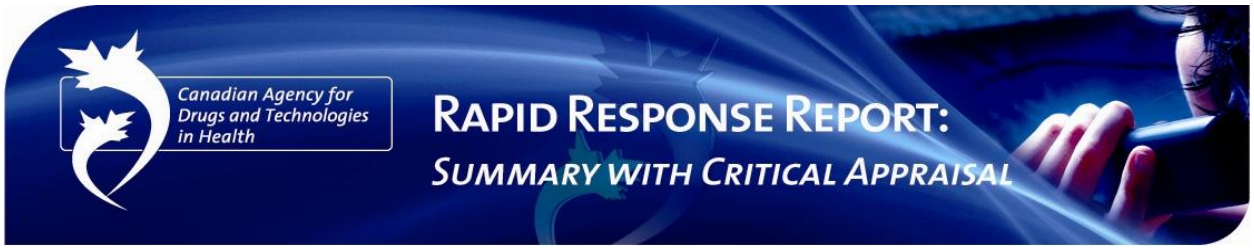

TITLE: Continuous versus Intermittent Intravenous Pantoprazole for Acute Gastrointestinal Bleeding: A Review of the Clinical Effectiveness and Guidelines

DATE: 01 May 2015

CONTEXT AND POLICY ISSUES

The gastrointestinal (GI) tract stretches from the mouth to the anus and gastrointestinal bleeding describes any bleeding that starts in the GI tract. Acute GI bleeding refers to the passage of a clinically significant amount of blood (i.e., the passage of more than a scant amount of blood)[1] Acute bleeding in the upper part of the GI tract often presents with hematemesis (i.e., vomiting of blood or coffee-ground-like material) and/or melena (i.e., black, tarry stools).[1] Patients with acute bleeding in the lower part of the GI tract often present with hematochezia (i.e., bright red blood in the stool).[2] Acute GI bleeding represents a serious medical emergency that can result in death. For example, the mortality rate associated with acute lower GI bleeding is two to four percent.[2]

Proton pump inhibitors (PPIs) are an acid suppression medication used as part of the treatment for patients admitted to hospital with GI bleeding.[1] One such example of a PPI is the drug pantoprazole. Pantoprazole can be administered by different routes (e.g., intravenously, orally) and using different dosing regimens (e.g., continuously, intermittently). Given the potential for different routes and doses, the focus of this Rapid Response report will be the comparative clinical effect of continuous intravenous infusion relative to intermittent intravenous infusion of pantoprazole for the treatment of acute GI bleeding. This report will also review the evidence-based guidelines related to the use of PPIs for the treatment of acute GI bleeding.

The clinical evidence and guidelines presented in this Rapid Response report are intended to contribute to the standardization of clinical practice for the treatment of acute GI bleeding.

RESEARCH QUESTIONS

1. What is the comparative clinical effectiveness of continuous versus intermittent intravenous infusion of pantoprazole for acute gastrointestinal bleeding?

2. What are the evidence-based guidelines regarding the use of proton pump inhibitors for acute gastrointestinal bleeding?

KEY FINDINGS

The evidence found in this review addressed acute bleeding in the upper portion of the GI tract. The clinical studies were based on a randomized controlled trial and a non-randomized observational study which together provided evidence of both the efficacy and effectiveness of pantoprazole treatment for acute upper GI bleeding. Outcomes within the respective studies were similar for both the continuous and intermittent regimens. Across the studies more deaths occurred in the continuous pantoprazole group in the observational study than in the randomized controlled trial. The percentage of patients who experienced re-bleeding within three days post endoscopy was higher in the continuous arm in the randomized controlled trial compared to the observational study. The evidence-based guidelines recommended the use of an intravenous bolus followed by continuous infusion of PPI therapy for the treatment of acute upper GI bleeding post endoscopy.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were used to limit retrieval by publication type for question 1. A methodological filter was applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and guidelines for question 2. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and April 2, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with acute gastrointestinal bleeds
Intervention	Q1: Pantoprazole IV via continuous infusion Q2: Proton pump inhibitors
Comparator	Q1: Pantoprazole IV via intermittent infusion Q2: No comparator necessary
Outcomes	Q1: Clinical benefits and harms Q2: Guidelines
Study Designs	HTAs, Systematic reviews, Meta-analyses, Randomized controlled trials, Non-randomized studies, Evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2010.

Critical Appraisal of Individual Studies

The included randomized controlled trial[3] was critically appraised using the Cochrane Collaboration's tool for assessing the risk of bias,[4] the included non-randomized observational study was appraised using the SIGN checklist for cohort studies[5] and the guidelines were assessed with the AGREE II instrument.[6] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 193 citations were identified in the literature search. Following screening of titles and abstracts, 160 citations were excluded and 33 potentially relevant reports from the electronic search were retrieved for full-text review. Ten potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 37 publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of individual study characteristics are presented in Appendix 2.

Study Design

Two clinical studies[3,7] were identified that addressed the comparative clinical effectiveness of continuous versus intermittent intravenous infusion of pantoprazole for acute GI bleeding. One study[3] was a randomized controlled trial and the other study was a non-randomized retrospective cohort study.[7] Both studies were hospital based. The details of the included clinical studies are reported in Table A1, Appendix 2.

Four evidence-based guidelines[8-11] regarding the use of PPIs for acute gastrointestinal bleeding were also found. Details describing the objectives and methodology of the guidelines are presented in Table A2, Appendix 2.

Country of Origin

The clinical studies were based on evidence from patients presenting to hospitals in Thailand[3] and Spain.[7] The guidelines reflected a variety of perspectives including the United States of America,[9] the United Kingdom,[11] and Denmark[8] as well as one guideline that represented an international consensus.[10]

Patient Population

The randomized controlled trial[3] included 28 patients who were hospitalized for non-variceal upper gastrointestinal hemorrhage while the cohort study was based on the retrospective review of the medical charts of 272 patients who were hospitalized for peptic ulcer bleeding and who had high risk stigmata.[7]

All four of the guidelines referred to patients with upper GI bleeding. One guideline was based on bleeding due to gastric or duodenal ulcers,[9] another guideline related to patients with non-variceal bleeding,[10] another discussed treatment for patients who presented with haematemesis and/or melaena[11] and the final guideline applied to patients with chronic peptic ulcerations located in the stomach and/or duodenum.[8]

Interventions and Comparators

The randomized controlled trial investigated the efficacy of an intermittent intravenous injection relative to a continuous intravenous infusion of pantoprazole post endoscopy. The intermittent group was administered 40 mg bolus injections of pantoprazole twice daily for seven days. The continuous group was given continuous intravenous infusion of pantoprazole at a dose of 8 mg/hour for the first three days post endoscopy, followed by a 40 mg bolus injection twice daily from day four until day seven.[3] The cohort study examined the effectiveness of intravenous pantoprazole at a dose of at least 160 mg/day relative to a dose of less than 160 mg/day.[7] The guidelines provided recommendations on the use of proton pump inhibitors for the treatment of acute GI bleeding pre- and post-endoscopy.[8-11]

Outcomes

Both clinical studies considered re-bleeding, surgery, volume of blood units transfused, and mortality as outcomes.[3,7] The randomized controlled trial also included information on the length of hospital stay[3] and the cohort study included data on the number of patients with repeated endoscopy.[7]

Similarly, all four guidelines were based on evidence of the impact of PPIs on re-bleeding, surgery and mortality.[8-11] One guideline also considered evidence on the need for a transfusion and the length of hospital stay.[11] Three of the guidelines[9-11] used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to rate the strength of the recommendations and the quality of the evidence. The other guideline reported on the quality of the associated evidence, but did not discuss the strength of the recommendations.[8]

Summary of Critical Appraisal

Details of the critical appraisal of individual studies are presented in Appendix 3.

