Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Supplementary Appendix for

Pantoprazole in ICU patients at risk of a gastrointestinal bleeding

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Trial inclusion criteria[1]

All adult (18 years or older) patients who are acutely admitted to the ICU with one or more of the following risk factors for gastrointestinal bleeding:

- 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 normalized 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)

Trial exclusion criteria[1]

- Contraindications to proton pump inhibitors: any history of intolerance to proton pump inhibitors or additives, or treatment with atazanavir (HIV medication)
- Ongoing treatment with proton pump inhibitors and/or histamine-2-receptor antagonists on a daily basis. Ongoing is defined as treatment not being discontinued at ICU admission
- Gastrointestinal bleeding of any origin (both upper and lower gastrointestinal bleeding) during current hospital admission, documented in the patient charts
- Diagnosed with peptic ulcer confirmed by endoscopy or other method during current hospital admission
- Organ transplant during current hospital admission
- Withdrawal from active therapy or brain death documented in the patient charts
- Fertile woman with positive urine human chorionic gonadotropin (hCG) or plasma-hCG
- Consent according to national regulations not obtainable: patients where the clinician or investigator is unable to obtain necessary consent before inclusion of the patient according to the national regulations

Outcome definitions[1]

Primary outcome:

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

Secondary outcomes:

1) Proportion of patients with one or more of the following clinically important adverse events: clinically important gastrointestinal bleeding, pneumonia, *Clostridium Difficile* infection, and acute myocardial ischemia. The events are defined as follows:

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

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 hemoglobin of at least 2 g/dl (1.24 mmol/l)
d) transfusion of two units of packed red blood cells or more

*Overt gastrointestinal bleeding: hematemesis, coffee ground emesis, melena, hematochezia or bloody nasogastric aspirate

Pneumonia: episodes of newly confirmed pneumonia according to the modified CDC criteria[2]

- 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 (>38°C) with no other recognized cause
  2. leukopenia (white cell count < 4 x 10^9/l) or leukocytosis (white cell count >12 x 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 dyspnea, or tachypnea
3. rales or bronchial breath sounds
4. worsening gas exchange (hypoxemia, increased oxygen requirement, increased ventilator demand)

Clostridium difficile infection: Treatment with antibiotics (enteral vancomycin, intravenous or enteral metronidazole, enteral fidaxomicin) for suspected or proven *Clostridium difficile* infection

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, ischemic signs on electrocardiography and clinical presentation) AND receiving treatment as a consequence of this (reperfusion strategies (Percutaneous Coronary Intervention/thrombolysis) or initiation/increased antithrombotic treatment)

2) Proportions of patients with clinically important gastrointestinal bleeding: proportion of patients with one or more episodes of clinically important gastrointestinal bleeding as defined above

3) Proportion of patients with one or more infectious adverse events: proportion of patients with one or more episodes of pneumonia or *Clostridium difficile* infection

4) Percentage of days alive without use of life support: percentage of days alive without use of life support (mechanical ventilation, circulatory support or renal replacement therapy) in the 90-day period

5) Serious adverse reactions: any adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity. An adverse reaction is any untoward and unintended response to an investigational medicinal product related to any dose administered

Patients were monitored for onset of serious adverse reactions occurring between the first dose of trial medication and until discharge from the intensive care unit. If a patient was withdrawn from the trial intervention, serious adverse reactions was recorded for 24 hours after the last dose of trial medication or discharge from the intensive care unit. If the patient was readmitted to the intensive

care unit and trial intervention was reintroduced, data collection for serious adverse reactions was resumed.

Serious adverse reactions were defined as follows:

- Anaphylactic reactions defined as urticaria and at least one of the following
    - worsened circulation (>20% decrease in blood pressure or >20% increase in vasopressor dose)
    - increased airway resistance (>20% increase in the peak pressure on the ventilation)
    - clinical stridor or bronchospasm
    - subsequent treatment with bronchodilators
- Agranulocytosis defined as any new, acute and severe drop in granulocytes to $< 0.5 \times 10^9$/l requiring active monitoring or treatment
- Pancytopenia defined as any new, severe drop in red blood cells, white blood cells and platelets requiring active monitoring or treatment
- Acute hepatic failure defined as severe and progressing hepatic failure as judged by the treating doctor or the investigator
- Steven-Johnson syndrome and toxic epidermal necrolysis defined as severe dermatological reactions with a skin biopsy confirming the diagnosis
- Interstitial nephritis defined as a nephritis affecting the interstitium of the kidneys surrounding the tubules with a kidney biopsy confirming the diagnosis
- Angioedema (Quincke's edema) defined as a vascular reaction involving the deep dermis, subcutaneous or submucosal tissues, resulting in a characteristic localized edema

Trial criteria for discontinuation and withdrawal[1]

Discontinuation and withdrawal at the choice of the participant or surrogates

The patient or his/her surrogate could withdraw consent for trial participation at any time without need of further explanation, and without consequences for further treatment. The procedure of handling withdrawal of consent from a patient or his/her surrogate followed national regulations. If consent for further data registration was given daily data and follow-up was collected. Already collected data was used if accepted.

Discontinuation and withdrawal at the choice of the investigator

A patient could be withdrawn from the trial intervention by the investigator or responsible clinician at any time, if:

- the patient experienced intolerable adverse reactions suspected to be related to the trial intervention

AND/OR

- the patient developed upper gastrointestinal bleeding or another condition where the responsible clinician found indication for treatment with an acid suppressant. The intervention was stopped and the patient received relevant treatment

AND/OR

- if the responsible clinician found other reasons than the above for discontinuation of the trial medication, e.g. withdrawal from active therapy

AND/OR

- the patient experienced a serious adverse reaction

In cases where consent was not withdrawn, the collection of daily data was continued and the follow-up data was collected.
The patients remained in the intention-to-treat population.

Patients who were transferred to another intensive care unit continued in the trial if the intensive care unit receiving the patient was an active SUP-ICU trial site. Otherwise the patient was regarded as discharged from the intensive care unit. In any case, patients transferred to another

intensive care unit were followed up for the primary outcome measure and as many of the secondary outcome measures as possible.

Trial population

Definition of the intention-to-treat population

The intention-to-treat population is all patients randomized except:

a. patients withdrawing consent for the use of data
b. patients who were erroneously randomized AND who did not receive the trial medicine [3]

Definition of the per-protocol population

The per-protocol population is all randomized patients except those having one or more protocol violations defined as:

1. Patients who did not receive the allocated trial intervention at all
2. Patients who did not receive the trial intervention for at least two days in a row
3. Patients who received treatment (open label) with proton pump inhibitors or histamine-2-receptor antagonists except for those receiving it according to the protocol (i.e. occurrence of gastrointestinal bleeding after randomization)
4. Patients who withdrew from trial intervention, but consented to the use of data
5. Monitoring revealed that one or more in- or exclusion criteria were violated

Handling of missing data

Simplified Acute Physiology Score (SAPS) II[4] in the 24 hours prior to randomization.
This score is based on 17 variables, which were registered in the baseline case report form from source data. We had missing source data for one or more of the 17 variables in 134 patients in the pantoprazole group and 115 patients in the placebo group. SAPS II scores for these patients were not included in the baseline characteristics.

The Sepsis-related Organ Failure Assessment (SOFA) score [5] in the 24 hours prior to randomization.
The score grades organ failure with sub-scoring ranging from 0 to 4 for each of six 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. Variables were missing in 108 patients in the pantoprazole group and 85 patients in the placebo group. SOFA scores for these patients were not included in the baseline characteristics.

Missing outcome data
We had data for the primary outcome measure for 3282/3291 (99.7%) of the patients in the intention-to-treat population.

We had missing data on some trial days for all the secondary outcome measures in 20 patients in each group, because the patient or the surrogate decision-maker did not allow continued data registration. We did not impute any data for these outcome data, because they only represented 40/3291 (1.2%) of the patients. All the patients allowed the use of already collected data. Hence, in the analyses the patients were regarded as discharged from the ICU after the time of withdrawal of consent.

A total of 26 patients, who were discharged to non-trial ICUs, had a time period within the 90 days after randomization where data for the use of life support was unobtainable to trial investigators. Because we could not confirm the use of life-support during these periods, we included the days during these periods as no use of life support in the analysis of the secondary outcome measure days alive without the use of life support within 90 days.

