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A systematic review with meta-analysis and trial sequential analysis

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Prophylactic use of acid suppressants in adult acutely ill hospitalised patients: a systematic review with meta-analysis and trial sequential analysis

Running title: Prophylactic acid suppressants in acutely ill patients

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ABSTRACT

Background
Acutely ill patients are at risk of stress-related gastrointestinal bleeding and prophylactic acid suppressants are frequently used. In this systematic review, we assessed the effects of stress ulcer prophylaxis (SUP) with proton pump inhibitors or histamine-2 receptor antagonists versus placebo or no prophylaxis in acutely ill hospitalised patients.

Methods
We conducted the review according to the PRISMA statement, the Cochrane Handbook, and GRADE, using conventional meta-analysis and trial sequential analysis (TSA). The primary outcomes were all-cause mortality, clinically important gastrointestinal bleeding and serious adverse events (SAEs). The primary analyses included overall low risk of bias trials.

Results
We included 65 comparisons from 62 trials (n=9713); 43 comparisons were from intensive care units. Only 3 trials (n=3596) had overall low risk of bias. We did not find an effect on all-cause mortality (RR 1.03, 95% CI 0.94-1.14; TSA-adjusted CI 0.90-1.18; high certainty). The rate of clinically important gastrointestinal bleeding was lower with SUP (RR 0.62, 95% CI 0.43-0.89; TSA-adjusted CI 0.14-2.81; moderate certainty). We did not find a difference in pneumonia rates (moderate certainty). Effects on SAEs, Clostridium difficile enteritis, myocardial ischemia and health-related quality of life (HRQoL) were inconclusive due to sparse data. Analyses of all trials regardless of risk of bias were consistent with the primary analyses.

Conclusions
We did not observe a difference in all-cause mortality or pneumonia with SUP. The incidence of clinically important gastrointestinal bleeding was reduced with SUP, whereas any effects on SAEs, myocardial ischemia, Clostridium difficile enteritis and HRQoL were inconclusive.

Study registration
PROSPERO registration number CRD42017055676; published study protocol: Marker, et al 2017 in Systematic Reviews.

KEYWORDS
Acid suppressants, gastrointestinal bleeding, adverse effects, stress ulcer prophylaxis, proton pump inhibitors, histamine-2 receptor antagonists

Editorial Comment:

In this high quality systematic review, pooled results from available studies of prophylactic gastric acid suppressants address different important outcomes. This analysis shows that the treatment in hospitalized patients with acute illness has some beneficial effect on important gastrointestinal bleeding, even though no effect on overall survival or occurrence of pneumonia.
INTRODUCTION

Acutely ill patients are at risk of stress-related mucosal erosions.\textsuperscript{1} Although typically superficial and asymptomatic, they may further ulcerate into the submucosal layer where larger vessels reside, resulting in risk of gastrointestinal (GI) bleeding.\textsuperscript{2,3} GI bleeding is a potentially life-threatening condition with a mortality of up to 50\% among frail patients.\textsuperscript{4} The true incidence of GI bleeding due to stress ulcerations in acutely ill patients is unknown. Within the intensive care unit (ICU), where this has been studied the most, the reported incidence of overt GI bleeding ranges between 2-10\%, of which only 2-3\% are clinically important GI bleedings.\textsuperscript{5-11} However, most reported estimates include all conditions resulting in GI bleeding and not exclusively stress ulcers or other types of bleeding that may be prevented by acid suppressants.\textsuperscript{12} Stress ulcer prophylaxis (SUP) is widely used in many acutely ill patient categories.\textsuperscript{13,14} However, the overall balance between potential benefits and harms in hospitalised patients in general is unknown. Increased rates of hospital-acquired pneumonia, \textit{Clostridium (C.) difficile} enteritis and myocardial ischaemia with SUP may outweigh any beneficial effects, including decreased occurrence of GI bleeding.\textsuperscript{7,15-17} Further, the widespread use of acid suppressants is an expense for healthcare systems, which may not cause a clinical net-benefit, even in high-risk patients.\textsuperscript{18} Consequently, we conducted a systematic review on SUP with proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs) versus placebo or no prophylaxis in adult acutely ill hospitalised patients. We hypothesised that SUP would have no effect on mortality, reduce clinically important GI bleeding, and increase infectious adverse events and myocardial ischemia.
METHODS

This systematic review has been conducted according to a published protocol.\textsuperscript{18} We registered the protocol in the International Prospective Register of Systematic Reviews database (PROSPERO, CRD42017055676) and used the methodology of the Cochrane Handbook,\textsuperscript{19} the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (checklist available as S1 the Electronic Supplementary Material (ESM)),\textsuperscript{20} Jakobsen et al.,\textsuperscript{21} and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.\textsuperscript{22}

Eligibility criteria

We included randomised clinical trials (RCTs) comparing SUP with either PPI or H2RA versus placebo or no prophylaxis in acutely ill hospitalised adult patients (as defined by the investigators) irrespective of hospital setting. We accepted the intervention in any dose, formulation and treatment duration and excluded trials that were quasi-randomised, used cross-over, and trials where patients were not acutely admitted to the hospital.\textsuperscript{18}

Literature search

We searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; Ovid MEDLINE; Ovid EMBASE; Epistemonikos; Science Citation Index Expanded (Web of Science); Biosis Previews (Web of Science); and PubMed. The full systematic search string is available as S2 in the ESM. The literature search was updated on 17 October 2019. A hand-search of trial registries, the reference list of relevant trials and systematic reviews and meta-analyses on SUP were performed. Unpublished trials were sought identified. Authors were contacted for additional data if relevant. We did not restrict the search by language, date, publication status or any other trial characteristics.