The strengths of the randomized trial stemmed from the objective nature of the outcomes as well as the apparent absence of missing outcome data. However, this study also had potential limitations. These limitations included a failure to adequately describe the processes of random sequence generation and allocation concealment as well as a sample size that may not have been large enough to detect statistically significant differences. In addition, there may be

concerns regarding the applicability of the results based on a sample of patients from Southeast Asia relative to the general population of patients with acute upper gastrointestinal bleeding. As well, the study focused on patients with massive peptic ulcer bleeding and also a high percentage of patients had low risk lesions, which may also impact the applicability of the results. The strengths of the cohort study were based on a clearly focused question, a transparent process of patient selection, clearly defined outcomes and an observational design that may better reflect outcomes in the real world. Limitations included the retrospective nature of the study design, concerns about the comparability of the intervention and comparator groups as well as issues of applicability. In terms of the subgroup of importance for this Rapid Response report, it was not clear whether the intervention and comparator groups were selected from source populations that were comparable in all respects other than the dose of pantoprazole. Also, the results pertain to patients with high risk stigmata and may not be applicable to the general population of patients with GI bleeding. The critical appraisal of the clinical studies is presented in Table A3, Appendix 3.

In terms of strengths, all of the guidelines included a well specified scope and purpose and provided a clear presentation of the recommendations. Most of the guidelines discussed the relevant evidence base and disclosed financial support and potential competing interests. Limitations related primarily to a lack of patient input and concerns with the methods for evidence collection and selection. Specifically, there were concerns regarding the use of a single reviewer in two of the guidelines,[10,11] the limited use of search terms in one of the guidelines[9] and the reliance on only one database and/or the failure to search the grey/unpublished literature among a majority of the guidelines.[8,9,11] Details specific to the critical appraisal of the guidelines are reported in Table A4, Appendix 3.

Summary of Findings

Details of individual study findings are presented in Appendix 4.

What is the comparative clinical effectiveness of continuous versus intermittent intravenous infusion of pantoprazole for acute gastrointestinal bleeding?

Since patients in the continuous intravenous arm of the randomized controlled trial received intermittent injections starting on day four, this Rapid Response report is focused on outcomes measured within three days post endoscopy. Re-bleeding within three days post endoscopy was approximately 8% in the intermittent intravenous group and approximately 27% in the continuous intravenous group, though the statistical significance was not reported.[3] It is unclear from the results when surgery or blood transfusions occurred, so it was difficult to make comparisons at day three for these outcomes, however there was no statistical difference in these outcomes at study completion. Neither group experienced any deaths within the seven day follow-up period. For the cohort study[7] there was concern about possible exposure to oral proton pump inhibitor therapy, so again the results were limited to those measured at three days post endoscopy. The findings presented in this Rapid Response report refer to outcomes following treatment with intravenous pantoprazole among patients with high risk stigmata, stratified by dose. A patient was classified as having high risk stigmata if the ulcer was spurting bleeding, oozing bleeding, visible vessel or adherent clot on endoscopy.[7] The results for the low risk stigmata group were not considered as these patients could receive intravenous or oral pantoprazole. The percentage of patients who experienced re-bleeding or required surgery within three days post endoscopy were similar across study arms (i.e., 10.5% vs. 9.1% and

2.5% vs. 3.0%, respectively).[7] No deaths were reported at day three in the 33 patients receiving less than 160 mg/day of pantoprazole whereas six deaths were observed among the 239 patients who received at least 160 mg/day of intravenous pantoprazole. Two of the reported deaths were considered bleeding related.[7] The study findings are presented in Table A5, Appendix 4.

What are the evidence-based guidelines regarding the use of proton pump inhibitors for acute gastrointestinal bleeding?

All of the guidelines recommended the use of PPIs after endoscopy. Three of the guidelines specified that an intravenous bolus followed by continuous intravenous PPI therapy be used post-endoscopy.[8-10] Relative to the recommendation regarding proton pump inhibitors post-endoscopy there was more variability in terms of the recommended use of proton pump inhibitors pre-endoscopy. Of the three guidelines[9-11] that considered the use of PPIs pre-endoscopy, one guideline[9] provided a conditional recommendation and another guideline[10] provided a strong recommendation in support of their use. The remaining guideline[11] gave a strong recommendation against their use pre-endoscopy for patients with suspected non-variceal upper GI bleeding. The findings from the guidelines are presented in Table A5, Appendix 4.

