Application for inclusion of intravenous omeprazole in the WHO Model List of Essential Medicines 2015

Submitted by
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Potential conflicts of interest

Dr. Leontiadis declares that he has had no COI for the last 5 years (he acted as consultant for and received research grants from AstraZeneca, a pharmaceutical company producing PPIs, more than 5 years ago)

Dr. Schünemann declares that he has no COI.

Date: Dec 10, 2014
GENERAL ITEMS

1. Summary statement of the proposal for inclusion

At present, IV omeprazole is not included in the WHO Model List of Essential Medicines. This application proposes IV omeprazole for the core list of WHO Model List of Essential Medicines for:

1. patients with severe suspected nonvariceal upper gastrointestinal (GI) bleeding for whom endoscopy is unavailable or is expected to be delayed
2. patients with endoscopically documented peptic ulcer bleeding with high risk for detrimental outcomes (active bleeding or a non-bleeding visible vessel), regardless of the application of endoscopic hemostatic treatment (which may not be widely available in low recourse settings)

A series of systematic reviews of published randomized controlled trials, of previously published systematic reviews and clinical practice guidelines (CPG) were conducted for the needs of this application. All seven recent CPGs strongly commended PPI treatment in patients with peptic ulcer bleeding. Regarding the route of administration of PPIs, none of the CPGs recommended an exclusively oral route. Six CPG recommended an IV route for PPIs either exclusively for all patients or selectively for high risk populations, while the seventh CPG stated that there was no adequate evidence to make a decision on the route of administration.

The assessment of existing systematic reviews and the updated systematic review of RCTs that was performed for this application, as also reached the conclusion that IV omeprazole is safe medication that not only reduces rebleeding in the target population, but also saves lives. It was also concluded that IV omeprazole cannot be substituted with oral omeprazole, or histamine-2 receptor antagonists (oral or IV).

2. Name of the focal point in WHO submitting or supporting the application (where relevant)

Dr. Nicola Magrini

3. Name of the organization(s) consulted and/or supporting the application

Dr. Grigorios Leontiadis and Dr. Holger Schünemann,

Department of Medicine and of Clinical Epidemiology and Biostatistics & WHO collaborating center for evidence informed policy making
McMaster University, Hamilton, Ontario, Canada

4. International Nonproprietary Name (INN, generic name) of the medicine

Omeprazole

5. Formulation proposed for inclusion; including adult and paediatric (if appropriate)

Omeprazole 40 mg vial of powder and solvent for solution for injection. Each vial of powder for solution for injection contains omeprazole sodium 42.6 mg, equivalent to omeprazole 40 mg. After reconstitution, 1 ml contains omeprazole sodium 4.26 mg, equivalent to omeprazole 4 mg.
6. International availability - sources, of possible manufacturers and trade names

Omeprazole is being manufactured by AstraZeneca under the brand names of Losec and Prilosec and is available world-wide. However, omeprazole, as most of the other PPIs, is off-patent and therefore it is also available world-wide from generic manufacturers under various brand names. For example, Zefxon is a generic intravenous formulation of omeprazole that is available in Thailand \(^1\). IV omeprazole is not available in the US and Canada, but in these countries other IV PPIs are available (pantoprazole, esomeprazole, a successor of omeprazole, and lansoprazole in the US; pantoprazole in Canada).

7. Whether listing is requested as an individual medicine or as an example of a therapeutic group

As an individual medicine. However, the mechanism of action, efficacy and safety is identical to all other IV PPIs (pantoprazole, esomeprazole, lansoprazole).

8. Information supporting the public health relevance (epidemiological information on disease burden, assessment of current use, target population)

Main target populations
- Patients with acute bleeding from a peptic ulcer (diagnosed endoscopically)
- Patients with acute upper gastrointestinal (GI) bleeding who have not (yet) undergone endoscopy

Secondary target populations

There are other populations and indications for which IV omeprazole or other IV PPIs are currently used, especially in Western countries, but it is unlikely that these indications should influence the decision to include IV omeprazole in the WHO Model List of Essential Medicines 2015, because reasonable alternatives are available. The other populations and indications consist of:
- *High risk patients in ICU requiring stress ulcer prophylaxis.* There is low to moderate quality of evidence that PPIs are more efficacious than H\(_2\)RAs, but there is very low quality of evidence on the comparison of intravenous administration of PPIs vs. administration of a liquid PPI formulation via nasogastric tube \(^2\). According to the 2012 International Guidelines for Management of Severe Sepsis and Septic Shock, the recommendation for PPIs over histamine-2 receptor antagonists (H\(_2\)RAs) was weak \(^3\). Thus, alternatives to IV PPIs are available and it is not an absolute indication for IV PPIs (H\(_2\)RAs or oral PPIs can be used instead).
- *Severe erosive esophagitis when oral therapy is not possible.* PPIs are more efficacious than H\(_2\)RAs in healing erosive esophagitis, and H\(_2\)RAs are superior to placebo \(^4\). Although potentially more beneficial, alternatives to IV PPIs are available and it is not an absolute indication for IV PPIs (IV H\(_2\)RAs can be used instead).
- *Other conditions (trauma, malignancy) that render oral therapy impossible in patients who require treatment for or prevention of peptic ulcer disease.* PPIs are more efficacious than H\(_2\)RAs, but still H\(_2\)RAs are superior to placebo or no treatment \(^5\). Also here, although
potentially more beneficial, alternatives to IV PPIs are available and it is not an absolute indication for IV PPIs (IV H2RAs can be used instead).

Epidemiological information on disease burden

Nonvariceal upper gastrointestinal (GI) bleeding

Nonvariceal upper (GI) bleeding is a common emergency, affecting 44 to 99 per 100,000 persons every year\(^6,7\). The mortality from nonvariceal upper GI bleeding remains high; a recent UK national audit found a 9.6% in-hospital mortality rate\(^8\). Recurrence of bleeding occurs in 8-26% of patients and is associated with an even higher mortality\(^9\).

Peptic ulcer bleeding

Peptic ulcer bleeding is the principal cause of nonvariceal upper GI bleeding\(^10\), and is associated with substantial morbidity, mortality and health care cost\(^11\). The annual incidence of peptic ulcer bleeding in recent population-based studies varies from 22 per 100,000 persons\(^1\) to 57 per 100,000 persons\(^12\). Approximately 3.5% of patients die during the hospitalization in Canada\(^13\) and in the US\(^14\). A recent systematic review showed similar or higher in-hospital mortality in Europe and in Hong Kong\(^15\). The most recent UK national audit showed an 8.9% in-hospital mortality rate for patients with peptic ulcer bleeding\(^8\). All available evidence on the mortality of peptic ulcer bleeding originates from studies that had been conducted in high resource countries; there are no published data from low income countries\(^15\) where the mortality is expected to be even higher due to limited resources, especially with regards to access to emergency endoscopic treatment.

Bleeding from peptic ulcers stops spontaneously in 80% of patients. In the remaining 20%, bleeding continues or recurs, predominantly within the first 72 hours. These patients are at high risk for emergency surgery and death. Clinical factors predictive of a high risk of rebleeding, need for surgical intervention, and death are the presence of circulatory shock on admission; rebleeding itself; severe comorbidity; old age; and early endoscopic findings of active arterial bleeding, oozing of blood, or a nonbleeding visible vessel in the ulcer base\(^6,16,17,18\). Endoscopic appearances associated with a low risk of adverse outcomes include a clean ulcer base or, at most, a flat pigmented spot in the base. The finding of an adherent clot in the ulcer base carries an intermediate risk.

Description of recommended management for peptic ulcer bleeding

Current management of peptic ulcer bleeding may include resuscitation and fluid replacement, treatment of comorbidity, pharmacologic treatment, endoscopic hemostatic therapy, and surgery\(^19,20\).

Resuscitation and fluid replacement are of major importance and should precede endoscopy. Concurrent major diseases that could be further decompensated by the bleeding episode (e.g., ischemic heart disease, renal insufficiency, and hepatic insufficiency), as well as bleeding disorders should be carefully assessed and treated. Most deaths in patients with ulcer bleeding are caused by decompensation of pre-existing diseases rather than exsanguination\(^18\). Endoscopic hemostatic treatment of bleeding ulcers with high-risk endoscopic stigmata can control ongoing hemorrhage, as well as reduce mortality, rebleeding, and the need for surgical intervention\(^21\). Endoscopic treatment is unnecessary for patients with a clean-based ulcer or flat pigmented spot. The optimal endoscopic management of patients with adherent clots is still debated. Currently, endoscopic hemostatic therapy for high-risk endoscopic findings is the standard of practice.

However, recurrent bleeding still may be a problem after initial endoscopic hemostasis. Therefore, there is still room for improvement in the treatment of peptic ulcer bleeding. Pharmacotherapy with PPIs has been shown to further improve clinical outcomes. It must be emphasized that PPI treatment and endoscopic hemostatic therapy cannot and should not be regarded as a substituting alternative
(to each other). Both treatments are effective in reducing clinical outcomes, and the combination of PPI and initial endoscopic hemostasis have at least an additive effect. However, even with combination treatment, there is still a residual risk for rebleeding and death²⁰.

PPI treatment in peptic ulcer bleeding

How the intervention might work

In vivo studies have provided a plausible explanation as to why PPIs reduce rebleeding in patients with recent or ongoing bleeding from peptic ulcers. Hemostasis in the stomach and duodenum is antagonized by gastric acid and pepsin, which inhibit clot formation and promote lysis of previously formed clots. Plasma coagulation and platelet aggregation are compromised by 50% in the presence of gastric juice at pH 6.4. At pH 6.0, previously formed platelet aggregates break up; at pH 5.4, plasma coagulation and platelet aggregation are practically abolished; at pH 4.0, previously formed fibrin clots are dissolved.²² Such findings provided the rationale for rigorous acid suppression treatment in an attempt to maintain intragastric pH above 6.0 during the first one to three days following an episode of peptic ulcer bleeding. H₂RAs have been studied for decades, but systematic reviews and meta-analyses did not prove superiority compared to placebo²³, hence the research interest turned towards PPIs.

Evidence of efficacy of PPIs in peptic ulcer bleeding

PPIs have been shown to improve clinical outcomes in patients with peptic ulcer bleeding compared to H₂RAs or placebo in a Cochrane systematic review of 24 randomized controlled trials (RCTs) comprising 4373 participants²⁴. PPI treatment significantly reduced rebleeding (odds ratio, OR 0.49; 95% confidence interval (CI) 0.37 to 0.65), surgical interventions (OR 0.61; 95% CI 0.48 to 0.78) and further endoscopic hemostatic treatment (OR 0.32; 95% CI 0.20 to 0.51). There was no evidence of an effect of PPI treatment on all-cause mortality rates (OR 1.01; 95% CI 0.74 to 1.40). However, PPI treatment significantly reduced mortality when the analysis was restricted to patients with high-risk endoscopic findings (active bleeding or a non-bleeding visible vessel) (OR 0.53; 95% CI 0.31 to 0.91), and among trials that had been conducted in Asia (OR 0.35; 95% CI 0.16 to 0.74).

The evidence on the efficacy of PPIs in peptic ulcer bleeding will be further discussed in section #9, where the recommendations form recent guidelines is appraised.

Of note, the effect of PPIs in patients with acute peptic ulcer bleeding is considered to be a class effect. Meta-regression and subgroup analyses in the above-mentioned Cochrane review of RCTs that had compared PPIs with H₂RAs or placebo were consistent with a class effect of PPIs.²⁴ Standard doses of different PPIs may have quantitatively small but statistically significant differences in the degree of acid inhibition²⁵. However, these small differences are inconsistent when the PPIs are compared on a milligram basis, especially when clinical efficacy is assessed²⁶,²⁷.

Assessment of current use of IV PPIs

IV PPIs are widely used in hospitalized patients world-wide. Studies have consistently shown that hospital physicians tend to use intravenous PPIs outside of established indications. In a hospital in Lebanon only 31% of non-ICU hospitalized patients who received IV PPIs had a justified indication of PPI use, and of these, about half could have safely received PPIs orally instead of intravenously.²⁸ Similarly, in a Canadian hospital only 56% of the patients who received IV PPIs had nonvariceal upper GI bleeding, with the remainder of the patients receiving IV PPIs for non-proven indications (e.g. 18% for nothing by mouth status and 13% for abdominal pain).²⁹ However, the documented overutilization of IV PPIs does not mean that all IV PPI treatments are unjustified; as shown below in this application, IV PPI treatment is strongly indicated for a small proportion of patients.
9. Treatment details (dosage regimen, duration; reference to existing WHO and other clinical guidelines; need for special diagnostics, treatment or monitoring facilities and skills)

Existing clinical guidelines

A literature search for clinical practice guidelines (CPGs) on the management of peptic ulcer bleeding or non-variceal upper GI bleeding was performed in PubMed/Medline (http://www.ncbi.nlm.nih.gov/pubmed) using the following search strategy:

```
(Guideline[ptyp] OR Practice Guideline[ptyp]) OR (guideline[Title] OR guidelines[Title] OR consensus[Title] OR statement[Title] OR statement[Title]) OR recommendation[Title] OR recommendations[Title] OR monograph[Title] OR “taskforce” [Title])
AND
(“Peptic Ulcer Hemorrhage”[MESH] OR (“Gastrointestinal Hemorrhage”[MESH] OR “Melena”[ MESH] OR “Hematemesis”[MESH] OR bleed* OR rebleed* OR re-bleed* OR hemorrhag* OR haemorrhag*) AND (“peptic ulcer” OR “duodenal ulcer” OR “gastric ulcer” OR gastric OR stomach OR duodenal OR duodenum OR gastroduodenal OR “upper gastrointestinal” OR “upper GI” OR nonvariceal OR “non-variceal”)))
```

Filters activated: published in the last 5 years, Humans, English.

This search yielded 38 articles, which were screened. Eight CPGs on the management of peptic ulcer bleeding or non-variceal upper GI bleeding were identified, but one of them only addressed the role of endoscopy. The remainder seven CPGs were the following:

1. 2012 American Society for Gastrointestinal Endoscopy (ASGE) CPG
2. 2012 American College of Gastroenterology (ACG) CPG
3. 2012 National Institute for Health and Care Excellence (NICE) CPG
4. 2012 Danish Society of Gastroenterology and Hepatology CPG
5. 2011 Asia-Pacific Working Group Consensus CPG
6. 2011 Belgian CPGs
7. 2010 International Consensus Upper Gastrointestinal Bleeding Conference Group (ICON) CPG

WHO guidelines (http://www.who.int/publications/guidelines/en/) were searched, but there were no relevant guidelines.

The following online resources were also reached but did not reveal any additional CPGs:

- The National Guideline Clearinghouse (http://www.guideline.gov/
- The National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk/guidance)
- National professional associations guideline webpages, including the Canadian Association of Gastroenterology, American Gastroenterological Association, American College of Gastroenterology, American Society for Gastrointestinal Endoscopy, British Society of Gastroenterology.

All seven CPGs, had conducted systematic reviews, assessed the quality of evidence and reported methods. However only 2 CPGs reported the methods in adequate detail: the 2012 NICE CPG, and the 2010 ICON CPG.

The recommendations from these 7 CPGs are presented in the table below:
<table>
<thead>
<tr>
<th>CPG</th>
<th>Patients with acute upper GI bleeding who have not (yet) undergone endoscopy</th>
<th>Patients with acute bleeding from a peptic ulcer (diagnosed endoscopically)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2012 ASGE</strong></td>
<td><strong>Statement:</strong> “We recommend antisecretory therapy with PPIs for patients with suspected peptic ulcer bleeding awaiting endoscopy.”</td>
<td><strong>Statement:</strong> “We recommend antisecretory therapy with PPIs for patients with bleeding caused by peptic ulcers.”</td>
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<tr>
<td></td>
<td><strong>QoE:</strong> High</td>
<td><strong>QoE:</strong> High</td>
</tr>
<tr>
<td></td>
<td><strong>Supporting evidence:</strong> A 2010 Cochrane systematic review of 6 RCTs on pre-endoscopic PPI treatment⁴⁶. “The analysis found that patients with nonvariceal UGIB administered intravenous PPI therapy prior to endoscopy did not experience any statistically significant differences in the outcomes of mortality, rebleeding, or progression to surgery compared with patients in the control group. However, the analysis did show that before-procedure PPI therapy resulted in significantly reduced rates of high-risk stigmata identified on endoscopy (odds ratio [OR] 0.67; 95% confidence interval [CI], 0.54–0.84) and need for endoscopic therapy (OR 0.68; 95% CI, 0.50–0.93). Therefore, intravenous PPI therapy is recommended for patients who are suspected of having acute UGIB.”</td>
<td><strong>Supporting evidence:</strong> Two systematic reviews of RCTs on post-endoscopic PPI treatment ⁴⁶,⁴⁷. “The administration of a continuous infusion, high-dose, intravenous PPI for a period of 72 hours has been demonstrated to be effective in reducing rebleeding rates and mortality after endoscopic therapy of ulcers with high-risk stigmata.”</td>
</tr>
</tbody>
</table>
|  | **Our notes:**  
- Was pre-endoscopic PPI treatment recommended: Yes  
- What route of administration: intravenous | **Our notes:**  
- Was post-endoscopic PPI treatment recommended: Yes  
- What route of administration: intravenous for high risk stigmata; either route for low risk stigmata |

| **2012 ACG** | **Statement A:** “Pre-endoscopic intravenous PPI (e.g., 80 mg bolus followed by 8 mg / h infusion) may be considered to decrease the proportion of patients who have higher risk stigmata of hemorrhage at endoscopy and who receive endoscopic therapy. However, PPIs do not improve clinical outcomes such as further bleeding, surgery, or death.”  
- Conditional recommendation. **QoE:** High  
**Supporting evidence:** A 2010 Cochrane systematic review of 6 RCTs on pre-endoscopic PPI treatment ⁴⁶. | **Statement A:** “After successful endoscopic hemostasis, intravenous PPI therapy with 80 mg bolus followed by 8 mg/h continuous infusion for 72 h should be given to patients who have an ulcer with active bleeding, a non-bleeding visible vessel, or an adherent clot.”  
- Strong recommendation. **QoE:** High  
**Supporting evidence:** A systematic review of RCTs ⁴⁷. “Meta-analysis of randomized trials of intravenous PPI therapy (80 mg bolus followed by 8 mg / h continuous infusion) vs. placebo / no treatment for 72 h after endoscopic therapy of high-risk stigmata reveals a significant reduction in further bleeding (RR = 0.40, 0.28– 0.59; NNT = 12), surgery (RR = 0.43, 0.24–0.76; NNT = 29), and mortality (RR = 0.41, 0.20–0.84; NNT = 45)”  
- Strong recommendation. **QoE:** Moderate  
**Supporting evidence:** “Rates of serious rebleeding with lower risk stigmata (clean base, flat pigmented spot) are low⁴⁸ and thus standard antisecretory therapy to heal the ulcer is all that is recommended in patients with these findings.” |
|  | **Statement B:** “If endoscopy will be delayed or cannot be performed, intravenous PPI is recommended to reduce further bleeding.”  
- Conditional recommendation. **QoE:** Moderate  
**Supporting evidence:** A 2007 Cochrane systematic review of 24 RCTs on post-endoscopic PPI treatment ⁴⁹. A subgroup analysis from this systematic review separated the studies into two groups according to whether endoscopic hemostatic treatment was applied consistently and appropriately to patients who were found to have high risk stigmata of hemorrhage. In the group of studies that did not consistently apply – or never applied – endoscopic hemostatic treatment, “PPI therapy was associated with reduced rebleeding (OR = 0.38, 0.18– 0.81 (with significant heterogeneity); NNT = 10) and surgery (OR = 0.62, 0.44– 0.88; NNT = 17), but not mortality. This suggests that if endoscopy will be delayed or cannot be performed, PPI therapy may improve clinical outcomes.”  
- Our notes:**  
- Was pre-endoscopic PPI treatment recommended: Yes  
- What route of administration: intravenous | **Statement B:** “Patients with ulcers that have flat pigmented spots or clean bases can receive standard PPI therapy (e.g., oral PPI once daily).”  
- Strong recommendation. **QoE:** Moderate  
**Supporting evidence:** “Rates of serious rebleeding with lower risk stigmata (clean base, flat pigmented spot) are low⁴⁸ and thus standard antisecretory therapy to heal the ulcer is all that is recommended in patients with these findings.” |
|  | **Our notes:**  
- Was post-endoscopic PPI treatment recommended: Yes  
- What route of administration: intravenous for high risk stigmata; oral for low risk stigmata |}
### 2012 NICE

**Statement:** “Do not offer acid-suppression drugs (proton pump inhibitors or H2-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding.”

**QoE:** Moderate (GRADE)

**Supporting evidence:** The CPG committee members performed their own systematic review and meta-analysis of RCTs. “When PPIs are considered specifically in the context of routine admission prior to endoscopy in patients with suspected non-variceal bleeding, there is no statistically or clinically significant evidence that acid suppression therapy is beneficial in relation to any of the considered outcomes.”

“Proton pump inhibitors administered pre-endoscopy reduce the incidence of major stigmata or recent haemorrhage. However the evidence suggests that this does not translate into improved clinical outcomes.”

“There is no available evidence that makes a direct comparison between the administration of oral and iv. PPI prior to endoscopy.”

**Our notes:**
- Was pre-endoscopic PPI treatment recommended: No
- What route of administration: Not applicable

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### 2012 Danish

**Statement:** “Treatment with PPI prior to endoscopy cannot be recommended”

**QoE:** “Ia”

**Supporting evidence:** A 2010 Cochrane systematic review of 6 RCTs on pre-endoscopic PPI treatment

A Cochrane analysis has shown that treatment with PPI prior to endoscopy reduces the proportion of patients in whom endoscopic treatment is indicated. However, this is followed neither by a lower rebleeding rate, rate of surgery nor mortality. Furthermore treatment with PPI impedes the diagnosis of Helicobacter pylori infection. Treatment with PPI prior to endoscopy cannot be recommended and must not delay the timing of upper endoscopy.

**Our notes:**
- Was pre-endoscopic PPI treatment recommended: Yes
- What route of administration: not specified

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### 2012

**Statement:** “Offer proton pump inhibitors to patients with non-variceal upper gastrointestinal bleeding and stigmata of recent haemorrhage shown at endoscopy.”

**QoE:** Moderate (GRADE)

**Supporting evidence:** The CPG committee members performed their own systematic review and meta-analysis of RCTs. “When the results of the endoscopy are known, the considered evidence demonstrates statistically and clinically significant benefit of proton pump inhibitors, compared to placebo. Benefit was seen across all outcomes except mortality where there was a trend in favour of PPI which did not reach statistical significance. Proton pump inhibitors were also demonstrably superior to H2 receptor antagonists when considering re-bleeding, surgery and length of hospital stay but not mortality and blood transfusion requirements.”

“The considered evidence does not demonstrate a statistically or clinically significant difference between oral and intravenous proton pump inhibitors across all outcomes.”

“The GDG considered the available analysis by Leontiadis et al. 2007 which found oral PPIs to be more cost effective than iv PPI; however the GDG noted several limitations that may bias the analysis towards oral PPI over iv PPI. […] Taking into account the above potential limitations, the cost effectiveness of iv PPI could be improved on that indicated by Leontiadis et al. 2007. Therefore the GDG felt that either route of administration could be cost effective. Although direct comparisons exist, the quality of evidence comparing oral and intravenous proton pump inhibitors is of very low quality, and consequently it is inadequate to allow firm conclusions to be drawn.”

“The GDG did not feel able to make a firm recommendation on the preferred route of administration. A regimen of an 80mg bolus of Omeprazole or Pantoprazole followed by a 72 hour infusion of 8mg per hour was used in the majority of studies. In contrast studies of orally administered proton pump inhibitor drugs used comparable dosage but a shorter duration of therapy. We are therefore unable to recommend a specific dosage regimen.”

**Our notes:**
- Was post-endoscopic PPI treatment recommended: Yes
- What route of administration: No difference between oral or iv administration observed albeit very low quality evidence, but no recommendation for one over the other made.

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**Statement A:** “Treatment with PPI following endoscopy reduces the rebleeding rate and the need for surgical hemostasis”

**QoE:** “Ia”

**Supporting evidence:** A 2006 Cochrane systematic review of RCTs on post-endoscopic PPI treatment

A Cochrane analysis has shown that, overall, treatment with PPI reduces the rebleeding rate and the need for surgical haemostasis as compared with treatment with placebo or histamine-2 receptor antagonists.

**Statement B:** “Following successful endoscopic therapy, PPI treatment should be given as an intravenous bolus followed by continuous infusion, reducing rebleeding rate and mortality”

**QoE:** “Ib”

**Supporting evidence:** The analyses performed for the 2010 ICON CPG and 2 RCTs that compared 2 different doses of PPI treatment.
**2011 Asia-Pacific**

<table>
<thead>
<tr>
<th>Statement</th>
<th>Pre-endoscopy proton pump inhibitor is recommended where early endoscopy or endoscopic expertise is not available within 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>QoE</td>
<td>Low</td>
</tr>
<tr>
<td>Supporting evidence</td>
<td>A 2010 Cochrane systematic review of 6 RCTs on pre-endoscopic PPI treatment [45], one of the individual RCTs conducted in Hong Kong [59], and a cost-effectiveness analysis [58]. The recommendation should not be constructed as discouraging clinicians who use pre-emptive PPIs for all patients with UGIB. In fact, in a decision analysis based on the Hong Kong model, the use of a high-dose PPI before endoscopy increases the upfront cost but reduces subsequent procedures and hence duration of hospital stay, and thus is still a cost-effective measure. However, the working group considered that a pre-endoscopic PPI may be valuable in practices when early endoscopy or endoscopic expertise is not available within 24 h. Under these circumstances, pre-endoscopy PPI may buy time to stabilise patients before definitive treatment can be arranged. This may be the case for some countries or communities in Asia, especially in rural areas, when medical facilities are limited or in countries where only licensed endoscopists are allowed to perform therapeutic endoscopy.</td>
</tr>
<tr>
<td>Our notes:</td>
<td>- Was pre-endoscopic PPI treatment recommended: Yes - What route of administration: not explicitly stated; implied intravenous</td>
</tr>
</tbody>
</table>

| Statement A | A high-dose intravenous (IV) PPI is effective in reducing rebleeding and the need for surgery. |
| QoE       | High                                                                                                                      |
| Supporting evidence | An IV bolus followed by infusion of a high-dose PPI reduces recurrent bleeding, need for repeated endoscopy, surgery and blood transfusion. This is evident in the Cochrane meta-analysis of data, including 24 RCTs, which showed that even mortality is reduced with the use of intravenous high-dose PPIs. Indeed, high-dose PPI infusion has already been adopted as a standard of care in many Western countries. The initial discrepancy between European and Asian studies has also been resolved by a multinational prospective randomised trial using esomeprazole in the high-dose infusion regimen in the PUB study. The mortality in that study was relatively low and may not entirely reflect the real-life situation where peptic ulcer bleeding is managed in smaller centres with less experience. The use of high-dose intravenous PPIs has also been found to be cost effective in both Asia and America. |

| Statement B | A high-dose oral PPI may be effective in reducing rebleeding in Asian patients. |
| QoE       | Moderate                                                                                                                  |
| Supporting evidence | In some Asian studies, even oral PPIs have been found to be useful in preventing recurrent bleeding from peptic ulcers. Although the Cochrane pooled data showed that only high-dose IV PPIs, but not oral PPIs or low-dose IV PPIs, benefit patients and result in improved clinical outcome, there are obvious differences between Asian and non-Asian studies. Two studies from Asia showed that oral PPIs as an adjunct to endoscopic treatment reduced the risk of recurrent bleeding. [...] This observation is also considered in the ICON-UGIB, which suggest that oral doses of PPIs equivalent to four times the standard daily oral dose can be considered. |

| Statement C | Insufficient data exist on low-dose IV PPI to justify its use. |
| QoE       | Moderate to low                                                                                                             |
| Supporting evidence | Although strong evidence demonstrates the efficacy of high-dose IV PPI treatment after }
### 2011 Belgian

**Statement:** "PPIs are indicated BEFORE and AFTER endoscopy (40 mg IV bid or continuous infusion for 72 h depending on severity)"

**QoE:** 1a (Systematic review of RCTs including meta-analysis)

**Supporting evidence:** A 2010 Cochrane systematic review of 6 RCTs on pre-endoscopic PPI treatment, a systematic review of RCTs that compared 2 doses of PPIs post-endoscopically, and individual RCTs. "In patients with overt signs of UGIB but without persistent hypovolemic shock, an IV bolus of 80 mg omeprazole, followed by 8 mg/hour for 72 hours, administered after hemodynamic stabilization and before endoscopy, was reported to be effective in accelerating the resolution of signs of bleeding from ulcers and in reducing the need for therapeutic endoscopy. A recent Cochrane meta-analysis confirmed these findings [31] (1a-A). Another 2010 meta-analysis showed that there is no evidence that continuous high dose PPI (8 mg/h for 72 h) has a better outcome than fractionated low dose (2 x 40 mg/d) PPI for active ulcer bleeding [32]. Therefore the panel recommends using 2 x 40 mg/d, the first dose being given before endoscopy as soon as a tentative diagnosis of non-PHT related bleeding is made [5-D]. In low risk patients tolerating oral medication, the strategy of giving oral PPI before and after endoscopy, with endoscopic hemostasis for those with no major stigmata of recent hemorrhage, is likely to be the most cost-effective [31-38]."

**Our notes:**
- Was pre-endoscopic PPI treatment recommended: **Yes**
- What route of administration: **oral for low risk patients**

### 2010 ICON

**Statement:** "Pre-endoscopic PPI therapy may be considered to downstage the endoscopic lesion and decrease the need for endoscopic intervention but should not delay endoscopy."

**QoE:** Moderate

**Supporting evidence:** The CPG committee members performed their own update of the Cochrane systematic review of RCTs. "The updated meta-analysis in 2223 patients included 1 study that assessed oral PPI strategies and 5 studies that assessed intravenous strategies, only 1 of which used a high-dose regimen."

"Although pre-endoscopic PPI therapy has not been shown to affect rebleeding, surgery, or mortality, the beneficial effects on the need for intervention, supportive cost-effectiveness analyses, and excellent safety profile suggest that these agents may be useful, particularly in those suspected of having high-risk stigmata."

"The observed lesion down-staging attributable to PPI therapy before endoscopy may be even more beneficial in situations in which early endoscopy may be delayed or when available endoscopic expertise may be suboptimal."

**Our notes:**
- Was pre-endoscopic PPI treatment recommended: **Yes**
- What route of administration: **intravenous for high risk patients; oral for low risk patients**

### Supporting evidence:
- "An intravenous bolus followed by continuous-infusion PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy."

**QoE:** High

**Supporting evidence:** A Cochrane systematic review of RCTs. "Strong evidence demonstrates the efficacy of high-dose intravenous PPI therapy after successful endoscopy, but it is not possible to make conclusions regarding the efficacy of either lower intravenous doses or high-dose oral therapy. Indeed, head-to-head comparisons and subgroup analyses of high versus lower intravenous doses are underpowered, and no direct comparisons of high-dose intravenous therapy and high-dose oral therapy have been made. However, lower intravenous doses or high-dose oral PPI therapy (at doses equivalent to at least 4 times the standard daily oral dose) are also effective (especially in Asian populations) and can be considered when high-dose intravenous therapy is not available or feasible."

"Although recent data have linked PPI use to In-hospital Clostridium difficile infection, the participants felt that the benefits outweighed the risks in patients who have acute UGIB that requires PPI therapy."
The recommendations from the 7 CPGs are further summarized in the following table:

<table>
<thead>
<tr>
<th>CPG</th>
<th>Pre-endoscopic PPI treatment</th>
<th>Post-endoscopic PPI treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Recommended?</td>
<td>Route?</td>
</tr>
<tr>
<td>2012 ASGE</td>
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</tr>
<tr>
<td></td>
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<tr>
<td>2012 ACG</td>
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<td>Intravenous</td>
</tr>
<tr>
<td></td>
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<td>2012 NICE</td>
<td>No</td>
<td>Not relevant</td>
</tr>
<tr>
<td>2012 Danish</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
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<td></td>
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<tr>
<td>2011 Asia-Pacific</td>
<td>Yes</td>
<td>Not explicitly stated, implied intravenous</td>
</tr>
<tr>
<td>2011 Belgian</td>
<td>Yes</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>- Oral for low risk patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2010 ICON</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In summary, 6 out of 7 CPGs recommended pre-endoscopic PPI treatment in patients with suspected nonvariceal upper GI bleeding. With regards to the route of administration of pre-endoscopic PPIs, none of the CPGs recommended an exclusively oral route: 2 GPGs recommended an exclusively intravenous route, 3 CPG did not specify the route (although one of these implied that intravenous route is preferred), and one CPG recommended intravenous administration for high risk patients and oral administration for low risk patients.

All 7 CPG recommended post-endoscopic PPI treatment for patients who had been scoped and found to have peptic ulcer bleeding. Regarding the route of administration of post-endoscopic PPIs, none of the CPGs recommended an exclusively oral route: 5 GPGs recommended intravenous administration for high risk stigmata or high risk patients (of these, 3 recommended oral administration for low risk stigmata/patients, and 2 recommended either route for such patients), one CPG concluded that there was not adequate evidence to make a decision on the route of administration, and one CPG did not provide a clear recommendation (intravenous route was judged to be effective; oral route was judged as “may be effective in Asian patients”).

Therefore, with the exception of the 2012 NICE CPG (which did not recommend pre-endoscopic PPI treatment and did not make a decision on the preferred route of administration for the post-endoscopic PPI treatment), all other CPGs require the availability of intravenous omeprazole for the management of their target populations.

**Dosage regimen and duration**

The **dosage** of the IV regimen of PPIs for peptic ulcer bleeding proposed by the 7 aforementioned CPGs, ranged from 40 mg IV bolus administration twice daily to the “high-dose IV regimen”, i.e. 80 mg IV bolus followed by continuous IV infusion of 8 mg/h.
For high-risk patients, the duration used most studies and recommended by most guidelines in 72 hours, because this is the timeframe when the majority of the negative clinical outcomes (especially rebleeding) occur. However, the duration of treatment should be individualized. Patients should be switched to oral PPI, as soon as the risk of rebleeding is judged to be low (e.g. based on the severity of stigmata of bleeding at index endoscopy, the confidence of the endoscopist on the definitiveness of the endoscopic hemostasis, the absence of clinical evidence of rebleeding, and the absence of severe comorbidities or medications that inhibit hemostasis).

Need for special diagnostics, treatment or monitoring facilities and skills
There is no need for special diagnostics, treatment or monitoring facilities and skills

PUBLIC HEALTH NEED AND EVIDENCE APPRAISAL AND SYNTHESIS

10. Summary of comparative effectiveness in a variety of clinical settings:
A literature search was performed in PubMed on Dec 3, 2014 for systematic reviews and meta-analyses of RCTs on PPI treatment for peptic ulcer bleeding or upper GI bleeding. The search was limited to publications over the last 10 years, humans and English language. The search string was as follows:

("systematic review"[Title] OR "meta-analysis"[Title] OR Meta-Analysis[ptyp])
AND
("Peptic Ulcer Hemorrhage"[MESH] OR ("Gastrointestinal Hemorrhage"[MESH] OR "Melena"[ MESH] OR "Hematemesis"[MESH] OR "bleed" OR re-bleed* OR re-bleed* OR hemorrhag* OR haemorrhag*) AND (ulcer OR gastric OR stomach OR duodenal OR duodenum OR gastroduodenal OR "upper gastrointestinal" OR "upper GI" OR nonvariceal OR "non-variceal")]]
AND
("proton pump inhibitors" OR "proton-pump inhibitors" OR "proton pump inhibitor" OR "proton-pump inhibitor" OR PPI OR PPIs OR "acid suppression" OR omeprazole OR lansoprazole OR pantoprazole OR rabeprazole OR esomeprazole)

This search yielded 38 potentially eligible articles. After screening titles and abstracts, 17 eligible systematic reviews and meta-analyses of RCTs were identified:

Despite differences between meta-analyses (regarding the date of literature search, the databases searched, the exact definition of target population/interventions/comparators/outcomes of interest, and the methods applied) there was absolute agreement between all meta-analyses on the efficacy of PPIs (compared to H2RAs or placebo) in patients with endoscopically confirmed peptic ulcer bleeding.

In this population, PPIs compared to either H2RAs or placebo, have very consistently reduced rebleeding (clinically important and statistically significant difference) in all subgroup analyses (by risk of bias, route of PPI administration, type of control treatment or application of initial endoscopic haemostatic treatment) and sensitivity analyses. In the 2006 Cochrane review of 24 RCTs PPI treatment, PPIs significantly reduced rebleeding compared to control; odds ratio (OR) 0.49; 95% CI 0.37 to 0.65). There was statistically significant heterogeneity (P = 0.04) that was fully explained (eliminated by) a subgroup analysis by geographical location. PPI treatment was more efficacious in studies conducted in Asia compared to studies conducted elsewhere. The increased efficacy of PPIs in Asian studies may be related to the lower parietal cell mass and a higher prevalence of H. pylori infection and genetically determined slow metabolism of PPIs in Asian patients.

PPIs also have reduced the rate of emergency surgical interventions, although the effect was not as consistent in subgroup and sensitivity analyses as with the outcome of rebleeding. In the 2006 Cochrane review, PPI treatment significantly reduced surgery compared to control; OR 0.61; 95% CI 0.48 to 0.78, without statistically significant heterogeneity (P = 0.24).

The effect of PPI treatment on mortality was seen only in subgroup analyses. In the 2006 Cochrane review, PPI treatment was not associated with a statistically significant difference in all-cause mortality rates between PPI and control treatment, but the 95% CI could not exclude a clinically important benefit or harm; OR 1.01; 95% CI 0.74 to 1.40, without statistically significant heterogeneity (P = 0.24). However, PPI treatment reduced mortality in studies conducted in Asia. Also PPI reduced mortality also among patients with high-risk endoscopic stigmata (active bleeding or non-bleeding visible vessel); OR 0.53; 95% CI 0.31 to 0.91.

A 2009 update of the Cochrane review of PPIs vs control in peptic ulcer bleeding (only available as abstract publication) that was conducted for the needs of the 2010 ICON CPG, showed that among patients with high risk stigmata who were treated consistently and appropriately with endoscopic haemostatic treatment, only there was a statistically significant reduction in mortality only for the subgroup of studies that used the high dose intravenous PPI regimen – and not for the subgroup of studies that used other PPI regimens (oral or low-dose intravenous). This subgroup
analysis has been often been interpreted erroneously is subsequent publications. It has been mistakenly interpreted as indirect proof of superiority of the high dose intravenous regimen vs. other PPI regimens; this is not correct because the test for subgroup differences was not significant. In fact the subgroup of studies on non-high dose PPI regimens was seriously underpowered, resulting in a wide 95% CI that crossed the line of no effect and widely overlapped with the 95% CI for the high-dose IV regimen. Inversely, this subgroup analysis was considered by others as proof of equivalence between the two regimens, but this was also a mistaken interpretation. The authors of this application agree with the interpretation of the 2010 ICON CPG 19: we can only conclude that we have high quality of evidence that the high-dose IV reduces rebleeding and surgery in the high-risk population the clinicians should be worried the most. On the other hand, the efficacy of lower-dose PPI regimens on mortality has not been proven as yet (the quality of evidence is moderate due to serious imprecision). Therefore, it seems prudent to recommend high-dose IV PPI treatment for these patients, until there is proof that lower-dose regimens are also efficacious.

Another common misinterpretation is that the recommendation for “high-dose IV PPI treatment in patients with high risk stigmata after successful endoscopic therapy” means that patients with high risk stigmata who will not undergo endoscopy, or will not have endoscopic therapy, or will have unsuccessful endoscopic therapy, will not need treatment with IV PPIs. Such patients are at even higher risk for rebleeding and death than patients who had successful endoscopic therapy, and therefore are at even higher need for the regimen that has been best documented to be successful. Such situations are more likely to occur in low-resource areas and counties. Nowadays, in most Western countries the standard of care for acute upper GI bleeding includes prompt endoscopy and, if high-risk stigmata are seen, endoscopic treatment with well-defined modalities.

Five recent systematic reviews and meta-analyses of RCTs that compared two different doses of PPIs for peptic ulcer bleeding:


Of those, four included a comparison of IV vs. oral PPIs in peptic ulcer bleeding:

- Sachar 2014: included a subgroup analysis on 4 RCTs that compared oral PPI treatment vs. high-dose continuous IV infusion. This analysis had used a noninferiority approach, and therefore only reported the point estimate of the relative risk (RR, 0.96) and the upper boundary of the 1-sided 95% CI (2.02), therefore suggesting noninferiority. RCTs that compared intermittent (bolus) IV PPI treatment were not included in this systematic review.
- Tsoi 2013: 6 RCTs were included that compared oral vs IV PPI treatment. There were no significant differences found for any clinical outcome. The 95% CIs for the pooled effects could not rule out clinically important benefit or harm.
- Neumann 2013: Included a subgroup analysis on 5 RCTs that had compared oral vs. IV PPI treatment. There were no significant differences found for any clinical outcome. The 95% CIs for the pooled effects could not rule out clinically important benefit or harm.
- Wang 2010: Included a subgroup analysis on 2 RCTs that had compared oral vs. high-dose continuous IV infusion PPI treatment. There were no significant differences found for any clinical outcome. The 95% CIs for the pooled effects could not rule out clinically important benefit or harm.
**UPDATED SYSTEMATIC REVIEW AND META-ANALYSIS**

One of the authors of this application was the senior author of the recent Cochrane review of RCTs that compared different regimens of PPI treatment for peptic ulcer bleeding \(^{62}\), and therefore had access to the data extraction forms and the RevMan file for all previously included RCTs. It was decided to update this systematic review and meta-analysis for the needs of this application.

**METHODS**

**Types of studies:**

RCTs that compared treatment with oral PPI with treatment with intravenous PPI (the same or different PPI) in patients with acute bleeding from peptic ulcer, provided that they met all the following criteria:

- concomitant therapy was applied equally to both intervention arms;
- acute bleeding from peptic ulcer was diagnosed endoscopically;
- for RCTs that included patients with other causes of upper GI bleeding, the data for patients with peptic ulcer bleeding had to be accessible and presented separately;
- at least one of the following outcomes was reported: mortality, rebleeding, surgical intervention, adverse effects

**Types of participants**

Patients with acute upper gastrointestinal bleeding with an endoscopically-confirmed diagnosis of bleeding peptic ulcer. The participants were patients admitted to hospital for the bleeding episode or in-patients who developed acute bleeding from a peptic ulcer while hospitalized for other reasons.

**Types of interventions**

The treatment group received intravenous PPI treatment (either PPI alone or in combination with other treatment) and the control group received oral PPI treatment (either PPI alone or in combination with the same concomitant treatment administered to the intravenous PPI group). Only studies in which treatment groups were treated similarly, apart from the dose of PPIs being compared, were included.

**Types of outcome measures**

Primary outcome:

- Death from any cause within 30 days of randomization, or at the reported time point closest to 30 days.

Secondary outcomes

- rebleeding within 30 days of randomization or at the reported time point closest to 30 days.
- surgical intervention (including angiographic embolization) for bleeding within 30 days of randomization, or at the reported time point closest to 30 days
- adverse effects within 30 days of randomization, or at the reported time point closest to 30 days

**Search methods for identification of the studies**

Since the authors of this application had access to the data extraction forms and the RevMan file of the 2013 Cochrane review on this topic, it was decided to use that Cochrane review as starting point\(^{62}\). That Cochrane review had included 22 RCTs that compared at least 2 different regimens of PPI treatment in patient with peptic ulcer bleeding. These RCTs had been identified via a comprehensive literature search in MEDLINE, EMBASE, CENTRAL and proceedings of major gastroenterology meetings up to September 2010, without language restrictions. That search
strategy could not be replicated for the updated search due to time restrictions related to the strict deadline for submission of this application. Instead, the following search methods were used:

1. The 22 RCTs that were included in the 2013 Cochrane review were re-assessed for identification of studies that had compared intravenous PPI treatment with oral PPI treatment

2. A literature search was conducted in PubMed on Dec 3, 2014 for RCTs that had compared IV omeprazole (or other IV PPIs) with oral omeprazole (or other oral PPIs) in patients with peptic ulcer bleeding. No filters for RCTs were applied so as not to limit the sensitivity of the search. The publication date was from Aug 1, 2010 (this was set one month earlier that the end of the literature search of our 2013 Cochrane systematic review on this topic 62). The search was limited to publications on humans and in English language. The search string was as follows:

   ("Peptic Ulcer Hemorrhage"[MESH] OR ("Gastrointestinal Hemorrhage"[MESH] OR "Melena"[ MESH] OR "Hematemesi"[MESH] OR bleed* OR re-bleed* OR re-bleed* OR hemorrhag* OR haemorrhag*)
   AND
   ("peptic ulcer" OR "duodenal ulcer" OR "gastric ulcer" OR gastric OR stomach OR duodenal OR duodenum OR gastroduodenal OR "upper gastrointestinal" OR "upper GI" OR nonvariceal OR "non-variceal")
   AND
   ("proton pump inhibitors" OR "proton-pump inhibitors" OR "proton pump inhibitor" OR "proton pump inhibitor" OR PPI OR PPIs OR "acid suppression" OR omeprazole OR lansoprazole dexlansoprazole OR pantoprazole OR rabeprazole OR esomeprazole)

3. The 17 systematic reviews and meta-analyses that were identified by the search described in the beginning of section 10, were searched for additional eligible RCTs

Data extraction and management
The data were extracted by a single reviewer using the data extraction form that was previously used for the 2013 Cochrane review.

Assessment of risk of bias in included studies
The risk of bias of the included studies was assessed using the "Risk of bias table" which is the tool recommended by The Cochrane Collaboration. For each study a description and a judgement was provided for each one of the following domains: sequence generation, allocation sequence concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias.

Measures of treatment effect and data synthesis
Pooled outcomes (all outcomes were dichotomous) were reported as risk ratio (RR) and risk difference with 95% CI. Data synthesis was performed with the Mantel-Haenszel random effects method with the use of the Review Manager software (RevMan 5.3.5).

Assessment of the quality of evidence
The quality of evidence was assessed according to the GRADE approach63. Summary of findings tables were produced. The quality of evidence for each outcome was classified as high, moderate, low, or very low. According to the GRADE framework evidence from RCTs starts as high quality, but can downgraded in quality for study limitations, inconsistency, imprecision, indirectness, and/or publication bias.

RESULTS
Re-assessment of the RCTs that were already included in the 2013 Cochrane systematic review identified 5 eligible RCTs:

The updated search for RCTs in Medline yielded 263 publications. Titles and abstracts were manually searched. For all publications that could not be confidently excluded at this stage, the full-text was retrieved and assessed for eligibility. Three eligible RCT were published following the literature search by the recent Cochrane systematic review:

The search of the included studies and reference lists of all other published systematic reviews and meta-analyses revealed two additional eligible RCTs:

Of note, the RCT named “Tsai 2008” that was included in the systematic review by Tsoi et al (Tsoi 2013), is apparently a typographical error; it was published in 2009, and has been included in the 2013 Cochrane review. The RCT named Sung 2012 that was included in the systematic review by Sachar et al (Sachar 2014) was the preliminary abstract publication of the study that was subsequently published in full (Sung 2014). Finally, Mostaghni 2011, which was included in the in the systematic review by Tsoi et al (Tsoi 2013), was not a true RCT (patients were allocated to the two treatments “based on even and odd days of the month”).

Therefore, 10 RCTs were included in the updated systematic review of RCTs that compared oral PPI treatment with intravenous PPI treatment in patients with peptic ulcer bleeding.

The characteristics of these 10 studies and the risk of bias are shown below.

**Characteristics of included studies**

**Bajaj 2007**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Single-centre RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Country: US. 25 participants. Mean age 63 years. SRH: spurring or oozing bleed 28%, NBBVV (or “red spot”) 36%, clean base 36%. Conflicting information with regards to the proportion of patients with high risk SRH who underwent initial endoscopic hemostasis: 86% according to table 2 in Results section, but 100% according to a statement in the Discussion section.</td>
</tr>
<tr>
<td>Interventions</td>
<td>IV regimen: pantoprazole 80 mg bolus IV, then IV infusion 8 mg/h for 3 days. Oral regimen: pantoprazole 80 mg PO every 12h for 3 days. After the initial 72 hours, all participants received pantoprazole 40mg PO once daily for at least 30 days.</td>
</tr>
</tbody>
</table>
### Focareta 2004

**Methods**
- Single-centre RCT

**Participants**
- Country: Italy. 87 participants. SRH: spurting bleed 15%, oozing bleed 20%, NBVV 28%, adherent clot 38%. They all received initial endoscopic hemostatic treatment (presumably successful)

**Interventions**
- **IV regimen**: omeprazole 80 mg IV bolus, then 40 mg three times daily
- **Oral regimen**: esomeprazole 40mg PO twice daily

**Outcomes**
- Rebleeding, surgery

**Notes**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No description (only available as abstract)</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
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</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Different schedules of PPI administration without measures to ensure blinding</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>No description (only available as abstract)</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>The study report does not include results for a key outcome that would be expected (mortality)</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No description (only available as abstract)</td>
</tr>
</tbody>
</table>

### Jae 2006

**Methods**
- RCT

**Participants**
- Country: Korea. 38 participants. SRH: spurting or oozing bleed 26%; NBBVV 74%. All patients initial endoscopic hemostasis

**Interventions**
- **IV regimen**: pantoprazole 80 mg IV bolus, then 40 mg three times daily, for 3 days, then 40 mg orally once daily for 8 weeks
- **Oral regimen**: pantoprazole 40mg orally twice daily, for 5 days, then 40 mg orally once daily for 8 weeks

**Outcomes**
- Rebleeding, mortality

**Notes**
- The article is not accessible. The description and outcomes are derived from the information reported in the meta-analysis by Tsoi et al. Aliment Phram Ther 2013.
### Jang 2006

**Methods**
- Single-centre RCT

**Participants**
- Country: South Korea. 40 participants (results were reported for 37 participants) SRH: all had either active bleeding or NBVV. Initial endoscopic hemostasis in 100%.

**Interventions**
- IV regimen: Pantoprazole 80 mg IV bolus, then infusion 8 mg/h IV for 72 h
- Oral regimen: Pantoprazole 40 mg PO twice daily for 5 days
- Thereafter, all patients received pantoprazole 40 mg PO once daily for 8 weeks.

**Outcomes**
- Mortality, rebleeding, surgery, length of stay

**Notes**
- Only available as abstract

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
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</tr>
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<td>No description (only available as abstract)</td>
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<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>The study protocol is not available but it is clear that the published report includes all expected outcomes</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>No description (only available as abstract)</td>
</tr>
</tbody>
</table>

### Javid 2009

**Methods**
- Three parallel RCTs, each RCT in a different centre

**Participants**
- Country: India. 90 participants (30 in each RCT) SRH: all had either active bleeding or NBVV. All had initial endoscopic hemostasis.

**Interventions**
- RCT-1:
  - IV regimen: Omeprazole 80 mg IV bolus, then infusion 8 mg/h IV for 72 h
  - Oral regimen: Omeprazole 80 mg PO initially, then 40 mg PO every 12 h for 72 h
- RCT-2:
  - IV regimen: Pantoprazole 80 mg IV bolus, then infusion 8 mg/h IV for 72 h
  - Oral regimen: Pantoprazole 80 mg PO initially, then 80 mg PO every 12 h for 72 h
- RCT-1:
  - IV regimen: Rabeprazole 80 mg IV bolus, then infusion 8 mg/h IV for 72 h
  - Oral regimen: Rabeprazole 80 mg PO initially, then 40 mg PO every 12 h for 72 h
- After 72 h, all patients (all three RCTs) who were H. pylori-infected received triple therapy and oral PPI daily for 8 weeks and patients who were not H. pylori infected received daily PPI for 8 weeks.

**Outcomes**
- Mortality, rebleeding, surgery

**Notes**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “Treatment assignments were made based on random numbers derived from a table of random numbers in blocks of four”</td>
</tr>
</tbody>
</table>
### Kim 2012

**Methods**
Two-centre RCT

**Participants**
Country: Republic of Korea. 106 participants. Mean age 57 years. 78% with "major" SRH (active bleeding or NBVV) and 22% with adherent clot. All had successful initial endoscopic hemostasis.

**Interventions**
- **IV regimen:** omeprazole 80 mg bolus, followed by continuous infusion at 8 mg/h for 72 h.
- **Oral regimen:** rabeprazole 20 mg orally 2 times daily for 72 h.
Both groups: From day 4 to week 6: oral rabeprazole 10 mg once daily.

**Outcomes**
Mortality, rebleeding, surgery

**Notes**
Terminated early due to slow recruitment

**Bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
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<tr>
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<td>detection bias)</td>
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</tr>
<tr>
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<tr>
<td>(attrition bias)</td>
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<tr>
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<td>Low risk</td>
<td>The study protocol is not available but it the published report includes all</td>
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<tr>
<td>bias)</td>
<td></td>
<td>expected outcomes.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>The study appears to be free of other sources of bias.</td>
</tr>
<tr>
<td>Bias</td>
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<td>Support for judgement</td>
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<tr>
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<td>-------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Not blinded. Compared intermittent vs. continuous administration of PPI without measures to ensure blinding</td>
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<tr>
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<td>Low risk</td>
<td>The study appears to be free of other sources of bias.</td>
</tr>
</tbody>
</table>

**Tsai 2009**

**Participants**
Country: Taiwan. 156 participants. Mean age 69 years. SRH: spurting bleed 2%, oozing bleed 39%, NBV 27%, adherent clot 31%. All had initial endoscopic hemostatic treatment.

**Interventions**
**IV regimen:** Omeprazole IV continuous infusion 40 mg per 12 h for 72 h. Followed by esomeprazole 40 mg PO once daily for 2 months.  
**Oral regimen:** Rabeprazole 20 mg PO twice daily for 72. Followed by rabeprazole 20mg PO once daily for 2 months.  
For both groups: patients with *H. pylori* infection received a 1-week course of triple eradication therapy (containing esomeprazole 40 mg PO twice daily) after discharge.

**Outcomes**
Mortality, rebleeding, surgery

**Notes**

**Yen 2012**

**Participants**
Country: Taiwan. 100 participants. Mean age 64 years. All patients had "major" SRH (active bleeding or NBV) and successful initial endoscopic hemostasis.

**Interventions**
**IV regimen:** esomeprazole 80 mg “continuous infusion every 6 h” for 3 days. Thereafter, oral esomeprazole 40 mg once daily for 2 months.  
**Oral regimen:** Lansoprazole 30 mg orally 4 times daily for 3 days. Thereafter, oral lansoprazole 40 mg once daily for 2 months.  
For both groups: Patients who had *H. pylori* infection received one week of triple eradication therapy after discharge.

**Outcomes**
Mortality, rebleeding, surgery, length of stay, and transfusion requirements.

**Notes**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>Quote: “derived from a random number table”.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;using sealed envelopes containing a therapeutic option&quot;. Unclear if the envelopes were opaque and consecutively numbered.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>High risk</td>
<td>Not blinded. Different routes of PPI administration without measures to ensure blinding</td>
</tr>
</tbody>
</table>
In complete outcome data (attrition bias) | Low risk | All randomized patients completed the study and were included in the analysis
--- | --- | ---
Selective reporting (reporting bias) | Low risk | The study protocol is available (NCT01123031). All pre-stated primary outcomes (at 14 days) have been reported (the 30-day outcomes that were included as secondary outcomes in the protocol have not been reported, but this is an issue of minor concern)
Other bias | Low risk | The study appears to be free of other sources of bias.

Yilmaz 2006

Methods | Single-centre RCT
Participants | Country: Turkey. 211 participants. Mean age 53 years; male 69%; comorbidities 36%; GU 24%, DU 76%. SRH: "old adherent clot" (clot dislodged easily by washing) 10%, flat spot 22%, clean base 68% (patients with active bleeding, NBV or "fresh" adherent clots were excluded for this RCT). Initial endoscopic hemostatic treatment in 6% (all patients had achieved spontaneous hemostasis at study entry).
Interventions | IV regimen: Omeprazole 80 mg IV bolus, then IV infusion 8mg/h for 72h
Oral regimen: Omeprazole 40 mg PO every 12 h for 72 h
After the first 72 h, both groups received omeprazole 40 mg PO once daily for 6 weeks (patients with H. pylori infection initially received a 2-week eradication therapy with omeprazole 20 mg PO twice daily)
Outcomes | Mortality, rebleeding, surgery
Notes

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>
| Random sequence generation (selection bias) | Low risk | Quote: "coded them based on random table numbers"
| Allocation concealment (selection bias) | Low risk | Quote: "A person outside the study staff placed the two drug formulations into sealed non-transparent envelopes and coded them [...] Only this person knew the codes". Ideally, the envelopes should have also been consecutively numbered, but the allocation concealment can still be considered adequate.
| Blinding (performance bias and detection bias) | High risk | Quote: "The research assistant, other medical personnel, the endoscopists, and patients were blind to this information. The study was conducted in a double-blind manner as all treatment assignments were revealed at the end of the study." The study was stated to be double blind, but there was no mention of dummy medications (without dummy regimens binding could not be possible for this study that compared oral vs. IV regimens).
| Incomplete outcome data (attrition bias) | Unclear risk | There were no losses to follow up or protocol violations in the first 72 h. Following discharge, completeness of follow up is uncertain, because the investigators relied on patients and relatives calling to inform in case negative outcomes had occurred.
| Selective reporting (reporting bias) | Low risk | The study protocol is not available but it is clear that the published report includes all expected outcomes
| Other bias | Low risk | The study appears to be free of other sources of bias.

Risk of bias graph for the 10 included RCTs

---

Risk of bias summary for the 10 included RCTs
EFFECTS OF INTERVENTIONS

The above-mentioned 10 studies were included in the meta-analysis of outcomes (Javid 2009 compromised of 3 independent RCTs, so the outcomes were included in the forest plots as Javid 2009-a, Javid 2009-b, and Javid 2009-c)

Mortality

Eight out of 10 studies reported numerical results on mortality (763 patients; 11 events in total). Only 5 studies contributed to the analysis (the remainder studies had zero events in both arms). There was no statistically significant or substantial heterogeneity among studies ($P = 0.77$; $I^2 = 0\%$). There was no statistically significant difference in mortality rates between IV and oral PPI treatment: the pooled relative risk (RR) was 0.83 ($95\%$ CI 0.27 to 2.53). The $95\%$ CI around the pooled estimate included the possibility of no difference, but it was not possible to exclude clinically relevant benefit or harm with IV PPI. Pooled risk difference (RD) 0 more deaths per 100 patients treated with IV PPI ($95\%$ CI from 2 fewer to 2 more deaths per 100 treated).
The quality of evidence for mortality was very low (see Summary of Evidence table). The reasons for downgrading the quality of evidence are as follows:

- **Study limitations:** Serious. All 8 trials included in the analysis on mortality had high risk of bias (main reason being that no trial was blinded, leading to performance bias)
- **Inconsistency:** Not serious. Statistical heterogeneity was not detected; however it must be noted that if inconsistency was present it would have been masked by the fact that the confidence intervals for the effect for each study were very wide and therefore broadly overlapping.
- **Imprecision:** Very serious. Very small number of events (11 in total). The 95% confidence interval for the pooled effect does not exclude a large clinically relevant benefit or a large clinically relevant harm.
- **Indirectness:** Serious: the low mortality rate (1.6% for the oral PPI group; 1.4% overall) suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice.
- **Publication bias:** Not detected (see funnel plot below; note that only 5 studies contributed to the analysis).

Rebleeding

All 10 studies (1894 participants) reported numerical results on rebleeding rates. There was no statistically significant or substantial heterogeneity among studies (P = 0.96; I² = 0%). There was no statistically significant difference in rebleeding rates between IV and oral PPI treatment: the pooled relative risk (RR) was 1.07 (95% CI 0.71 to 1.62). The 95% CI around the pooled estimate included the possibility of no difference, but it was not possible to exclude clinically relevant benefit or harm with IV PPI. Pooled risk difference (RD) 0 more rebleeds per 100 patients treated with IV PPI (95% CI from 2 fewer to 3 more rebleeds per 100 treated).
The quality of evidence for rebleeding was low (see Summary of Evidence table). The reasons for downgrading the quality of evidence are as follows:

- **Study limitations**: Serious. Nine out of 10 trials included in this analysis had high risk of bias (performance and detection bias due to lack of blinding). One trial had unclear risk of bias (possible attrition bias).

- **Inconsistency**: Not serious. Statistical heterogeneity was not detected; however it must be noted that if inconsistency was present it would have been masked by the fact that the confidence intervals for the effect for each study were very wide and therefore broadly overlapping.

- **Imprecision**: Serious. Small number of events (84 in total). The 95% confidence interval for the pooled effect does not exclude a clinically relevant benefit or harm.

- **Indirectness**: Possible: the low mortality rate (1.6% for the oral PPI group; 1.4% overall) among the 8 (out of 10) studies that reported mortality rates suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice.

- **Publication bias**: Not detected (see funnel plot below)

### Surgical interventions

Nine studies (1056 participants) reported numerical results on surgery rates. There was no statistically significant or substantial heterogeneity among studies (P = 0.90; I² = 0%). There was no statistically significant difference in surgery rates between IV and oral PPI treatment: the pooled relative risk (RR) was 0.94 (95% CI 0.39 to 2.24). The 95% CI around the pooled estimate included the possibility of no difference, but it was not possible to exclude clinically relevant benefit or harm with IV PPI. Pooled risk difference (RD) 0 more surgeries per 100 patients treated with IV PPI (95% CI from 2 fewer to 1 more surgeries per 100 treated).
The quality of evidence for surgery was low (see Summary of Evidence table). The reasons for downgrading the quality of evidence are as follows:

- **Study limitations:** **Serious.** Eight out of 9 trials included in the analysis on mortality had high risk of bias (performance bias due to lack of blinding). One trial had unclear risk of bias (possible attrition bias).

- **Inconsistency:** Not serious. Statistical heterogeneity was not detected; however it must be noted that if inconsistency was present it would have been masked by the fact that the confidence intervals for the effect for each study were very wide and therefore broadly overlapping.

- **Imprecision:** **Serious.** Small number of events (19 in total). The 95% confidence interval for the pooled effect does not exclude a clinically relevant benefit or harm.

- **Indirectness:** **Possible:** the low mortality rate (1.6% for the oral PPI group; 1.4% overall) among the 8 (out of 9) studies that reported mortality rates suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice.

- **Publication bias:** Not detected (see funnel plot below)
Summary of Findings table (clinical efficacy)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>2 per 100</td>
<td>2 per 100 (0 to 4)1</td>
<td>RR 0.83 (0.27 to 2.53)</td>
<td>763 (8 studies)</td>
<td>⊕⊕⊕⊕ very low2,3,4</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>7 per 100</td>
<td>7 per 100 (5 to 10)1</td>
<td>RR 1.07 (0.71 to 1.62)</td>
<td>1894 (10 studies)</td>
<td>⊕⊕⊕ low5,6,7</td>
</tr>
<tr>
<td>Surgery</td>
<td>2 per 100</td>
<td>2 per 100 (0 to 3)1</td>
<td>RR 1.33 (0.63 to 2.77)</td>
<td>1270 (9 studies)</td>
<td>⊕⊕⊕⊕⊕⊕⊕ very low8,9,10</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Notes

1. Pooled risk difference

2. Serious study limitations: All 8 trials included in the analysis on mortality had high risk of bias (main reason being that no trial was blinded)

3. Very serious imprecision: very small number of events (11 in total); the 95% CI of the pooled RR does not exclude a clinically relevant benefit or harm

4. Serious indirectness: the low mortality rate (1.6% for the oral PPI group; 1.4% overall) suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice

5. Serious study limitations: Nine out of 10 trials included in the analysis on rebleeding had high risk of bias (performance and detection bias due to lack of blinding). One trial had unclear risk of bias (possible attrition bias).

6. Serious imprecision: Small number of events (84 in total). The 95% confidence interval for the pooled effect does not exclude a clinically relevant benefit or harm.

7. Possible indirectness: the low mortality rate (1.6% for the oral PPI group; 1.4% overall) among the 8 (out of 10) studies that reported mortality rates suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice

8. Serious study limitations: Nine out of 10 trials included in the analysis on rebleeding had high risk of bias (performance and detection bias due to lack of blinding). One trial had unclear risk of bias (possible attrition bias).

9. Serious imprecision: Small number of events (84 in total). The 95% confidence interval for the pooled effect does not exclude a clinically relevant benefit or harm.

10. Possible indirectness: the low mortality rate (1.6% for the oral PPI group; 1.4% overall) among the 8 (out of 10) studies that reported mortality rates suggests that the study populations included in this analysis are not representative of the patients with peptic ulcer bleeding seen in clinical practice.
DISCUSSION

It is obvious that patients with peptic ulcer bleeding who present with hematemesis cannot practically be treated with oral PPIs because of impaired absorption of oral PPI. This is only a proportion of the population with peptic ulcer bleeding, but it is understandable that for such patients there is no alternative to IV PPI treatment, at least during the acute phase.

Furthermore, it is important to note that all 10 RCTs that compared IV vs oral PPI treatment in patients with peptic ulcer bleeding used restrictive inclusion criteria so as to ensure the safety of the participants. These studies applied all or a combination of the following exclusion criteria:

- Delayed endoscopy (> 24 hours) and
- Coagulopathy
- Severe comorbidities
- Shock
- Unsuccessful endoscopic hemostatic
- persistent vomiting

Of course, none of the 10 RCTs had included patients who never had endoscopy because of very serious comorbidities or irreversible hemodynamic instability.

Therefore, the population of the published RCTs is different from the target population who is a candidate for IV omeprazole in the real world, especially in low-resource areas and countries were urgent endoscopy and appropriate endoscopic therapy might not be feasible. The restrictive inclusion criteria in the published RCTs would lead to study populations with an very low baseline risk for re-bleeding and mortality (as shown in this meta-analysis), and therefore would be likely to bias the results towards showing “non-significant” differences between the studied interventions effects.

The extent of this selection bias can be seen in the study by Sung et al (Sung 2014). “In a period of 60 months, 862 patients presented to the Prince of Wales Hospital with Forrest I or IIA / B bleeding ulcers. A total of 263 patients were enrolled into this study, and 599 were not randomized because of various reasons” Therefore only 30.5% of the real-life populations of patients with peptic ulcer bleeding were included in the study (see figure below).
11. Summary of comparative evidence on safety:

Long-term PPI treatment has been recently associated with a wide range of potential adverse effects (including C. difficile infection, bone fractures, respiratory infections, interaction with clopidogrel, hypomagnesemia, etc.), however, short-term treatment, either IV or oral, (even high dose regimens) for the median duration of 2-3 days required for peptic ulcer bleeding, have never raised safety concerns. 

Although more than 50 RCTs have assessed the efficacy of PPIs in peptic ulcer bleeding (compared to placebo, or an H2RA or another PPI regimen), not all publications have reported adverse effects in detail, and very few trials applied rigorous protocols to actively seek adverse effects. No systematic reviews and meta-analyses were able to extract data of adequate quality and granularity to perform a meta-analysis of adverse effects of PPIs vs. H2RAs, PPIs vs. placebo, or IV PPIs vs. oral PPIs. The best data were available in the Cochrane review of RCTs on PPIs vs placebo or H2RAs for peptic ulcer bleeding, where no serious adverse effects were associated with PPI treatment (oral or IV).

Regarding the 10 RCTs (comparing IV vs oral PPI in peptic ulcer bleeding) that were included in the systematic review that was conducted for this application, the adverse effects were as follows:

Bajaj 2007 reported that there were no adverse effects in either study arm (one patient on the IV pantoprazole arm developed renal failure, that resolved within 1 week, but this was not considered as adverse effect to the medication, presumably because acute, reversible renal failure is not an uncommon complication of GI bleeding itself).

Kim 2012 stated that: “There were few adverse events reported. Two adverse events in the oral rabeprazole group were elevation of hepatic enzyme levels and generalized tonic seizure-like activity. The elevated hepatic enzyme levels were resolved within several days. The seizure-like activity, possibly caused by hyperventilation, was resolved within 15–20 seconds by conservative management; no sequelae was seen during the 6-week follow-up period. The two adverse events in the IV omeprazole group were elevation of hepatic enzyme levels and premature ventricular beats. The elevated hepatic enzyme levels were resolved within several days. The patient with premature ventricular beats had a history of percutaneous coronary angioplasty because of angina and had no concomitant symptom. No severe adverse events resulted from withdrawal from the study in either group.”

The remainder eight studies did not report adverse effects. Two of these were only published as abstracts, one was not accessible (its evaluation was based on the information reported in the systematic review by Choi et al); five were available as full publications.
Summary of Findings table (Adverse effects)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Oral PPI</th>
<th>Intravenous PPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects</td>
<td>Could not be estimated</td>
<td>Could not be estimated</td>
</tr>
<tr>
<td></td>
<td>Could not be estimated</td>
<td>Could not be estimated</td>
</tr>
<tr>
<td>No of Participants (studies)</td>
<td>131 (2 studies)</td>
<td></td>
</tr>
<tr>
<td>Quality of the evidence (GRADE)</td>
<td>⊕⊝⊝⊝ very low</td>
<td></td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; GRADE Working Group grades of evidence

Notes

1. Very serious study limitations: High risk of bias for selective outcome reporting (only 2 out of 10 trials reported adverse effects), and for lack of blinding in the 2 trials that reported adverse effects (performance and attrition bias)

2. Very serious imprecision: very small number of events (few adverse effects were reported, none in more than 2 patients); only 131 participants

The following information on safety of IV esomeprazole is included in the "US prescribing information for NEXIUM® I.V. (esomeprazole sodium) for injection, for intravenous use" 76.
6 ADVERSE REACTIONS

6.1 Clinical Trials Experience with Intravenous NEXIUM

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults

The safety of intravenous esomeprazole is based on results from clinical trials conducted in four different populations including patients having symptomatic GERD with or without a history of erosive esophagitis (n=199), patients with erosive esophagitis (n=160), healthy subjects (n=204) and patients with bleeding gastric or duodenal ulcers (n=375).

Symptomatic GERD and Erosive Esophagitis Trials

The data described below reflect exposure to NEXIUM I.V. for Injection in 359 patients. NEXIUM I.V. for Injection was studied only in actively-controlled trials. The population was 18 to 77 years of age; 45% Male, 52% Caucasian, 17% Black, 3% Asian, 28% Other, and had either erosive reflux esophagitis (44%) or GERD (56%). Most patients received doses of either 20 or 40 mg either as an infusion or as an injection. Adverse reactions occurring in ≥ 1% of patients treated with intravenous esomeprazole (n=359) in clinical trials are listed below:

Table 2

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10.9</td>
</tr>
<tr>
<td>Flatulence</td>
<td>10.3</td>
</tr>
<tr>
<td>Nausea</td>
<td>6.4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3.9</td>
</tr>
<tr>
<td>Mouth dry</td>
<td>3.9</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>2.8</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.5</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>1.7</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Intravenous treatment with esomeprazole 20 and 40 mg administered as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole.
Pediatric
A randomized, open-label, multi-national study to evaluate the pharmacokinetics of repeated intravenous doses of once daily esomeprazole in pediatric patients 1 month to 17 years old, inclusive was performed. The safety results are consistent with the known safety profile of esomeprazole and no unexpected safety signals were identified. [See Clinical Pharmacology (12.3)]

Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers in Adults
The data described below reflect exposure to NEXIUM I.V. for Injection in 375 patients. NEXIUM I.V. for Injection was studied in a placebo-controlled trial. Patients were randomized to receive NEXIUM I.V. for Injection (n=375) or placebo (n=389). The population was 18 to 98 years old; 68% Male, 87% Caucasian, 1% Black, 7% Asian, 4% other, who presented with endoscopically confirmed gastric or duodenal ulcer bleeding. Following endoscopic hemostasis, patients received either 80 mg esomeprazole as an intravenous infusion over 30 minutes followed by a continuous infusion of 8 mg per hour or placebo for a total treatment duration of 72 hours. After the initial 72-hour period, all patients received oral proton pump inhibitor (PPI) for 27 days.

Table 3

<table>
<thead>
<tr>
<th>Incidence (%) of adverse reactions that occurred in greater than 1% of patients within 72 hours after start of treatment*</th>
<th>Number(%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Esomeprazole (n=375)</td>
</tr>
<tr>
<td>Duodenal ulcer hemorrhage</td>
<td>16 (4.3%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>16 (4.3%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (3.5%)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (1.1%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (1.1%)</td>
</tr>
</tbody>
</table>

*Incidence ≥1% in the esomeprazole group and greater than placebo group safety population

With the exception of injection site reactions described above, intravenous treatment with esomeprazole administered as an injection or as an infusion was found to have a safety profile similar to that of oral administration of esomeprazole.

12. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

- **Range of costs of the proposed medicine**

The International Drug Price Indicator Guide, Management Sciences for Health (MSH) (http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=dmp&language=english) does not provide price for IV omeprazole or other IV PPI formulations.

The price for oral omeprazole tablets (according to the International Drug Price Indicator Guide, MSG) is shown in the table below:
The authors of this application did not have access to pharmacy websites and databases providing prices for intravenous PPIs. A free internet search identified a document from the VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel \(^7\), that contained the following table for the cost of IV pantoprazole according to 2003 prices from VA Federal Supply Schedule. According to this, the daily cost of twice daily bolus administration of 40 mg IV pantoprazole was $7.64 in the US in 2003. Of note, pantoprazole came off patent in 2007, therefore it is expected that the price of IV pantoprazole will be significantly lower nowadays (2014), especially outside the US.
• Resource use and comparative cost-effectiveness presented as range of cost per routine outcome

A literature search for **cost-effectiveness studies** on the use of IV and oral PPIs in patients with peptic ulcer bleeding was performed in PubMed/Medline using the following search strategy:

```
("cost-benefit analysis"[MeSH Terms] OR "cost-benefit"[All Fields] AND "analysis"[All Fields]) OR "cost-benefit analysis"[All Fields] OR "cost"[All Fields] AND "effectiveness"[All Fields]) OR "cost effectiveness"[All Fields]) AND
("analysis"[Subheading] OR "analysis"[All Fields]) AND ("proton pump inhibitors" OR "proton-pump inhibitors" OR "proton pump inhibitor" OR "proton-pump inhibitor" OR PPI OR PPIs OR "acid suppression" OR omeprazole OR lansoprazole dexlansoprazole OR pantoprazole OR rabeprazole OR esomeprazole)
```

Filters activated: published in the last 10 years.

This search yielded 162 articles, which were screened. Several cost-effectiveness studies have been published on this topic⁷⁹,⁸⁰,⁸¹,⁸²,⁸³, but they are all limited by the assumptions of the relative efficacy of IV PPIs vs. oral PPIs. In the light of the results of the updated systematic review and meta-analysis that was conducted for this application (wide non-informative 95% confidence intervals), if updated cost-effectiveness analyses were to be performed, they would produce similarly non-conclusive, non-informative 95% confidence intervals for their results.

**REGULATORY INFORMATION**

13. Summary of regulatory status of the medicine (in various countries)

Intravenous esomeprazole (Nexium) was the first IV PPI to be approved in Europe to prevent peptic ulcer re-bleeding in adults⁸⁴.

The US Food and Drug Administration (FDA) approved one IV esomeprazole (Nexium) for “risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults” in March 2014, as shown in the extracts below:
FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis

NEXIUM I.V. for Injection is indicated for the short-term treatment of GERD with erosive esophagitis in adults and pediatric patients 1 month to 17 years, inclusively as an alternative to oral therapy when oral NEXIUM is not possible or appropriate.

1.2 Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults

NEXIUM I.V. for Injection is indicated for the risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in adults.

2.1 GERD with Erosive Esophagitis

Adult Patients

The recommended adult dose is either 20 mg or 40 mg NEXIUM given once daily by intravenous injection (no less than 3 minutes) or intravenous infusion (10 minutes to 30 minutes). Safety and efficacy of NEXIUM I.V. for Injection as a treatment of GERD patients with erosive esophagitis for more than 10 days have not been demonstrated.

Dosage adjustment is not required in patients with mild to moderate liver impairment (Child Pugh Classes A and B). For patients with severe liver impairment (Child Pugh Class C), a maximum dose of 20 mg once daily of NEXIUM should not be exceeded [see Use in Specific Populations (8.6), Clinical Pharmacology, (12.3)].

Pediatric Patients

The recommended doses for children ages 1 month to 17 years, inclusive, are provided below. Dose should be infused over 10 minutes to 30 minutes.

1 year to 17 years:
- Body weight less than 55 kg: 10 mg
- Body weight 55 kg or greater: 20 mg

1 month to less than 1 year of age: 0.5 mg/kg
The official indication for IV Nexium (esomeprazole) in the Wales, is reads: “Esomeprazole (Nexium® IV) is recommended as an option for use within NHS Wales for gastric antisecretory treatment when the oral route is not possible, such as gastro-oesophageal reflux disease (GORD) in patients with erosive reflux oesophagitis and/or severe symptoms of reflux for children and adolescents aged 1–18 years of age.”

The UK Summary of Product Characteristics for IV Nexium (esomeprazole) as provided by AstraZeneca states 85.

“Nexium for injection and infusion is indicated for:

**Adults**
- gastric antisecretory treatment when the oral route is not possible, such as:
- gastro-oesophageal reflux disease (GORD) in patients with oesophagitis and/or severe symptoms of reflux
- healing of gastric ulcers associated with NSAID therapy
- prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.
- prevention of rebleeding following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers.

**Children and adolescents aged 1-18 years**
- gastric antisecretory treatment when the oral route is not possible, such as:
- gastro-oesophageal reflux disease (GORD) in patients with erosive reflux oesophagitis and/or severe symptoms of reflux.”
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use NEXIUM L.V. safely and effectively. See full prescribing information for NEXIUM L.V.

NEXIUM® L.V. (esomeprazole sodium) for injection, for intravenous use
Initial US Approval: 2005

----------------------------RECENT MAJOR CHANGES----------------------------
• Indications and Usage. Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults (1.2) 03/2014
• Dosage and Administration. Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults (2.2) 03/2014
• Dosage and Administration. Preparation and Administration Instructions (2.3) 03/2014

----------------------------INDICATIONS AND USAGE----------------------------
NEXIUM L.V. is a proton pump inhibitor indicated for the treatment of:
• Gastroesophageal Reflux Disease (GERD) with erosive esophagitis (EE) in adults and pediatric patients greater than one month of age, when oral therapy is not possible or appropriate. (1.1)
• Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following therapeutic endoscopy in adults (1.2)

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE
1.1 Treatment of Gastroesophageal Reflux Disease (GERD) with Erosive Esophagitis
NEXIUM L.V. for Injection is indicated for the short-term treatment of GERD with erosive esophagitis in adults and pediatric patients 1 month to 17 years, inclusively as an alternative to oral therapy when oral NEXIUM is not possible or appropriate.

1.2 Risk Reduction of Rebleeding of Gastric or Duodenal Ulcers following Therapeutic Endoscopy in Adults
NEXIUM L.V. for Injection is indicated for risk reduction of rebleeding in patients following therapeutic endoscopy for acute bleeding gastric or duodenal ulcers in adults.

- British Pharmacopoeia: could not be searched; restricted access
• International Pharmacopoeia: not included
• United States Pharmacopoeia: included
• European Pharmacopoeia: included

15. Proposed (new/adapted) text that could be included in a revised WHO Model Formulary

The text for inclusion in a revised WHO Model Formulary will have to be worded carefully in collaboration with specialised pharmacists, after taking into consideration the special circumstances in low- and middle-income countries. Below is provided an example of text from the “US prescribing information for NEXIUM® I.V. (esomeprazole sodium) for injection, for intravenous use”, which obviously would need to be modified.
- Body weight 55 kg or greater: 20 mg
  - 1 month to less than 1 year of age: 0.5 mg/kg

- For patients with severe liver impairment (Child-Pugh Class C), a maximum dose of 20 mg once daily of NEXIUM should not be exceeded. (2.1, 8.6, 12.3)

Risk Reduction of Rebleeding of Gastric and Duodenal Ulcers in the first 72 hours following therapeutic endoscopy in Adults (2.2): 80 mg intravenous infusion given over 30 minutes, followed by a continuous infusion of 8 mg/h over 3 days (72 hours).

- Dose adjustments are needed in patients with liver impairment (2.2, 8.6, 12.3)
  - For patients with borderline gastrics or duodenal ulcers and mild to moderate liver impairment (Child-Pugh Classes A and B), a maximum continuous infusion of 6 mg/h should not be exceeded.
  - For patients with severe liver impairment (Child Pugh Class C), a maximum continuous infusion of 4 mg/h should not be exceeded.

--- DOSE FORMS AND STRENGTHS ---

NEXIUM I.V. for injection is supplied as a freeze-dried powder containing 20 mg or 40 mg of esomeprazole per single-use vial. (3)

--- CONTRAINDICATIONS ---

Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (metronidazole and sucralfate have occurred). (4)

- Patients treated with proton pump inhibitors and warfarin concurrently may need to be monitored for increases in INR and prothrombin time. (7)
- NEXIUM I.V. may reduce the plasma levels of atazanavir, nefazodone, and saquinavir. (7)
- Concomitant treatment with a combined inhibitor of CYP3A4 and CYP2C19, such as voriconazole, may result in more than doubling of the esomeprazole exposure. (7)
- May increase systemic exposure of cilostazol and an active metabolite. Consider dose reduction. (7)
- Clevidipine: NEXIUM I.V. decreases exposure to the active metabolite of clevidipine. (7)
- Tacrolimus: NEXIUM may increase serum levels of tacrolimus. (7.2)
- Methotrexate: NEXIUM may increase serum levels of methotrexate. (7.3)

--- USE IN SPECIFIC POPULATIONS ---

- Pregnancy: Based on minimal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 03/2014
REFERENCES


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