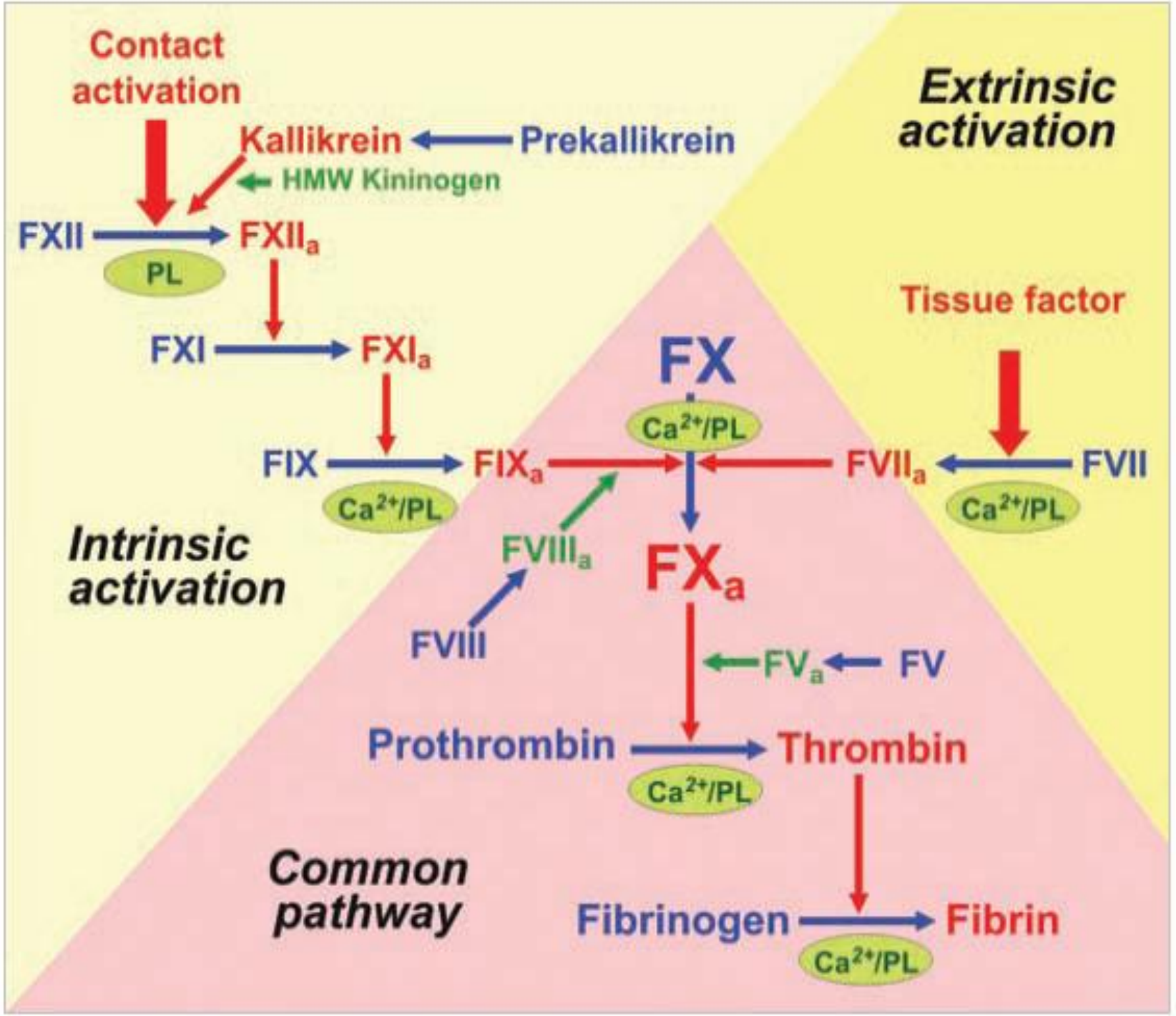
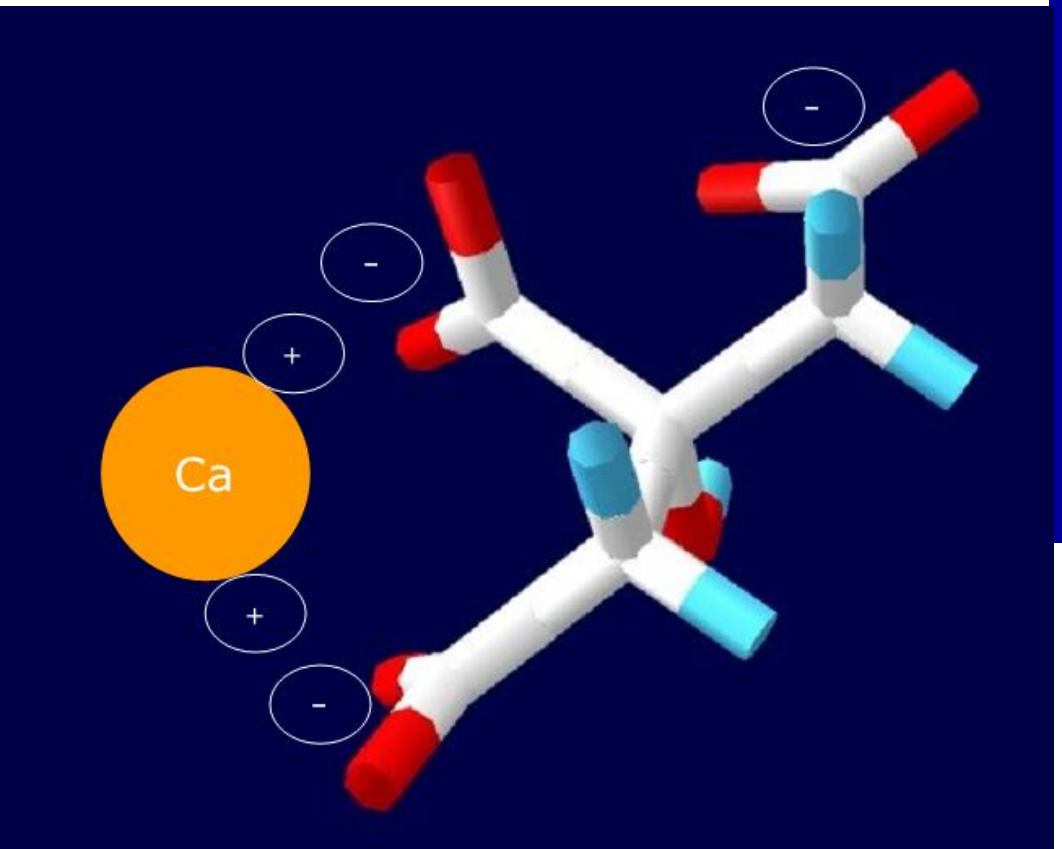
REGIONAL CITRATE ANTICOAGULATION IN CONTINUOUS RENAL REPLACEMENT THERAPY

INFECTIOUS DISEASE DEPARTMENT - 2017

Coagulation cascade





Sites of Action of Citrate

CONTACT PHASE
XII activation
XI IX

TISSUE FACTOR
TF:VIIa
monocytes / platelets / macrophages

Va
VIIIa
Ca^{++}
platelets

X
Xa

Phospholipid surface

prothrombin

CITRATE

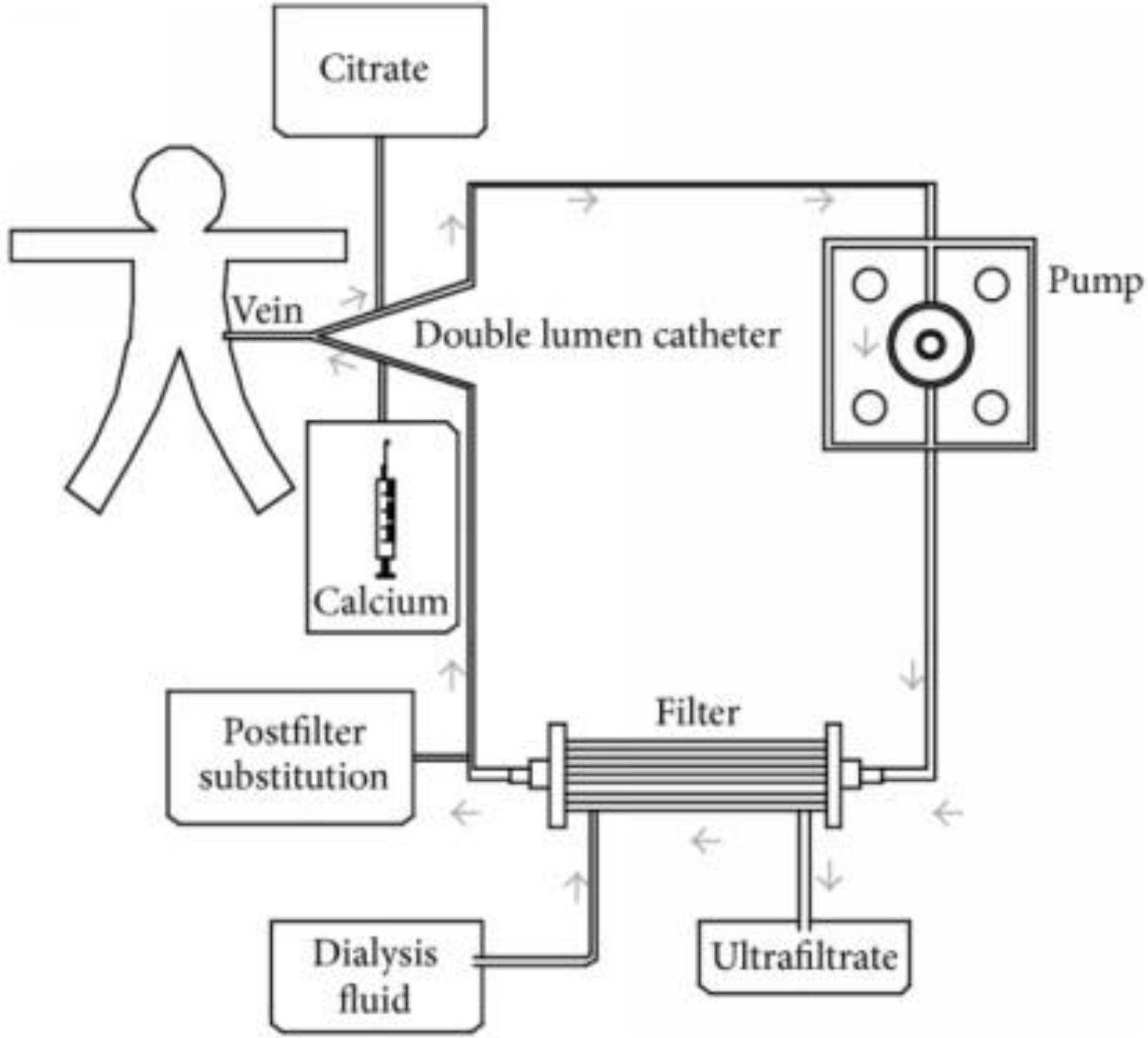
THROMBIN

NATURAL ANTICOAGULANTS (APC, ATIII)

fibrinogen

FIBRINOLYSIS ACTIVATION
FIBRINOLYSIS INHIBITION

CLOT


