involving patients with MWT who had flat pigmented spots or clean-

based ulcers and received endoscopic hemostatic therapy and on 4 studies involving those who did not receive endoscopic hemostatic therapy.[102,104,114,115] Overall, 6 patients received endoscopic hemostatic therapy, and 154 did not.[102,104,114,115] None of the studies provided data on the critical outcome of further bleeding, or important outcomes of mortality, units of blood transfusions received and the length of hospitalization. However, all studies provided data on 7-day rebleeding.

There was no direct evidence of adverse effects from endoscopic hemostatic therapy in patients with MWT with flat-pigmented spots or clean-based ulcers. Therefore, indirect evidence was obtained through proportional meta-analyses of single-arm cohort-type data from 9 studies on patients with bleeding MWT who underwent endoscopic hemostatic therapy.[100–102,106–109,111,113] A proportional meta-analysis was also performed of single-arm cohort-type data from 3 studies on patients with flat-pigmented spot or clean-based ulcers who did not receive endoscopic hemostatic therapy.[100–102]

The EtD framework is in Appendix 4.

**Benefits, harms, and burden.** The pooled rebleeding rate for patients who received endoscopic hemostatic therapy was 0% (95% CI, 0%–0.5%; range, 0%–0%).[104,115] For those who did not receive endoscopic hemostatic therapy, the pooled rebleeding rate was also 0% (95% CI, 0%–0.02%; range, 0%–0%).[102,104,114,115] The pooled rate of adverse effects with endoscopic hemostatic therapy was 5% (95% CI, 2%–12%),[100–102,106–109,111,113] and without endoscopic hemostatic therapy was 0% (95% CI, 0%–0.04%).[100–102] The panel judged that the desirable effects of endoscopic hemostatic therapy were trivial, and the undesirable effects were small.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness due to the lack of comparative data.

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the main outcome of rebleeding. The costs of endoscopic hemostatic therapy were deemed moderate. There was no published cost-effectiveness analysis. However, when benefits are minimal, even modest procedure costs can lead to poor cost-effectiveness ratios. The panel judged endoscopic hemostatic therapy likely to be acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with MWT with flat pigmented spots or clean-based ulcers, the panel determined that the balance of desirable and undesirable effects probably favors no endoscopic hemostatic therapy. These patients have a very low risk of rebleeding, which significantly reduces the potential benefits and increases the potential harms of endoscopic intervention. As a result, the panel issued a conditional recommendation against endoscopic hemostatic therapy based on very low certainty evidence. This aligns with PUB guidelines, which advise against endoscopic intervention for such lesions.[8,11]

## *Dieulafoy's Lesion*

**Question 8:** Should patients with UGIB from DL receive one endoscopic hemostatic therapy vs another endoscopic hemostatic therapy?

**Recommendation 8A: In patients with UGIB from DL, we suggest either EBL with or without epinephrine injection or endoscopic TTSC placement with or without epinephrine injection (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Recommendation 8B: In patients with UGIB from DL, we suggest either mechanical devices (EBL or endoscopic TTSC placement) with or without epinephrine injection or contact thermal devices (heater probe and bipolar electrocoagulation) with or without epinephrine injection (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Recommendation 8C: In patients with UGIB from DL, we cannot make a recommendation for or against the use of cap-mounted clips over conventional endoscopic hemostatic therapy.**

**Recommendation 8D: In patients with UGIB from DL, we suggest either mechanical devices (EBL or endoscopic TTSC placement) with or without epinephrine injection or injection of sclerosants with or without epinephrine injection (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 8A. Endoscopic Band Ligation With or Without Epinephrine Injection vs Endoscopic Through-the-Scope Clip Placement With or Without Epinephrine Injection*

**Evidence summary.** We identified 2 systematic reviews that addressed this question.[116,117] The first review combined observational data with RCT data in its meta-analyses, introducing potential bias due to the inherent differences in study designs.[116] The second review included 1 RCT relevant to this question.[117] To provide a more robust comparison between EBL and TTSC in patients with DL, we conducted our own systematic reviews and meta-analyses that included 2 RCTs and 2 comparative cohort studies, analyzed separately.[118–121] Epinephrine injection was used in some patients in both groups to reduce active bleeding and improve visualization, but no subgroup data for patients treated with and without epinephrine were available.[118–121] One comparative cohort study included in the first review was excluded from our meta-analyses, as it only provided data for 3 patients treated with EBL and 9 patients treated with TTSC, falling below our predetermined threshold of 10 patients for each treatment group.[122] All studies reported further bleeding, failure to achieve immediate hemostasis, rebleeding, and mortality.[118–121] Because all rebleeding episodes occurred within 7 days, we classified all rebleeding and further bleeding events as 7-day outcomes to avoid double counting 7-day and 30-day outcomes. One RCT did

not report the need for additional hemostatic therapy.[120] One RCT reported adverse effects.[121]

In addition, we conducted proportional meta-analyses of single-arm cohort-type data from 10 studies on EBL[118–121,123–128] and 13 studies on TTSC.[39,118–121,129–137] The results of the proportional meta-analyses were presented as supplementary data in the Evidence Profile Table, but were not included in the EtD framework due to the lack of direct comparison. The EtD framework is in Appendix 5.

