



Clinical trial results:

Feasible strategy for preventing blood clots in critically ill patients with acute kidney Injury

Summary

EudraCT number	2012-004368-23
Trial protocol	DK
Global end of trial date	20 February 2015

Results information

Result version number	v1 (current)
This version publication date	08 September 2016
First version publication date	08 September 2016
Summary attachment (see zip file)	Journal article (The Provision of Thromboprophylaxis and the Prediction of Renal Recovery in Critically Ill Patients with Acute Kidney Injury.pdf)

Trial information

Trial identification

Sponsor protocol code	20121005
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Odense University Hospital
Sponsor organisation address	Sdr. Boulevard 29 , Odense , Denmark, DK 5000
Public contact	Professor Palle Toft, Odense University Hospital , 45 65413947, palle.toft@rsyd.dk
Scientific contact	Professor Palle Toft , Odense University Hospital , 45 65413947, palle.toft@rsyd.dk

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	02 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2015
Global end of trial reached?	Yes
Global end of trial date	20 February 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To reduce the incidence of venous thromboembolism(VTE) among patients on continuous renal replacement therapy (CRRT) by using 1 mg/kg enoxaparin, versus the standard dose of 40 mg enoxaparin.

Protection of trial subjects:

The trial was approved by the Danish national scientific ethical committee and the Danish health and medicine authority. The study was conducted in accordance with the ethical principles set forth in the Declaration of Helsinki and monitored by Good Clinical Practice (GCP). The study was closed in February 2015-a decision made in conjunction with GCP and the project's data monitoring committee owing to poor accrual despite intense efforts to increase recruitment.

Background therapy:

All study patients were critically ill and received treatment therapies as indicated by their underlying conditions. As all study patients had acute kidney injury (AKI), they received CRRT. Once patients achieved diuresis of > 200 ml/day on CRRT, dialysis was discontinued.

Evidence for comparator:

Despite ICU patients receiving recommended doses of prophylactic low- molecular-weight heparin (LMWH), between 5 and 15.5% develop proximal leg deep-vein thrombosis (DVT).

Actual start date of recruitment	01 March 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	11
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Research physicians on the ICUs of the study hospitals obtained written informed consent from all potential trial participants or their designated surrogates for participation in the study.

Pre-assignment

Screening details:

Daily screening for consecutive eligible patients.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Patients, family members, clinicians, research personnel, radiologists, laboratory technicians, and the trial biostatistician were unaware of study-group assignments. They remained blinded until the study database was locked at the end of the trial. Nurses who administered the drug were the only party privy to the actual dose given to each patient as it was impossible to prepare an enoxaparin dose of 1 mg/kg beforehand.

Arms

Are arms mutually exclusive?	Yes
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Arm title	Control arm
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Arm description:

Patients received 40 mg enoxaparin sc QD upon commencement of CRRT

Arm type	control
Investigational medicinal product name	enoxaparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg enoxaparin sc QD

Arm title	Treatment arm
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Arm description:

Patients received 1 mg/kg enoxaparin sc QD upon commencement of CRRT

Arm type	intervention
Investigational medicinal product name	enoxaparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 mg/kg enoxaparin sc QD

Number of subjects in period 1	Control arm	Treatment arm
Started	10	9
Completed	10	9

Period 2

Period 2 title	Overall
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst, Assessor

Blinding implementation details:

Patients, family members, clinicians, research personnel, radiologists, laboratory technicians, and the trial biostatistician were unaware of study-group assignments. They remained blinded until the study database was locked at the end of the trial. Nurses who administered the drug were the only party privy to the actual dose given to each patient as it was impossible to prepare an enoxaparin dose of 1 mg/kg beforehand.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control arm

Arm description:

Patients received 40 mg enoxaparin sc QD upon commencement of CRRT

Arm type	control
Investigational medicinal product name	enoxaparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

40 mg enoxaparin sc QD

Arm title	Treatment arm
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Arm description:

Patients received 1 mg/kg enoxaparin sc QD upon commencement of CRRT

Arm type	intervention
Investigational medicinal product name	enoxaparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

1 mg/kg enoxaparin sc QD

Number of subjects in period 2	Control arm	Treatment arm
Started	10	9
Completed	10	9

Baseline characteristics

Reporting groups

Reporting group title	Control arm
Reporting group description:	
Patients received 40 mg enoxaparin sc QD upon commencement of CRRT	
Reporting group title	Treatment arm
Reporting group description:	
Patients received 1 mg/kg enoxaparin sc QD upon commencement of CRRT	

Reporting group values	Control arm	Treatment arm	Total
Number of subjects	10	9	19
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	62	57.6	
standard deviation	± 10.3	± 14.2	-
Gender categorical			
Units: Subjects			
Female	3	2	5
Male	7	7	14
weight			
Units: kg			
arithmetic mean	92.5	87.1	
standard deviation	± 24.7	± 20.6	-
APACHE II			
Units: none			
arithmetic mean	27.3	26.9	
standard deviation	± 5.1	± 10.4	-
SOFA			
Units: none			
arithmetic mean	11.2	10.4	
standard deviation	± 4.2	± 4.1	-

End points

End points reporting groups

Reporting group title	Control arm
Reporting group description: Patients received 40 mg enoxaparin sc QD upon commencement of CRRT	
Reporting group title	Treatment arm
Reporting group description: Patients received 1 mg/kg enoxaparin sc QD upon commencement of CRRT	
Reporting group title	Control arm
Reporting group description: Patients received 40 mg enoxaparin sc QD upon commencement of CRRT	
Reporting group title	Treatment arm
Reporting group description: Patients received 1 mg/kg enoxaparin sc QD upon commencement of CRRT	
Subject analysis set title	Renal Recovery
Subject analysis set type	Full analysis
Subject analysis set description: Renal recovery refers to the complete independence from renal replacement therapy after dialysis was discontinued.	
Subject analysis set title	Repeat Dialysis
Subject analysis set type	Full analysis
Subject analysis set description: Repeat Dialysis group: patients with continued dependence on renal replacement therapy after dialysis was discontinued.	

Primary: Venous thromboembolism (VTE)

End point title	Venous thromboembolism (VTE)
End point description:	
End point type	Primary
End point timeframe: Patients underwent daily bedside clinical assessment for VTE using validated tools. Bilateral lower extremity CUS was conducted on the first, third, and seventh day of inclusion. CUS was repeated on a weekly basis (more frequently if DVT was suspected).	

End point values	Control arm	Treatment arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: number	0	0		

Statistical analyses

Statistical analysis title	Primary endpoint analysis
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Statistical analysis description:

We estimated that with 133 patients in each group, the study would have 80% power to show a 40% reduction in the relative risk of VTE with 1 mg/kg enoxaparin sc QD, assuming an incidence rate of 40% in the control group, at a two-sided alpha level of 0.05.

Comparison groups	Treatment arm v Control arm
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Bleeding

End point title	Bleeding
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End point description:

End point type	Secondary
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End point timeframe:

Patients underwent daily bedside clinical assessment for bleeding.

End point values	Control arm	Treatment arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: number				
Major bleeding	0	0		
Minor bleeding	4	4		

Statistical analyses

Statistical analysis title	analysis for secondary endpoints
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Statistical analysis description:

All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).

Comparison groups	Control arm v Treatment arm
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Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Secondary: All other DVTs and catheter-related thrombus

End point title	All other DVTs and catheter-related thrombus
End point description:	
End point type	Secondary
End point timeframe:	
Patients underwent daily bedside clinical assessment for DVT using validated tools.	

End point values	Control arm	Treatment arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: number	0	0		

Statistical analyses

Statistical analysis title	analysis of secondary outcomes
Statistical analysis description:	
All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).	
Comparison groups	Control arm v Treatment arm
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: Haematology laboratory endpoints

End point title	Haematology laboratory endpoints
End point description: Peak anti-Xa was 0.47 IU/ml for 1 mg/kg enoxaparin compared to 0.16 IU/ml for 40 mg enoxaparin (P=0.17). Trough anti-Xa was 0.14 IU/ml for 1 mg/kg enoxaparin compared to 0.003 IU/ml for 40 mg enoxaparin (P=0.05). There was no significant difference in highest APTT, AT or lowest platelet count between groups.	
End point type	Secondary
End point timeframe: Peak and trough anti-Xa were measured on day three, and once weekly. Activated partial thromboplastin time (APTT), platelets and antithrombin (AT) were all measured at baseline. Daily platelet count was measured; AT and APTT as per department's norm.	