Limitations

The main limitations in this report are related to the clinical studies.[3,7] This review identified two clinical studies that addressed the comparative clinical effectiveness of continuous versus intermittent intravenous infusion of pantoprazole for acute GI bleeding. Interpretation of the results of these studies was not straightforward and in both studies only a subset of the results proved relevant to this review. Neither study focused specifically on the intervention and comparator of interest in this review, so the results must be interpreted with caution. For the randomized controlled trial[3] not all of the outcomes were relevant for the comparison between the intermittent and continuous arms and for the cohort study[7] the use of a comparator arm based on an intravenous pantoprazole dose of less than 160 mg/day may allow for the inclusion of both intermittent and continuous doses within a single arm of the study. Despite this possibility, the cohort study was included based on the likelihood that doses less than 160 mg/day may include those that would be characterized as intermittent.[12] In addition, there may be concerns regarding the applicability of the results from studies based in Thailand[3] and Spain[7] to the Canadian context. To the extent that the guidelines are based on evidence from multiple studies, issues of applicability may be less of a concern. However, none of the guidelines specifically represented a Canadian perspective.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The results of this review provided evidence on the efficacy and effectiveness of pantoprazole and recommended use of PPI therapy for the treatment of acute upper GI bleeding. While the evidence-based guidelines recommended the use of continuous intravenous PPI therapy post-endoscopy, in terms of pantoprazole, the evidence from the clinical studies suggested the effect of continuous compared with intermittent intravenous infusion may be similar. The two clinical studies[3,7] and their associated limitations speak to the need for further research in this area. Future research, especially with regards to real world observational studies, would help to strengthen the evidence upon which clinical decisions are based. Evidence that reflects the

clinical effectiveness of interventions based on how they are administered and to whom they are administered in real world hospital and emergency department settings would help to inform clinical decision making in those settings. Additional research focused on the use of pantoprazole in lower GI bleeds would also be beneficial to the standardization of clinical practice.

