Clinical trial results:
Regional citrate versus systemic heparin anticoagulation for continuous renal replacement therapy in critically ill patients with acute kidney injury (RICH-Trial).

Summary

EudraCT number	2014-004854-33
Trial protocol	DE
Global end of trial date	03 January 2020

Results information

Result version number	v1 (current)
This version publication date	08 January 2021
First version publication date	08 January 2021

Trial information

Trial identification

Sponsor protocol code	03-AnIt-14/UKM14_0066

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02669589
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Muenster
Sponsor organisation address	Albert-Schweitzer-Campus 1, D5, Münster, Germany, 48149
Public contact	Dept. of Anesthesiology, University Hospital Muenster, +49 02518347255, rich@anit.uni-muenster.de
Scientific contact	Dept. of Anesthesiology, University Hospital Muenster, +49 02518347255, rich@anit.uni-muenster.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Effect of regional citrate anticoagulation (RCA) for CRRT in critically ill patients on filter life span and all cause 90-day mortality compared to systemic heparin anticoagulation for CRRT

Protection of trial subjects:

All patients will receive standard intensive care therapy. As no pharmacological therapy for AKI exists, the management of AKI remains primarily supportive, with renal replacement therapy serving as a cornerstone of therapy in patients with severe kidney injury. None of the patients in both groups (‘early’ and ‘late’ group) will be exposed to additional risks. Participation in this study will be voluntary. Written informed consent will be obtained from patients.
This study will be performed in accordance with the revision of the Declaration ofHelsinki (2008). Study protocol, patient information and informed consent have been submitted to the ethics committees of the University of Münster for appraisal. Once the protocol is approved, the documents will be submitted to the ethics committees of all participating centers for appraisal. The study will be directly started in these centers, in which the local ethics committee has approved the study. The principal investigator will inform the ethics committee about any changes in the study protocol. The treating investigator will inform the patient about the nature of the trial, its aims, expected advantages as well as possible risks. Each patient must consent in writing to participate in the study. The patient must be given enough time andopportunity to decide on participation and to clarify any questions before the beginning of documentation of the study.

Background therapy:

The patient’s primary physicians will determine the remainder of patient management consistent with established best practices with the management of critically ill patients.

Evidence for comparator:

Multiple pharmacologic interventions have shown promise in animal models of AKI, however no agents have been demonstrated to be efficacious in clinical practice. As a result, the management of AKI remains primarily supportive, with CRRT serving as the cornerstone of therapy in critically ill patients with severe AKI. To investigate the best anticoagulant for CRRT, we will randomly assign patients with CRRTdependent AKI to receive either regional citrate or systemic heparin anticoagulation. A placebo group of patients treated with continuous CRRT without any anticoagulation is ethically not acceptable.

Actual start date of recruitment	04 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 596
Worldwide total number of subjects	596
EEA total number of subjects	596

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	217
From 65 to 84 years	360
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from March 2016 (First Patient In) until January 2019 and followed up until January 2020 (Last Patient Out)

Pre-assignment

Screening details:

A total of 5069 patients were screened for inclusion, of whom 638 patients were enrolled and randomized. 42 patients had to be excluded from the analysis due to incomplete consent process according to the European regulations. 596 patients were included in the primary analysis.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Regional citrate anticoagulation

Arm description:

Anticoagulation for continuous renal replacement therapy via regional citrate

Arm type	Experimental
Investigational medicinal product name	Regional anticoagulation with citrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Extracorporeal use

Dosage and administration details:

Individual doses according to published protocols (target aPPT: 45-60s)

Arm title	Systemic heparin anticoagulation

Arm description:

Continuous renal replacement therapy with systemic heparin anticoagulation

Arm type	Active comparator
Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

Dose of anticoagulation: individual doses according to published protocols (target aPPT: 45-60s)

Number of subjects in period 1	Regional citrate anticoagulation	Systemic heparin anticoagulation
Started	300	296
Completed	300	296