End point values	Control arm	Treatment arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: See table				
arithmetic mean (standard deviation)				
Highest aPTT in the study period (seconds)	64.2 (± 51)	80.4 (± 20)		
Lowest platelet count in the study period (×10 ⁹ /L)	130 (± 118)	133 (± 80)		
AT (%)	86 (± 26)	60 (± 0)		

Statistical analyses

Statistical analysis title	secondary endpoints analysis
Statistical analysis description: All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).	
Comparison groups	Control arm v Treatment arm
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: Heparin - induced thrombocytopenia

End point title	Heparin - induced thrombocytopenia
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End point description:

End point type	Secondary
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End point timeframe:

All patients had daily platelet count measured during the study period and were evaluated by the 4 T's clinical scoring system.

End point values	Control arm	Treatment arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: number	1	1		

Statistical analyses

Statistical analysis title	secondary endpoints analysis
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Statistical analysis description:

All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).

Comparison groups	Control arm v Treatment arm
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: ICU endpoints

End point title	ICU endpoints
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End point description:

No significant difference was observed in ICU length of stay or ventilator free days.

End point type	Secondary
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End point timeframe:

Trial period.

End point values	Control arm	Treatment arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: See table				
arithmetic mean (standard deviation)				
Length of stay on the ICU (days)	11.6 (± 10.8)	9.6 (± 11.2)		
Ventilator free days	5.4 (± 4.4)	4.2 (± 3.7)		

Statistical analyses

Statistical analysis title	secondary endpoints analysis
Statistical analysis description:	
All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).	
Comparison groups	Treatment arm v Control arm
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: CRRT-related outcomes

End point title	CRRT-related outcomes
End point description:	
Patients in the group that received 40 mg enoxaparin showed a trend towards needing higher doses of regional UFH during CRRT (P=0.06) , and five patients in that group compared with none in the group that received 1 mg/kg enoxaparin needed regional citrate (P= 0.03).	
End point type	Secondary
End point timeframe:	
Trial period.	

End point values	Control arm	Treatment arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	9		
Units: See table				
arithmetic mean (standard deviation)				
Duration of CRRT (hours)	79.5 (± 45.3)	86 (± 109)		
Number of filters used	3.6 (± 2)	4.3 (± 5)		
Dose of UFH (IU)	845 (± 900)	211 (± 342)		

Statistical analyses

Statistical analysis title	secondary endpoints analysis
Statistical analysis description:	
All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).	
Comparison groups	Treatment arm v Control arm
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: Renal outcomes: general

End point title	Renal outcomes: general
End point description:	
The main cause of AKI was sepsis or septic shock (42%). In 63% of the patients, the reason for starting dialysis was either anuria or electrolyte disturbances. 26% of patients were dialysis-dependent after the first dialysis-free period on the ICU. Eight patients in the enoxaparin 1 mg/kg group, and six patients in the enoxaparin 40 mg group experienced renal recovery. The number of patients needing vasopressors did not differ significantly between the renal recovery and non-renal recovery groups ($P = 1$), mean arterial pressure was not significantly different ($P = 0.18$), and patients had similar fluid balances before CRRT was discontinued ($P = 0.4$). The number of patients with sepsis was evenly distributed between non-renal recovery and renal recovery groups ($P = 0.6$). During the dialysis -free interval, the mean urine volume was similar but, non-renal recovery patients had a trend towards needing higher doses of furosemide to maintain urine volume ($P = 0.05$).	
End point type	Secondary
End point timeframe:	
Trial period.	

End point values	Renal Recovery	Repeat Dialysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	5		
Units: See table				
arithmetic mean (standard deviation)				
MAP (mm Hg)	83 (\pm 13)	93 (\pm 13)		

Initial plasma creatinine (umol/l)	345 (± 228)	354 (± 106)		
Time to initiation of CRRT after admission (days)	1 (± 1.3)	1.6 (± 1.5)		
Duration of CRRT (hours)	81.6 (± 87)	84.1 (± 51)		
Urine volume (ml)	731 (± 931)	826 (± 950)		
Dose of furosemide (mg)	103 (± 207)	371.5 (± 350)		

Statistical analyses

Statistical analysis title	secondary endpoints analysis
Statistical analysis description:	
All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).	
Comparison groups	Renal Recovery v Repeat Dialysis
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Secondary: Renal outcomes:NGAL