**Benefits, harms, and burden.** Based on meta-analyses of 2 RCTs, the relative and absolute effects of EBL compared with TTSC on 7-day further bleeding and rebleeding in patients with DL were highly uncertain due to the small sample size and very low event rates (RR, 0.66; 95% CI, 0.09–5.03; ARR, 22 fewer per 1000; 95% CI, 59 fewer to 260 more).[120,121] Thirty-day mortality and adverse effects were not estimable due to double-zero events. Failure to achieve immediate hemostasis was also not estimable due to double-zero events. When considering "immediate hemostasis," EBL showed no difference compared with TTSC (RR, 1.00; 95% CI, 0.92–1.09; ARR, 1 fewer per 1000; 95% CI, 1 fewer to 1 fewer). EBL also appeared to have no impact on additional hemostatic therapy (RR, 1.00; 95% CI, 0.07–14.34; ARR, 0 fewer per 1000; 95% CI, 72 fewer to 1000 more), although this estimate was very imprecise.[121]

A systematic review of 2 comparative cohort studies suggested that EBL may reduce 7-day further bleeding, rebleeding, and additional hemostatic therapy in patients with DL.[118,119] The RR was the same for all 3 outcomes (RR, 0.22; 95% CI, 0.05–0.95, ARR, 166 fewer per 1000; 95% CI, 202 fewer to 11 fewer).[118,119] Failure to achieve immediate hemostasis and 30-day mortality were not estimable due to double-zero events. Compared with TTSC, EBL showed no difference in achieving immediate hemostasis (RR, 1.00; 95% CI, 0.95–1.06; ARR, 1 fewer per 1000; 95% CI, 1 fewer to 1 fewer).[118,119]

The panel prioritized the systematic review of RCTs over cohort studies, given the limitations and inherent selection bias with the latter. They judged the effect estimates of 7-day further bleeding and rebleeding highly uncertain due to low event rates and the fragility of the RCT and observational data. Yet, both EBL and TTSC appeared highly effective in achieving immediate hemostasis. Therefore, the desirable effects of EBL compared with TTSC remain unclear, while the undesirable effects of EBL relative to TTSC were deemed trivial.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and very serious imprecision.

**Other evidence-to-decision criteria and considerations.** There was no research evidence on patients' values and preferences in the context of DL. However, the panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The cost difference between EBL and TTSC was considered negligible, with no cost-effectiveness studies comparing the 2. The panel judged EBL probably acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with UGIB from DL, the panel could not determine whether the balance of effects favored EBL or TTSC due to very low certainty evidence. Consequently, the panel issued a conditional recommendation for either EBL or TTSC, both of which can be performed with or without epinephrine injection. They highlighted the need for more comparative studies. However, conducting RCTs on DL is challenging due to their rarity, intermittent nature of bleeding, and inter-observer variability in diagnosis, as they may be misdiagnosed as small ulcers. Until more evidence becomes available, clinicians should consider individual patient factors (eg, lesion location and accessibility), the availability of devices, and clinician expertise when choosing between these 2 interventions. The panel expressed concerns that TTSC might be less effective than EBL, as EBL can aspirate and ligate vessels originating from the submucosal layers.

### *Recommendation 8B. Mechanical Modalities (Endoscopic Band Ligation/Endoscopic Through-the-Scope Clip Placement) With or Without Epinephrine Injection vs Contact Thermocoagulation With or Without Epinephrine Injection*

**Evidence summary.** We did not find any RCTs addressing this question. Two comparative cohort studies compared mechanical vs contact thermal therapies in patients with UGIB from DL.[126,138] One prospective cohort study compared EBL with bipolar electrocoagulation in patients with nonvariceal UGIB and provided subgroup data on DL.[126] Another study provided subgroup data from 2 RCTs and prospective cohort studies, comparing Doppler endoscopic probe (DEP)-guided treatments vs visually guided hemostasis.[138] This study included 77 patients who were treated with either mechanical modalities, such as TTSC or cap-mounted clips or thermal modalities, like heater probe or multipolar electrocoagulation, regardless of DEP use.[138] Only 7 patients received cap-mounted clips, and no subgroup data were provided to differentiate between TTSC or cap-mounted clips.[138] Patients in the DEP cohort were more likely to undergo mechanical treatments than the visually guided cohort (100% vs 49.2%; $P < .001$), which could introduce a confounding factor.[138] Epinephrine injection was used in some patients in both groups, but no subgroup data were provided.[126,138]

One study provided data on 7-day further bleeding, 7-day rebleeding, and failure to achieve immediate hemostasis,[126] while another reported 30-day rebleeding and adverse effects.[138] Both studies reported additional hemostatic therapy, but neither reported mortality.[126,138]

We performed proportional meta-analyses using single-arm cohort-type data from 10 studies on EBL,[118–121,123–128] 13 studies on TTSC,[39,118–121,129–137] and 4 studies on thermal modalities.[126,139–141] The results were provided as

supplementary data in the Evidence Profile Table. However, due to the lack of direct comparative data, they were not included in the EtD framework, which is available in Appendix 5.

