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# Outcomes of Prophylactic Pantoprazole in Adult Intensive Care Unit Patients Receiving Dialysis: Results of a Randomized Trial

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**Keywords**

Acute kidney injury · Continuous renal replacement therapy · Sepsis · Critical illness · Stress ulcer prophylaxis · Gastrointestinal bleeding

**Abstract**

***Background:*** Intensive care unit (ICU) patients with acute kidney injury requiring renal replacement therapy (RRT) are considered at high risk of gastrointestinal (GI) bleeding and stress ulcer prophylaxis (SUP) is often prescribed. We aimed to assess the incidence of GI bleeding and effects of SUP in these patients. ***Methods:*** We assessed GI bleeding in ICU patients receiving RRT at baseline (and at any time in the ICU) and effects of prophylactic pantoprazole versus placebo in the international SUP in the ICU (SUP-ICU) trial. All analyses were conducted according to a published protocol and statistical analysis plan. ***Results:*** Data of 3,291 acutely admitted adult ICU patients with one or more risk factors for GI bleeding randomized to pantoprazole or placebo intravenously once daily during ICU stay (until ICU discharge, death, or a maximum of 90 days) were analyzed. Some 20 out of 258 (7.8%, 95% CI 4.5–11.1%) and 52 out of 568 (9.2%, 95% CI 6.8–11.6%) of the patients receiving RRT at baseline and at any time in ICU, respectively, developed clinically important GI bleeding in the ICU. We did not observe statistically significant differences in the intervention effect (pantoprazole vs. placebo) in the proportion of patients with clinically important GI bleeding, clinically important events, infectious adverse events, use of interventions to stop GI bleeding, or

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90-day mortality in patients with versus without RRT at baseline. ***Conclusions:*** In adult ICU patients receiving RRT at baseline, we observed high incidences of clinically important GI bleeding, but did not observe effects of pantoprazole versus placebo in this subgroup. 

## Introduction

Around 5% of adult patients in the intensive care unit (ICU) experience gastrointestinal (GI) bleeding [1], and 3 out of 4 adult ICU patients receive stress ulcer prophylaxis (SUP) as recommended in clinical practice guidelines [2]. In the recently published SUP in the ICU (SUP-ICU) trial – a European, investigator-initiated, randomized clinical trial on prophylactic pantoprazole versus placebo in ICU patients at risk of GI bleeding – clinically important GI bleeding occurred in 41 of 1,644 (2.5%) and 69 of 1,647 (4.2%) of patients, respectively [3]. In the SUP-ICU trial, no differences were observed in 90-day mortality or the number of clinically important events between patients allocated to pantoprazole versus placebo, but fewer patients in the pantoprazole group developed clinically important GI bleeding [3].

In critically ill patients with acute kidney injury (AKI), the incidence of GI bleeding may be increased due to uremia-induced effects on platelets and coagulation cascades [4–9]. In addition, renal replacement therapy (RRT) is known to activate the coagulation cascades via contact of patient blood with foreign material and RRT often requires anticoagulation [5–14]. AKI is frequently observed in ICU patients and significantly affects morbidity and mortality [4, 14–16], and previous data comparing continuous versus intermittent RRT modalities in critically ill patients have indicated that up to 30% of adult RRT-treated general ICU patients may experience clinically important all-cause bleeding episodes during ICU stay [7, 17]. However, no specific data on GI bleeding episodes are available.

We therefore aimed to assess the incidence of clinically important GI bleeding and the benefits and harms of SUP in critically ill patients receiving RRT in patients randomized in the SUP-ICU trial.

## Materials and Methods

*Study Design*

This was a preplanned observational study (SUP-ICU RENal, SIREN) [18] of the SUP-ICU trial [3]. We prepared this manuscript according to the Strengthening the Reporting of Observational Studies in Epidemiology statement [19]. A filled-in Strengthening the Reporting of Observational Studies in Epidemiology checklist is available in the electronic supplementary material.

