Supplementary Online Content 3

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

Effect of Regional Citrate Anticoagulation vs Systemic Heparin Anticoagulation During Continuous Kidney Replacement Therapy on Dialysis Filter Lifespan and Mortality Among Critically Ill Patients with Acute Kidney Injury: A Randomized Clinical Trial

The RICH Investigators

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Supplementary Methods

Inclusion of unconscious patients

According to the European regulation and the requirements of the institutional review boards for including unconscious patients into trials, patients can be included into trials if there is no indication that the patient was unwilling to participate in clinical trials. This has to be evaluated by telephone calls to the family members, close relatives or the general practitioner who knows the patient personally. In this case, the patient has to be asked for consent as soon as he/she regains consciousness but at the latest two weeks after inclusion into the trial. If it is foreseeable that the patient does not regain consciousness, a guardianship procedure has to be initiated and the guardianship needs to provide consent for the patient to participate in the trial. Reasons for including but not analyzing patients were: refusal of the guardianship procedure by the local court, no written consent of guardian prior to the death of the patient, no written consent of the guardian at all, or timeline of two weeks not fulfilled.

Randomization

Randomization was performed centrally by the Clinical Trials Centre Leipzig in a 1:1 proportion. A computerized minimization method with random component was used that provided treatment assignment to be balanced by the factors study center, sex, cardiovascular sequential organ failure assessment (SOFA) score (0-2 versus 3-4) and by the presence or absence of oliguria.

Pocock's minimization method is a method of stratified randomization that leads to balanced marginal treatment totals for each stratification factor.[1] After each recruited patient the allocation ratio of the next patient is adjusted continually based on the up-to-date marginal distribution of stratification factors and the new patient's expression of his/her stratification factors. Instead of a 1:1 allocation ratio, the allocation ratio is shifted so that after inclusion of the new patient the chance of more balanced marginal totals of stratification factors is increased. The random component refers to the fact that the shift of the allocation ratio is never carried so far that it results in the deter-ministic assignment of a treatment. Instead of that in case of all recruited patients there is an (uneven but still >0) chance to receive each of the two treatments.

Procedures

Participating centers utilized the standard dialysis machines used in daily clinical care (Fresenius, Baxter, BBraun) and adapted the mode of dialysis according to the patients' condition. 22 centers used Fresenius Medical Care machines (with 4% sodium citrate, K2 or K4 as dialysate, and Multibic as substitution fluid where applicable), 3 centers used Prismaflex by Baxter (Prismocitrate 10/2 or 18/0, Prismocal and Phoxilium), 1 center used BBraun machines (with 30% sodium citrate, HDE 2/0 as dialysate, and sodium chloride as substitution fluid where applicable). Modality of continuous kidney replacement therapy was described using machine-centric terminology. All participating centers used published citrate protocols.[2,3] To prevent thromboembolic complications, prophylactic heparin anticoagulation was permitted in the regional citrate anticoagulation group.[4]

Further outcomes

Chronic kidney disease and new onset of chronic kidney disease were exploratory outcomes. Chronic kidney disease was defined according to the estimated GFR criterion of the KDIGO recommendations for chronic kidney disease in all patients using the Chronic Kidney Disease Epidemiology Collaboration formula at day 90 and 1 year.[5] New onset of chronic kidney disease was defined as an estimated GFR <60ml/min/1.73m^2 in patients without prior chronic kidney disease.

Stopping rules

Regarding the first co-primary outcome of filter lifespan, there was no specified stopping rule for futility. Regarding the second co-primary outcome of 90-day mortality, a non-binding stopping rule for futility was specified. The sample size was limited to a maximal total number of 1450 patients. In the interim analysis it was determined if the (unadjusted) p-value of favorable survival in the citrate group is 0.5 or larger, and if stochastic curtailment shows a conditional power of the final statistical analysis with 1450 patients that is lower than 50%. Both above stopping criteria may lead to the decision to stop recruitment, but were not strictly binding. The final decision to stop or continue recruitment was drawn by the principal investigator based on the recommendation of the data and safety monitoring board.

Interim analysis

The interim analysis included 470 patients who were recruited up to the cutoff date June 30, 2018 (235 patients in the regional citrate group and the systemic heparin group, respectively), and was conducted at the time when primary outcome data of all recruited patients were available. The study statistician (JG) performed the interim analysis and delivered the results to the data and safety monitoring board confidentially.

In total, 1680 filters were used (n=749 in the citrate and n=931 in the heparin group). Filter lifespan was significantly longer in the citrate as compared to the heparin group (48h [IQR: 20h, 71h] vs. 27h [IQR: 13h, 53h]; $P<0.001$). 90-day all-cause mortality was 51.4% in the citrate and 54.6% in the systemic heparin group (one-sided $P=0.17$). The calculated (one-sided) conditional error function was alpha(P) = 0.033 (inverse normal method). Based on the observed difference of 3.2 percentage points the calculated number of additional patients for a required 70% conditional power of the final statistical analysis was 2754. According to the study protocol, the maximal total number of recruited patients was n=1450. With a number of 1450 patients included in the final statistical analysis, the calculated conditional power was 33.4%.

In the light of the results from the interim analysis, the preplanned end of the trial according to the protocol was reached and the data and safety monitoring board deemed that completion of enrollment was unlikely to change the results of the trial significantly and recommended that the trial be stopped. The recommendation was followed and recruitment was stopped by the principal investigator at the 4th of January 2019 for two reasons: regarding the first co-primary endpoint filter lifespan, significant superiority of regional citrate over systemic heparin anticoagulation was proven; and regarding the second co-primary endpoint overall survival in a 90-day follow-up period, the calculated conditional power of a final statistical analysis with 1450 patients was 33.4% < 50%, so that the preplanned stopping criterion was reached.

After patient no. 470 was recruited and before the decision to stop recruitment could be drawn, recruitment was carried on until patient no. 470 completed the 90-day follow-up period. In the meantime, additional patients were recruited up to the 3rd of January 2019. After the additional patients completed the 90-day follow-up period, the final analysis was conducted, including 638 recruited patients in total (596 evaluable patients). The results of the final analysis are reported in the main body of the manuscript.

Post-hoc Statistical analyses

In post-hoc sensitivity analyses beyond the primary statistical analysis, 90-day overall survival was evaluated with additional adjustment for the patients' baseline fluid balance as well as the time-dependent factor new infection since start of dialysis using multivariable Cox regression. In a further post-hoc sensitivity analysis filter lifespan was evaluated with censoring at 72 hours using survival analytic methods, in order to account for the obligatory filter

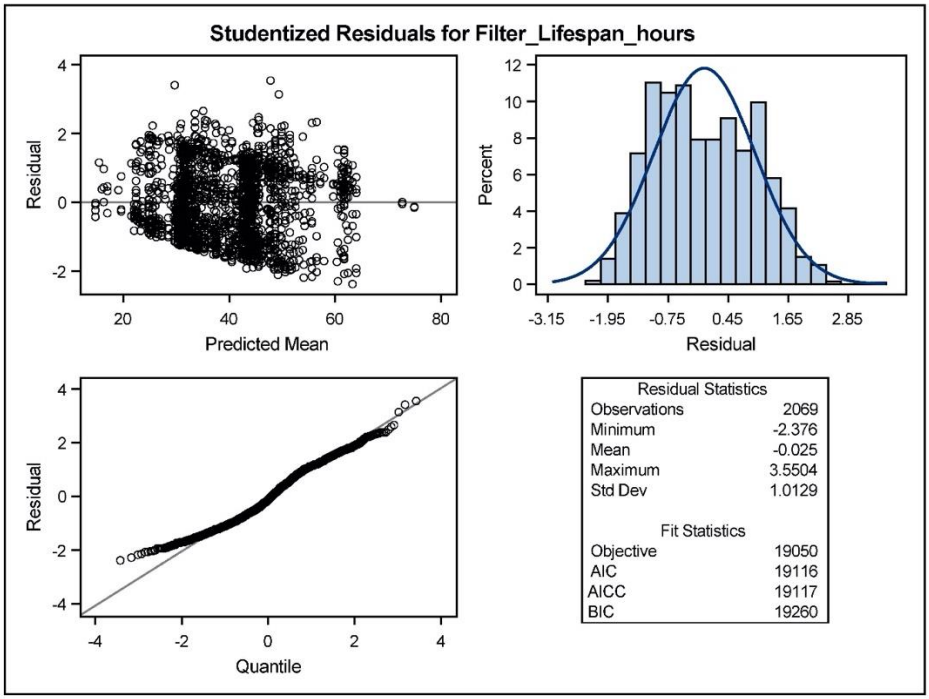
change after 72 hours (manufactures recommend to change the filter after 72 hours and most of the centers generally view this as completion of a filters lifespan). A pre-planned subgroup analysis of surgical and non-surgical patients was conducted by including an interaction effect of the randomized treatment and the subgroup indicator in the respective multivariable models. Statistical tests for significant interaction were performed and differences in the treatment effect size among subgroups were quantified based on the estimated interaction effect. The impact of filter lifespan on the occurrence of infections was evaluated by multivariable logistic regression with the factors anticoagulation strategy, study center, baseline cardiovascular SOFA Score, presence or absence of oliguria, sex, pre/post amendment 1, and aggregated filter lifespan.

Further statistical analyses were performed using descriptive and inferential statistical methods, including pre-specified secondary endpoints, subgroup analyses, safety analyses, and additional exploratory analyses. The results of all secondary analyses were considered exploratory. P-values were regarded significant in case $p \leq 0.05$ without adjustment for multiplicity. Categorical variables were compared with the use of the chi-square test, and continuous variables were compared with the use of Student's t-Test or Wilcoxon test, as appropriate. Results are generally reported by mean parameter estimates and associated 95%CIs. For non-normal data the absolute difference between groups was reported using the Hodges-Lehmann estimator of location shift. All applied hypothesis tests were two-sided unless otherwise stated.

Supplementary Results

Model diagnostics of the linear mixed model of filter lifespan

The basic model assumptions of the linear mixed model are the normality and constant variance of the random effect and the random error term. Model diagnostics were performed using the Studentized conditional residuals. Histograms, normal q-q plots, and residual versus predicted plots revealed that the basic model assumptions were met.



Model diagnostics of the Cox regression of 90-day mortality

The proportionality assumption was tested and confirmed based on the Schoenfeld residuals using the Grambsch-Therneau method.

	Chi-Square	Degrees of freedom	p-value (Grambsch-Therneau test)
anticoagulation strategy	1.0657	1	0.302
study center	35.7837	25	0.075
sex	0.1337	1	0.715
cardiovascular SOFA score (0-2 versus 3-4)	0.0291	1	0.865
presence or absence of oliguria	0.3879	1	0.533
pre/post amendment 1	0.8211	1	0.365
GLOBAL	38.2092	30	0.144

Sensitivity analysis for partial unbalance of randomized treatment groups

Filter lifespan (adjusted for the factors study center, cardiovascular SOFA score, presence or absence of oliguria, sex, pre/post amendment 1, diabetes and chronic kidney disease) remained significantly longer in the citrate group (P<0.001). In the multivariable model neither diabetes nor chronic kidney disease reached significance (P=0.079 and P=0.664, respectively).

Mortality at day 90 (adjusted for the factors study center, cardiovascular SOFA score, presence or absence of oliguria, sex, pre/post amendment 1, diabetes and chronic kidney disease) was still not significantly different in both randomized treatment groups (HR, 0.87 (95% CI, 0.60 to 1.10); P=0.247). In the multivariable model neither diabetes nor chronic kidney disease reached significance (P=0.697 and P=0.561, respectively).

In terms of the secondary outcomes, it was concluded that the significant differences in new onset of CKD and persistent kidney dysfunction at day 90 emerged by chance, as these results are only detectable at day 90 and not at other time points. Therefore it was not put emphasis on these findings.

Sensitivity analysis adjusting for modality of kidney replacement therapy

Filter lifespan (adjusted for the factors anticoagulation strategy, study center, cardio-vascular SOFA score, presence or absence of oliguria, sex, pre/post amendment 1, CKRT modality) was still significantly longer in the citrate group than in the heparin group (Mean difference = 10.58 (95%CI 7.76-13.40); P<0.001). In the multivariable model CKRT modality showed a significant effect on filter lifespan (P=0.002). In pairwise comparisons of modalities, it was found that CVVHD had the longest filter lifespan, followed by CVVHDF and CVVH.

CVVHD versus CVVH: Mean difference = 14.68 (95%CI 5.71-23.65), P=0.001

CVVHDF versus CVVH: Mean difference = 9.54 (95%CI 0.23-18.85), P=0.045

CVVHD versus CVVHDF: Mean difference = 5.14 (95%CI 0.23-10.05), P=0.040

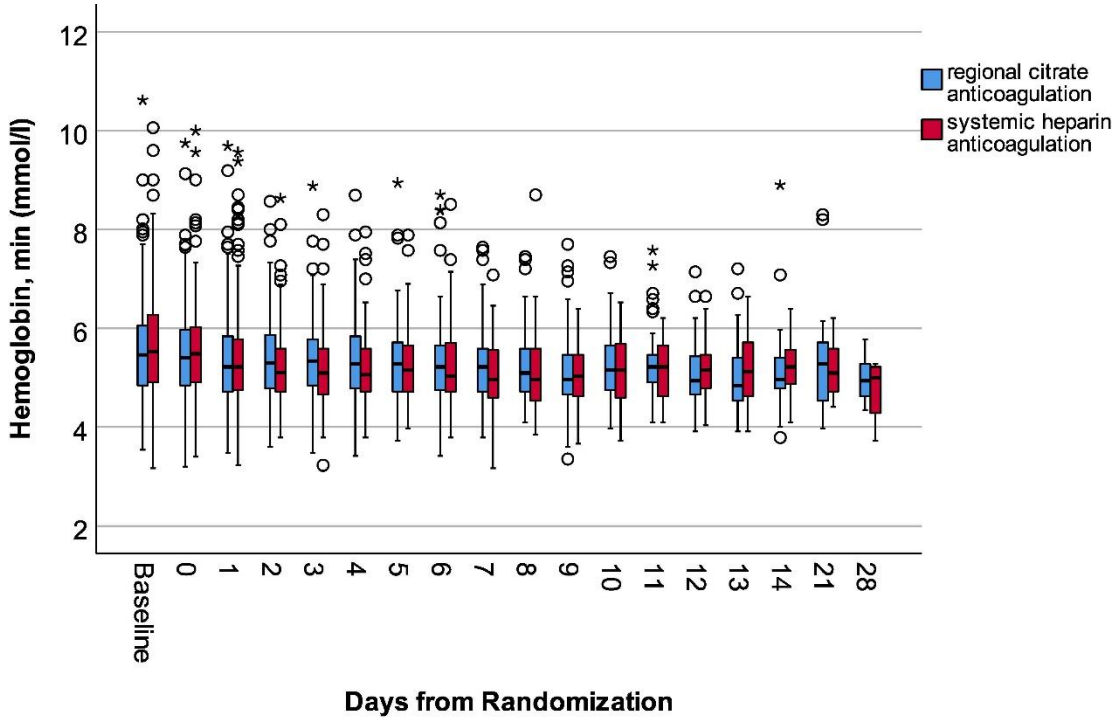
In terms of 90-day mortality, CKRT modality had no impact. 90-day Mortality, adjusted for the factors anticoagulation strategy, study center, base-line cardiovascular SOFA Score, presence or absence of oliguria, sex, pre/post amendment 1, CKRT modality:

RCA versus SHA: Hazard Ratio HR=0.90 (95%CI 0.70-1.16), P=0.434

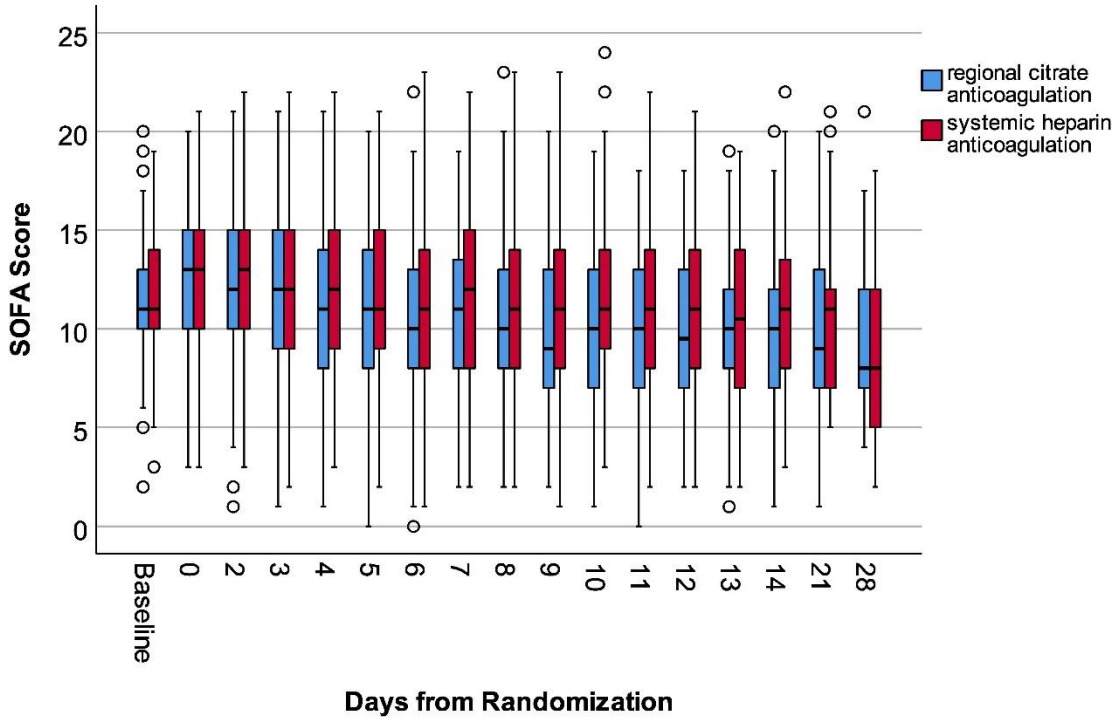
CKRT modality (CVVH versus CVVHD versus CVVHDF): P=0.141

Supplementary Figures

eFigure 1: Hemoglobin values at different time points

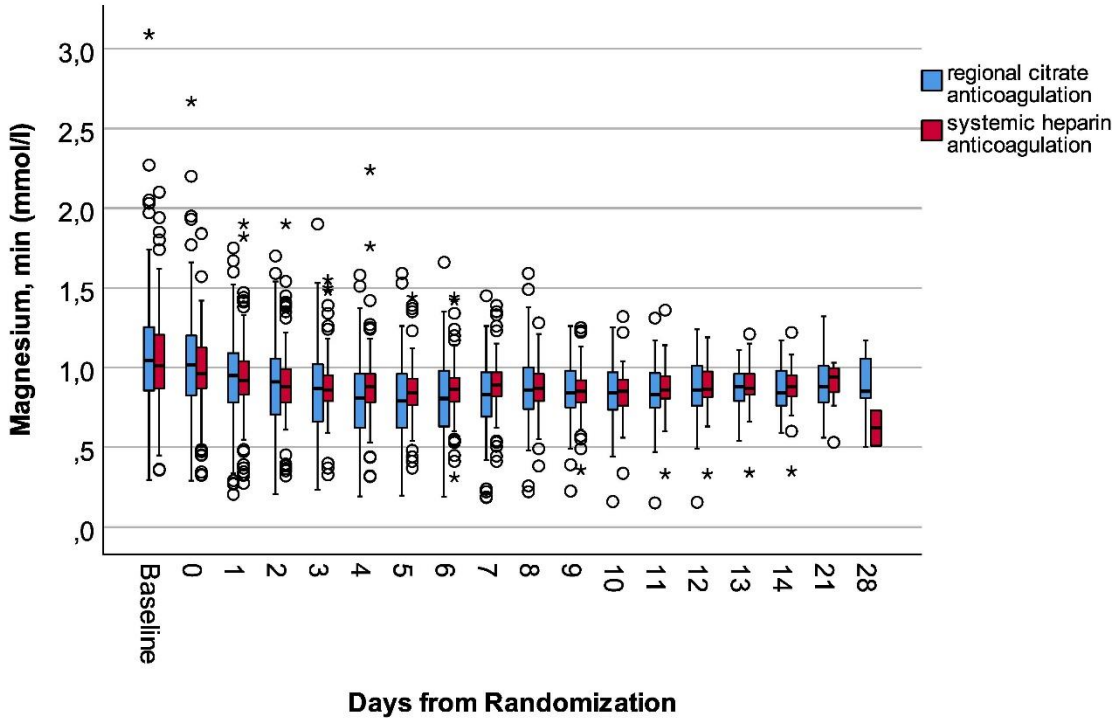


eFigure 2: SOFA Score at different time points



SOFA is a score that evaluates the degree of organ dysfunction and helps determine the mortality risk of a patient. SOFA score values range from 0 to 24 with higher values indicating highest risk of mortality (SOFA 10-11: 50% mortality)

eFigure 3: Magnesium levels at different time points



Supplementary Tables

eTable 1: Protocol changes after amendment	
Old version	**New version**
Patients with increased bleeding risk (e.g. an active bleeding from ulcers in the gastro-intestinal tract, hypertension with a diastolic blood pressure higher than 105 mm Hg, injuries (intracranial haemorrhage, aneurysm of brain arteries)of or surgical procedures on the central nervous system if a heparinization with a target aPTT 45-60 s is not allowed by the treating neurologist or neurosurgeon, severe retinopathies, bleeding into the vitreum, ophthalmic surgical procedures or injuries, active tuberculosis; infective endocarditis)	Patients with increased bleeding risk (e.g. active bleeding from ulcers in the gastro-intestinal tract, hypertension with a diastolic blood pressure higher than 105 mmHg, injuries (intracranial haemorrhage, aneurysm of brain arteries) of or surgical procedures on the central nervous system if a heparinization with a target PTT 45-60 s is not allowed by the treating neurologist or neurosurgeon, severe retinopathies, bleeding into the vitreum, ophthalmic surgical procedures or injuries, active tuberculosis, infective endocarditis)
Diseases or organ damage related with haemorrhagic diathesis (coagulopathy, thrombocytopenia, severe liver or pancreas disease)	Diseases or organ damage related with haemorrhagic diathesis (coagulopathy, thrombocytopenia, severe liver or pancreas disease)
Pre-existing kidney disease KDOQI IV not requiring RRT (GFR < 30 mL/min)	Removed.
Previous renal-replacement therapy due to acute kidney injury in the last 90 days	Removed.
Dialysis-dependent chronic kidney insufficiency	Dialysis-dependent chronic kidney insufficiency
Need of therapeutic systemic anticoagulation	Need of therapeutic anticoagulation (PTT> 60 s)
Allergic reaction to one of the anticoagulants or ingredients, Heparin-induced thrombocytopenia	Allergic reaction to one of the anticoagulants or ingredients, Heparin-induced thrombocytopenia
AKI caused by permanent occlusion or surgical lesion of the renal artery	AKI caused by permanent occlusion or surgical lesion of both renal arteries
AKI caused by (glomerulo-)nephritis, interstitial nephritis, vasculitis or postrenal obstruction	AKI caused by (glomerulo-)nephritis, interstitial nephritis, vasculitis or postrenal obstruction
Do-not-resuscitate order	Do-not-resuscitate order
Hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura	Hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura
Persistent and severe lactate acidosis in the context of an acute liver failure and/or shock	Persistent and severe lactate acidosis in the context of an acute liver failure and/or shock

Kidney transplant within the last 12 months	Kidney transplant within the last 12 months
Pregnancy and nursing period	Pregnancy and nursing period
Abortus imminens	Abortus imminens
No hemofiltration machine free for use at the moment of inclusion	No hemofiltration machine free for use at the moment of inclusion
Participation in another clinical intervention trial in the last 3 months	Participation in another clinical intervention trial in the last 3 months
Persons with any kind of dependency on the investigator or employed by the sponsor or investigator	Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
Persons held in an institution by legal or official order	Persons held in an institution by legal or official order

This amendment was compiled with the steering committee due to the slow recruitment process mainly caused by the two exclusion criteria previous kidney replacement therapy due to acute kidney injury within the last 90 days and preexisting kidney disease with a eGFR < 30ml/min/m^2. The institutional review board approved this amendment on July 24th 2017. The amendment was applied on August 18th 2017.

eTable 2: Additional inclusion criteria for dialysis initiation				
	Regional citrate anticoagulation (n=300)	**Systemic heparin anticoagulation (n=296)**	**p-value**	**Absolute difference [95% CI]**
Severe sepsis/ septic shock, No./No. total (%)	165/293 (56.3)	159/284 (56.0)	0.94	0.3 (-7.8, 8.4)[a]
High doses of vasopressors, No./No. total (%)[b]	221/299 (73.9)	215/296 (72.6)	0.73	1.3 (-5.8, 8.4)[a]
Fluid overload or worsening pulmonary edema, No./No. total (%)	189/290 (65.2)	198/289 (68.5)	0.39	-3.3 (-11.0, 4.3)[a]
Number of additional inclusion Criteria, No. (%)			0.79	
1	98 (32.7)	98 (33.1)		
2	129 (43.0)	120 (40.5)		
3	73 (24.3)	78 (26.4)		

[a] Absolute difference in percentages

[b] defined as norepinephrine or epinephrine ≥ 0.1 µg/kg/min or norepinephrine ≥ 0.05 µg/kg/min + dobutamine (any dose) or norepinephrine ≥ 0.05 µg/kg/min + vasopressin (any dose) or epinephrine + norepinephrine ≥ 0.1 µg/kg/min

p-values should be interpreted descriptive, not in terms of statistical testing

eTable 3: Characteristics of kidney replacement therapy				
	Regional citrate anticoagulation (n=300)	**Systemic heparin anticoagulation (n=296)**	**p-value**	**Absolute difference [95% CI]**
Filters	965	1104		
Reason for filter change, No./Total No. filters with non-missing data (%)				
Change after 72h (as recommended by the manufacturers)	297/839 (35.4)	167/999 (16.7)	<0.001	18.7 (14.7, 22.7)[a]
Clotting	265/839 (31.6)	566/999 (56.7)	<0.001	-25.1 (-29.5, -20.7)[a]
Others (e.g., surgery)	256/839 (30.5)	224/999 (22.4)	<0.001	8.1 (4.0, 12.1)[a]
Change of anticoagulation	21/839 (2.5)	42/999 (4.2)	0.046	-1.7 (-3.3, -0.1)[a]
Effectiveness of anticoagulation therapy, median (IQR)	iCa^{2+} (mmol/l) 0.3 (0.3- 0.3)	PTT (s) 50.0 (42.0- 58.5)	n/a	n/a
Filtration fraction, median (IQR), %	16.8 (15.2-19.3)	15.6 (13.3-17.6)	<0.001	1.8 (0.8, 2.9)[b]
CKRT dose (delivered), mean (SD), ml/kg/h[c]	27.0 (6.3)	25.6 (6.2)	<0.001	1.4 (0.9, 2.0)
Modality of CKRT[d], No./Total No. filters with non-missing data (%)				
CVVHD	512/965 (53.1)	366/1104 (33.2)	<0.001	19.9 (15.7, 24.1)[a]
CVVHDF	402/965 (41.7)	613/1104 (55.5)	<0.001	-13.9 (-18.1, -9.6)[a]
Pre-dilution	149/388 (38.4)	191/550 (34.7)	0.249	3.7 (-2.6, 9.9)[a]
Post-dilution	239/388 (61.6)	359/550 (65.3)	0.249	-3.7 (-9.9, 2.6)[a]
CVVH	51/965 (5.3)	125/1104 (11.3)	<0.001	-6.0 (-8.4, -3.7)[a]
Blood flow, median (IQR), ml/h	10.0 (100.0- 120.0)	110.0 (105.5-144.2)	<0.001	-8.0 (-10.0, -2.2)[b]
Dialysate flow, mean (SD), ml/h	1593.1 (754.9)	1603.2 (792.5)	0.87	-10.08 (-135.8, 115.6)
Total replacement flow, median (IQR), ml/h	1367.2 (1221.5-1591.7)	1150.0 (900.0-1329.2)	<0.001	253.7 (171.3, 346.7)[b]
CVVHD	–	–	–	–