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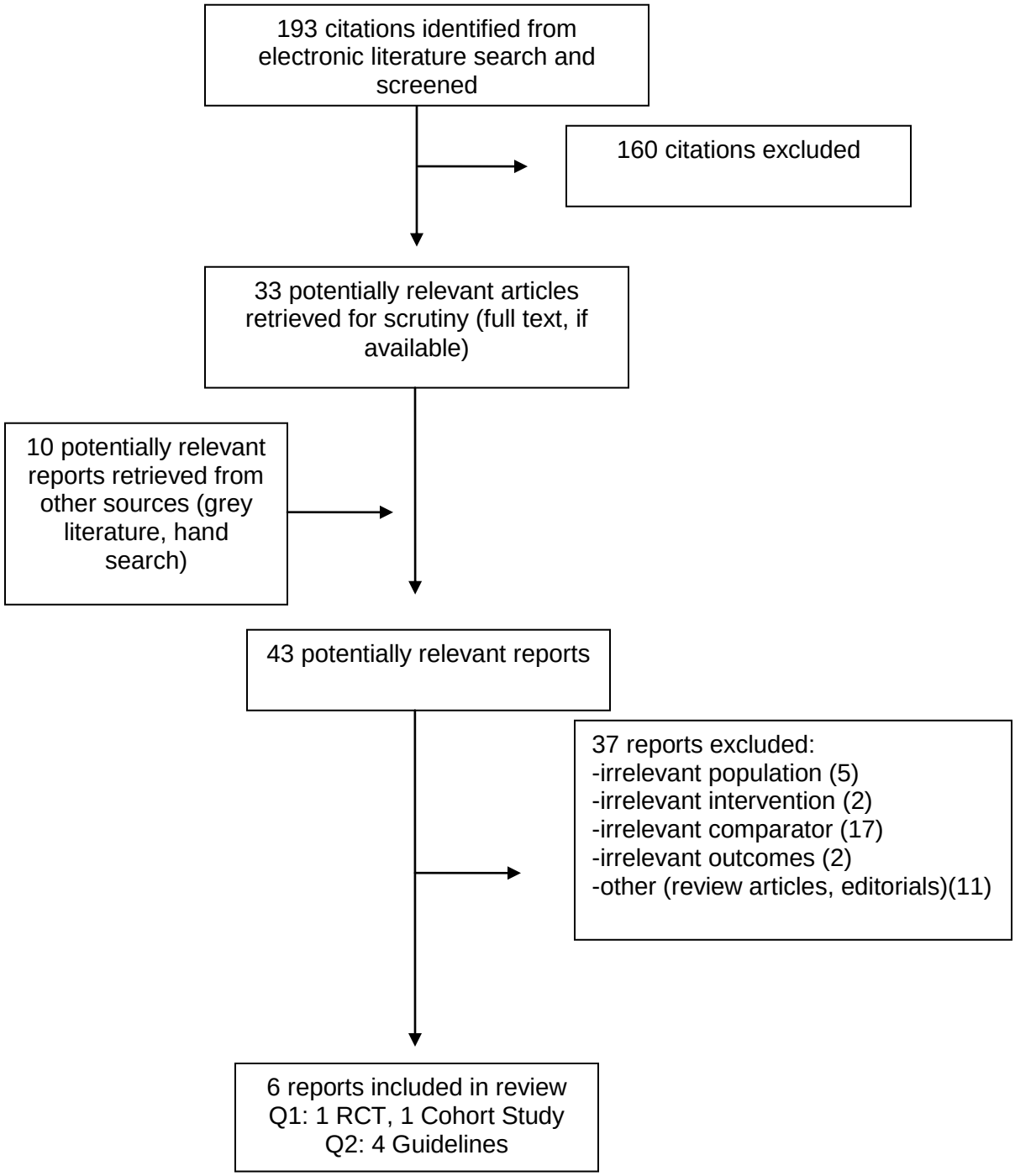
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Yamada,[3] 2012, Thailand	RCT	Patients admitted between August 2005 and October 2007 to the department of surgery Maharaj Nakorn Chiang Mai Hospital with non-variceal upper gastrointestinal hemorrhage	High dose of pantoprazole, 40 mg bolus intravenous injections twice daily for seven days, then 20 mg oral pantoprazole once daily for two months	Continuous intravenous infusion of pantoprazole, 8 mg per hour for the first three days, followed with a 40 mg bolus injection twice daily from day four until day seven, then 20 mg oral pantoprazole once daily for two months	Re-bleeding Surgery Volume of blood transfusion Length of hospital stay Mortality
Lanas,[7] 2014, Spain	Retrospective cohort	Consecutive patients hospitalized for peptic ulcer bleeding were identified retrospectively, based on medical records, starting in December 2009 and going back to January 2006	Intravenous pantoprazole dose >= 160 mg/day After initial post-endoscopy PPI therapy, patients received further PPI treatment, either oral or intravenous	Intravenous pantoprazole dose < 160 mg/day After initial post-endoscopy PPI therapy, patients received further PPI treatment, either oral or intravenous	Re-bleeding Surgery All-cause mortality Bleeding related mortality Repeated endoscopy Blood units transfused

Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; RCT = randomized controlled trial

Table A2: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Laine, 2012[9]						
Patients with overt upper gastrointestinal bleeding due to gastric or duodenal ulcers	Proton pump inhibitors pre and post endoscopy	Mortality Re-bleeding Surgery	Searched MEDLINE using MeSH term "gastrointestinal hemorrhage" limited to clinical trials and meta-analysis for the years 1996-2010 Reviewed clinical trials and reviews known to authors Two reviewers	Used GRADE system	Authors considered the quality of the evidence, the balance between the desirable effects and the undesirable effects of an intevention, the variability in the values and preferences of patients and the use of resources	Not stated
Barkun, 2010[10] -International Consensus Upper Gastrointestinal Bleeding Conference Group						
Patients with non-variceal upper gastrointestinal bleeding	Proton pump inhibitors pre and post endoscopy	Mortality Re-bleeding Surgery	Searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials and ISI	Used GRADE system	All participants contributed to the development and evaluation of the recommendations using a modified Delphi process until consensus	Not stated, though ongoing work was planned to describe the criteria for monitoring and auditing purposes

