Check for updates

Received: 15 March 2024 | Accepted: 27 March 2024

DOI: 10.1111/aas.14426

REVIEW ARTICLE

acta Anaesthesiologica Scandinavica

# Proton pump inhibitors for gastrointestinal bleeding prophylaxis in critically ill patients: A systematic review protocol

Ying Wang[1] | Diane Heels-Ansdell[1] | Long Ge[2] | Sameer Parpia[3] | Quazi Ibrahim[1] | Deborah Cook[1,4] | Adam Deane[5] | Francois Lauzier[6,7] | Naomi Hammond[8,9] | Morten H. Møller[10,11] | Mette Krag[10,12] | Anders Perner[10,11] | Gordon H. Guyatt[1,4]

[1]Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

[2]Evidence Based Social Science Research Center, School of Public Health, Lanzhou University, Lanzhou, China

[3]Department of Oncology, McMaster University, Hamilton, Ontario, Canada

[4]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[5]Department of Critical Care, Melbourne Medical School, University of Melbourne, Melbourne, Victoria, Australia

[6]Population Health and Optimal Health Practice Research Unit (Trauma—Emergency—Critical Care Medicine) CHU de Québec-Université Laval Research Centre, Québec City, Québec, Canada

[7]Department of Medicine, Anesthesiology and Critical Care, Université Laval, Québec, Québec, Canada

[8]Critical Care Program, The George Institute for Global Health, UNSW Sydney, Sydney, New South Wales, Australia

[9]Malcolm Fisher Department of Intensive Care, Royal North Shore Hospital, Sydney, New South Wales, Australia

[10]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

[11]Department of Intensive Care, Copenhagen University Hospital–Rigshospitalet, Copenhagen, Denmark

[12]Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet, Copenhagen, Denmark

**Correspondence**
Ying Wang, Department of Health Research Methods, Evidence and Impact, McMaster University, Hamilton, ON, Canada.
Email: yingwwy@163.com

## Abstract

**Background:** Proton pump inhibitors (PPIs) are the most commonly prescribed drugs for preventing upper gastrointestinal bleeding in critically ill patients. However, concerns have arisen about the possible harms of using PPIs, including potentially increased risk of pneumonia, *Clostridioides difficile* infection, and more seriously, an increased risk of death in the most severely ill patients. Triggered by the REVISE trial, which is a forthcoming large randomized trial comparing pantoprazole to placebo in invasively mechanically ventilated patients, we will conduct this systematic review to evaluate the efficacy and safety of PPIs versus no prophylaxis for critically ill patients.

**Methods:** We will systematically search randomized trials that compared gastrointestinal bleeding prophylaxis with PPIs versus placebo or no prophylaxis in adults in the intensive care unit (ICU). Pairs of reviewers will independently screen the literature, and for those eligible trials, extract data and assess risk of bias. We will perform

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2024 The Authors. *Acta Anaesthesiologica Scandinavica* published by John Wiley & Sons Ltd on behalf of Acta Anaesthesiologica Scandinavica Foundation.

meta-analyses using a random-effects model, and calculate relative risks for dichotomous outcomes and mean differences for continuous outcomes, and the associated 95% confidence intervals. We will conduct subgroup analysis to explore whether the impact of PPIs on mortality differs in more and less severely ill patients. We will assess certainty of evidence using the GRADE approach.

**Discussion:** This systematic review will provide the most up-to-date evidence regarding the merits and limitations of stress ulcer prophylaxis with PPIs in critically ill patients in contemporary practice.

**KEYWORDS**

gastrointestinal bleeding prophylaxis, proton pump inhibitors, stress ulcer prophylaxis, systematic review protocol

## 1 | INTRODUCTION

Patients who are critically ill, typically cared for in the intensive care unit (ICU), are at risk of stress ulceration in the upper gastrointestinal tract, which may cause bleeding.[1] Clinicians have long been concerned about the risk of clinically important upper gastrointestinal bleeding (CIB), which may be associated with additional diagnostic tests, blood transfusions, the use of vasoactive agents, increased length of ICU stay, and an increased risk of death.[2] Clinical practice guidelines have supported the use of acid suppressing drugs for critically ill patients at high risk of bleeding.[3–5] In current practice, proton pump inhibitors (PPIs) are the most commonly prescribed drugs for this purpose.[6,7]

Stress-ulcer prophylaxis has generated controversy in recent years. The epidemiology of critical illness has changed, advances in critical care practice have occurred, and perceptions have emerged about low rates of gastrointestinal bleeding that may not be associated with a poor prognosis.[1] Moreover, concerns have arisen about the potentially increased risk of pneumonia and *Clostridioides difficile* infection with acid suppression.[8,9] A large, international, multicenter randomized controlled trial (RCT) published in 2018 (the SUP-ICU trial) raised the possibility that use of PPIs for bleeding prevention, while effective, may increase mortality relative to placebo in the most severely ill patients but not in the less severely ill.[10] Together, these concerns have raised questions about whether the possible harms of prophylaxis may outweigh any possible benefits, especially for the sickest patients in the ICU.

The REVISE trial is an international parallel-group RCT that investigated the effects of pantoprazole versus placebo among invasively mechanically ventilated patients.[11] We will conduct this systematic review to evaluate the efficacy and safety of PPIs versus no prophylaxis for critically ill patients.

The forthcoming REVISE trial report[11] will conduct within-trial subgroup analysis to explore whether the impact of PPIs on mortality differs in more severely ill and less severely ill patients, aligned with the SUP-ICU trial.[10] In this systematic review, we will combine these two within-trial subgroup analyses and assess the credibility of the subgroup effect on this issue.

## 2 | METHODS

We will register this protocol with PROSPERO (CRD42023461695). This systematic review will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[12]

### 2.1 | Eligibility criteria

This review will include RCTs that, in adult critically ill patients, compared gastrointestinal bleeding prophylaxis with PPIs versus placebo or no prophylaxis, prescribed to prevent upper gastrointestinal bleeding, and in which authors reported any of the following outcomes: mortality at any time, CIB, pneumonia, *Clostridioides difficile* infection, overt upper gastrointestinal bleeding, duration of mechanical ventilation, duration of ICU stay (or ICU-free days), and duration of hospital stay. To be eligible, trials have to explicitly include critically ill patients or patients admitted to an ICU.

We will apply no restriction on the PPI drug (dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole), dose, duration, or route of administration. We will consider trials without restriction by language or publication status (published or preprint). We will exclude quasi-randomized studies and abstracts. We will exclude trials that did not report sufficient information to pool data on any outcome (for example, an uncertain number of events or number of patients in each group). We will check for retractions in the Retraction Watch Database (http://retractiondatabase.org/) to exclude retracted trials.

We will accept trial definitions of CIB. Trial definitions typically include evidence of overt upper gastrointestinal bleeding with any of the following: significant hemodynamic changes not explained by other causes, a significant decrease in hemoglobin level, transfusion of two or more units of red blood cells, upper gastrointestinal endoscopy, angioembolization, or the need for surgery to control bleeding. We will accept trial definitions of overt bleeding, which typically include hematemesis, coffee-ground emesis, oro- or naso-gastric aspirate of frank blood or coffee-grounds, melaena, or hematochezia.

13996576, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/aas.14426 by National Health And Medical Research Council, Wiley Online Library on [02/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

**BOX 1 Trial feature**

- Type of ICU(s)
- Number of participating centers
- Participating countries
- Number of participants
- Year of publication
- Source of funding

1. Population characteristics

- Number of participants randomized to each group
- Eligibility criteria
- Mean age
- Mean illness severity score (APACHE II score or SAPS II score)
- Percent female
- Percent receiving mechanical ventilation
- Percent receiving enteral nutrition

2. Intervention and control

- Drug, dose, frequency, route, and duration of administration for intervention
- Control (placebo or no prophylaxis)

3. Outcomes

- All-cause mortality at longest follow-up, up to 90 days
- Clinically important upper gastrointestinal bleeding
- Patient important upper gastrointestinal bleeding
- Pneumonia
- *Clostridioides difficile* infection
- Overt upper gastrointestinal bleeding (if a trial reported only clinically important bleeding without mention of overt bleeding, we will consider all clinically important bleeding events as overt bleeding events)
- Duration of mechanical ventilation
- Duration of ICU stay (or ICU-free days)
- Duration of hospital stay
- Units of red blood cells transfused.