Citrate
Vein
Double lumen catheter
Pump
Calcium
Postfilter
substitution
Filter
Dialysis
fluid
Ultrafiltrate

Regional Citrate Versus Heparin Anticoagulation for Continuous Renal Replacement Therapy: A Meta-Analysis of Randomized Controlled Trials

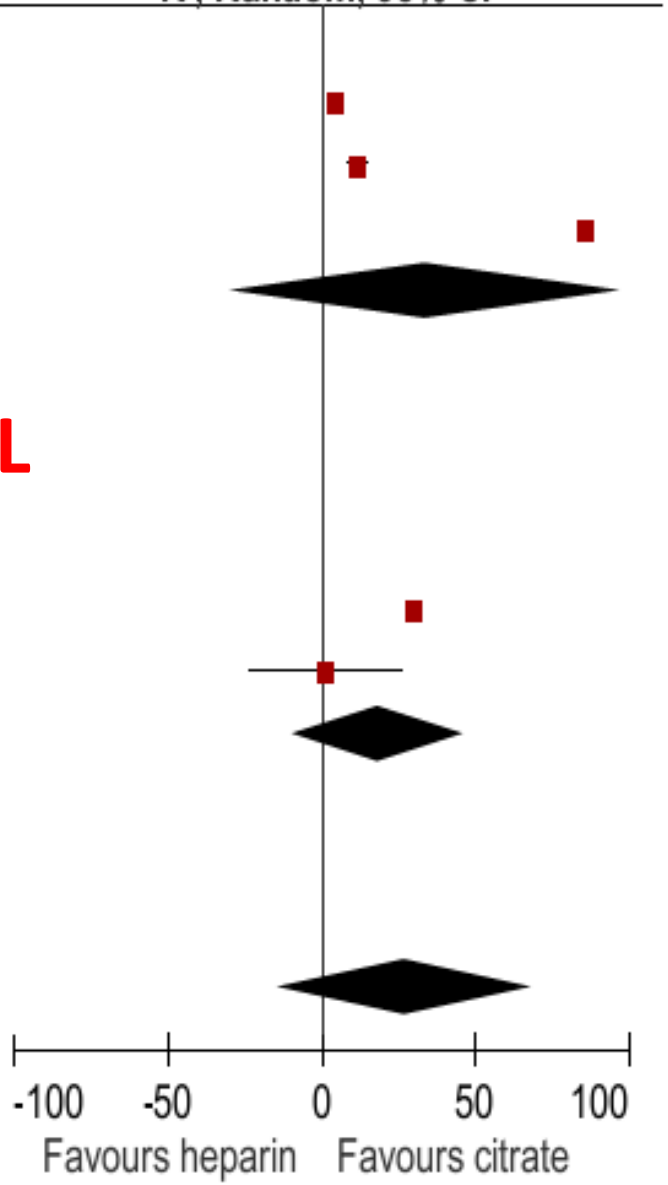
Mei-Yi Wu, MD,[1] Yung-Ho Hsu, MD,[1] Chyi-Huey Bai, PhD,[2] Yuh-Feng Lin, MD,[1] Chih-Hsiung Wu, MD, PhD,[3] and Ka-Wai Tam, MD, MS[4]