Abstract written before breaking the randomization code *

BACKGROUND

Stress ulcer prophylaxis is frequently used in intensive care unit (ICU) patients, but its risks and benefits have not been established.

METHODS

In this international, multicenter, parallel-group, blinded trial, we randomly assigned adult patients who were acutely admitted to the ICU and at risk of gastrointestinal bleeding to intravenous pantoprazole 40 mg or placebo daily during ICU admission. The primary outcome was death by 90 days after randomization.

RESULTS

We analyzed 3282 of the 3298 patients (99.5%) who underwent randomization in the primary analysis. At 90 days, 510 of the 1642 patients (31.1%) assigned to 0 had died as compared with 499 of the 1640 patients (30.4%) assigned to 1 (relative risk, 1.02; 95% confidence interval, 0.87-1.18; P=0.76). In the ICU, 21.9% of those assigned to 0 and 22.6% of those assigned to 1 had at least one clinically important event – a composite of clinically important gastrointestinal bleeding, pneumonia, *clostridium difficile* infection, or myocardial ischemia (relative risk, 0.96; 95% confidence interval, 0.81-1.14; P=0.57). Fewer patients in the 0 group had clinically important gastrointestinal bleeding in the ICU. The numbers of patients with infectious adverse events and serious adverse reactions in the ICU were similar in the two interventions groups; so were the percentages of days alive without life support at 90 days.

CONCLUSIONS

Among acutely admitted adult ICU patients at risk of gastrointestinal bleeding, mortality at day 90 and the number of clinically important events were similar in those assigned to 0 and those assigned to 1.

* Following breaking of the randomization code, minor inconsistencies in the 95% confidence intervals were discovered. Accordingly, the 95% confidence intervals given above differ from the final ones given in the final abstract and in the main text.

Figure S1. Masking of trial medication

Nomeco CTSM was responsible for storage, blinding, packaging and distribution of vials with pantoprazole 40 mg [Actavis] and placebo vials [Pharma-Skan Aps] to national and international trial sites. All services were performed by qualified and trained personnel and according to Good Manufacturing Practice (GMP) and Good Distribution Practice (GDP).

Table S1. Risk factors for gastrointestinal bleeding

Risk factors	Pantoprazole (N=1644)	Placebo (N=1647)
	no. (% of patients)	
Chronic liver disease*	45 (3)	49 (3)
Chronic renal replacement therapy	20 (1)	17 (1)
Coagulopathy†	352 (21)	299 (18)
Use of anti-coagulants‡	513 (31)	484 (29)
Use of NSAID or acetylsalicylic acid	278 (17)	255 (15)
Use of intravenous thrombolysis	25 (2)	22 (1)
Invasive mechanical ventilation	1273 (77)	1316 (80)
Vasopressors or inotropes	1103 (67)	1093 (66)
Acute renal replacement therapy	123 (7)	99 (6)

* Liver disease was defined as portal hypertension, cirrhosis proven by biopsy, CT scan or ultrasound, history of variceal bleeding or hepatic encephalopathy in the past medical history

† Coagulopathy included both acute coagulopathy defined as platelets < 50 x 10^9/l or international normalized ratio > 1.5 or prothrombin time > 20 seconds at ICU admission and history of coagulopathy defined as coagulopathy within 6 months prior to hospital admission.

‡ Anticoagulants were defined as 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 were not included

Table S2. Protocol violations

Violation	Pantoprazole (N=1644) *	Placebo (N=1647) *
	no. (% of patients)	
Patients who did not receive the trial medicine at all	0 (0.0)	0 (0.0)
Patients who did not receive the trial medicine for two consecutive days or more (major protocol violation)	29 (1.7)	27 (1.6)
Patients who in error received open-label proton pump inhibitor or histamine-2-receptor antagonist in addition to trial medicine	16 (1.0)	16 (1.0)
Patients in whom monitoring revealed that all inclusion criteria or one or more exclusion criteria were violated	1 (0.1)	0 (0.0)

* This population comprised 3291 patients. Of these, 593 discontinued the trial protocol (criteria for discontinuation and withdrawal are presented on page 10). Two-hundred-sixty-seven patients had the trial medication stopped on patient or surrogate request with consent to use of collected data (Fig 1). Of these 227 gave further permission to continue data registration.
Protocol violations were registered in the intensive care unit up to a maximum of 90 days. In case of withdrawal, protocol violations were registered until withdrawal.

Table S3. Enteral nutrition in the first 5 days from enrolment

	Pantoprazole	**Placebo**
Enteral nutrition *	*no. (% of patients)* †	
Day 1	956/1644 (58.2)	929/1647 (56.4)
Day 2	1176/1598 (73.6)	1201/1579 (76.1)
Day 3	1088/1359 (80.1)	1118/1372 (81.5)
Day 4	955/1145 (83.4)	950/1133 (83.8)
Day 5	825/962 (85.8)	802/940 (85.3)

*Defined as use of enteral feeding and/or oral nutrition on this day.

†The total number of patients declined over time due to discharge from the ICU or death.

Table S4. Results of the unadjusted analyses of outcomes

Outcome	Pantoprazole	Placebo	Relative Risk* (95% CI)	P-value*
Primary outcome measure	*no./total no. (%)*			
Dead at day 90	510/1642 (31.1)	499/1640 (30.4)	1.02 (0.92 - 1.13)	0.71
Secondary outcome measures	*no./total no. (%)*			
One or more clinically important events (clinically important GI bleeding, pneumonia, *Clostridium difficile* infection or myocardial ischemia)	360/1644 (21.9)	372/1647 (22.6)	0.97 (0.85 - 1.10)	0.64
One or more episodes of clinically important GI bleeding	41/1644 (2.5)	69/1647 (4.2)	0.60 (0.41 - 0.87)	
One or more infectious adverse events (pneumonia or *Clostridium difficile* infections)	276/1644 (16.8)	279/1647 (16.9)	0.99 (0.85 - 1.15)	
Severe adverse reactions†	0/1644 (0.0)	0/1647 (0.0)	-	
median percentage of days (IQR)‡				
Days alive without the use of life support	92 (60-97)	92 (65-97)	-	

CI denotes confidence interval; GI, gastrointestinal; IQR, interquartile range.

* Results of Fisher's test. Secondary outcomes (except 'clinically important events' presented without p-values because of lack of adjustment for multiple comparisons.

† Defined as anaphylactic reactions, agranulocytosis, pancytopenia, acute hepatic failure, Steven-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis or angioedema (Quincke's edema) related to the intervention as adjudicated by the treating clinicians and investigators.[6] We present specific events of participants adjudicated not to be related to the intervention, including the reasoning in Table S11.

‡ Calculated as the number of days without mechanical ventilation/ vasopressor/renal replacement therapy divided by the number of days alive in the 90-day follow-up period.

Table S5. Results of the primary analyses presented as odds ratio

Outcome	Pantoprazole	Placebo	Odds Ratio* (95% CI)	P-value*
Primary outcome measure	*no./total no. (%)*			
Death by day 90	510/1642 (31.1)	499/1640 (30.4)	1.02 (0.88 - 1.19)	0.76
Secondary outcome measures	*no./total no. (%)*			
One or more clinically important events (clinically important gastrointestinal bleeding, pneumonia, *Clostridium difficile* infection or myocardial ischemia)	360/1644 (21.9)	372/1647 (22.6)	0.95 (0.80 - 1.13)	0.57
One or more episodes of clinically important gastrointestinal bleeding	41/1644 (2.5)	69/1647 (4.2)	0.57 (0.38 - 0.85)	
One or more infectious adverse events (pneumonia or *Clostridium difficile* infection)	276/1644 (16.8)	279/1647 (16.9)	0.98 (0.81 - 1.19)	
Severe adverse reactions†	0/1644 (0.0)	0/1647 (0.0)	-	

CI denotes confidence interval; ICU, intensive care unit.

*Logistic regression analyses adjusted for the stratification variables (site and hematologic malignancy). Secondary outcomes (except 'clinically important events') presented without p-values because of lack of adjustment for multiple comparisons.

† Defined as anaphylactic reactions, agranulocytosis, pancytopenia, acute hepatic failure, Steven-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis or angioedema (Quincke's edema) related to the intervention as adjudicated by the treating clinicians and investigators.[6] We present specific events of participants adjudicated not to be related to the intervention, including the reasoning in Table S11.

Table S6. Results of the adjusted analyses of 90-day mortality in the pantoprazole group vs. the placebo group

	Primary analysis (adjusted for stratification variables)*	**Secondary analyses (adjusted for stratification and design variables†)**
Populations	Relative risk (95% confidence interval) P value	Relative risk (95% confidence interval) P value
Intention-to-treat N = 3282 N-pantoprazole = 1642 N-placebo = 1640	1.02 (0.91 - 1.13) 0.76	1.00 (0.89 - 1.12) 0.96
Per-protocol N = 2865 N-pantoprazole = 1430 N-placebo = 1435	1.00 (0.89 - 1.13) 0.95	NA

N = number of patients in the total population
N-pantoprazole = number of patients in the pantoprazole group
N-placebo = number of patients in the placebo group
NA = Not applicable

*The primary analyses (Column 1) were adjusted for the stratification variables (hematological malignancy and site).

† The secondary analyses were adjusted for stratification and design variables (age, type of admission (medical, elective surgery or emergency surgery), Sepsis-related Organ Failure Assessment (SOFA) score).[5] The SOFA score had more than 5% missing variables. We therefore used multiple imputation with 25 imputed data sets.

Table S7. Single components of the composite outcome clinically important adverse events*

Outcome†	Pantoprazole	Placebo	Relative Risk (95% CI)
Clinically important gastrointestinal bleeding	41/1644 (2.5)	69/1647 (4.2)	0.58 (0.40 - 0.86)
Pneumonia	266/1644 (16.2)	266/1647 (16.2)	1.00 (0.84 - 1.19)
Clostridium difficile infection	19/1644 (1.2)	25/1647 (1.5)	0.76 (0.42 – 1.39)
Acute myocardial ischemia	77/1644 (4.7)	66/1647 (4.0)	1.17 (0.84 - 1.65)

CI denotes confidence interval

* Presented without p-values because of lack of adjustment for multiple comparisons.

† The outcome definitions are presented on page 7 of this supplementary appendix.

Table S8. Gastrointestinal bleeding characteristics

	Pantoprazole (N=1644)	**Placebo (N=1647)**
	no. (% of patients)	
Overt gastrointestinal bleeding	88/1644 (5.4)	148/1647 (9.0)
Clinically important gastrointestinal bleeding	41/1644 (2.5)	69/1647 (4.2)
Criteria for clinically important gastrointestinal bleeding*		
Spontaneous drop of systolic, diastolic, or mean arterial pressure of 20 mmHg or more	25/41	46/69
Vasopressor initiated or increased by 20% or more	22/41	35/69
Hemoglobin decrease by at least 2 g/dl (1.24 mmol/l)	23/41	41/69
Transfusion of 2 units of packed red blood cells or more	29/41	39/69
Intervention		
Endoscopy	16	28
Surgery	3	5
Coiling	2	4
Source of gastrointestinal bleeding (if confirmed)		
Ulcer	10	17
Gastritis	4	4
Varices	0	0
Other	6	14
No. of patients transfused with red blood cells during the intervention period	535/1644 (32.5)	488/1647 (29.6)
No. of red blood cell units transfused per patient during the intervention period - median (interquartile range)	0 (0 - 1)	0 (0 - 1)

* Patients having overt gastrointestinal bleeding AND at least one of the four criteria within 24 hours of the gastrointestinal bleed (in the absence of other causes). Some patients fulfilled more than one criterion for clinically important gastrointestinal bleeding. The full definitions are presented above (page 7).

Table S9. Simplified acute physiology scoring (SAPS) II in the SUP-ICU trial[4]

Part 1

Variable	Points:	26	13	12	11	9	7	6	5	4	3	2	0
Age													< 40
Heart rate					< 40							40-69	70-119
Systolic blood pressure mmHg			< 70						70-99				100-199
Body temperature °C °F													< 39 <102.2
Only if ventilated PaO_2 mmHg/FiO_2 PaO_2 kPa/FiO_2					< 100 <13.3	100-199 13.3-26.5		≥200 ≥26.6					
Urinary output ml/day					<500					500-999			> 1000
Serum urea level mmol/l (g/dl)													< 10.0 (< 0.6)
WBC 10^9/l				<1.0									1.0-19.9
Serum potassium mmol/l											<3.0		3.0-4.9
Serum sodium mmol/l									<125				125-144
Serum bicarbonate mEq/l								<15			15-19		≥20
Bilirubin umol/l (mg/dl)													< 68.4 (<4.0)
Glasgow coma scale score	<6	6-8					9-10		11-13				14-15
Chronic disease													
Type of admission													Scheduled surgical

Part 2

Variable	1	2	3	4	6	7	8	9	10	12	15	16	17	18
Age						40-59				60-69	70-74	75-79		≥80
Heart rate				120-159		≥160								
Systolic blood pressure mmHg		≥200												
Body temperature °C °F			≥39.0 ≥102.2											
Only if ventilated PaO_2 mmHg/FiO_2 PaO_2 kPa/FiO_2														
Urinary output ml/day														
Serum urea level mmol/l (g/dl)					10.0-29.9 0.60-1.79				≥30.0 ≥1.80					
WBC 10^9/l			≥20.0											
Serum potassium mmol/l			≥5.0											
Serum sodium mmol/l	≥145													
Serum bicarbonate mEq/l														
Bilirubin umol/l (mg/dl)				68.4-102.5 (4.0-5.9)				≥102.6 (≥6.0)						
GCS score														
Chronic disease								Metastatic cancer	Hematologic malignancy				AIDS	
Type of admission					Medical		Unscheduled surgical							
Sum of points														

Table S10. Sepsis-related organ failure assessment scoring (SOFA) in the SUP-ICU[5]

	0	1	2	3	4
Respiration					
PaO_2/FiO_2					
(mmHg)	≥ 400	< 400	< 300*	< 200†	< 100†
(KPa)	≥ 53	< 53	< 40*	< 27†	< 13†
Coagulation					
Platelets (x 10^3/mm3)	≥ 150	101-150	51-100	21-50	≤ 20
Liver					
Bilirubin					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
(umol/l)	< 20	20-32	33-101	102-204	> 204
Cardiovascular					
Hypotension*			Dopamine ≤ 5☼ **OR**	Dopamine ≥ 5☼ **OR**	Dopamine > 15☼ **OR**
(MAP)	≥ 70	< 70	Dobutamine (any dose) **OR**	Norepinephrine ≤ 0.1☼ **OR**	Norepinephrine > 0.1☼ **OR**
			Milrinone (any dose) **OR**	Adrenaline ≤ 0.1☼ **OR**	Adrenaline > 0.1☼
			Levosimendan (any dose) **OR**	Vasopression (any dose) **OR**	
				Phenylephrine (any dose) **OR**	
CNS					
Glasgow coma scale score	15	13-14	10-12	6-9	< 6
Renal					
Creatinine					
(mg/dl)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
(umol/l)	< 110	110-170	171-299	300-440	>440
OR					
Urine output				<500 ml/day	<200 ml/day

* without respiratory support

† with respiratory support

☼Adrenergic agents administered for at least one hour (doses given are in ug/kg/min).

Table S11. Refuted serious adverse reactions

Participant ID	Suggested Serious Adverse Reaction	Rationale for refutation
DK06064	Pancytopenia related to the intervention on this day	Cytopenia only affecting red blood cells (no leucopenia or thrombocytopenia)
NY01363	Acute hepatic failure related to the intervention on this day	Rapid increase in bilirubin (along with severe multiple organ failure) preceding randomization by three days
UK01144	Pancytopenia related to the intervention on this day	No pancytopenia. Site investigators concerned about occurrence of a gastrointestinal bleeding (not a Serious Adverse Reaction, but a Serious Adverse Event, reported separately in the electronic Case Report Form).

The list does not include patients where all Serious Adverse Reactions were initially and erroneously reported in the electronic Case Report Form, due to the entire column answered ‘yes’ instead of ‘no’. This was the case for 3 participants: DK06014, DK06046 and DK04613.

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