Citrate Anticoagulation in CKRT

Nattachai Srisawat, M.D., Ph.D., EDIC

Division of Nephrology, Department of Medicine, Chulalongkorn University, Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, and Academy of Science, Royal Society of Thailand

- I have no conflicts of interest which relate to my presentation

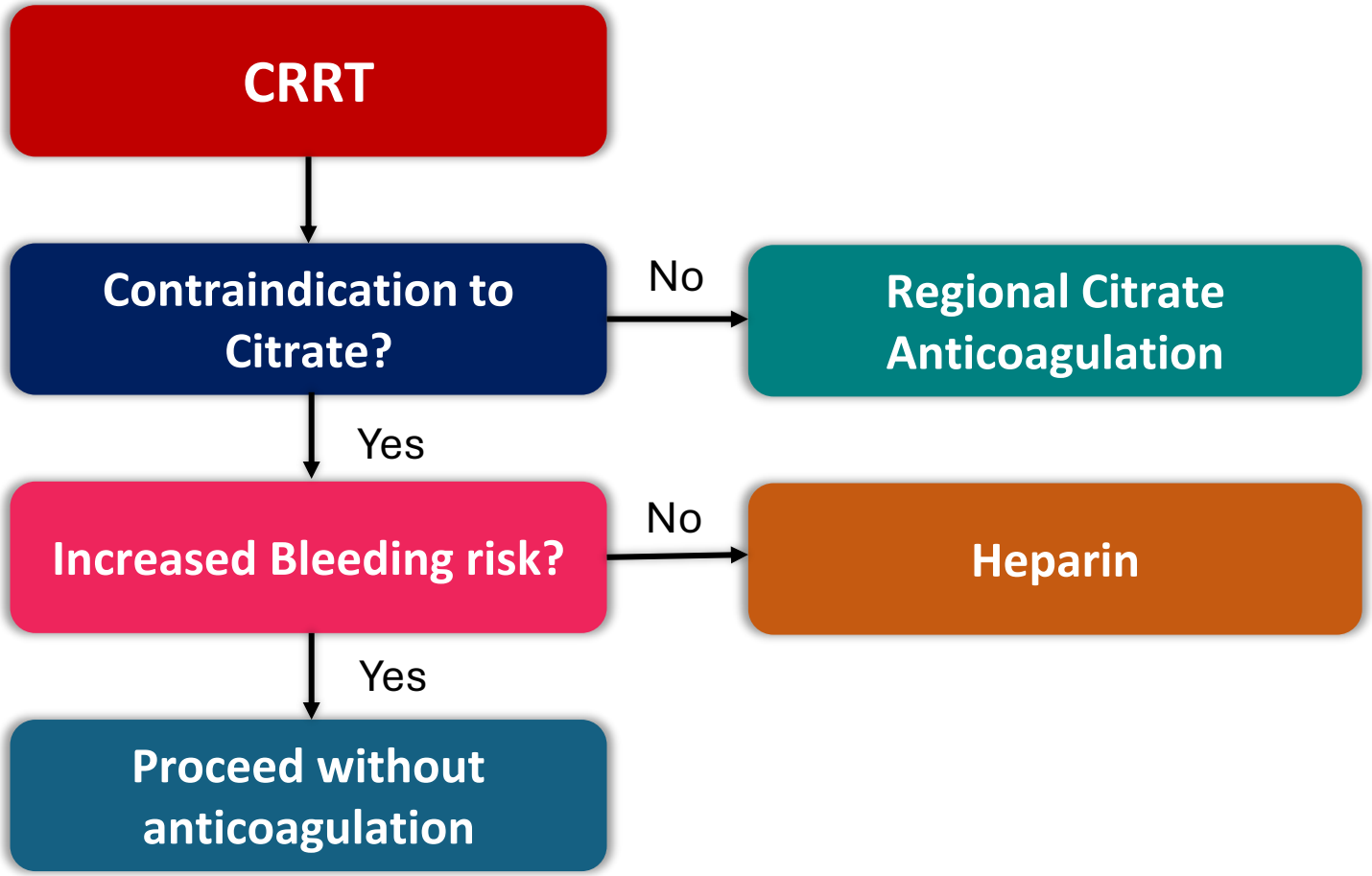
Outline

- Principle of RCA
- How to prescription RCA and monitoring ?
- Benefit and safety of RCA compare with heparin
- Our experience and case sharing

CHOICE OF ANTICOAGULATION IN CRRT: KDIGO 2012 RECOMMENDATION

- Severe lactic acidosis (lactate > 8 mmol/L)
- Shock state (hypoperfusion)
- ALF or ACLF (AST/ALT > 1000, TB/DB > 8)

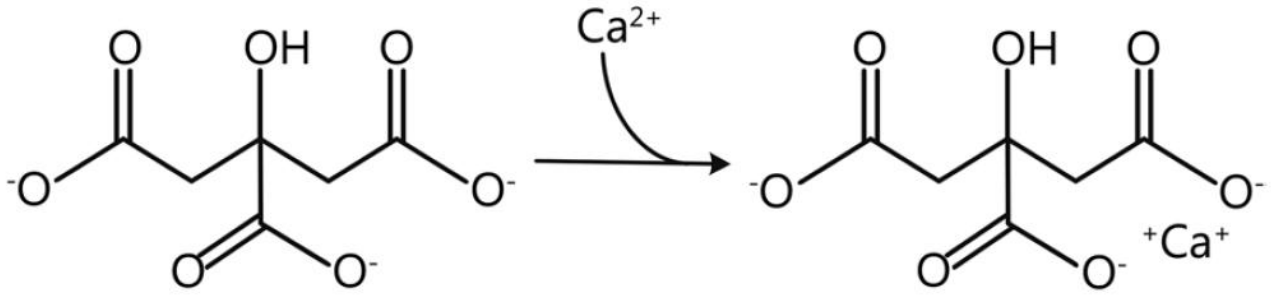
- Active bleeding
- Post-operative surgery within 48 hours
- Platelet < 50000
- INR > 2, aPTT > 45
- Uncontrolled HTN
- Presence of epidural catheter



Kidney International Supplement (2012) 2, 8-12

Principle of RCA

- During CRRT, when citrate is infused at the access end of the extracorporeal circulation, the concentration of calcium in the extracorporeal circulation is rapidly reduced
- Ionized calcium ions play a critical role in the coagulation process both endogenous and exogenous coagulation pathway.
- Binding of calcium ions removes free calcium ions, preventing circuit clotting



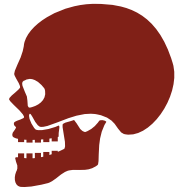
Citrate^{3-} Calcium citrate complex (CCC)

NDT Plus . 2009 Dec;2(6):439-47.
Mil Med Res. 2023 May 29;10(1):23.

ANTICOAGULATION IN CRRT: RCA VS HEPARIN META-ANALYSIS

Prolong filter life span significantly in predilution CVVH and CVVHD, but not postdilution CVVH and CVVHDF

Prolong filter life span

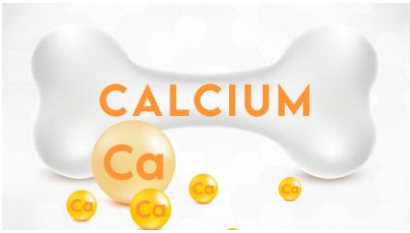


No difference in mortality (RR 0.97, 95% CI 0.84, 1.13, P > 0.05)

No difference in mortality

Reduce risk of bleeding (RR 0.31, 95% CI 0.19, 0.51, P < 0.01)

Decrease bleeding

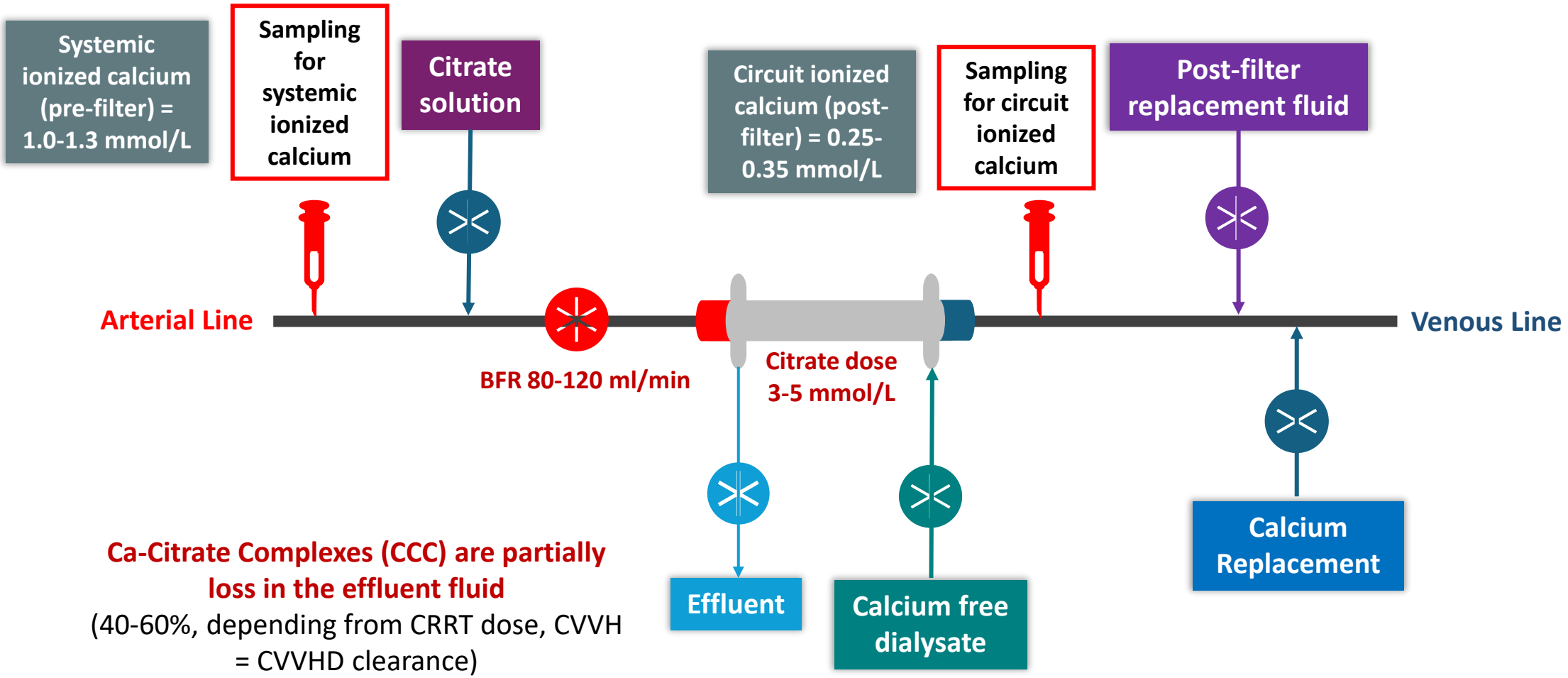


Higher number of hypocalcemia episode (RR 3.96, 95% CI 1.50, 10.43, P < 0.01)

Higher hypocalcemia

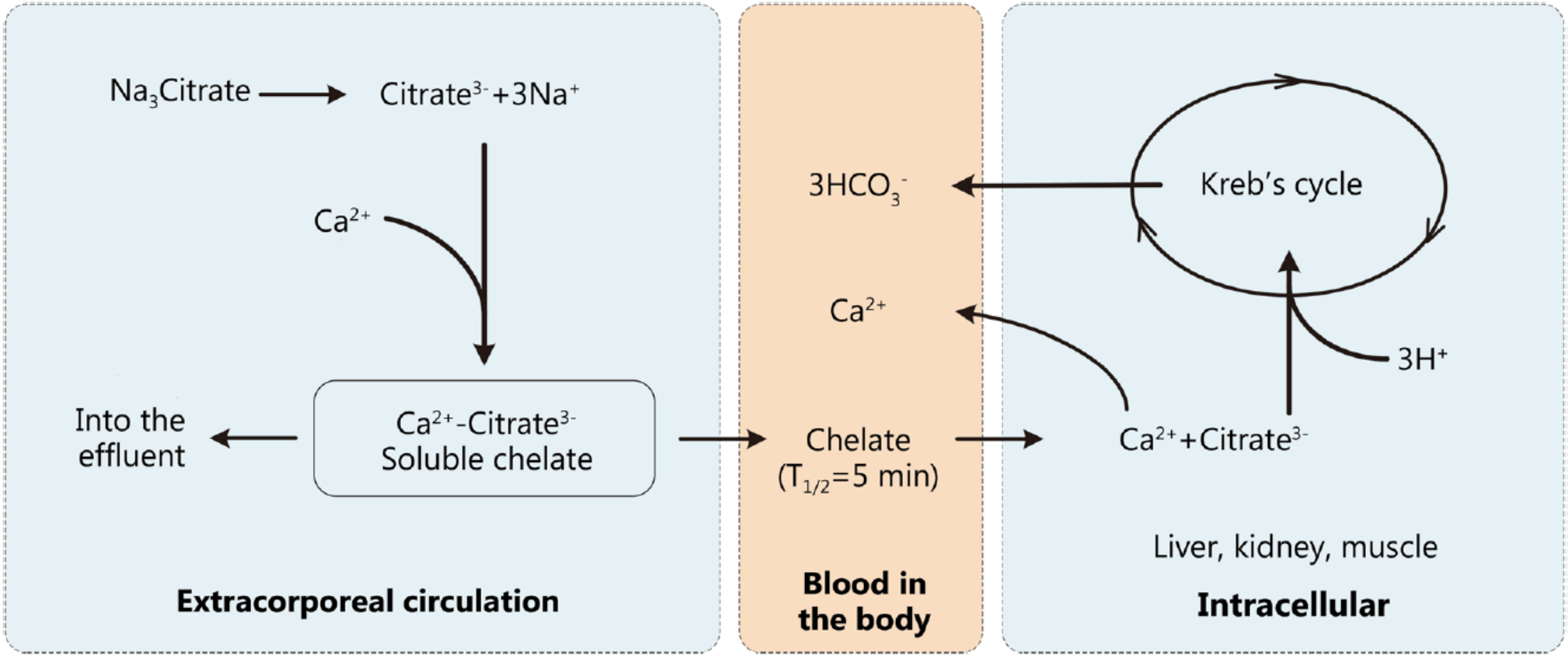
a meta-analysis with trial sequential analysis of randomized controlled trials. Crit Care 20, 144 (2016)

REGIONAL CITRATE ANTICOAGULATION CIRCUIT



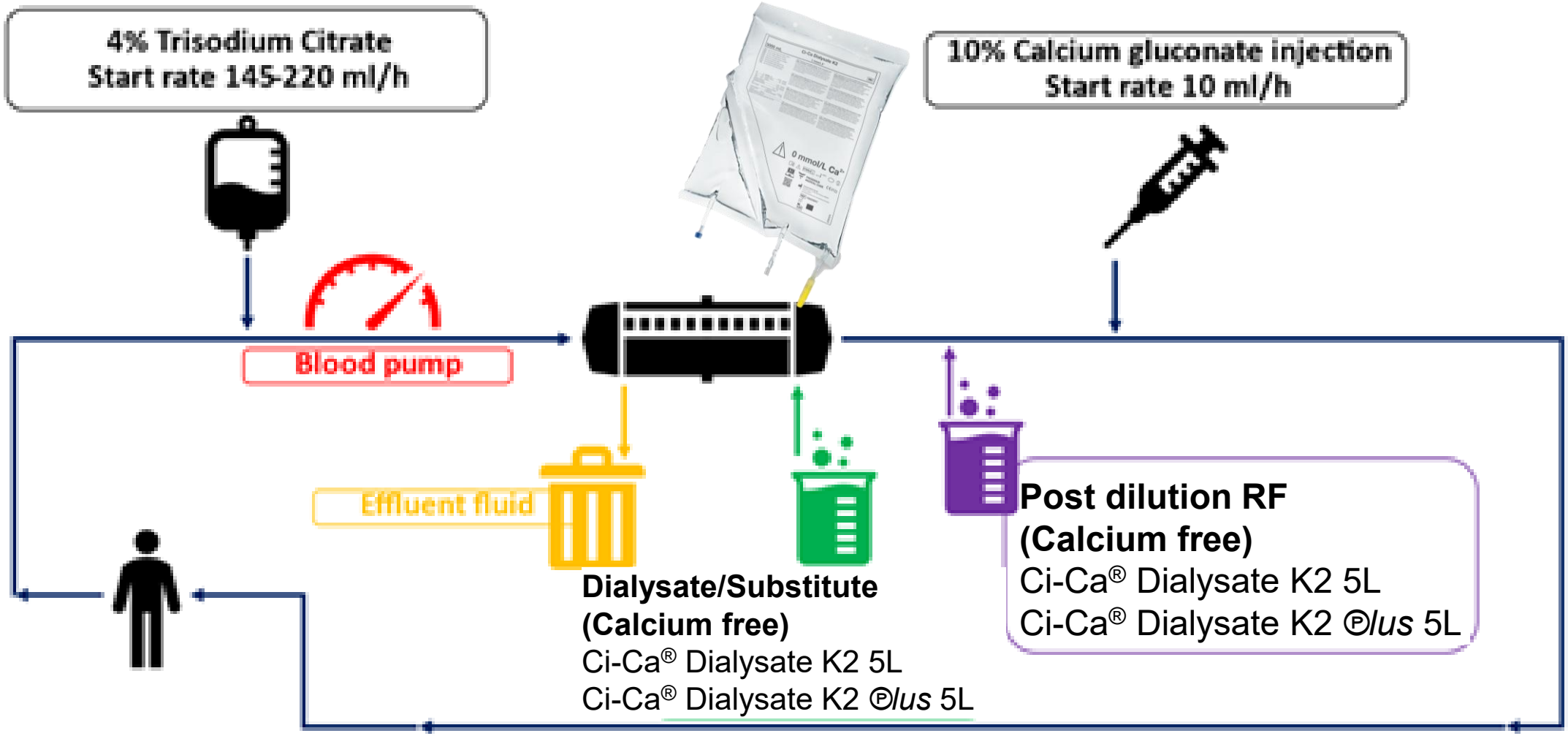
Ca-Citrate Complexes (CCC) are partially loss in the effluent fluid
(40-60%, depending from CRRT dose, CVVH = CVVHD clearance)

Citrate Metabolism



NDT Plus . 2009 Dec;2(6):439-47.
Mil Med Res. 2023 May 29;10(1):23.

Protocol: Hypertonic citrate protocol



Diffusion was used as a major solute clearance

Dialysates for Citrate : Ci-CA dialysate

Diffusion was used as a major solute clearance

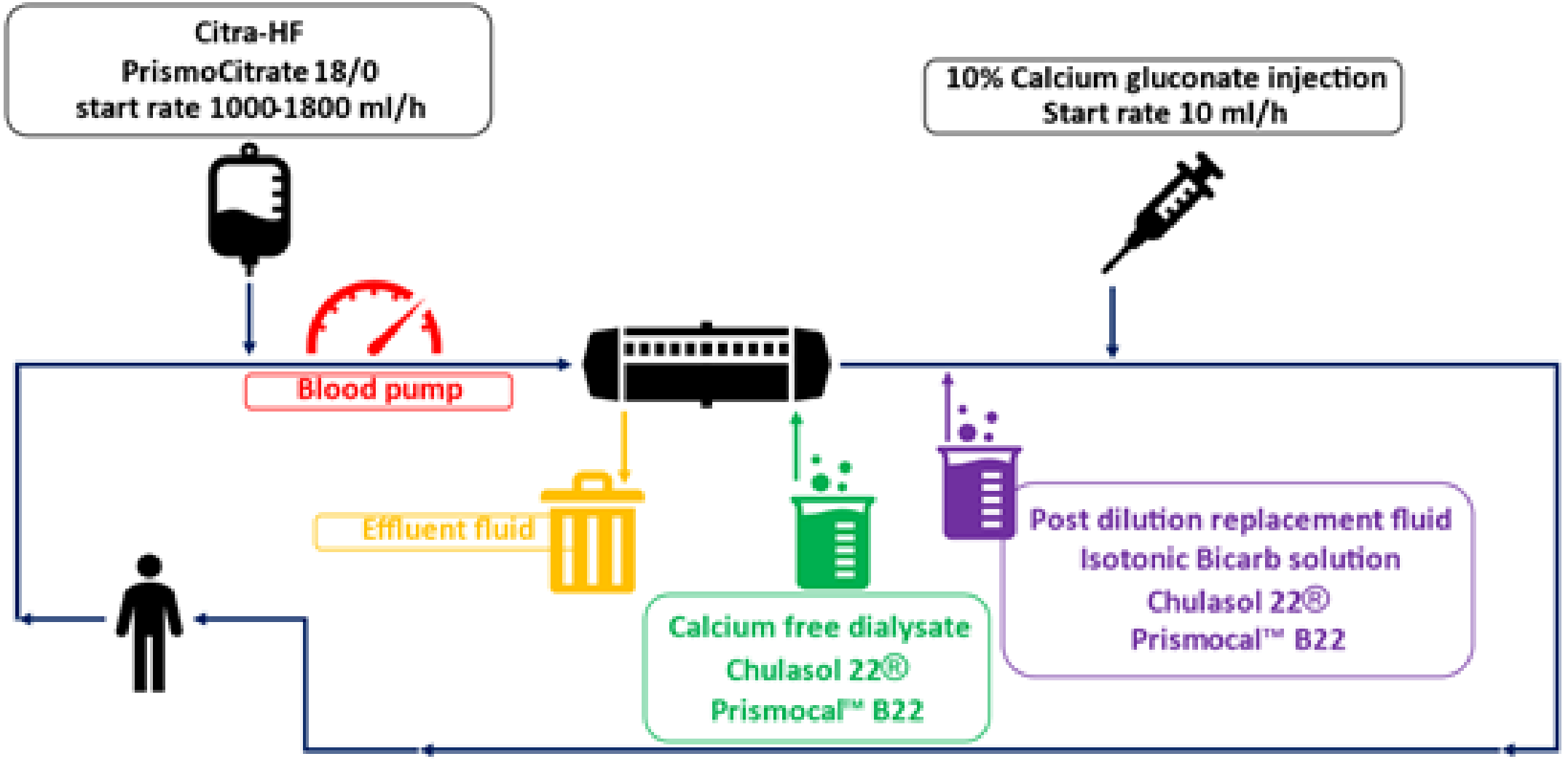
Compositions	Ci-Ca® Dialysate K2	Ci-Ca® Dialysate K2 Plus	4% Trisodium Citrate
Sodium	133 mmol/L	133 mmol/L	408 mmol/L
Potassium	2.0 mmol/L	2.0 mmol/L	-
Calcium	0 mmol/L	0 mmol/L	-
Magnesium	0.75 mmol/L	1.0 mmol/L	-
Chloride	116.5 mmol/L	115.75 mmol/L	-
Bicarbonate	20 mmol/L	20 mmol/L	-
Glucose	1.0 g/L	1.0 g/L	-
Citrate	-	-	136 mmol/L
Dihydrogen phosphate	-	1.25 mmol/L	-
Preparation	Two-chamber	Two-chamber	Premixed
Volume per bag	5L	5L	500 mL

Initial prescription of the patients

the DFR to BFR ratio of 20:1 to avoid hypernatremia and metabolic alkalosis due to the solution's high concentration of citrate and sodium

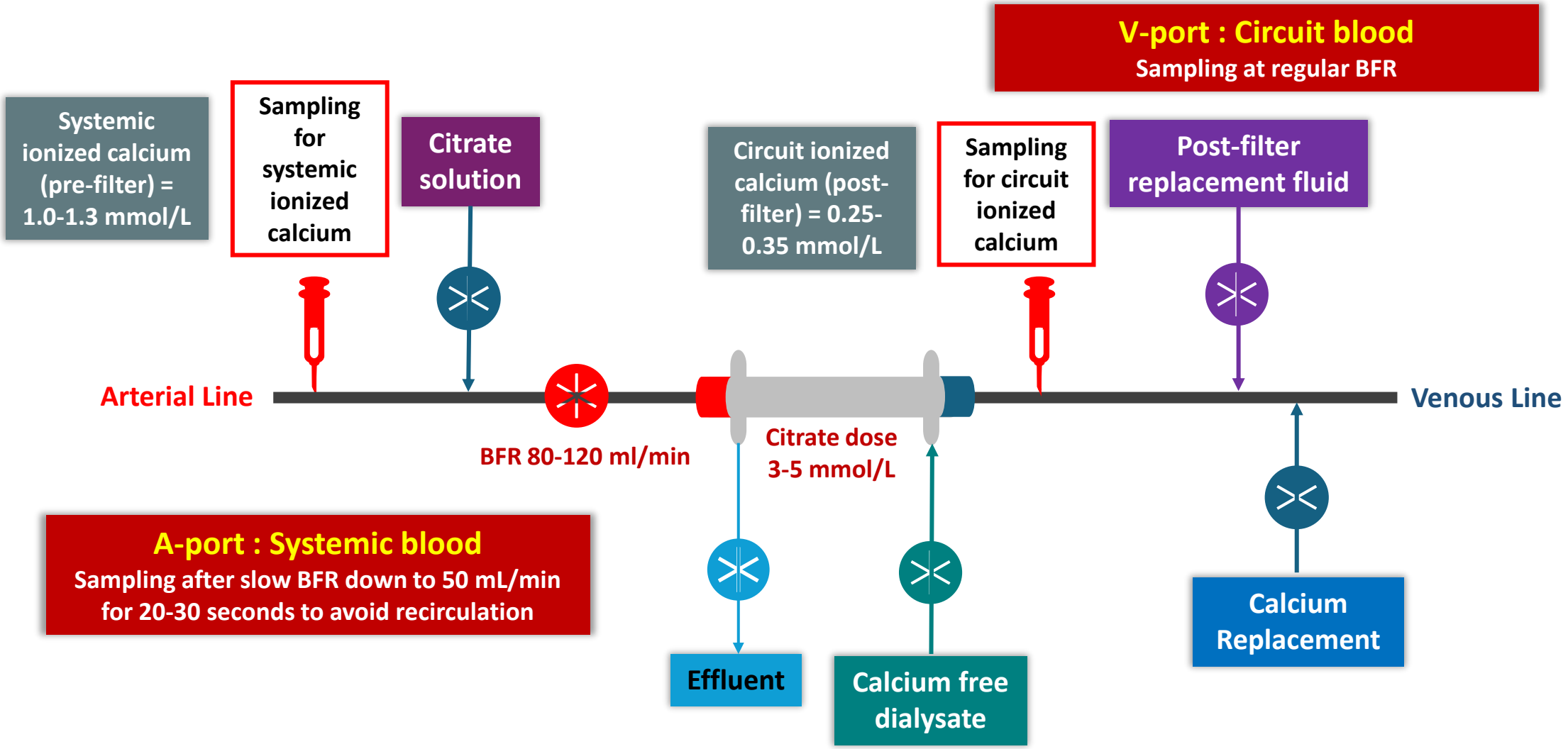
Ideal Body Weight	< 60 kg	60-90 kg	>90 kg
BFR	80 ml/min	100 ml/min	120 ml/min
PBP	145 ml/h	185 ml/h	220 ml/h
DFR	1600 ml/h	2000 ml/h	2400 ml/h
Post RFR	100 ml/h	100 ml/h	100 ml/h
Citrate dose	4 mmol/L	4 mmol/L	4 mmol/L
10% Calcium gluconate rate	10 ml/h	10 ml/h	10 ml/h
Magnesium	6 g/d	6 g/d	6 g/d
Phosphate	20-40 mmol/d	20-40 mmol/d	20-40 mmol/d
DFR + Post RFR combined for effluent 30 ml/kg/h			

Protocol: Isotonic citrate protocol

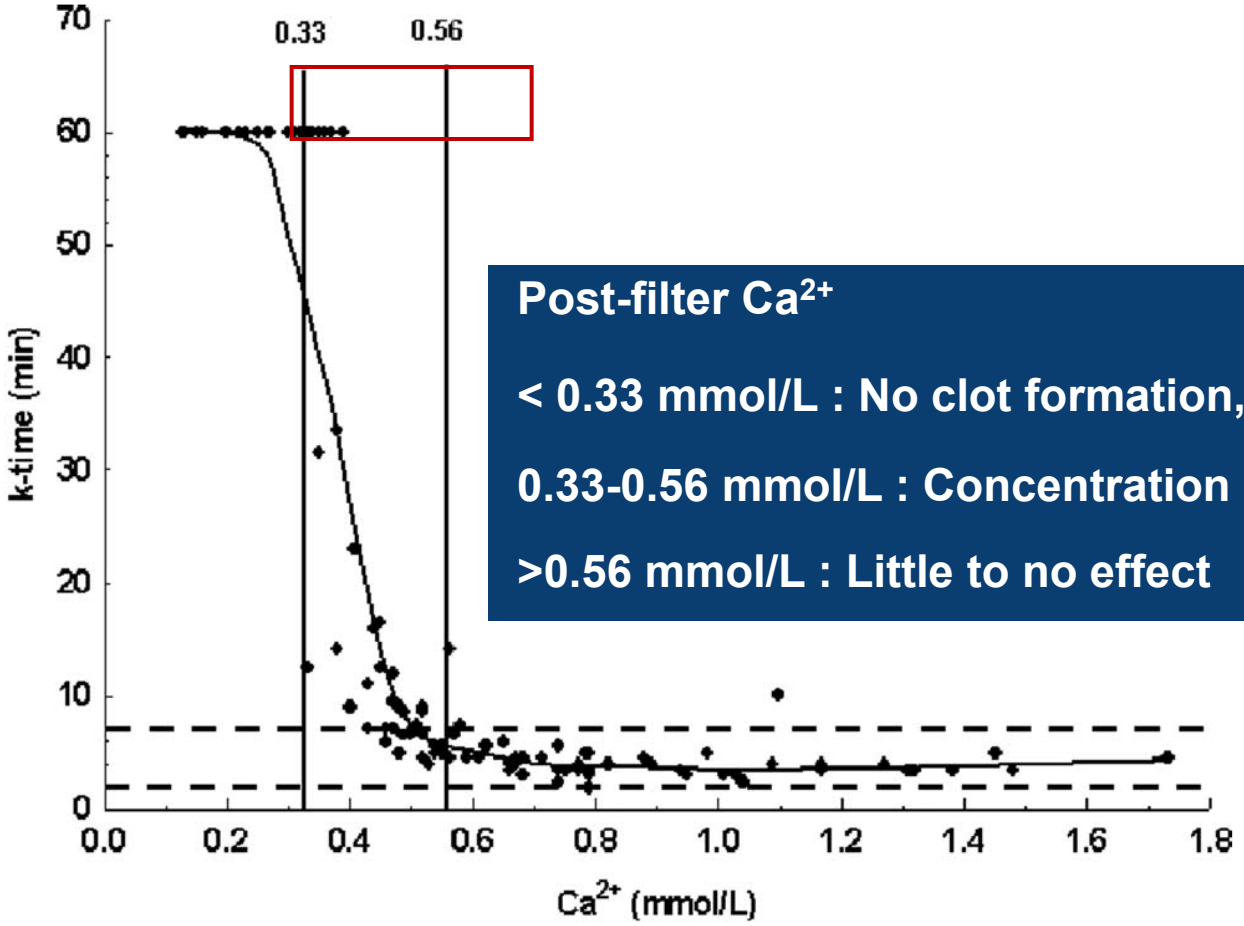


Convection was used as a major solute clearance

MONITORING OF IONIZED CALCIUM



Dose-response relationship between iCa^{2+} level and clot formation



Post-filter Ca^{2+}

< 0.33 mmol/L : No clot formation, Bleeding time → ∞

0.33-0.56 mmol/L : Concentration dependent

>0.56 mmol/L : Little to no effect

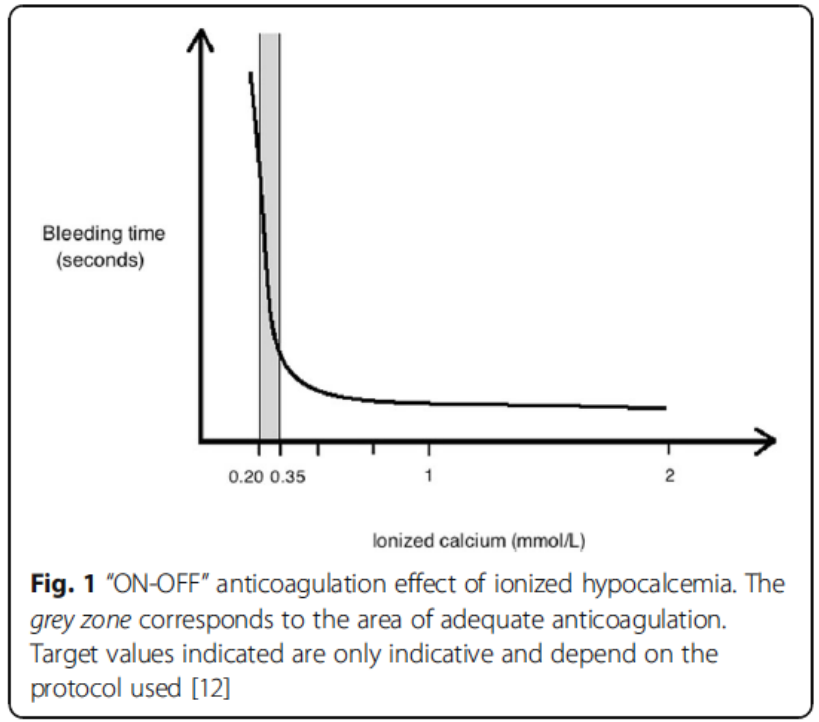


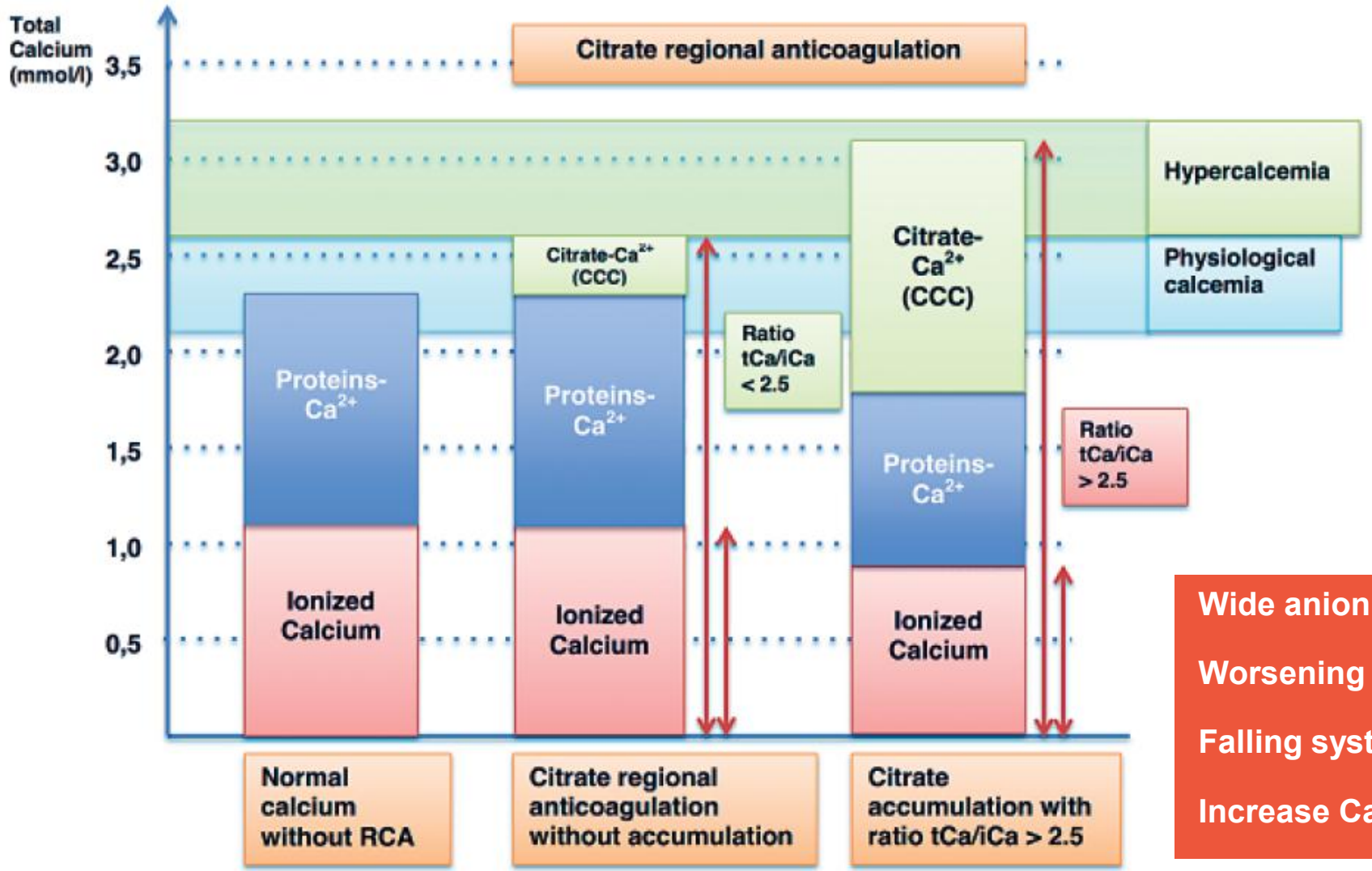
Fig. 1 "ON-OFF" anticoagulation effect of ionized hypocalcemia. The *grey zone* corresponds to the area of adequate anticoagulation. Target values indicated are only indicative and depend on the protocol used [12]

On-Off anticoagulation effect

J Cardiothorac Vasc Anesth . 2004 Oct;18(5):581-6.

Circuit ICa (mmol/L)	Citrate dose	Citrate rate (BFR 80)	Citrate rate (BFR 100)	Citrate rate (BFR 120)
< 0.30	↓ dose by 0.2 mmol/L	↓ 10 ml/h	↓ 10 ml/h	↓ 15 ml/h
0.30-0.40	**No change**	**No change**	**No change**	**No change**
0.41-0.50	↑ dose by 0.2 mmol/L	↑ 10 ml/h	↑ 10 ml/h	↑ 15 ml/h
> 0.50	↑ dose by 0.4 mmol/L	↑15 ml/h	↑20 ml/h	↑25 ml/h

Systemic iCa (Prefilter iCa^{2+})	10% Calcium gluconate IV drip adjustment
< 1.00	Increase 4 mL/h + 10 ml IV bolus
1.00-1.11	Increase 2 mL/h
1.12-1.20	**No adjustment**
1.21-1.35	Decrease 2 mL/h
> 1.35	Decrease 4 mL/h



Wide anion gap

Worsening metabolic acidosis

Falling systemic iCa2+

Increase Ca2+ gap

Target HCO_3 22-26 mmol/L

HCO3 < 21
BE < -10

Ratio < 2.5
AG 5-15

- Treat cause
- Give bicarbonate
- "Citrate deficit"

Ratio > 2.5
AG >15

"Citrate accumulation"
"Citrate toxicity"

- **Stop citrate**
- **Decrease BFR or citrate dose**
- **Increase dialysate or post RF rate**

$$\frac{\text{Total calcium (mg/dL)}}{\text{Systemic ionized calcium (mmol/L) x 4}}$$

HCO3 > 27
BE > -10

"Citrate overload"
"Citrate excess"

- **Decrease BFR or citrate dose**
- **Increase dialysate or post RF rate**

Adapted from Clin J Am Soc Nephrol 9: 2173-2188, December, 2014

RICH trial

QUESTION In critically ill patients with acute kidney injury, what is the effect of using regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality?

CONCLUSION This randomized trial showed that in patients with acute kidney injury, anticoagulation with regional citrate, vs systemic heparin anticoagulation, increased filter life span, but the trial was underpowered to reach conclusions regarding mortality.