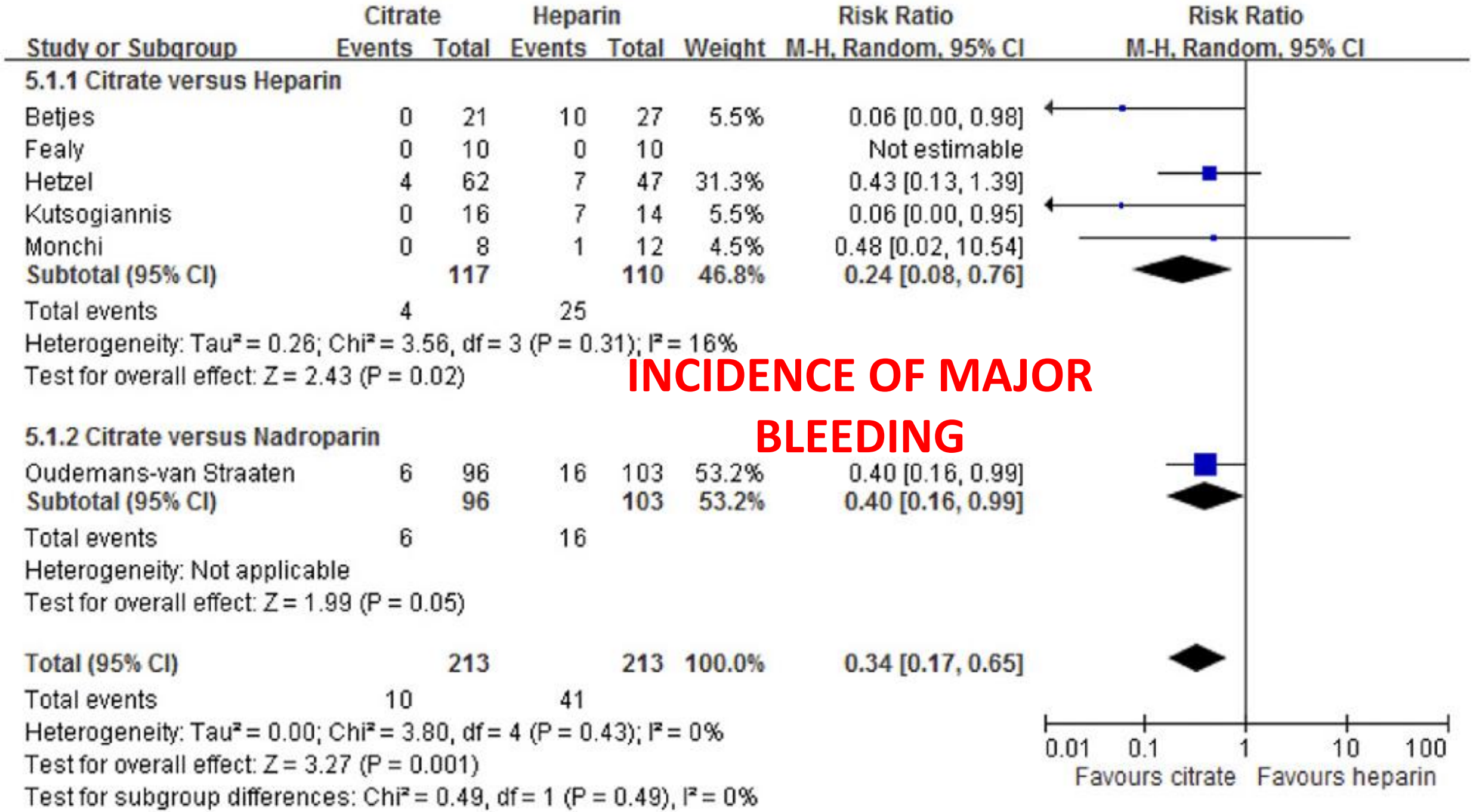
Am J Kidney Dis. 2012;59(6):810-818

- **Population**: Patients admitted to ICU with AKI that required CRRT
- **Intervention**: Regional citrate vs heparin anticoagulation in CRRT
- 6 RCTs with 488 patients were identified

Study or Subgroup	Mean Difference	SE	Citrate Total	Heparin Total	Weight	Mean Difference IV, Random, 95% CI
8.1.1 Pre-dilution						
Fealy	4	1.325	10	10	20.3%	4.00 [1.40, 6.60]
Hetzel	11.4	1.85	87	81	20.3%	11.40 [7.77, 15.03]
Kutsogiannis	86.2	0.141	36	43	20.3%	86.20 [85.92, 86.48]
Subtotal (95% CI)			**133**	**134**	**60.8%**	**33.88 [-29.83, 97.59]**
Heterogeneity: Tau² = 3168.23; Chi² = 5391.27, df = 2 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 1.04 (P = 0.30)						
8.1.2 Post-dilution						
Monchi	30	0.873	26	23	20.3%	30.00 [28.29, 31.71]
Oudemans-van Straaten	1	12.88	97	103	18.9%	1.00 [-24.24, 26.24]
Subtotal (95% CI)			**123**	**126**	**39.2%**	**18.35 [-9.52, 46.21]**
Heterogeneity: Tau² = 337.17; Chi² = 5.05, df = 1 (P = 0.02); I² = 80%						
Test for overall effect: Z = 1.29 (P = 0.20)						
Total (95% CI)			**256**	**260**	**100.0%**	**26.89 [-14.47, 68.25]**
Heterogeneity: Tau² = 2194.11; Chi² = 9282.17, df = 4 (P < 0.00001); I² = 100%						
Test for overall effect: Z = 1.27 (P = 0.20)						
Test for subgroup differences: Chi² = 0.19, df = 1 (P = 0.66), I² = 0%						