Table A2: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
			Web of Knowledge Manual searches of bibliographies of key articles and conference abstracts Searched for updated topics from 2002 and new topics from 1966 to October 2008 Prioritized data from RCTs and performed meta-analyses Search terms were derived from previous Cochrane meta-analyses and through input from methodologists One reviewer with results		was reached	

Table A2: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
			reviewed by both methodological and content experts			
National Institute for Health and Clinical Excellence, 2012[11]						
Patients with acute upper gastrointestinal bleeding who present with haematemesis and/or melaena	Proton pump inhibitors for the management of non-variceal bleeding pre and post endoscopy	Mortality Re-bleeding Surgery Need for transfusion Length of hospital stay	Searched MEDLINE, Embase, Cinahl, The Cochrane Library, PsycInfo (for patient experience) for literature published up to September 23, 2011 Search terms included medical subject headings and free-text terms All references sent by stakeholders	Used GRADE system	The Guideline Development Group took into account the balance between issues such as potential benefits, harms, costs, patient preferences and equality issues Expert opinion was used when evidence was of poor quality, conflicting or absent	The guidance was subject to an eight week period of public consultation, including stakeholder feedback

Table A2: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
			were also considered Grey literature or unpublished literature were not searched Evidence was identified and reviewed by a single reviewer with a portion quality assured by a second reviewer Meta-analyses were conducted to synthesize data			
Laursen, 2014[8]						
Patients with bleeding from chronic peptic ulcerations located in the stomach and/or duodenum	Medical treatment with proton pump inhibitors post endoscopy	Mortality Re-bleeding Surgery	Searched published studies up to June 2014	Presented the level of quality for the evidence associated with the recommendation The strength of the recommendation	Recommendations were based on evidence from Cochrane systematic reviews, case series, cohort and case control studies	Not stated

Table A2: Characteristics of Included Guidelines						
Objectives			**Methodology**			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
				was not provided		

Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health, GRADE=Grading of Recommendations Assessment, Development and Evaluation

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of the Randomized Controlled Trial using the Cochrane Collaboration's tool for assessing the risk of bias[4] and the SIGN checklist for cohort studies[5]

Strengths	Limitations
Yamada[3]	
• Blinding of participants, personnel or outcome assessors was not discussed, but the outcomes and their measurement were unlikely to be influenced by the lack of blinding. Due to the objective nature of the outcomes, the risk of bias was judged to be low • The trial was at low risk for attrition bias as no missing outcome data were reported and the outcome data were analyzed based on an intention-to-treat approach	• The authors referred to a process of block randomization; however, there was insufficient information about the process to permit judgement of whether the risk of bias was low or high • The method of allocation concealment was not described in sufficient detail to judge the risk of bias, but there was no evidence (at the 5% level) of statistically significant imbalances in demographic characteristics between the intervention and comparator arms • There was insufficient information to allow judgement of the risk of bias due to selective outcome reporting • The risk of bias due to the applicability of the results to the general population of patients with acute upper gastrointestinal bleeding may be considered high because of a high prevalence of Helicobacter pylori infection and a potential difference in drug metabolism among Asian populations as well as a difference in clinical management of upper gastrointestinal bleeding due to variable socioeconomic environments in Asia relative to the general population of patients.[13] • Also, the study consisted of patients with massive peptic ulcer bleeding and a high percentage of patients had low risk lesions • The sample size calculation indicated that at least 50 patients were required for each arm in order to detect a clinically meaningful effect size. Consequently, the absence of an observed difference between the intervention and comparator arms may simply reflect a lack of statistical power to detect a statistically significant effect • It should also be noted that as of day four both arms received a 40 mg bolus injection twice daily and after the seventh day both groups were given 20 mg of oral

