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SYSTEMATIC REVIEW

Stress ulcer prophylaxis with proton pump inhibitors or histamin-2 receptor antagonists in adult intensive care patients: a systematic review with meta-analysis and trial sequential analysis

Marija Barbateskovic[1,2*], Søren Marker[2,3], Anders Granholm[3], Carl Thomas Anthon[3], Mette Krag[3], Janus Christian Jakobsen[1,2,4], Anders Perner[2,3], Jørn Wetterslev[1,2] and Morten Hylander Møller[2,3]

Abstract

Purpose: Most intensive care unit (ICU) patients receive stress ulcer prophylaxis. We present updated evidence on the effects of prophylactic proton pump inhibitors (PPIs) or histamine 2 receptor antagonists (H2RAs) versus placebo/no prophylaxis on patient-important outcomes in adult ICU patients.

Methods: We conducted a systematic review with meta-analysis and trial sequential analysis (TSA) of randomised clinical trials assessing the effects of PPI/H2RA versus placebo/no prophylaxis on mortality, gastrointestinal (GI) bleeding, serious adverse events (SAEs), health-related quality of life (HRQoL), myocardial ischemia, pneumonia, and *Clostridium (Cl.) difficile* enteritis in ICU patients.

Results: We identified 42 trials randomising 6899 ICU patients; 3 had overall low risk of bias. We did not find an effect of stress ulcer prophylaxis on mortality [relative risk 1.03, 95% confidence interval (CI) 0.94–1.14; TSA-adjusted CI 0.94–1.14], but the occurrence of any GI bleeding was reduced as compared with placebo/no prophylaxis (0.60, 95% CI 0.47–0.77; TSA-adjusted CI 0.36–1.00). The conventional meta-analysis indicated that clinically important GI bleeding was reduced (RR 0.63, 95% CI 0.48–0.81), but the TSA-adjusted CI 0.35–1.13 indicated lack of firm evidence. The effects of stress ulcer prophylaxis on SAEs, HRQoL, pneumonia, myocardial ischemia and *Cl. difficile* enteritis are uncertain.

Conclusions: In this updated systematic review, we were able to refute a relative change of 20% of mortality. The occurrence of GI bleeding was reduced, but we lack firm evidence for a reduction in clinically important GI bleeding. The effects on SAEs, HRQoL, pneumonia, myocardial ischemia and *Cl. difficile* enteritis remain inconclusive.

Keywords: Critical care, Peptic ulcer, Gastrointestinal haemorrhage, Meta-analysis, Proton pump inhibitors, Histamine-2 receptor antagonists, Stress ulcer prophylaxis

*Correspondence: marija.barbateskovic@ctu.dk
[1] Copenhagen Trial Unit, Centre for Clinical Intervention Research, 2100 Copenhagen, Denmark
Full author information is available at the end of the article

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Introduction

Patients admitted to the intensive care unit (ICU) are at risk of stress-related gastrointestinal (GI) mucosal damage that may evolve to ulceration and bleeding [1]. The reported prevalence of GI bleeding ranges from 5 to 10% in recent reports, and GI bleeding is associated with an increased risk of death and length of stay in the ICU [2–5]. Stress ulcer prophylaxis is routinely used in the ICU, even though recommendations in international guidelines are conflicting [6, 7]. However, the quantity and quality of evidence supporting use of stress ulcer prophylaxis in adult ICU patients is low with no firm evidence for benefit or harm [8, 9]. Importantly, increased rates of myocardial ischaemia, *Clostridium (Cl.) difficile* enteritis and hospital-acquired pneumonia with the use of stress ulcer prophylaxis have been suggested [1, 8, 10, 11]. Several randomised clinical trials (RCT) and systematic reviews have compared the effects of proton pump inhibitors (PPIs) and histamine-2-receptor antagonist (H2RAs), but neither PPIs nor H2RAs have demonstrated superiority as compared with placebo or no prophylaxis [10, 12–15].

Recently, new relevant trials, including the SUP-ICU trial, have been published [3, 5, 16–18]. Consequently, we performed an updated systematic review on stress ulcer prophylaxis with PPI or H2RA versus placebo or no prophylaxis in adult ICU patients. We hypothesised an absence of effect on mortality, a reduction of GI bleeding, and an increase of infectious adverse events and myocardial ischemia.

Take-home message

Stress ulcer prophylaxis with PPI or H2RA did not seem to affect mortality, but likely reduced the occurrence of gastrointestinal bleeding.

Methods

We conducted this systematic review according to the preplanned statistical analysis plan of the published protocol [19]. We registered the protocol in the international prospective register of systematic reviews database (PROSPERO) (CRD42018089151) and used the methodology of the Cochrane Collaboration [20], the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [S1, Electronic Supplementary Material, (ESM)] [21], Keus et al. [22], Jakobsen et al. [23], and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [24].

Eligibility criteria

We included any RCT comparing stress ulcer prophylaxis with either PPI or H2RA versus placebo or no prophylaxis in adult ICU patients. We accepted any dose, formulation and duration of intervention [19].

Search methods for identification of studies

We did not restrict the search by language, date, publication status or any other trial characteristics. MB searched the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; Ovid MEDLINE; Ovid Embase; Science Citation Index Expanded (Web of Science); Biosis Previews (Web of Science); and PubMed. The systematic search included the following keywords: peptic ulcer; gastrointestinal haemorrhage; proton pumps; histamine h2 receptor antagonists; critical illness; critical care; intensive care units; artificial respiration; craniocerebral trauma; heart arrest; myocardial infarction; sepsis; and surgery. The full search is available in the ESM. The literature search was updated on 11 October 2018. We manually identified additional potential eligible trials by screening the reference lists of the included studies, other relevant systematic reviews, and searched trial registries.

Selection of studies

At least two authors (MB, SM, AG or CTA) independently screened each title and abstract. Reports deemed potentially relevant were obtained in full-text and assessed for inclusion in accordance with the inclusion criteria. Disagreements were resolved by consensus and MHM/JW were consulted when agreement could not be met.

Data extraction and management

Two review authors (MB and SM) independently extracted predefined data of the included trials using a predefined data collection form (S2, ESM). The following data were collected: (1) Trial: country, duration of the trial, date of publication, and type of trial (single versus multi centre); (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 [19].

Outcomes

Predefined co-primary outcomes were all-cause mortality and the proportion of participants with any GI bleeding (overt and clinically important bleeding defined by trialists). Co-secondary outcomes were: the proportion of participants with one or more serious adverse events (SAEs) (as defined by trialists using the term 'serious

adverse event', 'severe adverse event', 'serious adverse reaction', 'serious complication', 'severe complication' or similar terms fulfilling the criteria of the Good Clinical Practice Guideline of the International Conference on Harmonization (ICH-GCP) definition [25]); health-related quality of life (HRQoL) (any valid scale used by trialists); proportion of participants with myocardial ischemia (as defined by trialists); proportion of participants with hospital-acquired pneumonia (as defined by trialists); proportion of participants with *CI. difficile* enteritis (as defined by trialists).

For all outcomes, we used the trial results reported at time-points closest to 90 days.

Risk of bias

MB and SM independently assessed the risk of systematic errors (bias) in the included trials using the Cochrane Collaboration's risk of bias tool [20], with additional prespecified criteria (ESM) [19]. Two review contributors not involved in the SUP-ICU trial [3] assessed risk of bias and extracted data from this trial. We specifically 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 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' when unclear or high risk of bias was judged in one or more domains [26].

We assessed publication bias by inspecting funnel plots for signs of asymmetry when ten or more trials were included in an analysis [20, 23]. We tested asymmetry with the Harbord test [27].

Data synthesis

Summary measures

We calculated relative risks (RRs) with 95% confidence intervals (CIs) and trial sequential analysis (TSA)-adjusted CIs [28] for all outcomes. We hypothesised an absence of effect on mortality, a reduction of GI bleeding, and an increase of infectious adverse events and myocardial ischemia, assuming a required information size corresponding to a relative risk reduction (RRR) or a relative risk increase (RRI) of 20% [19, 29].

Meta-analyses

The primary analysis included trials with overall low risk of bias. We calculated pooled effect estimates using Review Manager [30]. We considered a P value of $0.05/[(2+1)/2] = 0.033$ or less as statistically significant in the analyses of each primary outcome, and we considered a P value of $0.05/[(5+1)/2] = 0.017$ or less as statistically significant in the analyses of each secondary outcome, in order to restrict the family-wise error rates (FWER) to 0.05 [23]. We calculated Bayes factor to assess if the summary effect estimates fitted better with the null hypothesis than alternative hypotheses of the anticipated intervention effects [23].

Dealing with missing data

Corresponding authors were contacted to clarify important missing data related to the methods, data reporting, or if further trial details were needed (S4, ESM).

We conducted a predefined sensitivity analysis by imputing missing outcome data in a best-/worst-case scenario and a worst-/best-case scenario to assess the potential impact of loss to follow-up. In the best-/worst-case scenario analysis, it was assumed that all participants lost to follow-up in the experimental group did not experience the event, and that all those with missing outcomes in the control group did experience the event. In the worst-/best-case scenario analysis, it was assumed that all participants lost to follow-up in the experimental group did not experience the event, and that all those with missing outcomes in the control group did experience the event [19, 23].

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots, the inconsistency statistics (I^2) and the estimates of diversity (D^2) [31]. When $I^2 = 0$, we used a fixed effects model [32, 33], and when I^2 was above zero, we used both fixed and random effects models [32, 34, 35], and reported the most conservative estimate being the point estimate closest to no effect or the estimate with the widest CI.

Subgroup analyses

We planned to conduct the following predefined subgroup analyses: high versus low risk of bias; medical versus surgical versus mixed ICU setting; shock versus no shock; renal replacement therapy (RRT) versus no RRT; invasive mechanical ventilation versus no invasive mechanical ventilation versus unknown status; PPI versus H2RA; and placebo versus no prophylaxis [19]. In addition, we conducted post hoc subgroup analyses on the co-primary outcomes: one according to a dose of PPI (max 40 mg daily versus > 40 mg daily) and one according to publication year (median publication date 1993/1994). We accepted the definitions used in the included trials, and only trials defining subgroups on a trial level were included. Presence of statistical heterogeneity was

assessed by the χ^2 test with significance set at $P<0.10$ [19].

Sensitivity analyses

We conducted a sensitivity analysis to assess the potential impact of reporting bias by excluding trials not reporting on clinically important bleeding [19].

In two post hoc sensitivity analyses, we estimated 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 the ESM).

Trial sequential analysis

TSA is a sequential meta-analysis considering how much information (randomised patients) is needed to conclude on a specific a priori anticipated intervention effect in updated, repetitive testing meta-analyses. If information size is smaller than required in the meta-analysis, the TSA-adjusted CI becomes wider than the conventional naïve, meta-analytic 95% CI, and the threshold for statistical significance becomes more restrictive. However, if the required information size is reached, the TSA-adjusted CI and the naïve CI, anticipating a specific intervention effect, becomes identical.

We used TSA to assess the risk of random errors due to sparse data and multiple testing of accumulating data [36–44], and to calculate the required information size [31]. The calculated required information size takes into account the control event proportion, the anticipated heterogeneity variance (D^2) [22] of the meta-analysis, and the assumption of a plausible RRR or RRI.

We used a FWER of 5% [23] leading to a statistical significance level of 3.3% and 96.7% CIs for each of the two co-primary outcomes and 1.7% and 98.3% CIs, respectively, for each of the five co-secondary outcomes [19]. We used a beta of 10%, and a D^2 [31] as suggested by the trials in the meta-analysis [23], or a D^2 of 20% if the measured heterogeneity was zero [45]. As anticipated intervention effects for the primary and secondary outcomes in the TSA, we used a realistic a priori RRR or RRI of 20%. Furthermore, we used an RRR or RRI based on the 95% confidence limit closest to a null effect in the traditional meta-analysis [19]. In addition, we have made a TSA anticipating a 15% RRR of mortality on the meta-analysis of new trials published after our first review [34].

We present 95% CIs and TSA-adjusted CIs, adjusted for multiplicity of outcomes, sparse data, and repetitive testing for all estimates. For a more detailed description of the statistical analysis plan and TSA, we refer to the published protocol [19].

Grading quality of evidence

We used the GRADE approach [24] to assess the overall certainty of evidence for all outcomes. We appraised the certainty of evidence and our confidence in the effect estimates based on risk of bias, inconsistency, indirectness, imprecision and publication bias. Thus, we rated the overall certainty of evidence as high, moderate, low or very low.

Results

Study selection

We identified 10,054 references (Fig. 1) and included 41 RCTs [3–5, 12, 16–18, 46–79] with a total of 6790 participants. Some 37 trials were in English, 2 in German [75, 78], 1 in Portuguese [54], and 1 in French [61].

Characteristics of the included studies

The included trials were published between 1977 and 2018. Some 35 trials were published as full trial reports and 6 as conference abstracts. The 41 included trials covered 44 trial comparisons; 32 trials assessed H2RAs and 12 assessed PPIs. The control group was placebo in 31 trials and no prophylaxis in 13 trials. Details and additional information of the included trials are presented in S3 and S4, ESM. Characteristics of the excluded studies and ongoing trials are summarised in S5, ESM.

Risk of bias assessment

Three trials were judged as having overall low risk of bias [3–5]; the remaining 38 all had overall high risk of bias (Figs. 2 and S4 in the ESM) [12, 16–18, 46–79].

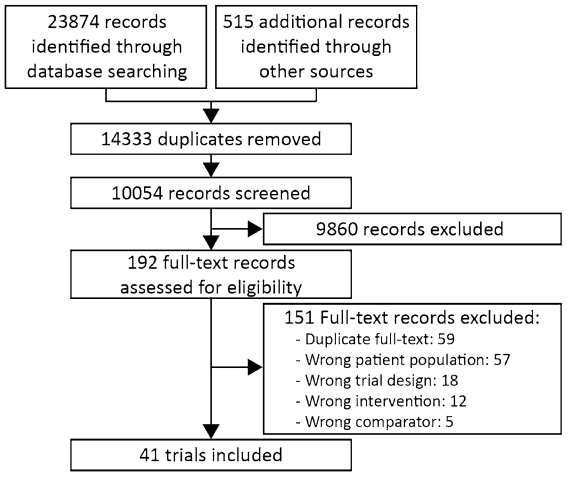


Fig. 1 PRISMA flowchart

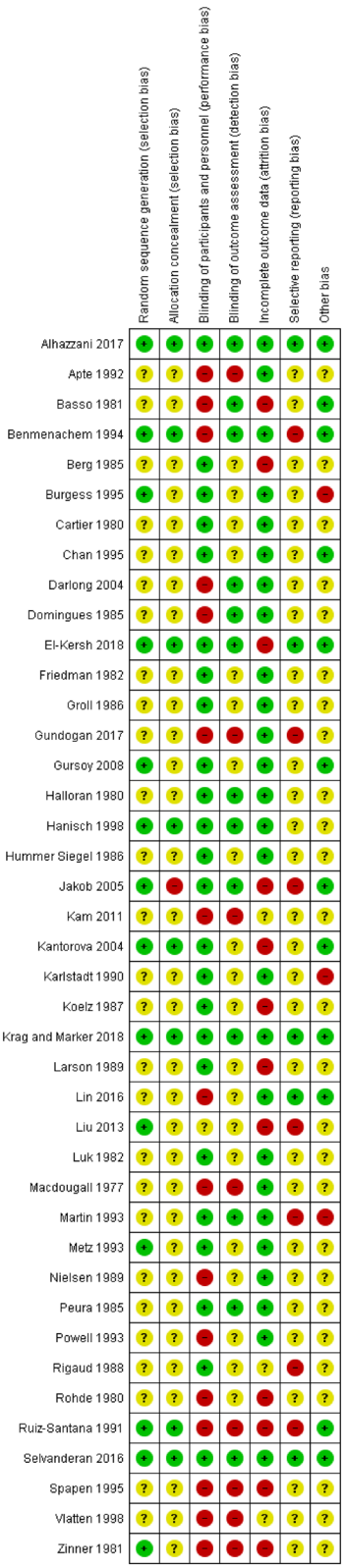


Fig. 2 Risk of bias summary as per the Cochrane Handbook. *Green* represents a low risk of bias, *yellow* an unclear risk of bias, and *red* a high risk of bias

Outcomes

Mortality

A total of 28 trials with 5656 participants reported data on all-cause mortality, including the 3 trials with overall low risk of bias with 3587 participants.

The meta-analysis of the three trials with overall low risk of bias did not show any difference in all-cause mortality between stress ulcer prophylaxis and placebo/no prophylaxis: RR 1.03 (95% CI 0.94, 1.14; $P=0.52$; $I^2=0\%$; TSA-adjusted CI 0.94, 1.14; Bayes factor 239,649) (Fig. 3) (S6–S9, ESM). TSA showed that the boundary for futility was crossed, indicating firm evidence for no difference in mortality between the groups. The certainty of evidence, using the GRADE approach, was high (Table 1).

The corresponding summary estimate of all 28 trials ($n=5656$) regardless of risk of bias was RR 1.01 (95% CI 0.93, 1.10; $P=0.75$; $I^2=0\%$; TSA-adjusted CI was 0.93, 1.10; Bayes factor 941,833) (Fig. 3).

The sensitivity analyses on missing data were consistent with the primary analysis (S10–S11, ESM), and Harbord's test did not indicate asymmetry [$P=0.83$ (S12, ESM)]. The certainty of evidence was moderate due to risk of bias (Table 1).

The subgroup analyses of PPI versus H2RA and placebo versus no prophylaxis showed no interaction (Table S6, ESM). We observed an interaction in the subgroup analysis of ICU setting (test-of-interaction $P=0.08$), suggesting that surgical ICU patients had lower risk of mortality with stress ulcer prophylaxis, compared with medical ICU patients (S6, ESM). Additional subgroup analyses were consistent with the primary analysis (Table S6, ESM). The subgroup analyses of RRT versus no RRT and shock versus no shock could not be performed as no trials (nor stratified subgroups) were eligible for inclusion in these analyses. In the post hoc subgroup analyses of dosing of PPI and publication year, there was no interaction (Table S6, ESM). TSA anticipating a 15% RRR showed that the boundary for futility was crossed, indicating firm evidence for no difference in mortality between the groups (S8, ESM).

GI bleeding

A total of 39 trials with 6627 participants reported on GI bleeding, including the three trials with overall low risk of bias with 3596 participants.

The meta-analysis of the three trials with overall low risk of bias showed a reduction in GI bleeding with stress ulcer prophylaxis versus placebo/no prophylaxis: RR 0.60 (95% CI 0.47, 0.77; $P<0.0001$; $I^2=0\%$; TSA-adjusted CI 0.36, 1.00; Bayes factor 0.004) (Fig. 4), and TSA showed that the required information size to detect a 20% relative

(See figure on next page.)

Fig. 3 **a** Forest plot of 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 pooled analysis. *Horizontal bars* represent 95% confidence intervals. **b** Trial sequential analysis of all 28 trial regardless of risk of bias of the effect of proton pump inhibitors/histamine 2 receptor antagonists versus placebo/no prophylaxis on mortality using a control event proportion of 26.7% (from the included trials), a diversity (D2) of 0%, an alpha of 3.3%, a power of 90%, and a relative risk reduction of 20%. The relative risk was 1.01 with a TSA-adjusted CI 0.93, 1.10. The required information size of 2985 was reached, suggesting that a 20% relative risk increase/reduction can be excluded"

difference had been reached (S13, ESM). The certainty of evidence was high (Table 1).

The corresponding summary effect estimate of all 39 trials ($n=6627$) regardless of risk of bias was RR 0.52 (95% CI 0.45, 0.61; $P<0.00{,}001$; $I^2=43\%$; TSA-adjusted CI 0.39, 0.68; Bayes factor 9×10^{-9}) and TSA showed that the required information size to detect a 20% relative difference had been reached (Fig. 4).

The sensitivity analyses on missing data were consistent with the primary analysis (S10 and S11, ESM), and Harbord's test did not indicate asymmetry [$P=0.33$ (S16, ESM)]. The certainty of evidence was low due to risk of bias and inconsistency (Table 1).

The subgroup analyses of PPI versus H2RA and placebo versus no prophylaxis showed no interaction (Table S6, ESM). Additional subgroup analyses were consistent with the primary analysis (S6, S14 and S15, ESM). In the post hoc subgroup analyses of dosing of PPI and publication year, there was no interaction (Table S6, ESM).

A total of 14 trials ($n=4833$) reported on clinically important GI bleeding. The meta-analysis showed a reduction in clinically important GI bleeding with stress ulcer prophylaxis versus placebo/no prophylaxis: RR 0.63 (95% CI 0.48, 0.81; $P=0.0005$; $I^2=1\%$, Bayes factor 0.017) (S17, ESM). However, this was not confirmed by TSA (TSA-adjusted CI 0.35, 1.13), indicating that the required information size to detect or reject a 20% relative difference had not been reached (S18, ESM).

Serious adverse events

Four trials (three with overall low risk of bias, $n=3587$ participants) reported on SAEs [3, 12, 52, 64], although not defining the adverse events according to ICH-GCP. All four trials reported zero events in each group despite reporting mortality and GI bleeding.

A total of 42 trials reported on outcomes categorised by us as SAEs according to the ICH-GCP definition [25] (S19 and S24, ESM).

The two post hoc analyses estimating the number of patients with one or more SAEs were inconclusive. Details of the analyses are available in S19–S29, ESM . The certainty of evidence was judged to be low/very low due to risk of bias, inconsistency, imprecision, very serious indirectness and strongly suspected publication bias (Table 1).

Health-related quality of life

No trials reported data on HRQoL.

Myocardial ischaemia

We identified one trial (low risk of bias, 3291 participants) which reported on myocardial ischaemia [3]; RR 1.07 (95% CI 0.85, 1.61). TSA highlighted that only 11% of the required information size had been reached. The certainty of evidence was judged to be low due to very serious imprecision (Table 1).

Hospital-acquired pneumonia

A total of 16 trials with 4951 participants reported data on pneumonia, including the three trials with overall low risk of bias with 3596 participants.

The meta-analysis of the three trials with overall low risk of bias showed no difference in hospital-acquired pneumonia between stress ulcer prophylaxis and placebo/no prophylaxis: RR 1.01 (95% CI 0.87, 1.18; $P=0.64$; $I^2=0\%$; TSA-adjusted CI 0.77, 1.33; Bayes factor 82) (S30 and S31, ESM), and TSA showed that only 52% of the required information size had been reached. The certainty of evidence was moderate due to imprecision (Table 1).

The corresponding summary estimate of all 16 trials ($n=4951$) regardless of risk of bias was RR 1.07 (95% CI 0.94, 1.21; $P=0.34$; $I^2=0\%$; TSA-adjusted CI 0.89, 1.27; Bayes factor 7465) (S32 and S33, ESM), and TSA showed that only 70% of the required information size had been reached. The sensitivity analyses of missing data were consistent with the primary analysis (S34 and S35, ESM). Harbord's test did not indicate asymmetry [$P=0.17$ (S36, ESM)]. The certainty of evidence was low due to risk of bias and imprecision (Table 1).

The subgroup analyses of PPI versus H2RA and placebo versus no prophylaxis showed no interaction (Table S6, ESM). Additional subgroup analyses were consistent with the primary analysis; however, there was interaction in the analysis of ICU setting (test-of-interaction $P=0.06$), suggesting that medical ICU patients had higher risk of hospital-acquired pneumonia, compared with surgical or mixed ICU patients (S6, ESM).

a

Study or Subgroup	PPI/H2RA Events	PPI/H2RA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Trials with overall low risk of bias						
Alhazzani 2017	17	49	13	42	1.9%	1.12 [0.62, 2.03]
Krag and Marker 2018	510	1642	499	1640	67.8%	1.02 [0.92, 1.13]
Selvanderan 2016	30	106	25	108	3.4%	1.22 [0.77, 1.93]
Subtotal (95% CI)		**1797**		**1790**	**73.0%**	**1.03 [0.94, 1.14]**
Total events	557		537			
Heterogeneity: Chi² = 0.64, df = 2 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.2.2 Trials with overall high risk of bias						
Apte 1992	11	16	7	18	0.9%	1.77 [0.91, 3.44]
Benmenachem 1994	28	100	19	100	2.6%	1.47 [0.88, 2.46]
Burgess 1995	1	16	0	18	0.1%	3.35 [0.15, 76.93]
El-Kersh 2018	7	55	8	47	1.2%	0.75 [0.29, 1.91]
Groll 1986	13	114	13	107	1.8%	0.94 [0.46, 1.93]
Gursoy 2008	6	60	2	15	0.4%	0.75 [0.17, 3.35]
Halloran 1980	8	26	10	24	1.4%	0.74 [0.35, 1.56]
Hanisch 1998	7	57	12	57	1.6%	0.58 [0.25, 1.37]
Jakob 2005	5	20	5	20	0.7%	1.00 [0.34, 2.93]
Kantorova (H2RA) 2004	11	71	6	37	1.1%	0.96 [0.38, 2.38]
Kantorova (PPI) 2004	14	72	7	38	1.2%	1.06 [0.47, 2.39]
Karlstadt 1990	5	54	2	33	0.3%	1.53 [0.31, 7.43]
Lin 2016	2	60	0	60	0.1%	5.00 [0.25, 102.00]
Liu (H2RA) 2013	14	58	10	26	1.9%	0.63 [0.32, 1.22]
Liu (PPI) 2013	17	58	10	27	1.9%	0.79 [0.42, 1.49]
Macdougall 1977	20	26	31	36	3.5%	0.89 [0.70, 1.14]
Martin 1993	8	65	7	66	0.9%	1.16 [0.45, 3.02]
Nielsen 1989	0	12	0	13		Not estimable
Peura 1985	7	21	7	18	1.0%	0.86 [0.37, 1.98]
Powell (H2RA) 1993	0	11	0	5		Not estimable
Powell (PPI) 1993	1	20	0	5	0.1%	0.86 [0.04, 18.45]
Rohde 1980	7	14	6	14	0.8%	1.17 [0.52, 2.60]
Ruiz-Santana 1991	7	19	7	30	0.7%	1.58 [0.66, 3.79]
Spapen 1995	4	20	2	10	0.4%	1.00 [0.22, 4.56]
Zinner 1981	9	100	17	100	2.3%	0.53 [0.25, 1.13]
Subtotal (95% CI)		**1145**		**924**	**27.0%**	**0.96 [0.82, 1.13]**
Total events	212		188			
Heterogeneity: Chi² = 16.53, df = 22 (P = 0.79); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**2942**		**2714**	**100.0%**	**1.01 [0.93, 1.10]**
Total events	769		725			
Heterogeneity: Chi² = 18.04, df = 25 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.75)						
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² = 0%						

Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favours PPI/H2RA Favours control

b

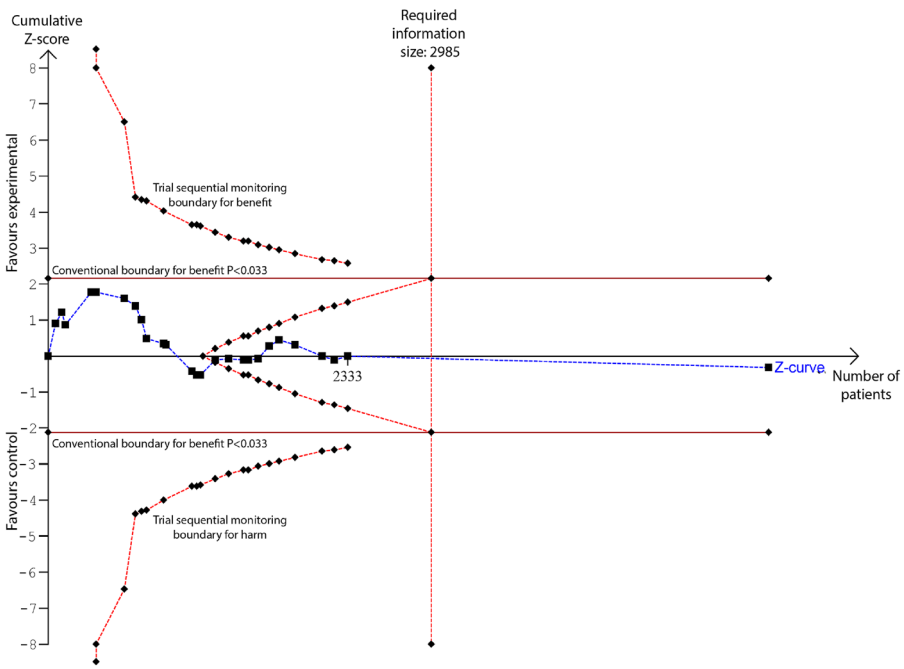


Table 1 Summary of findings

Proton pump inhibitors or histamin-2 receptor antagonists compared to placebo/no prophylaxis for stress ulcer prophylaxis in adult ICU patients										
Certainty assessment							**Summary of findings**			
No. of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% naive CI)**	**Anticipated absolute effects**
							With control	**With PPI/H2RA**		**Risk with control**	**Risk difference with PPI/H2RA**
Mortality—low risk of bias trials											
3557 (3 RCTs)	Not serious	Not serious[a]	Not serious[b]	Not serious[c]	None	⊕⊕⊕⊕ High	537/1790 (30.0%)	557/1767 (31.5%)	RR 1.03 (0.94–1.14)	300 per 1000	9 more per 1000 (18 fewer to 42 more)
Mortality—all trials											
5656 (28 RCTs)	Serious[d]	Not serious[e]	Not serious[f]	Not serious[g]	None	⊕⊕⊕◯ Moderate	725/2714 (26.7%)	769/2942 (26.1%)	RR 1.01 (0.93–1.10)	267 per 1000	3 more per 1000 (19 fewer to 27 more)
GI bleeding—low risk of bias trials											
3596 (3 RCTs)	Not serious	Not serious[h]	Not serious[i]	Not serious[j]	None	⊕⊕⊕⊕ High	157/1797 (8.7%)	95/1799 (5.3%)	RR 0.60 (0.47–0.77)	87 per 1000	35 fewer per 1000 (46 fewer to 20 fewer)
GI bleeding—all trials											
6627 (39 RCTs)	Serious[k]	Serious[l]	Not serious[m]	Not serious[n]	None	⊕⊕◯◯ Low	395/3223 (12.3%)	218/3404 (6.4%)	RR 0.52 (0.45–0.61)	123 per 1000	59 fewer per 1000 (48 fewer to 67 fewer)
Serious adverse events (highest proportion)—low risk of bias trials											
3587 (3 RCTs)	Not serious	Not serious[o]	Very serious[p]	Not serious[q]	None	⊕⊕◯◯ Low	537/1790 (30.0%)	557/1797 (31.0%)	RR 1.03 (0.94–1.14)	300 per 1000	9 more per 1000 (18 fewer to 42 more)
Serious adverse events (highest proportion)—all trials											
6744 (42 RCTs)	Serious[r]	Serious[s]	Very serious[t]	Not serious[u]	Publication bias strongly suspected[v]	⊕◯◯◯ Very low	852/3252 (26.2%)	822/3492 (23.5%)	RR 0.92 (0.85–1.00)	262 per 1000	21 fewer per 1000 (39 fewer to 0 fewer)
Serious adverse events (cumulated)—low risk of bias trials											
3587 (3 RCTs)	Not serious	Serious[w]	Very serious[x]	Serious[y]	None	⊕◯◯◯ Very low	1130/1790 (63.1%)	1073/1797 (59.7%)	RR 1.04 (0.85–1.26)	631 per 1000	25 more per 1000 (95 fewer to 164 more)
Serious adverse events (cumulated)—all trials											
6748 (42 RCTs)	Serious[z]	Serious[aa]	Very serious[ab]	Not serious[ac]	None	⊕◯◯◯ Very low	1627/3254 (50.0%)	1521/3494 (43.5%)	RR 0.89 (0.85–0.93)	500 per 1000	55 fewer per 1000 (75 fewer to 35 fewer)
Health-related quality of life											
0 (0 RCTs)						–					

Table 1 (continued)

Proton pump inhibitors or histamin-2 receptor antagonists compared to placebo/no prophylaxis for stress ulcer prophylaxis in adult ICU patients										
Certainty assessment							Summary of findings			
No. of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% naive CI)	Anticipated absolute effects
							With control	With PPI/H2RA		Risk with control	Risk difference with PPI/H2RA
Myocardial ischaemia										
3291 (1 RCT)	Not serious	Not serious	Not serious	Very serious[ad]	None	⊕⊕◯◯ Low	66/1647 (4.0%)	77/1644 (4.7%)	RR 1.17 (0.85–1.61)	40 per 1000	7 more per 1000 (6 fewer to 24 more)
Pneumonia—low risk of bias trials										
3596 (3 RCTs)	Not serious	Not serious[ae]	Not serious[af]	Serious[ag]	None	⊕⊕⊕◯ Moderate	273/1797 (15.2%)	278/1799 (15.5%)	RR 1.01 (0.87–1.18)	152 per 1000	2 more per 1000 (20 fewer to 27 more)
Pneumonia—all trials										
4951 (16 RCTs)	Serious[ah]	Not serious[ai]	Not serious[aj]	Serious[ak]	None	⊕⊕◯◯ Low	358/2401 (14.9%)	400/2550 (15.7%)	RR 1.07 (0.94–1.21)	149 per 1000	10 more per 1000 (9 fewer to 31 more)
Cl. difficile—low risk of bias trials										
3596 (3 RCTs)	not serious	Not serious[al]	Not serious[am]	very serious[an]	None	⊕⊕◯◯ LOW	26/1797 (1.4%)	22/1799 (1.2%)	RR 0.84 (0.48–1.47)	14 per 1000	2 fewer per 1000 (8 fewer to 7 more)
Cl. difficile—all trials										
3698 (4 RCTs)	Serious[ao]	Not serious[ap]	Not serious[aq]	Very serious[ar]	None	⊕◯◯◯ Very loW	29/1844 (1.6%)	23/1854 (1.2%)	RR 0.78 (0.46–1.34)	16 per 1000	3 fewer per 1000 (8 fewer to 5 more)

CI confidence interval, *cumulated* all reported serious adverse events cumulated in each trial, *highest proportion* highest proportion of reported serious adverse events in each trial, *RR* risk ratio

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

[b] All trials assess PPI versus placebo. Duration of intervention differed slightly

[c] TSA-adjusted CI 0.69, 1.55 with the *Z*-curve reaching futility area for an RRR/RRI of 20%

[d] 25/28 trials had overall high risk of bias

[e] $I^2 = 0\%$, $P = 0.84$, overlap of confidence intervals

[f] 20 trials assessed H2RA and nine trials assessed PPI (no subgroup difference, test-of-interaction $P = 0.51$). Some 22 trials compared intervention to placebo and seven trials compared to no prophylaxis (no subgroup difference, test-of-interaction $P = 0.51$). Duration of intervention differed

[g] 95% CI CI 0.90.93, 1.10 with the *Z*-curve reaching required information size

[h] $I^2 = 0\%$, $P = 0.66$, overlap of confidence intervals

[i] All trials assessed PPI versus placebo. Treatment duration differed slightly

[j] TSA-adjusted CI 0.36, 1.00 with the *Z*-curve reaching the trial sequential monitoring boundary for benefit

[k] 36/39 had overall high risk of bias

Table 1 (continued)

[l] $I^2 = 43\%$, $P = 0.005$. Signs of heterogeneity in forest plot

[m] 11 trials assessed PPI and 28 trials assessed H2RA (no subgrup difference, $P = 0.38$). 28 trials compared intervention to placebo and 11 compared to no prophylaxis (no subgroup difference, $P = 0.59$). Treatment duration differed

[n] TSA-adjusted CI 0.31, 0.84 with the *Z*-curve crossing the trial sequential monitoring boundary for benefit

[o] $I^2 = 0\%$, $P = 0.72$, overlap of confidence intervals

[p] Method used in meta-analysis and under-reporting of serious adverse events in trials

[q] TSA-adjusted CI 0.69, 1.55 with the cumulative *Z*-curve reaching the futility area for an RRR of 20%

[r] 39/42 trials had overall high risk of bias

[s] $I^2 = 44\%$, $P = 0.002$. Signs of heterogeneity in forest plot

[t] Method used in meta-analysis and under-reporting of serious adverse events in trials

[u] TSA-adjusted CI 0.84, 1.02 with the cumulative *Z*-curve crossing the trial sequential monitoring boundary for benefit

[v] Funnel plot indicated asymmetry and Harbord's test did indicated this publication bias ($P = 0.019$)

[w] $I^2 = 53\%$, $P = 0.12$. Signs of heterogeneity in forest plot

[x] Method used in meta-analysis and under-reporting of serious adverse events in trials

[y] TSA-adjusted CI 0.64, 1.68 with the cumulative *Z*-curve not reaching the trial sequential monitoring boundary and not reaching the futility area

[z] 39/42 trials had overall high risk of bias

[aa] $I^2 = 59\%$, $P < 0.00001$. Signs of heterogeneity in forest plot

[ab] Method is an indirect method of estimating SAE

[ac] TSA-adjusted CI was 0.85, 0.94 with the cumulative *Z*-curve reaching the trial sequential monitoring boundary

[ad] Only one trial included, with wide CI around effect estimate. However, it included 3291 analysed patients

[ae] $I^2 = 0\%$, $P = 0.64$, overlap of confidence intervals

[af] All trials assess PPI versus placebo. Treatment duration differed slightly

[ag] According to the 95% CI and TSA-adjusted CI there are still a risk of 20% RRR/RRI

[ah] 13/16 were overall high risk of bias

[ai] $I^2 = 0\%$, $P = 0.50$, overlap of confidence intervals

[aj] Six trials assessed PPI and 10 assessed H2RA (no subgroup difference, $P = 0.18$). 13 trials assess placebo and 3 trials assessed no prophylaxis (no subgroup difference,$P = 0.16$). Duration of intervention differed

[ak] According to the 95% CI and TSA-adjusted CI there are still a risk of 20% RRR/RRI

[al] $I^2 = 0\%$, $P = 0.58$, overlap of confidence intervals

[am] All trials assessed PPI versus placebo. Minor differences in intervention period

[an] TSA was not possible due to too little information. Optimal information size criterion is therefore not met

[ao] 1/4 trials had overall high risk of bias

[ap] $I^2 = 0\%$, $P = 0.59$, overlap of confidence intervals

[aq] All trials assessed PPI versus placebo. Minor differences in intervention period

[ar] TSA was not possible due to too little information. Optimal information size criterion is therefore not met

(See figure on next page.)

Fig. 4 **a** Forest plot of 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 pooled analysis. *Horizontal bars* represent 95% confidence intervals. **b** Trial sequential analysis of all 39 trials regardless of risk of bias of the effect of proton pump inhibitors/histamine 2 receptor antagonists versus placebo/no prophylaxis on GI bleeding using a control event proportion of 12.26% (from the included trials), a diversity (D2) of 0%, an alpha of 3.3%, a power of 90%, and relative risk reduction of 20%. The relative risk was 0.52 with a TSA-adjusted CI 0.39, 0.68. As the cumulative *Z*-curve reached the trial sequential monitoring boundary for benefit there is evidence of at a 20% relative risk reduction in the risk of GI bleeding from proton pump inhibitors or histamine 2 receptor antagonists

Cl. difficile enteritis

A total of four trials with 3698 participants reported data on *Cl. difficile* enteritis, including the three trials with overall low risk of bias with 3596 participants.

The meta-analyses of trials with overall low risk of bias and trials regardless of risk of bias were both inconclusive (S37, ESM). TSA highlighted that less than 5% of the required information size had been reached. The certainty of evidence was low/very low due to very serious imprecision and risk of bias (Table 1).

Subgroup analyses of PPI versus H2RA and placebo versus no prophylaxis were not applicable. The sensitivity analyses of missing data and subgroup analyses were consistent with the primary analysis (S38 and S39, ESM).

Discussion

In this updated systematic review, we did not find a difference in mortality between adult ICU patients receiving PPI or H2RA versus placebo/no prophylaxis, and TSA highlighted that the required information size to detect a 20% (and even a 15%) relative difference in mortality had been reached, indicating firm evidence. Furthermore, we found a reduction in the occurrence of any GI bleeding and clinically important GI bleeding, and TSA highlighted that firm evidence for such a reduction in any GI bleeding had been reached; however, this was not the case for clinically important GI bleeding. The effects on the other outcomes, including SAEs, HRQoL, myocardial infarction, pneumonia, and *CI. difficile* enteritis, were inconclusive.

Strengths and limitations

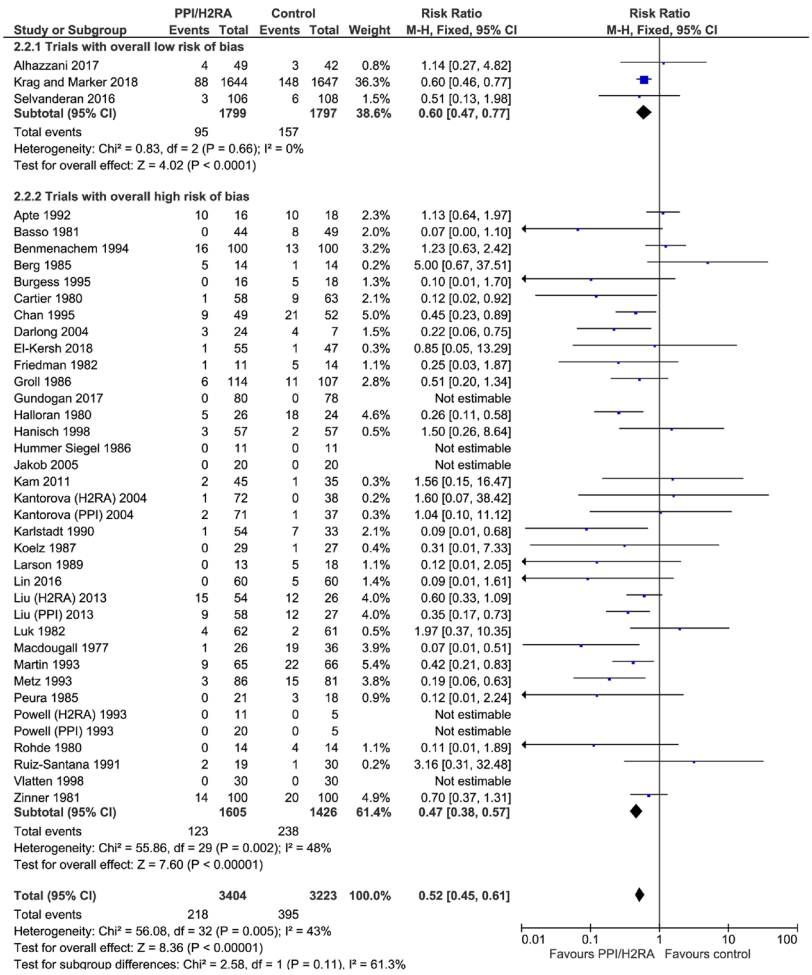
Strengths of this review include the systematic, transparent and robust methodology used, including the use of the Cochrane Handbook [20], the PRISMA statement [21], a prespecified protocol [19], an up-to-date comprehensive literature search, and the independent study selection, data extraction, and risk of bias assessment by two authors. Also, we used TSA to assess the overall risk of random error to increase the reliability of the results of the meta-analysis, and to identify the required information size. Finally, we assessed the certainty of evidence using GRADE.

Limitations of our review include a risk of clinical heterogeneity between trials. Furthermore, statistical heterogeneity was present in the analyses of GI bleeding and SAEs. To account for systematic errors and missing data in the included trials, we conducted subgroup analyses comparing trials of overall high risk of bias with trials of overall low risk of bias, and sensitivity analyses to account for missing data. We cannot exclude a biased effect estimate of the trials of overall high risk of bias; hence, the certainty of evidence for all trials irrespective of risk of bias was downgraded one level for risk of bias. We were unable to include the losses to follow-up from four trials ($n=81$) in the sensitivity analyses exploring uncertainty due to missing data, as the trial reports did not specify to which intervention group these patients belonged. The uncertainty due to loss to follow-up is therefore higher. None of the included trials reported detailed data on SAEs according to the ICH-GCP recommendation [25]; however, four trials reported zero SAEs in both groups, although mortality, clinically important GI bleeding and hospital-acquired pneumonia were reported [12, 52, 64]. Accordingly, SAEs are likely considerably underreported. To estimate the effect on SAEs actually reported in the included trials we conducted two post hoc analyses aiming to estimate the effect on the proportion of patients having one or more SAEs expected to lie between these two extremes. Analysing SAEs according to ICH-GCP may not be optimal in ICU patients who may experience numerous SAEs each day, making it difficult to register them all; thus, a composite outcome as defined by ICH-GCP may be inappropriate. Although we had two co-authors not involved in the SUP-ICU trial to assess the risk of bias in this trial, we acknowledge the potential for indirect conflicts of interests from review authors being involved in the SUP-ICU trial. Finally, limited data on SAEs, HRQoL, myocardial ischemia, pneumonia, and *CI. difficile* enteritis resulted in no firm evidence on the balance between the benefits and harms for these outcomes.

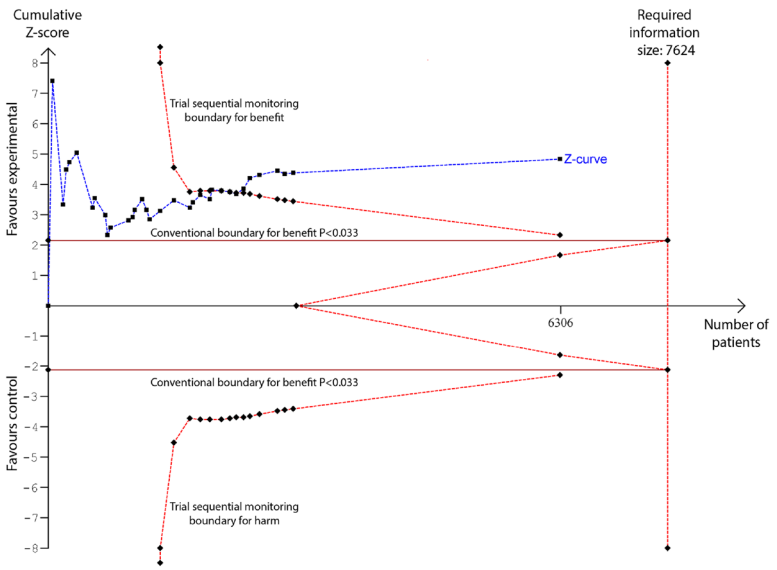
Our results in relation to previous systematic reviews

Previous systematic reviews have not observed a difference in mortality between PPI/H2RA and placebo/no prophylaxis [80–83], which our results, including TSA, confirm. Previous reviews have shown conflicting results regarding the effects of stress ulcer prophylaxis on any GI bleeding [80, 82, 83]. Our results show an absolute

a


PPI/H2RA
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
2.2.1 Trials with overall low risk of bias
Alhazzani 2017 4 49 3 42 0.8% 1.14 [0.27, 4.82]
Krag and Marker 2018 88 1644 148 1647 36.3% 0.60 [0.46, 0.77]
Selvanderan 2016 3 106 6 108 1.5% 0.51 [0.13, 1.98]
Subtotal (95% CI) 1799 1797 38.6% 0.60 [0.47, 0.77]
Total events 95 157
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 4.02 (P < 0.0001)
2.2.2 Trials with overall high risk of bias
Apte 1992 10 16 10 18 2.3% 1.13 [0.64, 1.97]
Basso 1981 0 44 8 49 2.0% 0.07 [0.00, 1.10]
Benmenachem 1994 16 100 13 100 3.2% 1.23 [0.63, 2.42]
Berg 1985 5 14 1 14 0.2% 5.00 [0.67, 37.51]
Burgess 1995 0 16 5 18 1.3% 0.10 [0.01, 1.70]
Cartier 1980 1 58 9 63 2.1% 0.12 [0.02, 0.92]
Chan 1995 9 49 21 52 5.0% 0.45 [0.23, 0.89]
Darlong 2004 3 24 4 7 1.5% 0.22 [0.06, 0.75]
El-Kersh 2018 1 55 1 47 0.3% 0.85 [0.05, 13.29]
Friedman 1982 1 11 5 14 1.1% 0.25 [0.03, 1.87]
Groll 1986 6 114 11 107 2.8% 0.51 [0.20, 1.34]
Gundogan 2017 0 80 0 78 Not estimable
Halloran 1980 5 26 18 24 4.6% 0.26 [0.11, 0.58]
Hanisch 1998 3 57 2 57 0.5% 1.50 [0.26, 8.64]
Hummer Siegel 1986 0 11 0 11 Not estimable
Jakob 2005 0 20 0 20 Not estimable
Kam 2011 2 45 1 35 0.3% 1.56 [0.15, 16.47]
Kantorova (H2RA) 2004 1 72 0 38 0.2% 1.60 [0.07, 38.42]
Kantorova (PPI) 2004 2 71 1 37 0.3% 1.04 [0.10, 11.12]
Karlstadt 1990 1 54 7 33 2.1% 0.09 [0.01, 0.68]
Koelz 1987 0 29 1 27 0.4% 0.31 [0.01, 7.33]
Larson 1989 0 13 5 18 1.1% 0.12 [0.01, 2.05]
Lin 2016 0 60 5 60 1.4% 0.09 [0.01, 1.61]
Liu (H2RA) 2013 15 54 12 26 4.0% 0.60 [0.33, 1.09]
Liu (PPI) 2013 9 58 12 27 4.0% 0.35 [0.17, 0.73]
Luk 1982 4 62 2 61 0.5% 1.97 [0.37, 10.35]
Macdougall 1977 1 26 19 36 3.9% 0.07 [0.01, 0.51]
Martin 1993 9 65 22 66 5.4% 0.42 [0.21, 0.83]
Metz 1993 3 86 15 81 3.8% 0.19 [0.06, 0.63]
Peura 1985 0 21 3 18 0.9% 0.12 [0.01, 2.24]
Powell (H2RA) 1993 0 11 0 5 Not estimable
Powell (PPI) 1993 0 20 0 5 Not estimable
Rohde 1980 0 14 4 14 1.1% 0.11 [0.01, 1.89]
Ruiz-Santana 1991 2 19 1 30 0.2% 3.16 [0.31, 32.48]
Vlatten 1998 0 30 0 30 Not estimable
Zinner 1981 14 100 20 100 4.9% 0.70 [0.37, 1.31]
Subtotal (95% CI) 1605 1426 61.4% 0.47 [0.38, 0.57]
Total events 123 238
Heterogeneity: Chi² = 55.86, df = 29 (P = 0.002); I² = 48%
Test for overall effect: Z = 7.60 (P < 0.00001)
Total (95% CI) 3404 3223 100.0% 0.52 [0.45, 0.61]
Total events 218 395
Heterogeneity: Chi² = 56.08, df = 32 (P = 0.005); I² = 43%
Test for overall effect: Z = 8.36 (P < 0.00001)
Test for subgroup differences: Chi² = 2.58, df = 1 (P = 0.11), I² = 61.3%
0.01 0.1 1 10 100
Favours PPI/H2RA Favours control

b


Cumulative Z-score
Required information size: 7624
Trial sequential monitoring boundary for benefit
Z-curve
Favours experimental
Conventional boundary for benefit P<0.033
6306
Number of patients
Conventional boundary for benefit P<0.033
Favours control
Trial sequential monitoring boundary for harm

difference in any GI bleeding of 3.4%, corresponding to a number needed to treat of 35 (CI from 46 fewer to 20 fewer) in trials with overall low risk of bias. Previous reviews have also shown inconsistent results in clinically important GI bleeding [81, 83]. In accordance with previous reviews, we did not observe a statistically significant difference in hospital-acquired pneumonia, indicating no firm evidence for benefit or harm [80–83]. A recently published systematic review did not report a difference in *CI. difficile* enteritis which is supported by our results [82]. SAEs, HRQoL, and myocardial ischemia have not been assessed in previous reviews.

Clinical implications and perspectives

Nowadays, GI bleeding, including clinically important GI bleeding, is an important but rare event in adult ICUs. Yet, stress ulcer prophylaxis is used in three out of four acutely admitted adult ICU patients [2], and recommendation on its use is conflicting [6, 7].

Our results indicate that, although we did not find an effect of stress ulcer prophylaxis on mortality, GI bleeding is reduced by almost 50% and clinically important bleeding a little less, which could be used as an argument for using PPI/H2RA as a prophylactic intervention in intensive care patients. Conversely, GI bleeding occurs in 12% of intensive care patients and clinically important GI bleeding in only 5% of the patients with placebo or no intervention. Furthermore, as mortality does not seem to be reduced using PPI/H2RA, it could be argued that the prophylactic use is unnecessary and that treatment with antacids should be reserved for patients developing active GI bleeding. Moreover, a pre-planned subgroup analysis in the recently published SUP-ICU trial suggested excess mortality among patients with a Simplified Acute Physiology Score II greater than 53 allocated to PPI compared with placebo, indicating that the most severely ill patients may be harmed from prophylactic PPI [3]. On the other hand, prophylactic PPI does not appear to substantially increase the number of SAEs, including nosocomial infections and myocardial ischemia. Accordingly, additional data on the importance of disease severity on the overall effects of stress ulcer prophylaxis are needed, along with data on long-term outcomes, HRQoL, and an economic analysis [84].

Conclusions

In this updated systematic review, we were able to refute a relative change of 20% of mortality when prophylactic PPI or H2RA were compared with placebo or no prophylaxis in adult ICU patients. GI bleeding was reduced with PPI or H2RA, but firm evidence for a reduction in clinically important GI bleeding was not found. The effects on SAEs, HRQoL, myocardial ischemia, pneumonia, and *CI. difficile* enteritis remain inconclusive.

Discrepancy between protocol and review

We used a power of 90%, and not 80% as reported in the protocol [19], as meta-analyses should use a higher (or the same) power as its included trials to be able to communicate the best available evidence.

We choose to report two post hoc analyses of the effect of PPI/H2RA on SAEs as none of the trials reported these according to the ICH-GCP criteria. Furthermore, we conducted two post hoc subgroup analyses according to dose of PPI and publication year. In addition, we have made a TSA anticipating a 15% RRR of mortality on the meta-analysis of new trials published after our first review [34].

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-019-05526-z) contains supplementary material, which is available to authorized users.

Author details

[1] Copenhagen Trial Unit, Centre for Clinical Intervention Research, 2100 Copenhagen, Denmark. [2] Centre for Research in Intensive Care, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [3] Department of Intensive Care, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [4] Department of Cardiology, Holbaek Hospital, Holbaek, Denmark.

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Compliance with ethical standards

Conflicts of interest

Marija Barbateskovic: PhD student at the Copenhagen Trial Unit and the Centre for Research in Intensive Care. Søren Marker: PhD student at the Department of Intensive Care at Rigshospitalet and the Centre for Research in Intensive Care. Coordinating investigator of the randomised clinical trial 'Stress Ulcer Prophylaxis in the Intensive Care Unit' (SUP-ICU). Anders Granholm: Coordinating investigator of the SUP-ICU trial. Carl Thomas Anthon: Coordinating investigator of the SUP-ICU trial. Mette Krag: Coordinating investigator of the SUP-ICU trial. Janus Christian Jakobsen: Director of Research, Chief Physician, Department of Cardiology, Holbæk Sygehus, Holbæk, Denmark. Anders Perner: Head of Research at the Department of Intensive Care at Rigshospitalet. The intensive care unit receives support for research from CSL Behring, Fresenius Kabi, Ferring Pharmaceuticals and the Novo Nordisk Foundation. Dr Perner is initiator of the SUP-ICU trial. Jørn Wetterslev: Member of the Copenhagen Trial Unit task force for developing Trial Sequential Analysis theory, manual and software which is presently free-ware at www.ctu.dk/tsa. Dr Wetterslev is member of the SUP-ICU trial steering group. Morten Hylander Møller: Sponsor and initiator of the SUP-ICU trial.

Ethical approval

An approval by an ethics committee was not applicable.

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