

Meta-analysis: proton-pump inhibition in high-risk patients with acute peptic ulcer bleeding

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SUMMARY

Background: Recent data suggest that profound acid suppression may improve outcomes of patients in peptic ulcer bleeding.

Aim: To better characterize the role of different pharmacological therapies in this population.

Methods: MEDLINE was used to identify randomized trials (01/1990–04/2003) that assessed the efficacy of pharmacological treatments for patients with bleeding peptic ulcers exhibiting high-risk stigmata (Forrest Ia–IIb). Three groups of treatment were assessed: proton-pump inhibitors given as high-dose bolus followed by intravenous constant infusion (40–80 mg and at least 6 mg/h), high-dose oral proton-pump inhibitors (at least twice the standard dosage), non-high-dose proton-pump inhibitors (other proton-pump inhibitors dosing schedules). Mixed-effect models were used to determine rate differences between treatment and control groups.

Results: Eighteen studies (1855 patients) were included. High-dose intravenous proton-pump inhibitors significantly reduced rebleeding (–14.6%), surgery (–5.4%) and mortality (–2.7%) compared with placebo, and rebleeding (–20.6%) compared with H₂RA. Compared with placebo, high-dose oral proton-pump inhibitors significantly reduced only rebleeding (–11.8%), while non-high-dose proton-pump inhibitor treatment significantly improved all three outcomes.

Conclusions: High-dose intravenous proton-pump inhibitor significantly decreases ulcer rebleeding, surgery and mortality. Early data on high-dose oral proton-pump inhibitor suggest improved rebleeding. The non-high-dose proton-pump inhibitor regimens, including a broad range of dosing, also improved outcomes, suggesting that doses inferior to those in the high-dose intravenous proton-pump inhibitor may be effective.

INTRODUCTION

Acute upper gastrointestinal (GI) haemorrhage is a major cause of morbidity and mortality. Based on hospital admission,¹ and discharge data,^{2–4} the estimated annual incidence of upper GI haemorrhage is 50–150 per 100 000 subjects. The most common cause of acute haemorrhage in the upper GI tract is

peptic ulcer disease, which accounts for approximately 50% of cases.^{5–7} Overall mortality has been estimated at 7–10% for the past 30 years,^{8, 9} despite the advent of effective endoscopic therapies,¹⁰ likely due to the older age and increased comorbidity among patients presenting with upper GI haemorrhage.¹¹ A trend towards a decrease in mortality was, however, recently observed in one epidemiological study,¹² but not another.¹³

No single controlled clinical trial has been able to demonstrate improvements in mortality, but two meta-analyses in the early 1990s showed that selected, older, methods of endoscopic haemostasis

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were capable of significantly reducing the death rate by 30–50%.^{14, 15}

Recently, trials have investigated the effect of pharmacological treatments, including intravenous proton-pump inhibitors (IV-PPI) on the clinical outcomes of mortality, rebleeding and surgery. These trials have reported conflicting results on patient outcomes,¹⁶ but an authoritative consensus conference recently recommended the use of high-dose (HD) IV-PPI administration following endoscopic haemostasis.¹⁰ We therefore performed a series of meta-analyses to better determine the role of contemporary pharmacological treatments aimed at improving outcomes in selected patients with bleeding ulcers.

MATERIAL AND METHODS

Search strategy

Literature review methods for relevant articles included MEDLINE searches and manual searches of bibliographies of key articles published in English or French between January 1990 and April 2003. Search terms included 'peptic ulcer bleeding', 'peptic ulcer haemorrhage', 'upper GI bleeding', 'upper GI haemorrhage' and 'treatment'. The abstracts of all randomized trials published in full form were manually screened and assessed.

Inclusion and exclusion criteria

Trials were included in the meta-analyses only if they provided adequate information concerning the number of patients randomized in each treatment group, the treatment procedures, and the rates of rebleeding, surgery and mortality. Only studies that included patients with bleeding peptic ulcers exhibiting high-risk stigmata for rebleeding (Forrest Ia, Ib, IIa and IIb)¹⁷ were considered for inclusion. Dual publications were excluded; if multiple publications of the same patient groups were retrieved, only the more recent version was included. Pharmacodynamic studies, uncontrolled trials and studies of treatment in upper GI tract bleeding from unspecified causes or aetiologies other than peptic ulcer disease were also excluded.

Validity assessment

The quality of the studies was assessed independently by two investigators with a third resolving discrepancies.

Studies were graded using 10 quality criteria, defined *a priori*, and adapted from those described by Cook *et al.*¹⁵ (Table 1). Each component of the scoring system was graded '1' if the study met the quality criterion and '0' if it did not.

Potential sources of heterogeneity

Clinical heterogeneity was assessed, especially with regards to the patient populations of the different

Table 1. Methodological quality assessment of the treatment for upper GI bleeding

Population	
Patients selection	1 Consecutive eligible consenting patients 0 Selected patients/not described
Patients characteristics	1 Comparable with respect to all the characteristics 0 Non-comparable with respect to at least two characteristics
Intervention	
Randomization	1 Randomization process clearly stated 0 No randomization or randomization process not described
Blinding	1 Assessment of outcome blinded to evaluation treatment 0 Unblinded or cannot tell
Endoscopic treatment	
Injection	1 Volume, concentration of injectate and number of applications stated 0 At least one of the above not stated
Other endoscopic treatments (laser, heat probe, bicap, clips, microwave, APC)	1 Technique fully stated according to the endoscopic procedure 0 Technique poorly or not enough described to be reproduced
Pharmacological treatment	
	1 Dose, duration and route stated even for GI drugs not randomized 0 At least one of the above not stated
Outcome	
Rebleeding definition	1 Objective direct or indirect evidence of upper GI bleeding 0 Subjective evidence or criteria not explicitly stated
Indication for surgery	1 Criteria stated explicitly 0 Criteria not explicitly stated
Cause of death	1 Cause clearly stated with no need to obvious relation to bleeding 0 Cause of death not clearly stated

GI, gastrointestinal; APC, argon plasma coagulation.

studies. As a result, the mean age of patients, the percentage of patients in shock at inclusion, the time period during which the study was conducted (dichotomized as 'prior to' or 'after' 1996, midpoint of the study period), were recorded as potential sources of heterogeneity and interstudy variance. These and the aforementioned quality scores were all considered possible confounders of outcomes. Age and shock were identified based on the Rockall¹⁸ risk scoring system and a systematic review of the literature.¹⁰ The time period of the study was considered in order to control for possible changes in supportive care over time.¹⁹ Comorbid conditions may also influence outcomes; unfortunately such information was not available in the majority of included trials.

Statistical heterogeneity was also taken into account in the modelling (see Meta-analytic Statistical Methods and Modelling section below).

Treatment group

It is widely believed, based on a number of physiological arguments, that profound acid suppression may improve outcomes for patients with bleeding peptic ulcers, which would explain the observed effectiveness of HD-PPIs.^{16, 20} Based on these underlying considerations and available data in the literature, we *a priori* decided to categorize treatments into three subgroups: HD-IV-PPI (the use of a bolus followed by a constant infusion of at least 6 mg/h), high-dose oral PPI (HD-PO-PPI; at least twice the standard dosage) and non-HD-PPI (PPI dosing schedules other than the former two).

Meta-analytic statistical methods and modelling

The number of patients experiencing each outcome (mortality, rebleeding and surgery) was used to calculate the outcome rates for each study according to treatment (or placebo) received. Each pharmacological treatment subgroup was compared with all others as much as possible depending on the actual head-to-head comparisons carried out in the studies as it is critical to note that comparisons were only made 'within the groups' that patients were initially randomized to for each study, and not across randomization schemes, in order to preserve the balancing effect of randomization and the comparability of populations. For example, to assess the performance of the HD-IV-PPI we considered all studies that compared HD-IV-PPI to any other

treatment. Crude rate differences were calculated for individual studies as has been reported in the literature.^{21, 22}

All analyses were performed in two steps. First, a linear mixed-effect model was created to determine the between- and within-study variations in differences in outcome rates.²³ Studies that compared three or more treatments were entered into the model more than once. Each study was weighted according to the ratio of the total number of patients to the number of times the study appeared in the model, to avoid over-representation of any individual trial. The weighted rate differences between the selected treatment and control groups were regressed against the year of publication, quality score, mean age, sex (number of male patients). Specific treatment was considered a random effect.

In the second step of the analysis, the mean effects of a given pharmacotherapy were compared with each specific control (placebo or another pharmacotherapy) separately. The 95% confidence intervals (CI) were determined by taking into account the within- and between-study variances as proposed by DerSimonian and Laird.²⁴ The within- and between-study variances were the fixed effect and random effect variances, respectively, given by the mixed-effect model while adjusted for the weights. Details on the mixed-effect models method used for the analyses are described by Stram.²⁵ Statistical analyses were performed using the SAS software (version 8.2; Cary, NC, USA).

RESULTS

Included studies

We reviewed 126 English or French abstracts, as well as several reviews and meta-analyses^{14–16, 26–32} and their bibliographies. After a manual review of over 85 fully published manuscripts that potentially fulfilled the selection criteria, 18 articles (14.3% of the initially identified 126 abstracts) were ultimately considered adequate using the aforementioned criteria. The other articles were excluded because they reported results on case series, lacked sufficient details to recalculate crude rates for each outcome, did not allow for adequate assessment of treatments, because the analysis was not restricted to patients with high-risk endoscopic lesions (Forrest Ia–IIb), or as the trial focused exclusively on H₂-receptor antagonists, somatostatin (SST)/octreotide or endoscopic treatment. The QUOROM flow diagram³³

is shown in Figure 1. The 18 selected studies included a total of 1855 patients, all exhibiting high-risk endoscopic stigmata, as defined above.

Treatment subgroups

Four studies,^{34–37} including 682 patients, were found to fulfil the preset inclusion criteria for the evaluation of HD-IV-PPI. We excluded a study on HD-IV-PPI³⁸ because the study population included patients with a Forrest IIc (pigmented spot) ulcer lesion which is not considered a high-risk stigmata. We also excluded the trial by Schaffalitzky de Muckadell *et al.*³⁹ because the primary efficacy measure was the worst ranking of an overall outcome scale that did not allow us to reconstruct corresponding 2 × 2 tables. In these four studies HD-IV-PPI was administered as a bolus (80 mg except for one study³⁷ where it was 40 mg) followed by a continuous infusion of 6.7–8 mg/h for up to 3 days.

Four trials,^{40–43} including 448 patients, comprised the evaluation of HD-PO-PPI. We did not include a study by Khuroo *et al.*⁴⁴ in this treatment subgroup because no initial endoscopic haemostasis was carried out. Furthermore, because endoscopic therapy was administered to only 13% of patients in the study by Michel *et al.*⁴³ a sensitivity analysis was also done excluding its results. Treatment regimen ranged from 60 mg of lansoprazole once a day to omeprazole 80 mg/day (40 mg twice a day or 20 mg four times a day).

The effects of non-HD-PPI, i.e. excluding HD-IV-PPI and HD-PO-PPI, were evaluated in 10 studies^{44–53} comprising 725 patients. Treatment regimens ranged from 40 mg/day oral omeprazole to 160 mg/day IV omeprazole administered via different protocols

(20–40 mg bolus every 3–6 h) and other IV regimens such as 40 mg bolus followed by 80 mg/day continuous infusion, 40 mg q12 h for 3 days, 80 mg bolus followed by 40 mg q12 h, or 40 mg q12 h for 2 days followed by 40 mg/day oral.

Efficacy of high-dose IV-PPI therapy

Compared with placebo, HD-IV-PPI, which was administered after endoscopic treatment in 52% of all analysed patients, was associated with a significant decrease in rebleeding (–14.6%; 95% CI: –16.2 to –12.9), surgery (–5.4%; 95% CI: –8.4 to –2.4) and mortality (–2.7%; 95% CI: –9.2 to 3.8) (Table 2, Figure 2). Compared with H₂RA, HD-IV-PPI significantly reduced rebleeding (–20.6%; 95% CI: –24.7 to –16.6), but not surgery (–1.0%; 95% CI: –8.0 to 6.1) or mortality (–2.4%; 95% CI: –17.7 to 12.9). Finally, when compared with a combination of H₂RA and SST given together, HD-IV-PPI significantly reduced rebleeding (–13.2%; 95% CI: –22.3 to –4.1), but neither surgery (–14.7%; 95% CI: –30.5 to –0.1) nor mortality (+7.8%, 95% CI: –26.4 to 42.0; Table 2).

No analysis could be performed comparing HD-IV-PPI with other IV or oral PPI regimens because at this time there exist no head-to-head trials of these strategies.

A sensitivity analysis was performed using three of the four studies,^{34, 36, 37} but excluding the study by Hasselgren *et al.*,³⁵ which had an unexpectedly low mortality rate in the placebo group (0.6%). Exclusion of this study increased the magnitude of the beneficial effect of HD-IV-PPI on rebleeding, and, reaching statistical significance, on mortality (–5.0%; 95% CI: –7.7 to –2.3) compared with placebo (Table 3, Figure 2).

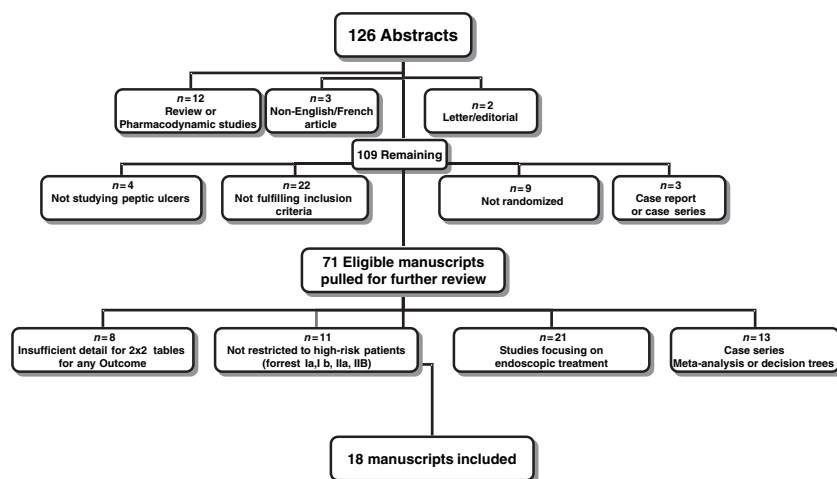


Figure 1. Flowchart of studies and abstracts exclusion.

Table 2. Role of high-dose intravenous proton-pump inhibitors (HD-IV-PPI) in the acute management of peptic ulcer bleeding

Control to HD-IV-PPI	Rebleeding (%)	Surgery (%)	Mortality (%)
Placebo	-14.6 (-16.2 to -12.9)	-5.4 (-8.4 to -2.4)	-2.7 (-9.2 to 3.8)
H ₂ RA	-20.6 (-24.7 to -16.6)	-1.0 (-8.0 to 6.1)	-2.4 (-17.7 to 12.9)
H ₂ RA + SST	-13.2 (-22.3 to -4.1)	-14.8 (-30.5 to 1.0)	7.8 (-26.4 to 42.0)

SST, somatostatin; H₂RA, H₂-receptor antagonists.

The expressed values are mean (95% CI).

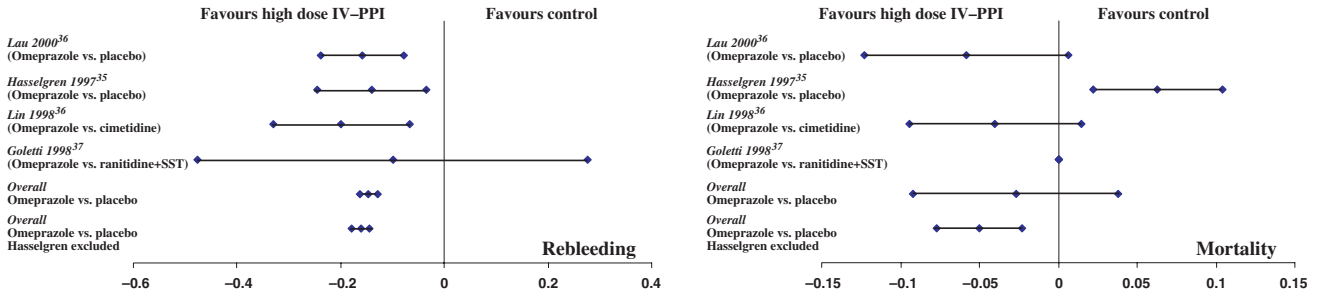


Figure 2. Included studies and results of the model for high-dose intravenous proton-pump inhibition vs. placebo. Panel (a) is rebleeding and panel (b) mortality. Results represent combined rate differences (in %) between treatment groups for each outcome with their respective 95% confidence intervals. SST, somatostatin.

Table 3. Role of high-dose intravenous proton-pump inhibitors (HD-IV-PPI) in the acute management of peptic ulcer bleedings: sensitivity analysis after excluding the study by Hasselgren *et al.*³⁵

Control to HD-IV-PPI	Rebleeding (%)	Surgery (%)	Mortality (%)
Placebo	-16.2 (-17.9 to -14.4)	-5.1 (-6.0 to -4.3)	-5.0 (-7.7 to -2.3)
H ₂ RA	-19.5 (-22.3 to -16.7)	0.2 (-1.0 to 1.5)	-4.7 (-8.9 to -0.6)
H ₂ RA + SST	-7.3 (-13.5 to -1.1)	-8.8 (-11.6 to -5.9)	-3.6 (-12.9 to 5.7)

SST, somatostatin; H₂RA, H₂-receptor antagonists.

The expressed values are mean (95% CI).

Efficacy of high-dose oral PPI therapy

Compared with placebo, HD-PO-PPI significantly reduced rebleeding (-15.3%; 95% CI: -16.5 to -14.0) but not surgery (-3.3%; 95% CI: -6.3 to 0.3) or mortality (-1.4%; 95% CI: -2.7 to 0.2) (Table 4, Figure 3). Compared with H₂RA or SST, no significant reduction of any of the three outcomes was noted (Table 4). The exclusion of the study by Michel *et al.*⁴³ did not significantly alter these findings (data not included).

Efficacy of non-high-dose PPI therapy

Compared with placebo, non-HD-PPI treatment was associated with reduced rebleeding (-25.0%; 95% CI: -29.3 to -20.7), surgery (-16.2%; 95% CI: -18.1 to -14.2) and mortality (-3.5%; 95% CI: -4.6 to -2.4; Table 5, Figure 4). Compared with H₂RA or SST, only the difference in rebleeding (-14.4%; 95% CI: -21.2 to -7.7) was statistically significant (Table 5).

Table 4. Role of high-dose oral proton-pump inhibitors (HD-PO-PPI) in the acute management of peptic ulcer bleedings

Control to HD-PO-PPI	Rebleeding	Surgery	Mortality
Placebo	-15.3 (-16.5 to -14.0)	-3.3 (-6.3 to 0.3)	-1.4 (-2.7 to 0.2)
H ₂ RA	1.7 (-2.1 to 5.4)	-1.6 (-10.4 to 7.2)	2.1 (-1.9 to 6.0)
SST	15.0 (-9.4 to 39.4)	6.0 (-4.2 to 16.2)	2.2 (-3.0 to 7.4)

SST, somatostatin; H₂RA, H₂-receptor antagonists.

The expressed values are mean (95% CI).

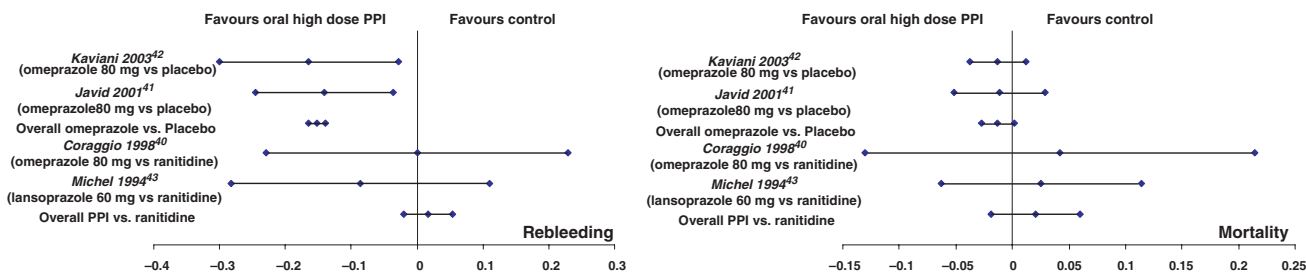


Figure 3. Included studies and results of the model for high-dose oral proton-pump inhibition vs. placebo. Panel (a) is rebleeding and panel (b) mortality. Results represent combined rate differences (in %) between treatment groups for each outcome with their respective 95% confidence intervals.

Control to	Rebleeding	Surgery	Mortality
non-HD-PPI			
Placebo	-25.0 (-29.3 to -20.7)	-16.2 (-18.1 to -14.2)	-3.5 (-4.6 to -2.4)
H ₂ RA	-14.4 (-21.2 to -7.7)	0.1 (-2.9 to 3.1)	0.8 (-2.7 to 4.4)
SST	9.4 (-11.7 to 30.5)	7.1 (0.2-14.0)	0.3 (-7.3 to 7.8)

Table 5. Role of non-high-dose proton-pump inhibitors (HD-PPI) in the acute management of peptic ulcer bleedings

SST, somatostatin; H₂RA, H₂-receptor antagonists. The expressed values are mean (95% CI).

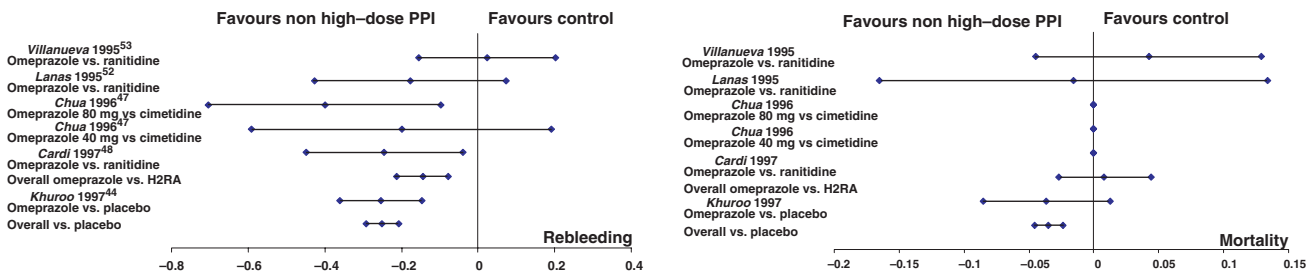


Figure 4. Included studies and results of the model for non-high-dose proton-pump inhibition (all routes combined) vs. placebo. Panel (a) is rebleeding and panel (b) mortality. Results represent combined rate differences (in %) between treatment groups for each outcome with their respective 95% confidence intervals. Only studies where placebo or H₂-receptor antagonists were the control groups are presented on the graph.

DISCUSSION

This study assesses the most common pharmacological options currently available for the acute management of patients with a high-risk bleeding peptic ulcer. The use of pharmacotherapy in the acute setting is widely practiced^{54, 55} and has traditionally included H₂RAs. Since their introduction, IV-PPIs have become very commonly used, especially as the widely diffused publication of a randomized trial showing decreased rebleeding in patients with high-risk lesions having first undergone endoscopic haemostasis.³⁶ To date, four studies have shown similar findings, using slightly different study populations, endoscopic therapies,

HD-IV-PPI dosing regimens, comparators and outcomes.^{35-37, 39} However, no single study or meta-analysis of PPI therapy following endoscopy has demonstrated a reduction in mortality compared with placebo until this present analysis,^{28, 54, 55} although a trend in this direction had been noted in the largest clinical trial, performed by Lau *et al.*³⁶ (4.2% vs. 10% for the HD-IV-PPI and placebo groups, respectively, *P* = 0.13). A recent meta-analysis by Leontiadis *et al.*⁵⁶ found that PPI did not decrease mortality compared with control (i.e. placebo or H₂RAs). This discrepancy might be explained by a less restrictive inclusion of patients at high risk as in the present study. Indeed, whereas our population was restricted to Forrest Ia-IIb

patients, the Leontiadis *et al.*⁵⁶ study included even a study that enrolled patients with clean-based ulcers. Furthermore, even if it is now generally understood that H₂RAs have little if any role in the management of acute ulcer bleeding, they decrease intragastric pH and their combination with placebo in the control group of this meta-analysis might explain in part the conclusions of this study. An inability to show statistical benefits on mortality may be due to small single trial sample sizes and meta-analyses of heterogeneous groups of studies, including one study³⁵ in which the mortality of the placebo-treated group was extremely low. The current meta-analysis, included 339 patients in the HD-IV-PPI group, thus providing a larger sample size, and the increased statistical power needed to show statistical significance, while, in contrast to most of other meta-analyses, adjusting for possible confounding including year of publication, quality score, as well as mean age and sex of included patients. Improved mortality rates attributable to PPI use were recently suggested by predictive modelling carried out on data from a large national registry, the registry on non-variceal Upper Gastrointestinal Bleeding and Endoscopy or RUGBE initiative, although the study design could not indisputably determine a specific dose threshold or method of administration.⁷

Recent recommendations from a consensus conference,¹⁰ suggested that PPI therapy may be effective and could be considered in the management of all patients with upper GI bleeding while awaiting endoscopy. But randomized-clinical trial evidence to date, including all studies in the current meta-analysis, only support the efficacy of HD-IV-PPI if administered to patients with high-risk lesions, usually after successful endoscopic treatments. The concept that endoscopic therapy should be the mainstay of treatment with pharmacotherapy considered only as adjuvant treatment has recently been re-emphasized by Sung *et al.*⁵⁷ who noted that, in patients with Forrest IIa and IIb lesions, combination endoscopic treatment (injection followed by thermal coagulation) followed by the administration of HD-IV-PPI was significantly superior to HD-IV-PPI alone in terms of rebleeding (0% and 9%, respectively, $P = 0.01$) but not mortality (2.6% and 5.1%, respectively, $P > 0.20$).⁵⁷ The only other study that has compared endoscopic therapy with HD-PPI therapy, in this case oral, failed to show significant differences in patients with Forrest IIa–IIb lesions, but this trial lacked

sufficient statistical power to rule out a type II error or confidently claim equivalence.⁵¹

As in the meta-analysis by Gisbert *et al.*,⁵⁴ HD-IV-PPIs and non-HD-PPI were also shown to be superior to H₂RAs in terms of rebleeding, but not for either mortality or surgery, although in their analysis Gisbert *et al.*⁵⁴ did not separate out HD-IV-PPIs.

The HD-PO-PPI following endoscopic treatment significantly decreased rebleeding (−15.3%; 95% CI: −16.5 to −14.0), but not surgery or mortality compared with placebo. These findings may be related to a lack of statistical power to detect such a beneficial effect, as the incidence of mortality in these studies was very low. Indeed, except in the study by Corragio *et al.*⁴⁰ where the mortality was 9.6% (8.3% in the ranitidine group and 12.5% in the omeprazole group) the mortality rate in the three other studies^{41–43} ranged from 0.7 to 2.7% (and more specifically from 1.3 to 2.4% in the placebo groups). In all, differences in mortality were in favour of the HD-PO-PPI regimen, and there was an overall trend towards reduced mortality in the meta-analysis (−1.4%; 95% CI: −2.7 to 0.2). However, many have questioned the possibility of generalizing these results as, except in the study by Michel *et al.*,⁴³ the oral PPI were given to non-Caucasian patients who are known to be physiologically and genetically different from Caucasians with resultant pharmacological differences.^{58, 59}

Non-HD-PPI use was also associated with improved outcomes, but this finding is harder to interpret and convert into a recommendation compared with the results of HD-IV-PPI or HD-PO-PPI administration. Indeed, the non-HD-PPI subgroup included a wide assortment of methodologies and quite disparate PPI regimens (please refer to 'Treatment Subgroups' paragraph of the 'Results' section). Moreover, the large, well designed single study by Daneshmend *et al.*⁶⁰ did not show IV-PPI bolus (80 mg plus three dose 40 mg q8 h) to be efficacious, although only 40% of included patients were bleeding from peptic ulcers. As a result, in light of this wide heterogeneity in dosing schedules, we do not feel that this component of the meta-analysis can be used, at this time, to provide a confident recommendation with regards to a specific non-HD method of IV or oral PPI administration. It however, raises the very pertinent question of an effective threshold dose that may be less than that of the HD-IV-PPI regimen, as has been suggested in exploratory analyses performed on the RUGBE data.^{20, 61}

Head-to-head studies comparing HD with non-HD-PPIs are needed.

In the current meta-analysis, we only included published randomized-controlled trials and therefore, might have missed data unpublished because of negative results. Although possible, this is unlikely as many of the trials included in fact did not favour the therapeutic intervention under study. A large multicentre trial was very recently presented in abstract form and found that HD pantoprazole was not superior to HD ranitidine in preventing negative outcomes, including mortality, at 72 h but favoured IV-HD pantoprazole over IV-HD ranitidine only in planned subgroup analyses (in patients with Forrest Ia lesions and those with bleeding gastric ulcers). Concerns about the selection criteria and interobserver variability amongst the participating endoscopists from 155 centres in 15 countries limit the interpretability of these preliminary data and additional perusal of a full publication would be needed before adding these results to any meta-analysis.⁶²

Heterogeneity between study results can also be a problem in meta-analytical work. Identifying its presence, investigating its cause, and correctly accounting for such variability are critical and need to be guided by clinical and methodological considerations. In the present meta-analysis, we assumed the presence of clinical and statistical heterogeneity between studies because of differences in experimental designs, patient populations and treatments, which is why we used a mixed-effect model, a meta-analytic approach that is adapted to the existence of between-study heterogeneity.⁶³ We also, as a result, performed adjustment for several potential confounders, including age and shock at admission. Although concomitant disease is of recognized clinical importance, we were unable to control directly for this latter factor as this information was rarely reported in any detail. Transfusion requirements and duration of hospital stay were not assessed as these are not reported in a standardized fashion, or was this outcome defined *a priori* in many of the trials.

In conclusion, for a patient with a bleeding peptic ulcer with high-risk stigmata, successful endoscopic treatment should be followed by HD-PPI administration, either IV or oral, although the strongest evidence and most generalizable data currently favour HD-IV administration, which can reduce both rebleeding and mortality. Such a recommendation was recently endorsed by a panel of international experts during a consensus conference on the optimal management of patients with

high-risk bleeding peptic ulcers.¹⁰ Lower PPI dosing appears to also be effective, but additional research is required to better define at what effective dose threshold and the optimal method of administration.

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