POPULATION

413 Men
183 Women

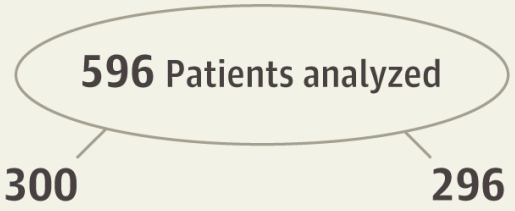
Adults with acute kidney injury or indication for kidney replacement therapy, an additional condition, and planned intensive care

Mean age: **67.5** years

LOCATIONS

26
Centers in Germany

INTERVENTION



Regional citrate anticoagulation

Citrate added continuously to the blood before the filter of extracorporeal circuit; adjusted to ionized calcium levels

Systemic heparin anticoagulation

Heparin administered through IV lines at 30 mL/kg/h; adjusted to partial thromboplastin time of 45-60 seconds

COPRIMARY OUTCOMES

Filter life span and 90-day all-cause mortality

FINDINGS

Median filter life span

Regional citrate anticoagulation	Systemic heparin anticoagulation
47 hours	26 hours

The median filter life span difference was significant:
15 hours (95% CI, 11 to 20); $P < .001$

90-day mortality

Regional citrate anticoagulation	Systemic heparin anticoagulation
51%	54%

Adjusted 90-day mortality was not significant:
HR, **0.79** (95% CI, 0.63-1.004),
but the trial was underpowered for this outcome

Zarbock A, Küllmar M, Kindgen-Milles D, et al. Effect of regional citrate anticoagulation vs systemic heparin anticoagulation during continuous kidney replacement therapy on dialysis filter life span and mortality among critically ill patients with acute kidney injury. *JAMA*. doi:10.1001/jama.2020.18618

Outlines

- Principle of RCA
- How to prescription RCA and monitoring ?
- Benefit and safety of RCA compare with heparin
- Our experience and case sharing

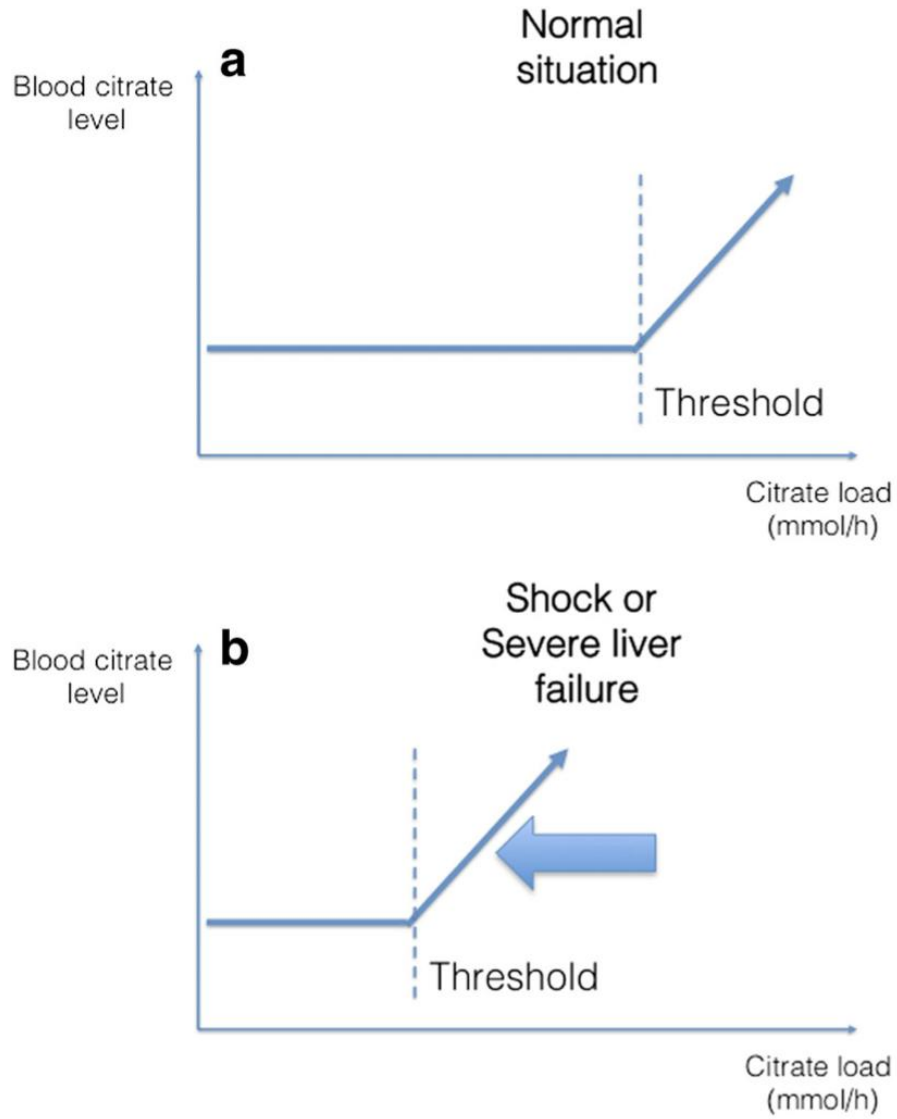
Decreasing Citrate Metabolization

Capacity to metabolize citrate is a dynamic process depending on:
- Baseline characteristics
- Hemodynamic status
- Mitochondrial function.

Acute liver failure, Acute-on-chronic liver failure
- Decrease but not “Null”
- Protocol with low citrate load

Circulatory shock
- Decreased oxygen delivery to the cells with decreased Krebs cycle activity

Medications
- Biguanides (e.g., metformin), cyclosporine, paracetamol, trichloroethylene, or propofol



Crit Care. 2017; 21(1):281

scientific reports

Citrate in Liver Failure

OPEN

Citrate pharmacokinetics in critically ill liver failure patients receiving CRRT

Peerapat Thanapongsatorn[1,2,3,9], Weerachai Chaijamorn[4,9], Phatadon Sirivongrangson[2,3,7], Sasipha Tachaboon[2,3], Sadudee Peerapornratana[2,3], Nuttha Lumlertgul[2,3], Aroonrut Lucksiri[5] & Nattachai Srisawat[2,3,6,8]✉

	Critically ill ALF patients	Critically ill ACLF patients	Critically ill cirrhotic patients	Critically ill patients
AUC_{0-t}(mmol.min/L)	124.4 +/- 43.9	113.9 +/- 73.3	N/A	69.9 +/- 66.6
AUC_{0-inf}(mmol.min/L)	267.2 +/- 111.7	372.6 +/- 399.3	282 +/- 130	87.5 +/- 95.5
T max (min)	100.0 +/- 60.0	113.8 +/- 32.8	115 +/- 12	106.6 +/- 21.7
Vd (L)	45.6 +/- 8.0	58.2 +/- 49.7	27 +/- 9	50.6 +/- 21.7
Cl_{body}(ml/min)	152.5 +/- 50.9	195.6 +/- 174.3	340 +/- 185	686.6 +/- 353.6
$C_{baseline}$(mmol/l)	0.24 +/- 0.12	0.21 +/- 0.12	0.51 +/- 0.13	0.02 +/- 0.04
C_{max}(mmol/l)	0.76 +/- 0.27	0.72 +/- 0.44	1.6 +/- 0.5	0.56 +/- 0.45
Total dose (mmol)	39.9	39.9	77 +/- 21	57.1 +/- 10.5

AUC, area under the concentration time curve; T_{max} Time to maximal concentration; V_d Volume of distribution; Cl_{body} Citrate body clearance; $C_{baseline}$ Citrate concentration at baseline; C_{max} Maximal citrate concentration

Ludwig Kramer, et al. Crit Care Med. 2003 Oct; 31(10):2450-5.
Zheng et al. Plos One. 2013; 8(6): e65992
Sci Rep **12**, 1815 (2022).

PROBLEM WITH POST-FILTER IONIZED CALCIUM

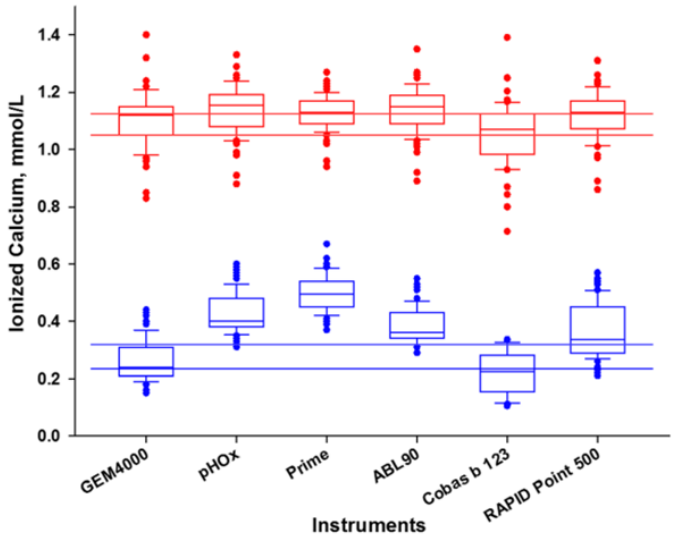
Schwarzer *et al. Critical Care* (2015) 19:321
DOI 10.1186/s13054-015-1027-1

CRITICAL CARE

RESEARCH Open Access

Discrepant post filter ionized calcium concentrations by common blood gas analyzers in CRRT using regional citrate anticoagulation

Patrik Schwarzer[1], Sven-Olaf Kuhn[2], Sylvia Stracke[3], Matthias Gründling[2], Stephan Knigge[2], Sixten Selleng[2], Maximilian Helm[1], Sigrun Friesecke[4], Peter Abel[4], Anders Kallner[5], Matthias Nauck[1] and Astrid Petersmann[1*]



Different blood gas analyzers result in different ionized calcium^{2+} levels

Oudemans-van Straaten and Ostermann *Critical Care* (2015) 19:429
DOI 10.1186/s13054-015-1148-6

CRITICAL CARE

COMMENTARY Open Access

Citrate anticoagulation for CRRT: don't always trust the postfilter iCa results!

Heleen M. Oudemans-van Straaten[1*] and Marlies Ostermann[2]

Abstract

Citrate has been recommended as the first-line anticoagulant for continuous renal replacement therapy (CRRT) in critically ill patients. Compared with heparin, citrate anticoagulation is safer and more efficacious. Citrate inhibits the coagulation cascade by lowering the ionized calcium (iCa) concentration in the filter. Monitoring of systemic iCa concentrations is inherent to the protocol, and monitoring of postfilter iCa is recommended to adjust citrate flow and optimize anticoagulation. While systemic iCa targets are in the physiological range, postfilter iCa concentrations are targeted between 0.20 and 0.35 mmol/l. In a previous issue of *Critical Care*, Schwarzer et al. compared systemic and postfilter iCa measurements of patients receiving citrate-based CRRT between six devices. They highlight the unreliability of iCa concentrations in the postfilter range, because the instruments cannot be validated in the low iCa range. The maximum mean difference between two instruments was as high as 0.33 mmol/l (range 0.21–0.50 mmol/l). The authors call for dialysis companies to revise their protocols. However, the first implication of their study is that the accuracy of blood gas analyzers to measure iCa in the low range needs to improve; and, secondly, clinicians using citrate anticoagulation need to be aware that the postfilter iCa result may be falsely high or low. This is particularly relevant when frequent premature filter clotting is observed despite postfilter iCa results in the seemingly target range. In these situations, citrate flow can be safely increased up to 4 mmol/l blood flow under monitoring of signs of citrate accumulation.

Ionized calcium measurement cannot be validated in the low iCa^{2+} range.

PROBLEM WITH POST-FILTER IONIZED CALCIUM

- Many analyzers may not be properly calibrated ionized calcium measurement especially at **low concentration levels**
- **Increase the risk of metabolic complication** from subsequent citrate dose adjustment
- For example
  - If pfCa level is **false high**, the citrate dose may be increased and lead to systemic hypocalcemia, citrate overload, or citrate accumulation.
  - If the pfCa level is **false low**, the citrate dose may be decreased and then lead to metabolic acidosis from inadequate buffer.
- Increase **workload** and **cost (25 USD per test)**

ORIGINAL ARTICLE

Standard versus no post-filter ionized calcium monitoring in regional citrate anticoagulation for continuous renal replacement therapy (NPC trial)

Peerapat Thanapongsatorn[1,2], Tanyapim Sinjira[3], Piyanut Kaewdoungtien[2], Prit Kusirisin[2], Win Kulvichit[2], Phatadon Sirivongrangson[4], Sadudee Peerapornratana[2,5,6,7], Nuttha Lumlertgul[2,5,6] and Nattachai Srisawat[2,5,6,8]

Peerapat Thanapongsatorn, et al. *Clinical Kidney Journal*, 2023

Clinical Kidney Journal

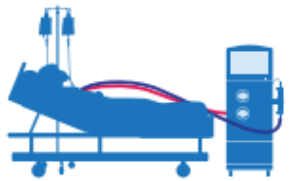
Standard versus no post-filter ionized calcium monitoring in regional citrate anticoagulation for continuous renal replacement therapy (NPC trial)

Post-filter ionized calcium (pfCa) is monitored to determine the citrate efficiency. However, the reliability of pfCa raises the question of whether routine monitoring is required. We aimed to test the efficiency of having no pfCa monitoring in RCA-CRRT.

Methods

King Chulalongkorn Memorial Hospital, Thailand

RCT, non-inferiority N=50



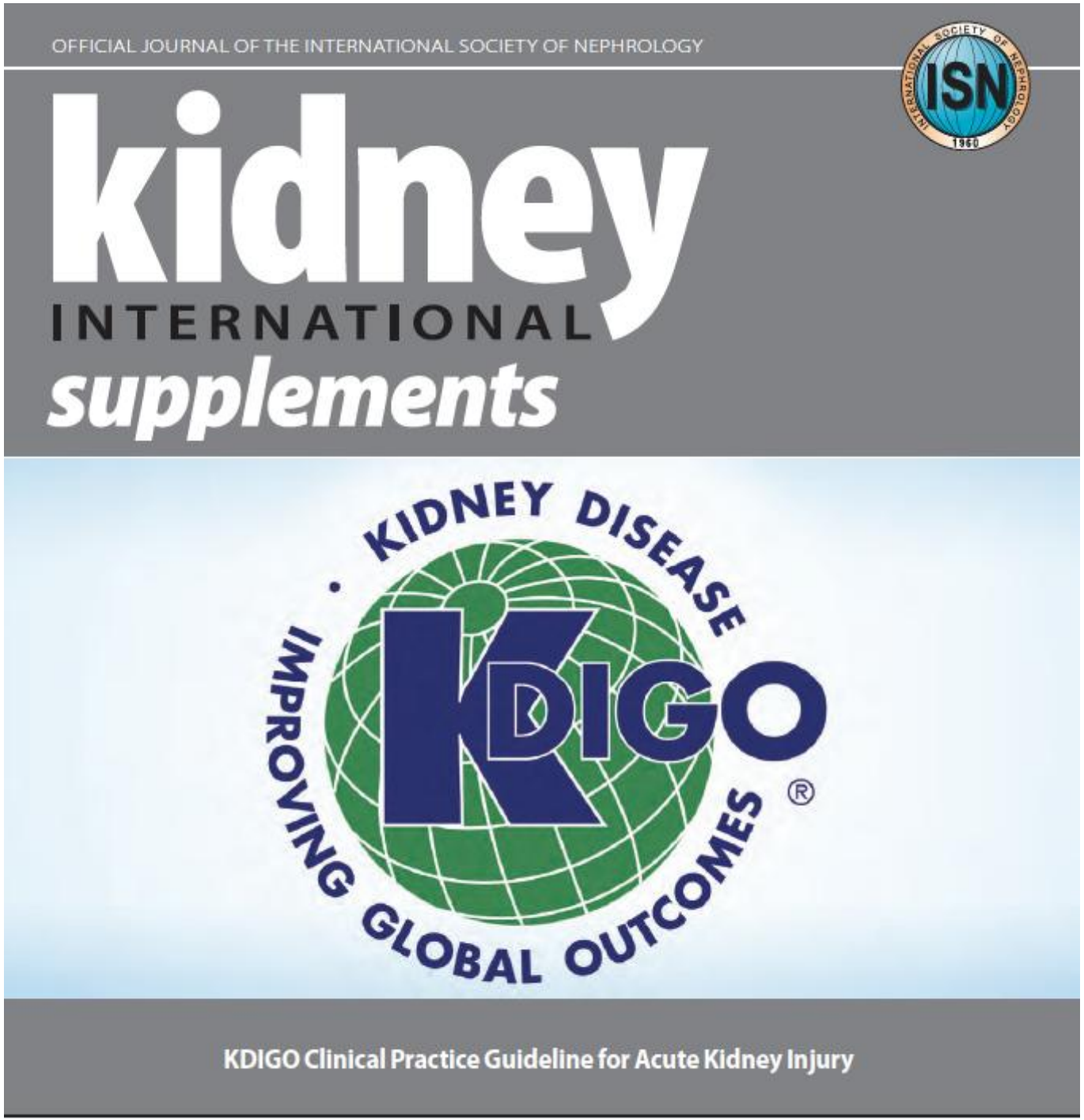
Critically ill patients receiving CRRT with RCA starting citrate concentration of 4 mmol/L

Results

Intervention	Filter lifespan (h)	Citrate dose (mmol/L)	Severe hypocalcemia
Standard pfCa monitoring (N=25) Adjust citrate dose to achieve a pfCa level of 0.25–0.35 mmol/L	54 ± 20	4.43 ± 0.32	44%
	Difference (95% CI) 7.1 (−5.3, 19.5) p=0.25	p<0.001	p=0.13
No pfCa monitoring (N=25) Blind the pfCa level and maintain the initial citrate dose without adjustment	47 ± 23	4.00 ± 0.00	20%

Conclusion: Amongst critically ill patients receiving RCA-CRRT, no pfCa monitoring by maintaining the citrate concentrations of 4 mmol/L is feasible. Larger RCT should be conducted to ensure this strategy.

Thanapongsatorn, P., et al. Clinical Kidney Journal (2023) @CKJsocial



Current KDIGO AKI 2012 guideline did not mention on which RCA protocol is better ?

Blood Purification

Critical Care Nephrology

Blood Purif
DOI: 10.1159/000546579

Received: September 26, 2024
Accepted: May 21, 2025
Published online: May 30, 2025

Hypertonic Citrate Solution Protocol Associated with Longer Filter Lifetime in Critically Ill Patients Requiring Continuous Kidney Replacement Therapy

Anyarin Wannakittirat[a, b] Khanittha Yimsangyad[b, c, d]
Nuttha Lumlertgul[b, c, d] Sadudee Peerapornratana[b, c, d, e]
Nattachai Srisawat[b, c, d, f]

[a]Division of Nephrology, Department of Medicine, Faculty of Medicine, Naresuan University Hospital, Phitsanulok, Thailand; [b]Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [c]Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [d]Center of Excellence for Critical Care Nephrology, Chulalongkorn University, Bangkok, Thailand; [e]Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [f]Academy of Science, Royal Society of Thailand, Bangkok, Thailand

Method

- Retrospective cohort study focused on critical care patients requiring CRRT during their admission to the KCMH, Bangkok, Thailand.

- The study was conducted in accordance with the Declaration of Helsinki and received approval from the Chulalongkorn University

IRB No. 89/66

- Data were collected from February 2023 to September

2023

Definition

- **Premature filter clotting:** defined as a filter lifetime of less than or equal to 72 h.

- **Total filter lifetime** refers to the duration from the initiation of the first filter of CRRT until filter replacement due to any cause, including termination of RRT, clotting, or nonclotting

events, with a maximum duration of 72 h.

- **Adjusted filter lifetime** includes only filters that reached the maximum circuit lifetime (72 h) or experienced clotting, while actual filter lifetime accounts for the true filter lifetime after excluding filter changes due to nonclotting events, with a maximum duration of 120 h, as per current practice.

Results

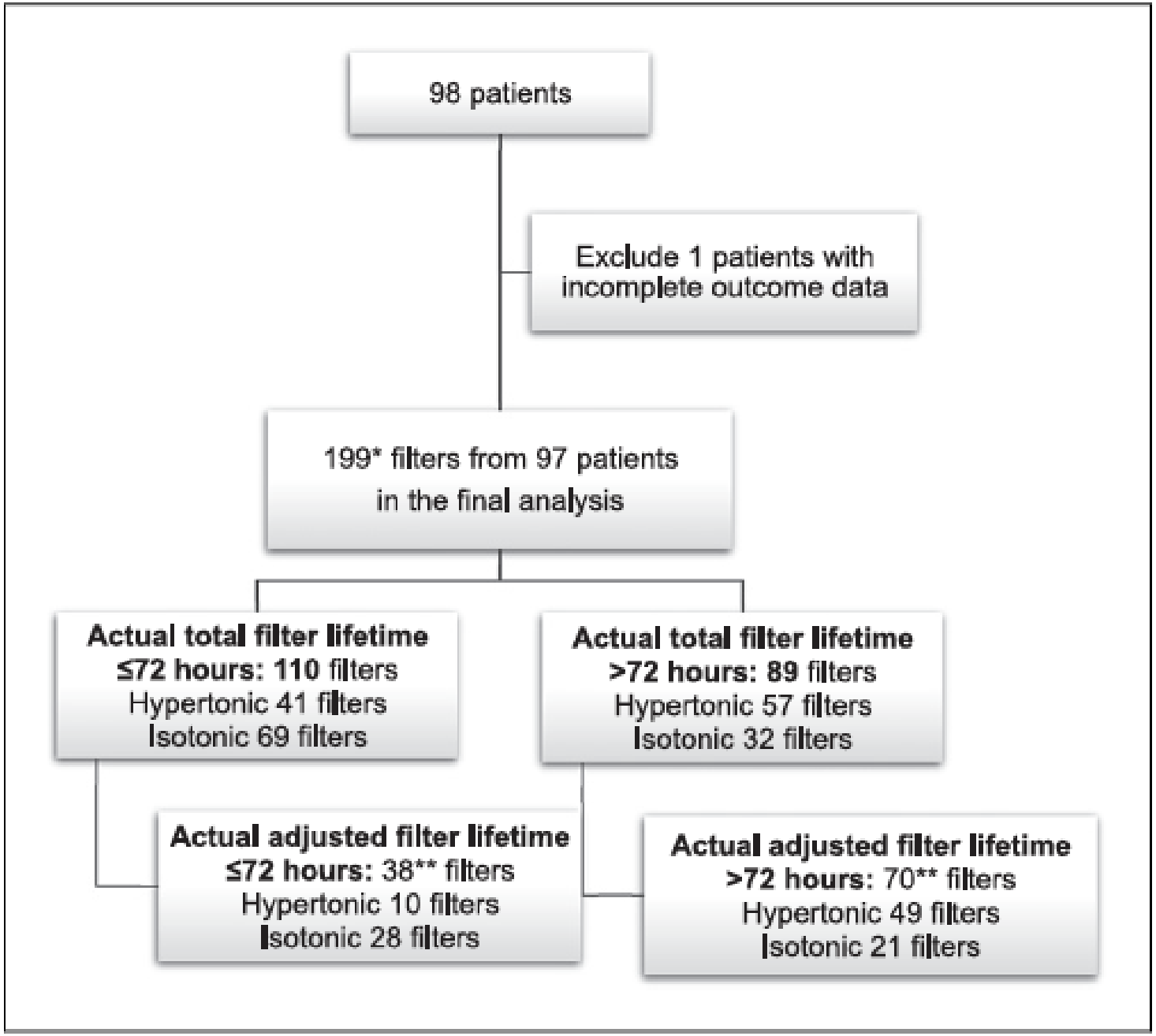


Fig. 1. Data flow chart. *There are multiple data points from different filters for individual patients having actual total filter lifetime, without exclusion of filter changes due to non-clotting events, with maximum duration of 120 h per our current practice. **There are multiple data points from different filters for individual patients having actual adjusted filter lifetime, with exclusion of filter changes due to non-clotting events, with maximum duration of 120 h per our current practice.

Table 1. Baseline characteristics of patients by filter premature clotting by actual adjusted filter lifetime (≤72 vs. >72 h) – 108 filters from 66 patients

Characteristics	≤72 h	>72 h	*p* value
	N = 38	*N* = 70	
Age, years	61 (44–71)	67 (57–75)	0.15
Gender			0.63
Male	21 (55)	42 (60)	
Female	17 (45)	28 (40)	
BW	52 (48–74)	55 (48–70)	0.84
Height	161 (150–170)	160 (150–161)	0.12
BMI	20.8 (19.1–26.3)	23.4 (20.6–29.3)	0.063
ICU			0.081
Medical	19/35 (54)	50 (71)	
Surgical	16/35 (46)	20 (29)	
Underlying disease			
Hypertension	20 (53)	49 (70)	0.073
End stage renal disease (ESRD)	4 (11)	27 (39)	0.002
Chronic kidney disease (CKD)	12 (32)	22 (31)	0.99
Cardiac disease	19 (50)	37 (53)	0.78
Congestive heart failure	11 (29)	15 (21)	0.38
Diabetes mellitus	11 (29)	33/69 (48)	0.058
Cirrhosis	7 (18)	11 (16)	0.72
Cause of AKI			
Sepsis	14/35 (40)	25/69 (36)	0.71
Ischemic	9/35 (26)	27/69 (39)	0.17
Nephrotoxic	4/35 (11)	2/69 (3)	0.078
Multifactorial	17/35 (49)	36/69 (52)	0.73
Severity of illness			
Baseline SOFA score	14 (3)	12 (4)	0.063
Baseline Apache II score	19 (7)	21 (8)	0.46
Baseline serum creatinine, mg/dL	0.98 (0.79–1.25)	1.66 (0.86–4.19)	0.005
Baseline blood urea nitrogen (BUN), mg/dL	19 (15–51)	28 (21–48)	0.49
Serum creatinine at KRT initiation, mg/dL	2.59 (1.76–3.70)	3.00 (2.10–5.62)	0.26
Blood urea nitrogen (BUN) at KRT initiation, mg/dL	65 (33–92)	58 (27–85)	0.93
Vasopressor Inotrope	33 (87)	58 (83)	0.59
Mechanical ventilation	37 (97)	63 (90)	0.16
Cause of KRT Initiation			
Volume overload	16/37 (43)	37 (53)	0.34
Oliguria/anuria	20/37 (54)	41 (59)	0.65
Uremia	13/37 (35)	24/69 (35)	0.97
Refractory acidosis	5/37 (14)	14/69 (20)	0.39
Refractory hyperkalemia	0/37 (0)	1/69 (1)	0.46

Table 2. Comparison of patient and CKRT factors by actual adjusted filter lifetime (≤72 vs. >72 h) – 108 filters from 66 patients

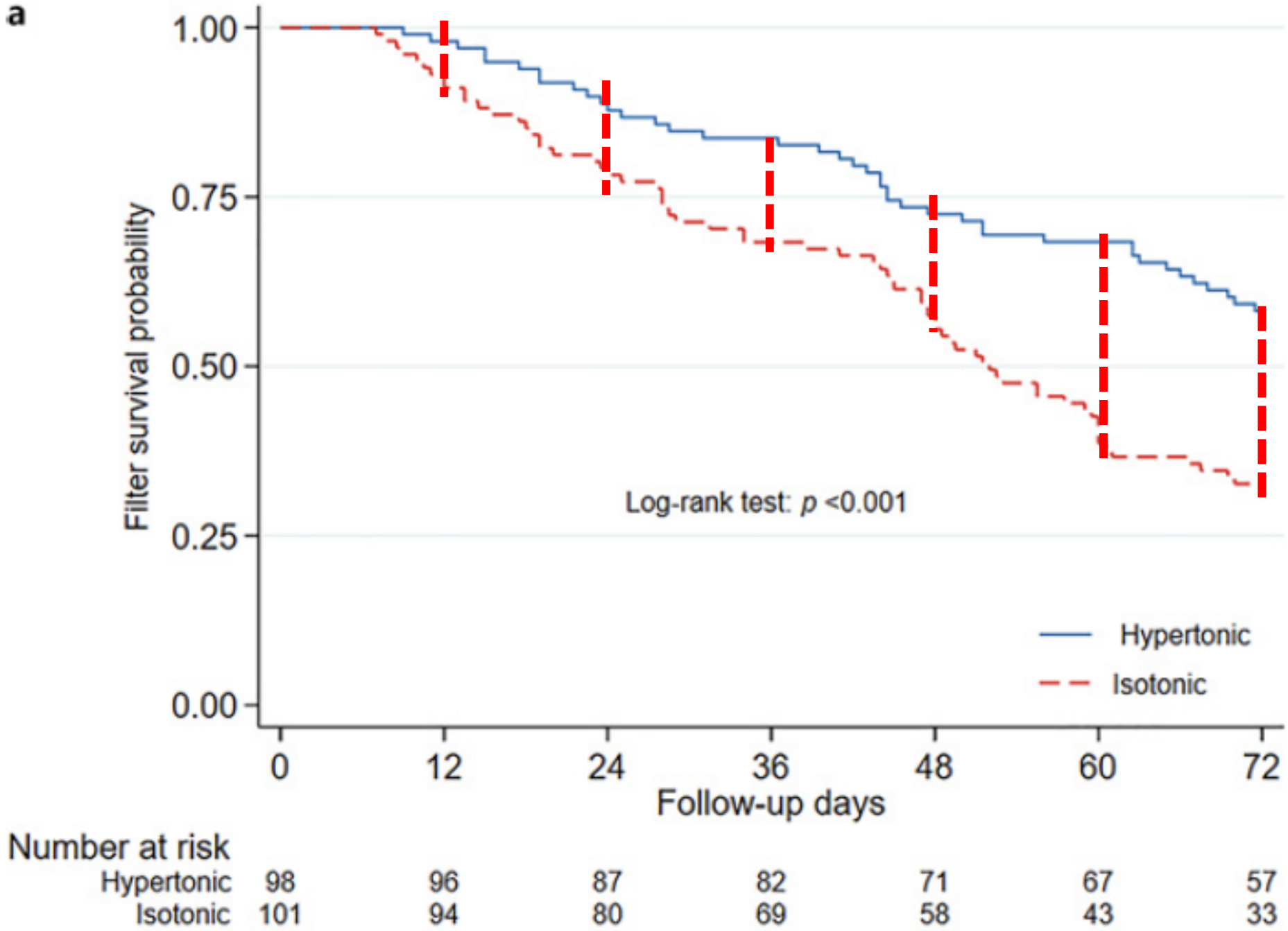
	≤72 h	>72 h	*p* value
	N = 38	*N* = 70	
Hematocrit level[b]	28.2 (25.0–30.3)	28.2 (24.2–31.3)	0.81
Platelets level (×10^3)[b]	78.5 (18–117)	75 (45–174)	0.38
Serum INR[b]	1.50 (1.17–1.64)	1.51 (1.40–1.87)	0.54
Blood transfusion			
Red cell	1 (0–2)	1 (0–2)	0.30
Platelet	1 (0–2)	1 (0–4)	0.42
Freeze frozen plasma	0 (0–4)	0 (0–2)	0.42
Mode of CRRT			
CVVH	13 (34)	9 (13)	0.021
CVVHD	0 (0)	2 (3)	
CVVHDF	25 (66)	59 (84)	
BFR[b]	100 (80–115)	80 (80–90)	<0.001
Dialysate flow rate[b]	500 (0–1,450)	1,500 (1,200–1,600)	<0.001
Pre-dilution replacement rate[b]	1,110 (857)	438 (587)	<0.001
Post-dilution replacement rate[b]	266 (140)	206 (78)	0.006
Net ultrafiltration rate[b]	20 (0–50)	0 (0–35)	0.11
Filtration fraction[a]	23.3 (11.8)	14.2 (8.9)	<0.001
Circuit ionized calcium[a]	0.42 (0.07)	0.45 (0.05)	0.010
Citrate doses[a]	4.32 (1.46)	4.12 (0.69)	0.35
Corrected citrate doses[a]	3.15 (0.85)	3.70 (0.58)	<0.001
Citrate formulations			<0.001
Hypertonic	10 (26)	49 (70)	
Isotonic	28 (74)	21 (30)	

"Citrate dose" calculated from citrate concentration in each solution, and "corrected citrate dose," which accounted for dilution factors from pre-dilution rates. Data are presented as mean (SD) or median (IQR: Q1–Q3) for continuous measures. INR, international normalized ratio. [a]Data were aggregated from multiple measurements (days) using mean. [b]Data were aggregated from multiple measurements (days) using median due to skewness of the data.

Table 3. Uni- and multi-variable analyses of factors associated with actual adjusted filter lifetime (≤72 vs. >72 h)

	Univariable analysis		Multivariable analysis[a]	
	unadjusted RR (95% CI)	*p* value	adjusted[a] RR (95% CI)	*p* value
Citrate protocols				
Hypertonic citrate	Reference	Reference	Reference	Reference
Isotonic citrate	3.37 (1.79, 6.34)	<0.001	2.45 (1.17, 5.14)	0.018
Mode of CRRT				
CVVH	2.03 (1.23, 3.36)	0.006	0.89 (0.46, 1.72)	0.74
CVVHD/CVVHDF	Reference	Reference	Reference	Reference
Daily CRRT factors				
Filtration fraction	1.05 (1.03, 1.07)	<0.001	0.97 (0.92, 1.03)	0.39
Blood flow rate (BFR)	1.16 (1.02, 1.32) per 10-unit increment	0.022	1.00 (0.87, 1.15)	1.00
Dialysate flow rate (DFR)	0.94 (0.90, 0.97) per 100-unit increment	0.001	Excluded since highly correlated	
Pre-dilution replacement rate	1.06 (1.04, 1.09) per 100-unit increment	<0.001	with filtration fractions	
Post-dilution replacement rate	1.03 (1.01, 1.04) per 10-unit increment	0.001	1.02 (0.99, 1.04)	0.19
Net ultrafiltration rate	1.04 (0.98, 1.12) per 10-unit increment	0.19	1.01 (0.95, 1.06)	0.81
Circuit ionized calcium	0.53 (0.29, 0.98) per 0.1-unit increment	0.044	0.61 (0.35, 1.06)	0.08
Citrate doses	1.12 (0.84, 1.50)	0.45	1.34 (0.81, 2.23)	0.26
Corrected citrate doses	0.61 (0.48, 0.78)	<0.001	0.48 (0.27, 0.87)	0.016
Blood transfusion				
Red cell	0.95 (0.85, 1.07)	0.397		
Platelet	0.90 (0.82, 0.99)	0.044	0.98 (0.88, 1.1)	0.74
Freeze frozen plasma	1.02 (0.97, 1.07)	0.533		

Dialysate flow rate and pre-dilution replacement rate were not adjusted in multivariable analysis due to highly correlated with filtration fractions. Correlation between FF, DFR, and pre-dilution replacement rate were shown in online supplementary Figure 1. Model used: mixed-effects Poisson regression model. RR, risk ratio; CI, confidence interval. Baseline characteristics with $p < 0.15$ and <5% missing data from crude comparison between groups were included in the univariate analysis. [a]Adjusted for citrate protocol, filtration fraction, BFR, post-dilution replacement rate, net ultrafiltration rate, circuit ionized calcium, citrate doses, corrected citrate doses, and platelet transfusion.


a
1.00
0.75
0.50
0.25
0.00
Filter survival probability
Log-rank test: p <0.001
Hypertonic
Isotonic
0
12
24
36
48
60
72
Follow-up days
Number at risk
Hypertonic 98 96 87 82 71 67 57
Isotonic 101 94 80 69 58 43 33

Summary :CRRT settings which associated with premature clotting include

- Lower dialysate flow rates (DFR) (500 mL/h vs. 1,500 mL/h, $p < 0.001$), and
- Lower corrected citrate doses
- Hypertonic citrate protocol had longer filter lifetime than the isotonic RCA protocol (total filter lifetime; 72 h vs. 52 h, $p < 0.001$; adjusted filter lifetime; 72 h vs. 56 h, $p < 0.001$ and actual filter lifetime)

Comparing the RCA protocols using concentrated and diluted citrate

Relevant studies generally still very limited

- 2021, prospective observational study (Switzerland)
- 2024, prospective quasi-experimental study (Spain)
- 2025, retrospective cohort study (Thailand)

1. Cassina T, et al. Minerva Anestesiol. 2021 Dec;87(12):1309-1319.
2. Mateos-Dávila A, et al. Nurs Crit Care. 2024 Sep;29(5):1005-1014.
3. Wannakittirat A, et al. Blood Purif. 2025 May 30:1-20.

RCA protocol using concentrated citrate associated with **longer filter lifespan and better clearance** (2021, Switzerland, prospective observational study)

CVVHD with citrate 136 mmol/L (31 pts.) vs. CVVH with citrate 13.3 mmol/L (45 pts.)

- RCA-CVVHD (citrate 136 mmol/L) was (showed by multivariable analysis) associated with a
- **longer filter lifespan (HR=0.47**; 95% CI: 0.28-0.78), **66 h vs. 48 h**;
- higher total cost (1362 CHF [782-1901] vs. 976 CHF [671-1353], P<0.001), but *cost per hour is similar for the two groups (23 CHF/hour)*;
- higher number of anticoagulation adjustments (9 [IQR, 4-14] vs. 2 [IQR, 1-4]).
- Significantly **higher mean urea and creatinine reduction ratios** at the first 24 hours were in the RCA-CVVHD group (**T 24, 43**±16% vs. 24±15% (P<0.001); and **41**±17% vs. 26±15%).
- Significantly **higher mean urea reduction ratios** at the 72 hours were in the RCA-CVVHD group (**T72, 55±28% vs. 39±27% (P=0.038)**
- Higher alkalosis incidence in the RCA-CVVHD group (log-rank test $\chi 2(1)=8.18$, P=0.004)

Cassina T, et al. Minerva Anestesiol. 2021 Dec;87(12):1309-1319.

RCA protocol using concentrated citrate had **longer circuit lifespan and less electrolyte loss** (2024, Spain, prospective, quasi-experimental study)

CVVHD with citrate 136 mmol/L (43 pts.) vs. **CVVHD with citrate 18 mmol/L (23 pts.)**

Both protocols using a starting **citrate dose** of 3.5 mmol/L (the original shall be 4 for concentrated and 3 for diluted)

Dialysis solution was used; post-filter replacement was not used, and the **citrate** solution was the only fluid administered pre-filter (the diluted protocol must still have more significant convective effect).

Main results:

- The concentrated citrate group had a **longer filter life** (Kaplan–Meier survival curves, $p < .05$), **76% vs. 48%** lasting longer than 48 hours; and there was a slight trend toward alkalosis (not statistically significant).
- A lower **need for electrolyte replacement** (K, Mg, P) was observed in the concentrated group ($p < .001$).

Mateos-Dávila A, et al. Nurs Crit Care. 2024 Sep;29(5):1005-1014.

Reason hypertonic citrate has longer filter life time

Unclear explanation

Possible mechanism

- lower filtration fraction
- lower iCa2+ in the circuit during first 24-48 hr

Reason hypertonic citrate has higher rate of metabolic alkalosis

Unclear explanation

Possible mechanism

- higher load of sodium content in hypertonic citrate solution (Na 408 mmol/L) → lead to higher SID

- hypertonic citrate solution combined with lower bicarbonate concentration in dialysiate solution strategy → may not sufficient enough to clear citrate-calcium complex

CONCLUSIONS

- Regional citrate anticoagulation is the gold standard of anticoagulation in CKRT – **prolong filter lifetimes** and **decrease bleeding complication**
- **Pre-filter (systemic) ionized calcium**, and **calcium ratio** was monitored to avoid **citrate toxicity and citrate complications.**
- **Simplified protocol for no post-filter ionized calcium**
  - Low risk of impaired citrate metabolism
  - Pre-determined citrate concentrations of 4 mmol/L
  - Monitoring of systemic iCa^{2+}, calcium ratio, and promptly correction of metabolic complications
- Citrate protocol may affect to filter lifetime

Acknowledgements

National Collaborators

- **12 hospitals in Sisaket and Nakhon Si Thammarat Province**
  - Dr. Chayomon Dokpong
  - Dr. Theerapon Sukmark

National Center for Genetic Engineering and Biotechnology (BIOTEC)

- Dr. Sittiruk Roytrakul

International Collaborators

UCLA

- Prof. David Haake
- Prof. Fayyaz Sutterwala

Duke University

- Prof. Megan Reller

Chang Gung University College of Medicine, Taiwan

- Prof. Chih-Wei Yang

Northern Arizona University

- David M Wagner
- Nathan Eric Stone

National fund

- Excellence Center for Critical Care Nephrology, King Chulalongkorn Memorial Hospital
- Center of Excellence in Critical Care Nephrology, Faculty of Medicine, Chulalongkorn University.
- Tropical Medicine Cluster, Chulalongkorn University
- The Second Century Fund Chulalongkorn University (C2F)

International fund

- NIH P01AI168148
- NIH R01AI183353

National Institutes of Health

Thank you very much

ศูนย์ความเป็นเลิศทางการแพทย์ด้านโรคไตในภาวะวิกฤต

EC-CCN
Excellence Center for Critical Care Nephrology
King Chulalongkorn Memorial Hospital
The Thai Red Cross Society

โรงพยาบาลจุฬาลงกรณ์ สภากาชาดไทย

Electrolyte imbalance

Systemic ionized hypercalcemia	Excessive calcium replacement	Reduce calcium infusion rate
Systemic ionized hypocalcemia	Inadequate calcium replacement	After excluding inadequate citrate metabolism, increase calcium infusion rate (check infusion pump to exclude technical issues)
	Inadequate citrate metabolism preventing calcium release from calcium-citrate complexes	In the presence of signs of citrate accumulation, increase calcium infusion rate and consider the measures suggested for citrate accumulation
Hypernatremia	Use of high-concentration trisodium citrate solutions without adequate lowering of sodium concentration in the dialysate/replacement fluid	Use a low-sodium dialysate/ replacement fluid in protocols based on hypertonic citrate solutions
Hyponatremia	Accidental omission of hypertonic citrate solution in protocols adopting hypotonic dialysate/replacement fluid (rarely observed)	Verify the correct matching of RCA solutions
Hypomagnesemia	Inadequate magnesium replacement	Increase magnesium replacement (check infusion pump to exclude technical issues)