**Benefits, harms, and burden.** Based on 1 cohort study, the relative and absolute effects of mechanical modalities (EBL) compared with thermal modalities on 7-day further bleeding (RD, −0.21; 95% CI, −0.45 to 0.02; ARR, 210 fewer per 1000; 95% CI, 450 fewer to 20 more), failure to achieve immediate hemostasis (RD, −0.14; 95% CI, −0.36 to 0.07; ARR, 140 fewer per 1000; 95% CI, 360 fewer to 70 more), and 7-day rebleeding (RD, −0.07; 95% CI, −0.25 to 0.11; ARR, 70 fewer per 1000; 95% CI, 250 fewer to 110 more) were highly uncertain due to the small sample size and very low event rates.[126] Based on 1 cohort study, the relative and absolute effects of mechanical modalities (TTSC) compared with thermal modalities on 30-day rebleeding were also highly uncertain (RR, 0.81; 95% CI, 0.40 to 1.64; ARR, 61 fewer per 1000; 95% CI, 194 fewer to 206 more).[138] A meta-analysis of the 2 cohort studies suggested that mechanical modalities may reduce the need for additional hemostatic therapy, with surgery being the most common form (RR, 0.14; 95% CI, 0.03 to 0.77; ARR, 153 fewer per 1000; 95% CI, 172 fewer to 41 fewer), but the effect estimate was very imprecise.[126,138] For adverse effects, mechanical modalities appeared to have little to no impact compared with thermal modalities (RR, 1.35; 95% CI, 0.13 to 14.23; ARR, 11 more per 1000; 95% CI, 28 fewer to 427 more), but the effect estimate was very imprecise.[138]

The panel judged the desirable and undesirable effects of mechanical modalities as uncertain compared with contact thermal modalities.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and very serious imprecision. The evidence was not further downgraded for indirectness related to the small number of patients who received cap-mounted clips.

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The cost difference between mechanical and thermal modalities was considered negligible, and no cost-effectiveness studies were found. The panel judged mechanical modalities as probably acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with UGIB from DL, the panel was unable to ascertain whether the balance of effects favored mechanical (EBL/TTSC) or contact thermal modalities due to very low certainty evidence from cohort studies and highly imprecise results. Because both modalities appeared effective and safe, the panel issued a conditional recommendation for using either mechanical or contact thermal modalities, with or without epinephrine injection. The panel emphasized the need for more comparative studies, including the need for combination with epinephrine injection.

### *Recommendation 8C. Cap-Mounted Clip vs Conventional Endoscopic Hemostatic Therapy*

**Evidence summary.** We found 1 RCT comparing cap-mounted clips with conventional endoscopic hemostatic therapy (TTSC or bipolar electrocoagulation) in patients with nonvariceal UGIB.[142] A small subgroup of patients had DLs (2 in the cap-mounted clip group and 3 in the standard endoscopic treatment group), but the data were insufficient for meaningful analysis.[142]

Most evidence for cap-mounted clips in treating DLs came from case series and case reports, with those involving fewer than 10 patients excluded from this guideline's evidence synthesis. A retrospective cohort study evaluated cap-mounted clips for nonvariceal UGIB, perforations, and fistulas.[143] This study also used propensity score matching to compare cap-mounted clips with "standard endoscopic therapy" for DL, although it did not define the latter, aside from excluding epinephrine injection as a monotherapy.[143] Further bleeding, failure to achieve immediate hemostasis, mortality, and the need for additional hemostatic therapy were not reported for the "standard endoscopic therapy" group. All rebleeding occurred within 5 days and was the only outcome available for comparative analysis.[143] Adverse effects were not reported.[143]

Another cohort study included patients from 2 RCTs and prospective cohort studies, comparing DEP-guided treatments with visually guided hemostasis.[138] It included 77 patients with DLs treated with either mechanical modalities like TTSC or cap-mounted clips or thermal modalities, such as heater probe or bipolar electrocoagulation, regardless of DEP use.[138] However, only 7 patients received cap-mounted clips, and no subgroup data were provided.[138] This study was excluded from our evidence synthesis as it did not meet our predefined threshold of 10 patients per treatment group.[138]

A large retrospective study provided indirect evidence regarding the safety of cap-mounted clips in 1517 patients with refractory bleeding, perforation, fistula, and anastomotic dehiscence.[144]

The EtD framework is in Appendix 5.

**Benefits, harms, and burden.** Based on data from a comparative cohort study, the relative and absolute effects of cap-mounted clips vs conventional endoscopic therapy on 7-day rebleeding in patients with DL were highly uncertain due to the small sample size and very low event rates (RR, 0.50; 95% CI, 0.14–1.73; ARR, 150 fewer per 1000; 95% CI, 258 fewer to 219 more).[143] Among the 20 patients treated with cap-mounted clips for DL, 15.0% had 7-day further bleeding, none failed to achieve immediate hemostasis, and 10.0% required additional hemostatic therapy.[143]

Based on 1 cohort study, the overall and severe adverse event rates of cap-mounted clips were 1.7% and 0.59%, respectively.[144]

The panel judged the effect estimate of 7-day rebleeding as highly uncertain due to low event rates, small sample size, and the inherent bias associated with observational design. As a result, the desirable effects of cap-mounted clips over conventional endoscopic hemostatic therapy remained

unclear. Due to a lack of comparative data, the undesirable effects of cap-mounted clips were also uncertain.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness due to the lack of a clear definition for "standard endoscopic therapy" in the cohort study.

**Other evidence-to-decision criteria and considerations.** The panel assumed that patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The costs of cap-mounted clips compared with conventional endoscopic therapy were considered moderate. There were no cost-effectiveness studies. The panel deemed cap-mounted clips to be probably acceptable and unlikely to adversely impact equity-deserving groups. Nevertheless, feasibility may vary depending on access and training to ensure the safe and effective application of these systems, as well as proper management of any complications or failures.

**Conclusions and research needs.** For patients with UGIB from DL, the panel was unable to ascertain whether the balance of effects favored cap-mounted clips or conventional endoscopic therapy due to very low certainty evidence from a cohort study and highly imprecise results. The panel also expressed concerns about the higher upfront costs of the cap-mounted clips and the challenges involved in retrieval if misapplication occurs. Consequently, the panel was unable to make a recommendation for or against the use of cap-mounted clips over conventional endoscopic hemostatic therapy for DL. They emphasized the need for well-designed RCTs.

### *Recommendation 8D. Mechanical Modalities (Endoscopic Band Ligation/Endoscopic Through-the-Scope Clip Placement) With or Without Epinephrine Injection vs Injection of Sclerosants With or Without Epinephrine*

**Evidence summary.** We did not identify any RCTs that compared EBL with injection of sclerosants. One RCT included 107 patients with UGIB due to DL and compared aethoxysklerol injection with TTSC placement alone or combined with aethoxysklerol injection.[145] Epinephrine injection was not used in this study. The study defined "successful endoscopic hemostasis" as the cessation of bleeding during the index endoscopy without subsequent rebleeding and "unsuccessful endoscopic hemostasis" as any rebleeding occurring within 48 hours post index endoscopy. The study did not provide outcome data for further bleeding, failure to achieve immediate hemostasis, need for additional hemostatic therapy, mortality, or adverse effects.[145] All rebleeding cases occurred within 48 hours and were considered in the 7-day rebleeding outcome.[145]

No comparative cohort study was identified.

We performed proportional meta-analyses using single-arm cohort-type data from 13 studies on TTSC[39,118–121,129–137] and 3 studies on injection of sclerosants,[133,146,147] with some patients in both groups receiving epinephrine injections. The results were provided as supplementary data in the Evidence Profile Table but were not included in the EtD framework due to the lack of direct comparative data.

The EtD framework is in Appendix 5.

**Benefits, harms, and burden.** Based on data from 1 RCT, the relative and absolute effects of TTSC vs injection of sclerosants on 7-day rebleeding in patients with DLs were highly uncertain due to the small sample size and very low event rates (RR, 0.80; 95% CI, 0.36–1.77; ARR, 57 fewer per 1000; 95% CI, 181 fewer to 218 more).[145] No comparative data were available for other outcomes.

The study also reported a higher risk of 7-day rebleeding with TTSC alone compared with when combined with sclerosant injection (RR, 6.77; 95% CI, 0.80¯51.80; ARR, 192 more per 1000; 95% CI, 4 fewer to 1000 more).[145] However, the effect estimate was very imprecise due to very low event rates and the small sample size.[145] As this comparison was not part of our predefined question and the study had serious risk of bias—such as unclear allocation sequence generation and concealment—the panel deemed it inappropriate to draw conclusions regarding the effects of combining TTSC with sclerosant injection over either treatment alone.

Proportional meta-analyses of single-arm cohort-type data suggested that both TTSC and injection of sclerosants had similar 7-day further bleeding rates (14%; 95% CI, 11%–19% vs 14%; 95% CI, 8%–23%) and adverse effects (0%).[39,118–121,129–137,146,147]

The panel judged the effect estimates as highly uncertain due to low event rates, small sample size, and high risk of bias. As a result, the desirable effects of TTSC over injection of sclerosants remained unclear. Due to a lack of comparative data, the undesirable effects of TTSC compared with injection of sclerosants were also uncertain.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and very serious imprecision. Specifically, the panel expressed concerns about the lack of reporting of allocation sequence generation and baseline characteristics of the included patients in the RCT.[145]

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the main outcome of rebleeding. The costs of TTSC compared with injection of sclerosants were considered negligible. There were no cost-effectiveness studies. The panel judged TTSC to be probably acceptable, feasible, and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with UGIB from DL, the panel was unable to determine whether the balance of effects favored mechanical modalities (EBL/TTSC) or injection of sclerosants due to very low certainty evidence from an RCT and highly imprecise results. Because both interventions appeared to be effective and safe, the panel issued a conditional recommendation for using either mechanical modalities or injection of sclerosants, with or

without epinephrine injection. The panel highlighted the need for more comparative studies, including the need for combination with epinephrine injection.