CVVHDF	1357.3 (1222.0-1562.3)	1171.6 (975.3-1333.3)	<0.001	224.6 (142.0, 307.3)[b]
Pre-dilution	1460.0 (235.0-2125.3)	791.7 (238.0-1350.0)	0.449	201.2 (-322.1, 800.0)[b]
Post-dilution	1356.3 (1283.0-1477.1)	1200.0 (1050.0-1329.2)	<0.001	187.0 (128.1, 245.7)[b]
CVVH	–	–	–	–
Calcium substitution, No. (%)				
Calcium chloride	251 (83.6)	50 (16.9)	<0.001	66.8 (60.8, 72.8)[a]
No substitution	26 (8.7)	237 (80.1)	<0.001	-71.4 (-77.0, -65.9)[a]
Calcium gluconate	23 (7.7)	9 (3.0)	0.012	4.6 (1.0, 8.2)[a]
Citrate product[e], No. (%)				
Prismocitrate 18/0	125 (41.7)	17 (5.7)	<0.001	35.9 (29.8, 42.1)[a]
SodiumCitrate 4 %	111 (37.0)	33 (11.1)	<0.001	25.9 (19.3, 32.4)[a]
Citrate K2	35 (11.7)	6 (2.0)	<0.001	9.6 (5.7, 13.6)[a]
30 % Citrate	31 (10.3)	8 (2.7)	<0.001	7.6 (3.7, 11.5)[a]
Citrate K4	7 (2.3)	0	0.008	2.3 (0.6, 4.0)[a]
Prismocitrate 10/2	2 (0.7)	0	0.159	0.7 (-0.3, 1.6)[a]
Time on CKRT, median (IQR) days[f]	5.9 (3.2- 11.1)	5.7 (3.1- 10.6)	0.58	0.2 (-0.6, 0.9)
Change to intermittent technique, No./No. total (%)	60/294 (20.4)	54/292 (18.5)	0.56	1.9 (-4.5, 8.3)[a]

[a] Absolute difference in percentages
[b] Hodges-Lehmann estimator of location shift
[c] CKRT dose per filter
[d] modality of CKRT using machine-centric terminology
[e] all percentages refer to randomized patients in respective groups, patients may have received more than one product.
[f] censored at day of death or end of follow-up
p-values should be interpreted descriptive, not in terms of statistical testing

eTable 4: Characteristics of the catheters used for kidney replacement therapy			
	Regional citrate anticoagulation (n=300)	**Systemic heparin anticoagulation (n=296)**	**p-value**
Catheters[a], No.	447	430	
Catheter per patient, Median (IQR)	1.0 (1.0- 2.0)	1.0 (1.0- 2.0)	0.50
Catheter diameter, No./No. total (%)			0.14
11	10/438 (2.3)	7/411 (1.7)	
11.5	3/438 (0.7)	11/411 (2.7)	
12	112/438 (25.6)	99/411 (24.1)	
13	282/438 (64.4)	256/411 (62.3)	
13.5	31/438 (7.1)	38/411 (9.2)	
Catheter localization, No./No. total (%)			0.79
V. jugularis	278/443 (62.8)	269/417 (64.5)	
V. subclavia	41/443 (9.3)	40/417 (9.6)	
V. femoralis	124/443 (28.0)	108/417 (25.9)	
Type of catheters, No./No. total (%)			0.63
2-lumen	169/427 (39.6)	164/398 (41.2)	
3-lumen	258/427 (60.4)	234/398 (58.8)	
Catheter length, No./No. total (%)			0.94
150 mm	116/411 (28.2)	119/376 (31.6)	
160 mm	12/411 (2.9)	11/376 (2.9)	
175 mm	36/411 (8.8)	34/376 (9.0)	
200 mm	163/411 (39.7)	141/376 (37.5)	
240 mm	51/411 (12.4)	44/376 (11.7)	
250 mm	33/411 (8.0)	27/376 (7.2)	

[a] All catheters were neither tunneled nor coated with antibiotics.

p-values should be interpreted descriptive, not in terms of statistical testing

eTable 5: Fluid balance at different days

	Regional citrate anticoagulation (n=300)	Systemic heparin anticoagulation (n=296)	p-value	Absolute difference [95% CI]
Secondary outcomes, Median (IQR)				
Fluid balance at day 0, ml	632.0 (-262.0-1720.0)	759.0 (-210.0-2350.0)	0.19	-218.0 (-544.0, 108.0)[a]
Fluid balance at day 1, ml	144.0 (-924.0-1857.0)	480.0 (-786.0-1845.0)	0.31	-195.0 (-558.0, 187.0)[a]
Fluid balance at day 2, ml	-244.5 (-1287.5-1015.0)	200.0 (-939.0-1509.0)	0.019	-396.0 (-731.0, -63.0)[a]
Fluid balance at day 3, ml	-294.0 (-1200.0-789.0)	-107.0 (-1346.0-1001.0)	0.34	-163.0 (-486.0, 171.0)[a]
Fluid balance at day 4, ml	-356.0 (-1560.0-564.0)	-228.0 (-1000.0-995.0)	0.020	-355.0 (-669.0, -53.0)[a]
Fluid balance at day 5, ml	-396.0 (-1540.0-422.0)	-262.0 (-1406.0-757.0)	0.29	-169.0 (-486.0, 149.0)[a]
Fluid balance at day 6, ml	-203.0 (-1247.0-789.0)	-304.0 (-1285.0-927.0)	0.94	11.0 (-299.0, 320.0)[a]
Fluid balance at day 7, ml	13.0 (-1056.0-740.0)	-387.0 (-1290.0-701.0)	0.16	238.0 (-100.0, 564.0)[a]
Cumulative fluid balance at days 0 to 2, ml	533.0 (-2290.0-4812.0)	1195.0 (-1918.0-5103.0)	0.33	-470.0 (-1382.0, 442.0)[a]
Cumulative fluid balance at days 0 to 7, ml	-301.0 (-4879.5,-3878.0)	-229.0 (-5135.0-4775.0)	0.79	-197.5 (-1864.0, 1457.0)[a]

[a] Hodges-Lehmann estimator of location shift

p-values should be interpreted descriptive, not in terms of statistical testing

eTable 6: Further dialysis and kidney associated outcomes					
	Regional citrate anticoagulation (n=300)	**Systemic heparin anticoagulation (n=296)**	**Absolute difference [95% CI]**	**OR or HR [95% CI]**	**p-value**
Outcomes at day 28					
KRT free days through day 28, median (IQR), days[a]	22.0 (15.0-25.0)	23.0 (13.0-25.0)	-1.0 (-2.0, 1.0)	HR: 1.04 (0.84, 1.29)	0.70
Requirement of RRT on day 28, No./Total No. patients alive at day 28 (%)	60/176 (34.1)[b]	50/160 (31.3)[c]	2.8 (-7.2, 12.9)[d]	OR: 1.14 (0.72, 1.80)	0.58
Persistent kidney dysfunction on day 28, No./Total. No. patients alive at day 28 (%)	19/71 (26.8)[e]	21/61 (34.4)[f]	-7.7 (-23.4, 8.1)[d]	OR: 0.70 (0.33, 1.47)	0.34
Major adverse kidney events on day 28, No./Total No. patients at risk (%)	182/207 (87.9)[g]	187/203 (92.1)[h]	-4.2 (-10.0, 1.6)[d]	OR: 0.62 (0.32, 1.21)	0.16
Outcomes at day 60					
Requirement of RRT on day 60, No./Total No. patients alive at day 60 (%)	33/154 (21.4)[i]	28/140 (20.0)[j]	1.4 (-7.8, 10.7)[d]	OR: 1.09 (0.62, 1.92)	0.76
Persistent kidney dysfunction on day 60, No./Total. No. patients alive at day 60 (%)	15/41 (36.6)[k]	9/40 (22.5)[l]	14.1 (-5.5, 33.7)[d]	OR: 1.99 (0.75, 5.28)	0.17
Major adverse kidney events on day 60, No./Total No. patients at risk (%)	175/197 (88.8)[m]	178/205 (86.8)[n]	2.0 (-4.4, 8.4)[d]	OR: 1.21 (0.66, 2.20)	0.54
Outcomes at day 90					
Requirement of RRT on day 90, No./Total No. patients alive at day 90 (%)	22/138 (15.9)[o]	18/131 (13.7)[p]	2.2 (-6.3, 10.7)[d]	OR: 1.19 (0.61, 2.34)	0.61
Persistent kidney dysfunction on day 90, No./Total.	27/95 (28.4)[q]	15/100 (15.0)[r]	13.4 (2.0, 24.9)[d]	OR: 2.25 (1.11, 4.56)	0.023

No. patients alive at day 90 (%)					
Major adverse kidney events on day 90, No./Total No. patients at risk (%)	186/246 (75.6)[s]	181/258 (70.2)[t]	5.5 (-2.3, 13.2)[d]	OR: 1.32 (0.89, 1.96)	0.17
New onset of CKD at day 90, No./Total No. patients without CKD at Baseline and alive at day 90 (%)	39/64 (60.9)[u]	21/52 (40.4)[v]	20.6 (2.6, 38.5)[d]	OR: 2.30 (1.09, 4.86)	0.028
Outcomes at year 1					
Requirement of RRT on year 1, No./Total No. patients alive at 1 year (%)	8/87 (9.2)[w]	7/88 (8.0)[x]	1.2 (-7.1, 9.5)[d]	OR: 1.17 (0.41, 3.38)	0.77
Persistent kidney dysfunction on year 1, No./Total. No. patients alive at year 1 (%)	11/44 (25.0)[y]	8/44 (18.2)[z]	6.8 (-10.3, 24.0)[d]	OR: 1.50 (0.54, 4.18)	0.44
Major adverse kidney events at 1 year, No./Total No. patients at risk (%)	196/228 (86.0)[aa]	189/223 (84.8)[ab]	1.2 (-5.3, 7.7)[d]	OR: 1.10 (0.65, 1.86)	0.72
CKD at 1 year, No./Total No. patients alive at 1 year (%)	27/44 (61.4)[ac]	28/44 (63.6)[ad]	-2.3 (-22.5, 18.0)[d]	OR: 0.91 (0.38, 2.15)	0.83
New onset of CKD at 1 year, No./ Total No. patients without CKD at Baseline and alive at 1 year (%)	20/30 (66.7)[ae]	13/23 (56.5)[af]	10.1 (-16.2, 36.5)[d]	OR: 1.54 (0.50, 4.72)	0.45

Abbreviations: CKD, chronic kidney disease; KRT, kidney replacement therapy; OR, odds ratio.

Major adverse kidney events is a combined endpoint consisting of persistent kidney dysfunction, kidney replacement therapy and mortality.

[a] censored at the day of death or end of follow-up according whatever occurred first

[b] 178 patients were alive at day 28. Two patients were excluded from the calculation of percentage, as no RRT was started

[c] 162 patients were alive at day 28. Two patients were excluded from the calculation of percentage, as no RRT was started

[d] Absolute difference in percentages

[e] 107 patients were excluded from the calculation of percentage, as data on PKD was missing.

[f] 101 patients were excluded from the calculation of percentage, as data on PKD was missing.

[g] 93 patients were excluded from the calculation of percentage due to missing data.

[h] 93 patients were excluded from the calculation of percentage due to missing data.

[i] 155 patients were alive at day 60. One patient was excluded from the calculation of percentage, as no RRT was started.

[j] 142 patients were alive at day 60. Two patients were excluded from the calculation of percentage, as no RRT was started.

[k] 114 patients were excluded from the calculation of percentage, as data on PKD was missing.

[l] 102 patients were excluded from the calculation of percentage, as data on PKD was missing.

[m] 103 patients were excluded from the calculation of percentage due to missing data.

[n] 91 patients were excluded from the calculation of percentage due to missing data.

[o] 139 patients were alive at day 90. One patient was excluded from the calculation of percentage, as no RRT was started.

[p] 132 patients were alive at day 90. One patient was excluded from the calculation of percentage, as no RRT was started.

[q] 44 patients were excluded from the calculation of percentage, as data on PKD was missing.

[r] 32 patients were excluded from the calculation of percentage, as data on PKD was missing.
[s] 54 patients were excluded from the calculation of percentage due to missing data.
[t] 38 patients were excluded from the calculation of percentage due to missing data.
[u] 23 patients were excluded from the calculation of percentage due to missing data.
[v] 20 patients were excluded from the calculation of percentage due to missing data.
[w] 88 patients were alive at day 365. One patient was excluded from the calculation of percentage, as no RRT was started.
[x] 89 patients were alive at day 365. One patient was excluded from the calculation of percentage, as no RRT was started.
[y] 44 patients were excluded from the calculation of percentage, as data on PKD was missing.
[z] 45 patients were excluded from the calculation of percentage, as data on PKD was missing.
[aa] 72 patients were excluded from the calculation of percentage due to missing data.
[ab] 73 patients were excluded from the calculation of percentage due to missing data.
[ac] 88 patients were alive at day 365. 44 patients were excluded from the calculation of percentage, as data on CKD was missing.
[ad] 89 patients were alive at day 365. 45 patients were excluded from the calculation of percentage, as data on CKD was missing.
[ae] 23 patients were excluded from the calculation of percentage due to missing data.
[af] 25 patients were excluded from the calculation of percentage due to missing data.

eTable 7: Details on Infections					
	Regional citrate anticoagulation (n=300)	**Systemic heparin anticoagulation (n=296)**	**Absolute difference [95% CI]**	**OR or HR [95% CI]**	**p-value**
New infection since start of dialysis, No./Total No. (%)	204/300 (68.0)	164/296 (55.4)	12.6 (4.9, 20.3)[a]	OR: 1.71 (1.23, 2.39)	0.002
Pathogen, No./Total No. (%)					
Gram positive	123/300 (41.0)	97/296 (32.8)	8.2 (0.5, 16.0)[a]	OR: 1.43 (1.02, 1.99)	0.037
Gram negative	105/300 (35.0)	88/296 (29.7)	5.3 (-2.2, 12.8)[a]	OR: 1.27 (0.90, 1.80)	0.17
Gram positive and negative	38/300 (12.7)	33/296 (11.1)	1.5 (-3.7, 6.7)[a]	OR: 1.16 (0.70, 1.90)	0.57
Multi resistant	37/300 (12.3)	21/296 (7.1)	5.2 (0.5, 10.0)[a]	OR: 1.84 (1.05, 3.23)	0.031
Fungal infection	112/300 (37.3)	100/296 (33.8)	3.6 (-4.1, 11.2)[a]	OR: 1.17 (0.83, 1.63)	0.37
Source of infection, No./Total No. (%)					
Bacteremia	57/204 (27.9)	49/164 (29.9)	-1.9 (-11.3, 7.4)[a]	OR: 0.91 (0.58, 1.43)	0.68
Pneumonia	82/204 (40.2)	71/164 (43.3)	-3.1 (-13.2, 7.0)[a]	OR: 0.88 (0.58, 1.34)	0.55
UTI	25/204 (12.3)	18/164 (11.0)	1.3 (-5.3, 7.9)[a]	OR: 1.13 (0.59, 2.16)	0.70
Others	97/204 (47.5)	91/164 (55.5)	-7.9 (-18.2, 2.3)[a]	OR: 0.73 (0.48, 1.10)	0.13
Time to infection, median (IQR), days[b]	4 (2-10)	6 (2-14)	-1 (-4, 0)	HR: 1.38 (1.12, 1.69)	0.001

Abbreviation: UTI, urinary tract infection.

[a] Absolute difference in percentages

[b] censored at the day of death or end of follow-up according whatever occurred first

eTable 8: Subgroup analysis surgical vs. non-surgical patients							
	Surgical			**Non-Surgical**			
	Regional citrate anticoagulation (n=225)	**Systemic heparin anticoagulation (n=228)**	**p-value**	**Regional citrate anticoagulation (n=75)**	**Systemic heparin anticoagulation (n=68)**	**p-value**	**p-value (Inter-action test)**
Filter, No.	668	810		297	294		
Primary outcomes							
Filter lifespan, median (IQR), hours	45.0 (18.1- 69.0)	25.5 (11.8- 50.7)	<0.001	48.2 (20.9- 71.2)	27.2 (13.7- 50.3)	<0.001	0.683
90-day all-cause mortality, No. (%)	108 (49.1)	111 (49.4)	0.77	42 (57.7)	45 (67.8)	0.072	0.125
Secondary and other outcomes							
Duration of kidney replacement therapy, median (IQR), days[a]	9.0 (3.5- 60.0)	7.9 (3.2- 39.0)	0.23	11.9 (5.0- 45.0)	13.8 (4.6- 60.0)	0.84	0.650
Kidney replacement therapy free days through day 28, median (IQR), days[a]	22.0 (15.0- 25.0)	23.0 (12.0- 25.0)	0.84	21.0 (11.0- 24.0)	22.0 (16.0- 24.0)	0.73	0.853
Bleeding and transfusion							
Bleeding, No. (%)	12 (5.4)	41 (18.4)	<0.001	3 (4.2)	8 (11.9)	0.094	0.750
Transfusion requirement (red blood cells), No. (%)	149 (67.1)	148 (66.4)	0.87	48 (67.6)	36 (53.7)	0.10	0.174
Transfusion volume (red blood cells), median (IQR), ml	300 (0- 1000)	600 (0- 1200)	0.29	600 (0- 1250)	250 (0- 1000)	0.19	0.707

Infection							
New onset of infection, No. (%)	148 (65.8)	132 (57.9)	0.084	56 (74.7)	32 (47.1)	<0.001	0.035
ICU and Hospital stay							
ICU length of stay, median (IQR), days	14.5 (7.0- 26.5)	13.5 (7.0- 26.0)	0.69	17.0 (8.0- 34.0)	13.5 (6.0- 23.0)	0.043	0.038
ICU length of stay, median (IQR), days[a]	22.0 (11.0- 42.0)	25.0 (12.0- 55.0)	0.67	33.0 (18.0- 60.0)	29.0 (16.0- 35.0)	0.14	0.256
Hospital length of stay, median (IQR), days	27.0 (14.0- 51.0)	29.5 (15.0- 50.0)	0.80	25.0 (11.0- 55.0)	21.0 (12.5- 42.0)	0.35	0.731
Hospital length of stay, median (IQR), days[a]	45.0 (27.0- 86.0)	55.0 (34.0- 91.0)	0.82	64.0 (30.0- 112.0)	52.0 (32.0- 96.0)	0.84	0.883
Outcomes at day 28							
28-day all-cause mortality, No. (%)	84 (38.0)	93 (41.2)	0.47	30 (40.8)	35 (52.5)	0.16	0.398
Requirement of kidney replacement therapy on day 28, No./Total No. patients alive at day 28 (%)	47/135 (34.8)	41/(131-2) (31.8)	0.60	13/(43-2) (31.7)	9/31 (29.0)	0.81	0.986
Persistent kidney dysfunction on day 28, No./Total. No. patients alive at day 28 (%)	15/(135-85) (30.0)	18/(131-81) (36.0)	0.52	4/(43-22) (19.0)	3/(31-20) (27.3)	0.59	0.842
Major adverse kidney events on day 28, No./Total No. patients at risk (%)	137/(225-71) (89.0)	142/(228-74) (92.2)	0.33	45/(75-22) (84.9)	45/(68-19) (91.8)	0.28	0.684