Baseline characteristics

Reporting groups	
Reporting group title	Regional citrate anticoagulation
Reporting group description:	
Anticoagulation for continuous renal replacement therapy via regional citrate	
Reporting group title	Systemic heparin anticoagulation
Reporting group description:	
Continuous renal replacement therapy with systemic heparin anticoagulation	

Reporting group values	Regional citrate anticoagulation	Systemic heparin anticoagulation	Total
Number of subjects	300	296	596
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	67.5	67.6	
standard deviation	± 12.3	± 12.5	-
Gender categorical			
Units: Subjects			
Female	94	89	183
Male	206	207	413

End points

End points reporting groups	
Reporting group title	Regional citrate anticoagulation
Reporting group description: Anticoagulation for continuous renal replacement therapy via regional citrate	
Reporting group title	Systemic heparin anticoagulation
Reporting group description: Continuous renal replacement therapy with systemic heparin anticoagulation	

Primary: Filter life span	
End point title	Filter life span
End point description:	
End point type	Primary
End point timeframe: During continuous renal replacement therapy up to 1 year	

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	290		
Units: hours				
median (inter-quartile range (Q1-Q3))	46.5 (18.8 to 70.3)	26.0 (12.0 to 50.6)		

Statistical analyses

Statistical analysis title	Primary efficacy analysis (filter life span)
Comparison groups	Regional citrate anticoagulation v Systemic heparin anticoagulation
Number of subjects included in analysis	583
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	11.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.16
upper limit	14.31

Primary: Overall survival

End point title	Overall survival
End point description:	

End point type	Primary
End point timeframe:	
up to 90 days	

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: days				
median (confidence interval 95%)	78.4 (48.0 to 999)	55.0 (28.0 to 999)		

Statistical analyses

Statistical analysis title	Primary analysis (overall survival)
Comparison groups	Regional citrate anticoagulation v Systemic heparin anticoagulation
Number of subjects included in analysis	596
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0538
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.792
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.626
upper limit	1.004

Secondary: ICU length of stay

End point title	ICU length of stay
End point description:	

End point type	Secondary

End point timeframe:
up to 1 year

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: days				
median (inter-quartile range (Q1-Q3))	16.0 (8.0 to 29.0)	13.5 (7.0 to 25.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital length of stay

End point title	Hospital length of stay

End point description:

End point type	Secondary

End point timeframe:
during primary hospital stay

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: days				
median (inter-quartile range (Q1-Q3))	27.0 (13.0 to 51.0)	27.0 (14.0 to 49.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of renal replacement therapy

End point title	Duration of renal replacement therapy

End point description:

End point type	Secondary

End point timeframe:
during primary continuous renal replacement therapy

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	294	292		
Units: days				
median (inter-quartile range (Q1-Q3))	9.6 (3.9 to 57.0)	8.4 (3.6 to 45.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bleeding complication

End point title	Bleeding complication

End point description:

End point type	Secondary

End point timeframe:
during ICU stay

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: Number of patients	15	49		

Statistical analyses

No statistical analyses for this end point

Secondary: Transfusion requirement

End point title	Transfusion requirement

End point description:

End point type	Secondary

End point timeframe:
during primary continuous renal replacement therapy

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	293	290		
Units: Number of patients	197	184		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Infection

End point title	Rate of Infection

End point description:

The rate of infection during ICU stay is defined as new infection in patients with pre-existing infection but with another pathogen than baseline or without baseline infection at baseline after initiation of renal replacement therapy up to the end of ICU stay or day 28 (whatever occurred first).

End point type	Secondary

End point timeframe:

during primary ICU stay

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: Number of patients	204	164		

Statistical analyses

No statistical analyses for this end point

Secondary: MAKE 28

End point title	MAKE 28

End point description:

Major adverse kidney event (MAKE) will be defined as the composite of death, use of renal replacement therapy and missing renal recovery

End point type	Secondary

End point timeframe:

from randomization up to day 28

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	207	203		
Units: Number of patients with MAKE	182	187		

Statistical analyses

No statistical analyses for this end point

Secondary: MAKE on day 60

End point title	MAKE on day 60

End point description:

Major adverse kidney event (MAKE) will be defined as the composite of death, use of renal replacement therapy and missing renal recovery

End point type	Secondary

End point timeframe:

from randomization up to day 60

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	197	205		
Units: number of patients with MAKE	175	178		

Statistical analyses

No statistical analyses for this end point

Secondary: MAKE on day 90

End point title	MAKE on day 90

End point description:

Major adverse kidney event (MAKE) will be defined as the composite of death, use of renal replacement therapy and missing renal recovery

End point type	Secondary

End point timeframe:

from randomization up to day 90

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246	258		
Units: Patients with MAKE	186	181		

Statistical analyses

No statistical analyses for this end point

Secondary: MAKE after 1 year

End point title	MAKE after 1 year

End point description:

Major adverse kidney event (MAKE) will be defined as the composite of death, use of renal replacement therapy and missing renal recovery

End point type	Secondary

End point timeframe:

from Randomization up to 1 year

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	223		
Units: Patients with MAKE	196	189		

Statistical analyses

No statistical analyses for this end point

Secondary: Recovery of renal function day 28

End point title	Recovery of renal function day 28

End point description:

End point type	Secondary

End point timeframe:

28 days after randomization

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	93	76		
Units: Number of patients with renal recovery	20	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal recovery on day 60

End point title	Renal recovery on day 60

End point description:

End point type	Secondary

End point timeframe:

60 days after randomisation

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	58		
Units: Number of patients with renal ercovery	22	25		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal Recovery on day 90

End point title	Renal Recovery on day 90

End point description:

End point type	Secondary

End point timeframe:

90days after randomization

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	102		
Units: No of patients with renal recovery	55	73		

Statistical analyses

No statistical analyses for this end point

Secondary: Renal recovery after 1 year

End point title	Renal recovery after 1 year

End point description:

End point type	Secondary

End point timeframe:

1 year after randomization

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: No of patients with renal recovery	25	32		

Statistical analyses

No statistical analyses for this end point

Secondary: Requirement of renal replacement therapy on day 28

End point title	Requirement of renal replacement therapy on day 28

End point description:

End point type	Secondary

End point timeframe:

28 days after randomization

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	160		
Units: No of patients with RRT	60	50		

Statistical analyses

No statistical analyses for this end point

Secondary: Requirement of renal replacement therapy on day 60

End point title	Requirement of renal replacement therapy on day 60

End point description:

End point type	Secondary

End point timeframe:

60 days after randomisation

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	140		
Units: No of patients with RRT	33	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Requirement of renal replacement therapy on day 90

End point title	Requirement of renal replacement therapy on day 90

End point description:

End point type	Secondary

End point timeframe:

90 days after randomisation

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	138	131		
Units: No of patients with RRT	22	18		

Statistical analyses

No statistical analyses for this end point

Secondary: Requirement of renal replacement therapy after 1 year

End point title	Requirement of renal replacement therapy after 1 year

End point description:

End point type	Secondary

End point timeframe:

1 year after randomisation

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	88		
Units: No of patients with RRT	8	7		

Statistical analyses

No statistical analyses for this end point

Secondary: SOFA-Score at baseline

End point title	SOFA-Score at baseline

End point description:

End point type	Secondary

End point timeframe:

at baseline

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	282	270		
Units: points				
median (inter-quartile range (Q1-Q3))	11.0 (10.0 to 13.0)	11.0 (10.0 to 14.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: SOFA score at day 14

End point title	SOFA score at day 14
End point description:	
SOFA scores was documented during the primary ICU stay.	
End point type	Secondary
End point timeframe:	
14 days after randomisation	

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	95	88		
Units: points				
median (inter-quartile range (Q1-Q3))	10.0 (7.0 to 12.0)	11.0 (8.0 to 13.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: SOFA score at day 21

End point title	SOFA score at day 21
End point description:	
SOFA scores was documented during the primary ICU stay.	
End point type	Secondary
End point timeframe:	
21 days after randomisation	

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	50		
Units: points				
median (inter-quartile range (Q1-Q3))	9.0 (7.0 to 13.0)	11.0 (7.0 to 12.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: SOFA score at day 28

End point title	SOFA score at day 28

End point description:

SOFA scores was documented during the primary ICU stay.