Table A3: Strengths and Limitations of the Randomized Controlled Trial using the Cochrane Collaboration's tool for assessing the risk of bias[4] and the SIGN checklist for cohort studies[5]	
Strengths	**Limitations**
	pantoprazole once daily for two months; therefore, for this rapid review report it is only appropriate to compare outcomes for the two arms until day three
Lanas[7]	
• The study addressed an appropriate and clearly focused question • The process by which consecutive patients were selected was well documented, including reasons for exclusion from the study • The outcomes were clearly defined • The observational nature of the study may better reflect the relative effectiveness of continuous versus intermittent intravenous pantoprazole in a real world setting	• The study design was retrospective • For the subgroup of importance, in terms of this Rapid Response report, potential confounders were not identified and it was not clear whether the intervention and comparator groups were selected from source populations that were comparable in all respects other than the dose of pantoprazole • Confidence intervals were not provided and it was not clear whether the statistical power of the study was sufficient to identify statistically significant differences between the intervention and comparator arms • The results pertain to patients with high risk stigmata and may not be applicable to the general population of patients with acute gastrointestinal bleeding • Possible exposure to oral PPI therapy, especially after day three, should also be noted for both the intervention and comparator arms • For the pantoprazole <160 mg/day arm it is not clear whether this might include both intermittent and continuous doses

Table A4: Strengths and Limitations of Guidelines using AGREE II [6]	
Strengths	**Limitations**
Laine[9]	
• The scope and purpose were well specified • The supporting evidence and the associated strength of each recommendation was explicitly stated • The guidelines were clearly presented • Financial support and potential competing interests were disclosed	• Though the authors referred to patient input they did not describe how this was sought • For the electronic portion of the literature search only one database and one search term were used
Barkun[10]	
• The scope and purpose were well specified • Health benefits, side effects and risks were considered in formulating the recommendations • The methods for formulating the recommendations were clearly described • The guidelines were clearly presented • The authors provided advice on how the recommendations could be applied to clinical practice • Financial support and potential competing interests were disclosed	• While a multidisciplinary group of 34 experts from 15 countries developed the guidelines, patient input was not considered • The specific strengths and limitations of the body of evidence were not clearly described • Though the results of the literature review were reviewed by both methodological and content experts and approved by the entire group, the initial review of the evidence was conducted by a single reviewer
National Institute for Health and Clinical Excellence[11]	
• The scope and purpose were well specified • Guideline development group members included patient/carer representatives • The guideline was subject to an external validation process based on public consultation and stakeholder feedback • The potential resource implications of applying the recommendations were considered • The methods for formulating the recommendations were clearly described • A procedure for updating the guideline was provided • Financial support and potential competing interests were disclosed	• The grey literature or unpublished literature was not searched • While a portion of the results from the review of the clinical evidence were quality assured by a second reviewer, the bulk of the review was undertaken by a single reviewer
Laursen[8]	
• The scope and purpose were well specified • The evidence underlying the recommendations was described	• The methods used to search for evidence were not fully documented • Electronic databases were not specified and no grey literature was searched

Table A4: Strengths and Limitations of Guidelines using AGREE II [6]	
Strengths	**Limitations**
• The guidelines were clearly presented	• The methods for formulating the recommendations were not clearly described • No discussion of patient input, health benefits, side effects, or risks was provided • Neither financial support nor competing interests were disclosed

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Yamada, 2012[3]	
Intervention- Intermittent (n=13) Number of patients with re-bleeding: n=4 (30.8%) Number of patients with re-bleeding at 3 days: n=1 (7.7%) Number of patients requiring surgery: n=3 (23.1%) Mean blood transfusion (units): 6.31 (standard deviation=3.8) Mean Hospital stay (days): 10.15 (standard deviation=3.2) Mortality: n=0 (0%) *Comparator- Continuous (n=15)* Number of patients with re-bleeding: n=5 (33.3%) Number of patients with re-bleeding at 3 days: n=4 (26.7%) Number of patients requiring surgery: n=5 (33.3%) Mean blood transfusion (units): 6.07 (standard deviation=3.8) Mean Hospital stay (days): 9.93 (standard deviation=4.3) Mortality: n=0 (0%)	The authors concluded that both intermittent intravenous injection and continuous intravenous infusion of pantoprazole were equally efficacious

