



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
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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 of Helsinki (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 and opportunity 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 CRRT-dependent 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
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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
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End point description:

End point type	Primary
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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)
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Comparison groups	Regional citrate anticoagulation v Systemic heparin anticoagulation
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Number of subjects included in analysis	596
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.0538
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Method	Regression, Cox
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Parameter estimate	Cox proportional hazard
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Point estimate	0.792
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.626
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upper limit	1.004
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Secondary: ICU length of stay

End point title	ICU length of stay
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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 recovery	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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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 randomisation	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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Regional citrate anticoagulation
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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
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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			
Arrhythmia			

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 occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 355 (0.28%) 0 / 1 0 / 0	1 / 333 (0.30%) 0 / 1 0 / 0	
Pneumonia legionella subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 355 (0.28%) 0 / 1 0 / 0	0 / 333 (0.00%) 0 / 0 0 / 0	
Septic shock subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 355 (0.56%) 0 / 2 0 / 0	3 / 333 (0.90%) 0 / 3 0 / 1	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 355 (0.00%) 0 / 0 0 / 0	2 / 333 (0.60%) 0 / 2 0 / 0	
Lactic acidosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 355 (0.28%) 1 / 1 1 / 1	2 / 333 (0.60%) 2 / 2 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 occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Colectomy subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
General disorders and administration site conditions			
Catheter site haemorrhage subjects affected / exposed occurrences (all)	3 / 355 (0.85%) 4	2 / 333 (0.60%) 3	
Chest pain subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Hypothermia subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Perforation subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Puncture site haemorrhage subjects affected / exposed occurrences (all)	2 / 355 (0.56%) 2	0 / 333 (0.00%) 0	
Vessel puncture site haematoma subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Reproductive system and breast disorders			
Vaginal haemorrhage subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Respiratory, thoracic and mediastinal disorders			
Aspiration subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Epistaxis subjects affected / exposed occurrences (all)	2 / 355 (0.56%) 2	2 / 333 (0.60%) 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 occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Restlessness subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Investigations acid balance abnormal subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Blood bicarbonate increased subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Blood calcium decreased subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Blood sodium increased subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	2 / 333 (0.60%) 3	
Lipase increased subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Platelet count decreased subjects affected / exposed occurrences (all)	2 / 355 (0.56%) 2	3 / 333 (0.90%) 3	
Transaminases increased subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Injury, poisoning and procedural complications Abdominal wound dehiscence subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Citrate toxicity			

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

Tachycardia subjects affected / exposed occurrences (all)	2 / 355 (0.56%) 2	0 / 333 (0.00%) 0	
Nervous system disorders			
Brain oedema subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Cerebral infarction subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Cerebrovascular accident subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 2	
Epilepsy subjects affected / exposed occurrences (all)	2 / 355 (0.56%) 2	2 / 333 (0.60%) 2	
Headache subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Hemianopia subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Myoclonus subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Partial seizures subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Seizure subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	2 / 333 (0.60%) 2	
Status epilepticus subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 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 occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Pupils unequal subjects affected / exposed occurrences (all)	2 / 355 (0.56%) 2	1 / 333 (0.30%) 1	
Gastrointestinal disorders			
Anal ulcer haemorrhage subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Ascites subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Constipation subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	1 / 333 (0.30%) 1	
Duodenal ulcer haemorrhage subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Dysphagia subjects affected / exposed occurrences (all)	2 / 355 (0.56%) 2	0 / 333 (0.00%) 0	
Faeces pale subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	
Gastrointestinal haemorrhage subjects affected / exposed occurrences (all)	4 / 355 (1.13%) 4	4 / 333 (1.20%) 4	
Haematochezia subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	3 / 333 (0.90%) 3	
Intestinal haemorrhage subjects affected / exposed occurrences (all)	0 / 355 (0.00%) 0	1 / 333 (0.30%) 1	
Intestinal ischaemia subjects affected / exposed occurrences (all)	1 / 355 (0.28%) 1	0 / 333 (0.00%) 0	

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

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

subjects affected / exposed occurrences (all)	3 / 355 (0.85%) 3	0 / 333 (0.00%) 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	<p>Inclusion and exclusion criteria have been amended.</p> <ul style="list-style-type: none">- patients with previous renal replacement therapy due to acute 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 <p>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.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported