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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are higher doses of proton pump inhibitors better in acute peptic bleeding?

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Abstract

Although there is broad consensus about the benefits of proton pump inhibitors in acute upper peptic bleeding, there is still controversy over their optimal dosing. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified six systematic reviews including 27 randomized trials addressing this question. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded high-dose proton pump inhibitors probably result in little or no difference in re-bleeding rate or mortality. The risk/benefit and cost/benefit balance probably favor use of low-doses.

Problem

Acute upper peptic bleeding is a serious clinical problem often requiring management in critical care units, and is associated with important morbidity and mortality.Proton pump inhibitors effectively block gastric acid secretion, favoring the healing of ulcer and halting of bleeding. The benefits of these drugs in acute upper peptic bleeding are widely recognized, but there is still controversy over their optimal dosing in this setting.
Methods

We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- High-dose proton pump inhibitors probably result in little or no difference in re-bleeding
- The risk/benefit and cost/benefit balance probably favor the use of low-doses.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found six systematic reviews [1],[2],[3],[4],[5],[6] that included 27 randomized controlled trials [7], [8],[9],[10],[11],[12],[13], [14], [15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28], [29],[31],[32],[33].
What types of patients were included	All of the studies included adult patients hospitalized for acute upper peptic bleeding. In 19 studies all patients achieved endoscopic hemostasis prior to receiving proton pump inhibitors [7], [8],[11],[13],[14], [15], [17], [18],[19],[20],[21],[22],[23],[24],[25],[26],[27], [28],[31],[32] In six studies prior endoscopic hemostasis was achieved in some but not all patients [10],[12],[16],[25],[30],[33].In two studies the information about endoscopic hemostasis was not available [9],[29]. In 14 studies ulcer characteristics were used as inclusion criteria. Thirteen studies exclusively included patients with bleeding secondary to Forrest IA to IIB ulcers [7],[8], [14],[15],[16],[17], [18],[19],[26], [27], [28],[31],[32], and only one study included Forrest IA to III ulcers [9].
What types of interventions were included	All studies compared 'high-dose' proton pump inhibitors (accumulated dose of 600 mg or more in the first 72 hours) against 'non-high' dose (accumulated dose of less than 600 mg in first 72 hours). In all studies 'high-dose' consisted in 80 mg bolus followed by a continuous infusion of 8 mg/hour for at least 72 hours. In 18 studies 'non-high' dose was administered by intermittent intravenous bolus [7],[8],[10],[11], [12],[13],[14],[15],[16], [17],[18],[19],[20], [22],[24],[26],[28],[30],[31]. In eight studies it was administered orally [9],[15],[21],[23],[25],[27],[29],[32], while only one study used a low dose continuous infusion [33].
What types of outcomes were measured	The systematic reviews identified pooled the following outcomes: • Mortality • Re-bleeding • Need for new endoscopic therapy • Need of surgery • Need of transfusions • Length of hospital stay

Summary of findings

The information about the effects of different doses of proton pump inhibitors in acute upper peptic bleeding is based on 21 of 27 randomized studies identified, including 2565 patients. Thirteen studies evaluated mortality [7],[9],[10],[13],[16],[19],[21],[25],[26],[29],[30],[31],[33] and 21 studies evaluated re-bleeding [7],[8],[9],[10],[13],[14], [15],[16], [17],[18], [19],[21], [25],[26], [27],[28], [29],[30],[31],[32],[33]. In the remaining six studies the data could not be extracted for meta-analysis [11],[12],[20],[22],[23],[24]. The summary of the results is the following:

- High dose proton pump inhibitors may result in little or no difference in mortality. The certainty of the evidence is low.
- High dose proton pump inhibitors probably result in little or no difference in re-bleeding risk. The certainty of the evidence is moderate.

High versus low- doses of proton pump inhibitors in acute upper peptic bleeding

Patients Acute upper peptic bleeding
Intervention High-dose proton pump inhibitors (>600 mg in 72 hours)
Comparison Non-high-dose proton pump inhibitors (<600 mg in 72 hours)

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITH non-high-dose	**WITH high-dose**		
	Difference: patients per 1000			
Mortality	29 per 1000	25 per 1000	RR 0.86 (0.49 to 1.50)	⨁⨁◯◯[1,2] Low
	Difference: 4 patients less per 1000 (Margin of error: 15 less to 15 more)			
Re-bleeding	87 per 1000	104 per 1000	RR 1.2 (0.96 to 1.51)	⨁⨁⨁◯[1] Moderate
	Difference: 17 patients more per 1000 (Margin of error: 3 less to 44 more)			

Margin of error = confidence interval 95%.
RR: Relative Risk.
GRADE: grade levels of evidence of the GRADE Working Group (see later in this article).