End point title	Renal outcomes:NGAL
End point description:	
Plasma NGAL levels were higher in non-renal recovery (1074 [± 694] ng/mL) compared to renal recovery patients (296[± 197] ng/mL; P = 0.01) during the dialysis-free interval (Figure 1). Urine NGAL levels were higher in non-renal recovery (3885 [± 2722] ng/mL) compared to renal recovery patients (597 [± 565] ng/mL; P= 0.006) during dialysis -free interval (Figure 2). Though both plasma and urine NGAL levels appear to be significantly related to renal recovery, multiple regression analysis showed that only urine NGAL could independently predict recovery from AKI (P = 0.006).	
End point type	Secondary
End point timeframe:	
Urine and plasma NGAL were measured at baseline and during CRRT-free intervals.	

End point values	Renal Recovery	Repeat Dialysis		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	5		
Units: ng/mL				
arithmetic mean (standard deviation)				
Initial plasma NGAL (ng/ml)	731 (± 657)	881 (± 472)		
Initial urine NGAL (ng/ml)	3277 (± 2607)	3863 (± 2470)		

Attachments (see zip file)	Chart 2/Figure 2 Secondary endpoints.pdf
	Chart 1/Figure 1 Secondary endpoints.pdf

Statistical analyses

Statistical analysis title	secondary endpoints analysis
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Statistical analysis description:

All baseline demographic values for these two groups were compared using the Student's t-test or Mann-Whitney rank sum test for continuous variables, and Fisher's exact test for categorical variables. The prediction ability of urine output and NGAL for successful discontinuation of CRRT was assessed with multiple regression analysis. We analyzed data from all patients according to their assigned group (intention-to-treat principle).

Comparison groups	Repeat Dialysis v Renal Recovery
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	t-test, 2-sided
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Recording of adverse events was from time of enrolment in the study until 24 hours after end of study. All serious adverse events were immediately reported to the sponsor. The immediate reports were followed within 24 hours by detailed written reports.

Adverse event reporting additional description:

The investigator complied with regulatory requirements for reporting unexpected serious adverse drug reactions to the Danish national scientific ethical committee and the Danish Health and Medicines Authority. The sponsor expedited the reporting of all adverse drug reactions that were both serious and unexpected within the timeframe specified.

Assessment type	Systematic
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Dictionary used

Dictionary name	ICD
Dictionary version	9

Reporting groups

Reporting group title	Control arm
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Reporting group description:

Patients received 40 mg enoxaparin sc QD upon commencement of CRRT

Reporting group title	Treatment arm
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Reporting group description:

Patients received 1 mg/kg enoxaparin sc QD upon commencement of CRRT

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Heparin - induced thrombocytopenia was reported as a secondary endpoint, not as an adverse event, as per our protocol.

Serious adverse events	Control arm	Treatment arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Death	Additional description: Further therapy was judged futile and active therapy was withdrawn, resulting in death.		
subjects affected / exposed	0 / 10 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Control arm	Treatment arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 10 (0.00%)	0 / 9 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 August 2012	This was the first amendment made on a version of the protocol that had been submitted to the Danish Health and Medicines Authority and the Danish national scientific ethical committee. At the request of Danish Health and Medicines Authority changes were made to the exclusion criteria so that patients with chronic renal failure or acute-on-chronic renal failure were ineligible. The methods section was also updated to indicate that a patient who changed from CRRT to intermittent hemodialysis would have reached the end of the study period. In addition, further details about the reporting of adverse events were included. The comparator dose which was unconfirmed until this point was included in this new protocol version.
21 January 2013	At the request of the Danish national scientific ethical committee a separate information sheet for the designated surrogates was developed. The methods section was also revised due to the acquisition of new dialysis machines at Odense University Hospital.
06 June 2013	A change in the exclusion criteria: platelet count of $<75 \times 10^9/l$, changed to $<50 \times 10^9/l$ and INR or APTT $\geq 1\frac{1}{2}$ times the upper limit of normal changed to ≥ 2 times the upper limit of normal.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 February 2015	The study was closed in February 2015-a decision made in conjunction with GCP and the project's data monitoring committee owing to poor accrual despite intense efforts to increase recruitment.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Our study did not recruit enough patients to test the primary hypothesis, and this is an obvious limitation. It is also possible that the characteristics of NGAL may not be the same in clinical settings. Urine NGAL was in absolute concentration.

Notes: