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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
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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.

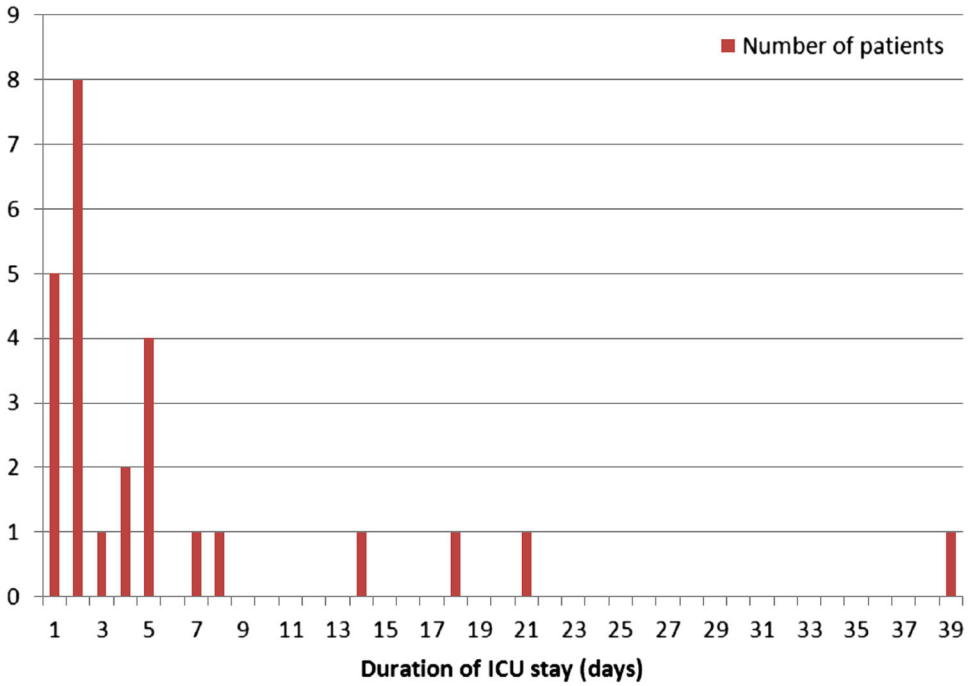

Fig. 1 Number of patients with clinically important gastrointestinal bleeding according to duration of ICU stay

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

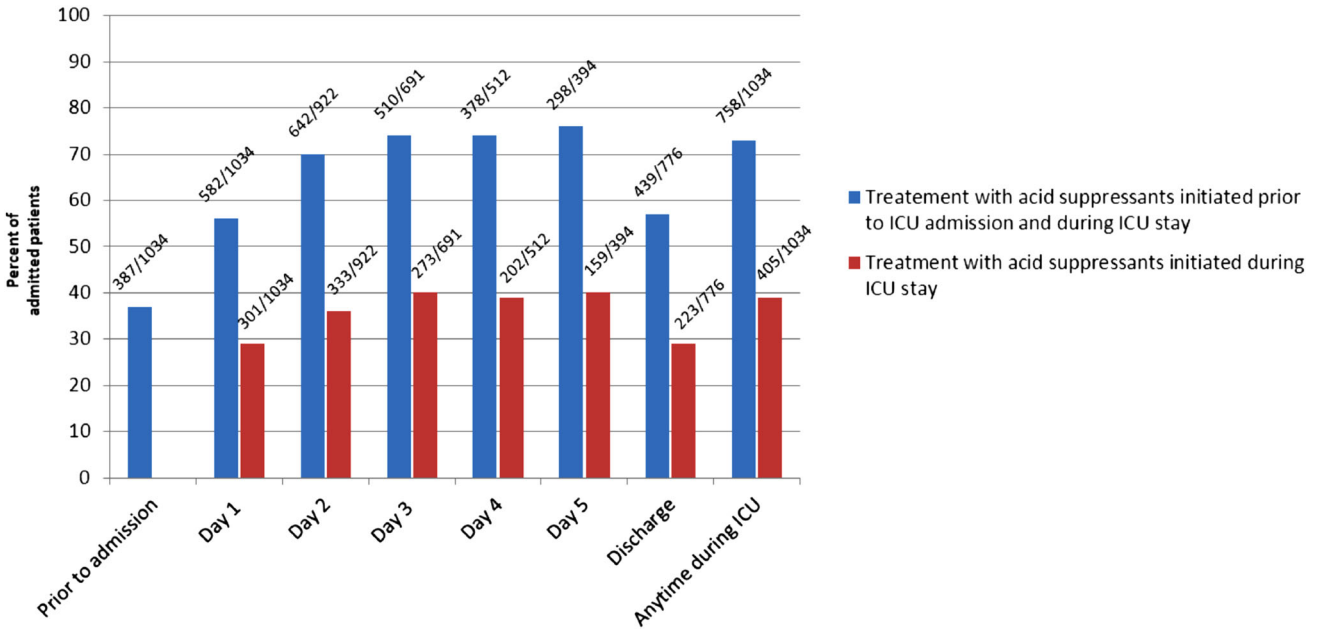

Fig. 2 Use of acid suppressing agents and number of patients with clinically important gastrointestinal bleeding during ICU stay

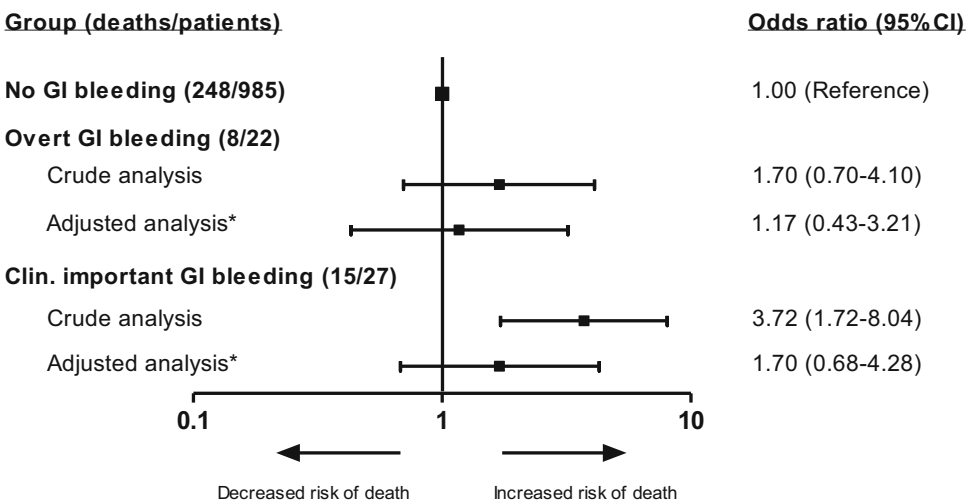

Fig. 3 Odds ratios (95 % confidence intervals) for 90-day mortality in patients who had no gastrointestinal (GI) bleeding, overt GI bleeding and clinically important GI bleeding during ICU stay. *Binary logistic regression analysis with adjustment for the following covariates according to the statistical 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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