CIRCUIT SURVIVAL TIME

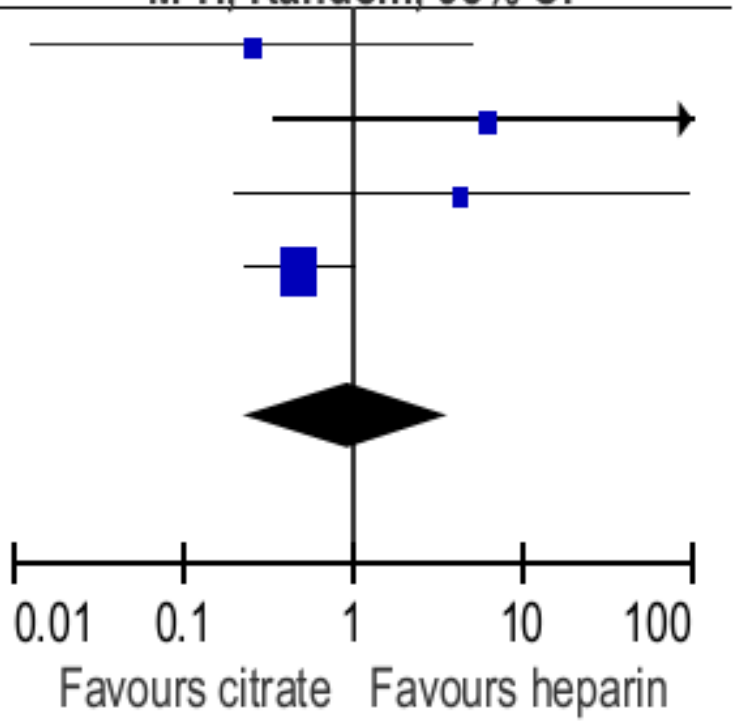



Citrate
Heparin
Risk Ratio
Risk Ratio
Study or Subgroup
Events Total Events Total Weight
M-H, Random, 95% CI
M-H, Random, 95% CI
5.1.1 Citrate versus Heparin
Betjes 0 21 10 27 5.5% 0.06 [0.00, 0.98]
Fealy 0 10 0 10 Not estimable
Hetzel 4 62 7 47 31.3% 0.43 [0.13, 1.39]
Kutsogiannis 0 16 7 14 5.5% 0.06 [0.00, 0.95]
Monchi 0 8 1 12 4.5% 0.48 [0.02, 10.54]
Subtotal (95% CI) 117 110 46.8% 0.24 [0.08, 0.76]
Total events 4 25
Heterogeneity: Tau² = 0.26; Chi² = 3.56, df = 3 (P = 0.31); I² = 16%
Test for overall effect: Z = 2.43 (P = 0.02)
INCIDENCE OF MAJOR BLEEDING
5.1.2 Citrate versus Nadroparin
Oudemans-van Straaten 6 96 16 103 53.2% 0.40 [0.16, 0.99]
Subtotal (95% CI) 96 103 53.2% 0.40 [0.16, 0.99]
Total events 6 16
Heterogeneity: Not applicable
Test for overall effect: Z = 1.99 (P = 0.05)
Total (95% CI) 213 213 100.0% 0.34 [0.17, 0.65]
Total events 10 41
Heterogeneity: Tau² = 0.00; Chi² = 3.80, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.27 (P = 0.001)
Test for subgroup differences: Chi² = 0.49, df = 1 (P = 0.49), I² = 0%
0.01 0.1 1 10 100
Favours citrate Favours heparin

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI
Betjes	0	21	2	27	15.9%	0.25 [0.01, 5.03]
Kutsogiannis	3	16	0	14	16.7%	6.18 [0.35, 110.11]
Monchi	1	8	0	12	15.1%	4.33 [0.20, 94.83]
Oudemans-van Straaten	9	97	20	103	52.3%	0.48 [0.23, 1.00]
Total (95% CI)		**142**		**156**	**100.0%**	**0.92 [0.23, 3.68]**
Total events	13		22			

Heterogeneity: $Tau^2 = 0.81$; $Chi^2 = 4.88$, df = 3 ($P = 0.18$); $I^2 = 38\%$

Test for overall effect: $Z = 0.11$ ($P = 0.91$)

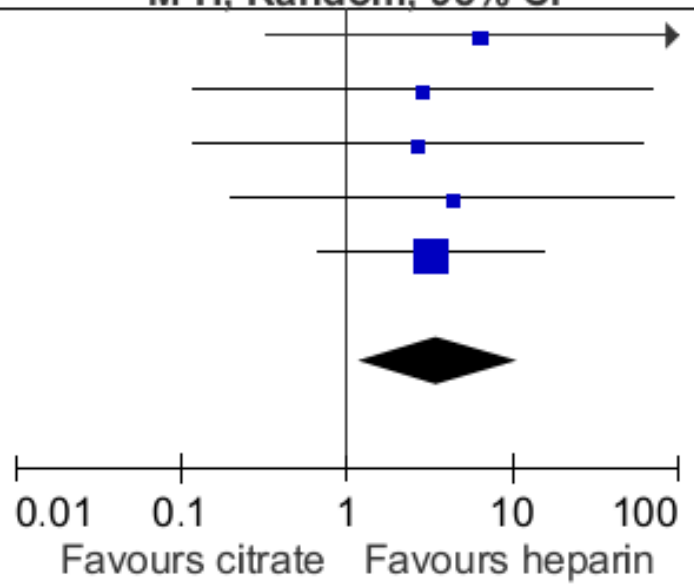


INCIDENCE OF METABOLIC ALKALOSIS

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Random, 95% CI
Betjes	2	21	0	27	13.7%	6.36 [0.32, 125.86]
Hetzel	1	87	0	83	12.0%	2.86 [0.12, 69.32]
Kutsogiannis	1	16	0	14	12.5%	2.65 [0.12, 60.21]
Monchi	1	8	0	12	12.8%	4.33 [0.20, 94.83]
Oudemans-van Straaten	6	97	2	103	49.0%	3.19 [0.66, 15.41]
Total (95% CI)		**229**		**239**	**100.0%**	**3.51 [1.17, 10.60]**
Total events	11		2			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.23$, df = 4 (P = 0.99); $I^2 = 0\%$

Test for overall effect: Z = 2.23 (P = 0.03)



INCIDENCE OF HYPOCALCEMIA

Conclusion:

- The efficacy of citrate and heparin anticoagulation for CRRT was similar.
- Citrate anticoagulation decreased the risk of bleeding with no significant increase in the incidence of metabolic alkalosis.
- We recommend citrate as an anticoagulation agent in patients who require CRRT but are at high risk of bleeding.

Intensive Care Med (2012) 38:20–28
DOI 10.1007/s00134-011-2438-3

SYSTEMATIC REVIEW

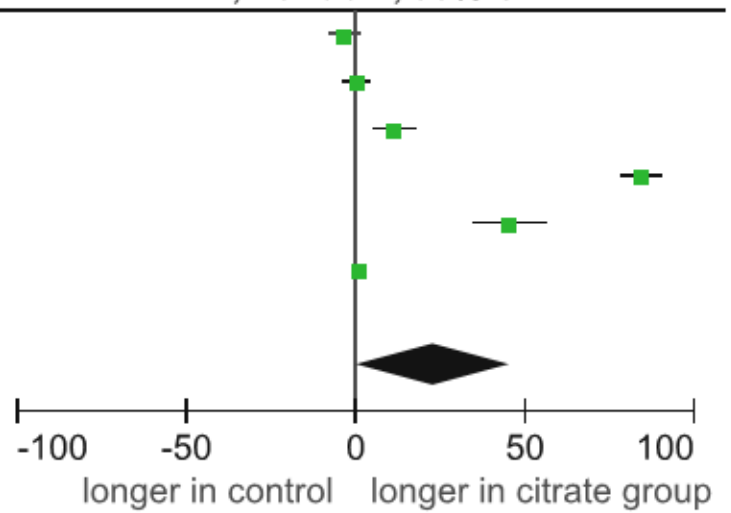
Efficacy and safety of regional citrate anticoagulation in critically ill patients undergoing continuous renal replacement therapy

- Six studies met our inclusion criteria, involved a total of 658 circuits
- Anticoagulation strategies of the control arm were not restricted.
- The study had to be conducted in critically ill patients treated with CRRT

Study or Subgroup	citrate Mean	citrate SD	citrate Total	control Mean	control SD	control Total	Weight	Mean Difference IV, Random, 95% CI
Betjes MG 2007	39	15.7	70	42.3	13.6	72	16.8%	-3.30 [-8.14, 1.54]
Fealy N 2007	16.3	2.4	10	16	6.3	10	16.8%	0.30 [-3.88, 4.48]
Hetzel GR 2011	37.5	23	87	26.1	19	81	16.7%	11.40 [5.04, 17.76]
Kutsogiannis DJ 2005	125.5	16.8	36	40.9	9.9	43	16.7%	84.60 [78.37, 90.83]
Monchi M 2004	81.4	27	26	36.1	8.9	23	16.2%	45.30 [34.30, 56.30]
Oudemans-van Straaten HM 2009	28.5	8.8	97	27.5	7.2	103	16.9%	1.00 [-1.24, 3.24]
Total (95% CI)			**326**			**332**	**100.0%**	**23.03 [0.45, 45.61]**

Heterogeneity: Tau² = 785.58; Chi² = 696.77, df = 5 (P < 0.00001); I² = 99%

Test for overall effect: Z = 2.00 (P = 0.05)

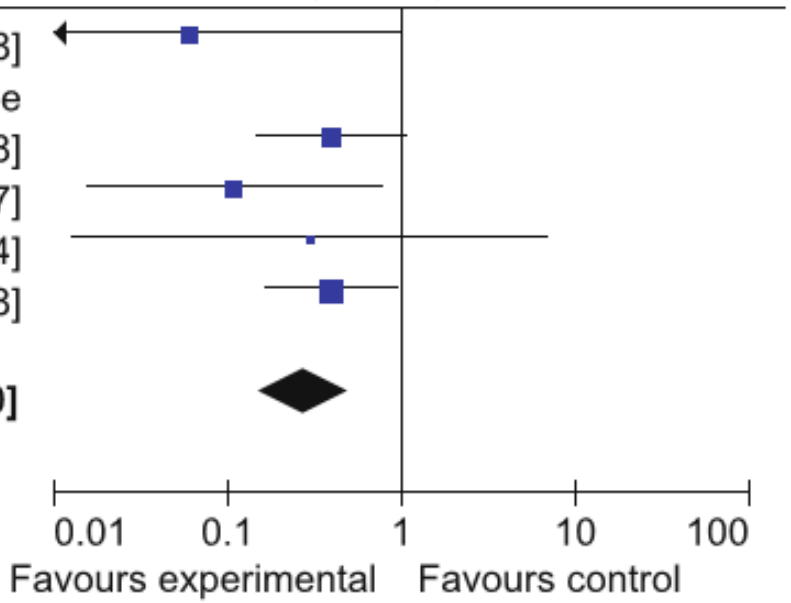


CIRCUIT LIFE SPAN

Study or Subgroup	citrate Events	Total	control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Betjes MG 2007	0	21	10	27	19.6%	0.06 [0.00, 0.98]
Fealy N 2007	0	10	0	10		Not estimable
Hetzel GR 2011	5	87	12	83	26.0%	0.40 [0.15, 1.08]
Kutsogiannis DJ 2005	1	16	8	14	18.1%	0.11 [0.02, 0.77]
Monchi M 2004	0	26	1	23	3.4%	0.30 [0.01, 6.94]
Oudemans-van Straaten HM 2009	6	97	16	103	32.9%	0.40 [0.16, 0.98]
Total (95% CI)		**257**		**260**	**100.0%**	**0.28 [0.15, 0.50]**
Total events	12		47			

Heterogeneity: Chi² = 3.16, df = 4 (P = 0.53); I² = 0%

Test for overall effect: Z = 4.27 (P < 0.0001)



RISK OF BLEEDING

Metabolic events

- **Hypernatremia**: was neglectable and occurred equally in both groups
- **Alkalosis**: two studies reported more episodes of alkalosis in the citrate group, another two reported more such events in the control group
- **Systemic hypo-calcemia**: occurred more frequently in the citrate group, which however could be resolved easily and caused no clinically important consequences.

Mortality

Two studies:

- Mortality rates per day were similar between the two groups during both treatment and follow-up period (3.1 vs. 3.1% and 3.8 vs. 3.4%, respectively)
- Compared with nadroparin, citrate could reduce both hospital and 3-month mortality by 15% ($P<0.05$)

Conclusions:

- RCA is effective in maintaining circuit patency and reducing the risk of bleeding, and thus can be recommended for CRRT if and when metabolic monitoring is adequate and the protocol is followed.
- However, the safety of citrate in pts with liver failure cannot be concluded from current analysis. The metabolic stability can be easily controlled during RCA.
- Survival benefit from RCA is still controversial.

?

Review Article

Citrate Anticoagulation During Continuous Renal Replacement Therapy in Pediatric Critical Care

T. Keefe Davis, MD[1]; Tara Neumayr, MD[2]; Kira Geile, RN, CPNP[1,3]; Allan Doctor, MD[2]; Paul Hmeil, MD, PhD[1]

Pediatr Crit Care Med 2014; 15:471–485

Data Extraction and Data Synthesis: In the pediatric population, there are no prospective interventional or randomized studies comparing regional versus systemic anticoagulation. However, there are 11 (retrospective and prospective observational studies) in the pediatric population using citrate anticoagulation. These studies have shown that regional citrate anticoagulation in the pediatric population can be effective, provide equivalent circuit survival, and decrease bleeding compared with heparin

TABLE 2. Regional Citrate Protocols in Pediatric and Adults

References	Citrate Solution and Dose	Circuit Ionized Calcium Goal mmol/L (mg/dL)	Modality
Bunchman et al (7, 8) (Pediatrics)	ACD-A Rate: 2.5% of Q_b (1.5× the Q_b in mL/hr)	0.35–0.5 (1.4–2)	CVVHD; CVVH
Chadha et al (9) (Pediatrics)	ACD-A Rate: 1.6–3.7% of Q_b	< 0.5 (< 2)	CVVH
Elhanan et al (21) (Pediatrics)	ACD-A Rate: 2.5–3.3% of Q_b	0.3–0.4 (1.2–1.6)	CVVH
St. Louis Children's Hospital[a] (Pediatrics)	ACD-A Rate: 2.5% of Q_b	0.3–0.35 (1.2–1.4)	CVVHDF

SUMMARY

- Regional citrate anticoagulation is an ideal option in a critically ill child especially with coagulopathy.
- Complications of citrate anticoagulation can be avoided with a greater understanding of the properties and clearance of citrate.

→ require well-designed protocol

Thank you for listening!

Citrate Protocol

1. Prime in CVVHDF Mode using ordered dialysate and replacement solutions.
   Dialysate : HCO3-based without Ca
   Replacement: normal saline or bicarb-based industry made solution

2. Place a 3 way stop cock to both the "arterial" and venous ports of the dialysis access. Attach the Citrate ACD(A) Solution 1000cc to a regular IV pump and then attach it to the "arterial" stop cock.

3. When ready to start the citrate rate in ccs/hr will be 1.5 x the blood flow rate of the PRISMA machine at ccs/min. (eg Start Citrate at 150 mls/hr if the BFR is 100 mls/min)

4. Set up the Ca++ infusion (ie. 8gms Calcium Chloride in 1L NS or 23.5 gms of Calcium Gluconate in 1L of NS) as ordered via central line other than the dialysis access. This will run at 40% of the citrate flow rate. (eg citrate rate = 150 mls/hr then CaCl rate = 60 mls/hr)

5. Set the flow rates in Hemofiltration machine as ordered.

6. Patient Fluid Removal Rate is calculated by:
Net Ultrafiltration rate + Citrate rate + Calcium infusion rate = Pt. Fluid Removal Rate.

7. Connect the Hemofiltration machine circuit to the dialysis catheter as per procedure and press start.

8. 2 hour after initiation of therapy and every 6 hours thereafter, send the following blood work

    Post-filter ionized Ca++ (drawn from the return line, blue sample port)
    Systemic ionized Ca++ (drawn from patient (true) arterial line or peripheral draw)
    Chemistries (eg Lytes, Bun, Cr, Ca, Phos, Albumen)
    (see # 14 for citrate and calcium adjustment)

9. Metabolic alkalosis occurs due to citrate metabolism to bicarbonate and due to bicarbonate in the Dialysate. Call Peds Nephrologist if the Serum Bicarb is> 35 meq/l In that case the Peds Nephrologist will add in NS as a replacement soln by 200-400 cc/hr and decrease the dialysate rate by the same amount. This will give an acid load from the NS and diminish the HCO3 from the bath at the same time

10. Notify MD for the following :

a. Systemic Ionized Ca++ < 0.75 mmol/L. (Consider holding citrate for 1 hours and resuming infusion at 30% of the citrate flow rate and bolus with 10 mg/kg of CaCl and increase Ca infusion by 10%)
b. Na+ > 150 mmol/L. Consider changing replacement solution to 0.45% NaCl.

11. If the filter clots, stop the Citrate and Ca++ infusions and discontinue the filter.

12. **In children less then 10 kg who require a blood transfusion when going on, avoid the use of citrate for the first 15 minutes for it may exacerbate the Bradykinin release syndrome seen in some children.**

13. Citrate Lock occurs when the total calcium rises with a dropping ionized calcium. This is due to the fact of the citrate infusion exceeds the clearance on dialysis and from hepatic metabolism. When this is seen, stop the citrate for 2-4 hours then restart at 70% of the previous dose. Watch the ionized calcium during this time to avoid inadequate anticoagulation of the circuit (i.e. the ionized calcium of the system rising causing system clotting).

14. Titrate the Citrate infusion according to the citrate sliding scale below :

Prisma ionized Ca++ (mmol/L)	**Citrate Infusion Adjustment**	
	> 20 kg	< 20 kg
< 0.35	↓ rate by 10 ml/hr	↓ rate by 5 ml/hr
0.35 – 0.5 (Optimum Range)	No adjustment	
0.5 – 0.6	↑ rate by 10 ml/hr	↑ rate by 5 ml/hr
> 0.6	↑ rate by 20 ml/hr	↑ rate by 10 ml/hr
NOTIFY MD IF CITRATE INFUSION RATE > 200 ml/hr		

Titrate the Calcium infusion according to the calcium sliding scale below :

Patient ionized Ca++ (mmol/L)	**Calcium Infusion Adjustment**	
	> 20 kg	< 20 kg
> 1.3	↓ rate by 10 ml/hr	↓ rate by 5 ml/hr
1.1-1.3 (Optimum Range)	No adjustment	
0.9-1.1	↑ rate by 10 ml/hr	↑ rate by 5 ml/hr
< 0.9	↑ rate by 20 ml/hr	↑ rate by 10 ml/hr
NOTIFY MD IF Calcium INFUSION RATE > 200 ml/hr		