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Lanas, 2014[7]	
Intervention- continuous (n=239) *Outcomes within 72 hours* Number of patients with re-bleeding: n=25 (10.5%) Number of patients requiring surgery: n=6 (2.5%) All-cause mortality: n=4 (1.7%) Bleeding related mortality: n=2 (0.8%) Repeated endoscopy: n=22 (9.2%) Mean blood units transfused: 2.9 (standard deviation=4.2) *Comparator- intermittent (n=33)* *Outcomes within 72 hours* Number of patients with rebleeding: n=3 (9.1%) Number of patients requiring surgery: n=1 (3.0%) All cause mortality: n=0 (0.0%) Bleeding related mortality: n=0 (0.0%) Repeated endoscopy: n=7 (21.2%) Mean blood units transfused: 2.9 (standard deviation=4.2) 2.10	These results were based on a subgroup analysis and as such the authors did not present conclusions specific to the comparison of pantoprazole doses

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Laine, 2012[9]	
For pre-endoscopic medical therapy the authors found the following: 1) Intravenous proton pump inhibitor therapy may decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy 2) Proton pump inhibitors do not improve clinical outcomes such as further bleeding, surgery or mortality 3) If endoscopy will be delayed or cannot be performed, intravenous proton pump inhibitor therapy may reduce further bleeding For post-endoscopic medical therapy the authors found the following: 1) Intravenous proton pump inhibitor therapy with 80 mg bolus followed by 8 mg/hour continuous infusion for 72 hours should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel, or an adherent clot 2) Patients with ulcers that have flat pigmented spots or clean bases can receive standard proton pump inhibitor therapy (e.g., oral once daily)	For pre-endoscopic medical therapy the authors concluded the following: For findings 1 and 2 the authors appraised the evidence as being of high quality and assigned a conditional recommendation. For finding 3 the authors appraised the evidence as being of moderate quality and assigned a conditional recommendation. For post-endoscopic medical therapy the authors concluded the following: For finding 1 the authors appraised the evidence as being of high quality and assigned a strong recommendation For finding 2 the authors appraised the evidence as being of moderate quality and assigned a strong recommendation

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
Barkun, 2010[10]	
For pre-endoscopic medical therapy the authors found the following: 1) Proton pump inhibitor therapy may be considered to down-stage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy For endoscopic management the authors found the following: 1) Endoscopic therapy may be considered for adherent clots although proton pump inhibitor therapy alone may be sufficient For post endoscopic pharmacologic management the authors found the following: 1) An intravenous bolus followed by continuous infusion proton pump inhibitor therapy should be used to decrease rebleeding and mortality in patients with high risk stigmata who have undergone successful endoscopic therapy 2) Patients should be discharged with a prescription for a single daily dose oral proton pump inhibitor for a duration dictated by the underlying etiology	For pre-endoscopic medical therapy the authors concluded the following: For finding 1 the authors appraised the evidence as being of moderate quality and assigned a strong recommendation For endoscopic management the authors concluded the following: For finding 1 the authors appraised the evidence as being of moderate quality and assigned a weak recommendation For post endoscopic pharmacologic management the authors concluded the following: For finding 1 the authors appraised the evidence as being of high quality and assigned a strong recommendation For finding 2 the authors appraised the evidence as being of low quality and assigned a strong recommendation

Table A5: Summary of Findings of Included Studies	
Main Study Findings	**Author's Conclusions**
National Institute for Health and Clinical Excellence, 2012[11]	
For pre-endoscopic medical therapy the authors found the following: 1) Do not offer proton pump inhibitors before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding For post-endoscopic medical therapy the authors found the following: 1) Offer proton pump inhibitors to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy	For pre-endoscopic medical therapy the authors concluded the following: For finding 1 the authors appraised the evidence as being of moderate to low quality and assigned a strong recommendation For post-endoscopic medical therapy the authors concluded the following: For finding 1 the authors appraised the evidence as being of moderate to very low quality and assigned a weak recommendation
Laursen, 2014[8]	
For post-endoscopic medical therapy the authors found the following: 1) Treatment with proton pump inhibitors reduces the rebleeding rate and the need for surgical haemostasis 2) Proton pump inhibitor therapy should be given as an intravenous bolus followed by continuous infusion for 72 hours	For post-endoscopic medical therapy the authors concluded the following: For finding 1 the authors appraised the evidence as being of high quality based on systematic reviews of randomized controlled trials For finding 2 the authors appraised the evidence as being of low quality based on case series or poor quality cohort or case control studies The strength of the recommendations was not discussed