



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 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 |
|------------------|----------------------------------|

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 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 |
|-----------------|--|

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 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 |
|-----------------|------------|

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 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 occurrences (all) | 0 / 355 (0.00%) 0 | 2 / 333 (0.60%) 2 | |
| Deep vein thrombosis subjects affected / exposed occurrences (all) | 1 / 355 (0.28%) 1 | 2 / 333 (0.60%) 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 | | | |

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| 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 | |

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| 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 | | | |

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| 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 | | | |

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| 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 | |

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| 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 | | | |

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| 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 | | | |

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

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

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| 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 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 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