Study selection

Two authors (SM and AG, CTA or MB) independently and in duplicate screened titles and abstracts. Reports considered potentially relevant were obtained in full-text and assessed for inclusion in accordance with the inclusion and exclusion criteria. Disagreements were resolved by consensus and upon consultation with MHM or JW if necessary.

Extraction and management of data
Two review authors (SM and MB) independently and in duplicate extracted predefined data of the included trials using a predefined data collection form (S3, ESM). The following data were collected: (1) trial: country, duration of the trial, date of publication, and type of trial (single- versus multicentre); (2) participants: numbers randomised, numbers analysed, numbers lost to follow-up/withdrawn, type of population, mean/median age, sex, inclusion criteria, and exclusion criteria; (3) interventions: intervention, comparator, and concomitant interventions; (4) outcomes: predefined primary and secondary outcomes.\(^1\)

Outcomes
Predefined co-primary outcomes were all-cause mortality, the proportion of participants with clinically important GI bleeding (as defined by the investigators) and the proportion of patients with one or more serious adverse events (SAEs) (as defined by the investigators).\(^2\)
Co-secondary outcomes were: health-related quality of life (HRQoL) (any valid scale used by the investigators); proportion of participants with myocardial ischemia (as defined by the investigators); proportion of participants with hospital-acquired pneumonia (as defined by the investigators); proportion of participants with \textit{C. difficile} enteritis (as defined by the investigators).
All outcomes were primarily assessed at the time point closest to 90 days. Secondly, we assessed all outcomes at maximum time of follow-up (only possible for all-cause mortality).

Risk of bias
SM and MB independently and in duplicate assessed the risk of systematic errors (bias) in the included trials using the risk of bias tool from the Cochrane Collaboration,\(^3\) with additional prespecified criteria (S4, ESM) developed for a similar review in the ICU setting.\(^4\) Two review contributors not involved in the SUP-ICU trial (which the majority of authors of this review were involved in) assessed risk of bias and extracted data from this trial. We assessed the following domains: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; and (7) other biases, including baseline imbalance, early stopping and risk of bias due to vested financial interest or academic bias. The included trials were judged as ‘overall low risk of bias’ when all bias domains were judged as low risk of bias. Conversely, trials were judged as ‘overall high risk of bias’ if unclear or high risk of bias was judged in one or more domains.\(^5\) Effort was made to resolve unclarities by contact to relevant trial authors. We assessed publication bias when 10 or more comparisons were included by inspecting funnel plots and using Harbord’s test for funnel plot asymmetry (with P<0.05 considered statistically significant).\(^6,7,8\)
Data synthesis

Summary measures
We calculated relative risks (RRs) with 95% confidence intervals (CIs) and Trial Sequential Analysis (TSA)\(^2\)-adjusted CIs for all outcomes. Details on statistical software used is available in S5, ESM.

Meta-analysis
Our primary analyses included trials with overall low risk of bias; secondary analyses included all trials regardless of risk of bias. We calculated pooled effect estimates using Review Manager version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark). As we had 3 co-primary outcomes and 3 secondary outcomes (protocolised as 4, but none of the included trials reported on HRQoL) we considered a P value of <0.025 (0.05/[(3+1)/2]) statistically significant in the analysis of each outcome, in order to restrict the family-wise error rates (FWER) to 0.05.\(^2\)

Dealing with missing data
Attempts were made to contact corresponding investigators to clarify important missing information related to methods, data reporting, or if further data were needed (S6, ESM). We conducted a preplanned sensitivity analysis of our primary outcomes by imputing data in a best-/worst-case scenario and a worst-/best-case scenario to assess the potential impact of loss to follow-up.\(^18,21\)

Heterogeneity assessment
We assessed heterogeneity by visual inspection of the forest plots, the inconsistency statistics ($I^2$) and the diversity estimates ($D^2$).\(^2\) When $I^2 = 0$, we used a fixed effect model\(^3\) and when $I^2 > 0$ we used both fixed effect and random effects models,\(^3,32,33\) and reported the most conservative estimate being the point estimate closest to no effect or the estimate with the widest CI if point estimates concurred.\(^2\)

Subgroup analyses
We conducted the following predefined subgroup analyses\(^18\) for the primary outcomes:

1. Comparison of estimates of the pooled intervention effect in trials with overall low risk of bias versus overall high risk of bias.
2. Comparison of estimates of the pooled intervention effect in trials using PPI versus H2RA.
3. Comparison of estimates of the pooled intervention effect in trials using placebo versus no
treatment.

4. Comparison of estimates of the pooled intervention effect in the included subpopulations (defined post-hoc) of critically ill patients.

5. Comparison of estimates of the pooled intervention effect in ICU patients versus non-ICU patients.

We used the Chi² test to provide an indication of heterogeneity between trials, with P<0.10 considered significant.

Sensitivity analyses
We conducted a preplanned sensitivity analysis by performing empirical continuity corrections in the zero event trials. Additionally, we conducted a post-hoc sensitivity analysis to assess any effect on overt GI bleeding (defined as visible GI bleeding without further specification), as not all trials reported on our co-primary outcome clinically important GI bleeding. Furthermore, as no trials reported on the proportion of participants with one or more SAEs according to the ‘International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use: guideline for Good Clinical Practice’ (ICH-GCP) definition, we conducted two post-hoc sensitivity analyses of this outcome in which we assessed the number of patients with one or more SAEs: (1) highest proportion of reported SAEs in each trial, and (2) all reported SAEs cumulated in each trial (information available in S7, ESM), respectively.

Trial Sequential Analysis
We used TSA to assess the risk of random errors due to sparse data and multiple testing of accumulating data, and to calculate the required information size for clinically relevant predefined effect sizes.

We used conservative estimates of the anticipated intervention effect estimates to reduce the risk of random errors. We applied trial sequential monitoring boundaries according to a realistic a priori 15% relative risk difference (reduction or increase), with a beta of 90% and a control event proportion as suggested by all the trials reporting the respective outcome.

We present TSA-adjusted CIs adjusted for multiplicity of outcomes, sparse data, and repetitive testing for all primary analyses and analyses of low risk of bias trials.

Certainty of evidence
We assessed the overall certainty of evidence for each outcome measure according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

In short, we downgraded the certainty of evidence (our confidence in the effect estimates) for
each outcome for identified risk of bias, inconsistency (unexplained heterogeneity), indirectness (including other patient populations or use of surrogate outcomes), imprecision (wide CI around the effect estimate) and publication bias to allow overall certainty of evidence ratings as ‘high’, ‘moderate’, ‘low’, or ‘very low’.
RESULTS

Trial selection
We identified 10810 unique citations and included 62 RCTs8–10,43–101 with a total of 9713 participants (Figure 1).

Characteristics of included trials
The included trials were published between 1977 and 2019 with 53 trials being in English, 3 in Chinese,72,96,97 2 in Spanish,53,90 2 in German,86,92 1 in French,61 and 1 in Portuguese.51 Some 53 trials were published as full trial reports and 9 as conference abstracts only.48,57,63,68,71–73,80,92 The 62 included trials covered 65 comparisons (for simplicity subsequently termed ‘trials’ throughout this manuscript); 45 trials intervened with H2RAs and 20 with PPIs. A total of 43 trials were conducted in ICU, 21 outside ICUs (not specified in 1 trial). Some 15 trials investigated patients with intracerebral pathology, 8 trials investigated patients with acute ischemic heart disease, 3 trials investigated patients having a renal transplant, and the remaining 39 trials investigated other acutely ill patients. The control group was placebo in 40 trials and no prophylaxis in 25 trials. Of note, 5 trials did not report on any of our outcomes and were thus not included in any quantitative analyses.51,71,85,96,101 Characteristics of the included trials are presented in table S8 and full schematic overview of results in table S9, in the ESM.

Risk of bias
Three trials were adjudicated as having overall low risk of bias;8–10 the remaining trials were adjudicated as having an overall high risk of bias (Figure 2).43–101 Only 6 and 8 trials were adjudicated as low risk of bias in the domains for ‘selective reporting’ and ‘allocation concealment’, respectively. More than 75% of the trials were at unclear or high risk of financial bias (‘other bias’ domain), mostly because there were no declarations about funding at all.

Outcomes
All-cause mortality
A total of 37 trials including 7576 patients (3 overall low risk of bias trials (n=3587)) reported on all-cause mortality. Meta-analysis of the 3 overall low risk of bias trials did not show evidence of a difference in all-cause mortality for SUP versus placebo/no prophylaxis: RR 1.03 (95% CI 0.93 to 1.14; TSA-adjusted CI 0.90 to 1.18; high certainty) (Table 1, Figure 3 and S12, ESM). This was consistent in the analysis of all trials (regardless of risk of bias): RR 0.99 (95% CI 0.90 to 1.08; TSA-adjusted CI 0.87 to 1.11; high certainty) (Table 1, Figure 2 and 3).
Importantly, TSA showed that the boundary for futility was reached, indicating that a 15% RRR/RRI from stress ulcer prophylaxis can be refuted (Figure 3 and S12, ESM).

The predefined sensitivity analyses on missing data (best-worst case/worst-best case) and mortality at longest follow-up were consistent with the primary analyses (Table S9, Figure S16-18, ESM).

In the subgroup analysis on disease entity subpopulations of acutely ill patients (categorised post-hoc), we observed heterogeneity (test of interaction P=0.02), indicating that SUP may lower mortality for patients with intracerebral pathology compared with other acutely ill patients (Table S9, Figure S23, ESM). We observed no heterogeneity in the other subgroup analyses (Figure S19-22, ESM).

Clinically important GI bleeding
A total of 20 trials including 6227 patients reported on clinically important GI bleeding (3 overall low risk of bias trials (n=3596)). Conventional meta-analysis of the 3 overall low risk of bias trials indicated a lower risk of clinically important GI bleeding with SUP versus placebo/no prophylaxis: RR 0.62 (95% CI 0.43 to 0.89), however TSA highlighted that only 6.9% (3382/49136 patients) of the required information size had been accrued (TSA-adjusted CI 0.14 to 2.81) (Figure 4 and S25, ESM). The certainty of evidence was moderate due to imprecision as the range of possible effect sizes was small on the absolute scale (Table 1).

This finding was consistent with the analysis of all trials (regardless of risk of bias): RR 0.57 (95% CI 0.39 to 0.83; TSA-adjusted CI 0.12 to 2.63.), with moderate certainty of evidence due to imprecision (Figure 4 and Table 1).

The predefined sensitivity analyses on missing data were consistent with the primary analyses (Figure S29 and S30, ESM). In the subgroup analyses on ICU versus non-ICU patients and subpopulations of acutely ill patients, we observed heterogeneity (test of interaction P=0.008 and P=0.06, respectively), indicating that SUP may be more effectively reduce clinically important GI bleeding in acutely ill non-ICU patients compared with ICU patients (Figure S38, ESM) and in patients with acute ischemic heart disease compared with a mixed population of acutely ill patients (Figure S40, ESM), whereas in the other subgroup analyses we did not observe heterogeneity (Table S9, Figure S36, S37 and S39, ESM).

Overt GI bleeding (post-hoc sensitivity analysis)
A total of 52 trials including 8753 patients reported on overt GI bleeding (3 overall low risk of bias trials (n=3596)). Conventional meta-analysis of overall low risk of bias trials indicated a lower risk of overt GI bleeding with SUP versus placebo/no prophylaxis: RR 0.60 (95% CI 0.47 to 0.77),
However, TSA highlighted that only 16.8% (3596/21401 patients) of the required information size had been accrued (TSA-adjusted CI 0.22 to 1.65). The certainty of evidence was moderate due to imprecision (Table S10, Figure S31 and S32, ESM). This finding was consistent with the analysis of all trials (regardless of risk of bias): RR 0.48 (95% CI 0.38 to 0.60; TSA-adjusted CI 0.24 to 1.01), with low certainty of evidence as downgraded for inconsistency and imprecision (Figure S33-35, ESM).

**Serious adverse events**

Only 4 trials reported on SAEs. All 4 trials reported zero events in each group despite separately reporting GI bleeding and mortality. A total of 60 trials including 9393 patients reported an outcome categorised as an SAE according to the ICH-GCP definition (3 low risk of bias trials (n=3587)). The post-hoc sensitivity analyses on the highest individual proportion of any SAE and cumulative SAE proportion were inconclusive, but could not detect increased harm with SUP (very low to low certainty of evidence) (full results of analyses in S7 and S10, Figure S41-50, ESM).

**Hospital-acquired pneumonia**

A total of 20 trials including 5922 patients reported on hospital-acquired pneumonia (3 overall low risk of bias trials (n=3596)). Meta-analysis of the 3 overall low risk of bias trials did not show evidence of a difference in hospital-acquired pneumonia for SUP versus placebo/no prophylaxis: RR 1.02 (95% CI 0.87 to 1.18; TSA-adjusted CI 0.72 to 1.42) (Figure S51 and S52, ESM), with moderate certainty of evidence due to imprecision (Table 1). This finding was consistent with analysis of all trials (regardless of risk of bias): RR 1.05 (95% CI 0.93 to 1.18; TSA-adjusted CI 0.85 to 1.28) (Figure S53-55, ESM). According to TSA, the boundaries for futility were reached and a 15% RRR/RRI of pneumonia from stress ulcer prophylaxis could be refuted (Figure S55, ESM). The overall certainty of evidence was high (Table 1, Figure 2).

**Clostridium difficile enteritis**

A total of 4 trials including 3720 patients reported on *C. difficile* enteritis (3 overall low risk of bias trials (n=3596)). Meta-analysis of the 3 overall low risk of bias trials and all 4 trials (regardless of risk of bias) did not show any difference in *C. difficile* enteritis for SUP versus placebo/no prophylaxis: RR 0.84 (95% CI 0.48 to 1.47) (Figure S56, ESM) and RR: 0.79 (95% CI 0.46 to 1.36) (Figure S57 and S58, ESM), respectively. TSA was not possible as too little information was accrued (2.5% and 3.0%, respectively). Accordingly, the certainty of evidence was low due to very serious imprecision (Table 1).
Myocardial ischemia

One trial (overall low risk of bias) including 3291 patients reported data on myocardial ischemia, RR 1.17 (95% CI 0.85 to 1.61; TSA-adjusted CI 0.31 to 4.34) (Figure S59 and S60, ESM). TSA showed that only 5.9% (3291/55355 patients) of the required information size had been accrued to confirm/reject a 15% RRR/RRI. Accordingly, the certainty of evidence was low due to very serious imprecision (Table 1).

Health-related quality of life

No trials reported data on HRQoL.
DISCUSSION

In this systematic review with meta-analysis and TSA of 57 trials (60 comparisons), we found no evidence of a difference in mortality (high certainty of the evidence) with SUP versus placebo or no prophylaxis in adult acutely ill hospitalised patients. SUP may reduce the risk of clinically important GI bleeding (moderate certainty). SAEs were not reported according to the ICH-GCP definition, and a post-hoc sensitivity analysis did not point towards increased harm with SUP (very low to low certainty). We found moderate to high certainty evidence for no effect of SUP on the rates of hospital-acquired pneumonia with a point-estimate very close to one. Very few trials have assessed the rates of C. difficile enteritis (4 trials) and myocardial ischemia (1 trial) with SUP (low to very low certainty). No trials have investigated the effect of SUP on HRQoL.

As suggested by the predefined subgroup analyses, SUP may lower mortality in patients with intracerebral pathology, when compared with a mixed population of acutely ill patients, and may be more effective in lowering the incidence of clinically important GI bleeding for acutely ill non-ICU patients as compared with ICU patients and in patients with acute ischemic heart disease as compared with a mixed population of acutely ill patients. Importantly, subgroup analyses were multiple and substantially underpowered, thus these results should be interpreted with caution and merely serve the purpose of hypothesis generation.

Relation to other reviews

Well-conducted systematic reviews with meta-analysis on SUP in the ICU have been published. However, this review is the first to address the effects of SUP with PPI/H2RA in adult acutely ill hospitalised patients not limited to the ICU. As a result, we meta-analysed more trials (57 trials, 60 comparisons) than any previous reviews on SUP for acutely ill patients. The most recent systematic review in ICU patients (conducted by the present group of authors), including 6790 patients from 41 trials, did not find a difference in mortality (high certainty), confirmed a reduction in overt GI bleeding (high certainty), and results on potential adverse effects from SUP with PPIs or H2RA versus placebo or no prophylaxis were inconclusive. A comprehensive Cochrane review from 2018 evaluating any form of pharmacological SUP versus placebo or no prophylaxis found no difference in ICU mortality regardless of drug type, evidence of H2RAs reducing the incidence of clinically important GI bleeding, but not evidence for PPIs reducing clinically important GI bleeding. In a direct comparison, however, PPIs were found to be superior to H2RA in reducing clinically important GI bleeding.
A recent network meta-analysis, with a total of 7293 patients from 57 trials, showed that PPIs were more efficient in preventing clinically important GI bleeding than H2RAs and placebo, but that PPIs may increase the risk of pneumonia compared with H2RAs and placebo.\textsuperscript{15} We could not replicate the finding of an increased occurrence of pneumonia, which may be due to the inclusion of more trials, especially the large SUP-ICU trial, in our study.

**Strengths and limitations**

This review has several strengths. We have conducted this review using a robust, systematic and transparent approach according to the Cochrane Handbook,\textsuperscript{19} the PRISMA statement,\textsuperscript{20} and our preplanned and published protocol and statistical analysis plan including TSA to assess the precision of the results. Our literature search was comprehensive, and the population was broad. Last, we used the GRADE approach\textsuperscript{22} to assess the certainty of evidence for each outcome.

Our review has important limitations. The population was clinically heterogenous as expected, with different indications for SUP and different patient groups in various clinical settings. Thus, the risk of introducing potentially important clinical heterogeneity is imminent. To get clinically applicable results, we excluded trials in children, non-acute ill patients and patients admitted electively. Importantly, no trials conducted outside of the ICU were judged to be of overall low risk of bias. Thus, only ICU trials were included in the analyses of low risk of bias trials hampering the generalisability to acutely ill hospitalised patients in other hospital settings. Also, only 5\% of all included trials were adjudicated as overall low risk of bias. However, estimates from meta-analyses of overall low risk of bias trials and all trials regardless of risk of bias, were consistent. We assessed effects in subpopulations of acutely ill patients (subgroup analysis) as planned, however, based on our own post-hoc grouping of comparable trial populations. Thus, these subpopulations were data-driven and not prespecified. Only few trials reported SAEs\textsuperscript{10,49,64,65} and none according to the ICH-GCP definition.\textsuperscript{23} Thus, SAEs are likely to be seriously underreported. Further, as only trials with overall high risk of bias have assessed H2RAs the results for H2RAs should be interpreted with caution. Lastly, some may consider our predefined effects sizes in the TSAs to be large\textsuperscript{105} and not assessing the minimal clinically important difference (e.g. a 10\% relative difference could also be clinically relevant, but was not assessed for any of the outcomes in this paper).

**Clinical implications and unanswered questions**

It has become increasingly evident that any effect of SUP on all-cause mortality of acutely ill hospitalised patients in general is either non-existent or smaller than 15\% RRI/RRR. Whether this...
is also the case for SUP in the most severely ill patients is uncertain, and more research is likely needed to confirm or reject this.

Our review suggests that an absolute reduction in clinically important GI bleeding of 2.4% (from 5.0% to 2.6%) may be obtained with use of PPIs or H2Ras in in adult acutely ill hospitalised patients. However, it remains debatable which of these should be first choice. The upcoming cluster-randomised ‘Proton Pump Inhibitors versus Histamine-2 Receptor Blockers for Ulcer Prophylaxis Therapy in the Intensive Care Unit’ (PEPTIC) trial results may indicate the direction on the head-to-head effects and adverse events of these agents. Our results do not indicate increased risk of hospital-acquired pneumonia when comparing SUP with placebo or no prophylaxis, thereby not supporting suggestions of increased risk derived mainly from observational studies and head-to-head comparisons of different SUP agents. Clinically meaningful inferences of effects on overall SAEs, C. difficile enteritis, myocardial ischemia or HRQoL cannot be made due to insufficient data.

In conclusion, in this systematic review of SUP in acutely ill adult hospitalised patients, we did not observe an effect on all-cause mortality and hospital-acquired pneumonia, but a reduction in the incidence of clinically important GI bleeding. The results regarding serious adverse events, myocardial ischemia, C. difficile enteritis and HRQoL were inconclusive.
FIGURE LEGENDS AND TABLES

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart

Legend:

* Trials populations consisting of patients who were not hospitalised or were electively admitted to the hospital

Figure 2. Risk of bias summary for the trials included in the quantitative analyses

Legend:

Green represents low risk of bias, yellow an unclear risk of bias, and red a high risk of bias. The 5 trials not included in any meta-analysis are not depicted on figure.

Figure 3. Forest plot and Trial Sequential Analysis for all-cause mortality (all trials)

Legend:

Fig. 3 A. Forest plot of all-cause mortality in trials with overall low risk of bias versus trials with overall high risk of bias. Size of squares for risk ratio reflects weight of trial in the pooled analysis. Horizontal bars represent 95% confidence intervals.

Fig. 3 B. Trial Sequential Analysis of all 37 trial regardless of risk of bias of the effect of proton pump inhibitors/histamine 2 receptor antagonists versus placebo/no prophylaxis on all-cause mortality using a control event proportion of 22.4% (from the included trials), a diversity (D2) of 30%, an alpha of 2.5%, a power of 90%, and a relative risk reduction of 15%. The meta-analytic relative risk was 0.99 with a TSA-adjusted CI 0.87, 1.11. The required information size of 10283 was not reached, however, the cumulative Z-score reached the futility area. Thus, concluding that a 15% relative risk change is refutable.

Figure 4. Forest plot and Trial Sequential Analysis for clinically important GI bleeding (all trials)

Legend:

Fig. 4 A. Forest plot of clinically important gastrointestinal bleeding in trials with overall low risk of bias versus trials with overall high risk of bias. Size of squares for risk ratio reflects weight of trial in the pooled analysis. Horizontal bars represent 95% confidence intervals.
Fig. 4 B. Trial Sequential Analysis of all 20 trial regardless of risk of bias of the effect of proton pump inhibitors/histamine 2 receptor antagonists versus placebo/no prophylaxis on clinically important gastrointestinal bleeding using a control event proportion of 5.0% (from the included trials), a diversity (D2) of 50%, an alpha of 2.5%, a power of 90%, and a relative risk reduction of 15%. The meta-analytic relative risk was 0.57 with a TSA-adjusted CI 0.12 to 2.63. The required information size of 78739 was not reached (only 7.6% obtained) and trial sequential monitoring boundaries were not crossed. The information fraction was too small to produce an inner wedge futility area. Thus, the TSA highlights that we have insufficient information to reject/confirm a 15% change in relative risk.
Table 1. GRADE evidence profile

<table>
<thead>
<tr>
<th>Study event</th>
<th>№ of participants (studies)</th>
<th>Follow-up</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication bias</th>
<th>Overall certainty of evidence</th>
<th>Summary of findings</th>
<th>Anticipated absolute effects</th>
<th>Risk with control</th>
<th>Risk difference with PPI/H2RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality - low risk of bias trials</td>
<td>3587 (3 RCTs)</td>
<td>not serious</td>
<td>not serious a</td>
<td>not serious b</td>
<td>undetected</td>
<td>HIGH</td>
<td>537/1790 (30.0%)</td>
<td>557/1767 (31.5%)</td>
<td>RR 1.03 (0.94 to 1.14)</td>
<td>300 per 1,000 (18 fewer to 42 more)</td>
<td></td>
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<tr>
<td>All-cause mortality - all trials</td>
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<tr>
<td>Certainty assessment</td>
<td>Summary of findings</td>
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<tr>
<td>7576 (37 RCTs)</td>
<td>826/3 (22.4%)</td>
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<tr>
<td>not serious d</td>
<td>852/3 (21.9%)</td>
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<tr>
<td>not serious e</td>
<td>RR 0.99 (0.90 to 1.08)</td>
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<tr>
<td>undetected</td>
<td>224 per 1,000</td>
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<td>HIGH</td>
<td>2 fewer per 1,000</td>
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<tr>
<td>3596 (3 RCTs)</td>
<td>71/17 (4.0%)</td>
<td></td>
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<tr>
<td>not serious f</td>
<td>44/17 (2.4%)</td>
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<tr>
<td>not serious g</td>
<td>RR 0.62 (0.43 to 0.89)</td>
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<tr>
<td>undetected</td>
<td>40 per 1,000</td>
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<tr>
<td>MODE RATE</td>
<td>16 fewer per 1,000</td>
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<tr>
<td>6227 (20 RCTs)</td>
<td>151/3 (5.0%)</td>
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<tr>
<td>not serious h</td>
<td>84/31 (2.6%)</td>
<td></td>
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</tr>
<tr>
<td>not serious i</td>
<td>RR 0.57 (0.39 to 0.83)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>not serious j</td>
<td>50 per 1,000</td>
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</tr>
<tr>
<td>undetected</td>
<td>22 fewer per 1,000</td>
<td></td>
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<td></td>
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<tr>
<td>MODE RATE</td>
<td>2 fewer per 9 fewer</td>
<td></td>
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</tbody>
</table>

This article is protected by copyright. All rights reserved
<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong> <em>(no reported events)</em></td>
<td></td>
</tr>
<tr>
<td>3704 (4 RCTs)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Health-related quality of life</strong> <em>(no trials reporting this outcome)</em></td>
<td></td>
</tr>
<tr>
<td>0 (0 RCTs)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Myocardial ischaemia – low risk of bias trials</strong> <em>(only trial reporting this outcome)</em></td>
<td></td>
</tr>
<tr>
<td>3291 (1 RCT)</td>
<td>not serious</td>
</tr>
<tr>
<td><strong>Hospital-acquired pneumonia - low risk of bias</strong></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proton pump inhibitors or histamin-2 receptor antagonists compared to placebo or no prophylaxis for stress ulcer prophylaxis in adult hospitalized acutely patients</strong></td>
<td></td>
</tr>
<tr>
<td>3596 (3 RCTs)</td>
<td>not serious</td>
</tr>
<tr>
<td>273/1</td>
<td>797</td>
</tr>
<tr>
<td><strong>Hospital-acquired pneumonia - all trials</strong></td>
<td></td>
</tr>
<tr>
<td>5922 (20 RCTs)</td>
<td>not serious</td>
</tr>
<tr>
<td>411/2</td>
<td>892</td>
</tr>
<tr>
<td><strong>C. difficile enteritis - low risk of bias</strong></td>
<td></td>
</tr>
<tr>
<td>3596 (3 RCTs)</td>
<td>not serious</td>
</tr>
<tr>
<td>26/17</td>
<td>97</td>
</tr>
</tbody>
</table>
Proton pump inhibitors or histamin-2 receptor antagonists compared to placebo or no prophylaxis for stress ulcer prophylaxis in adult hospitalized acutely patients

<table>
<thead>
<tr>
<th>Certainty assessment</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C. difficile enteritis - all trials</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N</th>
<th>(RCTs)</th>
<th>not serious</th>
<th>not serious, not serious</th>
<th>very serious, undetected</th>
<th>GRADE</th>
<th>29/18</th>
<th>23/18</th>
<th>RR</th>
<th>CI</th>
<th>few per 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>3720</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>59</td>
<td>61</td>
<td>0.79</td>
<td>0.46 to 1.36</td>
<td>(9 fewer to 5 more)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio

GRADE evidence profiles for post-hoc sensitivity analyses on SAEs and overt GI bleeding available as S10, ESM.
**Explanations**

a. $I^2 = 0\%, P = 0.72$, overlap of confidence intervals.

b. TSA-adjusted 95% CI 0.90 to 1.18 with the Z-curve reaching futility area for an RRR/RRI of 15%.

c. 34/37 trials had overall high risk of bias. However, as the estimate is nearly identical to that of low risk of bias trials we have not downgraded.

d. $I^2 = 2\%, P = 0.43$, overlap of confidence intervals.

e. TSA-adjusted 95% CI 0.87 to 1.11 with the Z-curve reaching futility area for an RRR/RRI of 15%.

f. $I^2 = 0\%, P = 0.40$, overlap of confidence intervals.

g. TSA-adjusted 95% CI 0.14 to 2.80 (broad, inconclusive) and very few events (required information size: 49136 patients, 6.9% obtained).

h. 17/20 had overall high risk of bias. However, as the estimate is nearly identical to that of low risk of bias trials we have not downgraded.

i. $I^2 = 19\%, P = 0.23$, overlap of confidence intervals.

j. TSA-adjusted 95% CI 0.12 to 2.63 (broad, inconclusive) and very few events (required information size: 78041 patients, 7.6% obtained).

k. Only one trial included, with wide CI around effect estimate. TSA-adjusted 95% CI 0.31 to 4.34 (broad, inconclusive) (required information size: 55355 patients, 5.9% obtained).

l. $I^2 = 0\%, P = 0.64$, overlap of confidence intervals.

m. TSA-adjusted 95% CI 0.72 to 1.42, with the cumulative Z-curve not reaching futility area (required Information size: 11540, 31.2% obtained)

n. 17/20 were overall high risk of bias. However, as the estimate is nearly identical to that of low risk of bias trials we have not downgraded.

o. $I^2 = 0\%, P = 0.52$, overlap of confidence intervals.

p. TSA-adjusted 95% CI 0.85 to 1.28 with the cumulative Z-curve reaching the futility area for an RRR/RRI of 15%.

q. $I^2 = 0\%, P = 0.58$, overlap of confidence intervals.

r. TSA was not possible due to too little information. Thus, the required information size is far from reached.

s. 1/4 trials had overall high risk of bias. However, as the estimate is nearly identical to that of low risk of bias trials we have not downgraded.

t. $I^2 = 0\%, P = 0.64$, overlap of confidence intervals.

u. TSA was not possible due to too little information. Thus, the required information size is far from reached.
DECLARATIONS

Authors’ contribution
Protocol development: SM, JW, MB, JCJ, MK, AG, CTA and MHM
Search strategy development: MB, SM
Study search/procurement: MB
Selection of studies: SM, AG, CTA, MB
Data extraction: SM, MB
Interpretation of analyses: SM, MHM
Final review: all authors
Updating of final review: all authors

Acknowledgements
We sincerely thank Drs Ning Liang and Dezhao Kong for translating Chinese papers.

Declaration of interests
Most authors of this review (SM, AP, JW, MK, AG, CTA and MHM) were involved in the recent international placebo-controlled randomised clinical trial ‘Stress Ulcer Prophylaxis in the Intensive Care Unit’ (SUP-ICU), which was included in this review.10 All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.
Dr. Perner reports grants from the Novo Nordisk Foundation outside the submitted work

Funding
The primary author has received funding from: the Ehrenreich foundation and the Research Council at Copenhagen University Hospital Rigshospitalet. The funding parties are not involved in the conduct of this review.

Appendices

Appendix A: Electronic Supplementary Material
References


49. Chan KH, Lai ECS, Tuen H, Ngan JHK, Mok F, Fan YW, Fung CF, Yu WC. Prospective double-blind placebo-controlled randomized trial on the use of ranitidine in preventing

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59. Halloran LG, Zfass AM, Gayle WE, Wheeler CB, Miller JD. Prevention of acute gastrointestinal complications after severe head injury: A controlled trial of cimetidine...


69. Lin CC, Hsu YL, Chung CS, Lee TH. Stress ulcer prophylaxis in patients being weaned


78. Moesgaard F, Jensen LS, Christiansen PM, Thorlacius-Ussing O, Nielsen KT, Rasmussen NR, Bardram L, Nielsen HJ. The effect of ranitidine on postoperative infectious


98. Zach GA, Gyr KE, von Alvensleben E, Mills JG, Stalder GA, Dunn SL, Bloom S. A double-


Records identified through database searching (n = 37,522)

Additional records identified through other sources (n = 5,15)

Duplicates removed (n = 27,227)

Records screened (n = 10,810)

Records excluded (n = 10,603)

Full-text articles assessed for eligibility (n = 206)

Full-text articles excluded, with reasons (n = 144)
- Duplicate full-texts (n = 60)
- Not acutely ill patients* (n = 42)
- Wrong trial design (n = 24)
- Wrong intervention (n = 13)
- Wrong comparator (n = 5)

Studies included in qualitative synthesis (n = 62)

Studies included in quantitative synthesis (meta-analysis) (n = 57)
### 2.3.1 Trials with overall low risk of bias

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>H2RA/PPI</th>
<th>Placebo/no prophylaxis</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alhazrani 2017</td>
<td>3</td>
<td>2</td>
<td>4.1% 1.29 [0.23, 7.33]</td>
</tr>
<tr>
<td>Krag and Marker 2018</td>
<td>1644</td>
<td>69</td>
<td>27.4% 0.60 [0.41, 0.87]</td>
</tr>
<tr>
<td>Selvander 2016</td>
<td>108</td>
<td>0</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1789</td>
<td>1787</td>
<td>31.5% 0.62 [0.43, 0.89]</td>
</tr>
<tr>
<td>Total events</td>
<td>44</td>
<td>71</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 2.55 (P = 0.01)

### 2.3.2 Trials with overall high risk of bias

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>H2RA/PPI</th>
<th>Placebo/no prophylaxis</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benmenachem 1994</td>
<td>16</td>
<td>100</td>
<td>13 16.9% 1.23 [0.63, 2.42]</td>
</tr>
<tr>
<td>Chan 1995</td>
<td>9</td>
<td>49</td>
<td>21 17.0% 0.45 [0.23, 0.89]</td>
</tr>
<tr>
<td>El-Kenawi 2018</td>
<td>1</td>
<td>62</td>
<td>1 1.8% 1.00 [0.09, 15.63]</td>
</tr>
<tr>
<td>Hanisch 1998</td>
<td>3</td>
<td>57</td>
<td>2 4.1% 1.50 [0.26, 8.64]</td>
</tr>
<tr>
<td>Kantorova (H2RA) 2004</td>
<td>2</td>
<td>71</td>
<td>1 2.3% 1.04 [0.10, 11.12]</td>
</tr>
<tr>
<td>Kantorova (PPI) 2004</td>
<td>1</td>
<td>72</td>
<td>0 1.3% 1.60 [0.07, 38.42]</td>
</tr>
<tr>
<td>Karlstad 1993</td>
<td>1</td>
<td>54</td>
<td>7 3.1% 0.09 [0.01, 0.68]</td>
</tr>
<tr>
<td>Koeltz 1987</td>
<td>0</td>
<td>29</td>
<td>1 1.3% 0.31 [0.01, 7.33]</td>
</tr>
<tr>
<td>Lin 2016</td>
<td>0</td>
<td>60</td>
<td>1 1.3% 0.33 [0.01, 8.02]</td>
</tr>
<tr>
<td>Nikolic 2011</td>
<td>0</td>
<td>150</td>
<td>4 1.6% 0.11 [0.01, 2.03]</td>
</tr>
<tr>
<td>Poula 1985</td>
<td>0</td>
<td>21</td>
<td>3 1.6% 0.12 [0.01, 2.24]</td>
</tr>
<tr>
<td>Walter 1984</td>
<td>1</td>
<td>47</td>
<td>11 3.2% 0.10 [0.01, 0.72]</td>
</tr>
<tr>
<td>Wei 2016</td>
<td>0</td>
<td>123</td>
<td>3 1.5% 0.10 [0.01, 1.87]</td>
</tr>
<tr>
<td>Wu 2011</td>
<td>1</td>
<td>333</td>
<td>5 2.8% 0.20 [0.02, 1.70]</td>
</tr>
<tr>
<td>Zhang (PPI and atorvastatin) 2015</td>
<td>0</td>
<td>27</td>
<td>0 26 Not estimable</td>
</tr>
<tr>
<td>Zhang (PPI and rosuvastatin) 2015</td>
<td>0</td>
<td>26</td>
<td>0 25 Not estimable</td>
</tr>
<tr>
<td>Zinner 1981</td>
<td>5</td>
<td>100</td>
<td>7 8.7% 0.71 [0.23, 2.18]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1381</td>
<td>1250</td>
<td>68.5% 0.49 [0.23, 0.83]</td>
</tr>
<tr>
<td>Total events</td>
<td>40</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.25; Chi² = 19.38, df = 14 (P = 0.15); I² = 28%
Test for overall effect: Z = 2.05 (P = 0.008)

Total (95% CI) 3180 3047 100.0% 0.57 [0.39, 0.83]
Total events 84 151

Heterogeneity: Tau² = 0.10; Chi² = 19.78, df = 16 (P = 0.23); I² = 19%
Test for overall effect: Z = 2.96 (P = 0.003)

Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%

---

**Cumulative Z-Score**

- **Trial sequential monitoring boundary for benefit**
- **Required information size = 78369**

---

**Z-curve**

- **Conventional boundary for benefit P=0.025**

---

**Number of patients (Linear scaled)**

- **Trial sequential monitoring boundary for harm**
- **Conventional boundary for harm P=0.025**

---

- **5909**