End point type	Secondary

End point timeframe:

28 days after randomization

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	33		
Units: points				
median (inter-quartile range (Q1-Q3))	8.0 (7.0 to 12.0)	8.0 (5.0 to 12.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: 28-day all cause mortality

End point title	28-day all cause mortality

End point description:

End point type	Secondary

End point timeframe:

from randomisation up to day 28

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: No of patients alive at d28	178	162		

Statistical analyses

No statistical analyses for this end point

Secondary: 60-day all cause mortality

End point title	60-day all cause mortality

End point description:

End point type	Secondary

End point timeframe:

60 day after randomisation

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: No of patients alive at day 60	155	142		

Statistical analyses

No statistical analyses for this end point

Secondary: 1 year all cause mortality

End point title	1 year all cause mortality

End point description:

End point type	Secondary

End point timeframe:

1 year after randomisation

End point values	Regional citrate anticoagulation	Systemic heparin anticoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	296		
Units: No of patients alive 1 year after rando	88	89		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs including SAEs will be recorded from the time the first dose of heparin or citrate is administered (day 1). Documentation on the AE form will be required up to discharge of the ICU.

Adverse event reporting additional description:

AKI is frequently caused by severe sepsis/septic shock, extended surgical procedures or traumatic events. Death and other AKI or Sepsis-related events was documented as clinical results. These were only be documented as AE if a reasonable causal relationship to the IP was suspected or they were unexpected in the context of the underlying disease.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Regional citrate anticoagulation

Reporting group description:

300 patientes were randomized to receive anticoagulation for continuous renal replacement therapy with regional citrate. 6 patients do not receive primary continuous renal replacement therapy. 61 were randomized to receive anticoagulation with heparine, but later they also received regional citrate anticoagulation.
Adverse events were analysed for all patients who receive regional citrate anticoagulation.

Reporting group title	Systemic heparin anticoagulation

Reporting group description:

Adverse events were analysed for all patients who receive systemic anticoagulation. 296 patientes were randomized to receive anticoagulation for continuous renal replacement therapy with systemic heparin. 4 patients do not receive primary continuous renal replacement therapy. 41 were randomized to receive anticoagulation with citrate, but later they also received systemic heparin anticoagulation.

Serious adverse events	Regional citrate anticoagulation	Systemic heparin anticoagulation	
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 355 (16.06%)	61 / 333 (18.32%)	
number of deaths (all causes)	212	204	
number of deaths resulting from adverse events	17	20	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Haemodynamic instability			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	3 / 355 (0.85%)	6 / 333 (1.80%)	
occurrences causally related to treatment / all	3 / 3	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Shock haemorrhagic			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Endotracheal intubation			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Resuscitation			
subjects affected / exposed	3 / 355 (0.85%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	3 / 355 (0.85%)	3 / 333 (0.90%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	1 / 3	1 / 3	

Necrosis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	2 / 355 (0.56%)	3 / 333 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bronchial haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary embolism			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory disorder			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 355 (0.28%)	3 / 333 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Thoracic haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Citrate toxicity			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Endotracheal intubation complication			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrythmia			

subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 355 (0.56%)	3 / 333 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 355 (0.28%)	4 / 333 (1.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 4	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cardiac failure			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myocardial infarction			

subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Right ventricular failure			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular fibrillation			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			

subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	3 / 355 (0.85%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic diathesis			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heparine induced thrombocytopenia			

subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric perforation			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	5 / 355 (1.41%)	5 / 333 (1.50%)	
occurrences causally related to treatment / all	1 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Intestinal ischaemia			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	4 / 355 (1.13%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 4	0 / 1	
Acute on chronic liver failure			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic failure			
subjects affected / exposed	0 / 355 (0.00%)	3 / 333 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle necrosis			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia legionella			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 355 (0.56%)	3 / 333 (0.90%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Regional citrate anticoagulation	Systemic heparin anticoagulation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 355 (27.32%)	85 / 333 (25.53%)	
Vascular disorders			
Arterial haemorrhage			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences (all)	0	2	
Deep vein thrombosis			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences (all)	1	2	

Extremity necrosis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	1 / 355 (0.28%)	3 / 333 (0.90%)	
occurrences (all)	1	3	
Haemorrhage			
subjects affected / exposed	8 / 355 (2.25%)	11 / 333 (3.30%)	
occurrences (all)	9	12	
Hypertensive crisis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Hypoperfusion			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences (all)	1	2	
Hypotension			
subjects affected / exposed	2 / 355 (0.56%)	0 / 333 (0.00%)	
occurrences (all)	3	0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Peripheral ischaemia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Shock haemorrhagic			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Thrombosis			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences (all)	2	1	
Venous thrombosis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Arterial aneurysm repair			

subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Colectomy			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	3 / 355 (0.85%)	2 / 333 (0.60%)	
occurrences (all)	4	3	
Chest pain			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Hypothermia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Perforation			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Puncture site haemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	0 / 333 (0.00%)	
occurrences (all)	2	0	
Vessel puncture site haematoma			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences (all)	2	2	

Haemothorax			
subjects affected / exposed	3 / 355 (0.85%)	2 / 333 (0.60%)	
occurrences (all)	3	2	
Hypercapnia			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Pharyngeal haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	3 / 355 (0.85%)	2 / 333 (0.60%)	
occurrences (all)	3	2	
Pneumothorax			
subjects affected / exposed	1 / 355 (0.28%)	3 / 333 (0.90%)	
occurrences (all)	1	3	
Pulmonary haemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	3 / 333 (0.90%)	
occurrences (all)	2	4	
Pulmonary oedema			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
respiratory failure			
subjects affected / exposed	3 / 355 (0.85%)	4 / 333 (1.20%)	
occurrences (all)	3	4	
Tachypnoea			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	3 / 355 (0.85%)	1 / 333 (0.30%)	
occurrences (all)	3	1	
Hallucination			

subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Investigations			
acid balance abnormal			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Blood bicarbonate increased			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Blood calcium decreased			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Blood sodium increased			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences (all)	0	3	
Lipase increased			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Platelet count decreased			
subjects affected / exposed	2 / 355 (0.56%)	3 / 333 (0.90%)	
occurrences (all)	2	3	
Transaminases increased			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Citrate toxicity			

subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Post procedural haematoma			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Post procedural haemorrhage			
subjects affected / exposed	3 / 355 (0.85%)	3 / 333 (0.90%)	
occurrences (all)	3	3	
Procedural haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Tracheal haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Wound haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 355 (1.13%)	3 / 333 (0.90%)	
occurrences (all)	4	3	
Bradycardia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Cardiac failure			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Cardiomyopathy			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Extrasystoles			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Tachyarrhythmia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	