* The risks **WITHOUT non-high-dose** are based on the risk in the control group of the studies. The risk **WITH high-dose** (and its margin of error) is calculated from the relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded in one level because of risk of bias of most of the included studies.
[2] The certainty of evidence was downgraded in one level because of imprecision, as the confidence interval includes both the superiority of high or non-high doses.

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

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Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence applies to adult patients hospitalized for acute upper peptic bleeding, after endoscopy and hemostatic procedures if needed. This evidence does not apply to patients with variceal upper bleeding.

About the outcomes included in this summary

- The selected outcomes were mortality and re-bleeding, which are critical for decition making in clinical practice based on the opinion of the authors of this summary. These are the outcomes mentioned in the main guidelines too [34],[35],[36].

Balance between benefits and risks, and certainty of the evidence

- The outcome for which more certainty exists is re-bleeding, with higher-doses of proton pump inhibitors probably not modifying its incidence. Although the certainty of the evidence is lower for mortality, because of its tight relationship with re-bleeding there is no reason to expect a different effect over it.
- In theory, some known adverse effects of proton pump inhibitors such as Clostridium difficile infection and pneumonia may be influenced by the dose used. This would turn the balance even more towards the use of non-high doses.

Resource considerations

- High-dose proton pump inhibitors are associated with higher costs, considering the amount of drug used and the need for a continous infusion pump.
- Considering there is probably no clinical benefit with higher doses of proton pump inhibitors, the cost/benefit balance favors non-high dose.

Differences between this summary and other sources

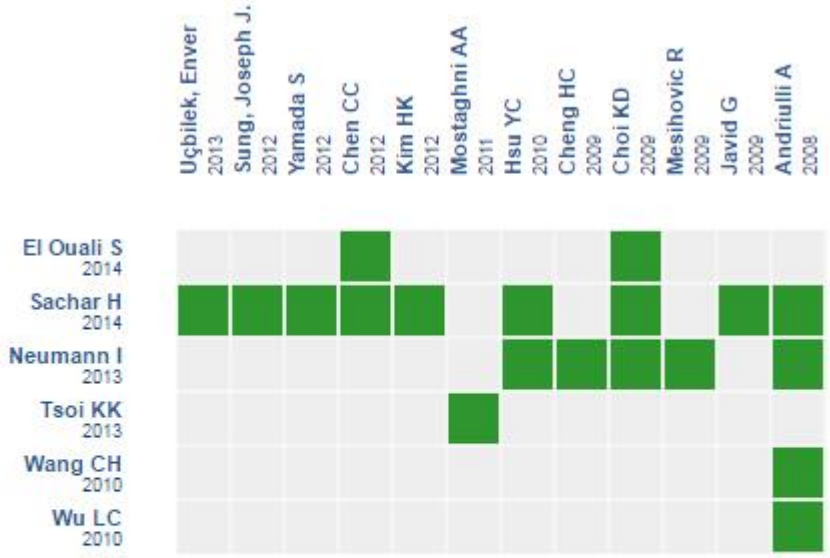
- The conclusions of this summary agree with most systematic reviews identified[2],[3],[5],[6], but partially disagree with two of them, which point out that more evidence is needed before making any conclusion [1],[4].
- The conclusions of this summary disagree with the most important clinical guidelines. While the NICE guideline does not make a specific statement about the dose of proton pump inhibitors, both the American Collegue of Gastroenterology [34] and the American Society of Gastrointestinal Endoscopy guidelines recommend the use of proton pump inhibitors in high dose in patients with "high risk" ulcers. It is important to highlight that these guidelines have considered only a small amount of the evidence included in this summary, basing their recommendation mostly in studies comparing proton pump inhibitors with placebo. None of them cites the available systematic reviews comparing high versus non-high doses, and only cite a small number of the primary studies included in this summary. For example, the American College of Gastroenterology guideline [34] cites only five of them [7],[14],[17],[19],[31], while the American Society of Gastrointestinal Endoscopy guideline does not cite any of them.

Could this evidence change in the future?

- The probability that future studies change the conclusions of this summary is low because of the certainty of the available evidence
- A substantial proportion of the studies is lacking in all systematic reviews, so a new or updated review may increase the certainty of the evidence

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** High-dose versus non-high-dose proton pump inhibitors for bleeding peptic ulcer

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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