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Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU)

PhD Thesis

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Original Papers

The present PhD Thesis is based on the following papers:

I. Krag M, Perner A, Wetterslev J, Møller MH. Stress ulcer prophylaxis in the intensive care unit: is it indicated? A topical systematic review. Acta Anaesthesiol Scand 2013, 57:835–847

II. Krag M, Perner A, Wetterslev J, Wise MP, Møller MH. Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis. Intensive Care Med 2014, 40:11–22.

III. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, Keus F, Guttormsen AB, Moller AD, Møller MH and the SUP-ICU collaborators. Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries. Acta Anaesthesiol Scand 2015, 59:576–585.

IV. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, McArthur C, Cook D, Nielsen N, Pelosi P, Keus F, Guttormsen AB, Moller AD, Møller MH and the SUP-ICU collaborators. Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients. Intensive Care Med 2015, 41:833–845.

V. Krag M, Perner A, Wetterslev J, Wise MP, Borthwick M, Bendel S, Pelosi P, Keus F, Guttormsen AB, Moller AD, Møller MH. Stress ulcer prophylaxis with proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial): study protocol for a randomised controlled trial. Trials (submitted January 18, 2016).

Preface

This thesis is based on research carried out during my employment at the Department of Intensive Care, 4131 at Rigshospitalet.

Morten Hylander Møller developed the idea of the SUP-ICU research programme and emphasised that further research in this area was extremely important. I was honoured when Morten, in 2011, introduced me to his ideas and asked me to get involved in this research. Without any hesitation, we planned the first meeting and the journey began. It has been a pleasure working with Morten as a dedicated supervisor and clinician. Morten, thanks for all your support, for endless scientific discussions, for your friendship and for entrusting me with the major responsibility for coordinating the SUP-ICU trial.

I have been fortunate to be part of a growing research environment, and to have Anders as my primary supervisor. His door is always open for seeking highly skilled academic advises. Anders, thanks for believing in the idea of this research programme, especially the trial, for sharing your experiences, and for spending hours and hours fundraising in support of the programme. I admire your ability to see research ideas in their wider context and that you always strive to answer clinically relevant questions.

Having Jørn as one of my supervisors has been priceless. A great mentor, always willing to explain the finesses of statistics and always aiming for the best methodology - never seeking short cuts!

The project manager in CRIC, Birgit Agerholm Larsen, deserves a special thank for her invaluable practical and administrative support. Without her it is difficult to see how we would ever have managed to get the trial medication for the SUP-ICU trial produced.

Thanks to my invaluable fellow researchers for being part of an environment with plenty of scope for searching questions and discussions and for sharing their experiences. Thanks to former and present research nurses for their efforts and thanks to all the SUP-ICU investigators and patients for contributing to this important research. Thanks to dedicated doctors and nurses at Rigshospitalet for helping with the SUP-ICU trial, even when clinical work was busy.

A special thanks to Jan Bonde for hosting me and for supporting and encouraging me when fundraising felt like climbing a mountain.

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Finally, I am extremely grateful for the endless support I have received from the other Morten in my life, my soulmate and best friend. Thanks for taking the time to get involved in my research, for endless advices, discussions across the dining table, coaching and patience when working days became too long. I could not have done this without you.

Definitions

Overt gastrointestinal (GI) bleeding

One or more of the following:

1) Haematemesis
2) Coffee ground emesis
3) Melaena
4) Haematochezia
5) Bloody nasogastric aspirate

Clinically important GI bleeding

Overt GI bleeding AND at least one of the following within 24 hours of overt GI bleeding in the absence of other causes (clinical evaluation):

1) Decrease in blood pressure of 20 mmHg or more
2) Start of/increase of vasopressor of 20% or more
3) Decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
4) Transfusion of two or more units of red blood cells during the bleeding episode

Abbreviations

ARD	Absolute Risk Difference
ARR	Absolute Risk Reduction
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
DMSC	Data Monitoring and Safety Committee
GCP	Good Clinical Practice
GI	Gastrointestinal
GRADE	Grading of Recommendations Assessment, Development and Evaluation
H2RA	Histamine-2-Receptor Antagonist
hCG	Human Chorion Gonadotropin
ICU	Intensive Care Unit
OR	Odds Ratio
PICO	Population, Intervention, Comparator and Outcome
PPI	Proton Pump Inhibitor
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	Prospective Register of Systematic Reviews
RCT	Randomised Clinical Trial
RRI	Relative Risk Increase
RRR	Relative Risk Reduction
SAR	Serious Adverse Reaction
SOFA	Sequential Organ Failure Assessment
SUP	Stress Ulcer Prophylaxis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSA	Trial Sequential Analysis

Summary

Background

Critically ill patients in the intensive care unit (ICU) are at risk of stress related gastrointestinal (GI) bleeding which is considered a serious condition associated with adverse outcome. Accordingly, stress ulcer prophylaxis (SUP) with acid suppressants is considered standard of care in adult ICU patients and is recommended internationally. However, the evidence supporting SUP has been questioned, potential serious side effects have been suggested, and clinical equipoise exists.

The aims of the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) research programme were to summarize existing evidence on SUP in adult ICU patients and to collect contemporary data on GI bleeding and use of SUP in these patients, in order to design a large randomised clinical trial with low risk of bias assessing the benefits and harms of SUP. We hypothesised that the evidence supporting SUP in adult ICU patients is low and that SUP is widely used.

Methods

The SUP-ICU research programme comprised five studies. Study I and II summarised the existing evidence in two systematic reviews. Study III was an international survey assessing use of SUP on a departmental level. Study IV was a 7-day inception cohort study collecting contemporary data on GI bleeding and use of SUP in adult critically ill patients. Study V was a protocol for a large randomised clinical trial with low risk of bias assessing benefits and harms of SUP with a proton pump inhibitor.

Results

Study I: The incidence of GI bleeding varied considerably. Trial sequential analysis did not support a 30% relative risk reduction in the incidence of GI bleeding in patients treated with histamine-2receptor antagonists compared to placebo or sucralfate.

Study II: Twenty trials were identified. All trials assessed histamine-2-receptor antagonist and two trials additionally assessed proton pump inhibitors. All trials had high risk of bias and most were underpowered. No significant difference in mortality between SUP and placebo was found.

Study III: Ninety-seven ICUs in 11 countries participated. Twenty-three different indications for prescribing SUP were reported. One in four departments reported using SUP in all ICU patients and 19% did not stop SUP when discharging the patient from the ICU. Nosocomial pneumonia and *Clostridium difficile* infection were the most frequently reported concerns.

Study IV: A total of 1034 patients were included. Twenty-seven patients (2.6%) developed clinically important GI bleeding. Independent risk factors for GI bleeding were: three or more co-existing diseases, co-existing liver disease, use of renal replacement therapy, co-existing or acute coagulopathy, use of acid suppressants and higher organ failure score. Seventy-three per cent of the patients received acid suppressants during ICU stay; primarily a proton pump inhibitor. The crude and adjusted association (odds ratio and 95% confidence interval) between clinically important GI bleeding and 90-day mortality was 3.7 (1.7-8.0) and 1.7 (0.7-4.3), respectively.
Study V: A protocol for a trial assessing pantoprazole versus placebo in 3350 adult ICU patients with risk factors for GI bleeding has been developed. The primary outcome measure will be mortality to balance benefits and harms of SUP.

Conclusion

The quantity and quality of evidence supporting use of SUP in adult ICU patients is low and clinical equipoise exists. Acid suppressants are frequently used in the ICU, risk factors for development of GI bleeding can be readily identified upon ICU admission, and the prognosis of GI bleeding is ambiguous. A large high-quality randomised clinical trial with low risk of bias assessing benefits and harms of SUP in adult critically ill patients is needed, prepared and initiated.

Summary in Danish (dansk resumé)

Baggrund

Kritisk syge patienter på intensivafdeling er i risiko for at udvikle stress-relateret gastrointestinal (GI) blødning, hvilket betragtes som en alvorlig tilstand associeret med øget morbiditet og mortalitet. Stress ulcus profylakse (SUP) med syrehæmmende medicin anvendes som standardbehandling til voksne intensivpatienter og anbefales internationalt. Der er imidlertid sået tvivl om den evidens der ligger til grund for brugen af SUP, og der er samtidig bekymring for potentielt alvorlige bivirkninger.

Formålet med forskningsprogrammet "Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU)" var, at opsummere den eksisterende viden om SUP til voksne intensivpatienter og at indsamle tidssvarende data om hyppigheden af GI blødning og brugen af SUP til disse patienter, for at kunne designe et stort randomiseret klinisk forsøg med lav risiko for bias, der skal undersøge fordele og ulemper ved brug af SUP til voksne intensivpatienter.

Hypotesen var, at evidensen der ligger til grund for brugen af SUP blandt voksne intensivpatienter er mangelfuld, og at SUP anvendes hyppigt.

Metode

SUP-ICU forskningsprogrammet omfattede fem delprojekter. Delprojekt I og II opsummerede den eksisterende viden vedrørende SUP i to systematiske reviews. Delprojekt III var en international spørgeskemaundersøgelse, der undersøgte intensivafdelingers brug af SUP. Delprojekt IV var et 7-dages inceptionskohortestudie hvor tidssvarende data vedrørende hyppigheden af GI blødning og brugen af SUP blev indsamlet. Delprojekt V var en protokol der beskriver et stort randomiseret klinisk forsøg med lav risiko for bias, der skal undersøge fordele og ulemper ved brugen af SUP med protonpumpehæmmer til voksne patienter på intensivafdeling.

Resultater

Delprojekt I: Incidensen af GI blødning varierede betydeligt. Trial sequential analysis understøttede ikke en 30% relativ risiko reduktion i incidensen af GI blødning blandt patienter behandlet med histamine-2-receptor antagonister sammenlignet med placebo eller sucralfat.

Delprojekt II: Tyve forsøg blev identificeret. Alle forsøg undersøgte histamine-2-receptor antagonister og to undersøgte desuden protonpumpehæmmere. Alle forsøg havde høj risiko for bias og de fleste havde for lille sample size (power). Vi fandt ingen signifikant forskel i mortalitet mellem SUP og placebo.

Delprojekt III: I alt 97 intensivafdelinger i 11 lande deltog i undersøgelsen. Der blev rapporteret 23 forskellige indikationer for ordination af SUP. En ud af fire afdelinger rapporterede at alle intensivpatienter blev behandlet med SUP og 19% stoppede ikke behandlingen når patienten blev udskrevet fra intensivafdeling. Nosokomiel pneumoni og *Clostridium difficile* infektion var de hyppigst rapporterede bekymringer omkring brugen af SUP.

Delprojekt IV: Der blev inkluderet 1034 patienter og heraf udviklede 27 (2.6%) klinisk betydende GI blødning. Følgende var uafhængige risikofaktorer for udvikling af GI blødning: tre eller flere co-morbiditeter, leversygdom, brug af dialyse, kronisk og akut koagulopati, brug af syrehæmmende medicin samt stigende Sequential Organ Failure Assesment (SOFA) score. I alt fik 73% af patienterne syrehæmmende medicin under deres intensivindlæggelse, oftest i form af en protonpumpehæmmer. Den ujusterede og justerede association (odds ratio and 95% konfidensinterval) mellem klinisk betydende GI blødning og 90-dages mortalitet var henholdsvis 3.7 (1.7-8.0) og 1.7 (0.7-4.3).

Delprojekt V: Vi har udviklet en protokol til et randomiseret klinisk forsøg der skal undersøge pantoprazol versus placebo til 3350 voksne intensivpatienter med risikofaktorer for udvikling af GI blødning. For at kunne opveje fordele og ulemper ved brug af SUP, er det primære effektmål mortalitet.

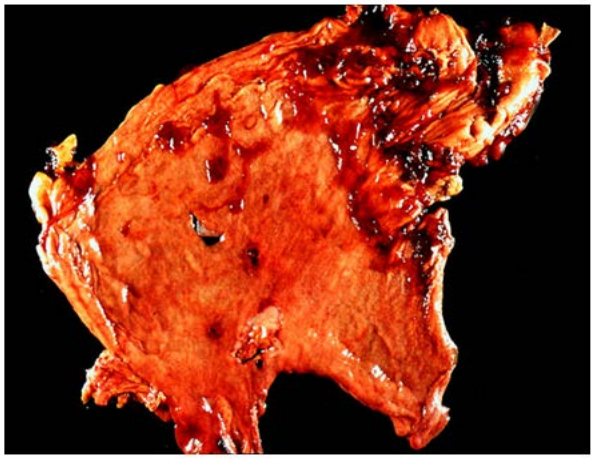
Konklusion

Kvaliteten og kvantiteten af den evidens der ligger til grund for brugen af SUP til voksne intensivpatienter er lav. Syrehæmmende medicin anvendes hyppigt på intensivafdelinger, risikofaktorer for at udvikle GI blødning kan identificeres ved indlæggelsen, og prognosen ved GI blødning er uafklaret. Der er behov for et stort randomiseret klinisk forsøg med lav risiko for bias for at undersøge fordele og ulemper ved brug af SUP til kritisk syge patienter på intensivafdeling.

Background

Gastrointestinal bleeding in critically ill patients

Critically ill patients in the intensive care unit (ICU) are at risk of developing stress-related mucosal damage.[1] The pathophysiology is not completely understood, but it has been hypothesised that stress ulcerations are caused by decreased mucosal blood flow, ischaemia and reperfusion injury, and hence are less related to acid secretion than peptic ulcers.[2] The majority of stress ulcerations are superficial and asymptomatic, but the ulceration can progress and erode larger vessels resulting in gastrointestinal (GI) bleeding.[3]



GI bleeding among ICU patients is a serious condition which has been estimated to result in a 1-4 times increased risk of mortality and an excess length of ICU stay of 4-8 days.[1,4] Reported estimates of the prevalence of GI bleeding among the general ICU population vary between 0.6% and 6% which may be due to heterogeneous populations, varying definitions of GI bleeding, and difficulties in diagnosing stress ulcers.[1,5,6]

Several studies have sought to identify risk factors for developing GI bleeding. A landmark multicentre, prospective cohort study by Cook et al. from 1994 (n=2252) highlighted mechanical ventilation ≥ 48 hours (odds ratio (OR) 15.6) and coagulopathy (OR 4.3) as major risk factors for GI bleeding in critically ill patients.[7] Acute kidney injury has also been shown to be independently associated with increased risk of GI bleeding in patients mechanically ventilated for more than 48 hours.[8] Additionally, severe head or spinal injury, burn injury, long lasting surgery, high dose corticosteroids and acute lung injury have been proposed as risk factors for GI bleeding, but the evidence supporting these findings is weak, because of the high risk of systematic and random errors.[9–11] Finally, it has been suggested that enteral feeding decreases the risk of GI bleeding.[12] Most guidelines distinguish between high-risk and low-risk patients.[10,13] However, existing evidence on risk factors is ambiguous, and adequate risk stratification is difficult.

Stress ulcer prophylaxis

To prevent GI bleeding in critically ill patients, stress ulcer prophylaxis (SUP) was introduced more than 40 years ago.[14] Different agents for the prevention of GI bleeding have been used throughout the years. Initially antacids and later sucralfate were the preferred agents, but with the introduction

of histamine-2-receptor antagonists (H2RAs) the opportunity of intravenous administration became available. In a randomised clinical trial (RCT) from 1998, a significantly lower incidence of GI bleeding in patients receiving H2RA compared with sucralfate was reported.[15] In the late eighties proton pump inhibitors (PPI) were introduced in Europe and the superior efficacy of PPIs over H2RAs was demonstrated in various GI disorders, including peptic ulcer disease and gastroesophageal reflux disease.[16]

Today, SUP with PPI is recommended in international guidelines.[13] However, the evidence base for SUP in critically ill patients has been questioned[17,18] and concerns of serious side effects have been expressed.[19]

Potential harm of SUP

Because acid suppressants increase pH in the stomach, the host immunity may be compromised. This may increase bacterial growth in the stomach and increase the risk of infectious complications.[20] It has been suggested that the more efficient an acid suppressant increases pH in the stomach, the higher the risk of nosocomial infections.[19]

Nosocomial pneumonia

Ventilator associated (nosocomial) pneumonia is the most common nosocomial infection in the ICU with a prevalence of 15% and hence a significant in-hospital burden.[21,22] Trials and meta-analyses have assessed the association between the use of different SUP agents and the risk of nosocomial pneumonia.[12,15,18,23] Four meta-analyses have compared sucralfate with H2RA and all of them showed an increased risk of pneumonia in patients treated with H2RA.[24–27] This difference between agents was not confirmed in two meta-analyses comparing PPI with H2RA.[18,28] Very limited data on SUP versus placebo have been published, but one meta-analysis comparing H2RA with placebo suggested increased risk of pneumonia in patients receiving the combination of SUP and enteral nutrition.[12]

Clostridium difficile infection

The increased pH induced by acid suppressants is hypothesised to increase the risk of *Clostridium difficile* infections.[29–32] The risk of *Clostridium difficile* infection among ICU patients is higher than in the general hospital population, and is associated with increased mortality, excess length of stay and significantly higher mean costs.[31,33,34] Clinical trials investigating the risk of *Clostridium difficile* infection in ICU patients prescribed acid suppressants are lacking, but a recently published observational study comprising 35,312 critically ill patients concluded that mechanically ventilated

patients receiving PPI have higher risk of *Clostridium difficile* infection than patients receiving H2RA.[19]

Cardiovascular events

Observational data have suggested an association between ischemic cardiovascular events and treatment with PPI.[35–39] It has been hypothesised that the combination of Clopidogrel and PPI results in an increased risk of adverse cardiac events, but data on this are ambiguous.[35–39] An observational study of 56,406 patients showed increased risk of cardiovascular events in non-ICU patients treated with PPI independent of treatment with Clopidogrel.[36] No trials in ICU patients have investigated the potential association between treatment with PPI and ischemic cardiovascular events. Consequently the evidence is weak and high quality data are needed before drawing conclusions.

In summary, the rationale for using SUP in critically ill patients in the ICU is ambiguous, and clinical equipoise exists. Estimates of GI bleeding in the ICU are 15-20 years old, data on risk factors for and prognosis of GI bleeding in contemporary ICU populations are lacking, and the balance between benefits and harms of SUP in ICU patients is unknown.

Aim of studies

The overall aims of the Stress Ulcer Prophylaxis in the Intensive Care Unit (SUP-ICU) research programme were to summarise existing evidence on SUP in adult ICU critically ill patients, and to collect contemporary data on GI bleeding and use of SUP in these patients in order to design a large RCT with low risk of bias assessing the benefits and harms of SUP in the ICU.
We hypothesised that SUP is widely used, and that the evidence supporting this is ambiguous.

This thesis comprises five papers:

I. A topical systematic review
II. A systematic review of RCTs comparing SUP with PPI/H2RA versus placebo/no prophylaxis with meta-analysis and trial sequential analysis
III. A survey assessing the contemporary use of SUP on a departmental level
IV. An inception cohort study describing the prevalence of, risk factors for, and prognostic importance of GI bleeding and the use of acid suppressants in acutely ill adult ICU patients
V. A protocol for a RCT comparing PPI (pantoprazole) with placebo

Presentation of studies I-V

Study I: Stress ulcer prophylaxis in the intensive care unit: is it indicated? A topical systematic review

Aim and hypothesis

The aim of this review was to highlight unanswered clinical research questions on SUP in ICU patients. We hypothesised that the rationale for SUP in the ICU is ambiguous and that the quality of evidence is low.

Methods

Overview and design

The review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[40] and was registered in the Prospective Register of Systematic Reviews (PROSPERO), no. CRD42012002579.

The review was descriptive, conducted systematically with a predefined protocol, a systematic literature search and assessment of the quality of evidence.

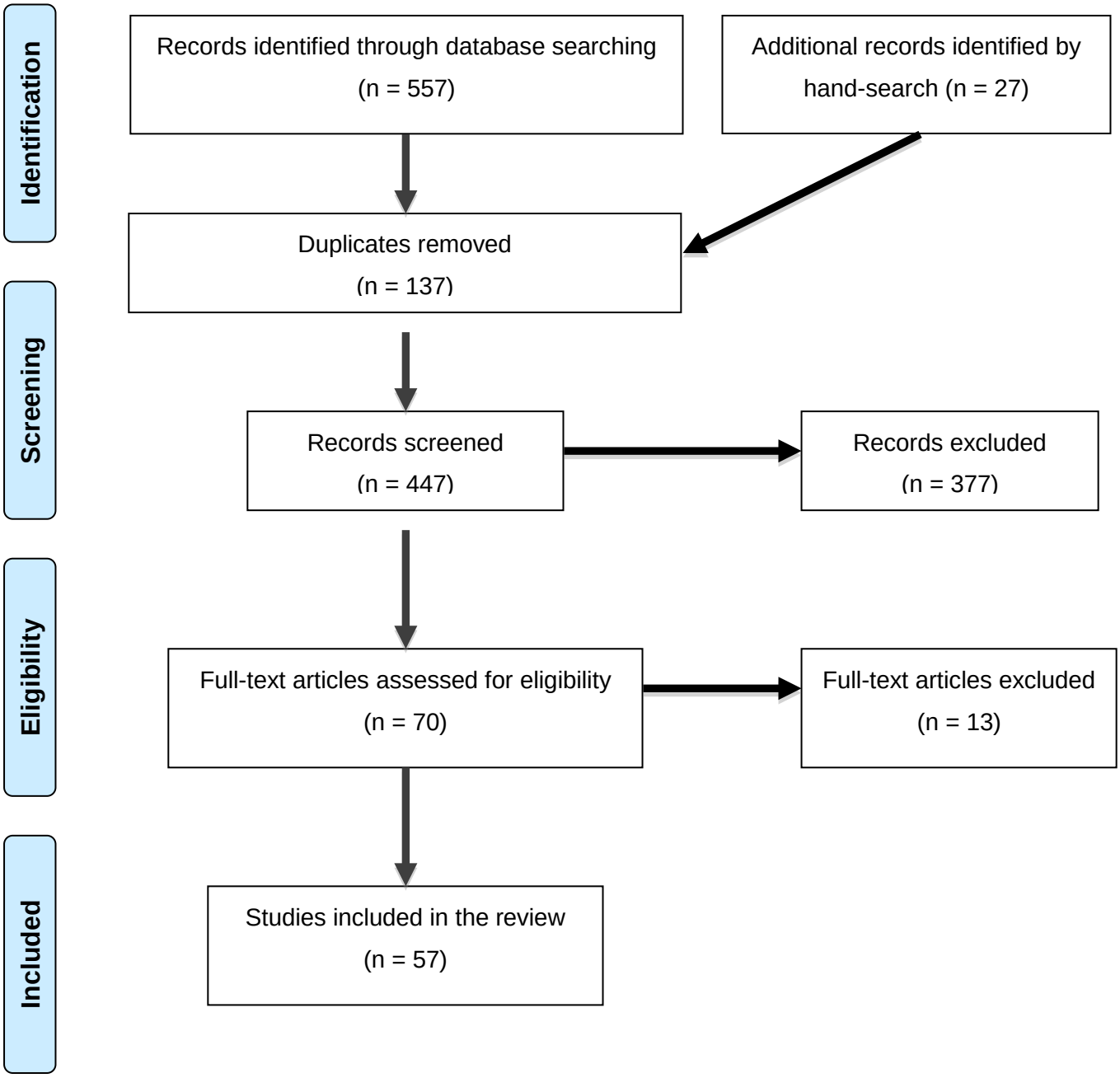
Search strategy

A population, intervention, comparator and outcome (PICO) question was performed.[41] Medline including MeSH, EMBASE and the Cochrane Library were searched. No study-designs were *per se* excluded.

Evaluation of included studies

Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[42] was used to evaluate the quality of evidence of the included studies and RCTs. The risk of random errors (imprecision) was assessed by trial sequential analysis (TSA).[43,44]

Figure 1. Flow diagram of retrieved studies.



Results

Epidemiology

Seven observational studies reported an incidence of GI bleeding between 0.3% and 3.5% throughout 1994-2009.[1,6,7,11,45–47] Few studies reported data from European general ICUs.[45]

Use of SUP in the ICU

The quality of evidence for a reduction in GI bleeding in trials comparing H2RA vs. sucralfate or placebo was low.[5,15,17,48–50] This was confirmed by TSA of the trials with lowest risk of bias (Jadad score of 5), showing that the cumulative z-curve did not cross the trial sequential monitoring boundary for benefit, indicating no firm evidence for a 30% relative risk reduction (RRR) between H2RA and sucralfate/placebo. We found no statistically significant difference between PPI vs. H2RA in the conventional cumulative meta-analysis or TSA in terms of GI bleeding.

Harm of SUP

A 2010 meta-analysis comparing H2RA to placebo did not find an overall increased risk of pneumonia in patients receiving H2RA compared with placebo.[12] Data on patients receiving PPI were too sparse to draw firm conclusions. Observational studies assessing the association between acid suppressants and *Clostridium difficile* infection in non-ICU patients showed increased risk of *Clostridium difficile* infection in patients receiving acid suppressants.[29,51] We were not able to identify any studies including critically ill patients in the ICU. Studies assessing the association between cardiovascular events and PPI in ICU patients were not identified.

Conclusion

This topical systematic review was conducted to summarise existing evidence. The evidence-base for the use of SUP in the ICU is low, and the following unanswered questions exist: 1) what is the prevalence of GI bleeding in contemporary ICU patients?; 2) which is the preferred SUP agent in contemporary ICUs?; 3) on which criteria are SUP prescribed?; 4) do ICU patients benefit from SUP with H2RA or PPI compared with placebo?; and 5) if they do, is PPI superior to H2RA or inversely?

Limitations

The review comes with limitations. First, we included all study designs resulting in a somewhat heterogeneous evidence-base. Second, although the literature search was conducted systematically, the search criteria were very simple and broad, which might have increased the risk of not identifying all relevant studies. Third, the studies included assessed ICU patients in general, which may limit generalisability to specific ICU subgroups. Fourth, we did not consider RCTs in the

estimate of the incidence of GI bleeding. Estimates of GI bleeding from RCTs may provide important data. Fifth, we assessed the quality of evidence using GRADE, but we did not assess all risk of bias domains systematically.

Study II: Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients. A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis

Aim and hypothesis

The objective was to assess the effects of PPI or H2RA versus placebo or no prophylaxis on all-cause mortality, GI bleeding and pneumonia in adult critically ill patients in the ICU. We hypothesised that the quality of evidence supporting SUP is low.

Methods

Overview and study design

Study II was a systematic review including RCTs assessing PPI or H2RA compared with placebo or no prophylaxis. The review was conducted according to the recommendations provided by the Cochrane Collaboration, including assessment of the risk of bias.[52] Furthermore, cumulative meta-analyses, and TSAs were performed. It was prepared according to the PRISMA statement[40] and a protocol was registered pre-experimentally in PROSPERO, no. CRD42013004142.

Eligibility criteria

We included RCTs if they assessed adult ICU patients, had an intervention group receiving PPI or H2RA and a control group receiving placebo or no prophylaxis. More than one intervention group was allowed, and trials were included irrespective of language. Trials including paediatric patients and non-ICU patients, trials reporting non-patient-centred outcome measures only, and animal studies were excluded.

Search strategy

A PICO question was performed[41] and Medline including MeSH, EMBASE and the Cochrane Library were searched for relevant trials. Additionally, we hand-searched reference lists and other relevant systematic reviews.

Outcome measures

The primary outcome was all-cause mortality, and secondary outcomes were GI bleeding and nosocomial pneumonia. The outcome measures of interest were defined according to the definition used by the authors of the original trials.

Data extraction and evaluation of risk of bias

Two authors independently reviewed all titles and abstracts identified in the literature search. Risk of bias was assessed according to the Cochrane Collaboration.[52] The following seven domains were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, baseline imbalance and bias due to vested financial interest. We classified a trial as having overall low risk of bias if all domains had low risk of bias.

Statistical analyses

We calculated summary relative risks with 95% confidence intervals (CIs), and assessed the risk of random errors using TSA[44].

Trial sequential analysis

TSA challenges the conventional meta-analysis. The required information size needed to show an effect in a single trial is calculated and heterogeneity is taken into account.[44] The required information size is combined with an adjusted threshold for statistical significance in the cumulative meta-analysis (like an interim analysis).

The required information sizes in this study were calculated based on a RRR of 20% for each outcome. We adjusted all TSAs for heterogeneity (diversity adjustment) according to an overall type I error of 5% and a power of 80%, considering early and repetitive testing.

Sensitivity- and subgroup analyses

Continuity correction in the zero event trials were performed[53] and five predefined subgroup analyses and one post-hoc subgroup analysis were conducted.

Results

Trial characteristics

A total of twenty RCTs randomising 1971 patients were included. All trials reported data on GI bleeding, mortality was assessed in 15 trials, and seven trials reported data on pneumonia. All 20 trials assessed H2RA and two of the trials additionally assessed PPI. All 20 trials had high risk of bias, primarily because of inadequate random sequence generation, inadequate allocation concealment and inadequate blinding.

All-cause mortality

We found no significant difference in mortality between patients treated with PPI/H2RA compared with those treated with placebo/no prophylaxis (fixed effect: RR 1.00, 95 % CI 0.84–1.20). The

subgroup analyses were consistent with the primary result. In the TSA, the Z curve reached the futility area, indicating firm evidence for exclusion of a 20% RRR in mortality in patients treated with PPI/H2RA, as compared with placebo/no prophylaxis.

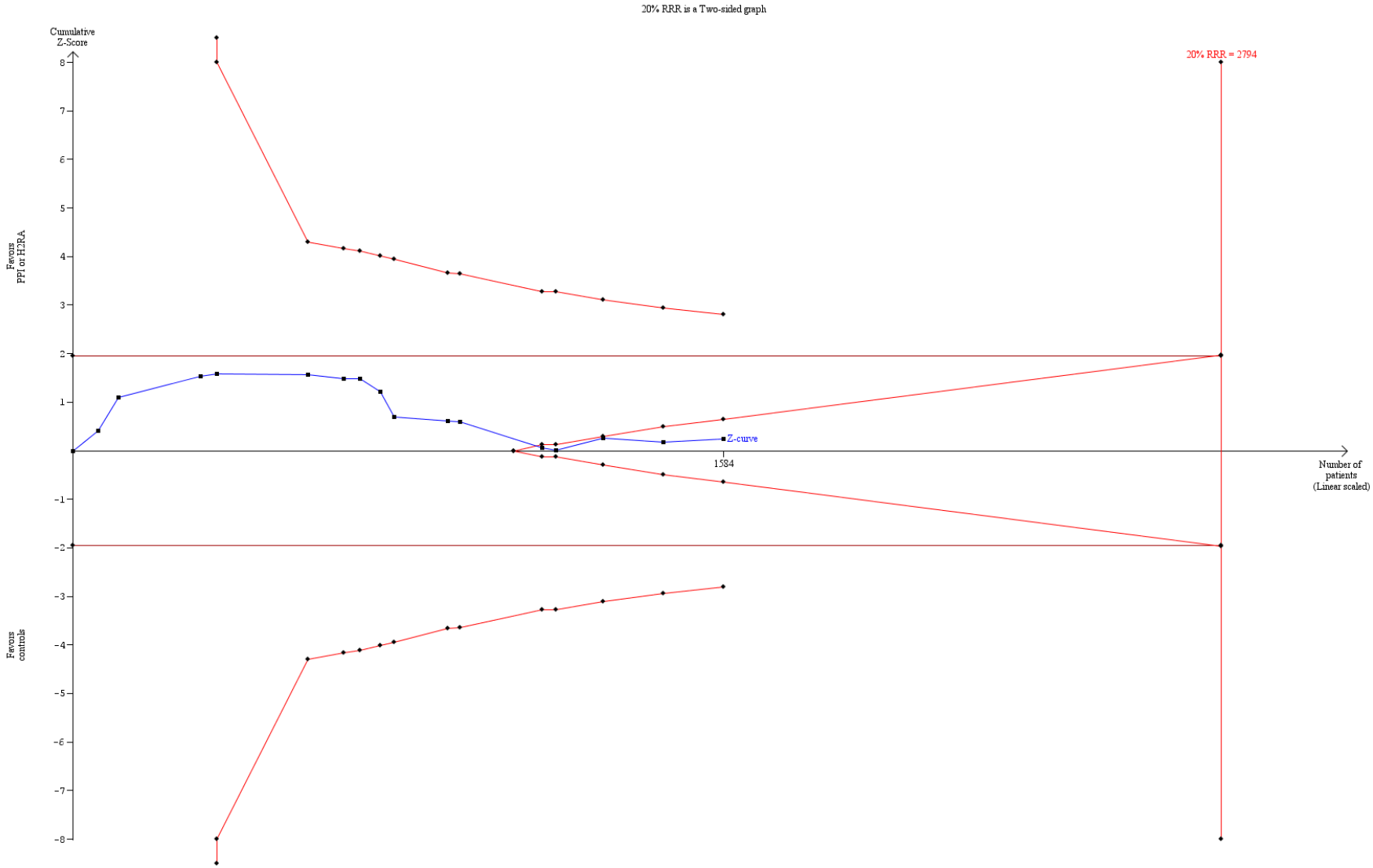
GI bleeding

The conventional meta-analysis suggested a statistically significant difference in GI bleeding between patients in the PPI or H2RA group compared with the placebo or no prophylaxis group (fixed effect: RR 0.41, 95 % CI 0.31–0.53). However, this was not confirmed in the TSA, which highlighted that only 22% of the required information size of 8707 patients had been accrued. Subgroup analyses were consistent with the primary finding.

Nosocomial pneumonia

Neither the conventional meta-analysis, nor the TSA showed a statistically significant difference between patients treated with acid suppressants and placebo/no prophylaxis (fixed effect: RR 1.16, 95 % CI 0.84–1.58). All but one subgroup analysis (placebo versus no prophylaxis; which surprisingly showed increased intervention effect in the placebo group) were consistent with the primary finding. TSA highlighted that only 12% of the required information size had been accrued.

Figure 2. Trial sequential analysis of all-cause mortality (15 trials). A diversity adjusted information size of 2794 patients was calculated using α=0.05 (two sided), β=0.20 (power 80%), D^2=0%, an anticipated relative risk reduction of 20%, and an event proportion of 21% in the placebo/control arm. The blue cumulative z curve was constructed using a fixed effects model.



Conclusion

In this systematic review with meta-analysis and TSA we systematically assessed RCTs on PPI/H2RA versus placebo/no prophylaxis in adult ICU patients. The quantity and quality of evidence supporting use of SUP in adult ICU patients is low, and there is no firm evidence for benefit or harm in terms of mortality, nosocomial pneumonia and GI bleeding. The rejection of a 20% RRR (futility), however, is dubious as the vast majority of trials come with a high risk of bias thereby potentially concealing an excess mortality associated with PPI/H2RA.

Limitations

This review comes with limitations. First, we did not define the three outcomes of interest; rather we used the definitions of the included trials. This may – combined with inclusion of ICU patients in general - increase the risk of trial heterogeneity. Second, we did not report data on C*lostridium difficile* infection and cardiovascular complications; otherwise serious side effects. Third, no subgroup analysis of old versus new RCTs was performed (hypothesised direction of subgroup effect: increased intervention effect in the old trials). Additionally, no analyses of subgroups of patients e.g. burn or neurosurgical patients were performed. Fourth, we did not distinguish between RCTs assessing PPI and H2RA, but assessed differences in a subgroup analysis exclusively.

Study III: Stress ulcer prophylaxis in the intensive care unit. An international survey of 97 units in 11 countries

Aim and hypothesis

We aimed to describe reported SUP practices in adult ICUs. We hypothesised that patient selection for SUP varies within individual ICUs as well as internationally.

Methods

Overview and study design

Study III was a survey conducted in departments participating in the SUP-ICU cohort study (Study IV). The questionnaire had to be completed before participation in Study IV. A pre-experimental protocol, including a statistical analysis plan was prepared and made available publicly.

Data

The following information was collected: country, type and size of ICU, presence of a SUP guideline, the preferred SUP agent, indications for prescribing SUP, criteria for discontinuing SUP, and potential concerns for adverse effects.

Statistics

Data were presented as frequencies and per cent. Tabulation of SUP preference by country, type of hospital, and type and size of ICU was performed. Fisher's exact test was used to assess differences.

Results

All 97 ICUs in the 11 countries accepting the invitation to participate in Study IV returned the questionnaire. Of the 97 ICUs, 62 (64%) reported having a guideline for the use of SUP. The majority of ICUs (66%) used PPI as first choice, but British ICUs preferred H2RAs.

Initiating and discontinuing SUP

Twenty-three different indications for prescribing SUP were reported. Among the most frequently reported were mechanical ventilation, coagulopathy and inadequate enteral feeding. One in four reported using SUP in all ICU patients. Full enteral feeding and discontinuation of mechanical ventilation were the two most frequently reported reasons for discontinuing SUP, and 19% did not stop SUP when discharging the patient from the ICU.

Concerns

Nosocomial pneumonia and *Clostridium difficile* infection were the most frequently reported concerns (81% and 53% respectively), and *Clostridium difficile* infection were more frequently reported as a concern among sites using H2RA.

Table 1. Preferences for stress ulcer prophylaxis (SUP). Frequencies (%)

Variable		No. of units (n = 97)
Local SUP guideline		62 (64)
Preferred SUP agent	PPI	64 (66)
	H_2 receptor antagonist	30 (31)
	Sucralfate	1 (1)
	Antacids	1 (1)
	None	1 (1)
Indications for SUP[1]		
	Mechanical ventilation	43 (45)
	Miscellaneous (17 different)*	41 (43)
	High risk patients (unspecified)	28 (29)
	All ICU patients	25 (26)
	Coagulopathy	16 (17)
	Incomplete enteral feeding	12 (13)
	Shock	11 (11)
	None	1 (1)
Criteria for discontinuing SUP	Full enteral feeding	31 (32)
	Discharge from ICU	21 (22)
	No discontinuation of SUP	18 (19)
	Discontinuation of mechanical ventilation	13 (13)
	Other	5 (5)
Concerns when prescribing SUP[1]	Nosocomial pneumonia	78 (80)
	Clostridium difficile infection	51 (53)
	Interactions	26 (27)
	Allergy	11 (11)
	Delirium	9 (9)
	None	8 (8)
	Other**	5 (5)

[1] More than one answer allowed

* Abdominal aortic aneurysm, acute kidney or liver failure, burn injury, renal replacement therapy, expected stay in the ICU for > 48 hours/1 week, therapeutic hypothermia after cardiac arrest, neurosurgery or cerebral infarction, pancreatitis, portal hypertension, previous or present use of PPI or H2RA, previous ulcer or GI bleeding, severe head injury, multiple trauma, treatment with NSAID, treatment with steroids

** Cost, high plasma aluminium, diarrhoea, liver dysfunction

PPI: Proton pump inhibitor

H2RA: Histamine 2 receptor antagonist

Conclusion

SUP is used routinely in the ICU and PPI seems to be the most frequently prescribed SUP agent. However, the majority of ICUs did not have a guideline for the use of SUP. Most of the participating departments expressed concern of serious side effects. Nevertheless, one in four departments did not discontinue SUP when discharging the patient from the ICU to the ward.

Limitations

This survey has several limitations. First, only departments that had already accepted the invitation to participate in the 7-day inception cohort study (Study IV) were invited. Clinicians accepting the invitation may be interested in the topic which could create a convenience sample. This may explain the high response rate in this survey compared with other surveys. Second, the majority of ICUs accepting the invitation were British (38/97) or Danish (24/97) with few ICUs from the remaining countries. This may limit the external validity outside these two countries. Third, a prerequisite limitation of surveys is the risk of answers not reflecting actual practice. Despite thorough instruction there is a risk of investigators answering the questionnaire according to their own preferences, which may not reflect the practice of the department. Fourth, since the most frequently answered side effects also were the first listed in the questionnaire, there is a risk of investigators choosing them because they were the first available options. Finally, no reliability testing or clinical sensibility testing of the questionnaire was conducted.

Study IV: Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients

Aim and hypothesis

We aimed to describe the prevalence of, risk factors for and prognostic importance of GI bleeding for all-cause mortality in adult critically ill patients in the ICU. Additionally, we aimed to describe the use of acid suppressants in the ICU. We hypothesised that the prevalence of clinically important GI bleeding as of today is low and that acid suppressants are frequently used.

Methods

Overview and study design

This 7-day inception cohort study was approved by the Danish Data Protection Agency and the Danish Health and Medicines Authorities. The ethical committees in all participating countries waived informed consent. A pre-experimental protocol and statistical analysis plan were available publicly.

Eligibility

Patients aged 18 years or above with an acute admission to the ICU were screened for inclusion. We excluded patients with GI bleeding upon admission to the ICU and patients with previous ICU admission during the same hospital stay.

Data extraction

We recorded co-existing diseases, disease severity and organ failure at admission, use of organ support and acid suppressants, data on coagulopathy and bleeding during the entire ICU stay, and after 90 days, we obtained vital status and date of hospital discharge.

Outcomes

The primary outcome measure was clinically important GI bleeding. Secondary outcome measures were overt GI bleeding and all-cause mortality 90-days after inclusion.

Statistics

We used binary logistic regression to determine baseline risk factors for overt and clinically important GI bleeding. The results were presented as crude and adjusted ORs with 95% CIs.

Additionally, we used binary logistic regression to determine crude and adjusted association between overt and clinically important GI bleeding and mortality.

Results

Some 1034 patients from 97 ICUs in 11 countries were included.

GI bleeding

Twenty-seven patients (2.6%) developed clinically important GI bleeding and 49 (4.7%) developed one or more episodes of overt GI bleeding. The majority of patients with clinically important GI bleeding bled within the first 5 days (n=20) with a median time from ICU admission to bleeding of 3 days (interquartile range 2-6 days)

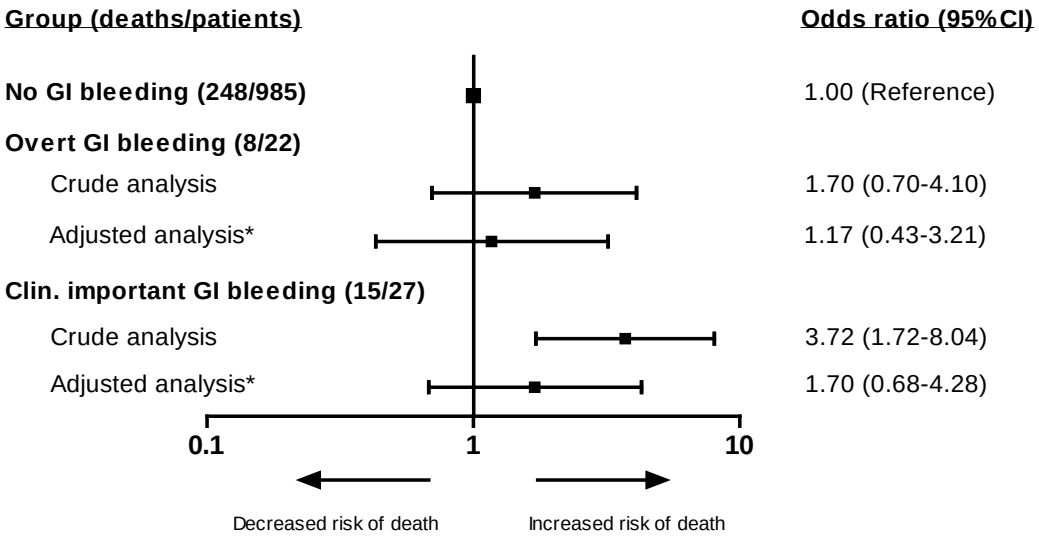
Risk factors

The following independent baseline risk factors for clinically important GI bleeding were identified: any three or more co-existing diseases, co-existing liver disease, renal replacement therapy, co-existing and acute coagulopathy, use of acid suppressants on ICU day 1, and higher SOFA score on ICU day 1. Circulatory support on ICU day 1 did not reach significance in the adjusted analysis (2.3, 95% CI 1.0-5.4), but as the estimates in the crude and adjusted analyses were consistent, this may be due to inadequate power end the resulting imprecision.

Mortality

The overall 90-day mortality was 26.2%. Fifteen of the 27 patients (55.6%) with clinically important GI bleeding were dead at day 90 compared with 256 of 1007 (25.4%) patients without GI bleeding. No statistically significant adjusted association between clinically important GI bleeding and 90-day mortality was present (Figure 3).

Figure 3. Odds ratios (95% confidence intervals) for 90-day mortality in patients who had no gastrointestinal (GI) bleeding, overt GI bleeding and clinically important GI bleeding during ICU stay



* Binary logistic regression analysis with adjustment for the following covariates according to the statistical analysis plan: Age on the first day of ICU admission, SOFA score on the first day of ICU admission, comorbidity (y/n), gender, type of admission (medical/emergency surgery/elective surgery), mechanical ventilation on the first day of ICU admission (y/n), coagulopathy on the first day of ICU admission (y/n), circulatory support on the first day of ICU admission (y/n), renal replacement therapy on the first day of ICU admission (y/n).

Acid suppressants

We found that 37% of the included patients received acid suppressants prior to ICU admission, increasing to 56% the first day in the ICU and to 70-76% the second to fifth day. The majority of patients received PPI (55%), with pantoprazole as the most frequently used (23%).

Conclusion

Clinically important GI bleeding still occurs in the ICU, but it is a rare condition. Patients with co-existing diseases and severe acute illness are at the highest risk of developing clinically important GI bleeding. No adjusted association between clinically important GI bleeding and 90-day mortality was found. Three out of four patients received acid suppressants during their ICU stay.

Limitations

This study comes with limitations, including limitations related to the observational design. First of all, no inferences on causalities can be drawn. The widespread use of acid suppressants in ICU patients today challenge the ability to draw firm conclusions about the prognosis of GI bleeding in patients not receiving acid suppressants. Second, there is a risk of residual confounding by unmeasured or unknown confounders and confounding by indication, including the fact that the most severely ill patients likely are at highest "risk" of receiving SUP. Third, we included patients with peptic ulcers (unless they had GI bleeding) and/or history of peptic ulcer, despite an *a priori* high risk of GI bleeding. Terminally ill patients and patients with treatment limitations were also included. Fourth, in accordance with Study III, participating ICUs were recruited by a national investigator and participation was voluntary. This may have resulted in a convenience sample with the risk of this sample differing form other ICUs. Fifth, the majority of patients were Danish or British, which may limit external validity outside these countries. Sixth, we used a slightly different definition of clinically important GI bleeding than the originally proposed definition by Cook et al.[7] This may explain some of the inter-study discrepancies, including the lack of association between mechanical ventilation and GI bleeding in the present study. We chose to modify the definition of clinically important GI bleeding, as initiating or increasing vasopressors can mask a decrease in blood pressure. Finally, we did not register data on the potential harms of SUP.

Study V: Stress ulcer prophylaxis with proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial): protocol for a randomised clinical trial

Aim and hypothesis

The aim of Study V was to outline the design and rationale for a high-quality RCT assessing the benefits and harms of SUP in adult ICU patients. We hypothesise that PPI reduces the rate of GI bleeding, but increases the rates of nosocomial infections and myocardial ischemia. The effect on overall mortality is therefore unpredictable.

Methods

Overview and study design

The trial is an investigator-initiated, international, RCT with blinding of patients, investigators, clinicians and statisticians. Randomisation will be performed in blocks with varying block sizes.

The trial is approved by the Danish Data Protection Agency (RH-2015-3203695), the Danish Health and Medicines Authorities (2015030166) and the Committee on Health Research Ethics (H-15003141). The trial is registered at clinicaltrials.gov (no. NCT02467621) and was initiated January 4, 2016. Some 50-75 ICUs in Europe are expected to participate during the trial period of maximum two years.

Eligibility

Adult patients acutely admitted to the ICU with at least one risk factor for clinically important GI bleeding[54] will be screened for inclusion. We will exclude patients with contraindications for PPI, current daily treatment with PPI or H2RA, GI bleeding, peptic ulcer or organ transplant during current hospital admission, fertile women with a positive urine human chorionic gonadotropin (hCG) or plasma-hCG, patients who are brain dead or where active therapy has been withdrawn, and patients in whom consent according to national regulations are unobtainable.

Inclusion and exclusion of the patients (including reasons for exclusion) will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[55]

Trial medication

Enrolled patients will be randomised to receive either pantoprazole 40 mg or placebo once daily intravenously from randomisation until ICU discharge or death for a maximum of 90 days.

Outcome measures

The primary outcome is all-cause mortality 90 days after randomisation. Secondary outcomes are 1) proportion of patients with one or more of the following events during ICU stay: clinically important GI bleeding, pneumonia, *Clostridium difficile* infection or myocardial ischemia; 2) proportion of patients with clinically important GI bleeding during ICU stay; 3) proportion of patients with one or more infectious adverse events (pneumonia or *Clostridium difficile* infection) during ICU stay; 4) 1 year 'landmark' mortality post-randomisation; 5) days alive without use of mechanical ventilation, renal replacement therapy or circulatory support in the 90-day period; 6) number of serious adverse reactions (SARs). Furthermore, a health economic analysis will be performed based on the results of the trial.

Safety

If indication for treatment with PPI or H2RA arises, enrolled patients will be withdrawn from the trial intervention and relevant treatment will be initiated. At any time the local investigator or the clinician responsible for the patient can withdraw the patient from the trial if they find clinical indication for discontinuing the trial medication. If the patient experiences a SAR or a Suspected Unexpected Serious Adverse Reaction (SUSAR) or the patient withdraws the consent, the trial medication will be discontinued.

An independent Data Monitoring and Safety Committee (DMSC) is responsible for safeguarding the interest of the trial participants, assessing the safety and efficacy of the interventions during the trial, including interim analyses, and for monitoring the overall conduct of the trial

The trial will be monitored at all trial sites according to the Good Clinical Practice (GCP) principles.

Statistics

A predefined detailed statistical analysis plan will be prepared and published before analysing data. Assuming a baseline 90-day mortality of 25%,[54] α=0.05 (two-sided), and β=0.1, 3350 patients (2 x 1675) will be needed to show a 20% RRR or relative risk increase (RRI) corresponding to a 5% absolute risk difference (ARD) in the primary outcome measure. The primary analysis will be a multiple regression analysis adjusted for stratification variables (active haematological cancer and site) in the intention-to-treat population comparing death by day-90 in the two groups. A secondary analysis will be performed adjusting the results for stratification variables and other known major prognostic co-variates (age, baseline sequential organ failure assessment (SOFA) score and type of admission (medical, elective or emergency surgery)). All statistical tests will be two-tailed and $P < 0.05$ is considered statistically significant. The prevalence and pattern of missing values for each variable will be analysed.[56] If variables are not *missing completely at random* multiple imputation will be performed.[57,58]

Discussion

Trial intervention

Because PPI in the form of pantoprazole is the most frequently used SUP[54,59] we chose to assess pantoprazole.

Sample size

It is difficult to produce reliable sample size estimations according to anticipated effects on GI bleeding, because we do not have reliable data describing mortality among patients with risk factors for GI bleeding not treated with PPI due to the widespread use of PPI.[54]

We do not know whether PPI benefits or harms the patients, and need to include both scenarios.

The sample size has been calculated from data in the SUP-ICU cohort study (Study IV) on patients fulfilling inclusion and exclusion criteria in the SUP-ICU trial and because few patients were not treated with acid suppressants during ICU admission, the estimation is based on the group receiving acid suppressants (intervention group).

Table 2. Sample size estimations

ARR	Power	Patients per group
- 5%	80%	1091
	90%	1461
+ 5%	80%	1248
	90%	1671

TSA has highlighted that an information gap of around 3000 patients exists, which is why inclusion of an additional 3350 patients is expected to be adequate for the pooled effect to cross the boundary for benefit/harm or the boundary for futility. However, due to the fact that existing trials have high risk of bias we acknowledge that the information gap may be even larger.

Outcome considerations

It has been estimated that 39% of the patients receiving SUP in the ICU are discharged from the hospital with acid suppressants without an obvious indication for continuation of therapy.[60] Long-

term treatment with PPI is associated with several side effects e.g. an increased risk of fractures, hypomagnesaemia and rhabdomyolysis,[61,62] which may all have the potential to increase mortality. It is possible that PPI used as SUP reduces GI bleeding, but it may at the same time increase the risk of nosocomial infections and myocardial ischemia, and the overall effect on mortality is therefore unknown. Assessing mortality as the primary outcome will give us the opportunity to balance the sum of benefits and harms of PPI. Mortality has not been the primary outcome of previous trials and we are sceptical that these trials got reliable information on mortality other than short-term mortality (ICU/hospital), which may be biased mortality outcomes.[63–65] Nearly all previous trials assessing PPI or H2RA as SUP have had high risk of bias, which tend to overestimate benefit and underestimate harm.[63,66] Accordingly, previous trial results might be biased and even though they seem to find a neutral effect on mortality this may be a biased estimate actually concealing excess mortality in the SUP groups.[64]

The rationale for the choice of pneumonia, clostridium *difficile infection* and myocardial ischemia has previously been discussed. However, the power for even major effects on each of the possible side effects is small. To gain power on the potential harm of SUP we will report the outcomes as composite outcomes. All elements of the composite outcomes will be reported in the supplementary material of the primary publication.

Generalisability

RCTs are considered the 'gold standard' for evaluating interventions. They are aiming to maximise the internal validity, sometimes at the cost of limited generalisability due to specific inclusion and exclusion criteria that are often quite restrictive. The gained knowledge of risk factors for GI bleeding from the SUP-ICU research programme, including the inception cohort study was used to define the inclusion criteria resulting in inclusion of a broad population at risk of GI bleeding. Exclusion criteria are few, and represent patients with no indication for SUP in daily clinical practice, including patients already receiving acid suppressants. Consequently, we believe the SUP-ICU trial results will exhibit high external validity.

Discussion

Principal findings

The SUP-ICU research programme has provided contemporary data on GI bleeding and use of SUP in the ICU, and has highlighted that the quantity and quality of evidence supporting use of SUP in adult ICU patients is low.

The prevalence of GI bleeding

Data from Study IV outlined a contemporary prevalence of clinically important GI bleeding of 2.6% in general ICUs.[54] Importantly, conditions not prevented by acid suppressants e.g. variceal bleedings were also included. In 1994, Cook et al. reported a 1.5% prevalence of GI bleeding, and more than half of these patients received SUP before the bleeding episode.[7] Data by Cook et al. from 1999 support that sources of GI bleeding not prevented by SUP are frequent.[8] They identified stress ulcerations as the sole source of GI bleeding by endoscopy in less than 50% of the patients. Another study from 2001 including 1666 patients reported a slightly higher incidence of 3.5%, which could be explained by the fact that one of the inclusion criteria was mechanically ventilation for at least 48 hours, and hence a more severely ill population.[1] Consequently, the prevalence of GI bleeding in critically ill patients has not changed much the past 20 years.

Risk factors for GI bleeding in critically ill patients

Mechanically ventilation for more than 48 hours and coagulopathy are considered well-established risk factors for clinically important GI bleeding.[7] We did not identify mechanical ventilation as a risk factor in our cohort study. Case-mix may partly explain this, as 93% of the patients in our study were from mixed ICUs with a mortality rate of 25-35%,[54,67,68] whereas Cook et al. included primarily cardiovascular surgical patients with an all-cause mortality rate of less than 10%.[7] We found that SOFA score at the first day in ICU was independently associated with increased risk of clinically important GI bleeding. To the best of our knowledge this has not been reported previously, and suggests that severity of illness contributes or predisposes to the development of GI bleeding in critically ill patients. Furthermore, it supports the hypothesis that stress ulcerations are caused by ischemia and reperfusion injury and is not as related to acid secretion as peptic ulcers.

It has been suggested that patients not receiving enteral feeding have an increased risk of GI bleeding.[12,69] A systematic review by Marik et al. published in 2010 assessed this and found that SUP did not alter the risk of GI bleeding in patients enterally fed, but the combination of SUP and enteral feeding seemed to increase the risk of pneumonia and even death.[12] However, this was a subgroup analysis including just three trials. Furthermore, a predefined protocol was not published,

three trials were not identified, and the trials reporting enteral feeding did not have a pre-specified standardised protocol for administering enteral nutrition which could introduce a systematic error (bias). Despite these limitations and the ambiguous evidence of enteral nutrition, our survey reveals that clinicians take enteral nutrition into account when prescribing or discontinuing SUP.[59] Data from Study IV suggests that shock or circulatory support should be considered as risk factors for GI bleeding, which is consistent with the hypothesis of ischemia and reperfusion injury leading to stress ulcerations.[54] Coagulopathy, acute kidney injury and acute or chronic liver disease has previously been identified as risk factors for clinically important GI bleeding,[7,8,70] and since recent studies, including our cohort study, were able to confirm these findings, it appears that these factors are still valid.[19,54,70]

The prognostic importance of GI bleeding in critically ill patients

As described previously, GI bleeding in ICU patients has been considered a serious condition with increased mortality and excess length of ICU stay.[1,4] We confirmed a crude association between clinically important GI bleeding and increased mortality, but surprisingly, when adjusting for known confounders, including age, disease severity and comorbidities the association was no longer statistically significant, indicating that the excess mortality largely is explained by confounding and/or that the study was somewhat underpowered.[54] We believe that high-quality RCTs assessing mortality as the primary outcome measure are needed to confirm this finding.[64]

Stress ulcer prophylaxis

Acid suppressants are the most frequently prescribed off-label drugs in the ICU, and prophylaxis of stress ulcers the most frequent indication.[71] In a 2014 US survey, respondents indicated that a median of 90% of their ICU patients were started on SUP while in the ICU,[72] and Study III confirmed this finding. All but one of the participating ICUs reported use of SUP, but as described previously, indications varied considerably.[59] Other studies have highlighted that inappropriate use is common[73] and a 2013 study found that more than 60% of ICU patients treated with acid suppressants were discharged from the ICU without discontinuation of the drug. In 39% of these patients acid suppressants are unnecessarily continued at hospital discharge.[60] During the previous ten years the sale of PPI in Denmark has increased by 213%[74] and failure to discontinue PPI at discharge from hospital undoubtedly contributes to unnecessary long-term treatment. Besides increased cost for the patient and the society there is a risk of interactions and long-term side-effects related to continued use of acid suppressants.[75–77]

Current evidence for the use of SUP

For years, RCTs and systematic reviews have sought to provide evidence for a clinical benefit of acid suppressants compared with placebo or no prophylaxis.[5,12,17,78] However, as concluded in Study I and II, the evidence supporting use of SUP in ICU patients is low. No previous systematic review has assessed PPI versus placebo or no prophylaxis. Only two RCTs have assessed PPI; one of them was a pilot-study and altogether they comprise less than 400 patients,[17,79] which according to our sample size estimations are far from enough to draw valid conclusions on benefits and harms of SUP. Following Study II, one additional trial assessing PPI versus placebo in patients with intracerebral haemorrhage has been published,[78] and a recently published systematic review assessed PPI or H2RA versus placebo or no prophylaxis in adult neurocritical care patients.[80] The authors concluded that SUP is superior to placebo/no prophylaxis in reducing GI bleeding and all-cause mortality, while not increasing the risk of nosocomial pneumonia. However, this review holds important methodological limitations, as all included trials had high risk of bias, no predefined sensitivity analysis with continuity correction in the zero event trials was planned or performed, and the risk of random errors using TSA was not assessed.[81] Applying TSA to the three trials with lowest risk of bias[80] suggests that an estimated required information size of 2005 patients and 1790 patients are needed to confirm or reject a 20% RRR in GI bleeding and all-cause mortality, respectively. Consequently, the cumulative meta-analysis presented, comprising 829 patients, is severely underpowered, with high risk of presenting spurious findings.[81,82]

No other systematic reviews on SUP versus placebo/no prophylaxis in critically ill patients have been published, highlighting the fact that only few small high-risk of bias trials have been conducted after 2010.[78] In contrast, PPI and H2RA have been compared in several RCTs and meta-analyses.[17,18,23,83] The most recent meta-analysis (14 trials) was conducted in 2013 by Alhazzani et al., and found that PPI was more effective than H2RA in reducing both clinically important and overt GI bleeding.[18] However, whether PPIs are superior to H2RAs may not be relevant when H2RAs have not unequivocally been shown to be superior to placebo.

Conclusion

The SUP-ICU research programme has paved the ground for a large RCT with low risk of bias assessing the benefits and harms of SUP in adult critically ill patients by summarising existing data on GI bleeding and SUP in ICU patients, and by providing estimates on use of SUP and the prevalence of GI bleeding in contemporary ICUs.

Implications for research

The SUP-ICU research programme has provided a solid base for the design and conduct of a high-quality RCT of SUP versus placebo, which can provide important data on benefits and harms of prophylactic use of acid suppressants in adult critically ill patients. RCTs reporting long-term consequences of treatment with SUP, and studies focusing on low-risk vs. high-risk patients are warranted. Assessment of the benefits and harms of SUP in subgroups of ICU patients is of interest, and risk stratification upon ICU admission may be clinically relevant. Furthermore, following completion of the SUP-ICU trial, an updated systematic review of SUP with PPI versus placebo/no prophylaxis is needed.

Clinical implications

Acid suppressants are the most frequently prescribed off-label drugs in the ICU, and prophylaxis of stress ulcers the most frequent indication.[71] However, the prevalence of clinically important GI bleeding is low and there is no firm evidence for benefit or harm of SUP in adult critically ill patients. Accordingly, routine use of SUP in adult ICU patients is discouraged. The SUP-ICU research programme and the actively recruiting SUP-ICU trial will inform clinicians, guideline committee members and policy-makers on clinical use of prophylactic PPI in the ICU, as well as increase the quality of evidence on this topic.

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Conflicts of interest

None

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Paper I

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Review Article

Stress ulcer prophylaxis in the intensive care unit: is it indicated? A topical systematic review

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Stress ulcer prophylaxis (SUP) is regarded as standard of care in the intensive care unit (ICU). However, recent randomized, clinical trials (RCTs) and meta-analyses have questioned the rationale and level of evidence for this recommendation. The aim of the present systematic review was to evaluate if SUP in the critically ill patients is indicated. *Data sources:* MEDLINE including MeSH, EMBASE, and the Cochrane Library. *Participants:* patients in the ICU. *Interventions:* pharmacological and non-pharmacological SUP. *Study appraisal and synthesis methods:* Risk of bias was assessed according to Grading of Recommendations Assessment, Development, and Evaluation, and risk of random errors in cumulative meta-analyses was assessed with trial sequential analysis. A total of 57 studies were included in the review. The literature on SUP in the ICU includes limited trial data and methodological weak studies. The reported incidence of gastrointestinal (GI) bleeding varies considerably. Data on the incidence and severity of GI bleeding in general ICUs in the developed world as of today are lacking. The best intervention for SUP is yet to be settled by balancing efficacy and harm. In essence, it is unresolved if intensive care patients benefit overall from SUP. The following clinically research questions are unanswered: (1) What is the incidence of GI bleeding, and which interventions are used for SUP in general ICUs today?; (2) Which criteria are used to prescribe SUP?; (3) What is the best SUP intervention?; (4) Do intensive care patients benefit from SUP with proton pump inhibitors as compared with other SUP interventions? Systematic reviews of possible interventions and well-powered observational studies and RCTs are needed.

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Critically ill patients are at risk of stress-related gastrointestinal (GI) mucosal damage, which can progress to ulceration and GI bleeding. One of the first reports on GI stress ulcerations in patients in the intensive care unit (ICU) was published by Skillman and colleagues in 1969.[1] In 7 out of 150 patients (5%) with the triad of respiratory failure, sepsis, and hypotension, post-mortem examination revealed multiple superficial ulcers in the gastric mucosa. Following this report, older clinical trials have suggested that stress ulcer prophylaxis (SUP) can reduce the frequency of GI bleeding in ICU patients compared with placebo or no prophylaxis.[2–7] Based on this research, SUP is regarded as the standard of care in ICU, as outlined by the Joint Commission,* the Institute for Healthcare Improvement, and in the Surviving Sepsis Campaign guidelines.[8] A number of randomized, clinical trials (RCTs) and meta-analyses have sought to determine the best SUP agent by balancing benefit and harm.[9–12] However, recent research has questioned the rationale and level of evidence of SUP for ICU patients because of limited data and methodological flaws in some of the trials.[9–12]

The aim of the present review was to highlight the unanswered clinical research questions on SUP in ICU patients. We hypothesized that the rationale of SUP in the ICU is widely unresolved and that the level of evidence is low.

Methods

This review has been prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[13] and was registered in the Prospective Register of Systematic Reviews (PROSPERO), no. CRD42012002579.

**The Joint Commission. http://www.jointcommission.org/ [Accessed 15 November 2012].*

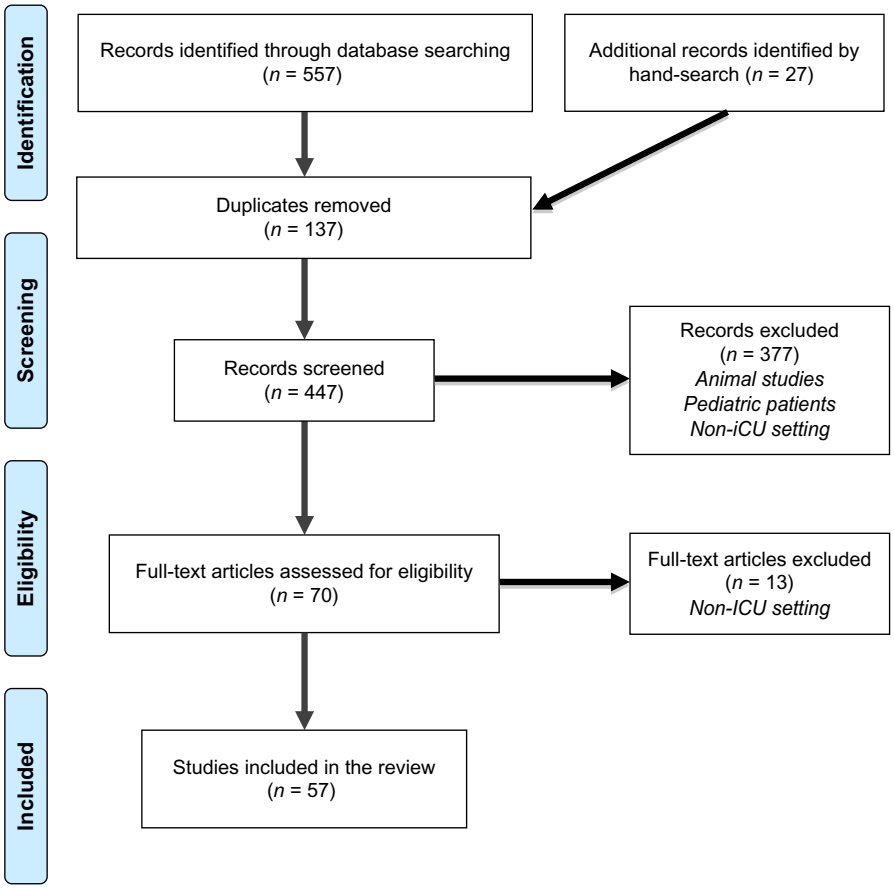

Fig. 1. Flow diagram of retrieved studies. ICU, intensive care unit.

We framed the following focused research question: Is SUP in critically ill patients indicated? A population, intervention, comparator, and outcomes–based (PICO) question and literature search were created:[14]

-*Population*: critically ill OR ICU OR intensive care unit OR intensive care

-*Intervention*: stress ulcer prophylaxis OR SUP

-*Comparator*: any

-*Outcomes*: mortality OR death OR GI bleeding OR gastrointestinal bleeding OR pneumonia OR morbidity OR clostridium difficile

Using this search string, the following databases were searched for literature: MEDLINE including MeSH (January 1966 to May 2012), EMBASE (January 1980 to May 2012), and the Cochrane Library (Issue 2, 2012). No study designs were *per se* excluded of the review. The search resulted in 557 hits. In addition, we hand-searched reference lists of relevant publications. A total of 57 studies were included in the review, see Fig. 1 and Table 1.

The level of evidence of the primary studies (observational studies and RCTs) was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE),[15] see Table 2. Based on the evaluation of five quality domains: (1) risk of bias, (2) imprecision, (3) inconsistency, (4) indirectness, and (5) publication bias, GRADE rates the quality of evidence as high, moderate, low, or very low. Furthermore, we evaluated the level of evidence of the cumulative meta-analyses histamine 2 receptor antagonists (H2RAs) vs. proton pump inhibitors (PPIs) and H2RAs vs. placebo by assessing the risk of random errors using trial sequential analysis (TSA).[16,17] We selected the two comparisons to be evaluated by TSA, as we anticipated them to be the two most frequently used SUP interventions in the ICU. In TSA, the addition of each trial in a cumulative meta-analysis is regarded as an interim meta-analysis and helps to clarify whether additional trials are needed. The idea in TSA is that if the cumulative *z*-curve crosses the boundary, a sufficient level of evidence is reached, and no further trials may be needed (firm evidence). If the *z*-curve does not cross the boundary, then there is insufficient evidence to reach a conclusion. To construct the trial sequential monitoring boundaries, the required information size is

Table 1

Overview of included studies.

Study	Year	Design	*n*	Country
Ali and Harty[29]	2009	Review	–	United States
Andersson et al.[26]	2005	Observational study	6119	Sweden
ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis[24]	1999	Guideline	–	United States
Ashraf and Ostrosky-Zeichner[45]	2012	Review	–	United States
Azevedo et al.[54]	1999	Randomized, clinical trial	108	Brazil
Baghaie et al.[33]	1995	Randomized, clinical trial	15	United States
Bavishi and Dupont[50]	2011	Systematic review	–	United States
Ben-Menachem et al.[23]	1994	Randomized, clinical trial	300	United States
Bhatt et al.[52]	2010	Randomized, clinical trial	3873	United States
Brett et al.[39]	2005	Review	–	United Kingdom
Bruno et al.[55]	2009	Observational study	100	United States
Choung and Talley[25]	2008	Review	–	United States
Conrad et al.[56]	2005	Randomized, clinical trial	359	United States
Cook et al.[3]	1996	Systematic review	7218	Canada
Cook et al.[4]	1991	Systematic review	4409	Canada
Cook et al.[18]	2001	Observational study	1666	Canada
Cook et al.[19]	1994	Observational study	2252	Canada
Cook et al.[20]	1999	Observational study	1077	Canada
Cook et al.[36]	1998	Randomized, clinical trial	1200	Canada
D'Ancona et al.[57]	2003	Observational study	11,058	Canada
Dellinger et al.[8]	2008	Guideline	–	United States
Driks et al.[46]	1987	Randomized, clinical trial	130	United States
Eddleston et al.[21]	1994	Randomized, clinical trial	26	United Kingdom
Ellison et al.[30]	1996	Observational study	874	United States
Faisy et al.[27]	2003	Observational study	3473	France
Fohl and Regal[32]	2011	Review	–	United States
Guyatt et al.[14]	2011	Guideline	–	Canada
Huang et al.[9]	2010	Systematic review	2092	China
Hurt et al.[43]	2012	Review	–	United States
The Joint Commission*	2012	Guideline	–	United States
Kantorova et al.[41]	2004	Randomized, clinical trial	287	Czech Republic
Koretz[44]	2009	Review	–	United States
Laine and Jensen[34]	2012	Guideline	–	United States
Lasky et al.[6]	1998	Observational study	60	United States
Leonard et al.[49]	2007	Systematic review	2948	Canada
Levy et al.[58]	1997	Randomized, clinical trial	67	United States
Lin et al.[10]	2010	Systematic review	936	Taiwan
Marik et al.[11]	2010	Systematic review	1836	United States
Martin[22]	1994	Randomized, clinical trial	100	United States
Messori et al.[37]	2000	Systematic review	2760	Italy
Miano et al.[48]	2009	Observational study	834	United States
Moher et al.[13]	2009	Guideline	–	Canada
Phillips et al.[7]	1996	Clinical trial	75	United States
Phillips et al.[59]	1998	Randomized, clinical trial	58	United States
Powell et al.[60]	1993	Randomized, clinical trial	41	United States
Prod'hom et al.[47]	1994	Randomized, clinical trial	244	Switzerland
Quenot et al.[12]	2009	Review	–	France
Sesler[28]	2007	Review	–	United States
Shuman et al.[2]	1987	Systematic review	2133	United States
Skillman et al.[1]	1969	Observational study	150	United States
Somberg et al.[61]	2008	Randomized, clinical trial	202	United States
Tryba[5]	1991	Systematic review	–	Germany
van Boxel et al.[51]	2010	Observational study	18,139	the Netherlands
Wilson[35]	1987	Review	–	United States
Zandstra and Stoutenbeek[62]	1994	Observational study	183	the Netherlands
Zinner et al.[42]	1989	Randomized, clinical trial	281	United States

–, not available.

calculated as the minimum number of participants needed in a well-powered single trial.[17,†] We used trial sequential monitoring boundaries according to a required diversity-adjusted information size based on an *a priori* 30% relative risk (RR) reduction,

†*Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for trial sequential analysis (TSA). Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark. 2011. p. 1–115. http://www.ctu.dk/tsa/ [Accessed 4 March 2013].*

Table 2

Rating the quality of evidence.

Study design	Quality of evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias –1 Serious –2 Very serious Inconsistency –1 Serious –2 Very serious Indirectness –1 Serious –2 Very serious Imprecision –1 Serious –2 Very serious Publication bias –1 Likely –2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Moderate		
Observational study →	Low		
	Very low		

From 'GRADE Guidelines 3: Rating the quality of evidence' by Balshem et al.[15]

employing $\alpha = 0.05$ and $\beta = 0.20$, and a Diversity found in the actual meta-analysis. We used the control event proportion suggested by all the available trial data.

Definitions

-*Stress ulceration*: Single or multiple mucosal defects, which can be complicated by GI bleeding during physiological stress in critically ill patients.

-*Occult GI bleeding*: A positive fecal or aspirate occult blood test without overt GI bleeding.

-*Overt GI bleeding*: Hematemesis, coffee ground emesis, melena, hematochezia, or bloody nasogastric aspirate.

-*Clinically important (significant) GI bleeding*: Overt GI bleeding and at least one of the following four features within 24 h of GI bleeding (in the absence of other causes): (1) spontaneous drop of systolic or diastolic blood pressure of 20 mmHg or more; (2) orthostatic increase in pulse rate of 20 beats per minute and a decrease in systolic blood pressure of 10 mmHg; (3) decrease in hemoglobin of at least 2 g/dl (1.24 mM); or (4) transfusion of 2 units of packed red blood cells or more.[18–20]

-*GUP*: Pharmacological and non-pharmacological methods of preventing stress ulcerations.

-*Critically ill patients*: Patients hospitalized in the ICU.

-*TSA*: A statistical tool combining a required information size calculation for meta-analyses with a threshold of statistical significance. TSA quantifies the statistical reliability of data in a cumulative meta-analysis, adjusting significance levels for sparse data, and repetitive testing on accumulating data.[16]

Stress ulcerations in the ICU

Epidemiology

Determining the incidence of GI bleeding in critically ill patients in the ICU is complicated by varying definitions of the outcome, difficulties in measuring the outcomes, and heterogeneity of the patient populations. Endoscopic studies have shown that gastric erosions are present in 10–25% of patients upon ICU admission and in up to 90% of patients by the third day in ICU.[21,22] In older RCTs and observational studies, the reported incidences of overt GI bleeding ranged from 1.5% to 8.5% among all ICU patients and were up to 15% among patients who do not receive SUP.[2,18,19,23] It has been suggested that the incidence of stress ulcer bleeding has decreased over time. In studies published before 1999, the reported incidence of clinically important GI bleeding in patients not receiving SUP ranges from 2% to 6%.[24] After the millennium, the reported incidence varies between 0.1% and 4% depending on the use of SUP.[25–27] In Table 3, the incidence of overt GI bleeding reported in recent observational studies is summarized. As outlined in the table, there are very limited observational data from multicenter studies in European general ICUs. In conclusion, as a result of substantially changed intensive care and practice through the last 10–20 years, the incidence of stress ulcerations in critically ill patients may have changed. However, we do not know, and the incidence of stress ulcerations in the 21st century is unknown.

Pathophysiology

Most episodes of overt GI bleeding in critically ill patients are due to gastric or esophageal ulcera-

Table 3

The incidence of overt GI bleeding in observational studies in critically ill patients.

Study	*n*	Population	Country	Design	GI bleeding incidence (%)	GI bleeding definition	GRADE rating[15]
Andersson 2005[26]	6.119	Post-cardiac surgery	Sweden	Prospective cohort study	0.3	Hematemesis, melena, or rectal bleeding, and transfusion of ≥ 2 units of blood	Low
Bruno et al. 2009[55]	100	Oncology in ICU	USA	Prospective cohort study	1.0	Clinically important*	Very low
Cook et al. 1994[19]	2.252	ICU	Canada	Prospective cohort study	1.5	Clinically important*	Moderate
Cook et al. 2001[18]	1.666	ICU	Canada	Prospective cohort study	3.5	Clinically important*	Moderate
D'Ancona et al. 2003[57]	11.058	Post-cardiac surgery	Canada	Prospective cohort study	0.3	None	Low
Faisy et al. 2003[27]	737	Medical ICU	France	Case-control study	1.1	Clinically important*	Low
Zandstra and Stoutenbeek 1994[62]	183	ICU and ≥ 48 h of mechanical ventilation	the Netherlands	Prospective cohort study	0.6	Bleeding from the upper GI tract and need of transfusion or bleeding mucosal lesions on endoscopy or mucosal lesions in the GI tract on post-mortem investigation	Very low

*Overt GI bleeding and at least one of the following four features within 24 h of GI bleeding (in the absence of other causes): (1) spontaneous drop of systolic or diastolic blood pressure of 20 mmHg or more; (2) orthostatic increase in pulse rate of 20 beats per minute and a decrease in systolic blood pressure of 10 mmHg; (3) decrease in hemoglobin of at least 2 g/dl (1.24 mM); or (4) transfusion of 2 units of packed red blood cells.

GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICU, intensive care unit.

tion.[18,19] Stress ulcerations are believed to result from an imbalance between mucosal protection and gastric acid production. Critical illness results in splanchnic hypoperfusion because of sympathetic nervous system activation, increased catecholamine release, and vasoconstriction. This leads to decreased gastric motility, delayed removal of acidic material, and impaired mucosal healing. Another important factor may be reperfusion injury. As blood flow is restored after periods of hypoperfusion, increased expression of nitric oxide synthase leads to hyperemia, cell death, and enhanced inflammation.[28] Hence, gastric ischemia and reperfusion result in mucosal injury, which may progress to significant mucosal damage and GI bleeding through acid secretion.[29]

Risk factors

A number of risk factors for overt GI bleeding have been identified. In a landmark, multicenter, prospective cohort study from 1994 comprising 2.252 ICU patients, Cook et al. identified mechanical ventilation ≥ 48 h [odds ratio (OR) 15.6] and coagulopathy (OR 4.3) as the two major risk factors for stress-related GI bleeding.[19] The incidence of clinically important GI bleeding among patients with one or both of these risk factors was 3.7% as compared with 0.1% among patients with neither of the risk factors. In a subsequent prospective, multicenter cohort study from 1996 ($n = 874$ and a 9% incidence of GI bleeding), several factors were found to be associated with increased risk of overt GI bleeding in multivariate analysis: acute hepatic failure (OR 6.7), nasogastric tube placement ≥ 5 days (OR 2.6), a history of alcohol abuse (OR 2.2), chronic renal failure (OR 3.0), and positive *Helicobacter pylori* serology (OR 1.9).[30] Despite using bootstrapping to validate the findings in this study, an increased risk of bias exists. With 35 tested variables, a two-sided alpha of 0.05, a power of 80%, and an anticipated small effect size, more than 1.300 patients would be needed to reduce the risk of multiple testing and type I errors,[31] so the study is underpowered by more than 400 patients. In another large cohort study by Cook and colleagues from 1999 ($n = 1.077$), acute kidney injury (RR and 95% confidence interval 1.16, 1.02–1.32) was independently associated with increased risk of GI bleeding in patients mechanically ventilated ≥ 48 h.[20] Other factors that have been associated with increased risk of GI bleeding in older and smaller – often methodological weak – studies include: severe head or spinal cord injury, thermal

injury involving more than 35% of the body surface area, surgery lasting more than 4 h, high-dose corticosteroids, and acute lung injury.[24]

In conclusion, mechanical ventilation ≥ 48 h and coagulopathy are the two major risk factors for stress-related GI bleeding.

Prognosis

Overt GI bleeding because of stress ulceration is associated with increased mortality. Cook et al. ($n = 2.252$) found that the mortality rate in ICU patients with clinically important GI bleeding was 49% as compared with 9% in those without GI bleeding ($P < 0.001$).[19] In another study, Cook and colleagues examined mortality and length of stay in the ICU in two multicenter databases ($n = 1.666$). They demonstrated that clinically important GI bleeding was associated with a significant increase in risk of mortality (RR 1.8–4.9) and 4–8 days longer stay in the ICU.[18]

SUP in the ICU

Pharmacological and non-pharmacological SUP agents

H2RAs. H2RAs have been widely used for acid suppression. H2RAs inhibit the stimulation of the H^+-K^+-adenosine triphosphatase (ATPase) by binding to the H2 receptor on the parietal cells.[32] This results in diminished gastric acid secretion. H2RAs can be administered enterally or intravenously, and continuous intravenous infusion is more effective than bolus injections at controlling gastric pH.[33]

PPIs. PPIs are among the most frequently prescribed drugs in the world.[32] They inhibit secretion of gastric acid by forming irreversible disulfide bonds with the H^+-K^+-ATPase pump. This leads to inhibition of the secretion of gastric acid. PPIs can be administered enterally or intravenously, and continuous intravenous infusion is more effective than bolus injections at controlling gastric pH.[34]

Sucralfate. Sucralfate is a basic aluminum salt. It coats the gastric mucosa and forms a thin protective layer between the mucosa and the gastric acid in the lumen without altering gastric acid secretion or buffering acid. Sucralfate can only be administered enterally.[32]

Antacids. Antacids neutralize gastric acid and inactivate the proteolytic enzyme of pepsin. They must be administered intragastrically at intervals of 1–2 h either orally or via nasogastric tube, and the dose depends on gastric pH, thus requiring frequently monitoring and dose titration. Antacids are not widely used for SUP in the ICU.[32]

Prostanoids. Prostanoids inhibit gastric acid secretion by selectively reducing the ability of the parietal cell to generate cyclic adenosine monophosphate in response to histamine and exert a cytoprotective effect by enhancing mucosal defense mechanisms.[35] They have not been extensively studied for use in SUP.

Enteral nutrition. Enteral nutrients buffer acid and may act as a direct source of energy for the mucosa, induce the secretion of cytoprotective prostaglandins and mucus, and increase mucosal blood flow.[11] Furthermore, the stress-triggered vagal stimulation may be blunted by enteral nutrition.[11]

In conclusion, H2RAs and PPIs are believed to be the two major SUP agents used; however, the distribution is currently unknown.

Efficacy of SUP

H2RAs vs. sucralfate or placebo. Several trials have compared sucralfate and H2RAs. Cook et al. conducted a multicenter, blinded RCT in 1.200 patients requiring mechanical ventilation.[36] Patients receiving H2RAs had a significantly lower incidence of clinically important GI bleeding than those receiving sucralfate. There were no significant differences in length of stay in the ICU, incidence of ventilator-associated pneumonia (VAP), or mortality.

In another fairly large RCT by Ben-Menachem et al., H2RA, sucralfate, and placebo were compared in 300 patients in a medical ICU in the United States.[23] No differences in incidence of stress-related hemorrhage and transfusion requirements, duration of stay, or nosocomial pneumonia were observed, but the trial may not have been powered to show clinically relevant differences in these outcomes.

In 2000, Messori et al. published a meta-analysis comparing H2RA, sucralfate, and placebo for the prevention of stress ulcerations ($n = 2.814$).[37] The authors concluded that trial data were too flawed to conclude on the better SUP agent and if SUP is needed in critically ill patients at all. In 2010, Huang et al. summarized existing evidence of H2RA vs. sucralfate.[9] They pooled 10 RCTs ($n = 2.092$) and concluded that no difference in the incidence of overt GI bleeding was observed. Furthermore, they asked for additional RCTs in order to establish the

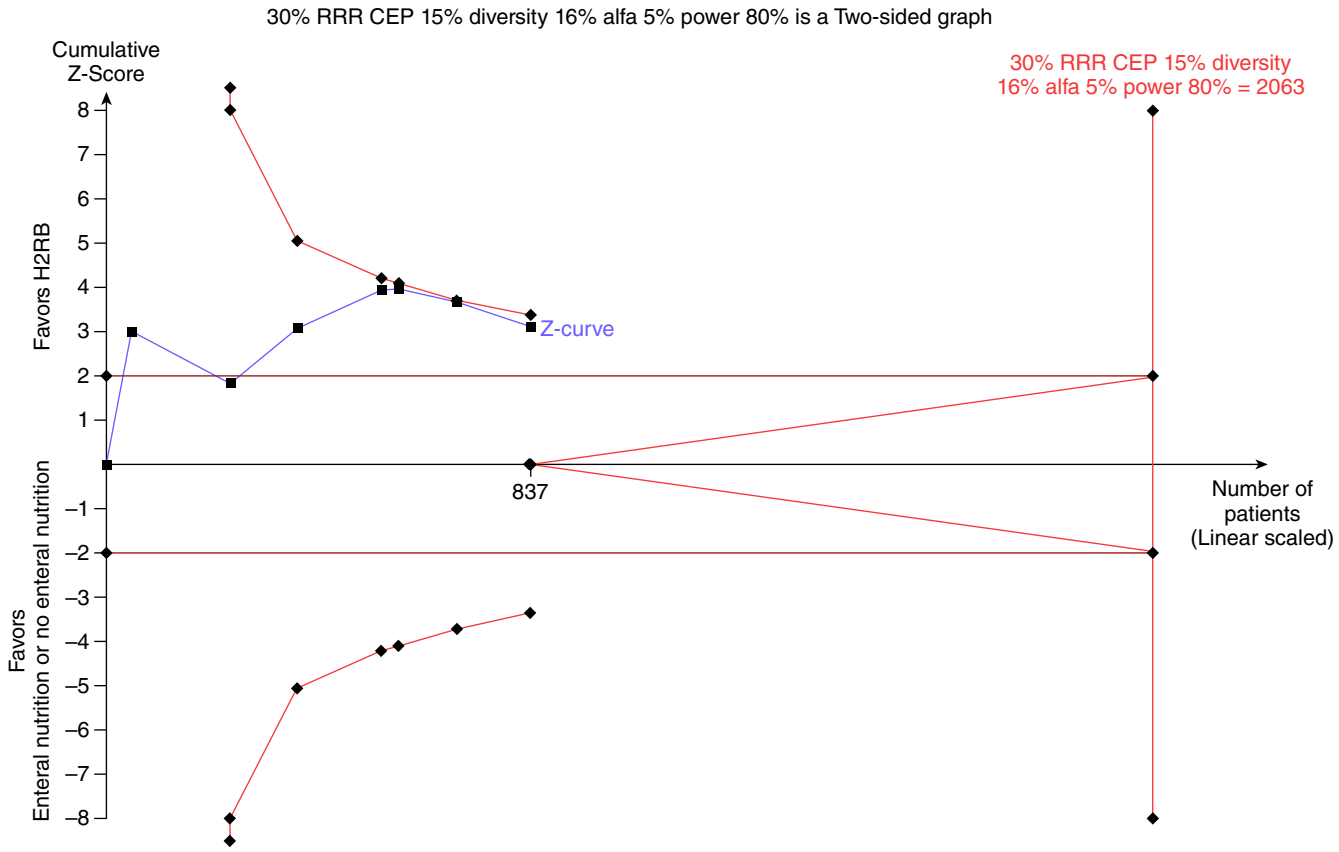

Fig. 2. Trial sequential analysis (TSA) of seven trials with least methodological bias and a Jadad score of 5.[38] Comparison of the effect of histamine 2 receptor antagonists (H2RAs) vs. placebo or sucralfate on the risk of gastrointestinal (GI) bleeding in a setting of no enteral nutrition. The required information size – anticipating a realistic 30% relative risk (RR) reduction, a heterogeneity with a diversity of 16% found in the trials, a control event proportion of 16%, and a risk of types 1 and 2 errors of 5% and 20%, respectively – is 2.063. The cumulative z-curve (—■—) in random-effects models after 837 randomized patients does not cross the boundary for benefit (—◆—). Even though there is a statistically significant effect of H2RA in a traditional random-effects meta-analysis with an RR of 0.42 [95% confidence interval (CI) 0.25–0.73], this is not confirmed in TSA (TSA-adjusted 95% CI 0.17–1.07). In conclusion, there is no firm evidence that H2RAs reduce the incidence of GI bleeding with a 30% RR reduction in the trials with lowest risk of bias.

net benefit and risks of H2RAs and sucralfate in mechanically ventilated patients. Finally, in a 2010 meta-analysis of H2RA vs. placebo, Marik et al. found that H2RA significantly reduced the risk of GI bleeding as compared with placebo ($n = 1.836$).[11] However, in the subgroup of patients receiving enteral nutrition, there was a signal of increased mortality with H2RA compared with placebo. Furthermore, in the trials with least risk of bias (Jadad score[38] of 5), TSA showed that the cumulative z-curve did not cross the trial sequential monitoring boundary for benefit. This indicates lack of firm evidence that H2RAs reduces GI bleeding even in patients not receiving enteral nutrition, see Fig. 2.

Taken together, there seems to be lack of reliable evidence of the efficacy of H2RAs vs. sucralfate (low level of evidence). Likewise, there seems to be low level of evidence for the use of H2RAs, as compared with placebo, in terms of reduced clinically significant GI bleeding. As this outcome measure has not been established as patient-important, the level of evidence may be downgraded because of indirectness (very low level of evidence).

PPIs vs. H2RAs or placebo. Today, PPIs are considered the drug of choice in the management of most acid-related GI disorders.[39] The superior efficacy of PPIs over H2RAs has been demonstrated in various GI disorders, including peptic ulcer disease, gastroesophageal reflux disease, and GI damage caused by nonsteroidal anti-inflammatory drugs.[39] However, the evidence for the use of PPIs in intensive care patients is limited. A recent meta-analysis comprising seven RCTs and 936 ICU patients (the character-

istics of the RCTs are shown in Table 4) compared PPIs and H2RAs.[10] The analysis did indicate a statistically significant difference in the incidences of clinically important GI bleeding in a random-effects model of RR but not in the incidences of pneumonia or mortality. However, the number of events was very small,[40] and TSA reveals lack of firm evidence that PPI reduces GI bleeding compared with H2RA, see Fig. 3. The authors themselves also concluded that evidence is inconclusive because of underpowered trials with limited data and inconsistent results.

In a four-armed, single-center RCT of 287 ICU patients, PPI was compared with placebo, sucralfate, and H2RA, respectively.[41] No differences in clinically important GI bleeding were observed, but the trial was not powered to show clinically important differences. To be able to detect a significant difference [15% RR reduction, $\alpha = 0.05$ (two-sided), and 80% power] in a composite outcome of mortality and clinically important GI bleeding, more than 1000 patients will be needed in a trial with two intervention groups.

In conclusion, the level of evidence for the use of PPIs for SUP in the critically ill patients is low (Table 2). There is lack of firm evidence that PPI reduces GI bleeding compared with H2RA or placebo in ICU patients.

Sucralfate vs. antacids. In 1996, Cook et al. reviewed existing RCTs of SUP in the critically ill[3] ($n = 7.218$). They found that patients receiving antacids, as compared with sucralfate, did not have a statistically significant lower rate of clinically important GI bleeding. When compared with placebo, antacids did not result in a statistically significant reduced incidence of GI bleeding (moderate level of evidence).

Misoprostol vs. antacids. No statistically significant differences were identified in a single RCT ($n = 281$) comparing antacid titration with fixed doses of misoprostol for preventing stress gastritis and bleeding[42] (moderate level of evidence).

Enteral nutrition. A number of smaller trials and several animal studies suggest that enteral nutrition provides protection against stress gastropathy.[43] It has been suggested that continuous enteral nutrition is more likely to raise gastric pH above 3.5 than H2RAs and PPIs, and that early enteral nutrition is more effective in preventing overt GI bleeding than H2RA and antacids.[11] However, the studies are limited by their retrospective nature, lack of rand-

Table 4

Overview of existing randomized, clinical trials evaluating the benefit and harm of proton pump inhibitors.

Study	*n*	Population	Intervention	Comparator	Outcome			GRADE rating[15]
					Mortality RR (95% CI)	GI bleeding RR (95% CI)	Pneumonia RR (95% CI)	
Azevedo et al. 1999[54]	108	ICU	Omeprazol IV	Ranitidin IV	–	–	1.25 (0.36–4.30)	Low
Conrad et al. 2005[56]	359	ICU	Omeprazol NG	Cimitidin IV	1.31 (0.77–2.22)	0.71 (0.28–1.83)	1.20 (0.65–2.21)	Low
Kantorova et al. 2004[41]	287	Surgical ICU	Omeprazol IV	Famotidine IV/sucralfate/placebo	0.89 (0.38–2.05)	0.49 (0.05–5.32)	1.13 (0.43–2.94)	Low
Levy et al. 1997[58]	67	ICU	Omeprazol PO	Ranitidin IV	1.00 (0.52–1.95)	0.20 (0.05–0.83)	0.22 (0.03–1.77)	Very low
Phillips et al. 1998[59]	58	ICU	Omeprazol NG	Ranitidine IV	–	0.03 (0.01–0.22)	1.14 (0.36–3.60)	Very low
Powell et al. 1993[60]	41	Post-cardiac surgery	Omeprazol IV	Ranitidin IV/placebo	–	–	–	Very low
Somberg et al. 2008[61]	202	ICU	Pantoprazol IV	Cimitidin IV	–	–	0.14 (0.09–0.23)	Low

CI, confidence interval; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; ICU, intensive care unit; IV, intravenous; NG, nasogastric; RR, relative risk.

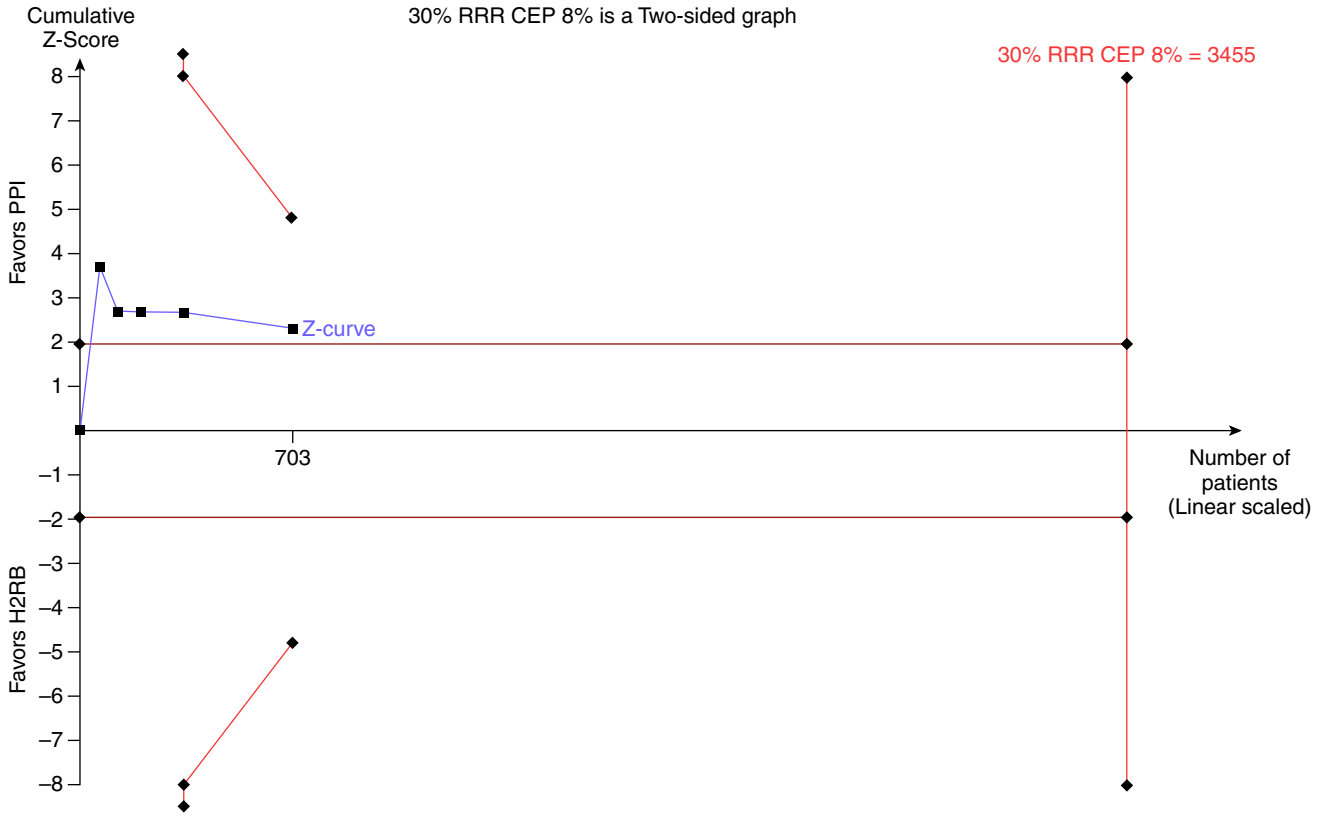

Fig. 3. Trial sequential analysis (TSA) of five trials, comparing the efficacy of proton pump inhibitors (PPIs) vs. histamine 2 receptor antagonists (H2RAs) on gastrointestinal (GI) bleeding. The required information size – anticipating a realistic 30% relative risk (RR) reduction, a heterogeneity with a diversity of 0% found in the trials, a control event proportion of 8%, and a risk of types 1 and 2 errors of 5% and 20%, respectively – is 3.455. The cumulative z-curve (—■—) in random-effects models does not cross the trial sequential monitoring boundary for benefit (—◆—). Even though there is a statistically significant effect of PPI in a traditional random-effects meta-analysis after 703 randomized patients with an RR of 0.44 [95% confidence interval (CI) 0.22–0.88], this is not confirmed in TSA (TSA-adjusted 95% CI 0.08–2.46). In conclusion, there is no firm evidence that PPIs reduce the risk of GI bleeding with 30% RR reduction compared with H2RAs.

omization, and their selection of acid suppressive therapy for the control group[43] (very low/low level of evidence).[44] Hence, an adequately powered RCT is needed to evaluate the efficacy of enteral nutrition vs. acid suppressive therapy in prevention of stress-related mucosal disease.[43]

Harm

Nosocomial pneumonia. Nosocomial infections are a significant in-hospital burden, and VAP is the most common nosocomial infection in the ICU, reaching 10–20% in patients receiving mechanical ventilation for more than 48 h.[45] It has been suggested that the SUP agents that increase gastric pH (PPIs, H2RAs, and antacids) may increase the frequency of nosocomial pneumonia compared with agents that do not alter gastric pH (sucralfate).[3,37,46,47] A meta-analysis by Cook et al. from 1996 ($n = 7.218$) revealed a nonstatistically significant higher incidence of nosocomial pneumonia in patients receiving H2RAs or antacids than in those receiving sucralfate.[3] In their RCT of H2RA vs. sucralfate in 1200 critically ill patients requiring mechanical ventilation from 1998,[36] there was no difference in the incidence of VAP between the two groups. In a 2010 meta-analysis by Huang et al. ($n = 2.092$), there was a statistically significant higher rate of VAP in the H2RA group as compared with the sucralfate group.[9] However, the majority of the included studies were performed before 2000. Marik et al. compared the incidence of VAP in patients receiving SUP with H2RA vs. placebo in a meta-analysis of 17 studies with a total of 1.836 patients, in 9 of which ($n = 1.157$) the incidence of nosocomial pneumonia was reported.[11] Overall, H2RAs did not increase the

risk of nosocomial pneumonia, but in the subgroup of patients who received both H2RA and enteral nutrition, the incidence of nosocomial pneumonia was increased, OR 2.81 (1.20–6.56). However, this subgroup finding is limited by the fact that no test of interaction was reported (low/moderate level of evidence).

The risk of VAP in patients receiving PPI is sparsely described. In a case-control study by Miano et al., cardiothoracic surgical patients receiving pantoprazole ($n = 377$) were compared with patients receiving ranitidine ($n = 457$).[48] Nosocomial pneumonia was observed in 35 out of 377 (9.3%) in the PPI group and in 7 out of 457 (1.5%) in the H2RA group ($P < 0.0005$). Limitations of this study include confounding, limited external validity (single-center study), and no causal relationship because of the observational study design (very low/low level of evidence).

In conclusion, RCTs are needed to assess if PPIs increase the risk of nosocomial pneumonia.

Clostridium difficile *enteritis.* Inhibition of the gastric acid may lead to increased risk of enteric infections. Gastric acid is an important barrier to colonization and infections by invading pathogens.[32] In a meta-analysis from 2007 ($n = 2.948$), Leonard et al. found a significantly increased risk of *Clostridium difficile* enteritis in non-ICU patients receiving H2RA or PPI as compared with placebo.[49] In a 2011 meta-analysis, Bavishi and Dupont found a statistically significant increased risk of *Clostridium difficile* enteritis in 17 out of 27 non-ICU studies.[50] We did not identify any studies reporting the incidence of *Clostridium difficile* infection among ICU patients receiving SUP (low/moderate level of evidence).

Cardiovascular events. An association between PPIs and increased risk of cardiovascular events in patients receiving clopidogrel have been suggested.[11,51] It may be that PPIs reduce the antiplatelet effects of clopidogrel, by interaction with the cytochrome P450 (CYP450) enzyme complex in the liver.[51] In a case-control study of 18.130 clopidogrel users, use of coexisting PPI was associated with an increased risk of cardiovascular complications.[51] However, in the only RCT published, no cardiovascular interaction between clopidogrel and PPI was observed[52] (moderate/high level of evidence).

Specific issues related to H2RAs. Although RCTs have demonstrated that H2RAs significantly reduce the risk of clinically significant GI bleeding, some important issues remain to be elucidated. There is a risk of tachyphylaxis during prolonged IV dosing.[39] It is believed to result from an increase in the release of endogenous histamine, which competes with the antagonist for the receptor sites. Tolerance can occur within 42 h, and pH control can deteriorate quickly.[39] Furthermore, H2RAs have been suggested not to inhibit vagally induced acid secretion, making them less effective in neurosurgical and head injury patients with vagal hyperactivity.[39] The use of H2RAs is associated with rare but serious adverse reactions such as thrombocytopenia, impaired liver function, and interstitial nephritis.[39] Finally, H2RAs are eliminated by the kidneys leading to reduced clearance in patients with kidney injury.

Specific issues related to sucralfate. Sucralfate must be administered intragastrically and is therefore unsuitable when patients cannot be fed enterally. In patients having kidney injury, attention must be paid to the risk of aluminum intoxication. Furthermore drug binding to sucralfate can reduce the effects of, e.g., digoxin, ciprofloxacin, and warfarin. Sucralfate may also interact with enteral feeding resulting in clotted feeding tubes.[11]

Specific issues related to PPIs. In general, PPIs are well tolerated. However, there have been reports that PPIs can cause abdominal pain, nausea, diarrhea, and headache.[28] As mentioned earlier, PPIs have the potential for drug interactions because they are metabolized by CYP450. Of the available PPIs, omeprazole has the highest potential for drug interactions including cyclosporin, diazepam, phenytoin, and warfarin.[28] Esomeprazol may interfere with CYP2C19 and has several potential drug interactions, most of which have little clinical relevance. Importantly though, esomeprazol decreases the metabolism of diazepam by 45% when given concomitantly. Pantoprazol has the lowest potential for drug interaction at least in theory.[28]

International recommendations for the use of SUP in the ICU

The 2012 Surviving Sepsis Campaign guidelines recommend as standard of care that H2RAs or PPIs are provided to patients with severe sepsis and septic shock.[8] The American Society of Health System Pharmacists published clinical practice guidelines in 1999.[24] They recommend SUP for patients with at least one major criteria including (1) coagulopathy [international normalized ratio (INR) > 1.5 or a partial thromboplastin time (PTT) > 2 times the

control value], (2) mechanical ventilation for more than 48 h, and (3) history of GI ulceration or bleeding within a year, or at least two minor criteria including (1) sepsis, (2) ICU admission lasting 1 week or more, (3) occult GI bleeding lasting 6 days or more, and (4) glucocorticoid therapy (more than 250 mg hydrocortisone or the equivalent).

Whether the current prescription of SUP to ICU patients is based on these recommendations is unknown.

Conclusion

In the present systematic review on SUP in ICU patients, we aimed at highlighting unanswered clinically research questions. Despite being considered standard of care, the evidence base for SUP in ICU patients is limited, and some studies are methodologically flawed. The incidence of GI bleeding varies considerably probably because no consensus definition of GI bleeding is used and because GI bleeding data derives from different ICU subpopulations. Data on the incidence and severity of GI bleeding in ICU patients are warranted. The present use of SUP in the ICU needs to be clarified, including the preferred SUP agent used. Which SUP agent has the best balance between efficacy and harm remains to be shown. Presently, the evidence that H2RAs reduces the risk of GI bleeding in ICU patients compared with placebo is unreliable. This is due to high risk of bias, increased risk of random error as the required information size for a reasonable intervention effect has not yet been reached, and possible design errors and insufficient data on the effect on mortality.[53] Whether PPI is superior to H2RA may not be entirely relevant as long as H2RAs have not unequivocally been shown to be superior to placebo. This situation has the imminent risk that even though PPI may be superior to H2RA, it may be inferior to placebo. Furthermore, data from RCTs do not reliably show that PPI is superior to H2RA, as the required information size in a random effect meta-analysis has not yet been reached and the boundary for benefit has not been crossed. An appropriate sample size/information size in a study with a high quality of evidence will need to include 2500–3000 patients. Accordingly, it is still unresolved if ICU patients benefit from SUP at all.

Answering the following key research questions will improve the level of evidence for SUP in the ICU:

1. What is the incidence of GI bleeding in general ICUs as of today?
2. What are the preferred SUP agents used in general ICUs as of today?
3. Based on what criteria is SUP prescribed?
4. Do ICU patients benefit from SUP with H2RAs or PPIs compared with placebo?
5. If patients in the ICU benefit from SUP with H2RA or PPI compared with placebo, is any agent superior to the other?

In order to answer these important questions, well-designed systematic reviews of possible interventions (question 4) and well-powered observational studies (question 1–3) and RCTs with low risk of bias are needed (question 5).

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Paper II

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SYSTEMATIC REVIEW

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Stress ulcer prophylaxis versus placebo or no prophylaxis in critically ill patients

A systematic review of randomised clinical trials with meta-analysis and trial sequential analysis

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Abstract *Purpose:* To assess the effects of stress ulcer prophylaxis (SUP) versus placebo or no prophylaxis on all-cause mortality, gastrointestinal (GI) bleeding and hospital-acquired pneumonia in adult critically ill patients in the intensive care unit (ICU). *Methods:* We performed a systematic review using meta-analysis and trial sequential analysis (TSA). Eligible trials were randomised clinical trials comparing proton pump inhibitors or histamine 2 receptor antagonists with either placebo or no prophylaxis. Two reviewers independently assessed studies for inclusion and extracted data. The Cochrane Collaboration methodology was used. Risk ratios/relative risks (RR) with 95 % confidence intervals (CI) were estimated. The predefined outcome measures were all-cause mortality, GI bleeding, and hospital-acquired pneumonia. *Results:* Twenty trials ($n = 1{,}971$) were included; all were judged as having a high risk of bias. There was no statistically significant difference in mortality (fixed effect: RR 1.00, 95 % CI 0.84–1.20; $P = 0.87$; $I^2 = 0$ %) or hospital-acquired pneumonia (random effects: RR 1.23, 95 % CI 0.86–1.78; $P = 0.28$; $I^2 = 19$ %) between SUP patients and the no prophylaxis/placebo patients. These findings were confirmed in the TSA. With respect to GI bleeding, a statistically significant difference was found in the conventional meta-analysis (random effects: RR 0.44, 95 % CI 0.28–0.68; $P = 0.01$; $I^2 = 48$ %); however, TSA (TSA adjusted 95 % CI 0.18–1.11) and subgroup analyses could not confirm this finding. *Conclusions:* This systematic review using meta-analysis and TSA demonstrated that both the quality and the quantity of evidence supporting the use of SUP in adult ICU patients is low. Consequently, large randomised clinical trials are warranted.

Keywords Stress ulceration · Gastrointestinal bleeding · All-cause mortality · Meta-analysis · Trial sequential analysis · Stress ulcer prophylaxis

Introduction

Critically ill patients are at risk of stress-related gastrointestinal (GI) bleeding [1]. The reported incidence of GI bleeding in the intensive care unit (ICU) ranges from 2 to 15 %, however this data derives from research published 15–20 years ago [2, 3]. Intensive care practice has changed substantially over recent decades and,

consequently, the incidence of GI bleeding in critically ill patients may also have changed.

GI bleeding due to stress ulceration has been associated with increased mortality and a prolonged length of ICU stay of 4–8 days [3, 4]. The results of older clinical trials indicate that stress ulcer prophylaxis (SUP) reduces the frequency of GI bleeding in ICU patients, and SUP is therefore regarded as a standard of care in ICU as outlined by the Surviving Sepsis Campaign guidelines [5]. However, the rationale and level of evidence of SUP in ICU patients has been questioned because of limited data, methodological flaws in some trials, possible increased incidence of hospital-acquired pneumonia and *Clostridium difficile* enteritis following the use of SUP and general improvements in intensive care [1, 6–9]. Furthermore, there is a lack of studies comparing the use of SUP versus no prophylaxis or placebo. Uncertainty over whether routine SUP is indicated in critically ill patients therefore exists amongst clinicians. As a result, there is a need to weigh the risks of SUP in ICU patients against the benefits of this approach in this patient group using up-to-date rigorous evidence-based methodology. The objective of our systematic review was to assess the effects of SUP versus placebo or no prophylaxis on all-cause mortality, GI bleeding and hospital-acquired pneumonia in critically ill patients using strict bias evaluation, cumulative meta-analysis and trial sequential analysis (TSA).

Methods

This systematic review is based on the methodology recommended by the Cochrane Collaboration [10], and the review has been prepared according to the PRISMA statement [11]. The protocol is published in the International Prospective Register of Systematic Reviews (PROSPERO), no. CRD42013004142.

Eligibility criteria

Potentially eligible trials had to be randomised, include adult patients admitted to the ICU, have an intervention group that received SUP with proton pump inhibitors (PPIs) or histamine 2 receptor antagonists (H2RAs) and include a control group that received placebo or no prophylaxis. We included trials irrespective of language and publication status. Trials were permitted to have more than one intervention group. Exclusion criteria were studies in animals, trials in patients aged <18 years, trials in patients not admitted to the ICU and trials only reporting non-patient-centred outcome measures [12], such as gastric pH and gastric colonisation.

Search strategy

We framed the following focused research question: "Is SUP with PPIs or H2RAs in critically ill patients in the ICU superior to placebo or no prophylaxis?"

A population, intervention, comparator and outcomes-based question and literature search was created [13] [Electronic Supplementary Material (ESM) 1].

The following databases were searched for literature: MEDLINE, including MeSH (January 1966 to March 2013), EMBASE (January 1980 to March 2013) and the Cochrane Library (Issue 2, March 2013). We also hand searched the reference lists of included trials and other systematic reviews of SUP in the critically ill patients. The electronic literature search was last updated March 20, 2013.

Study selection

Two authors (MK and MHM) independently reviewed all titles and abstracts identified in the literature search and excluded trials that were obviously not relevant. The remaining trials were evaluated in full text. Disagreements were resolved by JW.

Data extraction

Two authors (MK and MHM) independently extracted information from each included trial using a data extraction form. The extracted information included trial characteristics (year of publication, duration, country), characteristics of the trial participants (inclusion criteria, type of nutrition used), exclusion criteria, type of intervention/control (name, dosing, duration, route of administration, comparator) and outcomes. Trials were categorised as using enteral nutrition—if patients received any volume of enteral nutrition. The predefined primary outcome measure of this review was all-cause mortality, and the predefined secondary outcomes were GI bleeding and pneumonia. The outcome measures were the same as those defined by the authors of the original trials.

Risk of bias assessment

To determine the validity of the included trials, two authors (MK and MHM) independently assessed the risk of bias as advised by the Cochrane Collaboration [10], including the domains of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, baseline imbalance and bias due to vested financial interest. If one or more domains were judged as being high or unclear, we classified the trial as having a high risk of bias [10].

Statistical analyses

Review Manager 5.1.7 was used for statistical analyses, and for the TSA we used the TSA program version 0.9 beta (www.ctu.dk/tsa). For each included trial we calculated the relative risks (RR) with 95 % confidence intervals (CI) for the three dichotomous outcome measures, and we pooled these measures in the meta-analysis. Heterogeneity among trials was quantified with inconsistency factor (I^2) [14] and the Diversity (D^2) statistics [15]. If the I^2 statistic was 0, we reported the results from a fixed-effect model, and if the I^2 statistic was >0, we reported results from both a fixed-effect and random-effects model. The cumulative meta-analysis was challenged with the application of TSA—a sensitivity analysis that widens the confidence intervals in case the data are too sparse to draw firm conclusions [15–17] (ESM 2). In addition, the sensitivity analysis included application of continuity correction in trials of zero events [18]. Risk of small trial bias was assessed by Funnel plot asymmetry [19].

Subgroup analyses

We performed five predefined subgroup analyses and one post hoc subgroup analysis: (1) high versus low risk of bias trials (a possible increased intervention effect in trials with a high risk of bias); (2) adequate versus inadequate random sequence generation, allocation concealment and blinding (a possible increased intervention effect in trials with an inadequate random sequence generation, allocation concealment and blinding); (3) use of PPIs versus H2RAs (a possible increased intervention effect in the PPI group); (4) medical versus surgical versus mixed ICU (a possible increased intervention effect in surgical patients); (5) use of enteral nutrition versus no enteral nutrition (a possible increased risk of hospital-acquired pneumonia in patients receiving enteral nutrition); (6) placebo trials versus no prophylaxis trials (a possible increased intervention effect in the no prophylaxis trials).

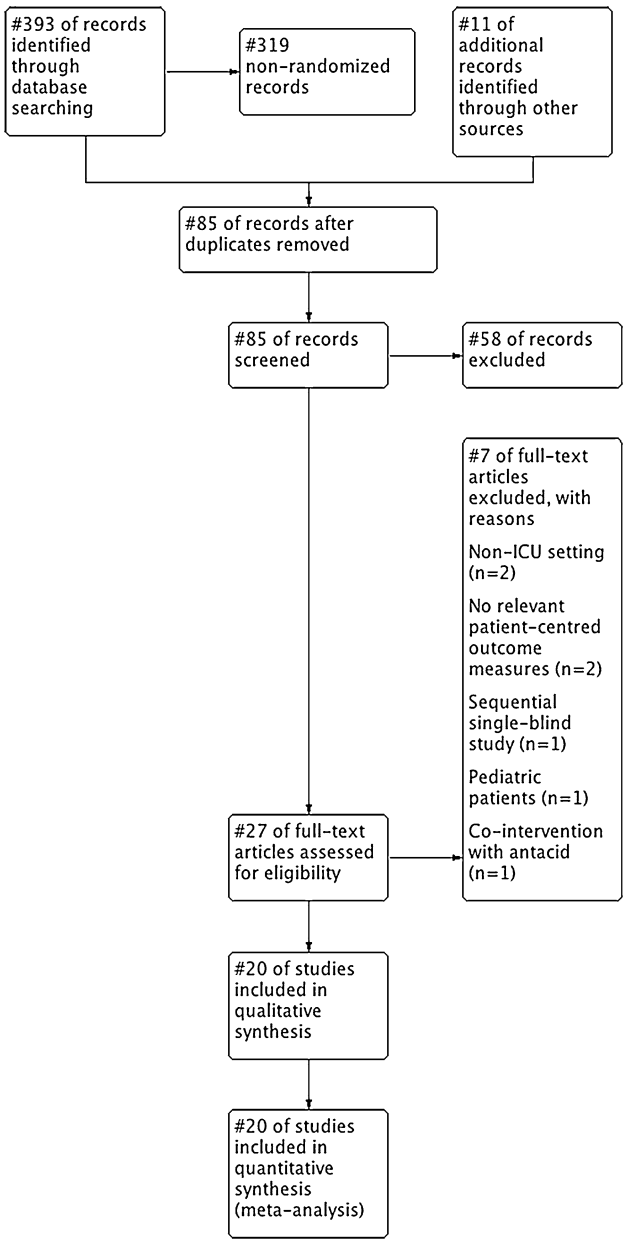

Fig. 1 Study flow diagram

Results

Figure 1 summarises the results of the search: 20 trials were included, all of which were published in English (Table 1) [20–39]. The main reasons for exclusion of trials were (1) no relevant patient-centred outcome measures were reported [40, 41] and (2) the trials were conducted in a non-ICU setting (ESM 3) [42, 43].

Characteristics of trials

Of the 20 trials included in this review, 16 (80 %) were single-centre trials [20–29, 31, 34–38]. The four multicentre trials were all from the USA and comprised a total of 585 patients (30 % of the included patients) [30, 32, 33, 39]. Twelve trials (60 %) used placebo as comparator [20–22, 24, 31, 36, 37, 39], whereas the remaining trials used no prophylaxis. In seven trials, patients were fed enterally [20, 22, 27, 32, 34, 36, 38].

Participants

The 20 included trials enrolled 1,971 adult patients in the ICU. Seven trials included patients from mixed ICUs [21,

Table 1 Characteristics of the included trials

First author of published trial	No. of patients in trial (*n*)	Setting/ country	Trial duration (months)	Intensive care unit	Enteral nutrition	Inclusion criteria (population)	Exclusion criteria	Intervention	Comparator	Outcomes
Control group: no prophylaxis										
Apte [20]	34	Single centre/ India	Unknown	Medical	Yes	Tracheotomised patients with tetatus	Pneumonia; SUP	Ranitidine 50 mg/every 6 h IV	No prophylaxis	Mortality Nosocomial pneumonia Overt GI bleeding[b]
Basso [21]	116	Single centre/ Italy	14	Surgical	No	High risk plastic- and neurosurgery[a]	GI bleeding; GI surgery; age <12 years; coagulopathy.	Cimetidine 200 mg/every 6 h IV or orally in at least 10 days	No prophylaxis	Overt GI bleeding
Ben-Menachem [22]	200	Single centre/ USA	10	Medical	Yes	Any	GI bleeding; GI surgery; age <18 years; expected ICU stay <24 h; SUP; anticoagulants; recent surgery/ anaesthesia; head injury; raised ICP; grade 4 hepatic encephalopathy; pregnancy or lactatation	Cimetidine loading dose of 300 mg IV and infusion titrated to maintain gastric pH >4	No prophylaxis	Hospital mortality Nosocomial pneumonia Clinically significant GI bleeding[c]
Darlong [24]	31	Single centre/ India	Unknown	Mixed	No	MV (>24 h expected duration) and NG tube in situ	GI bleeding; SUP; coagulopathy; anticoagulants	Ranitidine 50 mg/ every 8 h IV	No prophylaxis	Overt GI bleeding
MacDougall [31]	62	Single centre/ UK	18	Medical	No	Fulminant hepatic failure	GI bleeding	Metiamide 150 mg/ h (n = 10) or cimetidine 100 mg/h (n = 16) IVy giving pH >5	No prophylaxis	Mortality Overt GI bleeding
Reusser [36]	40	Single centre/ Switzerland	26	Surgical	No	Acute traumatic or spontaneous brain injury and neurosurgery and MV >48 h	GI bleeding; age <15 years; GI surgery; PUD; SUP	Ranitidine 50 mg/ every 8/6 h IV titrated to maintain gastric pH >4	No prophylaxis	Mortality Overt GI bleeding
Ruiz-Santana [37]	49	Single centre/ Spain	14	Mixed	Yes	MV (expected duration >6 days) and metabolic stress; no shock and no renal or hepatic disease; total parenteral nutrition	GI bleeding; GI surgery; PUD; SCI; AKI; hepatic failure, catabolic index score ≤0; SUP	Ranitidine 50 mg/ every 8 h IV	No prophylaxis	Mortality Overt GI bleeding
Zinner [39]	200	Multicentre/ USA	24	Surgical	No	Expected ICU duration >48 h	GI bleeding; GI surgery; PUD	Cimetidine 300 mg/every 6 h IV during ICU stay	No prophylaxis	Mortality Overt GI bleeding

Table 1 continued

First author of published trial	No. of patients in trial (*n*)	Setting/ country	Trial duration (months)	Intensive care unit	Enteral nutrition	Inclusion criteria (population)	Exclusion criteria	Intervention	Comparator	Outcomes
Control group: placebo										
Burgess [23]	34	Single centre/ USA	9	Surgical	No	Severe head injury and GCS ≤10	PUD; GI injury; SUP; oral intake	Ranitidine 6.25 mg/h IV for up to 72 h	Placebo	Mortality Overt GI bleeding
Friedman [25]	25	Single centre/ USA	18	Medical	No	MV	GI bleeding; AKI; SUP; pregnancy	Cimetidine 300 mg/every 6 h IV	Placebo	Overt GI bleeding
Groll [26]	221	Single centre/ Canada	21	Mixed	No	Any	GI bleeding; AKI; SUP; pregnancy; drug overdosage; AMI	Cimetidine 300 mg/every 6 h IV	Placebo	Mortality Overt GI bleeding
Halloran [27]	50	Single centre/ USA	21	Surgical	Yes	Severe head injury	Brain death; PUD; pregnancy; GI injury; severe hepatic or renal disease	Cimetidine 300 mg/every 4 h IV for up to 3 weeks	Placebo	Overt GI bleeding
Hanisch [28]	114	Single centre/ Germany	12	Surgical	No	MV	PUD; GI bleeding; age <18 years; transplanted patients (kidney, liver, heart); pneumonia; GI surgery	Ranitidine 50 mg × 3 IV	Placebo	Mortality Nosocomial pneumonia Clinically significant GI bleeding
Kantorova [29]	208	Single centre/ Czech Republic	29	Surgical	Yes	MV (expected duration >48 h) or coagulopathy; age >18 years; NG tube in situ	GI bleeding; GI surgery; pneumonia; SUP; PUD; anticoagulants; AKI, coagulopathy; life expectancy <3 months	Omeprazole 40 mg IV; Famotidine 40 mg × 2 IV	Placebo	Hospital mortality Nosocomial pneumonia Clinically significant GI bleeding
Karlstadt [30]	87	Multicentre/ USA	Unknown	Mixed	No	At least one of the following: major thoracic or abdominal surgery; multiple trauma; hypotension; hypovolemic shock; sepsis; acute respiratory failure	GI bleeding; hepatic failure; AKI; SUP; pregnancy or lactatation; age <16 years; hypersecretory disorders	Cimetidine 300 mg loading dose, followed by infusion at 50 mg/every hour	Placebo	Mortality Nosocomial pneumonia Clinically significant GI bleeding

Table 1 continued

First author of published trial	No. of patients in trial (*n*)	Setting/ country	Trial duration (months)	Intensive care unit	Enteral nutrition	Inclusion criteria (population)	Exclusion criteria	Intervention	Comparator	Outcomes
Martin [32]	131	Multicentre/ USA	7	Mixed	Yes	Expected ICU stay >36 h; NG tube in situ; at least one of the following: major surgery; multiple trauma; hypotension; hypovolemic shock; sepsis; acute respiratory failure; jaundice; burn>30%	GI bleeding; pregnancy or lactatation; age <16 years; GI surgery; SUP; anticoagulants	Cimetidine 300 mg loading dose, followed by 50 mg/h IV for up to 7 days	Placebo	30-day mortality Nosocomial pneumonia Overt GI bleeding
Metz [33]	167	Multicentre/ USA	20	Surgical	No	Severe head injury; GCS ≤10; NG tube in place	GI bleeding; age <18 years; expected ICU stay <72 h; burns>20 %; AKI; PUD; coagulopathy; SUP	Ranitidine 6.25 mg/h IV for up to 5 days	Placebo	Mortality Nosocomial pneumonia Overt GI bleeding
Peura [34]	39	Single centre/ USA	Unknown	Medical	Yes	Expected ICU stay >5 days	GI bleeding; age<18 years; GI surgery; AMI; pregnancy	Cimetidine 300 mg/every 6 h IV for 3–14 days	Placebo	Mortality Overt GI bleeding
Powell [35]	41	Single centre/ UK	Unknown	Surgical	No	Scheduled coronary artery bypass graft patients in ICU	PUD; GI surgery; SUP; severe allergy; AKI; hepatic disease; anticoagulants	Ranitidine 50 mg/ every 8 h IV; omeprazole 80 mg loading dose followed by 40 mg/every 8 h by bolus IV; omeprazole 80 mg loading dose followed by 40 mg/every 8 h by infusion	Placebo	Mortality Overt GI bleeding
Van den Berg [38]	28	Single centre/ Netherlands	Unknown	Mixed	Yes	MV	Unknown	Cimetidine 20 mg/ kg/every 24 h IV	Placebo	Overt GI bleeding

AKI acute kidney injury, *AMI* acute myocardial infarction, *EN* enteral nutrition, *GI* gastrointestinal, *GCS* Glasgow Coma Score; *ICP* intracranial pressure, *ICU* intensive care unit, *IV* intravenously, *MV* mechanical ventilation, *NG* nasogastric, *PUD* peptic ulcer disease, *SCI* spinal cord injury, *SUP* stress ulcer prophylaxis

[a] Neurosurgery; head injury, respiratory failure; sepsis; burns >20 %; hypotension; postoperative complications; acute renal failure; multiple trauma

[b] Overt GI bleeding included haematemesis, coffee ground emesis, melena, haematochezia or bloody nasogastric aspirate

[c] Clinically significant GI bleeding includes overt GI bleeding and clinically relevant changes in vital signs or haemoglobin

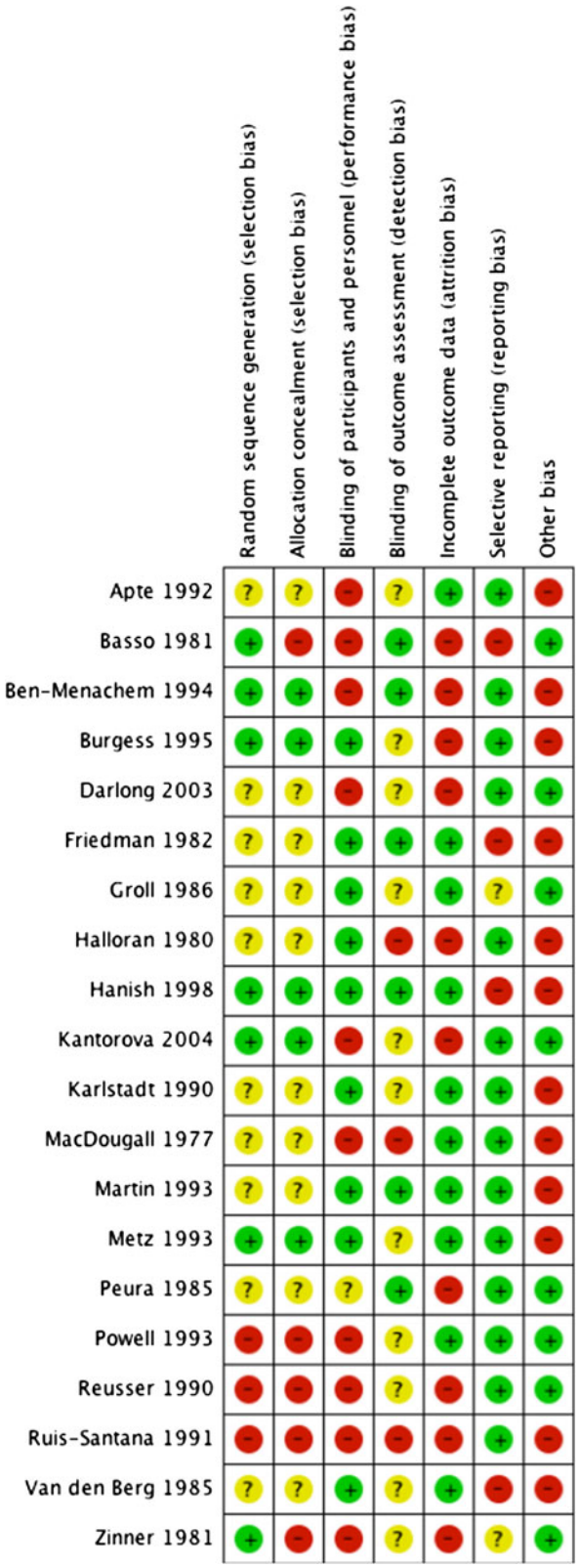

Fig. 2 Risk of bias summary. Review of authors' judgements about each risk of bias item for each included study. *Red* High risk, *green* low risk, *yellow* unclear

24, 26, 30, 32, 37, 38], eight trials included surgical ICU patients only (including trauma and neurosurgery) [23, 27–29, 33, 35, 36, 39] and five trials included patients in medical ICUs [20, 22, 25, 31, 34]. Inclusion and exclusion criteria varied considerably between trials (Table 1).

Interventions

Twenty trials evaluated H2RAs and two trials evaluated PPIs. Seven trials assessed ranitidine [20, 23, 24, 28, 33, 36, 37], ten trials assessed cimetidine [21, 22, 25–27, 30, 32, 34, 38, 39], two trials assessed omeprazole [29, 35] and three trials evaluated more than one intervention (e.g. both PPI and H2RA) [29, 31, 35]. The route of administration was intravenously in 19 trials [20, 22–39] and either orally or intravenously in one trial [21]. SUP dosing and duration of treatment varied across trials (Table 1).

Bias risk assessment

No trials were judged to be of low risk of bias in all six domains (Fig. 2). The main reasons for high risk of bias were inadequate random sequence generation, allocation concealment or blinding (ESM 4). One trial had adequate random sequence generation, allocation concealment and blinding [28] and was included in the subgroup analysis of adequate versus inadequate random sequence generation, allocation concealment and blinding. Eight trials had potential financial bias because of sponsorship by pharmaceutical companies [20, 23, 25, 27, 30–33].

Outcome measures

All-cause mortality

Mortality data were obtained from 15 trials including 1,604 patients [20, 22, 23, 26–32, 34–37, 39]. The meta-analysis of all 15 trials showed no significant difference in mortality in patients treated with SUP compared with those treated with placebo or no prophylaxis (fixed effect: RR 1.00, 95 % CI 0.84–1.20; $P = 0.87$; $I^2 = 0$ %; Fig. 3). Application of an empirical continuity correction of 0.01 in the two no-event trials did not change the result. The subgroup analysis of trials using PPIs versus trials using H2RAs showed no increased intervention effect in the PPI group (test of interaction $P = 0.68$). The subgroup analysis of trials with a low risk of bias versus a high risk of bias could not be done because there were no trials with a low risk of bias. In the subgroup analysis of trials with adequate versus inadequate random sequence generation, allocation concealment and blinding and in the placebo versus no prophylaxis subgroup analysis, no increased intervention effect was found in the inadequate

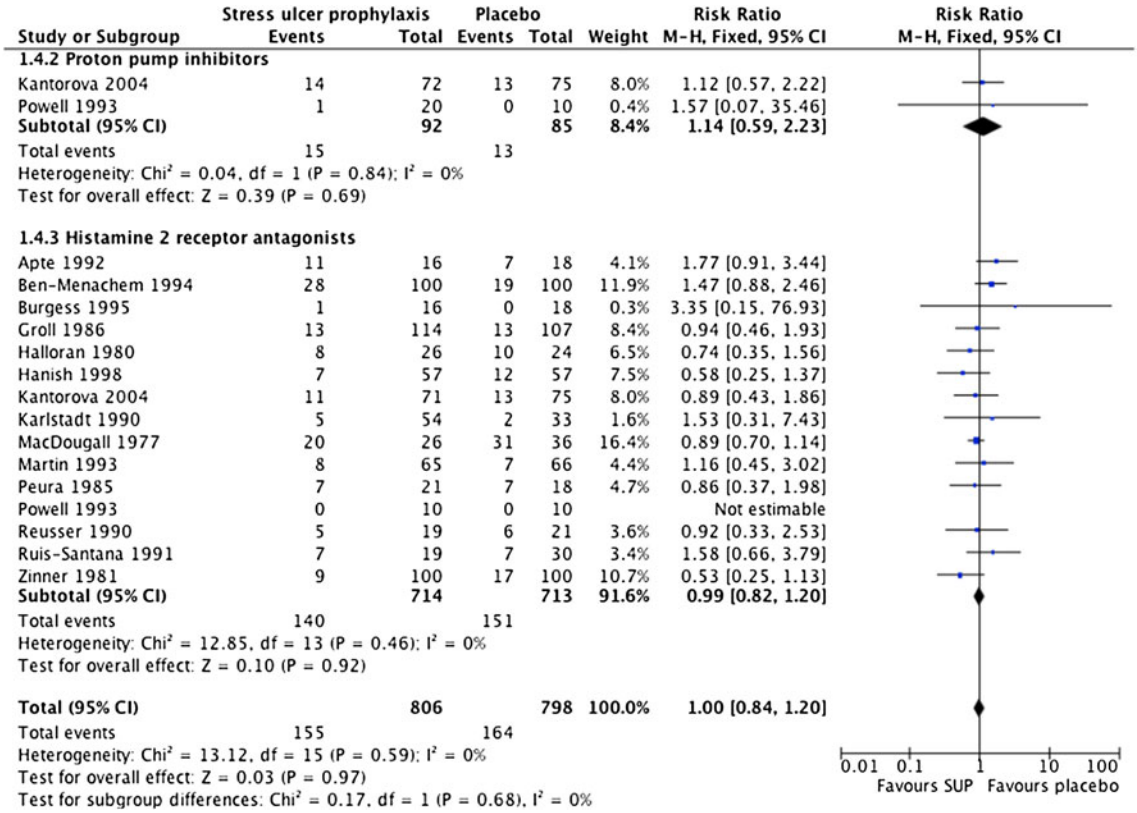

Fig. 3 Stress ulcer prophylaxis (SUP) and all-cause mortality. *Size of squares* for risk ratio (RR) reflects the weight of the trial in the pooled analyses. *Horizontal bars* 95 % Confidence intervals (CI)

group or in the no prophylaxis group. The subgroup analysis according to type of ICU, showed no increased intervention effect in the surgical ICU trials (test of interaction $P = 0.11$). Finally, no subgroup difference was found between enterally fed patients and non-enterally fed patients (test of interaction $P = 0.11$). The Funnel plot raised concern about small trial bias (ESM 8).

TSA showed that 57 % (1,594 patients) of the required information size to detect or reject a 20 % relative risk reduction (RRR) corresponding to 2,794 patients was accrued. The cumulative Z curve did not even touch the conventional boundary for harm or benefit ($P > 0.05$) or the trial sequential monitoring boundary for harm or benefit (ESM 5). However, the Z curve did reach the futility area, hereby excluding a 20 % RRR in mortality by using PPIs or H2RA.

GI bleeding

All 20 trials ($n = 1{,}971$) had data on GI bleeding [20–39]. The conventional meta-analysis showed a statistically significant difference in GI bleeding in patients treated with SUP compared with those treated with placebo or no prophylaxis (fixed effect: RR 0.41, 95 % CI 0.31–0.53; $P = 0.01$; $I^2 = 48$ %; random effects: RR 0.44, 95 % CI 0.28–0.68) (Fig. 4). Application of an empirical continuity correction of 0.01 in the four no-event trials did not change the result. In the subgroup analysis of trials using PPIs versus trials using H2RAs, no increased intervention effect in the PPI group was found (test of interaction $P = 0.54$). No trials had a low risk of bias, so the subgroup analysis of low versus high risk of bias trials could not be done. The adequate versus inadequate random sequence generation, allocation concealment and blinding subgroup analysis, and the placebo versus no prophylaxis subgroup analysis showed no signs of an increased intervention effect in the inadequate group or in the no prophylaxis group. The subgroup analysis according to type of ICU showed no increased intervention effect in the surgical ICU trials (test of interaction $P = 0.92$). No statistically significant subgroup difference between enterally fed patients and parenteral nutrition was found (test of interaction $P = 0.15$). The risk of smaller trial bias was low according to the Funnel plot (ESM 8).

TSA showed that only 22 % (1,881 patients) of the required information size of 8,707 patients was accrued. The cumulative Z curve crossed the conventional boundary for benefit ($P < 0.05$), but not the trial sequential monitoring boundary for benefit (ESM 9).

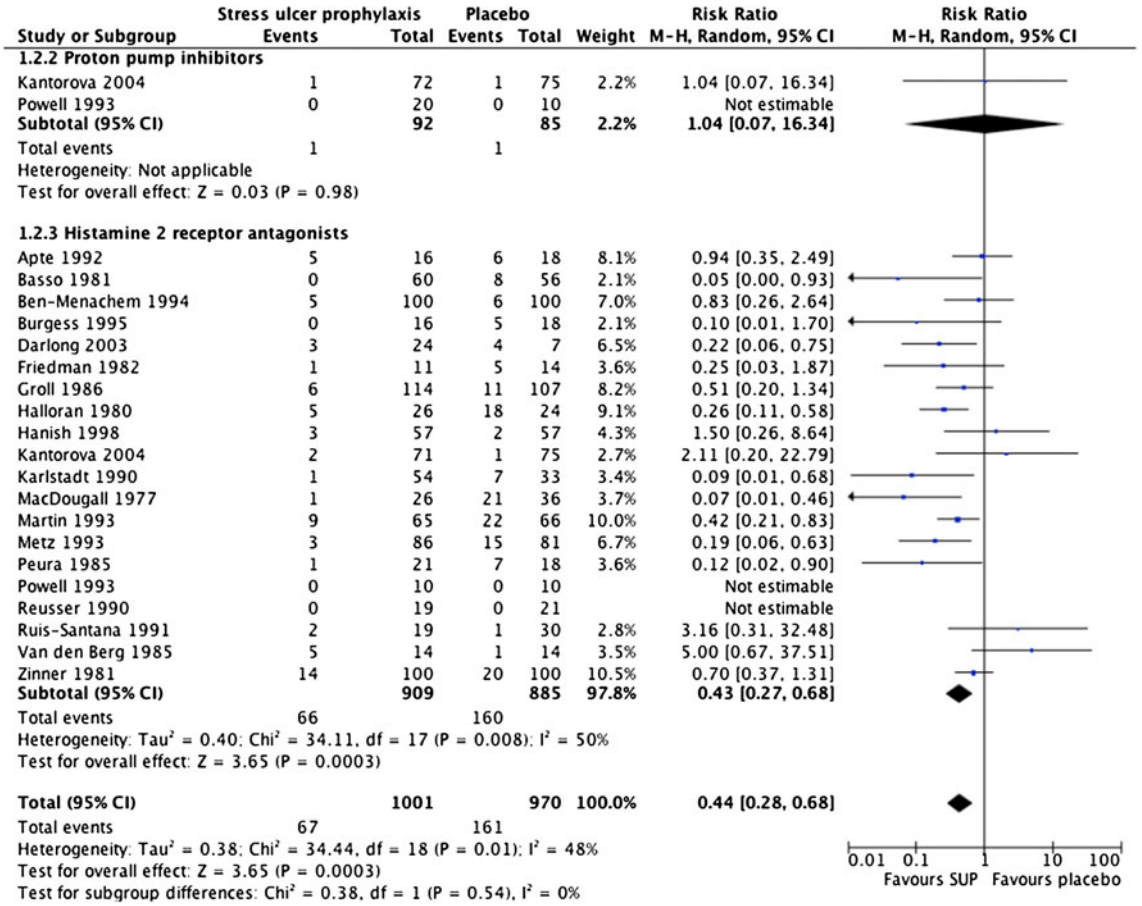

Fig. 4 SUP and gastrointestinal (GI) bleeding. *Size of squares* for RR reflects the weight of the trial in pooled analyses. *Horizontal bars* 95 % CI

Hospital-acquired pneumonia

Seven trials comprising 1,008 patients reported data on hospital-acquired pneumonia. The meta-analysis showed no statistically significant difference in pneumonia in patients treated with SUP compared with those treated with placebo or no prophylaxis (fixed effect: RR 1.16, 95 % CI 0.84–1.58; $P = 0.28$; $I^2 = 19$ %; random effects: RR 1.23, 95 % CI 0.86–1.78) (ESM 6). Application of an empirical continuity correction of 0.01 in the two no-event trials did not change the result. The subgroup analysis of trials using PPIs versus trials using H2RAs showed no increased intervention effect in the PPI group (test of interaction $P = 0.56$). The subgroup analysis of trials with a low risk of bias versus a high risk of bias could not be done. In the subgroup analysis of adequate versus inadequate random sequence generation, allocation concealment and blinding, no signs of an increased intervention effect in the inadequate group was found. An increased intervention effect in the placebo group was found in the placebo versus no prophylaxis subgroup analysis (test of interaction $P = 0.02$); however, significant statistical heterogeneity was present ($I^2 = 80$ %). The subgroup analysis according to type of ICU showed no increased intervention effect in the surgical ICU trials (test of interaction $P = 0.11$). Finally, no statistically significant increased risk of hospital-acquired pneumonia in the enteral nutrition group was found (test of interaction $P = 0.06$). No evidence of smaller trial bias was present in the Funnel plot (ESM 8).

TSA showed that a mere 12 % (1,008 patients) of the required information size of 8,694 patients was accrued. The cumulative Z curve did not touch the conventional boundary for harm or benefit, or the trial sequential monitoring boundary for harm or benefit (ESM 7).

Discussion

In the present systematic review using meta-analysis and TSA on SUP in adult critically ill patients in the ICU, SUP was not statistically significantly different from

placebo or no prophylaxis in terms of mortality, GI bleeding and pneumonia.

Mortality

The pooled analysis of mortality showed neither benefit nor harm of SUP with PPIs or H2RAs. No subgroup differences were present. The sensitivity analysis with TSA confirmed the finding in the conventional meta-analysis. Importantly, the TSA showed that it is unlikely that SUP will result in a relative mortality reduction of 20 % if further trials are conducted in adult ICU patients.

According to the risk of bias assessment [10], all trials had a high risk of bias. Thus, the pooled analyses may be influenced by the poor quality of existing trials, which could result in inflated point estimates and thus make interpretation difficult. Furthermore, the Funnel plot asymmetry with the absence of small negative trials increases the risk of overestimating the effect of SUP [44, 45].

GI bleeding

The conventional pooled analysis of GI bleeding showed a benefit of H2RAs. However, this finding could not be confirmed in the analysis of trials with adequate random sequence generation, allocation concealment and blinding ($n = 1$), and in the TSA. Consequently, an inflated point estimate in the conventional pooled analysis can be suspected. No subgroup differences were present. Considering the high risk of bias and sparse data, a genuine benefit of SUP on the risk of GI bleeding in adult ICU patients may be questioned.

Hospital-acquired pneumonia

No statistically significant benefit or harm of SUP on the risk of hospital-acquired pneumonia was demonstrated in the conventional meta-analysis or TSA. This was confirmed in the subgroup analyses. The overall high risk of bias in the trials warrants careful interpretation of the results because of an increased risk of falsely inflated estimates [44, 45].

Strengths and limitations of the review

The compliance with the recommendations of the Cochrane Collaboration is a strength of the present systematic review. The recommendations implemented in our review include a published protocol, an up-to-date literature search with no language restrictions, an independent literature search, data extraction and bias risk assessment by two authors and the inclusion of trials irrespective of publication and language status. In addition, we reduced the risk of random error in the meta-analysis with the application of TSA to increase the robustness of the analyses; this methodology has not been used in existing meta-analyses on SUP in the ICU. We excluded trials merely reporting non-patient-centered outcomes in order to make the results relevant for clinical practice. The subgroup analysis of trials with adequate versus inadequate random sequence generation, allocation concealment and blinding might have resulted in spurious findings. However, this analysis was introduced with the aim of estimating a possible bias effect. The heterogeneity of the included trials was considerable. We did not define the three outcome measures evaluated; rather, we used the definitions proposed by the authors, which may have resulted in trial heterogeneity. Most of the included trials have been conducted in high-risk patients, which must be kept in mind when interpreting the results. Overall, statistical heterogeneity did not seem to be a big issue, and we have reported both fixed-effect and random-effects pooled estimates when heterogeneity was present.

Relation to other reviews and implication for future research

No previous systematic reviews have been published on PPIs versus placebo or no prophylaxis, and only a few systematic reviews have evaluated H2RAs versus placebo or no prophylaxis. In 2010, Marik and colleagues suggested that in patients who are fed enterally, SUP does not reduce the risk of GI bleeding from stress ulcers and may even increase the risk of pneumonia and death [1]. However, there are a number of limitations to the review of these authors as three published trials were not identified or included [24, 25, 31], the risk of bias and precision assessment was not conducted as recommended by GRADE [46], no study protocol was published or registered and the increased risk of random errors in the conventional meta-analysis was not evaluated. These issues may have contributed to the discrepancies in relation to the present review. In 1996, Cook and colleagues conducted a thorough and comprehensive systematic review of SUP in critically ill patients [47]. However, the use of PPIs in the treatment of peptic ulcer disease began after 1996; consequently, the effect of PPIs was not evaluated in this meta-analysis. A number of methodological discrepancies between the Cook review and our review do exist. Not surprisingly, the placebo/no prophylaxis part of the Cook review included fewer trials and patients. Secondly, a different risk of bias assessment was used. Thirdly, no published protocol was identified. Finally, the increased risk of random errors due to possible multiple updating and sparse data was not assessed. Despite these dissimilarities, the pooled estimates in the conventional meta-analysis were of the same magnitude as those observed in our study.

The authors of recently published systematic reviews have suggested that PPIs significantly lower the risk of GI bleeding, without influencing the risk of hospital-acquired pneumonia, mortality or length of stay, as compared to H2RAs [6, 48]. However, whether PPIs are superior to H2RAs may not be relevant when H2RAs have not unequivocally been shown to be superior to placebo. This situation has the imminent risk that even though PPIs may be superior to H2RAs, they may not be better than placebo or no prophylaxis.

The TSA included in the present review adds important information to the area of SUP in adult ICU patients, as they highlight the lack of firm evidence for the use of SUP in this population. To ensure patient safety, well-powered trials with a low risk of bias are urgently needed.

Conclusion

This systematic review using meta-analysis and TSA has demonstrated that the quality and quantity of evidence for the use of SUP in adult ICU patients is low and that there is no firm evidence for benefit or harm of SUP as compared to placebo or no prophylaxis. Consequently, a genuine benefit of SUP in adult ICU patients may be questioned, and large randomised clinical trials should be conducted to answer the question of whether critically ill patients in the ICU should be treated with SUP or not.

Conflicts of interest None.

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Paper III

ORIGINAL ARTICLE

Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries

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One author (D. C.) received donated study drugs in 1992 from a company that does not exist anymore while leading an RCT funded by the Canadian government. On behalf of all other authors, the corresponding author states that there are no conflicts of interest.

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Background: Stress ulcer prophylaxis (SUP) may decrease the incidence of gastrointestinal bleeding in patients in the intensive care unit (ICU), but the risk of infection may be increased. In this study, we aimed to describe SUP practices in adult ICUs. We hypothesised that patient selection for SUP varies both within and between countries.

Methods: Adult ICUs were invited to participate in the survey. We registered country, type of hospital, type and size of ICU, preferred SUP agent, presence of local guideline, reported indications for SUP, criteria for discontinuing SUP, and concerns about adverse effects. Fisher's exact test was used to assess differences between groups.

Results: Ninety-seven adult ICUs in 11 countries participated (eight European). All but one ICU used SUP, and 64% (62/97) reported having a guideline for the use of SUP. Proton pump inhibitors were the most common SUP agent, used in 66% of ICUs (64/97), and H2-receptor antagonists were used 31% (30/97) of the units. Twenty-three different indications for SUP were reported, the most frequent being mechanical ventilation. All patients were prescribed SUP in 26% (25/97) of the ICUs. Adequate enteral feeding was the most frequent reason for discontinuing SUP, but 19% (18/97) continued SUP upon ICU discharge. The majority expressed concern about nosocomial pneumonia and *Clostridium difficile* infection with the use of SUP.

Conclusions: In this international survey, most participating ICUs reported using SUP, primarily proton pump inhibitors, but many did not have a guideline; indications varied considerably and concern existed about infectious complications.

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Editorial comment: what this article tells us
In this survey in 97 ICUs in 11 countries, most units reported routine use of stress ulcer prophylaxis, usually a proton pump inhibitor. Only two out of three units had written routines of its use, and indications varied.

Critically ill patients are at risk of developing gastrointestinal (GI) bleeding from stress ulcers.[1] The pathophysiology is not completely understood; however, it seems to differ from the aetiology of bleeding peptic ulcer. Stress ulcers may be less related to acid secretion, and more dependent on decreased mucosal blood flow, ischaemia and reperfusion injury.[2] The incidence of stress-related bleeding in the intensive care unit (ICU) has been estimated to vary from 0.6% to 6.0%,[1,3–5] which may be explained by heterogeneous populations, lack of a universally agreed definition and difficulties in diagnosing stress ulcers.[6] Not all stress ulcers progress to obvious GI bleeding, and not all GI bleeding is clinically relevant.[6] Significant GI bleeding in critically ill patients is associated with increased morbidity and mortality. In a landmark study by Cook and colleagues from 2001, patients with clinically significant GI bleeding had longer ICU stay (26 vs. 8 days, $P < 0.0001$) and higher ICU mortality (46% vs. 21%, $P < 0.0001$) in an unadjusted comparison to patients who did not experience bleeding.[1] Prior research has suggested a 50% lower GI bleeding rate when patients receive acid suppression vs. when they do not.[7]

The risk of stress ulcers in critically ill patients and the association of GI bleeding with mortality has encouraged the use of stress ulcer prophylaxis (SUP) in the ICU. There are many indications listed for SUP, including mechanical ventilation, coagulopathy, previous GI bleeding, prolonged duration of ICU stay and steroid therapy.[8,9] However, concern has been expressed about increased risk of nosocomial infections with its use in critically ill patients.[10,11] Today, SUP is recommended by several healthcare organisations, including the Surviving Sepsis Campaign (SSC),[8] the American Society of Health-System Pharmacists[9] and the Institute of Healthcare Improvement.[12]

These recommendations are based on research conducted 15–20 years ago, but the diagnostics, treatment and the process of care for critically ill patients have improved considerably over that period.[14] Accordingly, the *a priori* risk of developing stress ulcers in critically ill patients may have changed, so that the balance between benefit and harm of SUP may not be what it was 15–20 years ago.

In the present international survey, we aimed to describe reported SUP practices in adult ICUs. We hypothesised that patient selection for SUP varies within individual healthcare systems as well as internationally.

Methods

The present survey was approved by the Danish Data Protection Agency (No. 30–1115) and the Danish Health and Medicines Authorities (No. 3-3013-463/1/). The national ethical committees waived informed consent owing to the observational study design. The protocol was published prior to the conduct of the study (http://www.sup-icu.com). The manuscript has been prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[15]

National investigators were contacted and asked to invite local ICUs to participate in the survey and a concurrently conducted interna-

tional 7-day inception cohort study (http://www.sup-icu.com) on SUP in adult critically ill patients in the ICU. Due to practical and administrative considerations, the ICUs were invited to participate in both studies at the same time. Participation was voluntary and no fees were paid. The domains of interest were practice and attitudes rather than knowledge. Items of interest were generated by the Steering Committee of the SUP-ICU research programme, and the structured questionnaire was formatted with both open and closed responses. To make sure the objects of interest were answered from the questions, the questionnaire was pilot-tested and commented by five different clinicians at the coordinating site. Unclear questions were rephrased, and a question about indications for prescribing SUP was added. Between December 2013 and April 2014, an appointed principal investigator at each participating site completed the paper-based preformed questionnaire. The investigators were informed to answer all questions in the questionnaire according to the current practice in their ICU, and in each question it was highlighted whether one or multiple choices were allowed. The following variables were collected: country, type of hospital (university, teaching, district, general), type of ICU (mixed, surgical, medical, neurosurgical, cardiothoracic, cardiac), size of ICU (< 10 beds, 10–20 beds, > 20 beds), whether the ICU had a guideline for SUP (yes/no), the preferred SUP agent used [proton pump inhibitor (PPI), histamine 2 receptor antagonists (H_2RA), sucralfate, antacids or prostanoids], indications for prescribing SUP, criteria for discontinuing SUP, and potential concerns for adverse effects (Appendix S1). The outcome measure was the dominant SUP agent prescribed in each unit and indications for prescribing SUP.

The completed survey was returned by email to the coordinating investigator prior to inclusion of patients in the concurrently operating 7-day inception cohort study. Before data analysis, a statistical analysis plan was developed and published online (http://www.sup-icu.com). Data were analysed according to this plan using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Data are presented as distribution frequencies and per cent. Tabulation of SUP preference by country, type of hospital, type of ICU and size of ICU was performed. Fisher's exact test was used to assess statistically significant differences between groups. A two-sided P-value < 0.05 was considered statistically significant.

Results

A total of 97 ICUs treating adult patients in 11 countries participated (Australia, Canada, Denmark, Finland, Iceland, Italy, the Netherlands, New Zealand, Norway, Sweden and the United Kingdom (Table 1). All 97 sites returned the questionnaire before initiating the cohort study, and there were no missing data. The majority of ICUs were European, half of the hospitals were university hospitals, and 93% (90/97) of the ICUs admitted both medical and surgical patients (mixed ICU). Some 64% of the ICUs (62/97) reported having a guideline for the use of SUP (Table 1).

Sixty-six per cent (64/97) used PPI as the preferred SUP agent, and 31% (30/97) used primarily

Table 1 Characteristics of participating intensive care units (ICUs). Frequencies (%).

Variable	No. of units (n = 97)
Country	
United Kingdom	38 (39)
Denmark	24 (25)
Sweden	10 (10)
Finland	6 (6)
Canada	5 (5)
New Zealand	4 (4)
Australia	4 (4)
Norway	2 (2)
The Netherlands	2 (2)
Iceland	1 (1)
Italy	1 (1)
Type of hospital	
University	48 (49)
Teaching	26 (27)
District or general	23 (24)
Type of ICU	
Mixed	90 (93)
Neurosurgical	3 (3)
Cardiothoracic	2 (2)
Medical	1 (1)
Cardiac	1 (1)
Size of ICU	
< 10 beds	31 (32)
10–20 beds	43 (44)
> 20 beds	23 (24)

Table 2 Preferences for stress ulcer prophylaxis (SUP). Frequencies (%).

Variable		No. of units (n = 97)
Local SUP guideline		62 (64)
Preferred SUP agent	PPI	64 (66)
	H_2 receptor antagonist	30 (31)
	Sucralfate	1 (1)
	Antacids	1 (1)
	None	1 (1)
Indications for SUP*	Mechanical ventilation	43 (45)
	Miscellaneous (17 different)†	41 (43)
	High-risk patients (unspecified)	28 (29)
	All ICU patients	25 (26)
	Coagulopathy	16 (17)
	Incomplete enteral feeding	12 (13)
	Shock	11 (11)
	None	1 (1)
Criteria for discontinuing SUP	Full enteral feeding	31 (32)
	Discharge from ICU	21 (22)
	No discontinuation of SUP	18 (19)
	Discontinuation of mechanical ventilation	13 (13)
	Other	5 (5)
Concerns when prescribing SUP*	Nosocomial pneumonia	78 (80)
	Clostridium difficile infection	51 (53)
	Interactions	26 (27)
	Allergy	11 (11)
	Delirium	9 (9)
	None	8 (8)
	Other‡	5 (5)

*More than one answer allowed. †See Appendix S2. ‡Cost, high plasma aluminium, diarrhoea, liver dysfunction. H_2RA, histamine 2 receptor antagonist; ICU, intensive care unit; PPI, proton pump inhibitor.

H_2RA (Table 2). The preferred SUP agent differed significantly between countries, as H_2RAs were predominantly used in UK sites (Table 3). There was no difference in dominant SUP agent used across types of hospitals, types of ICUs or size of ICU. Only one unit (1%) did not use SUP at all.

A total of 23 different indications for SUP were reported (Table 2). The four commonest specific indications were mechanical ventilation (invasive and non-invasive) of any duration, coagulopathy, inadequate enteral feeding and shock. One in four ICUs used SUP in all ICU patients, and 29% (28/97) reported that SUP was only used in high-risk patients based on an individual assessment (Table 2). Full enteral feeding and discontinuation of mechanical ventilation were the two most frequent reasons for discontinuing SUP. One in five ICUs (19%) did not stop SUP upon discharge from the ICU.

In 81% (78/97) of the ICUs, concern was expressed about increased risk of nosocomial pneumonia when using SUP and in 53% (51/97) *Clostridium difficile* infection (CDI) (Table 2). In 8% (8/97) of the ICUs, no concerns were expressed about adverse effects of SUP. More sites using primarily H_2RA, as compared with PPI, expressed concern about CDI (P = 0.03), whereas concern about pneumonia was equally distributed between the two groups (P = 0.08).

Discussion

In this international survey of 97 ICUs, we found that all but one used SUP, primarily PPI. However, only 64% of ICUs had a guideline for SUP, the indications varied considerably, 19% did not stop SUP upon ICU discharge, and the majority expressed concern about increased risk of nosocomial pneumonia and CDI with the use of SUP.

Current SUP patterns for critically ill patients are not well described globally. However, in a

Table 3 Cross tabulation of subtypes of stress ulcer prophylaxis (SUP) and intensive care unit (ICU) characteristics. Frequencies (%).

			SUP agent, *n* (%)					
Variable		All (*n* = 97)	PPI (*n* = 64)	H_2RA (*n* = 30)	Sucralfate (*n* = 1)	Antacids (*n* = 1)	None (*n* = 1)	*P*-value*
Country								< 0.001
	United Kingdom	38	11 (29)	27 (71)	0 (0)	0 (0)	0 (0)	
	Denmark	24	24 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Sweden	10	7 (70)	1 (10)	1 (10)	1 (10)	0 (0)	
	Finland	6	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Canada	5	3 (60)	2 (40)	0 (0)	0 (0)	0 (0)	
	New Zealand	4	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Australia	4	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Norway	2	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	The Netherlands	2	1 (50)	0 (0)	0 (0)	0 (0)	1 (50)	
	Iceland	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Italy	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Type of hospital								0.654
	University	48	33 (69)	14 (29)	1 (2)	0 (0)	0 (0)	
	Teaching	26	15 (58)	9 (35)	0 (0)	1 (4)	1 (4)	
	District or general	23	16 (70)	7 (30)	0 (0)	0 (0)	0 (0)	
Type of ICU								0.801
	Mixed	90	57 (63)	30 (33)	1 (1)	1 (1)	1 (1)	
	Neurosurgical	3	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Cardiothoracic	2	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Medical	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
	Cardiac	1	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Size of ICU								0.211
	< 10 beds	31	24 (77)	6 (19)	0 (0)	1 (3.0)	0 (0)	
	10–20 beds	43	26 (60)	16 (37)	1 (2.0)	0 (0)	0 (0)	
	> 20 beds	23	14 (61)	8 (35)	0 (0)	0 (0)	1 (4)	

*Fischer's exact test. H_2RA, histamine 2 receptor antagonist; PPI, proton pump inhibitor.

retrospective Australian cohort study of two ICUs, 82% of patients were prescribed SUP.[16] In a UK survey from 2007, 81% of 198 ICUs stated that SUP was considered in all patients admitted,[17] and in a US survey from 2014 SUP was initiated in 90% of the patients.[18]

Taken together with our data, it appears that SUP is used in the majority of ICU patients today.

Despite use of SUP in the majority of patients, only 64% of the participating ICUs had a guideline for SUP prescription. In the 2007 UK survey, 90% had an SUP guideline.[17] In contrast, only 18% adhered to an SUP guideline in a survey based on answers from 501 US critical care physicians from different specialties,[19] and in 1999 Erstad and co-workers reported that 27% of 153 ICUs in the United States had an SUP guideline and only half of the available guidelines were updated within the last 2 years[20] (Table 4). These data suggest that even if ICUs have guidelines, they may not be current, and clinicians may prescribe SUP according to their own preferences, norms and cost structures.

We found that mechanical ventilation and coagulopathy were the two most frequent specific indications for SUP. Respiratory failure and coagulopathy appear to be widely accepted indications for SUP in clinical practice.[19] Even though one third of participating sites reported that high-risk patients should receive SUP, the finding of 23 different indications for prescribing SUP suggests that no consensus on use of SUP in adult critically ill patients exists. A recent survey from United States and Canada assessing appropriate and inappropriate use of SUP in 584 patients concluded that SUP is widely used even in patients with low risk of clinically significant GI bleeding and that several opportunities for improvement

Table 4 Characteristics of surveys on stress ulcer prophylaxis in the intensive care unit

Study	Setting	*n*	PPI (%)	H_2RA (%)	Sucralfate (%)	Antacids (%)	None (%)	Guideline (%)
Krag et al. (2014)	11 countries	97 ICUs	66	31	1	1	1	64
Preslaski et al. (2014)	United States	245 physicians	58	40	NA	NA	NA	NA
Gratrix et al. (2007)	United Kingdom	198 ICUs	20	67	13	0	0	90
Daley et al. (2004)	United States	501 physicians	23	64	12	0	0	NA
Erstad et al. (1999)	United States	153 physicians	3	77	20	0	0	27

H_2RA, histamine 2 receptor antagonist; ICU, intensive care unit; NA, not available; PPI, proton pump inhibitor.

exist.[22] Difficulties in identifying high-risk patients may lead to this under- or overuse of SUP. In a US survey from 2012, 53% either received SUP without a clinical indication or did not receive SUP when indicated.[23] Even though the evidence supporting the American Society of Health-System Pharmacists criteria is modest,[21,24] inappropriate use of SUP is common and overuse of SUP may be a more significant problem than underuse.

In our survey, 13% of units prescribed SUP to patients incompletely enterally fed, and one in three units discontinued SUP when the patient was fully enterally fed. Former surveys support that enteral nutrition is taken into consideration when evaluating the risk of stress-related bleeding and upon commencing SUP.[17,19,20] Current evidence is based on case reports, a limited number of serial studies in humans and several animal studies, and this explains why there is no firm evidence regarding the role of enteral nutrition in the prevention of stress ulcers.[21,25] Consequently, more research into this issue is needed.

Almost 20% of the participating sites did not stop SUP upon discharge to the ward. This is somewhat lower than previously reported, where 60% of patients with no risk factors for stress-related bleeding at discharge from ICU continued treatment with SUP in the ward.[26] Similarly, 31–39% of patients treated with SUP during ICU stay have been reported discharged from hospital with SUP.[16] This presumed inappropriate use of acid suppressants results in higher costs for patients and society.[27,28]

In contrast to the other participating countries, H_2RA was the preferred SUP agent in the United Kingdom. Gratrix and others demonstrated that 67% of the UK ICUs used H_2RA as first-line therapy or standard,[17] and in the present study 71% (27/38) of the participating UK ICUs preferred H_2RA compared with only 5% (3/59) of the other participating sites (Table 3). The reason for this discrepancy is not clear, but hospital penalties for high rates of CDI and concerns about PPIs increasing this risk more than H_2RAs may contribute. Studies conducted outside the ICU suggest that acid suppression is associated with increased risk of CDI, possibly because host immunity is compromised by higher gastric pH.[11,29,30] In a meta-analysis of observational studies from 2007, Leonard and others found a significantly increased risk of CDI in non-ICU patients receiving H_2RA or PPI, as compared with placebo.[31] Apparently, the risk of CDI is higher in patients receiving PPI as compared with H_2RA. In a recently published retrospective cohort study in adult critically ill patients requiring mechanical ventilation (n = 35,312), a two to four times increased risk of CDI was demonstrated in patients receiving PPIs as compared with H_2RAs.[32] Since CDI increases length of stay, mortality and healthcare costs, research evaluating the potential important association between SUP and CDI is warranted.[33,34]

Our survey revealed that nosocomial pneumonia and CDI are the two most frequently expressed concerns when prescribing SUP. It has been hypothesised that SUP increases the risk of nosocomial pneumonia for the same reasons as CDI, and several studies and trials have aimed to evaluate this potential increased risk.[4,35] Besides an increased risk of CDI, the before mentioned cohort study also found an increased risk of pneumonia in patients treated with PPI compared with H_2RA,[22] but the evidence regarding this is not firm, as recent meta-analysis has not been able to

identify an increased risk of nosocomial pneumonia when using SUP compared with placebo/no prophylaxis.[36]

Different guidelines have aimed to advise clinicians on which patients should receive SUP.[8,9,12] It seems that the evidence base for use of PPI in the treatment of gastro-oesophageal reflux and peptic ulcer bleeding has been widely applied to SUP in ICU patients. The SSC guidelines recommend that patients with sepsis and risk factors for GI bleeding should receive SUP (level of evidence 1B; strong recommendation based on moderate quality of evidence), and they suggest PPI as first-line therapy (level of evidence 2C; weak recommendation based on evidence of low quality).[8] One of the reasons for suggesting PPI as first-line therapy is a 2013 systematic review and meta-analysis where PPI was superior to H_2RA in reducing clinically important and overt GI bleeding (relative risk 1.36, 95% confidence interval 1.19–1.68, $P = 0.002$).[37] PPI may be superior to H_2RA, but as recently demonstrated in a systematic review of RCTs with meta-analysis and trial sequential analysis, both the quality and quantity of the evidence for the use of SUP as compared with placebo are low.[38] Correspondingly, no firm evidence for benefit or harm of SUP as compared with placebo exists.[21,39]

Strength of the present study includes the participation of 97 ICUs from 11 countries, a high response rate and no missing data, which increases the external validity of the results. We believe results are generalisable to ICUs in other countries. Furthermore, a protocol and statistical analysis plan were prepared and published before the survey was distributed. Limitations include our convenience sample of investigators interested in this topic. The majority of sites accepting the invitation to participate were Danish or from the United Kingdom with few sites from the remaining countries. As with any survey of reported practice, results may not reflect actual practice. Further, there is a risk that the investigators may have reported their individual SUP prescribing rather than departmental practices, despite survey instructions. Since our focus was a short simple survey with face validity, we conducted no reliability testing or clinical sensibility testing of the questionnaire itself.

In conclusion, we found that most ICUs used SUP, primarily PPI. However, many did not have a guideline, indications varied considerably, and concern was expressed about nosocomial pneumonia and CDI.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Questionnaire.
Appendix S2. Miscellaneous indications for prescribing stress ulcer prophylaxis.

Paper IV

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ORIGINAL

Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients

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The SUP-ICU co-authors are listed in the "Appendix".

Take home message: Acid suppressants are frequently prescribed as prophylaxis against gastrointestinal bleeding, but clinically important bleeding occurs infrequently. The increase in mortality in patients experiencing gastrointestinal bleeding may be explained by confounding variables. More research in this area is needed.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-015-3725-1) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* To describe the prevalence of, risk factors for, and prognostic importance of gastrointestinal (GI) bleeding and use of acid suppressants in acutely ill adult intensive care patients. *Methods:* We included adults without GI bleeding who were acutely admitted to the intensive care unit (ICU) during a 7-day period. The primary outcome was clinically important GI bleeding in ICU, and the analyses included estimations of baseline risk factors and potential associations with 90-day mortality. *Results:* A total of 1,034 patients in 97 ICUs in 11 countries were included. Clinically important GI bleeding occurred in 2.6 % (95 % confidence interval 1.6–3.6 %) of patients. The following variables at ICU admission were independently associated with clinically important GI bleeding: three or more co-existing diseases (odds ratio 8.9, 2.7–28.8), co-existing liver disease (7.6, 3.3–17.6), use of renal replacement therapy (6.9, 2.7–17.5), co-existing coagulopathy (5.2, 2.3–11.8), acute coagulopathy (4.2, 1.7–10.2), use of acid suppressants (3.6, 1.3–10.2) and higher organ failure score (1.4, 1.2–1.5). In ICU, 73 %

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(71–76 %) of patients received acid suppressants; most received proton pump inhibitors. In patients with clinically important GI bleeding, crude and adjusted odds for mortality were 3.7 (1.7–8.0) and 1.7 (0.7–4.3), respectively. *Conclusions:* In ICU patients clinically important GI bleeding is rare, and acid suppressants are frequently used. Co-existing diseases, liver failure, coagulopathy and organ failures are the main risk factors for GI bleeding. Clinically important GI bleeding was not associated with increased adjusted 90-day mortality, which largely can be explained by severity of comorbidity, other organ failures and age.

Keywords Stress ulcer prophylaxis · Gastrointestinal bleeding · Proton pump inhibitors · Histamine-2 receptor antagonists · Critically ill patients · Intensive care

Background

Critically ill patients are at risk of stress-related gastrointestinal (GI) mucosal damage, which can progress to ulceration and bleeding [1]. The aetiology and pathophysiology are not completely understood, but diminished blood flow, mucosal ischemia and reperfusion injury may be important [2]. Damage of the gastric mucosa can be found in up to 90 % of critically ill patients after 3 days in the intensive care unit (ICU) [3, 4]. However, the clinical relevance of these lesions may be limited, as only a small number of these ulcerations progress to overt and clinically important GI bleeding [5]. The reported incidence of GI bleeding in ICU patients varies from 0.6 % to 7.0 % [1, 6–10], which may be explained by case mix, lack of a universally agreed definition, and difficulties in diagnosing GI bleeding. GI bleeding in critically ill patients is associated with adverse outcomes, including 2–4 times increased risk of death and increased length of ICU stay of 4–8 days [1]. Most data on GI bleeding in critically ill patients are 15–20 years old, and diagnostics, treatment and the process of care for critically ill patients have improved considerably over that period of time [11, 12]. Consequently, the incidence of, risk factors for, and prognostic importance of GI bleeding in critically ill patients today are largely unknown.

To prevent GI bleeding in critically ill patients, stress ulcer prophylaxis (SUP) is today recommended in international guidelines and considered a standard of care in the ICU [13–15]. Despite this, indications for initiating SUP vary considerably [16–18]. These inconsistencies in initiation of SUP may be explained by ambiguous research data and variable recommendations [1, 6, 13–15, 19]. Also, the overall evidence for the use of SUP in critically ill patients has been questioned [20].

The aims of this international 7-day inception cohort study were to describe the prevalence of, risk factors for, and prognostic importance of GI bleeding for all-cause mortality in adult ICU patients, and to describe current use of acid suppressants. We hypothesised that the prevalence of clinically important GI bleeding in ICUs today is low, and that acid suppressants are frequently used.

Methods

This was an international 7-day inception cohort study with prospective data collection, which was approved by the Danish Data Protection Agency (No. 30-1115) and the Danish Health and Medicines Authorities (No. 3-3013-463/1/). The relevant ethical committees in each country waived informed consent because of the observational design. A protocol was developed and published prior to the conduct of the study, and a statistical analysis plan was prepared and published prior to analysis of data (www.sup-icu.com/downloads). The manuscript has been prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [21].

Organisation of the study

A steering committee was formed to design and coordinate the study. National and local research teams managed the study locally. ICUs were invited by email to participate in the study, participation was voluntary and no reimbursement was given. The principal investigator at each participating ICU chose an optional 7-day study period for patient enrolment between 1 December 2013 and 30 April 2014.

Study population

All patients admitted to the ICU in the 7-day period were eligible for enrolment in the study. We screened all patients for inclusion who were aged 18 years or above and acutely admitted to the ICU. We excluded patients with

GI bleeding upon admission to the ICU, and patients previously admitted to an ICU during the index hospital admission. If a patient was readmitted to the ICU, data collection was resumed.

Data extraction and management

A secure Web-based case report form (eCRF) was developed by the Steering Committee and Experlytics AB (Malmö, Sweden), pilot-tested on 20 patients by six investigators, and finalised.

We recorded co-existing diseases, disease severity and organ failure at admission, use of organ support and acid suppressants, data on coagulopathy and bleeding during the entire ICU stay, and after 90 days, we obtained vital status (alive/death) and date of hospital discharge (Supplement pages 3 and 4).

Definition of GI bleeding

Overt GI bleeding: one or more of the following: (1) haematemesis, (2) coffee ground emesis, (3) melaena, (4) haematochezia, (5) bloody nasogastric aspirate.

Clinically important GI bleeding: overt bleeding and at least one of the following features within 24 h of overt bleeding in the absence of other causes (clinical evaluation): (1) decrease in blood pressure of 20 mmHg or more, (2) start of/increase of vasopressor of 20 % or more, (3) decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l), (4) transfusion of two or more units of red blood cells during the bleeding episode.

Outcome measures

The primary outcome measure was clinically important GI bleeding during the ICU stay. Secondary outcome measures were overt GI bleeding in ICU and mortality 90 days after inclusion.

Statistical analysis

For this observational study with consecutive sampling, $\alpha = 0.05$, $\beta = 0.2$, and an estimated prevalence of clinically important GI bleeding in the ICU of 2–4 % [1, 22], we planned to include at least 1,000 patients to yield expected 95 % confidence intervals (CI) of 1.1–2.9 % (prevalence rate of 2 %) or 2.8–5.2 % (prevalence rate of 4 %) [23].

Data were validated and analysed according to the predefined statistical analysis plan using SAS version 9.3. Baseline data were stratified according to the occurrence of clinically important GI bleeding in ICU [24], and presented as medians with interquartile ranges (IQR) for continuous data, and numbers (%) for categorical data. Differences were assessed by X^2 test and Mann–Whitney U test, respectively. All statistical tests were two-tailed, and $P < 0.05$ was considered statistically significant.

The prevalence and pattern of missing values for each variable were collected and analysed according to the predefined statistical analysis plan. No outcome data were missing. There were no highly incomplete covariates (more than 33 % of observations missing) in the data set. Missing data were not missing completely at random (Little's test, $P < 0.001$). Consequently, multiple imputation for the missing values was performed [25, 26]. Fully conditional specification method with ten imputed data sets and with inclusion of the outcome measures and baseline variables (Supplement and Table 1) was used.

Binary logistic regression analysis was used to determine baseline (ICU admission) risk factors for overt and clinically important GI bleeding. To present the most conservative estimate, inclusion of known prognostic covariates was done in a single step/block (enter modelling) [27]. The regression models of the imputed data set were validated using goodness-of-fit tests and model diagnostics, and showed no indication of lack of fit. Results are presented as crude and adjusted odds ratios (ORs) with 95 % CIs. We adjusted for the following predefined covariates: (1) country, (2) type of hospital, (3) type of ICU, (4) size of ICU, (5) length of hospital stay prior to ICU admission.

Binary logistic regression analysis was also used to determine the crude and adjusted OR (95 % CI) for the association between GI bleeding and 90-day mortality. We adjusted for the following predefined covariates: age, gender, one or more co-existing diseases (y/n), acute/elective surgery prior to admission (y/n), invasive mechanical ventilation (y/n), renal replacement therapy (RRT) (y/n), circulatory support (y/n), coagulopathy (y/n) and SOFA score (continuous) on ICU admission. The results are presented as crude and adjusted ORs with 95 % CIs for patients with no GI bleeding, patients with overt GI bleeding and those with clinically important GI bleeding. Finally, the prevalence and pattern of acid suppressants use were assessed.

Results

A total of 97 ICUs in 11 countries participated: Australia (4), Canada (5), Denmark (24), Finland (6), Iceland (1), Italy (1), the Netherlands (2), New Zealand (4), Norway (2), Sweden (10) and the UK (38). Forty-nine per cent of the hospitals were university hospitals and 93 % of ICUs were mixed ICUs. The majority of ICUs (68 %) had more than ten beds (Supplement, page 5).

Table 1 Baseline characteristics of patients

Characteristic	All (n = 1,034)	No clinically important bleeding (n = 1,007)	Clinically important bleeding (n = 27)	P[a]	Patients with missing values, n (%)[†]
Age, years, median (IQR)	63 (48–74)	64 (48–75)	58 (51–70)	0.324	0 (0.0)
Male, gender, n (%)	576 (55.7)	562 (55.8)	14 (51.9)	0.683	0 (0.0)
SOFA score, median (IQR)	6 (4–8)	6 (4–8)	10 (7–14)	<0.001	245 (23.4)
SAPS II, median (IQR)	42 (31–54)	41 (31–53)	52 (45–66)	<0.001	180 (17.4)
Chronic obstructive pulmonary disease, asthma or other chronic lung disease, n (%)	205 (19.8)	201 (20.0)	4 (14.8)	0.508	0 (0.0)
Previous myocardial infarction, n (%)	101 (9.8)	99 (9.8)	4 (14.8)	0.394	0 (0.0)
Severe chronic heart failure (NYHA 3–4), n (%)	56 (5.4)	54 (5.4)	2 (7.4)	0.643	0 (0.0)
Chronic renal failure, n (%)	74 (7.2)	72 (7.1)	2 (7.4)	0.959	0 (0.0)
Liver cirrhosis or increased bilirubin (>33 μmol/l), n (%)	124 (12.0)	110 (10.9)	14 (51.9)	<0.001	38 (3.7)
Metastatic cancer, n (%)	46 (4.4)	44 (4.4)	2 (7.4)	0.450	0 (0.0)
Active haematologic cancer, n (%)	36 (3.5)	34 (3.4)	2 (7.4)	0.260	0 (0.0)
AIDS, n (%)	3 (0.3)	3 (0.3)	0 (0)	0.776	0 (0.0)
Immunosuppression[b], n (%)	50 (4.8)	49 (4.9)	1 (3.7)	0.781	0 (0.0)
Coagulopathy on ICU admission[c], n (%)	128 (12.4)	118 (11.7)	10 (37.0)	<0.001	0 (0.0)
Comorbidities, n (%)					
0	501 (48.5)	496 (4.9)	5 (18.5)	0.002	0 (0.0)
1	318 (30.8)	308 (30.6)	10 (37.0)	0.474	0 (0.0)
2	153 (14.8)	147 (14.6)	6 (22.2)	0.271	0 (0.0)
3	46 (4.4)	41 (4.1)	5 (18.5)	0.005	0 (0.0)
>3	16 (1.5)	15 (1.5)	1 (3.7)	0.347	0 (0.0)
Mechanical ventilation on ICU admission, n (%)	544 (52.6)	527 (52.3)	17 (63.0)	0.275	0 (0.0)
Circulatory support on ICU admission, n (%)	469 (45.4)	450 (44.7)	19 (70.3)	0.009	7 (0.7)
Renal replacement therapy on ICU admission, n (%)	70 (6.8)	61 (6.1)	9 (33.3)	<0.001	0 (0.0)
Treatment with NSAID or acetylsalicylic acid prior to hospital admission, n (%)	210 (20.3)	206 (20.5)	4 (14.8)	0.472	0 (0.0)
Treatment with NSAID or acetylsalicylic acid initiated during present hospital admission prior to ICU admission, n (%)	70 (6.8)	68 (6.8)	2 (7.4)	0.894	0 (0.0)
Treatment with anticoagulant drugs prior to hospital admission, n (%)	134 (13.0)	130 (12.9)	4 (14.8)	0.771	0 (0.0)
Treatment with anticoagulant drugs initiated during present hospital admission prior to ICU admission, n (%)	81 (7.8)	77 (7.6)	4 (14.8)	0.171	0 (0.0)
Use of acid suppressants on ICU admission, n (%)	387 (37.4)	374 (37.1)	13 (48.1)	0.243	0 (0.0)

AIDS acquired immune deficiency syndrome, *NSAID* non-steroidal anti-inflammatory drugs, *NYHA* New York Heart Association, *SAPS* Simplified Acute Physiology Score, *SOFA* Sepsis-related Organ Failure Assessment

[a] For the comparison of patients with vs. without clinically important GI bleeding

[b] Treatment with at least 0.3 mg/kg/day of prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission

[c] Defined as platelets $<50 \times 10^9$/l (50,000 mm^3) and/or INR >1.5 during current hospital admission

We included 1,034 patients with a median age of 63 (IQR 48–74) years, 56 % were men and the majority were medical patients (66 %). Median SAPS II and SOFA scores on admission were 42 (31–54) and 6 (4–8), respectively. These and several other baseline characteristics differed between the patients who did and did not develop clinically important GI bleeding during ICU stay (Table 1).

GI bleeding

Twenty-seven of 1,034 (2.6 %, 95 % CI 1.6–3.6) developed clinically important GI bleeding, and overall, 49 of 1,034 patients (4.7 %, 3.4–6.0) had at least one episode of overt GI bleeding during the ICU stay. Five of the 27 patients with clinically important GI bleeding bled on the first day of ICU stay, and eight bled on day 2 (Fig. 1 and Supplement, page 6). Median time from ICU admission to bleeding was 3 (IQR 2–6) days. Ten out of 27 patients with clinically important bleeding (37 %) had at least one diagnostic/therapeutic procedure performed. Nine patients (33 %) had oesophago-gastro-duodenoscopy performed. Two of the patients with clinically important GI bleeding (7 %) had an ulcer diagnosed at endoscopy, and no patients had varices or gastritis diagnosed. Following endoscopy, two patients (7 %) had a laparotomy performed, and 2 patients (7 %) were treated with coiling.

Baseline variables independently associated with overt and clinically important GI bleeding are presented in Table 2.

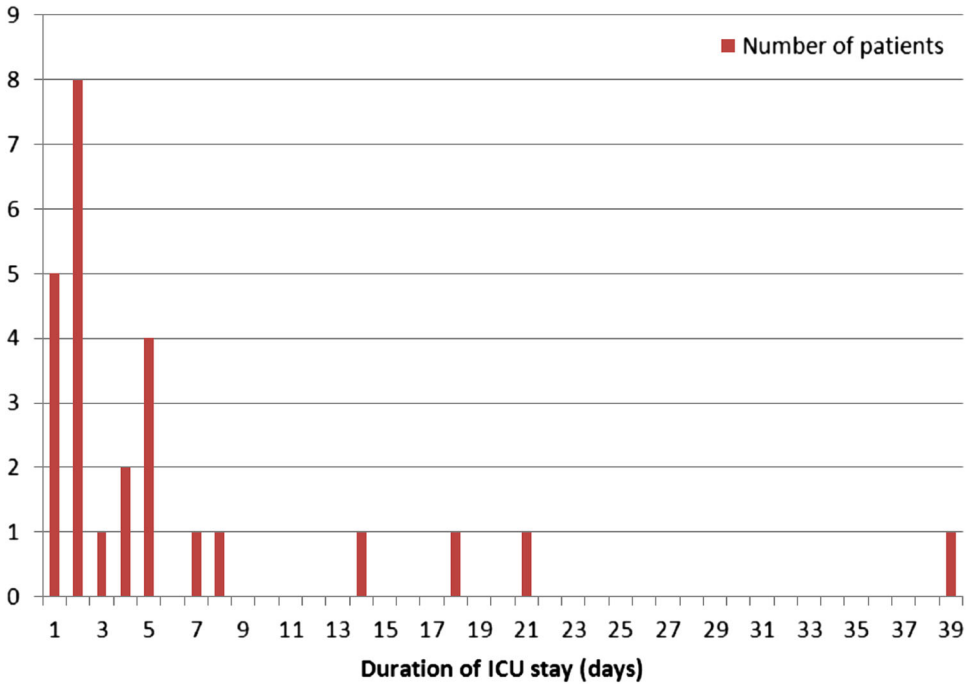

Fig. 1 Number of patients with clinically important gastrointestinal bleeding according to duration of ICU stay

Acid suppressants

Prior to ICU admission 378 (37 %) of the 1,034 patients received acid suppressants, on the day of admission this had increased to 56 % and on day 2–70 %. On the last day in ICU 57 % received acid suppressants (Fig. 2). Seventy-three per cent of all patients received acid suppressants at least one day during the ICU stay. Proton pump inhibitors (PPIs) were given to 573 of 1,034 patients (55 %) and histamine-2 receptor antagonists (H2RA) to 172 of patients (17 %). Pantoprazole was the most frequently used PPI [242/1,034 (23 %)]. All patients with clinically important GI bleeding were prescribed acid suppressants. Sixteen out of the 27 patients (59 %) received acid suppressants prior to the first GI bleeding episode, and in eight patients (30 %) use of acid suppressants was initiated on the day of GI bleeding.

Mortality

The overall 90-day mortality rate was 26.2 %; 256 of the 1,007 (25.4 %) patients without clinically important GI bleeding had died at day 90 as compared to 15 of 27 patients (55.6 %) with clinically important GI bleeding. The crude and adjusted association between overt GI bleeding and 90-day mortality was OR 1.70 (0.70–4.10) and 1.17 (0.43–3.21), whereas the crude and adjusted association between clinically important GI bleeding and 90-day mortality was 3.72 (1.72–8.04) and 1.70 (0.68–4.28), respectively (Fig. 3). The 90-day mortality was 25.0 % in patients without clinically important GI bleeding who had acid suppressants initiated during the ICU stay.

Discussion

In this international 7-day inception cohort study, 4.7 and 2.6 % of the patients experienced overt and clinically important GI bleeding, respectively. Independent baseline risk factors for clinically important GI bleeding were any three or more co-existing diseases, co-existing liver disease, RRT, co-existing and acute coagulopathy, use of acid suppressants on ICU day 1 and higher SOFA score on ICU day 1. The crude 90-day mortality was increased in patients with clinically important bleeding, but this was not statistically significant in the confounder-adjusted analysis. Fifty-six per cent of patients received acid suppressants on day 1 and 73 % received an acid suppressant during their ICU stay.

The strengths of our study include the 7-day inception cohort design with prospective and consecutive inclusion of a large number of patients from multiple ICUs in numerous countries, the prespecified and published protocol and statistical analysis plan [28], the complete follow-up of outcomes, the reporting and handling of missing data, and the adjustment for known potential confounders. Consequently, we believe that these results have a low risk of bias with high external validity. The limitations of our study include the observational design, which has an inherent risk of confounding, including residual confounding and confounding by indication, and

Table 2 Association between characteristics on first day of ICU admission and overt and clinically important gastrointestinal (GI) bleeding

Characteristic	Overt GI bleeding[a]		Clinically important GI bleeding[b]	
	Crude OR (95 % CI)	Adjusted[†] OR (95 % CI)	Crude OR (95 % CI)	Adjusted[†] OR (95 % CI)
Age, years	1.00 (0.99–0.12)	1.00 (0.99–1.02)	1.00 (0.98–1.02)	0.99 (0.97–1.01)
Male, gender	0.82 (0.46–1.46)	0.80 (0.44–1.45)	0.85 (0.40–1.83)	0.85 (0.39–1.89)
SOFA score on index day	1.24 (1.14–1.34)	1.25 (1.14–1.38)	1.39 (1.25–1.55)	1.37 (1.22–1.55)
ICU admission type				
Elective surgery	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
Emergency surgery	1.24 (0.27–5.60)	1.42 (0.29–7.02)	1.41 (0.17–11.51)	2.19 (0.23–20.95)
Medical	1.31 (0.30–5.59)	1.43 (0.31–6.65)	1.42 (0.19–10.84)	2.03 (0.23–18.03)
Comorbid conditions				
Chronic lung disease	0.66 (0.29–1.50)	0.65 (0.28–1.48)	0.70 (0.24–2.04)	0.69 (0.23–2.05)
Previous MI	0.80 (0.28–2.26)	0.60 (0.20–1.81)	1.60 (0.54–4.71)	1.13 (0.35–3.71)
Chronic heart failure	1.60 (0.55–4.60)	1.15 (0.37–3.59)	1.41 (0.33–6.12)	0.75 (0.15–3.87)
Chronic renal failure	1.51 (0.58–3.93)	1.94 (0.72–5.25)	1.04 (0.24–4.47)	1.34 (0.30–6.00)
Chronic liver disease	4.06 (2.18–7.56)	4.51 (2.30–8.86)	8.19 (3.75–17.89)	7.64 (3.32–17.57)
Metastatic cancer	2.62 (0.99–6.95)	2.32 (0.85–6.52)	1.75 (0.40–7.63)	1.36 (0.28–6.48)
Haematological cancer	2.65 (0.90–7.81)	3.08 (0.98–9.63)	2.29 (0.52–10.06)	2.69 (0.58–12.54)
AIDS	–	–	–	–
Immunosuppression[a]	1.81 (0.63–5.26)	1.56 (0.50–4.93)	0.75 (0.10–5.66)	0.64 (0.07–5.81)
Coagulopathy[b]	2.73 (1.41–5.30)	2.64 (1.29–5.42)	4.43 (1.98–9.91)	4.22 (1.74–10.23)
Number of comorbid conditions				
0	1.00 (REF)	1.00 (REF)	1.00 (REF)	1.00 (REF)
1	2.32 (1.11–4.89)	2.51 (1.15–5.46)	3.24 (1.10–9.56)	3.03 (1.00–9.25)
2	2.98 (1.30–6.84)	2.80 (1.17–6.67)	4.08 (1.23–13.55)	3.22 (0.94–11.06)
3	4.62 (1.56–13.65)	4.24 (1.31–13.72)	12.01 (3.34–43.19)	9.29 (2.34–36.94)
>3	5.47 (1.12–26.64)	6.66 (1.22–36.42)	6.63 (2.15–20.45)	8.88 (2.74–28.80)
Treatment with acid suppressants prior to hospital admission	1.27 (0.71–2.27)	1.39 (0.75–2.59)	1.57 (0.73–3.38)	1.47 (0.66–3.32)
Treatment with NSAID or acetylsalicylic acid prior to hospital admission	0.76 (0.35–1.64)	0.69 (0.31–1.54)	0.68 (0.23–1.98)	0.58 (0.19–1.75)
Treatment with anticoagulant drugs prior to hospital admission	1.55 (0.73–3.27)	1.26 (0.58–2.77)	1.17 (0.40–3.45)	0.87 (0.27–2.77)
Treatment with NSAID or acetylsalicylic acid initialised during present hospital admission prior to ICU admission	0.89 (0.27–2.95)	0.97 (0.28–3.36)	1.11 (0.26–4.76)	1.17 (0.25–5.39)
Treatment with anticoagulant drugs initialised during present hospital admission prior to ICU admission	2.05 (0.89–4.73)	2.04 (0.79–5.24)	2.10 (0.71–6.23)	1.84 (0.51–6.63)
Mechanical ventilation on first day of ICU admission	1.56 (0.88–2.87)	1.48 (0.79–2.78)	1.55 (0.70–3.42)	1.32 (0.57–3.06)
Circulatory support on first day of ICU admission	2.68 (1.47–4.90)	2.39 (1.28–4.46)	2.80 (1.24–6.28)	2.31 (0.99–5.40)
Renal replacement therapy on first day of ICU admission	6.64 (3.38–13.05)	7.35 (3.47–15.56)	7.75 (3.34–17.98)	6.89 (2.72–17.48)
Coagulopathy[b] on first day of ICU admission	3.93 (2.17–7.09)	4.06 (2.16–7.63)	5.50 (2.54–11.91)	5.21 (2.29–11.83)
Treatment with NSAID or acetylsalicylic acid on first day of ICU admission	0.41 (0.10–1.71)	0.41 (0.10–1.79)	–	–

Table 2 continued

Characteristic	Overt		Clinically important	
	GI bleeding[a]		GI bleeding[b]	
	Crude OR (95 % CI)	Adjusted[†] OR (95 % CI)	Crude OR (95 % CI)	Adjusted[†] OR (95 % CI)
Treatment with anticoagulant drugs on first day of ICU admission	2.06 (1.00–4.25)	2.25 (1.04–4.87)	1.78 (0.66–4.79)	1.77 (0.61–5.16)
Treatment with thrombolysis on first day of ICU admission	1.45 (0.19–11.21)	1.49 (0.17–12.90)	–	–
Treatment with acid suppressants on first day of ICU admission	2.23 (1.17–4.25)	2.95 (1.44–6.06)	3.51 (1.32–9.35)	3.61 (1.28–10.20)
Treatment with acid suppressants prior to hospital admission	1.27 (0.71–2.27)	1.39 (0.75–2.59)	1.57 (0.73–3.38)	1.47 (0.66–3.32)

Binary logistic regression with crude and adjusted odds ratios (ORs) with 95 % confidence intervals (CIs). –Analysis not possible because of too few events
Statistically significant association
AIDS acquired immune deficiency syndrome, *NSAID* non-steroidal anti-inflammatory drugs, *NYHA* New York Heart Association
[†] Adjustments for covariates (according to Statistical Analysis Plan): (1) country, (2) type of hospital, (3) type of ICU, (4) size of ICU, (5) length of hospital stay prior to index day
[a] Treatment with at least 0.3 mg/kg/day of prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission
[b] Defined as platelets $<50 \times 10^9$/l (50,000 mm^3) and/or INR >1.5 during current hospital admission

consequently an inability to draw conclusions on interventions and causation. The majority of participating sites were Danish or British. Study sites were not selected to be representative of all ICUs, participation was voluntary and participating sites may differ from those declining participation and those not invited. We did not exclude patients with known peptic ulcer disease and we did not evaluate mortality attributable to GI bleeding, and when adjusting mortality data we may not have included all important variables. Furthermore, we did not collect data on the potential harm associated with use of acid suppressants, including pneumonia [7, 22], *Clostridium difficile* infection [22, 29] and myocardial infarction [30]. Finally, we used a slightly different definition of clinically important bleeding as compared to the definition first described by Cook and colleagues in 1991 [31]. We chose to include a criterion involving use of vasopressors as they are frequently used in the ICU, and an increase would hide a decrease in blood pressure.

The reported prevalence of GI bleeding in our study was low as expected and, compared to previous reports using comparable definitions, the prevalence has not changed much in the last 20 years. In a systematic review of 46 randomised clinical trials (RCT) comprising 4,409 patients, Cook et al. [31] reported a 2.6 % incidence of clinically important GI bleeding in the ICU in 1991. In 2001, an incidence of clinically important GI bleeding of 3.5 % (2.7–4.6 %) was reported in 1,666 patients mechanically ventilated for more than 48 h [1]. The somewhat higher incidence reported in the latter study can most likely be attributed to the fact that the study was conducted in patients mechanically ventilated for longer than 48 h, a well-established risk factor for GI bleeding [6]. In a before and after study from 2003, Faisy et al. [19] compared the prevalence of GI bleeding in ICU patients during a period where SUP was used and a period where SUP was not used. In the period where SUP was used clinically important GI bleeding occurred in 1.4 % (1.5–2.2) of the patients, whereas in the period without use of SUP the prevalence was 1.1 % (0.3–1.8) [19]. In both time periods, the patients with clinically important GI bleeding had significantly higher SAPS II than those without important GI bleeding. In the present study, SAPS II and SOFA scores at admission were higher in patients with clinically important GI bleeding, and SOFA score on the first day in ICU was independently associated with clinically important GI bleeding, suggesting that severity of illness contributes or predisposes to the development of GI bleeding in critically ill patients.

Because of increased costs and potential harmful side effects, including pneumonia [7, 32] and *C. difficile* infection [22, 29], there is consensus on withholding SUP in patients without risk factors for GI bleeding [5, 13]. Over the years, attempts have been made to identify high-risk patients [6, 33], and a number of independent risk factors have been identified, including mechanical ventilation for

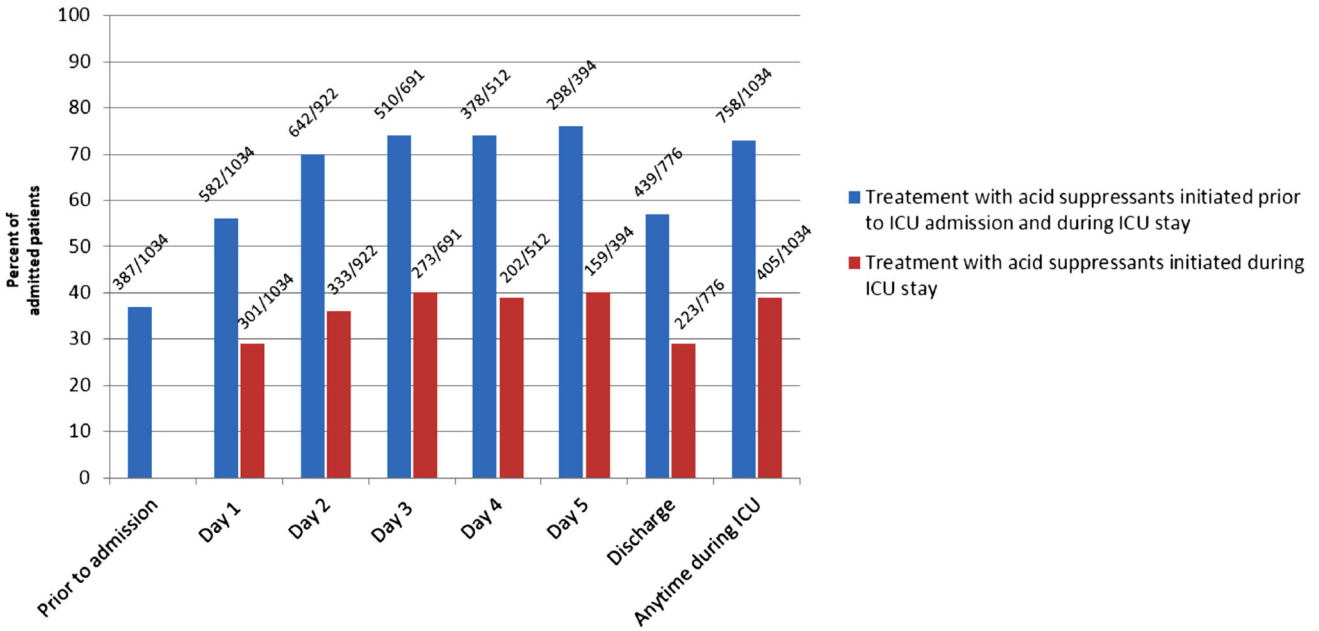

Fig. 2 Use of acid suppressing agents and number of patients with clinically important gastrointestinal bleeding during ICU stay

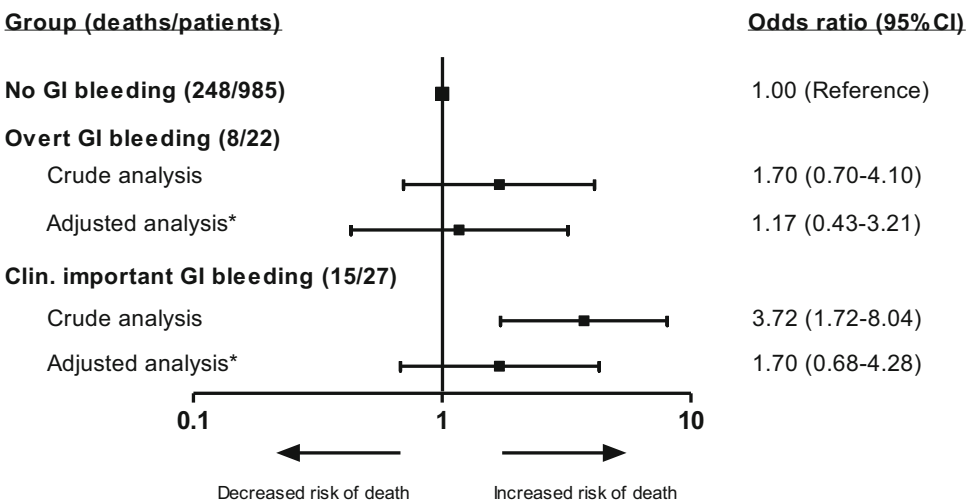

Fig. 3 Odds ratios (95 % confidence intervals) for 90-day mortality in patients who had no gastrointestinal (GI) bleeding, overt GI bleeding and clinically important GI bleeding during ICU stay. *Binary logistic regression analysis with adjustment for the following covariates according to the statistical analysis plan: age on the first day of ICU admission, SOFA score on the first day of ICU admission, comorbidity (y/n), gender, type of admission (medical/emergency surgery/elective surgery), mechanical ventilation on the first day of ICU admission (y/n), coagulopathy on the first day of ICU admission (y/n), circulatory support on the first day of ICU admission (y/n), renal replacement therapy on the first day of ICU admission (y/n)

more than 48 h [6], coagulopathy [6], acute kidney injury (AKI) [33] and acute or chronic liver disease [34]. It appears that these factors are still valid because we also found that co-existing and acute coagulopathy, AKI, and co-existing liver disease were independent risk factors for clinically important GI bleeding in the ICU. In contrast to the previous findings, we did not find that mechanical ventilation was a risk factor for GI bleeding [6]. This may be due to differences between the examined cohorts. Firstly, patients in [6] had low overall mortality (9.7 %) as compared to the overall 90-day mortality rate of 26 % in the present study. Secondly, 48.5 % of the patients in [6] underwent cardiovascular surgery and only 1.6 % were diagnosed with sepsis, which is very different from our cohort where 93 % of the patients were from mixed ICUs and all were emergency admissions [11, 35]. Our

finding of RRT on the first ICU day as an independent risk factor for clinically important GI bleeding is supported by observations in an RCT of ranitidine vs. sucralfate [33]. It was shown that AKI, defined as peak serum creatinine, was an independent risk factor for clinically important GI bleeding among 1,077 mechanically ventilated patients [33]. Despite differences in the populations studied and in the definition of AKI, there is evidence of an association between AKI and clinically important GI bleeding. We did not find a statistically significant association in the adjusted analysis between circulatory support and clinically important bleeding; this may be because of inadequate power and the resulting imprecision [36]. The point estimate, the unadjusted analysis and the estimates on overt GI bleeding all point towards a 2- to 3-fold increased risk of GI bleeding in patients receiving circulatory support. Acute or co-existing liver disease has been reported as an independent risk factor for GI bleeding in patients with sepsis or septic shock (OR 3.75, 2.19–6.44) [34]. Correspondingly, our data support that co-existing liver disease is a risk factor in the general ICU population. We also found that three or more co-existing diseases and co-existing coagulopathy were independent risk factors for clinically important GI bleeding, indicating that co-existing disease is an important risk factor for GI bleeding in critically ill patients in the ICU. The association between use of acid suppressants on ICU admission and clinically important GI bleeding may reflect that patients with co-existing diseases (comorbidity or increased disease severity) have an a priori higher chance of being prescribed acid suppressants prior to ICU admission on the basis of perceived increased risk of stress ulcer bleeding during critical illness (confounding by indication).

Our findings suggest that acid suppressants were commonly used drugs in the ICU and in the hospital in general in 2014, and that PPIs were most commonly used. In 2014, a point prevalence study in 584 patients in 58 ICUs found that 38 % of the patients received acid suppressants prior to ICU admission, and a total of 84 % received acid suppressants at some time during ICU stay [18]. In recent years, concerns have been raised about inappropriate use of SUP [37, 38]. A survey in the USA found that 53 % of critically ill patients either received SUP without a clear clinical indication, or did not receive SUP when it was perceived to be clinically indicated [39]. Moreover, discharge from hospital with acid suppressants after SUP was initiated in the ICU—despite the lack of indications for continued use—has received attention [38], as this results in additional drug costs, and possibly additional healthcare costs if long-term harm develop [40]. With the high proportion of patients being treated with acid suppressants, there is a pressing need to clarify the potential benefit versus harm of prophylaxis.

Conclusions

In our international 7-day inception cohort study we found that acutely ill patients in the ICU in 2014 still suffer from GI bleeding, and identification of patients with increased risk of GI bleeding is possible upon ICU admission. Clinically important GI bleeding is rare and was not associated with increased adjusted 90-day mortality, which largely can be explained by severity of comorbidity, other organ failures and age. Acid suppressants, in particular PPIs, are very frequently used in the ICU, but it still remains unresolved whether the use of acid suppressants prevents stress-related GI bleeding in ICU patients. Whether there is overall benefit or harm of SUP is ambiguous, and to ensure patient safety, there is a need for a large, high-quality RCT of SUP versus placebo in ICU patients at risk of clinically important GI bleeding.

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Conflicts of interest All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare the following interests: DC received donated study drugs in 1992 from a company that does not exist anymore while leading an RCT funded by the Canadian government. The ICU at Rigshospitalet receives support for other research projects from Fresenius Kabi and CSL Behring. MW reports personal fees from KaloBios Pharmaceuticals, personal fees from Wiley Publishing, personal fees from Fisher & Paykel, personal fees from Merck (MSD) and non-financial support from Qualitech Healthcare, outside the submitted work. On behalf of all other authors the corresponding author states that there are no conflicts of interest.

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Paper V

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Trials

STUDY PROTOCOL Open Access

Stress ulcer prophylaxis with a proton pump inhibitor versus placebo in critically ill patients (SUP-ICU trial): study protocol for a randomised controlled trial

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Abstract

Background: Critically ill patients in the intensive care unit (ICU) are at risk of clinically important gastrointestinal bleeding, and acid suppressants are frequently used prophylactically. However, stress ulcer prophylaxis may increase the risk of serious adverse events and, additionally, the quantity and quality of evidence supporting the use of stress ulcer prophylaxis is low. The aim of the SUP-ICU trial is to assess the benefits and harms of stress ulcer prophylaxis with a proton pump inhibitor in adult patients in the ICU. We hypothesise that stress ulcer prophylaxis reduces the rate of gastrointestinal bleeding, but increases rates of nosocomial infections and myocardial ischaemia. The overall effect on mortality is unpredictable.

Methods/design: The SUP-ICU trial is an investigator-initiated, pragmatic, international, multicentre, randomised, blinded, parallel-group trial of stress ulcer prophylaxis with a proton pump inhibitor versus placebo (saline) in 3350 acutely ill ICU patients at risk of gastrointestinal bleeding. The primary outcome measure is 90-day mortality. Secondary outcomes include the proportion of patients with clinically important gastrointestinal bleeding, pneumonia, *Clostridium difficile* infection or myocardial ischaemia, days alive without life support in the 90-day period, serious adverse reactions, 1-year mortality, and health economic analyses.
The sample size will enable us to detect a 20 % relative risk difference (5 % absolute risk difference) in 90-day mortality assuming a 25 % event rate with a risk of type I error of 5 % and power of 90 %. The trial will be externally monitored according to Good Clinical Practice standards. Interim analyses will be performed after 1650 and 2500 patients.

Conclusion: The SUP-ICU trial will provide high-quality data on the benefits and harms of stress ulcer prophylaxis with a proton pump inhibitor in critically ill adult patients admitted in the ICU.

Trial registration: ClinicalTrials.gov Identifier: NCT02467621.

Keywords: Stress ulcer prophylaxis, Gastrointestinal bleeding, Intensive care unit, Critically ill, Randomised clinical trial, Placebo, Adverse event

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Background

Critically ill patients are at risk of stress-related gastrointestinal (GI) mucosal damage, ulceration and bleeding [1]. Endoscopic studies have shown that gastric erosions are present in up to 90 % of patients by the third day in the intensive care unit (ICU) [2, 3]. These lesions are, in the vast majority of patients, superficial and asymptomatic, but some can progress and result in overt and clinically important GI bleeding [4]. Clinically important GI bleeding in the ICU is a serious condition, with an estimated one- to four-fold increased risk of death and excess length of ICU stay of 4–8 days [1, 5]. It has been suggested that prophylaxis with acid suppressants reduces the risk of GI bleeding and hence the risk of death [6]. In this context, stress ulcer prophylaxis (SUP) was introduced and is recommended in international guidelines [7–10] and regarded as standard of care in the ICU [5, 11]. However, clinical research has not been able to confirm that SUP improves outcome [12]. A recent meta-analysis comprising 20 randomised clinical trials (RCTs) comparing proton pump inhibitors (PPIs) and/or histamine-2-receptor antagonists (H2RAs) versus placebo or no prophylaxis did not find any differences in patient important outcome measures between the SUP and the placebo/no prophylaxis groups [12]. Furthermore, concern has been expressed about potentially increased risks of side effects in patients receiving prophylactic treatment with acid suppressants [13–16]. The higher gastric pH in these patients may compromise host immunity and increase the risk of pneumonia and *Clostridium difficile* infection (CDI) [15, 17]. However, no meta-analyses of randomised trials have shown a significantly increased risk of nosocomial pneumonia when using SUP compared to placebo/no prophylaxis [12, 18]. Additionally, no trials have assessed the incidence of CDI in an ICU setting, but a recently published large cohort study found a 2–4 fold increased risk of CDI in adult mechanically ventilated patients receiving PPIs compared to H2RAs [19]. Studies conducted outside the ICU have demonstrated similar findings [20, 21]. Also, an association between the use of PPIs and an increased risk of cardiovascular events has been suggested [18, 22, 23].

Taken together, the balance between benefits and harms of SUP is unclear in critically ill patients in the ICU. The aim of the SUP-ICU trial is to assess the benefits versus harms of PPI (pantoprazole) in acutely ill adults in the ICU. We hypothesise that a PPI reduces the rates of GI bleeding, but increases the rates of nosocomial infections and myocardial ischaemia. The effect on overall mortality is, therefore, unpredictable.

Methods

Trial design

The SUP-ICU trial is an investigator-initiated, pragmatic, international, multicentre, randomised, blinded, parallel-group trial of SUP with a PPI versus placebo.

Approvals

The trial is approved by the Danish Health and Medicine Agency (2015030166), the Committees on Health Research Ethics in the Capital Region of Denmark (H-15003141) and the Danish Data Protection Agency (RH-2015-3203695) and registered at ClinicalTrials.gov (Identifier: NCT02467621).

Setting

European ICUs admitting adult patients.

Population

Inclusion criteria

All adult (18 years or older) patients who are acutely admitted to the ICU with one or more risk factors for GI bleeding [5]:

- Shock (continuous infusion with vasopressors or inotropes, systolic blood pressure below 90 mmHg, mean arterial blood pressure below 70 mmHg or plasma lactate level 4 mmol/l or above)
- Acute or chronic intermittent or continuous renal replacement therapy (RRT)
- Invasive mechanical ventilation which is expected to last more than 24 hours
- Coagulopathy (platelets below 50×10^9/l, or international normalised ratio (INR) above 1.5, or prothrombin time (PT) above 20 s) documented within the last 24 hours
- Ongoing treatment with anticoagulant drugs (prophylactic doses excluded)
- History of coagulopathy (platelets below 50×10^9/l or INR above 1.5 or PT above 20 s within the 6 months prior to hospital admission)
- History of chronic liver disease (portal hypertension, cirrhosis proven by biopsy, computed tomography (CT) scan or ultrasound or history of variceal bleeding or hepatic encephalopathy)

Exclusion criteria

- Contraindications to PPIs (including intolerance of PPIs and treatment with atazanavir (anti-human immunodeficiency virus (HIV) medication))
- Current daily treatment with a PPI and/or a H2RA
- GI bleeding of any origin during current hospital admission

- Diagnosed with peptic ulcer during current hospital admission
- Organ transplant during current hospital admission
- Withdrawal from active therapy or brain death
- Fertile woman with positive test for urinary or plasma human chorionic gonadotropin (hCG)
- Consent according to national regulations not obtainable

Trial medication

Enrolled patients will be randomised to receive either pantoprazole 40 mg (pantoprazole, Actavis, Gentofte, Denmark) or placebo, given once daily intravenously, from randomisation until ICU discharge or death for a maximum of 90 days. Identical vials with and without pantoprazole powder will be masked with a full covering label. The nurse caring for the patient will have access to an electronic medication distribution system, which allows the allocation of the appropriate vial to the patient. The nurse will add 10 ml of sodium chloride to the vial, shake it, and administer the contents intravenously to the patient. As the powder immediately dissolves to a colourless fluid it will not be possible to distinguish dissolved pantoprazole in sodium chloride from sodium chloride alone.

Outcome measures

Primary outcome measure

All-cause mortality 90 days after randomisation

Secondary outcome measures

- Proportion of patients with one or more of the following adverse events during ICU stay: clinically important GI bleeding, pneumonia, CDI, or acute myocardial ischaemia
- Proportion of patients with clinically important GI bleeding during ICU stay
- Proportion of patients with one or more infectious adverse events (pneumonia or CDI) during ICU stay
- Days alive without use of mechanical ventilation, RRT or circulatory support in the 90-day trial period
- Number of serious adverse reactions (SARs) during ICU stay
- Mortality 1 year after randomisation
- A health economic analysis will be performed. The analytic details will be based on the results of the trial and specified at that time (cost-benefit versus cost-minimisation analyses)

The specific elements of the composite outcomes will be reported in the primary publication.

Definitions

See Appendix 1.

Screening

All patients referred to a participating clinical trial site will be considered for participation (screened). Patients will be eligible if they fulfil all of the inclusion criteria and none of the exclusion criteria listed. Inclusion and exclusion of patients (including reasons for exclusion) will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement [24].

Randomisation

Staff at trial sites will have 24-hour access to web-based central randomisation allowing immediate and concealed allocation of trial medication. Randomisation will be performed in blocks with varying block sizes according to the generation of the allocation sequence by the Copenhagen Trial Unit (CTU) [25]. A unique patient identification number will be entered into the system to ensure that the patient is not randomised twice. In addition, each patient will be allocated a unique patient number (screening number).

Blinding

The allocated trial medication will be blinded to the patient, the clinical staff caring for the patient, the investigators, the outcome assessors, the data manager, the statistician conducting the analyses, and the writing committee when drafting the abstract for the primary publication.

An independent company (Nomeco Clinical Trial Supply Management (CTSM) [26]) will handle masking, coding and distribution of the vials containing the investigational medicinal product (IMP)/placebo. A computer programme will generate the coding list (CTU) with numbers for the vials. Each trial site will have a sufficient number of vials to be allocated to participating patients. This will ensure that the patient only receives the trial intervention they are randomised to receive.

Safety

Patients can be withdrawn from the trial if:

- A clinical indication for treatment with a PPI/H2RA arises (GI bleeding and/or ulcer/gastritis/varices verified endoscopically). Patients will receive treatment for GI bleeding according to local standards
- Another clinical indication for withdrawal than the above mentioned (judged by responsible clinician or local investigator)
- A SAR/suspected unexpected serious adverse reaction (SUSAR) occurs (see below)
- The patient or next of kin withdraws consent

The independent Data Monitoring and Safety Committee (DMSC) can recommend pausing or stopping the trial. Details are provided in Appendix 2.

Serious adverse reactions

Adverse reactions are specified in the product characteristics of pantoprazole. The following conditions related to the intervention will be considered SARs:

- Anaphylactic reactions
- Agranulocytosis
- Pancytopenia
- Acute hepatic failure
- Stevens-Johnson syndrome and toxic epidermal necrolysis
- Interstitial nephritis
- Angioedema (Quincke's oedema)

The occurrence of SARs will be recorded daily in the electronic case report form (eCRF) during ICU stay and the distribution of SARs in the two groups will be compared by the DMSC at the interim analyses. During the trial the sponsor will send a yearly report to the ethics committees and medicine agencies.

SUSARs are defined as serious adverse events (SAEs) not described in the product characteristics for pantoprazole. SUSARs will be reported by the trial site investigators to the sponsor within 24 hours. The sponsor will report any SUSAR to the medicine agency within 7 days.

SAEs will not be recorded as an entity because the majority of ICU patients will experience a number of SAEs during their critical illness. SAEs will be captured in the secondary outcome measures.

Patient withdrawal

Patients who are withdrawn from the trial intervention will be followed-up and included in the intention-to-treat analysis. Patients may be withdrawn from the trial according to national consent regulations. In order to limit the amount of missing data, as much data as possible from each patient will be collected. All randomised patients will be reported, and all data available with consent will be used [27].

Patients who are transferred to another ICU will be regarded as discharged from the ICU unless the new ICU is an active SUP-ICU trial site. If so, the allocated trial intervention will be continued. All patients transferred to another ICU will be followed-up for the primary outcome measure.

Statistics

A predefined analysis plan will be prepared and published before data analysis.

The primary analysis will include the intention-to-treat population comparing mortality 90 days after randomisation in the two groups by binary logistic regression analysis with adjustment for stratification variables: site and active haematological cancer. A secondary analysis will be performed adjusting for stratification variables together with other known major prognostic covariates: age, baseline Sequential Organ Failure Assessment (SOFA) score, and type of admission (medical, elective surgery or emergency surgery). A sensitivity analysis will be conducted including the per-protocol population, excluding patients with a major protocol violation (patients who did not receive the allocated trial intervention at all, patients who did not receive the trial intervention for at least 2 days in a row, treatment with a PPI or a H2RA without clinical indication and withdrawal from trial intervention). The prevalence and pattern of missing values will be collected and analysed according to the predefined statistical analysis plan. If missingness exceeds 5 % and data is not missing completely at random (Little's test <0.05) multiple imputation with at least 10 imputations will be performed, and the primary result of the analysis will be from the aggregated intervention effects from the imputed datasets. All statistical tests will be two-tailed and $P < 0.05$ will be considered statistically significant.

Sample size estimation

Assuming a baseline 90-day mortality of 25 % [5] (see Appendix 3), $\alpha = 0.05$ (two-sided), and $\beta = 0.1$, 3350 patients (2×1675) will be needed to show a 20 % relative risk reduction (RRR) or increase (RRI) corresponding to a 5 % absolute risk reduction or risk increase in the primary outcome measure.

Interim analyses

Interim analyses will be performed after 1650 and 2500 patients. The DMSC may recommend pausing or stopping the trial if the group difference in the primary outcome measure, SARs or SUSARs is found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on the O'Brien-Fleming alpha-spending function, or otherwise finds that the continued conduct of the trial clearly compromises patient safety.

Data registration

Data will be entered into a web-based eCRF (CTU) by trial or clinical personnel. From the eCRF the trial database will be established. Paper case report forms (CRFs) will be used in case of technical difficulties with the eCRF. Details on data collection are shown in Appendix 1.

Data handling and retention

Data will be handled according to the national data protection agencies. All original records (including consent forms, CRFs, SUSAR reports and relevant correspondences) will be retained at trial sites or the CTU for 15 years to allow inspection by the Good Clinical Practice (GCP) Unit or local authorities. The trial database will be maintained for 15 years and anonymised if requested by the authorities.

Monitoring

The trial will be externally monitored according to a monitoring plan developed in collaboration with the GCP Unit in Copenhagen, which will coordinate the monitoring done by local GCP Units and/or monitors in all countries. Trial site investigators will give access to source data. A centralised day-to-day monitoring of the eCRF will be done by the coordinating investigator or her delegates.

Ethical justification

The trial will adhere to the latest version of the Helsinki Declaration [28] and the national laws in the participating countries. Inclusion will start after approval by the ethical committees, medicines agencies and data protection agencies.

Stress ulceration is a condition often seen in critically ill patients in the ICU [1]. The majority of patients will be temporarily incompetent because of severe illness or as a consequence of the treatment, including sedation. We cannot perform the trial in competent patients because less sick (and thus competent) patients do not suffer from stress ulcers. Patients requiring acute treatment in the ICU, e.g. mechanical ventilation, are in an acute life-threatening condition and it would expose the patient to great risk not to initiate the necessary treatment in order to obtain informed consent. To conduct clinical trials with the goal of improving the outcome for ICU patients at risk of stress-related GI bleeding, it is necessary to randomise and enrol patients before obtaining their informed consent. Informed consent will be obtained from all participants or representatives according to the national regulations. The process leading to the achievement of consent may differ in the participating countries, but will be described and be in compliance with all applicable local regulations.

No biological material will be collected for the trial; thus, no bio-bank will be formed.

Enrolment

Patients from Denmark, Finland, Italy, The Netherlands, Norway, Switzerland and the United Kingdom are expected to participate in the trial. The trial will be initiated in Denmark in January 2016 followed by the other countries when national approvals are obtained. The trial is expected to recruit patients during a 2-year period.

Trial management and organisation

The trial is part of the SUP-ICU research programme [29] and is supported by the Centre for Research in Intensive Care (CRIC) and the CTU.

A Steering Committee has been formed consisting of all national principal investigators and a Management Committee (see Appendix 4). The Steering Committee will manage and coordinate the trial centrally.

A local research team consisting of a principal investigator and a trial coordinator will manage and coordinate the trial locally. The principal investigator has the responsibility for data collection and maintenance of trial documentation.

Co-enrolment of participants in other interventional trials has to be approved by the SUP-ICU Steering Committee, but is generally allowed.

Publication

Upon trial completion the main manuscript with trial results, whether positive, negative or neutral, will be submitted for peer-review to one of the major clinical journals. Furthermore, the results will be published at the SUP-ICU web page [29].

The Steering Committee will grant authorship depending on personal input according to the Vancouver Principles. The DMSC and investigators not qualifying for authorship will be acknowledged with their names under the 'SUP-ICU trial investigators' in an appendix to the final manuscript.

Data sharing

According to the recommendations from the Institute of Medicine and the Scandinavian Trial Alliance a clean file dataset used for final analysis of the main results of the trial, the statistical analysis plan, a variable explanation, and the protocol will be made publicly accessible in an anonymised form 2 years after the last follow-up of the last patients [30].

Timeline

2014–2015: applications for funding, ethical committees and medicine agencies, development of an eCRF, development of monitoring plan and education of clinical staff

2016–2017: inclusion of patients

2018: data analyses, writing and submission of the main manuscript for publication

2021: data sharing according to the CRIC contract between partners [31]

Collaborators

The trial has been developed and conducted in collaboration with the Scandinavian Critical Care Trial Group (SCCTG). The trial is administered by the CRIC [31]. The CTU has developed the eCRF in close collaboration with the Steering Committee. The web-based randomisation system and the system for allocation of trial medication have been developed and administered by the CTU. Pharma-Skan ApS produces the placebo vials and Nomeco CTSM masks and distributes trial medication to all sites.

Finances

The trial is funded by the Innovation Fund Denmark and supported by the Aase and Ejnar Danielsens Foundation, the Ehrenreichs Foundation, the Scandinavian Society of Anaesthesia and Intensive Care Medicine (SSAI), the Danish Society of Anaesthesiology and Intensive Care Medicine (DASAIM), the Danish Medical Association, and the European Society of Intensive Care Medicine. Patient insurances will be sought financed from public and private funds. The funding sources will have no influence on trial design, trial conduct, data handling, data analysis or publication.

Discussion

Trial rationale

Clinical trials have suggested that there is a reduction in the incidence of GI bleeding among ICU patients receiving SUP compared with ICU patients receiving placebo or no prophylaxis [3, 32–38]. Based on this research conducted 15–20 years ago, and because of potentially increased mortality and morbidity in patients with clinically important bleeding, SUP is recommended as a standard of care in critically ill patients [7]. Around 75 % of critically ill patients in the ICU receive an acid suppressant during their ICU stay and PPIs are the most frequently used agents [5]. However, the quantity and quality of evidence supporting a reduction in clinically important GI bleeding and mortality with these agents is low [12]. Importantly, it has been suggested that PPIs may increase the risk of pneumonia, CDI, and acute myocardial ischaemia, and SUP may, in the worst case scenarios, increase mortality [13–16]. Taken together, SUP with a PPI is standard of care in ICUs worldwide but has never been tested in large high-quality clinically placebo-controlled trials. As a consequence, PPIs have been used as SUP for several years without convincing evidence of improved outcome.

Population

The population in this trial constitutes adult patients acutely admitted to the ICU with one or more risk factors for GI bleeding [5].

Intervention

In recent years a PPI has been considered the drug of choice in the management of most acid-related GI disorders [39]. The superior efficacy of PPIs over H2RAs has been demonstrated in various GI disorders, including peptic ulcer disease [39], and randomised trials and meta-analyses have assessed PPIs compared to H2RAs as SUP in the ICU. A recently published meta-analysis by Alhazzani et al. (14 trials, 1720 patients) compared a PPI and a H2RA [40], and found that a PPI was more efficient in reducing clinical important and overt GI bleeding, but no differences were shown regarding mortality, length of stay or incidence of pneumonia [40].

In most countries PPIs are more frequently used as SUP than H2RAs [5]. Since PPIs are considered equally effective, and pantoprazole is the most frequently used PPI [5], we chose this as the intervention.

Comparator

As described in the previous section, it has been suggested that a PPI is superior to a H2RA in the prevention of clinically important and overt GI bleeding. However, before comparing different SUP agents we need firm evidence of SUP being superior to placebo. This information is currently not available [12].

Outcome

Assessing mortality as the primary outcome has a number of advantages. First, mortality has not been the primary outcome of previous trials and we are sceptical that previous trials have collected high-quality data on mortality other than short-term mortality (ICU/hospital) [12]. Second, nearly all previous trials assessing PPIs or H2RAs as SUP have high risks of bias [12]. We know that trials with high risks of bias tend to overestimate benefit and underestimate harm [41]. Accordingly, previous trial results might be biased and even though they seem to find a neutral effect on mortality this may be a biased estimate actually concealing excess mortality in the SUP group. Third, meta-analysis of previous trials did not reach a realistic information size so even neutral mortality estimates may be misleading [12]. Fourth, as a consequence of the 6S trial [42], where we found that bleeding was associated with death and that death was partly mediated by bleeding (and renal insufficiency), it appears less likely that there should be a clinically significant reduction in GI bleeding (if PPIs do prevent GI bleeding) without any effect on mortality [43]. Consequently, assessing mortality as the primary outcome measure gives the opportunity to weigh up potential benefits and harms.

Sample size

It is difficult to produce reliable sample size estimations according to anticipated effects on GI bleeding because we have no reliable control group data due to the widespread use of PPIs [5]. As a consequence, it has been necessary to calculate sample size estimations given that something may change if we stop/avoid using PPIs until GI bleeding actually happens (see Appendix 3). The chosen intervention effect of 20 % RRR or RRI of the primary outcome may seem high, but in a population with septic shock or in, e.g. patients after cardiac arrest, a 20 % hazard ratio reduction corresponds to 1 month of extra median survival in patients with a median survival time of approximately 5 months. Furthermore, 3350 patients included in a low-risk-of-bias trial would make a huge contribution to existing evidence, more than doubling the number of randomised patients and providing trial results with low risk of bias on mortality and SAEs. Additionally, trial sequential analysis (TSA) [44, 45] of existing trials ($n = 16$) has shown that 34 % (1584 patients) of the required information size to detect or reject a 20 % RRR has been accrued; corresponding to a required information size of 4575 patients [12] (see Appendix 5). Consequently, there is an information gap of around 3000 patients assuming a 20 % RRR in mortality. With the inclusion of an additional 3350 patients it is expected that the pooled effect will cross the boundary for benefit/harm or the boundary for futility.

However, no single trial, whether large or well-conducted, gives the final answer and the SUP-ICU trial will not be an exception. Thus, existing meta-analyses of SUP should be updated with the SUP-IUC trial results.

Strengths

The SUP-ICU trial is a large multicentre clinical trial designed to provide high-quality data with low risk of bias. The trial is monitored according to GCP standards, and before data analyses a statistical analysis plan will be available. Furthermore, the strengths include concealed group assignment, blinding of the patient, the clinical staff caring for the patient, the investigators, the outcome assessors, the data manager, and the trial statistician. The trial design is pragmatic with routine practice maintained except from prescription of SUP; with resulting high generalisability.

Prior to designing the trial we have thoroughly described the available evidence in systematic reviews and a meta-analysis with TSA [12, 46]. Determining the incidence of GI bleeding in critically ill patients in the ICU is complicated by varying definitions of the outcome, difficulties in measuring the outcome, and differences in case mix. To make sure the available data on GI bleeding and risk factors were valid and up-to-date we conducted a large international observational study assessing the incidence of GI bleeding, risk factors for GI bleeding, and the use of SUP in more than 1000 adult critically ill patients in the ICU [5].

Limitations

As already described in previous sections the sample size estimation is based on estimates, as we do not have valid data describing mortality among patients with risk factors for GI bleeding not treated with a PPI due to the widespread use of acid suppressants. The power for even major effects on each of the possible side effects (pneumonia, CDI and acute myocardial ischaemia) may be reduced, but it will still make a large contribution to our knowledge on these outcomes that may seriously question, overthrow or confirm what we know so far. Furthermore, assessing the potential side effects as a composite outcome measure will increase the power. Additionally, there is a risk of excluding high-risk patients as patients already receiving daily treatment with a PPI or a H2RA cannot be enrolled in the trial due to the risk of discontinuing a therapy for another indication, e.g. history of peptic ulcer. The definition of overt GI bleeding includes haematochezia which might occur from a lower GI bleeding source not affected by PPI, e.g. colonic bleeding. Finally, we do not assess the use of a H2RA or other SUP agents and will not be able to draw conclusions about these drugs.

Perspective

The SUP-ICU trial will provide important high-quality data and the results will inform clinicians, guideline committee members and policy-makers on the use of SUP in ICU patients. Together with existing data the trial will establish a more solid evidence base for the use of a prophylactic PPI in critically ill patients in the ICU.

Trial status

Recruiting. First patient planned for inclusion in January 2016.

Appendix 1. Definitions used in the SUP-ICU trial

Definition of stratification variables

Site: all participating intensive care units (ICUs) will be assigned a number identifying the department.

Haematological malignancy includes any of the following:

Leukemia: acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL).

Lymphoma: Hodgkin's disease, non-Hodgkin lymphoma (e.g. small lymphocytic lymphoma (SLL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), hairy cell leukemia (HCL), marginal zone lymphoma (MZL), Burkitt's lymphoma (BL), post-transplant lymphoproliferative disorder (PTLD), T-cell prolymphocytic leukemia (T-PLL), B-cell prolymphocytic leukemia (B-PLL), Waldenström's macroglobulinemia, other NK- or T-cell lymphomas.

Multiple myeloma/plasma cell myeloma.

Definition of inclusion criteria

Acute admission to the ICU: a non-planned admission. It does not include planned recovery after surgery or similar planned admissions. ICU admission does not include admissions to semi-intensive care, intermediate intensive care or similar beds.

Age: the age of the patient in whole years at the time of randomisation. The age will be calculated from date of birth.

Shock: at least one of the following:

- Systolic pressure below 90 mmHg
- Mean arterial pressure below 70 mmHg
- Use of vasopressors or inotropes (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milirinone or levosimendan)
- Lactate level 4 mmol/l or above

Renal replacement therapy: acute or chronic intermittent or continuous renal replacement therapy.

Patients with expected duration of invasive mechanically ventilation longer than 24 hours: the treating clinician estimates that the patient will be invasively mechanically ventilated for more than 24 hours. When there is doubt about this forecast the patient should be enrolled.

Coagulopathy: platelets below 50×10^9/l or international normalised ratio (INR) above 1.5 or prothrombin time (PT) above 20 s documented within the last 24 hours.

Treatment with anticoagulant drugs: ongoing treatment with: dipyridamole, vitamin K antagonists, ADP-receptor inhibitors, therapeutic doses of low-molecular-weight heparin, new oral anticoagulant drugs, intravenous direct thrombin (II) inhibitors and similar drugs.

Acetylsalicylic acid (all doses) and low-molecular-weight heparin in prophylactic doses are *not* included.

History of coagulopathy: coagulopathy defined as platelets below 50×10^9/l *and/or* INR above 1.5 *and/or* PT above 20 s within the 6 months prior to hospital admission.

History of chronic liver disease: portal hypertension, cirrhosis proven by biopsy, CT scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history.

Definition of exclusion criteria

Contraindications to proton pump inhibitors (PPIs): any history of intolerance to PPIs or additives or treatment with atazanavir (HIV medication).

Ongoing treatment with PPIs and/or histamine-2-receptor antagonists (H2RAs): ongoing, documented daily treatment with the drugs in the patient charts.

Gastrointestinal (GI) bleeding during current hospital admission: GI bleeding of any origin (both upper and lower) documented in the patient charts.

Peptic ulcer: peptic ulcer confirmed by endoscopy or other method during current hospital admission.

Organ transplant: any kind of organ transplant during current hospital admission.

Withdrawal from active therapy or brain death: patients where withdrawal or brain death is documented in the patient charts.

Known pregnancy: fertile woman with a positive test for urinary or plasma human chorionic gonadotropin (hCG).

Consent not obtainable according to national regulations: patients where the clinician or investigator is unable to obtain the necessary consent before inclusion of the patient according to the national regulations.

Definition of baseline variables

Sex: the genotypic sex of the patient.

Age: defined in inclusion criteria.

Date of admission to hospital: the date of admission to the first hospital the patient was admitted to during the current hospital admission.

Elective surgery: surgery during the current hospital admission scheduled 24 hours or more in advance.

Emergency surgery: surgery during current hospital admission that was added to the operating room schedule 24 hours or less prior to that surgery.

Medical admission: when no surgery has been performed during the current hospital admission *or* surgery has been performed more than 1 week prior to ICU admission.

Treatment with anticoagulants at hospital admission and at ICU admission: anticoagulants are defined in the inclusion criteria.

Treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid at hospital admission: treatment with all doses of these drugs at hospital admission.

Treatment with intravenous thrombolysis: treatment with all kinds of intravenous thrombolysis within 3 days prior to randomisation.

Coagulopathy: defined in the inclusion criteria.

Treatment of suspected or confirmed *Clostridium difficile* infection (CDI) during current hospital admission.

Coexisting illnesses must have been present in the past medical history prior to ICU admission and are defined as follows:

- Chronic lung disease: chronic obstructive pulmonary disease (COPD), asthma or other chronic lung disease or treatment with any relevant drug indicating this at admission to hospital

- Previous myocardial infarction: history of myocardial infarction
- Chronic heart failure: New York Heart Association (NYHA) functional class III–IV. NYHA class III: the patient has marked limitations in physical activity due to symptoms (fatigue, palpitation or dyspnoea) even during less than ordinary activity (walking short distances 20–100 m or walking up one flight of stairs). The patient is only comfortable at rest. NYHA class IV: the patient is not able to carry out any physical activity (without discomfort (fatigue, palpitation or dyspnoea). Symptoms are present even at rest and the patient is mostly bedbound
- History of chronic renal failure: need of any form of chronic renal replacement therapy within the last year
- Liver disease: defined in baseline variables
- History of coagulopathy: defined in baseline variables
- Immunosuppression: patients treated with at least 0.3 mg/kg/day of prednisolone equivalent for at least 1 month in the 6 months prior to ICU admission
- Metastatic cancer: proven metastasis by surgery, CT scan or any other method
- Haematological malignancy: defined as stratification variable
- AIDS: HIV-positive patients with one or more HIV-defining diseases such as *Pneumocystis jerovechii* pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis or toxoplasma infection

The Simplified Acute Physiology Score (SAPS II) is based on the most extreme (highest or lowest) values from 24 hours prior to randomisation. The score consists of 17 variables: 12 physiological variables, age, type of admission, and 3 variables related to underlying disease, to give a total score ranging from 0 to 163, with higher scores indicating greater illness severity. The score will be calculated from data from the 24 hours prior to randomisation.

The Sequential Organ Failure Assessment (SOFA) score will be calculated from raw physiology and treatment data from the 24 hours prior to randomisation. The SOFA score consists of weightings for six organ systems to give a total score ranging from 0 to 24, with higher scores indicating a greater degree of organ failure.

Definition of daily collected variables

Delivery of trial medication: confirmation of administration of the trial drug.

Treatment with a PPI or a H2RA: prescription of any of these drugs in any dose (major protocol violation if the treatment is initiated (e.g. as prophylaxis) without clinical indication (e.g. GI bleeding).

Mechanical ventilation: invasive and non-invasive mechanical ventilation including continuous mask continuous positive airway pressure (CPAP) or CPAP via a tracheotomy. Intermittent CPAP is *not* mechanical ventilation.

Circulatory support: continuous infusion of vasopressor or inotrope (norepinephrine, epinephrine, phenylephrine, vasopressin or dopamine, dobutamine, milirinone or levosimendan).

Renal replacement therapy: any form of renal replacement therapy on this day. In patients receiving intermittent renal replacement therapy days between treatments are included.

Clinically important GI bleeding, onset of pneumonia, CDI, and acute myocardial ischaemia in the ICU are defined as outcomes.

Treatment with enteral feeding: any dose of enteral feeding (including oral nutritional intake) during the day.

Units of red blood cells: cumulated number of units of red blood cells transfused during the day.

Serious adverse reactions (SARs) are defined below.

Definition of bleeding variables

Confirmed diagnosis: diagnosis/origin of bleeding confirmed by endoscopy or other method.

Verification of ulcer/gastritis/bleeding oesophageal varices: confirmation of one of the three specific diagnoses by endoscopy or other method.

Haemostasis achieved or attempted: documentation in patient charts of haemostasis achieved or attempted by endoscopy, open surgery or coiling.

Definitions of outcome measures

Primary outcome:

90-day mortality: death from any cause within 90 days following the day of randomisation.

Secondary outcomes:

proportion of patients with one or more of the following adverse events: clinically important GI bleeding, pneumonia, CDI, and acute myocardial ischaemia. The events are defined as follows:

Clinically important GI bleeding: overt GI bleeding* and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) in the ICU:

1. Spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more

2. Start of vasopressor or a 20 % increase in vasopressor dose
3. Decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
4. Transfusion of two units of packed red blood cells or more

*Overt GI bleeding: haematemesis, coffee ground emesis, melaena, haematochezia or bloody nasogastric aspirate.

Pneumonia: episodes of newly confirmed pneumonia according to the modified CDC criteria [47]:

- Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):
  1. New or progressive and persistent infiltrate
  2. Consolidation
  3. Cavitation
- *and* at least one of the following:
  1. Fever (above 38 °C) with no other recognised cause
  2. Leucopoenia (white cell count below 4×10^9/l) or leucocytosis (white cell count above 12×10^9/l)
- *and* at least two of the following:
  1. New onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements
  2. New onset or worsening cough, or dyspnoea, or tachypnoea
  3. Rales or bronchial breath sounds
  4. Worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand)

CDI: treatment with antibiotics (enteral vancomycin, intravenous or enteral metronidazole, enteral fidaxomicin) for suspected or proven CDI.

Acute myocardial ischemia: ST elevation myocardial infarction, non-ST elevation myocardial infarction or unstable angina pectoris according to the criteria in the clinical setting in question (e.g. elevated biomarkers, ischaemic signs on an electrocardiogram (ECG) and clinical presentation) *and* receiving treatment as a consequence of this (reperfusion strategies (percutaneous coronary intervention(PCI)/thrombolysis) or initiation/increased antithrombotic treatment).

Proportions of patients with clinically important GI bleeding: proportion of patients with one or more episodes of clinically important GI bleeding as defined above.

Proportion of patients with one or more infectious adverse events: proportion of patients with one or more episodes of pneumonia or CDI.

One-year mortality: landmark mortality 1 year post randomisation.

Duration of life support in the ICU: the number of days alive and free from respiratory or circulatory support and off renal replacement therapy as defined below. The outcome will be days alive without the use of mechanical ventilation, circulatory support or renal replacement therapy in the 90-day period, and will be defined as the percentage of days without mechanical ventilation, circulatory support, and renal replacement therapy (as defined in daily collected variables) in the 90 days after randomisation.

SARs: number of SARs as defined below.

The elements of all composite outcomes will be reported in the supplementary material.

A health economic analysis will be performed. The analytic details will be based on the result of the trial and specified (cost-benefit versus cost-minimisation analyses).

Definitions of serious adverse reactions (SARs)

A SAR is defined as any adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, or results in persistent or significant disability or incapacity.

Patients will be monitored for onset of SARs occurring between the first dose of trial medication and until discharge from the ICU. If the patient is readmitted to the ICU and trial intervention is reintroduced, data collection for SARs will be resumed. If a patient experiences a SAR the patient will be withdrawn from the trial intervention but data collection and follow-up will be continued (see section 4.3.2).

SARs will be defined as follows:

Anaphylactic reactions defined as urticaria and at least one of the following:

- Worsened circulation (more than 20 % decrease in blood pressure or more than 20 % increase in vasopressor dose)
- Increased airway resistance (more than 20 % increase in the peak pressure on the ventilation)
- Clinical stridor or bronchospasm
- Subsequent treatment with bronchodilators

Agranulocytosis is defined as any new, acute and severe drop in granulocytes to below 0.5×10^9/l requiring active monitoring or treatment.

Pancytopenia is defined as any new, severe drop in red blood cells, white blood cells and platelets requiring active monitoring or treatment.

Acute hepatic failure is defined as severe and progressing hepatic failure as judged by the treating physician or the investigator.

Stevens-Johnson syndrome and toxic epidermal necrolysis are defined as severe dermatological reactions with a skin biopsy confirming the diagnosis.

Interstitial nephritis is defined as a nephritis affecting the interstitium of the kidneys surrounding the tubules with a kidney biopsy confirming the diagnosis.

Angioedema (Quincke's oedema) is defined as a vascular reaction involving the deep dermis, subcutaneous or submucosal tissues, resulting in a characteristic localised oedema.

Appendix 2. Charter for the independent Data Monitoring and Safety Committee (DMSC) of the SUP-ICU trial

ClinicalTrials.gov Identifier: NCT02467621.

Research ethical committee number: H-15003141.

Introduction

The DMSC will constitute its own plan of monitoring and meetings. However, this charter will define the minimum of obligations and primary responsibilities of the DMSC as perceived by the Steering Committee (SC), its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also outline the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DMSC, and an outline of the content of the open and closed reports which will be provided to the DMSC.

Primary responsibilities of the DMSC

The DMSC will be responsible for safeguarding the interests of trial patients, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the SC of the SUP-ICU trial. To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of patients, their management, improving adherence to protocol-specified regimens and retention of patients, and the procedures for data management and quality control.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC is planned by protocol to meet physically in order to evaluate the planned interim analyses of the SUP-ICU trial. The interim analyses will be performed by an independent statistician selected by the members of the DMSC (to be announced). The DMSC may additionally meet whenever they decide or contact each other by telephone or e-mail in order to discuss the safety of trial participants. The sponsor has the responsibility to report the overall number of serious adverse reactions (SARs) yearly to the DMSC. The DMSC can, at any time during the trial, request the distribution of events, including outcome measures and SARs according to intervention groups. Further, the DMSC can request unblinding of the interventions if suggested by the data; see section on 'Closed sessions'. The recommendations of the DMSC regarding stopping, continuing or changing the design of the trial should be communicated without delay to the SC of the SUP-ICU trial. As soon as possible, and no longer than 48 hours later, the SC has the responsibility to inform all investigators of the trial, and all the sites including patients in the trial, about the recommendation of the DMSC and the SC decision hereof.

Members of the DMSC

The DMSC is an independent multidisciplinary group consisting of clinicians and a biostatistician that, collectively, has experience in the management of ICU patients and in the conduct, monitoring and analysis of randomised clinical trials.

DMSC members

Anders Åneman, MD PhD.

Tim Walsh, professor, MD, PhD.

DMSC biostatistician

Aksel Karl Georg Jensen, Section of Biostatistics, University of Copenhagen.

Conflicts of interest

DMSC members will fill in and sign a declaration of conflicts of interests. DMSC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. Thus, neither trial investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DMSC. The DMSC members do not own stock in the companies having products being evaluated by the SUP-ICU trial.

The DMSC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial, with the Contract Research Organisation (CRO) for the trial (if any), or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial.

The DMSC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity.

The DMSC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the course of the trial. Any DMSC members who develop significant conflicts of interest during the course of the trial should resign from the DMSC.

DMSC membership is to be for the duration of the clinical trial. If any members leave the DMSC during the course of the trial, the SC will appoint their replacement(s).

Formal interim analysis meetings

Two formal interim analysis meetings will be held to review data relating to treatment efficacy, patient safety, and quality of trial conduct. The three members of the DMSC will meet when 90-day follow-up data of 1650 (approximately 50 % of sample size estimation) and 2500 (approximately 75 % of sample size estimation) patients have been obtained.

Proper communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DMSC has sole access to evolving information from the clinical trial regarding comparative results of efficacy and safety data, aggregated by treatment group. An exception will be made to permit access to an independent statistician who will be responsible for serving as a liaison between the database and the DMSC. At the same time, procedures will be implemented to ensure that proper communication is achieved between the DMSC and the trial investigators. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for open sessions and closed sessions will be implemented. The intent of this format is to enable the DMSC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DMSC and others who have valuable insights into trial-related issues.

Closed sessions

Sessions involving only DMSC members who generate the closed reports (called closed sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DMSC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DMSC will be blinded in its assessment of safety and efficacy data. However, the DMSC can request unblinding from the SC.

Closed reports will include analysis of the primary outcome measure. In addition, analyses of the secondary outcome measures and SARs will also be reported. These closed reports will be prepared by an independent biostatistician being a member of the DMSC, with assistance from the trial data manager, in a manner that allows them to remain blinded. The closed reports should provide information that is accurate, with follow-up on mortality that is complete to within 2 months of the date of the DMSC meeting.

Open reports

For each DMSC meeting, open reports will be made available to all who attend the DMSC meeting. The reports will include data on recruitment and baseline characteristics, pooled data on eligibility violations, completeness of follow-up, and compliance. The independent statistician, being a member of the DMSC, will prepare these open reports in cooperation with the trial data manager.

The reports should be provided to DMSC members approximately 3 days prior to the date of the meeting.

Minutes of the DMSC meetings

The DMSC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the DMSC meeting, including the listing of recommendations by the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the DMSC.

Recommendations to the Steering Committee

After the interim analysis meetings, the DMSC will make a recommendation to the SC to continue, hold or terminate the trial.

Interim analyses will be conducted after patient number 1650 and patient number 2500 have been followed-up for 90 days.

The DMSC will recommend pausing or stopping the trial if group difference in the primary outcome measure, SARs or SUSARs are found at the interim analyses with statistical significance levels adjusted according to the LanDeMets group sequential monitoring boundaries based on the O'Brien-Fleming alpha-spending function [48]. If an analysis of the interim data from 1650/2500 patients fulfils the LanDeMets stopping criterion the inclusion of further patients will be paused and an analysis including patients randomised during the analysis period will be performed. If this second analysis also fulfils the LanDeMets stopping criterion according to the group sequential monitoring boundaries the DMSC will recommend stopping the trial [49]. Furthermore, the DMSC can recommend pausing or stopping the trial if continued conduct of the trial clearly compromises patient safety. However, stopping for futility to show an

intervention effect of 15 % RRR will not be an option as intervention effects less than 15 % RRR of all-cause mortality may also be clinically relevant.

This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in this charter and the trial protocol.

The SC is jointly responsible with the DMSC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the trial made by the DMSC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue, hold or stop the trial based on the DMSC's recommendations.

The DMSC will be notified of all changes to the trial protocol or conduct. The DMSC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

Statistical monitoring guidelines

The outcome parameters are defined in the statistical analyses plan in the protocol. For the two intervention groups, the DMSC will evaluate data on:

The primary outcome measure

Mortality 90 days after randomisation of each patient ('landmark mortality').

The secondary outcome measures

- Proportion of patients with one or more of the following adverse events: clinically important gastrointestinal (GI) bleeding, pneumonia, *Clostridium difficile* infection (CDI), and acute myocardial ischaemia
- Proportion of patients with clinically important GI bleeding
- One-year mortality post randomisation
- The occurrence of SARs in the ICU

The DMSC will be provided with these data from the coordinating centre as:

Number of patients randomised.

Number of patients randomised per intervention group.

Number of patients stratified pr. stratification variable per intervention group.

Number of events, according to the outcomes, in the two groups.

Based on evaluations of these outcomes, the DMSC will decide if they want further data from the coordinating centre and when to perform the next analysis of the data.

For analyses, the data will be provided in one file as described below.

The DMSC should be informed yearly about SARs occurring in the two groups of the trial.

The DMSC may also be asked to ensure that procedures are properly implemented to adjust trial sample size or duration of follow-up to restore power if protocol-specified event rates are inaccurate. If so, the algorithm for doing this should be clearly specified.

Conditions for transfer of data from the coordinating centre to the DMSC

The DMSC will be provided with a file containing the data defined as follows:

Row 1 contains the names of the variables (defined below).

Row 2 to N (where $N-1$ is the number of patients having entered the trial) each contains the data of one patient.

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N rows the values of this variable.

The values of the following variables should be included in the database:

1. screening_id: a number that uniquely identifies the patient
2. rand_code: the randomisation code (group 0 or 1). The DMSC is not to be informed on what intervention the groups received
3. clin_imp_bleed: clinically important GI bleeding (1 = the patient had one or more episodes, 0 = the patient did not)
4. pneumonia: onset of pneumonia in the ICU after randomisation (1 = one or more episodes, 0 = no episodes)
5. clostridium: *Clostridium difficile* infection (1 = one or more episodes, 0 = no episodes)
6. ami: acute myocardial ischemia in the ICU (1 = one or more episodes, 0 = no episodes)
7. SAR: SAR indicator (1 = one or more SARs, 0 = no SARs).

Appendix 3. Power estimations

All power estimations have been calculated on data from the international 7-day inception cohort study [9].

Since we do not know whether treatment with acid suppressants reduce or increase mortality, a number of scenarios have been considered (±20 relative risk reduction):

1. 25.0 % mortality 90 days after inclusion among patients with:

At least one risk factor*.

No acid suppressants at ICU admission.

Treatment with acid suppressants during ICU admission.

No clinically important bleeding** during ICU admission.

Power estimation

ARR	Power	Patients per group
−5 %	80 %	1091
	90 %	1461
+5 %	80 %	1248
	90 %	1671

ARR absolute risk reduction

We do not know whether a PPI benefits or harms the patients, and need to include both scenarios. With 1671 patients in each group we will be able to show an absolute increase in risk of 5 % with 90 % power at the primary outcome, but also an absolute risk reduction of 5 % with 90 % power.

The sample size has been calculated on patients fulfilling inclusion and exclusion criteria in the SUP-ICU trial and because few patients were not treated with acid suppressants during ICU admission, the estimation is based on the group receiving acid suppressants (intervention group).

2. 25.9 % mortality 90 days after inclusion among patients with:

At least one risk factor*.
No acid suppressants at ICU admission.
Treatment with acid suppressants during ICU admission.
Bleeding (overt or clinically important**) or no bleeding during ICU admission.

Power estimation

ARR	Power	Patients per group
−5.2 %	80 %	1034
	90 %	1384
+5.2 %	80 %	1180
	90 %	1579

ARR absolute risk reduction

3. 29.2 % mortality 90 days after inclusion among patients with:

At least one risk factor*.
Acid suppressants and no acid suppressants at ICU admission.
Treatment with acid suppressants during ICU admission.
No bleeding (overt or clinically important**) during ICU admission.

Power estimation

ARR	Power	Patients per group
−5.8 %	80 %	901
	90 %	1206
+5.8 %	80 %	1014
	90 %	1357

ARR absolute risk reduction

4. 30.5 % mortality 90 days after inclusion among patients with:

At least one risk factor*.
Acid suppressants or no acid suppressants at ICU admission.
Treatment with acid suppressants during ICU admission.
Bleeding (overt or clinically important**) or no bleeding during ICU admission.

Power estimation

ARR	Power	Patients per group
−6.1 %	80 %	837
	90 %	1120
+6.1 %	80 %	937
	90 %	1254

ARR absolute risk reduction

*Risk factors are: shock, renal replacement therapy, coagulopathy, and coagulopathy and liver disease as comorbidities.

**Overt bleeding is defined as any episode of haematemesis, coffee ground emesis, melaena, haematochezia or bloody nasogastric aspirate.

Clinically important bleeding is defined as overt bleeding and at least one of the following four features within 24 hours of GI bleeding (in the absence of other causes) [1, 5] in the ICU:

a) Spontaneous drop of systolic blood pressure, mean arterial pressure or diastolic blood pressure of 20 mmHg or more
b) Start of vasopressor or a 20 % increase in vasopressor dose
c) Decrease in haemoglobin of at least 2 g/dl (1.24 mmol/l)
d) Transfusion of two units of packed red blood cells or more.

Appendix 4

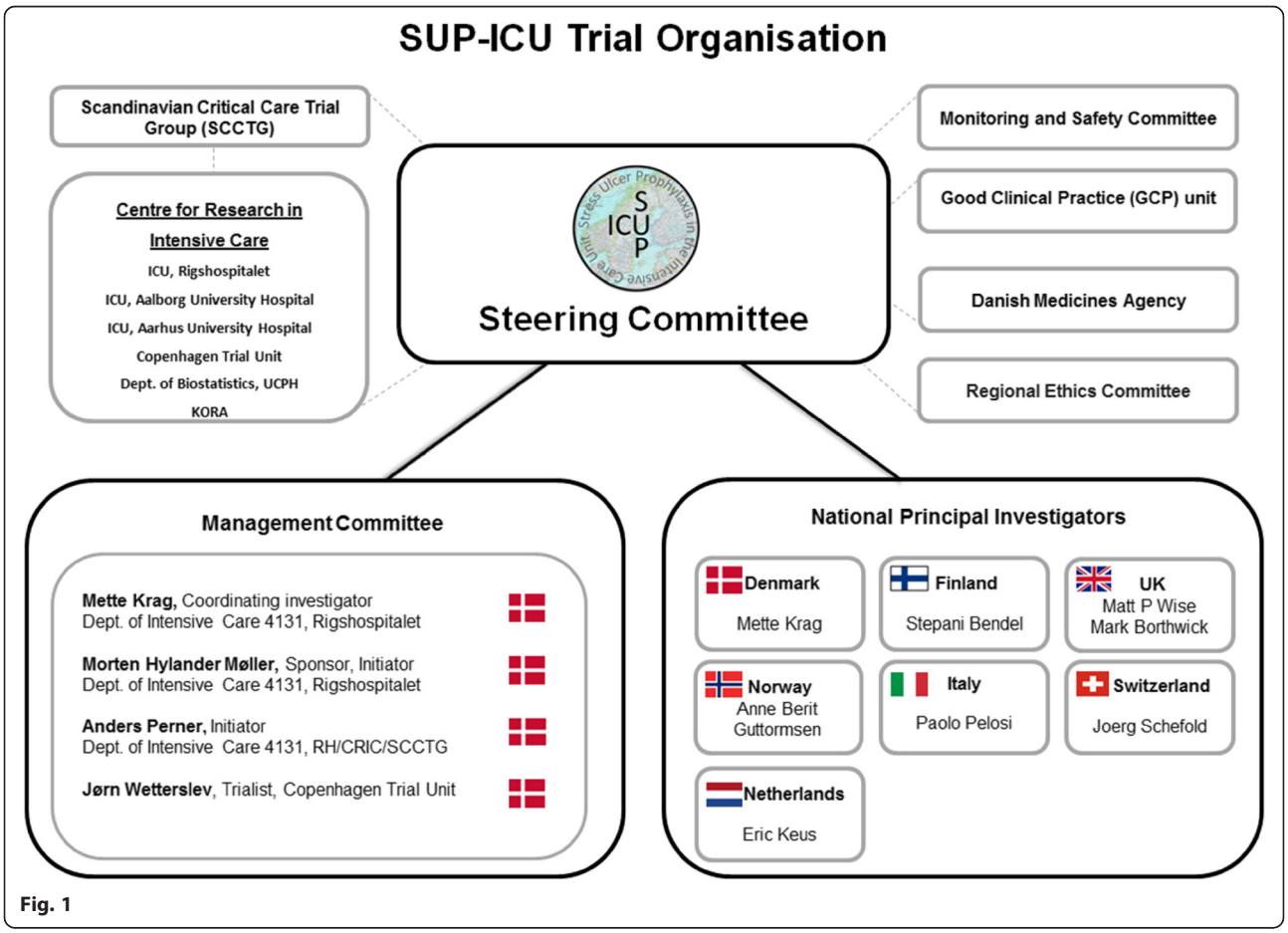

Fig. 1

Appendix 5. Trial sequential analysis of all-cause mortality (16 trials)

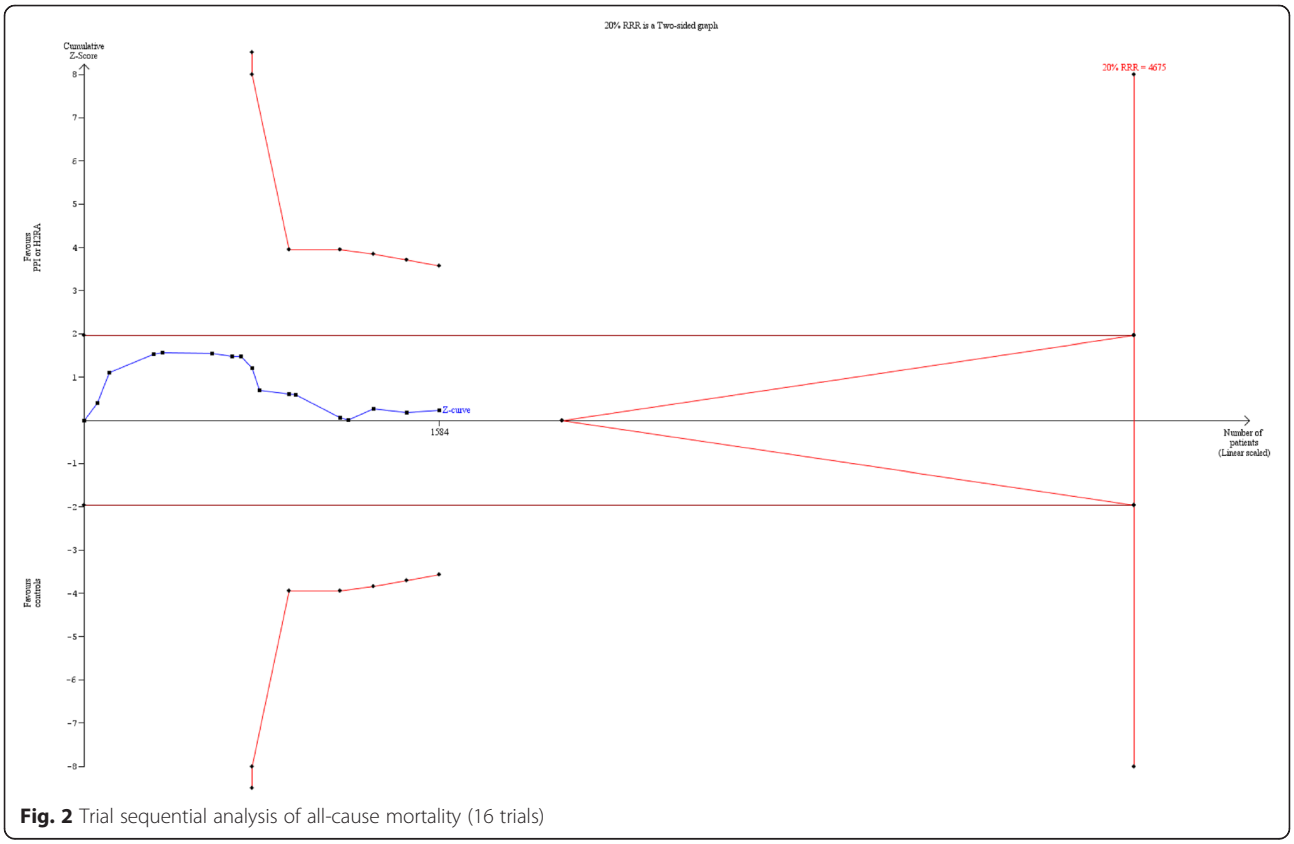

Fig. 2 Trial sequential analysis of all-cause mortality (16 trials)

Abbreviations

CDI: *Clostridium difficile* infection; CRF: case report form; CRIC: Centre for Research in Intensive Care; CT: computed tomography; CTSM: Clinical Trial Supply Management; CTU: Copenhagen Trial Unit; DASAIM: Danish Society of Anaesthesiology and Intensive Care Medicine; DMSC: Data Monitoring and Safety Committee; eCRF: electronic case report form; GCP: Good Clinical Practice; GI: gastrointestinal; H2RA: histamine-2-receptor antagonist; HIV: human immunodeficiency virus; hCG: human chorionic gonadotropin; ICU: intensive care unit; INR: international normalised ratio; PPI: proton pump inhibitor; PT: prothrombin time; RCT: randomised clinical trial; RRI: relative risk increase; RRR: relative risk reduction; RRT: renal replacement therapy; SAE: serious adverse event; SAR: serious adverse reaction; SCCTG: Scandinavian Critical Care Trial Group; SSAI: Scandinavian Society of Anaesthesia and Intensive Care Medicine; SUP: stress ulcer prophylaxis; SUSAR: severe unexpected serious adverse reaction; TSA: trial sequential analysis.

Competing interests

The ICU at Copenhagen University Hospital Rigshospitalet receives funds from Fresenius Kabi and CSL Behring for other research projects. Authors declare that they have no other competing interests.

Authors' contributions

MK and MHM drafted the protocol and the manuscript for this paper in close collaboration with AP and JW. MW, MB, SB, PP, FK, ABG and JCS all made substantial contributions to the process of developing the protocol and contributed with scientific input for the protocol and this manuscript. All authors read and approved the final manuscript. All authors are members of the SUP-ICU Steering Committee with MHM as principal investigator and sponsor of the SUP-ICU trial, MK as coordinating investigator, and MK, MW, MB, SB, PP, FK, ABG and JCS as national principal investigators. All authors have contributed significantly to the SUP-ICU research programme and the studies preparing the SUP-ICU trial.

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