## 2.2 | Data sources and searches

We will develop the search strategy in collaboration with a research librarian who is familiar with this topic. We will search Medline, Embase, the Web of Science, the Cochrane Central Register of Controlled Trials (CENTRAL), the International Clinical Trials Registry Platform (ICTRP), Latin American and Caribbean Health Sciences Literature (LILACS), clinicaltrials.gov, and medRxiv. Our team previously conducted a network meta-analysis comparing PPIs versus H2RAs versus sucralfate versus placebo or no intervention for gastrointestinal bleeding prophylaxis in critically ill patients, which searched up to February 2020.[13] We will update this search to February 2024.

**BOX 2 Risk of bias items**

- Item 1: Was the allocation sequence adequately generated?
- Item 2: Was the allocation adequately concealed?
- Item 3: Were participants blinded?
- Item 4: Were healthcare providers blinded?
- Item 5: Were outcome assessors blinded?
- Item 6
  - i. Extract the number of participants who were not included in the analysis in each group (because of missing outcome data or nonadherence).
  - ii. Was the proportion of participants not included in the analysis acceptably low? (<3% for definitely yes; 3% to <5% for probably yes; 5% to <8% for probably no; ≥8% for definitely no).

## 2.3 | Study selection

Pairs of reviewers will independently screen titles and abstracts, followed by full texts. They will resolve conflicts by discussion or, if necessary, by involving a third reviewer.

We will screen trials incorporated in our prior network meta-analysis,[13] and include trials that compared PPIs versus placebo or no prophylaxis (control group) that meet our eligibility criteria.

## 2.4 | Data extraction

For each eligible trial, pairs of trained reviewers will extract data independently using a pre-designed, piloted data extraction form and resolve disagreement by discussion or, if necessary, by a third reviewer. Box 1 presents the trial features, population, intervention characteristics, and outcomes we will extract. When available, we will extract the definition and timeframe of the outcomes.

## 2.5 | Risk of bias assessments

We will use a new risk of bias instrument that was developed by a recent international collaboration involving systematic collection and selection of items through a survey and intensive discussion among

13996576, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/aas.14426 by National Health And Medical Research Council, Wiley Online Library on [02/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

methodological experts.[14] This instrument is user-friendly and has a simple structure. Box 2 presents the seven items in the instrument. Response options for each item include definitely yes, probably yes, probably no, and definitely no, which allows systematic reviewers to make the best inference when the reporting in RCTs is unclear.[15]

Two reviewers, after training and calibration, will independently assess the risk of bias items and resolve conflicts by discussion or by involving a third reviewer as necessary.

## 2.6 | Data synthesis

All analyses will be performed in R (version 4.3.2, R Foundation for Statistical Computing), using the meta packages. Using a random-effects model, we will calculate relative risks (RRs) with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous outcomes. We will choose the method to estimate between-study variance $\tau^2$ based on the heterogeneity (if heterogeneity is low or moderate, we will use the restricted maximum-likelihood estimator;[16] if heterogeneity is high, we will use the Sidik-Jonkman estimator[17]). We will use the Hartung-Knapp method to calculate CIs for random effects estimate;[18,19] if this produces counterintuitive results, we will instead use the DerSimonian and Laird method.[20] For continuous outcomes, if trials did not report mean and standard deviation (SD), we will estimate them using sample size, median, and interquartile range.[21,22] The primary meta-analysis will include data derived from each trial's complete-case analysis.

For each outcome, we will conduct a subgroup analysis based on the overall risk of bias (trials with definitely/probably yes for all items versus trials with definitely/probably no for one or more items). If the interaction *p*-value is <.05, we will include only trials with definitely/probably yes for all items in generating the best effect estimate. Otherwise, we will include all trials in the meta-analysis.

For dichotomous outcomes, we will calculate the absolute effect based on RRs and baseline risks. We will use the event rates in the placebo arm in the REVISE trial as baseline risks.

The SUP-ICU trial[10] and the REVISE trial[23] conducted within-trial subgroup analysis on mortality based on disease severity. In REVISE, this was measured by an Acute Physiology and Chronic Health Evaluation (APACHE) II score of <25 versus APACHE II score ≥ 25. In SUP-ICU,[10] this was measured by the Simplified Acute Physiology Score (SAPS) II score ≤53 versus SAPS II score >53. To test the subgroup effect, we will pool the ratio of RRs (i.e., $RR_{sicker}/RR_{less\ sick}$) of the REVISE trial and SUP-ICU trial. Our hypothesis is that PPIs increase mortality in more severely ill patients, but not in less severely ill patients. We will use the Credibility of Effect Modification Analyses (ICEMAN) to assess the credibility of the subgroup effect.[24] If we find a subgroup effect with moderate or high credibility, we will separately calculate and report the effect of PPIs on mortality for more severely ill patients and less severely ill patients (i.e., pool the more severely ill subgroups as well as the less severely ill subgroups of these two trials).

To further test whether the effect of PPIs on mortality differs based on disease severity, we plan to collate individual patient data for the REVISE trial and the SUP-ICU trial, and conduct a regression analysis for the outcome of 90-day mortality involving all patients with disease severity as an independent variable. This will be performed in the current meta-analysis or a later individual patient data meta-analysis, depending on the timing of combined data availability. We will convert the SAPS II score (used in the SUP-ICU trial) to the APACHE II score (used in the REVISE trial) and use ICEMAN to assess credibility.

## 2.7 | Certainty of evidence

We will rate the certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[25] We will rate our certainty based on whether or not an effect exists (the target of the certainty rating is null). Evidence from RCTs starts with high certainty and can be rated down due to the risk of bias, inconsistency, indirectness, publication bias, and imprecision.

We will judge whether to rate down the risk of bias based on the relative contribution of trials with definitely/probably yes for all items and a definitely/probably no for any item on the overall estimate. If trials with definitely/probably yes for all items are dominant, we will not rate down; if trials with definitely/probably no for any item are dominant, we will rate down for risk of bias.

As for determining whether to rate down the certainty due to missing outcome data, we will challenge the robustness of the results by conducting sensitivity meta-analyses, imputing the missing data in each trial, and then pooling across trials.[26] For binary outcomes, we will impute missing data in the control group by assuming the incidence of outcome events in participants with missing data is the same as those with complete follow-up. As for the PPI group, we will impute missing data by assuming the incidence of outcome events in participants with missing data is as high as twice that of those with complete follow-up or as low as half of those with complete follow-up (depending on the direction of the result from primary analysis). If the result does not change materially, we will not rate down for the risk of bias due to missing data; otherwise, we will rate down.

For the sensitivity meta-analysis of continuous outcomes, if primary analysis suggests that PPIs decrease the duration of mechanical ventilation, ICU stay, or hospital stay, in the imputation we will use the largest mean score in the PPI group among trials as the mean score for those with missing data in the PPIs group, and use the smallest mean score in the control group among trials as the mean score for those with missing data in the control group. If the primary analysis suggests that PPIs increase the duration of mechanical ventilation, ICU stay, or hospital stay, we will use the smallest mean score in the PPI group as the mean score for those with missing data in the PPI group and the largest mean score in the control group as the mean score for those with missing data in the control group. The median SD in the control group will be used as the SD of those with missing data.

13996576, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/aas.14426 by National Health And Medical Research Council, Wiley Online Library on [02/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

If the result does not change materially, we will not rate down for missing data; otherwise, we will rate down.

We will assess inconsistency among trials with a visual inspection of differences in point estimates, overlap of Cis, and the $I^2$ statistic.[27] To assess publication bias, we will draw a funnel plot and perform the Egger test if 10 or more trials are available.[28] We will develop a summary of finding tables with a plain language summary using GRADE wording in MAGICapp.[29,30]

## 3 | DISCUSSION

This systematic review will focus on RCTs that compare PPIs to placebo or no prophylaxis, since PPIs are now the most frequently prescribed drug class for gastrointestinal bleeding prophylaxis.[6,7,31–33] Not only are histamine-2-receptor antagonists (H2RAs) and sucralfate less frequently used in practice,[6,7,31–33] but the RCTs comparing these agents to no prophylaxis or placebo were published more than two decades ago, not representing current practice.

This review will be limited by the definitions of morbidity outcomes that were used within the included trials, which are likely to be diverse or nonspecified. We anticipate that the outcome of patient-important bleeding will be available in only one trial such that no pooled estimate will be possible.[34] Other potentially concerning outcomes associated with acid suppression in observational studies are unlikely to be reported in these trials, such as the increased risk of colonization or infection with multidrug-resistant organisms.[35]

Results of the REVISE trial will more than double the number of patients contributing to previous trials evaluating the effect of a PPI versus no prophylaxis on upper gastrointestinal bleeding and other clinical outcomes. Given this addition to existing evidence and the exploration of subgroups related to disease severity, this systematic review will advance our understanding of the merits and limitations of stress ulcer prophylaxis in critically ill patients for contemporary practice.

### AUTHOR CONTRIBUTIONS

DC, GHG, DHA, LG, and YW conceived the study protocol. YW, DC, and GHG drafted the manuscript. All other authors revised the manuscript and approved the final version. YW registered the study protocol.

### FUNDING INFORMATION

No.

### CONFLICT OF INTEREST STATEMENT

DHA, AD, FL, NH, GHG, and DC are the investigators of the REVISE trial. MHM, MK, and AP are the investigators of the SUP-ICU trial. YW, LG, DC, MHM, AP, and GHG are the investigators of a prior network meta-analysis on this topic.

### DATA AVAILABILITY STATEMENT

YW would like to share other data upon request.

### ORCID

*Ying Wang* https://orcid.org/0000-0002-2296-1991

*Sameer Parpia* https://orcid.org/0000-0002-9407-5622

### REFERENCES

1. Cook D, Guyatt G. Prophylaxis against upper gastrointestinal bleeding in hospitalized patients. *N Engl J Med*. 2018;378(26):2506-2516. doi:10.1056/NEJMra1605507 [published Online First: 2018/06/28].
2. Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care*. 2001;5(6):368-375. [published Online First: 2001/12/12].
3. Evans L, Rhodes A, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for Management of Sepsis and Septic Shock 2021. *Crit Care Med*. 2021;49(11):e1063-e1143. doi:10.1097/CCM.0000000000005337
4. Madsen KR, Lorentzen K, Clausen N, et al. Guideline for stress ulcer prophylaxis in the intensive care unit. *Dan Med J*. 2014;61(3):C4811.
5. Ye Z, Reintam Blaser A, Lytvyn L, et al. Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline. *BMJ*. 2020;368:l6722. doi:10.1136/bmj.l6722
6. Barletta JF, Kanji S, MacLaren R, Lat I, Erstad BL, American-Canadian consortium for Intensive care Drug utilization (ACID) Investigators. Pharmacoepidemiology of stress ulcer prophylaxis in the United States and Canada. *J Crit Care*. 2014;29(6):955-960. doi:10.1016/j.jcrc.2014.06.025 [published Online First: 2014/08/02].
7. Krag M, Perner A, Wetterslev J, et al. Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. *Acta Anaesthesiol Scand*. 2015;59(5):576-585. doi:10.1111/aas.12508 [published Online First: 2015/04/17].
8. Buendgens L, Bruensing J, Matthes M, et al. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing Clostridium difficile-associated diarrhea. *J Crit Care*. 2014;29(4):696 e11-5. doi:10.1016/j.jcrc.2014.03.002 [published Online First: 20140307].
9. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA*. 2009;301(20):2120-2128. doi:10.1001/jama.2009.722 [published Online First: 2009/05/28].
10. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. *N Engl J Med*. 2018;379(23):2199-2208.
11. Deane AM, Alhazzani W, Guyatt G, et al. REVISE: Re-evaluating the inhibition of stress erosions in the ICU: a randomised trial protocol. *BMJ Open*. 2023;13(11):e075588. doi:10.1136/bmjopen-2023-075588 [published Online First: 20231115].
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71 [published Online First: 20210329].
13. Wang Y, Ge L, Ye Z, et al. Efficacy and safety of gastrointestinal bleeding prophylaxis in critically ill patients: an updated systematic review and network meta-analysis of randomized trials. *Intensive Care Med*. 2020;46(11):1987-2000. doi:10.1007/s00134-020-06209-w [published Online First: 2020/08/25].
14. Wang Y, Ghadimi M, Wang Q, et al. Instruments assessing risk of bias of randomized trials frequently included items that are not addressing risk of bias issues. *J Clin Epidemiol*. 2022;152:218-225. doi:10.1016/j.jclinepi.2022.10.018 [published Online First: 2022/11/26].
15. Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol*. 2012;65(3):262-267. doi:10.1016/j.jclinepi.2011.04.015 [published Online First: 20111224].

13996576, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/aas.14426 by National Health And Medical Research Council, Wiley Online Library on [02/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

16. Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat*. 2005;30:261-293.
17. Sidik K, Jonkman JN. Simple heterogeneity variance estimation for meta-analysis. *J R Stat Soc Ser C Appl Stat*. 2005;54(2):367-384.
18. Hartung J, Knapp G. A refined method for the meta-analysis of controlled clinical trials with binary outcome. *Stat Med*. 2001;20(24):3875-3889. doi:10.1002/sim.1009 [published Online First: 2002/01/10].
19. Hartung J, Knapp G. On tests of the overall treatment effect in meta-analysis with normally distributed responses. *Stat Med*. 2001;20(12):1771-1782. doi:10.1002/sim.791 [published Online First: 2001/06/15].
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2 [published Online First: 1986/09/01].
21. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27(6):1785-1805. doi:10.1177/0962280216669183 [published Online First: 2016/09/30].
22. Weir CJ, Butcher I, Assi V, et al. Dealing with missing standard deviation and mean values in meta-analysis of continuous outcomes: a systematic review. *BMC Med Res Methodol*. 2018;18(1):25. doi:10.1186/s12874-018-0483-0 [published Online First: 2018/03/09].
23. Heels-Ansdell D, Billot L, Thabane L, et al. REVISE: re-evaluating the inhibition of stress erosions in the ICU-statistical analysis plan for a randomized trial. *Trials*. 2023;24(1):796. doi:10.1186/s13063-023-07794-z [published Online First: 20231206].
24. Schandelmaier S, Briel M, Varadhan R, et al. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ*. 2020;192(32):E901-E906. doi:10.1503/cmaj.200077 [published Online First: 2020/08/12].
25. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi:10.1136/bmj.39489.470347.AD [published Online First: 2008/04/26].
26. Guyatt GH, Ebrahim S, Alonso-Coello P, et al. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. *J Clin Epidemiol*. 2017;87:14-22. doi:10.1016/j.jclinepi.2017.05.005 [published Online First: 20170518].
27. Deeks J, Higgins J, Altman D, et al. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. 0 (Updated March 2011)*. The Cochrane Collaboration; 2011.
28. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. [published Online First: 1997/10/06].
29. Carrasco-Labra A, Brignardello-Petersen R, Santesso N, et al. Improving GRADE evidence tables part 1: a randomized trial shows improved understanding of content in summary of findings tables with a new format. *J Clin Epidemiol*. 2016;74:7-18. doi:10.1016/j.jclinepi.2015.12.007 [published Online First: 20160111].
30. Santesso N, Glenton C, Dahm P, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol*. 2020;119:126-135. doi:10.1016/j.jclinepi.2019.10.014 [published Online First: 20191109].
31. Eastwood GM, Litton E, Bellomo R, et al. Opinions and practice of stress ulcer prophylaxis in Australian and New Zealand intensive care units. *Crit Care Resusc*. 2014;16(3):170-174.
32. Krag M, Perner A, Wetterslev J, et al. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Intensive Care Med*. 2015;41(5):833-845. doi:10.1007/s00134-015-3725-1 [published Online First: 2015/04/11].
33. Shears M, Alhazzani W, Marshall JC, et al. Stress ulcer prophylaxis in critical illness: a Canadian survey. *Can J Anaesth*. 2016;63(6):718-724. doi:10.1007/s12630-016-0612-3 [published Online First: 20160224].
34. Cook DJ, Swinton M, Krewulak KD, et al. What counts as patient-important upper gastrointestinal bleeding in the ICU? A mixed-methods study protocol of patient and family perspectives. *BMJ Open*. 2023;13(5):e070966. doi:10.1136/bmjopen-2022-070966 [published Online First: 20230519].
35. Willems RPJ, van Dijk K, Ket JCF, Vandenbroucke-Grauls CMJE. Evaluation of the association between gastric acid suppression and risk of intestinal colonization with multidrug-resistant microorganisms: a systematic review and meta-analysis. *JAMA Intern Med*. 2020;180(4):561-571. doi:10.1001/jamainternmed.2020.0009

**How to cite this article:** Wang Y, Heels-Ansdell D, Ge L, et al. Proton pump inhibitors for gastrointestinal bleeding prophylaxis in critically ill patients: A systematic review protocol. *Acta Anaesthesiol Scand*. 2024;68(7):983-988. doi:10.1111/aas.14426

13996576, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/aas.14426 by National Health And Medical Research Council, Wiley Online Library on [02/10/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License