*The SUP-ICU Trial*

In the SUP-ICU trial, 3,350 acutely admitted adult ICU patients with one or more risk factors for GI bleeding were randomized to 40 mg pantoprazole or placebo intravenously once daily during their ICU stay (administered until ICU discharge or death for a maximum of 90 days) [20]. In brief, adult ICU patients from 33 ICUs in 6 European countries with one or more of the following risk factors for GI bleeding were included: (1) shock (continuous infusion of vasopressors or inotropes, systolic blood pressure <90 mm Hg, mean arterial blood pressure <70 mm Hg, or plasma lactate level of ≥4 mmol/L); (2) need for intermittent or continuous RRT, (3) use of invasive mechanical ventilation expected to last >24 h, (4) acute (within previous 24 h) coagulopathy or history of coagulopathy (platelet count $<50 \times 10^9$/L) or international normalized ratio >1.5 or prothrombin time >20 s within the 6 months prior to hospital admission; (5) ongoing treatment with any anticoagulant (prophylactic doses excluded), or (6) history of chronic liver disease (portal hypertension, cirrhosis proven by biopsy, computed tomography scan, or ultrasound or history of variceal bleeding or hepatic encephalopathy).

Patients were excluded when any of the following criteria were met: contraindications to proton pump inhibitors, ongoing daily use of any proton pump inhibitor or any histamine-2-receptor antagonist, GI bleeding of any origin during current hospital admission, diagnosis of peptic ulcer during current hospital admission, organ transplant during current hospital admission, withdrawal from active therapy or brain death, fertile women with a positive test for urinary or plasma human chorionic gonadotropin, and patients in whom consent according to national regulations could not be obtained [20]. Additional details on the SUP-ICU protocol [20], statistical analysis plan [21], and trial results [3] are available elsewhere.

*Data Collection and Management*

We used data from the SUP-ICU trial database, which holds information on demographic and clinical characteristics at baseline, daily recordings during the entire stay in the ICU including GI bleeding events, potential infectious adverse events (pneumonia and *Clostridium difficile* infection [CDI]), and data on the usage of life support (daily use of mechanical ventilation, vasopressor/inotropes, and RRT).

*Outcome Measures*

The primary outcome measure in SIREN was the number of patients with clinically important GI bleeding (as defined below). Secondary outcomes included (1) the number of patients with one or more clinically important events in the ICU (clinically important GI bleeding, pneumonia, CDI, or acute myocardial ischemia); (2) the number of patients with serious adverse reactions related to the pantoprazole, (3) the number of patients with one or more infectious adverse events in the ICU (hospital-acquired pneumonia or CDI); (4) days alive without use of life support (mechanical ventilation, vasopressor/inotropes, or RRT) in the 90-day period, (5) 90-day mortality, (6) the number of patients receiving treatment (interventions) to stop GI bleeding (i.e., endoscopy, open or laparoscopic surgery, or coiling), and (7) the number of units of packed red blood cells (RBCs) transfused [18].

*Definitions*

Clinically important GI bleeding: overt GI bleeding (hematemesis, coffee ground emesis, melena, hematochezia, or bloody nasogastric aspirate) AND fulfillment of one or more of the following criteria within 24 h after the GI bleeding episode, in the absence of other causes: (A) spontaneous drop in systolic blood pressure, mean arterial pressure, or diastolic pressure of 20 mm Hg or more; (B) vasopressor (i.e., norepinephrine, epinephrine, dopamine, vasopressin, or terlipressin) initiated or increased by 20% or more; (C) hemoglobin decrease by at least 2 g/dL (1.24 mmol/L); (D) transfusion of 2 or more units of packed RBCs [20]. Clinically important events: clinically important GI bleeding, pneumonia, CDI, or myocardial ischemia. RRT included acute (i.e., need for dialysis at time of randomization) or chronic intermittent or continuous RRT [18, 20].

*Statistical Analyses*

The primary analysis was a conventional subgroup analysis of the effects of pantoprazole versus placebo in the intention-to-treat population in patients with and without use of RRT at baseline [18]. We included the interaction between baseline RRT and allocated treatment in the model and considered a $p$ value <0.1 as statistically significant. For clinically important GI bleeding and for the number of units of RBCs transfused, we used Cox regression analysis treating death as a competing risk, for days alive without use of life support we used Van Elterens test [22] and for the remaining secondary outcome measures we used logistic regression analyses.

The secondary analysis was a dynamically updated analysis using Cox models with delayed entry to assess ICU patients with need for RRT over time (start of RRT within 3 days was regarded typical in this clinical setting) and again treating death as a competing risk. We assessed the following 3 dynamical groups: (1) "no RRT" at baseline, (2) RRT at baseline and within 72 h from randomization ("RRT within 3 days"), and (3) RRT after 72 h from randomization ("RRT after 3 days") groups. If a patient later required RRT, she/he was moved from the "no RRT" group to the "RRT within 3 days" group or the "RRT after 3 days" group, respectively. Patients who died remained in the group that they were in at the time of death in the descriptive analyses, and they were not accounted for in the analyses after their death date. We adjusted the analysis for the following potential confounders: group allocation (pantoprazole vs. placebo), baseline Simplified Acute Physiology Score II [23], anticoagulation at hospital admission, age, and sex [18].

## Results

Out of 3,350 adult ICU patients included in the SUP-ICU trial, data were available for 3,291 patients [3]. Some 64% were males, 79% received mechanical ventilation at baseline, and most were medical ICU patients (Table 1). The median (interquartile range [IQR]) age and Simplified Acute Physiology Score II scores were 67 (IQR 56–75) and 48 (IQR 38–59), respectively. Some 258 ICU patients (7.8%) received RRT at baseline, and a total of 568 patients (17.3%) required RRT at any time during the ICU stay. Patients with the need for RRT at baseline had more coagulopathy and higher disease severity at baseline (Table 1).

Some 20 out of 258 (7.8%, 95% CI 4.5–11.1%) patients with RRT at baseline versus 90 out of 3,033 patients (3.0%, 95% CI 2.4–3.6%) without RRT at baseline developed clinically important GI bleeding (Table 2). In patients who received RRT within 3 days (either at baseline or within the first 72 h), 38 out of 449 patients (8.5%, 95% CI 5.9–11.1%) had one or more episodes of clinically important GI bleeding, as compared to 72 out of 2,842 patients (2.5%, 95% CI 1.9–3.1%) in those who did not receive RRT within 3 days. Further, in patients who received RRT at any time during ICU stay, a total of 52 out of 568 patients (9.2%, 95% CI 6.8–11.6%) had one or more episodes of clinically important GI bleeding, as compared to 58 out of 2,723 patients (2.1%, 95% CI 1.6–2.6%) in those who did not receive RRT.

*Primary Analysis*

We did not observe statistically significant interactions regarding the effect of pantoprazole between patients with versus without RRT at baseline in the number of patients with clinically important events, the number of patients with infectious adverse events, the number of patients who received interventions to stop GI bleeding, or in 90-day mortality (Table 2). We did observe higher transfusion rates and fewer days alive without life support in patients receiving RRT at baseline, but no interaction with trial allocation was observed (Table 2).

*Secondary Analysis*

In the dynamically updated groups, the hazard ratio for clinically important GI bleeding (95% CI) was 3.75 (2.41–5.83) and 6.86 (3.23–14.58) in the "RRT within 3 days" and "RRT after 3 days" groups, respectively, compared to patients without need for RRT (Fig. 1a, b). We did not observe a statistically significant interaction regarding the effect of pantoprazole in the dynamically updated RRT groups ($p = 0.146$).

## Discussion/Conclusions

In this preplanned observational study in a large sample of adult ICU patients at risk of GI bleeding, we observed that clinically important GI bleeding events

**Table 1.** Baseline characteristics of trial patients with and without RRT in the SUP-ICU trial*

| Characteristic | RRT ($n$ = 258) | | | No RRT ($n$ = 3,033) | | | All ($n$ = 3,291) |
|---|---|---|---|---|---|---|---|
| | pantoprazole | placebo | subtotal | pantoprazole | placebo | subtotal | total |
| Age, years | 70 (59–77) | 68 (60–75) | 69 (59–76) | 67 (56–75) | 67 (55–75) | 67 (55–75) | 67 (56–75) |
| Gender, male, *n* (%) | 89 (62) | 75 (65) | 164 (64) | 950 (63) | 992 (65) | 1,942 (64) | 2,106 (64) |
| *Comorbidities,* n *(%)* | | | | | | | |
| Chronic lung disease[a] | 26 (18) | 24 (19) | 50 (19) | 325 (22) | 282 (18) | 607 (20) | 657 (20) |
| Previous myocardial infarction | 13 (9) | 13 (11) | 26 (10) | 143 (10) | 129 (8) | 272 (9) | 298 (9) |
| Chronic heart failure (NYHA III–IV)[b] | 5 (4) | 15 (13) | 20 (8) | 95 (6) | 84 (5) | 179 (6) | 199 (6) |
| Use of glucocorticoids[c] | 4 (3) | 2 (2) | 6 (2) | 31 (2) | 25 (29 | 56 (2) | 62 (2) |
| Hematological malignancy[d] | 5 (4) | 8 (7) | 13 (5) | 59 (4) | 47 (3) | 106 (3) | 119 (4) |
| Metastatic cancer[e] | 6 (4) | 2 (2) | 8 (3) | 50 (3) | 53 (3) | 103 (3) | 111 (3) |
| AIDS[f] | 0 (0) | 0 (0) | 0 (0) | 6 (0.4) | 1 (0.03) | 7 (0.2) | 7 (0.2) |
| Coagulopathy[g] | 53 (37) | 39 (34) | 92 (36) | 299 (20) | 260 (17) | 559 (18) | 651 (20) |
| Admitted to university hospital | 110 (77) | 87 (76) | 197 (76) | 1,073 (71) | 1,102 (72) | 2,175 (72) | 2,372 (72) |
| Hours from ICU admission to randomization | 20 (10–40) | 20 (12–42) | 20 (10–41) | 14 (5–27) | 14 (5–25) | 14 (5–25) | 15 (5–26) |
| Days from hospital admission to randomization | 2 (1–6) | 2 (1–6) | 2 (1–6) | 1 (1–3) | 1 (1–3) | 1 (1–3) | 1 (1–3) |
| *ICU admission type,* n *(%)* | | | | | | | |
| Medical | 101 (71) | 80 (70) | 181 (70) | 945 (63) | 917 (60) | 1,862 (61) | 2,043 (62) |
| Emergency surgery | 31 (22) | 29 (25) | 60 (23) | 459 (31) | 529 (35) | 988 (33) | 1,048 (32) |
| Elective surgery | 11 (8) | 6 (5) | 17 (7) | 97 (6) | 86 (6) | 183 (6) | 200 (6) |
| Use of invasive mechanical ventilation | 94 (66) | 77 (67) | 171 (66) | 1,179 (79) | 1,239 (81) | 2,418 (80) | 2,589 (79) |
| Use of vasopressors or inotropes | 106 (74) | 78 (68) | 184 (71) | 997 (66) | 1,015 (66) | 2,012 (66) | 2,196 (67) |
| SAPS II[h] | 59 (50–68) | 59 (50–70) | 59 (50–68) | 48 (38–58) | 47 (37–58) | 47 (37–58) | 48 (38–59) |
| SOFA score[i] | 12 (10–14) | 12 (9–14) | 12 (10–14) | 8 (7–10) | 8 (6–10) | 8 (6–10) | 9 (7–11) |

* Values with ranges are medians (interquartile ranges). As per the STROBE statement [24] we applied no formal testing of statistically significant differences between the groups in any baseline characteristic. Full list of risk factors for gastrointestinal bleeding is provided in the online supplementary Appendix (see www.karger.com/doi/10.1159/000502732) of the main publication.

[a] Chronic lung disease was defined as any history of chronic obstructive pulmonary disease, asthma, or other chronic lung disease or treatment with any relevant drug indicating this at admission to hospital.

[b] Chronic heart failure was defined as NYHA III–IV. NYHA III: the patient has marked limitations in physical activity due to symptoms (fatigue, palpitation, or dyspnea) even during less than ordinary activity (walking short distances 20–100 m or walking up stairs to 1st floor). The patient is only comfortable at rest. NYHA IV: the patient is not able to carry out any physical activity without discomfort (fatigue, palpitation, or dyspnea). Symptoms are present even at rest and the patient is mostly bedbound.

[c] Use of corticosteroids was defined as 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.

[d] Hematological malignancy includes any of the following: acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, Hodgkin's disease, non-Hodgkin lymphoma (e.g., small lymphocytic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, hairy cell leukemia, marginal zone lymphoma, Burkitt's lymphoma, posttransplant lymphoproliferative disorder, T-cell prolymphocytic leukemia, B-cell prolymphocytic leukemia, Waldenström's macroglobulinemia, other NK- or T-cell lymphomas) and multiple myeloma/plasma cell myeloma.

[e] Metastatic cancer: proven metastasis by surgery, computed tomography scan or any other method.

[f] AIDS was defined as HIV positive patients with one or more AIDS defining diseases such as *Pneumocystis jirovecci* pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasma infection.

[g] Coagulopathy included both acute coagulopathy defined as platelets $<50 \times 10^9$/L or international normalised ratio >1.5 or prothrombin time >20 s at ICU admission and history of coagulopathy defined as coagulopathy within 6 months prior to hospital admission.

[h] In the 24 h prior to randomisation. The SAPS II [23] is calculated from 17 variables and ranges from 0 to 163 with higher scores indicating higher severity of disease.

[i] In the 24 h prior to randomisation. The SOFA score [27] grades organ failure with sub-scoring ranging from 0 to 4 for each of 6 organ systems (cerebral, circulation, lungs, liver, kidney and coagulation). The aggregated score ranges from 0 to 24 with higher scores indicating more severe organ failure.

RRT, renal replacement therapy; SUP-ICU, stress ulcer prophylaxis in the intensive care unit; NYHA, New York Heart Association Functional Class; CT, computed tomography; AIDS, Acquired Immune Deficiency Syndrome; SAPS, Simplified Acute Physiology Score; SOFA, Sepsis-related Organ Failure Assessment; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

**Table 2.** Primary and secondary outcome measures

| Outcomes | Baseline RRT (yes/no) | *n* (%) | OR/HR (95% CI) (pantoprazole vs. placebo) | *p* value for heterogeneity |
|---|---|---|---|---|
| *Primary outcome*[a] | | | | |
| Clinically important gastrointestinal bleeding in the ICU (time to event) | RRT<br>No RRT | 20/258 (7.8)<br>90/3,033 (3.0) | 0.53 (0.18–1.59)<br>0.66 (0.43–1.01) | 0.15 |
| *Secondary outcomes*[b] | | | | |
| Proportion of patients with one or more clinically important events (clinically important gastrointestinal bleeding, pneumonia, CDI or myocardial ischemia) | RRT<br>No RRT | 69/258 (2.7)<br>663/3,033 (2.2) | 1.19 (0.57–2.47)<br>0.95 (0.79–1.13) | 0.81 |
| Proportion of patients with serious adverse reactions in the ICU | RRT<br>No RRT | 0/258 (0)<br>0/3,033 (0) | NA<br>NA | NA |
| Proportion of patients with one or more in ectious adverse events (pneumonia or CDI) in the ICU | RRT<br>No RRT | 44/258 (17.1)<br>511/3,033 (16.8) | 1.30 (0.54–3.14)<br>0.96 (0.78–1.17) | 0.24 |
| 90-Day mortality | RRT<br>No RRT | 103/258 (39.9)<br>906/3,033 (29.9) | 0.80 (0.44–1.47)<br>1.02 (0.87–1.20) | 0.69 |
| Proportion of patients receiving interventions to stop GI bleeding[c] | RRT<br>No RRT | 10/258 (3.9)<br>40/3,033 (1.3) | 0.27 (0.04–1.69)<br>0.61 (0.32–1.17) | 0.19 |
| Percentage of days alive without use of mechanical ventilation, RRT, or circulatory support in the 90-day period[d], median (IQR) | RRT + pantoprazole<br>RRT + placebo<br>No RRT + pantoprazole<br>No RRT + placebo | 86 (40–94)<br>88 (33–96)<br>92 (60–97)<br>93 (67–97) | NA | 0.46 |
| Number of units of packed red blood cells transfused in the ICU[e], median (IQR) | RRT + pantoprazole<br>RRT + placebo<br>No RRT + pantoprazole<br>No RRT + placebo | 0 (0–3)<br>0 (0–2)<br>0 (0–1)<br>0 (0–1) | NA | 0.32 |

CI and *p* value are not adjusted for the comparisons of multiple secondary outcomes.

[a] Result of Cox regression model censoring at death or loss to follow-up adjusted for stratification variables (trial site and hematological malignancy) with allocated treatment (pantoprazole/placebo) as interaction variable. HR with 95% CI reported.

[b] Result of logistic regression model adjusted for stratification variables (trial site and hematological malignancy) with allocated treatment (pantoprazole/placebo) as interaction variable. OR with 95% CI reported.

[c] I.e. endoscopy, open or laparoscopic surgery, or coiling during ICU stay.

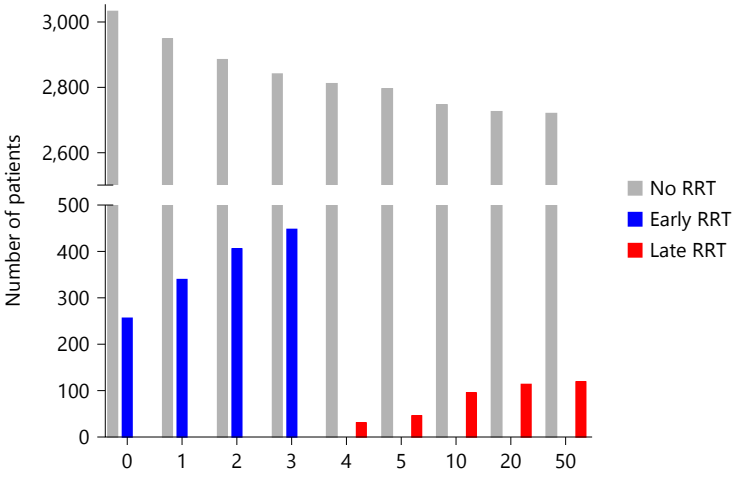
[d] Result of the van Elteren test adjusted for trial site. Medians and IQR reported.

[e] Raw medians with IQR presented. *p* value a result of Poisson regression model adjusted for stratification variables (trial site and hematological malignancy) with allocated treatment (pantoprazole/placebo) as interaction variable.

RRT, renal replacement therapy; ICU, intensive care unit; RR, relative risk; HR, hazard ratio; NA, not applicable; CDI, *Clostridium difficile* infection; GI, gastrointestinal; IQR, interquartile range.

were more frequent in patients receiving RRT as compared to patients not receiving RRT. We did not observe statistically significant interactions regarding the effects of pantoprazole in groups defined by either RRT at baseline or in dynamically updated RRT groups.

As previously demonstrated [7], ICU patients with AKI and need for RRT constitute a group with a high risk for all-cause bleeding episodes. Consequently, the current study augments previous data suggesting that clinically important GI bleeding episodes account for a considerable number of bleeding events in ICU patients on RRT. In the present study, we observed that 7.8% of patients treated with RRT at baseline had clinically important GI bleeding during their ICU stay; an absolute increase of 4.8% as compared to RRT-naïve patients. In ad-




a

Part 1. Dynamic group allocation for selected days[a]

| | Day 0 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 10 | Day 20 | Day 50 |
|---|---|---|---|---|---|---|---|---|---|
| No RRT | 3,033 | 2,950 | 2,884 | 2,842 | 2,812 | 2,796 | 2,748 | 2,728 | 2,723 |
| RRT within 3 days | 258 | 341 | 407 | 449 | 449 | 449 | 449 | 449 | 449 |
| RRT after 3 days | – | – | – | – | 30 | 46 | 94 | 14 | 119 |

Part 2. Time to clinically important gastrointestinal bleeding for RRT groups[b]

| | HR (95% CI) | *p* value for heterogeneity |
|---|---|---|
| RRT within 3 days | 3.75 (2.41–5.83) | 0.146 |
| RRT after 3 days | 6.86 (3.23–14.58) | |

b

Color version available online

**Fig. 1. a** Dynamic renal replacement group allocation for selected days. **b** Dynamic group allocation for selected days and time to clinically important GI bleeding for RRT groups. [a] Table shows number of patients in each group on selected days. Patients who die are counted in the group they were in at the time of death (also after their death) to ease the reading of the table. [b] Results from a Cox model with RRT status as a time-dependent covariate and controlled for Simplified Acute Physiology Score at baseline, anticoagulation at hospital admission, age, and sex. Patients are censored at the time of death as death is a competing risk. RRT, renal replacement therapy; GI, gastrointestinal.

dition, when compared to patients receiving RRT therapy at baseline, the number of patients with clinically important GI bleeding increased to 8.5% in patients with RRT within 3 days and to 9.2% in the group of patients receiving RRT at any time in ICU. Although the risk for clinically important GI bleeding in patients with RRT was higher, prophylaxis with pantoprazole did not statistically significantly reduce this risk or any of the other patient-important outcomes, including 90-day mortality in this subgroup.

Strengths of our study include use of data from a recent large, pragmatic international trial resulting in high generalizability. The level of missing data was low, and missing data were handled as recommended [24]. Moreover, all analyses were preplanned, and all outcome measures were patient-important [18]. The following limitations apply: the sample size was fixed with a limited number of events, which may imply a risk of inflated estimates (type 1 error) and low power (type 2 error). Further, no conclusions can be drawn on specific RRT modalities (e.g., continuous hemofiltration versus continuous hemodiafiltration or continuous versus intermittent RRT) [17, 25, 26], as these data were unavailable. In addition, no data were available on RRT-anticoagulation or dose. Importantly, the secondary analysis of the dynamically updated RRT groups is at risk of confounding, as this was not a baseline variable. Finally, we were unable to draw any conclusions on the underlying mechanisms leading to the increased risk of GI bleeding in this population.

In this preplanned observational study of a large sample of adult critically ill patients with risk factors for GI bleeding, we observed that clinically important GI bleeding events were more frequent in patients receiving RRT as compared to patients not receiving RRT. No statistically significant interactions were observed regarding the effects of pantoprazole in patients with versus without need of RRT.

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## Statement of Ethics

The trial was approved by the Danish Health and Medicine Agency (2015030166), the Committees on Health Research Ethics in the Capital Region of Denmark (H-15003141), the Danish Data Protection Agency (RH-2015-3203695), and by the national regulatory bodies in the participating countries. The Declaration of Helsinki was adhered to.

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## Author Contributions

J.C.S. and M.H.M.: proposed and initiated SIREN, defined the research strategy, and drafted the manuscript. T.L. and J.W.: provided statistical expertise and T.L., M.K., and S.M. conducted the analyses and drafted the tables. A.P., M.P.W., M.B., S.B., F.K., A.B.G., S.M., T.L., and M.K.: helped to draft the manuscript and revised it for important intellectual content. All authors read and approved the final version of the manuscript.

## Trial Registry

NCT02718261 (clinicaltrials.gov), date of registration March 14, 2016.

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