Outcomes at day 60							
60-day all cause mortality, No. (%)	100 (45.4)	108 (48.0)	0.52	37 (50.6)	39 (58.6)	0.24	0.492
Requirement of kidney replacement therapy on day 60, No./Total No. patients alive at day 60, (%)	27/120 (22.5)	23/(115-2) (20.4)	0.69	6/(35-1) (17.6)	5/27 (18.5)	0.93	0.802
Persistent kidney dysfunction on day 60, No./Total. No. patients alive at day 60 (%)	12/(120-86) (35.3)	8/(115-79) (22.2)	0.23	3/(35-28) (42.9)	1/(27-23) (25.0)	0.55	0.912
Major adverse kidney events on day 60, No./Total No. patients at risk (%)	130/(225-75) (86.7)	134/(228-70) (84.8)	0.64	45/(75-28) (95.7)	44/(68-21) (93.6)	0.65	0.781
Outcomes at day 90							
Requirement of kidney replacement therapy on day 90, No./Total No. patients alive at day 90 (%)	18/110 (16.4)	16/(111-1) (14.5)	0.71	4/(29-1) (14.3)	2/21 (9.5)	0.62	0.747
Persistent kidney dysfunction on day 90, No./Total. No. patients alive at day 90 (%)	22/(110-30) (27.5)	15/(111-22) (16.9)	0.095	5/(29-14) (33.3)	0/(21-10) (0)	0.033	0.965
Major adverse kidney events on day 90, No./Total No. patients at risk (%)	137/(225-35) (72.1)	134/(228-27) (66.7)	0.24	49/(75-19) (87.5)	47/(68-11) (82.5)	0.45	0.806

New onset of chronic kidney disease at day 90, No./Total No. patients without chronic kidney disease at Baseline and alive at day 90 (%)	32/(68-16) (61.5)	21/(63-15) (43.8)	0.075	7/(19-7) (58.3)	0/(9-5) (0)	0.042	0.972
Outcomes at 1 year							
1-year all-cause mortality, No. (%)	127 (58.0)	127 (56.7)	0.96	48 (66.5)	47 (71.1)	0.28	0.377
Requirement of kidney replacement therapy on year 1, No./Total No. patients alive at 1 year (%)	6/66 (9.1)	6/(75-1) (8.1)	0.84	2/(22-1) (9.5)	1/14 (7.1)	0.81	0.894
Persistent kidney dysfunction on year 1, No./Total. No. patients alive at year 1 (%)	5/(66-29) (13.5)	8/(75-35) (20.0)	0.45	6/(22-15) (85.7)	0/(14-10) (0.0)	0.006	0.958
Major adverse kidney events 1 year, No./Total No. patients at risk (%)	141 (225-53) (82.0)	141/(228-56) (82.0)	1.00	55/(75-19) (98.2)	48/(68-17) (94.1)	0.27	0.305
Chronic kidney disease at 1 year, No./ Total No. patients alive at 1 year (%)	21 (66-29) (56.8)	26/(75-35) (65.0)	0.46	6/(22-15) (85.7)	2/(14-10) (50.0)	0.20	0.166

New onset of chronic kidney disease at 1 year, No./ Total No. patients without pre-existing chronic kidney disease at baseline and alive at 1 year (%)	14/(39-16) (60.9)	13/(43-21) (59.1)	0.90	6/(14-7) (85.7)	0/(5-4) (0)	0.064	0.9639

[a] Censored at patients' date of death or end of follow-up whatever occurred first

eTable 9: Adverse events in surgical patients		
	Regional citrate anticoagulation (n=225)	**Systemic heparin anticoagulation (n=228)**
Heparin induced thrombocytopenia, No. (%)[a]	7 (3.2)	5 (2.2)
Thrombotic, thromboembolic complications, No. (%)	0 (0)	2 (0.9)
Hyperkalemia, No. (%)[b]	0 (0)	2 (0.9)
Severe hypocalcemia, No. (%)[c]	3 (1.4)	1 (0.4)
Severe alkalosis, No. (%)[d]	5 (2.3)	1 (0.4)
Metabolic acidosis, No. (%)[e]	1 (0.5)	2 (0.9)
Citrate accumulation, No. (%)[f]	2 (0.9)	0 (0)
Hypophosphatemia, No. (%)[g]	42 (18.9)	16 (7.2)
Gastrointestinal complications, No. (%)[h]	1 (0.5)	9 (4.0)
Respiratory complications, No. (%)[i]	2 (0.9)	3 (1.3)
Neurologic complications, No. (%)[j]	3 (1.4)	2 (0.9)
Sever cardiac-rhythm disorders, No. (%)	7 (3.2)	7 (3.1)
Other cardiovascular complications, No. (%)[k]	1 (0.5)	4 (1.8)

[a] positive antibody test
[b] extracted from adverse events terms
[c] ionized calcium <0.9mmol/l
[d] pH > 7.50 and HCO_3^- > 30mmol/L
[e] pH < 7.2 and HCO_3^-<20mmol/L (excluding lactic acidosis)
[f] Ca^{2+}total/Ca^{2+}ion ≥2.5
[g] phosphate <0.5mmol/l
[h] includes all gastrointestinal bleeding events requiring at least 1 packed red blood cell
[i] includes complications such as pneumonia, acute respiratory distress syndrome, Horowitz index < 200 for at least 1 hour, and respiratory complications with the need of re-intubation/re-cannulation
[j] includes complications such as seizures, delirium and hypoxic brain damage
[k] includes complications such as ischemia, cardiogenic shock, cardiac decompensation

eTable 10: Adverse events in non-surgical patients

	Regional citrate anticoagulation (n=75)	Systemic heparin anticoagulation (n=68)
Heparin induced thrombocytopenia, No. (%)[a]	1 (1.4)	4 (6.0)
Thrombotic, thromboembolic complications, No. (%)	0 (0)	1 (1.5)
Hyperkalemia, No. (%)[b]	0 (0)	2 (3.0)
Severe hypocalcemia, No. (%)[c]	1 (1.4)	0 (0)
Severe alkalosis, No. (%)[d]	2 (2.8)	0 (0)
Metabolic acidosis, No. (%)[e]	0 (0)	0 (0)
Citrate accumulation, No. (%)[f]	0 (0)	0 (0)
Hypophosphatemia, No. (%)[g]	3 (4.2)	2 (3.0)
Gastrointestinal complications, No. (%)[h]	1 (1.4)	1 (1.5)
Respiratory complications, No. (%)[i]	1 (1.4)	3 (4.5)
Neurologic complications, No. (%)[j]	1 (1.4)	2 (3.0)
Sever cardiac-rhythm disorders, No. (%)	3 (4.2)	2 (3.0)
Other cardiovascular complications, No. (%)[k]	1 (1.4)	1 (1.5)

[a] positive antibody test
[b] extracted from adverse events terms
[c] ionized calcium <0.9mmol/l
[d] pH > 7.50 and HCO_3^- > 30mmol/L
[e] pH < 7.2 and HCO_3^-<20mmol/L (excluding lactic acidosis)
[f] Ca^{2+}total/Ca^{2+}ion ≥2.5
[g] phosphate <0.5mmol/l
[h] includes all gastrointestinal bleeding events requiring at least 1 packed red blood cell
[i] includes complications such as pneumonia, acute respiratory distress syndrome, Horowitz index < 200 for at least 1 hour, and respiratory complications with the need of re-intubation/re-cannulation
[j] includes complications such as seizures, delirium and hypoxic brain damage
[k] includes complications such as ischemia, cardiogenic shock, cardiac decompensation

Supplementary References

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