**Question 9:** Should patients with UGIB from DL receive injection of epinephrine alone vs other endoscopic hemostatic therapies?

**Recommendations 9A: In patients with UGIB from DL, we suggest against epinephrine injection alone over mechanical devices (EBL or endoscopic TTSC placement) (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Recommendation 9B: In patients with UGIB from DL, we suggest against epinephrine injection alone over thermal devices (eg, heater probe, bipolar or multipolar electrocoagulation) (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

### *Recommendation 9A. Epinephrine Injection Alone vs Mechanical Modalities (Endoscopic Band Ligation/Endoscopic Through-the-Csope Clip Placement)*

**Evidence summary.** We identified 3 RCTs that addressed this question.[122,124,134] One RCT compared epinephrine injection alone with EBL, another compared epinephrine injection alone with endoscopic TTSC placement, and the third compared epinephrine injection alone with either EBL or TTSC.[122,124,134] We conducted meta-analyses of these 3 RCTs.[122,124,134] Two of them reported further bleeding, failure to achieve immediate hemostasis, and mortality,[122,134] while all 3 reported rebleeding and the need for additional hemostatic therapy. Notably, only 1 detailed the timing of the rebleeding, noting that all rebleeding events occurred within 48 hours after the initial endoscopy.[124] To avoid double-counting of 7-day and 30-day outcomes, we classified all rebleeding cases under the 7-day outcome. Adverse effects associated with the interventions were reported in only 1 RCT.[134]

We also found 2 comparative cohort studies that compared epinephrine injection alone with EBL or TTSC in DL.[148,149] However, both studies were excluded from evidence synthesis as they involved fewer than 10 patients for a specific type of endoscopic therapy.

The EtD framework is in Appendix 5.

**Benefits, harms, and burden.** Meta-analyses of 3 RCTs suggested that epinephrine injection alone may increase the risk of 7-day further bleeding (RR, 4.37; 95% CI, 1.43–13.33; ARR, 361 more per 1000; 95% CI, 46 more to 1000 more), failure to achieve immediate hemostasis (RR, 2.49; 95% CI, 0.52–11.82; ARR, 106 more per 1000; 95% CI, 34 fewer to 773 more), 7-day rebleeding (RR, 7.46; 95% CI, 1.81–30.76; ARR, 170 more per 1000; 95% CI, 21 more to 783 more), and additional hemostatic therapy (RR, 10.47; 95% CI, 2.62–41.86; ARR, 249 more per 1000; 95% CI, 43 more to 1000 more), with no significant subgroup differences between EBL, TTSC, or EBL/TTSC.[122,124,134] Thirty-day mortality and adverse effects were not estimable due to double-zero events.

The panel judged the desirable effects of epinephrine injection alone compared with EBL or TTSC as trivial, while the undesirable effects were large.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and very serious imprecision.

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The costs of epinephrine injection alone compared with EBL or TTSC were considered negligible. No cost-effectiveness studies were found. The panel judged epinephrine injection alone to be probably acceptable and feasible and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with UGIB from DL, the panel judged that the balance of effects likely favored EBL or TTSC over epinephrine injection alone. As a result, the panel made a conditional recommendation against epinephrine injection alone over mechanical modalities (EBL or TTSC). Although this conditional recommendation serves as guidance for current clinical practice, there is a need for more well-designed comparative studies to improve the precision of available data for the formulation of a stronger recommendation.

### *Recommendation 9B. Epinephrine Injection Alone vs Thermocoagulation*

**Evidence summary.** We did not identify any RCTs that addressed this question. We found 1 comparative cohort study involving 21 patients with DL, which compared epinephrine injection alone with epinephrine injection and heater probe coagulation.[139] All rebleeding cases occurred during hospitalization, although the exact timing was not specified. For consistency and to prevent double counting between 7-day and 30-day outcomes, we classified these rebleeding events under the 7-day outcome.

We did not identify any study that assessed noncontact thermocoagulation in DL.

The EtD framework is available in Appendix 5.

**Benefits, harms, and burden.** Based on 1 cohort study, epinephrine injection alone may increase the risk of 7-day further bleeding (RD, 0.45; 95% CI, 0.15 to 0.76; ARR, 450 more per 1000; 95% CI, 150 more to 760 more), failure to achieve immediate hemostasis (RD, 0.27; 95% CI, –0.01 to 0.56; ARR, 270 more per 1000; 95% CI, 10 fewer to 560 more), 7-day rebleeding (RD, 0.18; 95% CI, –0.08 to 0.44; ARR, 180 more per 1000; 95% CI, 80 fewer to 440 more), and the need for additional hemostatic therapy (RD, 0.45; 95% CI, 0.15 to 0.76; ARR, 450 more per 1000; 95% CI, 150 more to 760 more).[139] However, these effect estimates were very imprecise. Adverse effects were not estimable due to double-zero events.[139] Epinephrine injection alone may have little to no impact on 30-day mortality (RD, 0.09; 95% CI, –0.13 to 0.31; ARR, 90 more per 1000; 95% CI, 130 fewer to 310 more), but the estimate was also very imprecise.

The panel judged the desirable effects of epinephrine injection alone compared with contact thermocoagulation as trivial, while the undesirable effects were large.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias and very serious imprecision.

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcome of further bleeding. The costs of epinephrine injection alone compared with contact thermocoagulation were considered negligible. No cost-effectiveness studies were found. The panel judged epinephrine injection alone to be probably acceptable and feasible and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** For patients with UGIB from DL, the panel judged that the balance of effects likely favored contact thermocoagulation over epinephrine injection alone. As a result, the panel made a conditional recommendation against epinephrine injection alone over contact thermocoagulation. Although this conditional recommendation serves as guidance for current clinical practice, there is a need for well-designed comparative studies to improve the precision of available data, thereby facilitating the formulation of a stronger recommendation. In addition, RCTs comparing thermocoagulation with mechanical modalities are needed to inform clinical decision making, as both modalities appear superior to epinephrine injection alone.

### *Gastric Antral Vascular Ectasia*

**Question 10:** Should patients with GAVE receive one endoscopic hemostatic therapy vs another endoscopic hemostatic therapy?

**Recommendation 10: In patients with GAVE, we suggest against radiofrequency ablation (RFA) over APC (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Evidence summary.** We identified 5 RCTs that compared EBL with APC in patients with GAVE (presented in PICO question 11).[150–154] No RCTs were found for comparing 1 endoscopic hemostatic therapy vs another.

We identified 1 retrospective comparative cohort study that compared RFA with APC.[155] The study included 77 patients with GAVE, of whom 27 (33%) had cirrhosis.[155] Among these patients, 24 were treated with APC alone, 28 with RFA alone, and 25 received both modalities across multiple sessions.[155] Outcomes assessed were changes in Hgb level and the number of treatment sessions, evaluated 18 months before and after the index endoscopy.[155] Transfusion requirements, mortality, and adverse effects were not reported. It is possible that patients with more severe GAVE were preferentially selected for RFA due to its higher cost compared with APC.[155] No other comparative studies on different endoscopic hemostatic therapies for GAVE were found.

We identified a systematic review that included 33 noncomparative cohort studies on either RFA or APC.[155] However, this review did not include the comparative cohort study identified by our search.[155] Due to methodological concerns associated with comparing pooled results from single-arm noncomparative studies, this review was excluded from our evidence synthesis.[156]

We performed proportional meta-analyses of single-arm cohort-type data from 5 studies involving RFA in patients with "refractory" GAVE who had persistent anemia or GI bleeding despite prior APC, EBL, or Nd-YAG laser treatments.[157–161] We also performed proportional meta-analyses of single-arm cohort-type data from 9 studies involving APC in patients with GAVE.[45,162–169] The results of these analyses were presented as supplementary data in the Evidence Profile Table but were not included in the EtD framework due to the lack of direct comparison. The EtD framework is in Appendix 6.

We also found 6 single-arm cohort studies on Nd:YAG laser,[56,170–174] 1 on heater probe,[175] and 2 on cryotherapy[176,177] in patients with GAVE, each with more than 10 patients. However, the absence of comparative studies led the panel to conclude that there was insufficient evidence to form recommendations regarding these interventions. The results of these studies are summarized in Appendix 6.

**Benefits, harms, and burden.** Noncirrhotic patients treated with RFA alone underwent a mean of 2.2 treatment sessions, resulting in a mean Hgb increase of 0.7 g/L.[155] Cirrhotic patients treated with RFA alone averaged 2.4 sessions but showed no change in mean Hgb level (MD, 0 g/L).[155] In contrast, noncirrhotic patients treated with APC alone underwent a mean of 2.4 sessions, with a mean Hgb increase of 1.1 g/L, whereas cirrhotic patients averaged 2.7 sessions, with a mean Hgb increase of 0.3 g/L.[155] No data were available on the change in blood transfusion requirements, mortality, number of hospitalizations, or adverse effects.[155]

The minimally important difference in Hgb level in patients with GAVE is unknown. However, based on indirect evidence from 2 studies that assessed health-related quality of life in postmenopausal women and patients with arthritis, a 2-g/dL decrease was found to be associated with a statistically significant and clinically meaningful decline in health utility.[178,179] Consequently, the panel used a minimally important difference of 2 g/dL as our decision threshold.

The panel judged that the desirable effects of RFA, in terms of fewer treatment sessions, and its undesirable effects, in terms of change in Hgb level (a critical outcome) compared to APC in GAVE, were trivial.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness, particularly concerning the surrogate outcome of change in hemoglobin level in relation to the patient-important outcome of transfusion requirements.

**Other evidence-to-decision criteria and considerations.** There is no research evidence on patients' values

and preferences in the context of GAVE. However, the panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcomes of change in hemoglobin levels and the units of blood transfused, as well as important outcomes like the number of endoscopy sessions and hospitalizations. The costs of RFA compared with APC were considered large. There were no cost-effectiveness studies in patients with GAVE who had not failed prior APC treatments. The panel judged RFA probably acceptable and unlikely to adversely impact equity-deserving groups. However, feasibility may vary based on accessibility and expertise.

**Conclusions and research needs.** The panel judged that the balance of effects does not favor either RFA or APC in patients with GAVE. However, considering the large costs associated with RFA and its variable feasibility due to expertise and accessibility, the panel made a conditional recommendation against RFA over APC, particularly in patients who have not failed other treatments. The panel emphasized the need for RCTs that compare the effectiveness and safety of RFA vs APC or EBL in GAVE patients, focusing on long-term outcomes, such as recurrence rates and transfusion requirements. These studies should also examine health care resource utilization, including hospitalization, transfusion requirements, and follow-up procedures associated with each treatment. In addition, research should assess quality-adjusted life-years and patient-important outcomes to better understand the impact of endoscopic interventions on quality of life.

**Question 11:** Should patients with GAVE receive EBL vs other endoscopic hemostatic therapies?

**Recommendation 11: In patients with GAVE, we suggest EBL over APC (*conditional recommendation, very low certainty of evidence* ⊕⊖⊖⊖).**

**Evidence summary.** We identified 5 RCTs that addressed this question, involving patients with cirrhosis or portal hypertension.[150–154] Among these, 4 trials included adult patients, while 1 included only pediatric patients.[150–154] Most patients (69%) presented with symptoms of overt bleeding. In 2 studies, endoscopic appearances were described: 13.2% of cases showed the watermelon stripe pattern, whereas 86.8% exhibited the diffuse punctuate pattern.[150,152] Only 1 RCT confirmed GAVE through biopsy.[153] All studies followed their patients for 6 months. In accordance with the Cochrane policy for managing potentially problematic studies,[180] we did not include 3 of the RCTs in our systematic review because of internal data reliability issues that are further described in Appendix 6.[151,153,154]

A systematic review and meta-analysis of 2 RCTs compared EBL and APC in patients with GAVE.[150,152] Both studies reported changes in hemoglobin levels, the units of blood transfusions needed, the number of endoscopic sessions required to obliterate lesions, and adverse effects.[150,152] One study reported on the number of hospitalizations, and neither study provided data on mortality.[152]

We also performed a meta-analysis of 5 comparative cohort studies comparing EBL and APC in GAVE.[181–185] In these studies, 46% of the patients had cirrhosis and 49% presented with overt bleeding.[181–185] Only 1 study provided data on endoscopic patterns, indicating that patients showed either the watermelon stripe pattern or the diffuse punctate pattern, each occurring in 50% of cases.[181] The mean follow-up across these studies ranged from 10 to 26 months.[181–185] None of the studies conducted adjusted analyses to account for variations in prognostic factors between groups that could potentially affect the outcomes.

The details of our assessment of these studies and the EtD framework are in Appendix 6.

**Benefits.** Meta-analyses of 2 RCTs suggested that, compared with APC, EBL may increase Hgb level by 0.7 g/dL (95% CI, 0.08 lower to 1.49 higher) over 6 months.[150,152] EBL may also reduce the units of blood transfusions (MD, 3.30 lower; 95% CI, 4.45 lower to 2.15 lower), decrease the number of endoscopic sessions required for the obliteration of lesions (MD, 1.51 lower; 95% CI, 4.69 lower to 1.66 more), and lower the number of hospitalizations (MD, 1.30 lower; 95% CI, 2.24 lower to 0.36 lower).[150,152] However, these estimates were very imprecise.[150,152]

Similarly, meta-analyses of 5 comparative cohort studies suggested that EBL may increase Hgb level by 0.54 g/dL (95% CI, 0.30 higher to 0.77 higher).[181–185] EBL may also reduce the units of blood transfusions (MD, 1.90 lower; 95% CI, 5.74 lower to 1.94 higher), decrease the number of endoscopic sessions required for the obliteration of lesions (MD, 1.53 lower; 95% CI, 3.94 lower to 0.89 more), and reduce the number of hospitalizations (MD, 2.10 lower; 95% CI, 3.82 lower to 0.38 lower), but these estimates were very imprecise.[181–185] EBL appeared to have little to no impact on mortality (RR, 0.69; 95% CI, 0.31–1.58; ARR, 93 fewer per 1000; 95% CI, 207 fewer to 174 more).[182,184,185]

The panel judged that the desirable effects of EBL compared with APC were small.

**Harms and burden.** Meta-analyses of 2 RCTs suggested that EBL, compared with APC, may increase the risk of adverse effects (RD, 0.16; 95% CI, −0.29 to 0.61; ARR, 160 more per 1000; 95% CI, 290 fewer to 610 more).[150,152] Similarly, meta-analyses of 5 RCTs also suggested that EBL may increase the risk of adverse effects (RR, 1.93; 95% CI, 0.60–6.18; ARR, 32 more per 1000; 95% CI, 14 fewer to 179 more).[181–185] However, these estimates were very imprecise due to low event rates. The adverse effects associated with EBL included post-banding ulcers, hypertrophied polyps, abdominal pain, nausea, and vomiting. The panel considered these adverse effects to be minor. As a result, the panel judged that the undesirable effects of EBL compared with APC were small.

**Certainty in the evidence of effects.** Very low certainty of evidence due to serious risk of bias, very serious imprecision, and serious indirectness. The indirectness relates to using change in hemoglobin level as a surrogate outcome. Also, the RCTs included only patients with cirrhosis, who mostly presented with overt bleeding rather than occult bleeding with a diffuse punctate endoscopic pattern.

**Other evidence-to-decision criteria and considerations.** The panel assumed patients likely do not have important uncertainty or variability in valuing the critical outcomes and important outcomes. The costs of EBL compared with APC were considered negligible. No cost-effectiveness studies were found. The panel judged EBL to be probably acceptable and feasible and unlikely to adversely impact equity-deserving groups.

**Conclusions and research needs.** The panel judged that the balance of effects probably favored EBL over APC in patients with GAVE. Consequently, the panel issued a conditional recommendation for EBL over APC. The panel stressed the importance of conducting large, high-quality RCTs. Future research should also explore potential subgroup differences, focusing on different endoscopic patterns and patients with and without cirrhosis. These studies should prioritize long-term outcomes, such as recurrence rates and the durability of treatment effects in maintaining hemoglobin levels and reducing transfusion requirements. In addition, they should also examine health care resource utilization, including hospitalization, transfusion requirements, and follow-up procedures associated with each treatment.

## What Are Others Saying and What Is New in This Guideline?

This guideline is the first to specifically address the endoscopic management of NVNPUB caused by conditions such as malignant UGIB, MWTs, DLs, and GAVE. In addition, this guideline, in contrast to many, is based entirely on high-quality systematic reviews and adopted the GRADE approach with evidence profiles and EtD framework for each recommendation, thereby enhancing the transparency and trustworthiness of the decision-making process.

Recent guidelines from the United States, Canada, Europe, and Asia on nonvariceal UGIB have focused primarily on PUB and have not specifically addressed these conditions.[8,9,11,12] The European Society of Gastrointestinal Endoscopy's 2015 guidelines suggested consideration of endoscopic hemostasis for malignant UGIB, actively bleeding MWT, DLs, and upper GI angioectasias, but no specific modalities were recommended due to insufficient evidence.[10] The older American Society of Gastrointestinal Endoscopy 2004 guidelines advised endoscopic therapy for vascular abnormalities, such as DLs and vascular malformations, as well as for ongoing or severely bleeding MWTs, but they did not specify particular modalities or provide recommendations for malignant UGIB.[186]

### *Limitations of This Guideline*

The limitations of this guideline are inherent in the very low certainty of the evidence available for the questions addressed. For 2 recommendations concerning malignant UGIB (PICO questions 1A and 1B), there was no published direct or relevant indirect evidence. Consequently, the panel was surveyed to gather unpublished collective data to inform the decision-making process. It is important to note that the interpretation of these survey data is limited by factors, such as recall bias and variations in individual provider practices. This process is explicitly noted for relevant recommendations. Furthermore, this guideline focuses on the endoscopic management of these conditions and does not cover pre- and postendoscopic management. The consideration of the impact of antithrombotic therapy on NVNPUB was beyond the scope of this guideline, and readers are encouraged to refer to the joint American College of Gastroenterology–CAG clinical practice guideline on management of anticoagulants and antiplatelets during acute GI bleeding and the peri-endoscopic period.[187] We acknowledge that not all aspects of managing these conditions are included in this guideline. The panel prioritized questions for which there was clinical uncertainty or new information might guide decision making. Future updates could include new recommendations as evidence becomes available. The panel suggested actions based on the best evidence available when developing these guidelines. Some recommendations may change as new evidence emerges. Finally, the recommendations are intended to help clinicians and patients make informed decisions, but they should not replace careful consideration of the individual clinical circumstances and patients' values and preferences.

## Revision or Adaptation of This Guideline

### *Plans for Updating This Guideline*

After this guideline is published, the CAG will maintain it by monitoring new evidence, reviewing it with experts, and revising it regularly.

**Updating or adapting recommendations locally.** Although this guideline was developed for global application, adaptation will be necessary in many circumstances based on resource availability, feasibility, and acceptability of interventions. The EtD frameworks and the "adolopment" model should guide adaptations.[188] Local guideline groups may leverage the evidence already gathered and appraised in these frameworks. By adding relevant local information, they can efficiently create local recommendations, requiring fewer resources than developing a guideline de novo.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at 10.1053/j.gastro.2025.04.041.

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**Conflicts of interest**
The conflicts of interest of all participants were managed according to the CAG policies (https://www.cag-acg.org/_Library/clinical_cpgs_position_papers/CAG_Conflict_of_Interest_Policy_Nov17_2019.pdf), which are based on the recommendations of the Institute of Medicine (now the National Academy of Medicine) and the Guidelines International Network. Detailed conflict of interest management methods are in Appendix 1.

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