Tachycardia			
subjects affected / exposed	2 / 355 (0.56%)	0 / 333 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Cerebral infarction			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Cerebrovascular accident			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	2	
Epilepsy			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences (all)	2	2	
Headache			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Hemianopia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Myoclonus			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Partial seizures			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Seizure			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences (all)	0	2	
Status epilepticus			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	8 / 355 (2.25%)	3 / 333 (0.90%)	
occurrences (all)	8	3	
Heparin-induced thrombocytopenia			
subjects affected / exposed	22 / 355 (6.20%)	18 / 333 (5.41%)	
occurrences (all)	22	18	
Iron deficiency anaemia			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Pancytopenia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Splenic infarction			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Thrombocytopenia			
subjects affected / exposed	23 / 355 (6.48%)	20 / 333 (6.01%)	
occurrences (all)	24	21	
Application site haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	0	
Mydriasis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Optic disc haemorrhage			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Pupillary deformity			

subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Pupils unequal			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Anal ulcer haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Ascites			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Duodenal ulcer haemorrhage			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	2 / 355 (0.56%)	0 / 333 (0.00%)	
occurrences (all)	2	0	
Faeces pale			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal haemorrhage			
subjects affected / exposed	4 / 355 (1.13%)	4 / 333 (1.20%)	
occurrences (all)	4	4	
Haematochezia			
subjects affected / exposed	1 / 355 (0.28%)	3 / 333 (0.90%)	
occurrences (all)	1	3	
Intestinal haemorrhage			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Intestinal ischaemia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	

Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	2	2	
Large intestinal ulcer haemorrhage			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Large intestine perforation			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences (all)	2	1	
Megacolon			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Mouth haemorrhage			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences (all)	3	3	
Small intestinal perforation			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences (all)	2	2	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences (all)	1	2	
Hepatitis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Jaundice			

subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Portal vein thrombosis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Decubitus ulcer			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Dermatitis allergic			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Erythema			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Hidradenitis			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Lividity			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences (all)	3	3	
Rash			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences (all)	2	1	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Hypothyroidism			

subjects affected / exposed	3 / 355 (0.85%)	0 / 333 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Compartment syndrome			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences (all)	0	2	
Rhabdomyolysis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 355 (0.00%)	2 / 333 (0.60%)	
occurrences (all)	0	2	
Candida infection			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Cellulitis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Device related infection			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Genital candidiasis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	1	
Herpes zoster			

subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Pneumonia viral			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Postoperative wound infection			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Sepsis			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Tracheobronchitis			
subjects affected / exposed	0 / 355 (0.00%)	1 / 333 (0.30%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Alkalosis			
subjects affected / exposed	2 / 355 (0.56%)	1 / 333 (0.30%)	
occurrences (all)	2	1	
Electrolyte imbalance			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences (all)	2	2	
Hypercalcaemia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Hyperkalaemia			
subjects affected / exposed	1 / 355 (0.28%)	2 / 333 (0.60%)	
occurrences (all)	1	2	
Hypernatraemia			
subjects affected / exposed	5 / 355 (1.41%)	0 / 333 (0.00%)	
occurrences (all)	5	0	

Hypoalbuminaemia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	2 / 355 (0.56%)	2 / 333 (0.60%)	
occurrences (all)	2	2	
Hypoglycaemia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	1 / 355 (0.28%)	1 / 333 (0.30%)	
occurrences (all)	1	1	
Hypophosphataemia			
subjects affected / exposed	2 / 355 (0.56%)	0 / 333 (0.00%)	
occurrences (all)	2	0	
Hypovolaemia			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	3	0	
Lactic acidosis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Metabolic acidosis			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	
Metabolic alkalosis			
subjects affected / exposed	5 / 355 (1.41%)	2 / 333 (0.60%)	
occurrences (all)	5	2	
Metabolic disorder			
subjects affected / exposed	1 / 355 (0.28%)	0 / 333 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2017	Inclusion and exclusion criteria have been amended. - patients with previous renal replacement therapy due to acude kidney injury in the last 90 days were also allowed - patients with pre-existing kidney disease not requiring RRT with GFR < 30mL/min were also allowed In addition, the definition of Sepsis and septic shock followed the new guidelines. In 2016, the Surviving Sepsis Campaign introduced the new Sepsis3 guidelines. According to this new definition, the inclusion criteria regarding sepsis was amended.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported