Anticoagulation for CRRT

Ashita Tolwani, MD, MSc
University of Alabama at Birmingham
2019

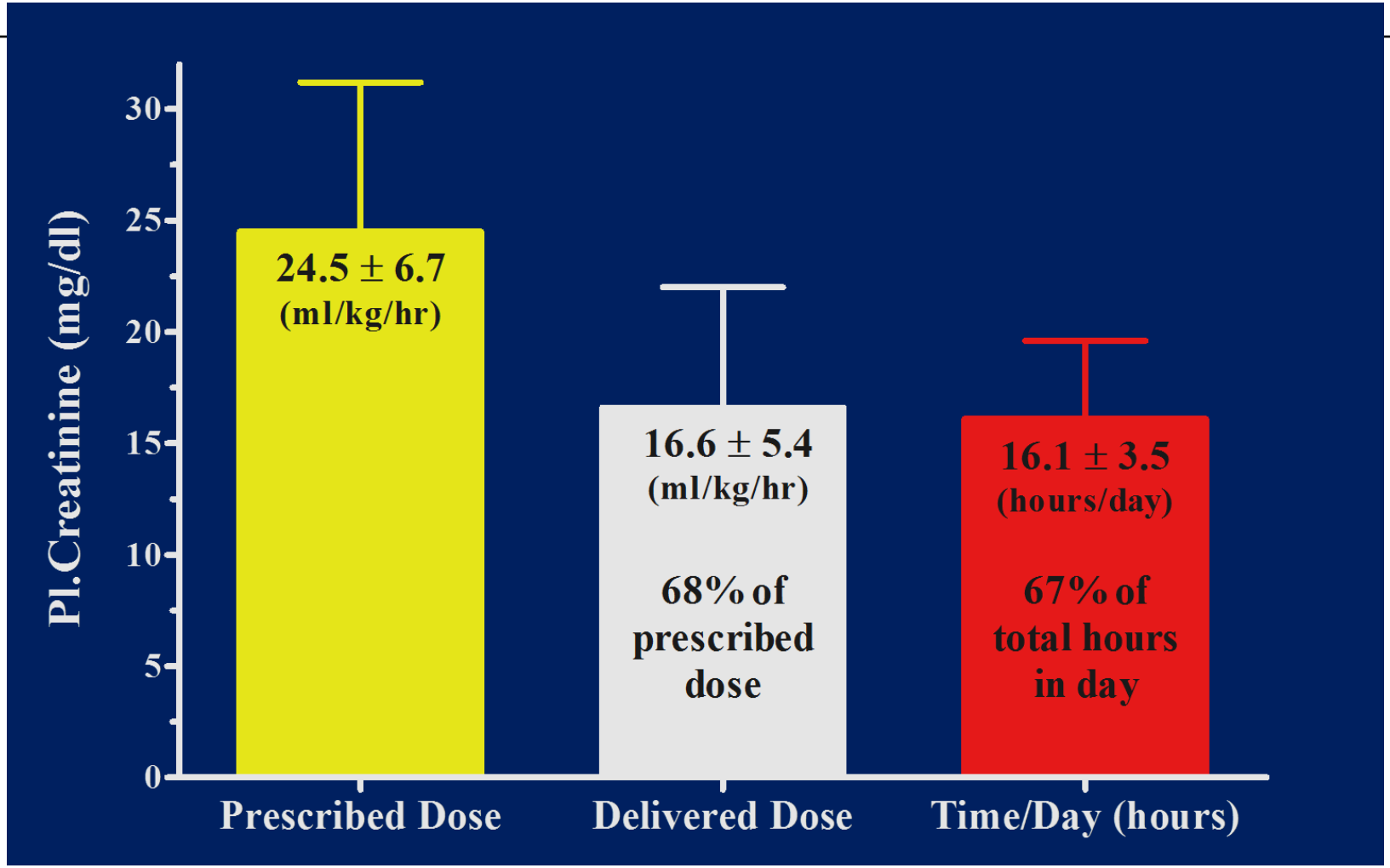
Disclosures

- Consultant for Baxter
- Patent on 0.5% citrate formulation

Why Anticoagulation During CRRT?

- To preserve life of extracorporeal circuit
- To maximize CRRT dose
- To minimize blood loss caused by clotting during CRRT

CRRT Prescription vs. Delivery



Venkataraman et al, *J Crit Care, 2002*

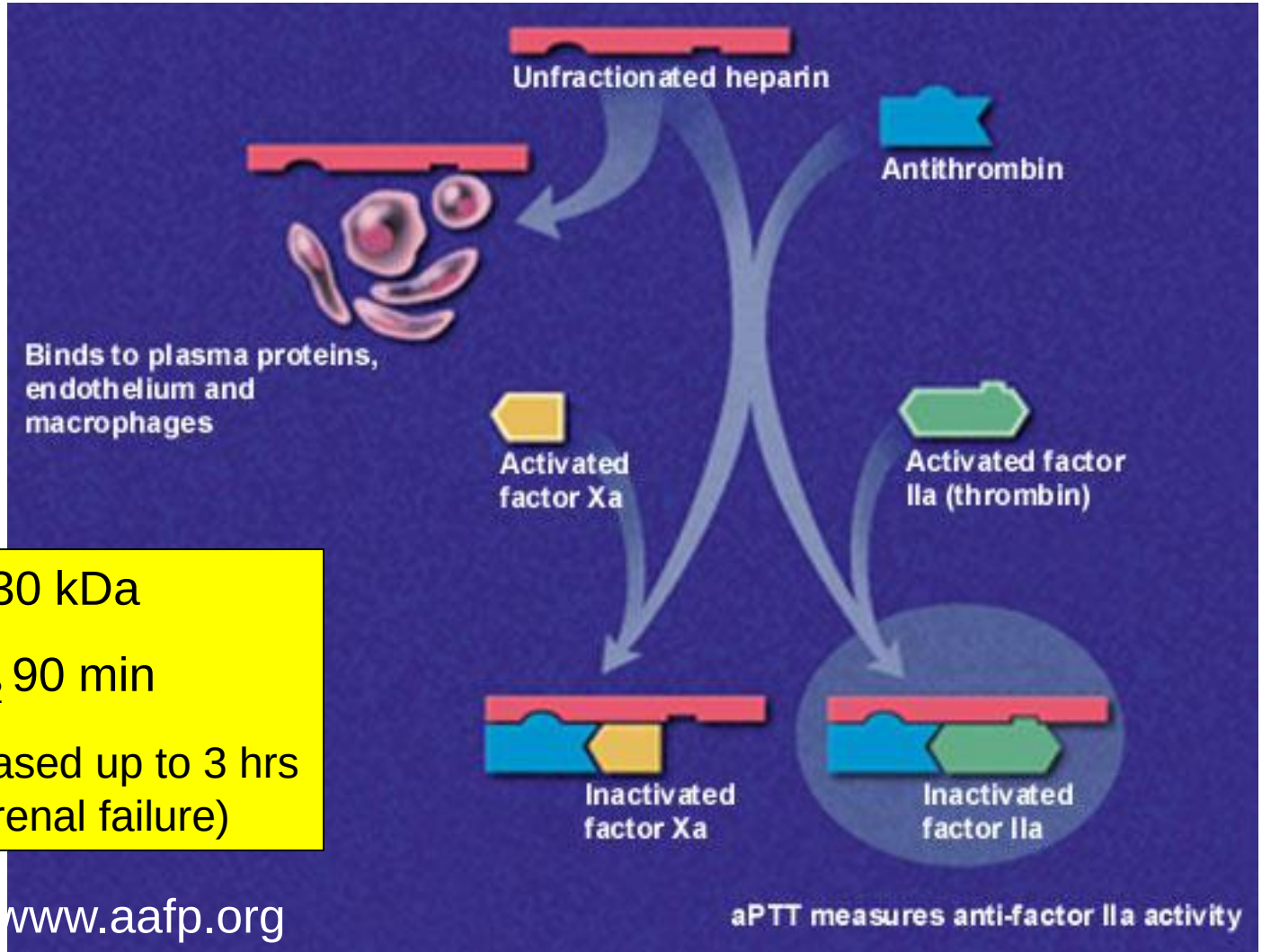
Clotting of Filter and Circuit

- Circuit Factors
  - Filtration Fraction
  - De-aeration chamber
- Vascular Access
- Insufficient Anticoagulation

Anticoagulation Options

- Heparin
- Citrate
- Other options
  - Regional heparin with protamine
  - LMWH
  - Thrombin inhibitors
    - Hirudin
    - Argatroban
    - Bivalrudin
  - Prostacyclin
  - Nafamostat

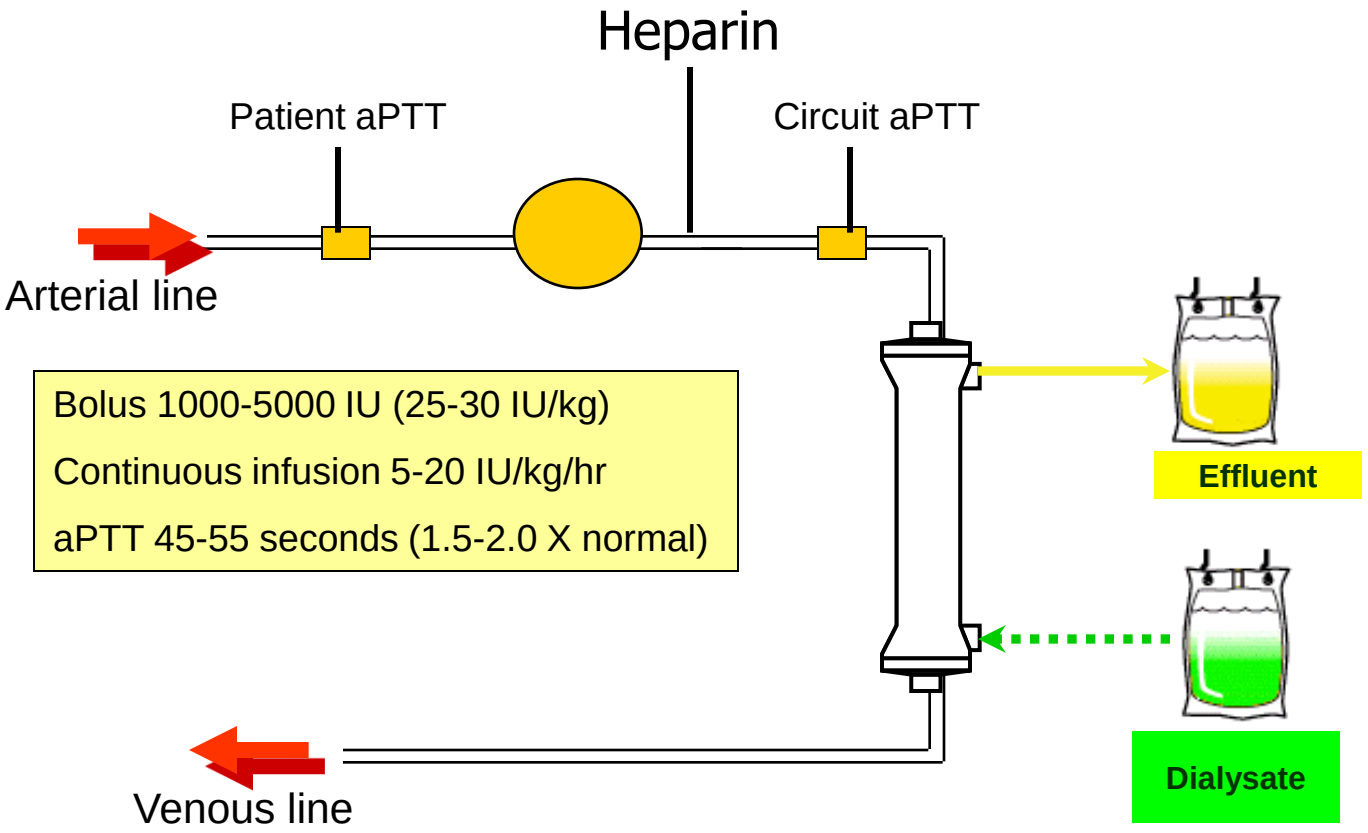
Unfractionated Heparin (UFH): Mechanism



- 5-30 kDa
- $t_{1/2}$ 90 min

(increased up to 3 hrs in renal failure)

UFH Protocol



UFH

Advantages

- Effective
- Widely available
- Simple monitoring (aPTT)
- Reversed with protamine
- Inexpensive
- Short half life

Disadvantages

- Systemic bleeding
- Unpredictable kinetics
- PTT not reliable predictor for bleeding
- Heparin resistance due to low patient antithrombin levels
- HIT

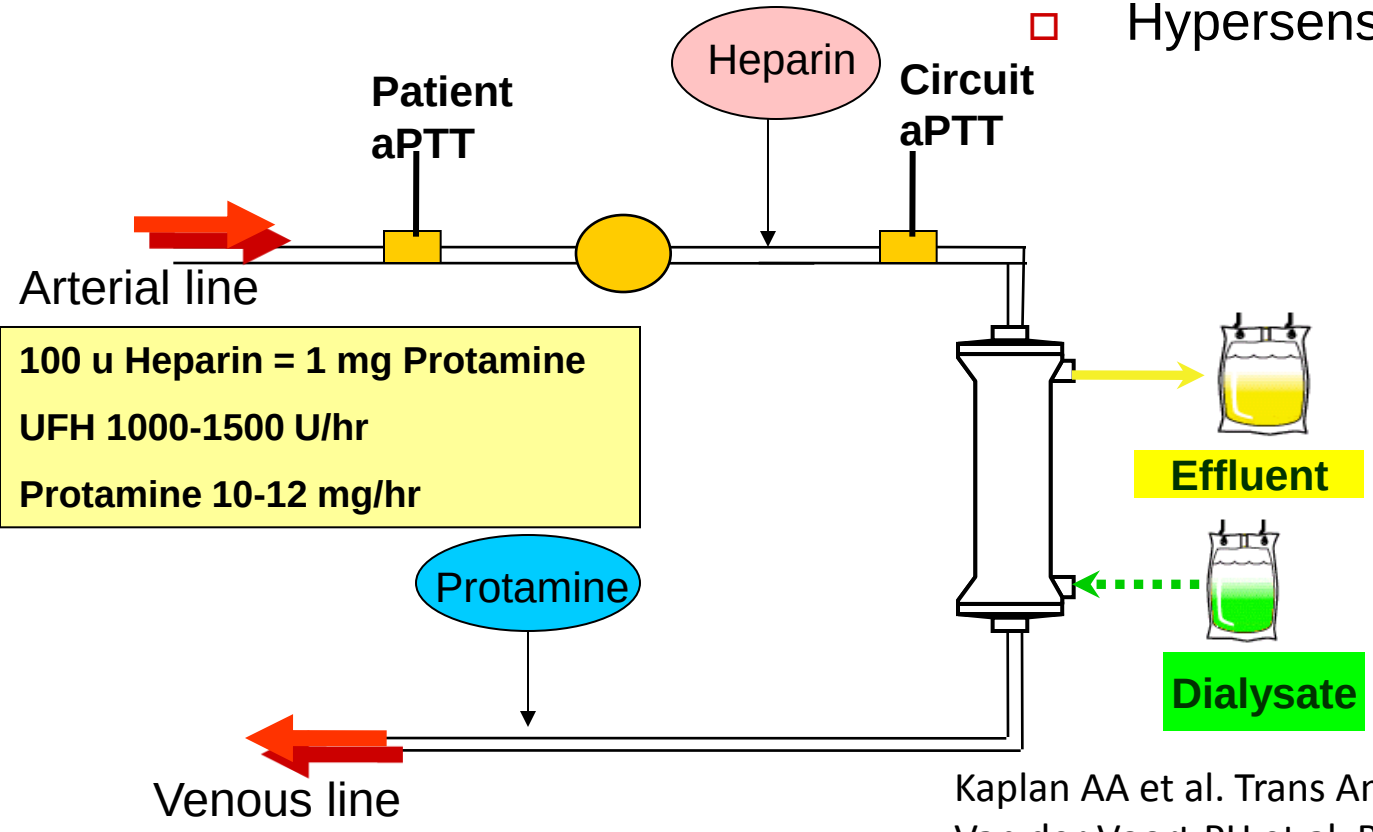
UFH – Protamine Regional Anticoagulation

Advantages

- Anticoagulation effects restricted to extracorporeal circuit

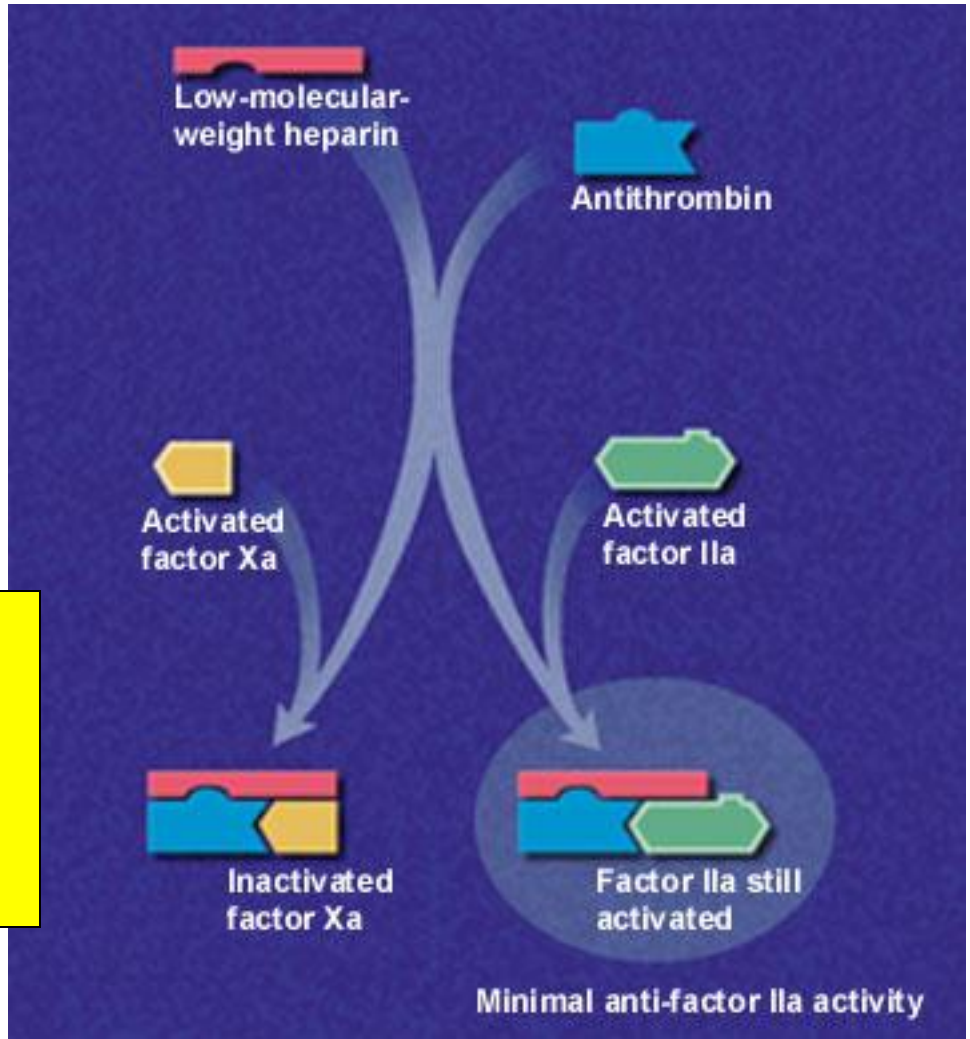
Disadvantages

- Rebound (instable heparin-protamine complex)
- Hypotension
- Hypersensitivity



Kaplan AA et al. Trans Am Soc Artif Organs 1987
Van der Voort PH et al. Blood Purif 2005

Low Molecular Weight Heparin (LMWH): Mechanism



- 4.5-6 kDa
- $t_{1/2}$ 2-4 hrs

(increased in renal failure)

LMWH Protocols

- Fixed dose vs. dose based on anti-Xa
- Target anti-Xa level 0.25-0.35 U/ml
- Enoxaparin
  - Loading dose 0.15 mg/kg
  - Maintenance dose 0.05 mg/kg/hr
  - Mean filter life 31 hrs
- Nadroparin, dalteparin
  - Loading dose 15-25 IU/kg
  - Maintenance dose 5-10 IU/kg/hr
  - Median filter life 18-50 hrs

Pont AC de et al. Crit Care Med 2000
Reeves JH et al. Crit Care Med 1999
Journois D et al. Ann Fr Anesth Reanim 1990
Joannidis M et al. Intensive Care Med 2007

LMWH

Advantages

- Effective
- Predictable pharmacokinetics
- Lower incidence of HIT
- Less effect on lipids

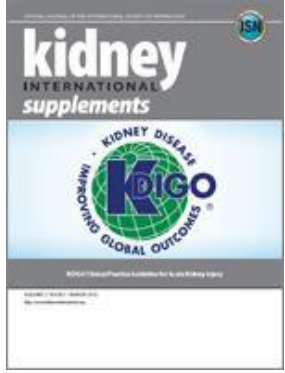
Disadvantages

- Systemic bleeding
- Only partially reversed with protamine
- anti Xa activity not everywhere available
- Expensive

Dosing

Anticoagulant	Loading dose	Rate	Monitoring
Heparin 500 units/mL	2500-5000 units	5-10 units/kg/hr	Target aPTT 1-1.4 times control Or pre-filter systemic aPTT 45-55 sec
Enoxaparin	0.15 mg/kg	0.05 mg/kg/hr	Target anti Xa 0.25-0.35
Dalteparin	15-25 units/kg	5 units/kg/hr	Target anti Xa 0.25-0.35
Argatroban	250 mcg/kg	2 mcg/kg/min	Target aPTT 1.5-3 times baseline Reduce initial dose to 0.5 mcg/kg/min in the setting of liver failure

AKI Guideline 5.3

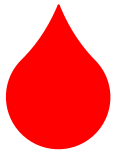


- 5.3.2: For patients without an increased bleeding risk or impaired coagulation and not already receiving effective systemic anticoagulation, we suggest the following:
  - 5.3.2.2: For anticoagulation in CRRT, we suggest using regional citrate anticoagulation rather than heparin in patients who do not have contraindications for citrate. (2B)
- 5.3.3: For patients with increased bleeding risk who are not receiving anticoagulation, we suggest the following for anticoagulation during RRT:
  - 5.3.3.1: We suggest using regional citrate anticoagulation, rather than no anticoagulation, during CRRT in a patient without contraindications for citrate. (2C)

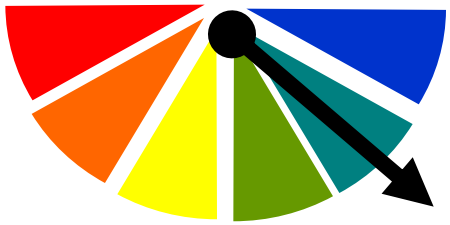
Citrate vs. Heparin Anticoagulation: Updated Meta-analysis of RCTs

11 RCTs with 992 patients

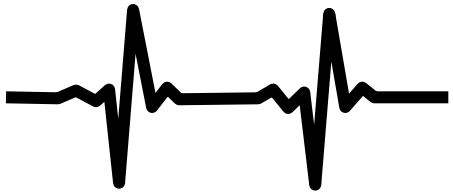
Less circuit loss
Compared to regional (HR 0.52, P=0.001) and systemic (HR 0.76, P=0.04) heparin



Less bleeding
Compared to the systemic heparin group (RR 0.36, P<0.001)



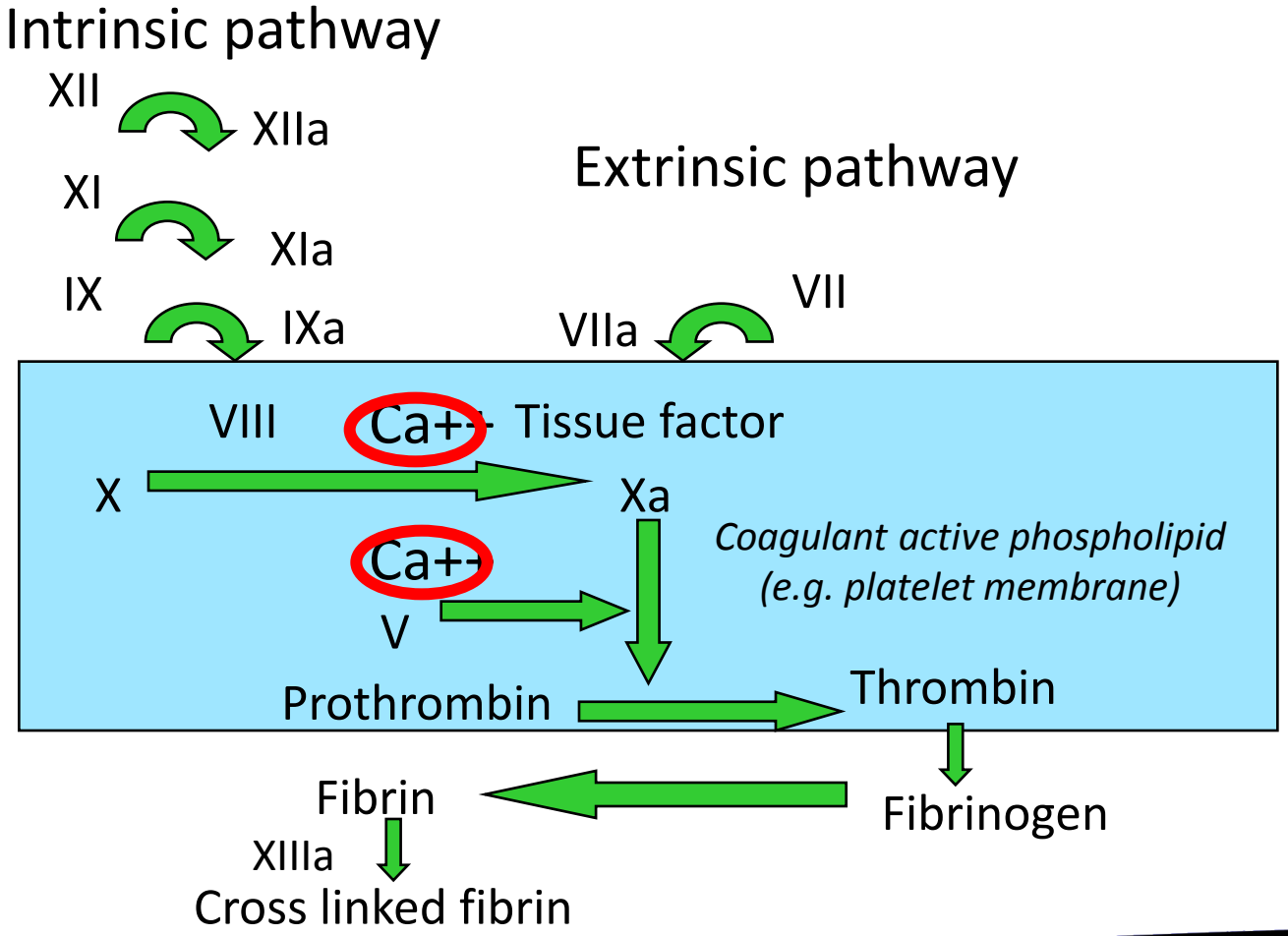
No change in metabolic alkalosis
(RR 1.39, 95% CI 0.40-4.85, P=0.60)



No change in mortality
(HR 0.80, 95% CI 0.61-1.04, P=0.10)

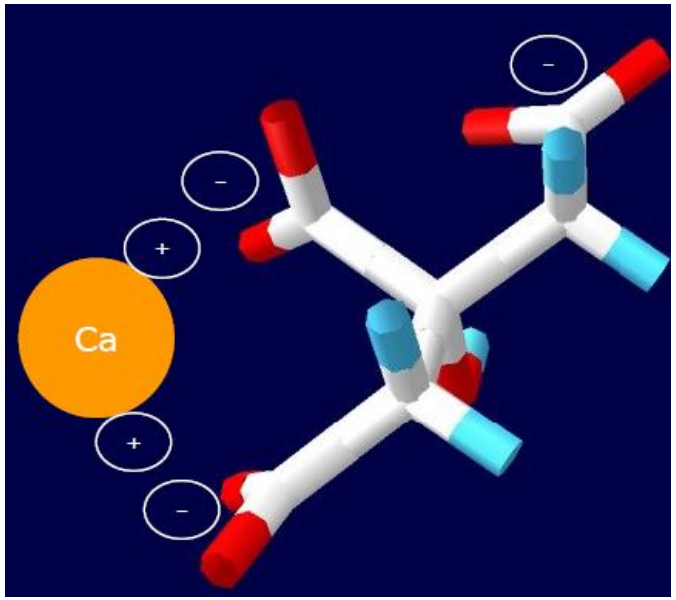
Bai M, *et al*. Intensive Care Med 2015;41:2098-2110

Citrate Anticoagulation



Citrate Anticoagulation

- Chelates free Ca^{+2} in extracorporeal circuit
- Prevents activation of Ca^{+2}-dependent procoagulants
- Anticoagulant effect measured by iCa^{+2}
- Anticoagulation reversed by Ca^{+2} infusion



Citrate + iCa → Calcium citrate

Biologically inactive
measurable as total Ca

Citrate Metabolism

- Citric acid has plasma half life of 5 mins
- Rapidly metabolized by liver, kidney and muscle cells

$$Na_3Citrate + 3H_2CO_3$$

$$\updownarrow$$

$$Citric\ Acid + 3NaHCO_3$$

$$\downarrow$$

$$3H_2CO_3 + H_2O + 3NaHCO_3$$

$$\updownarrow$$

$$4H_2O + 6CO_2$$

Flanagan MJ et al. *AJKD* 27: 519-24, 1996

Citrate

- Normal blood levels of citrate: 0.05 mmol/L
- Bleeding time $\rightarrow \infty$ at citrate levels of 4 to 6 mmol/L ($iCa^{2+} < 0.35$ mmol/L)
- Levels of 12 to 15 mmol/L required for stored blood products for transfusion therapy

Clearance of Citrate

- Extracorporeal clearance
  - Clearance same as urea
  - Sieving coefficient 0.87- 1.0
  - CVVH = CVVHD clearance
  - Depends on citrate concentration in the filter and filtration fraction

Chadha V et al. Pediatr Nephrol 2002, 17:819-824

Citrate

- Advantages
  - Regional, avoids bleeding complications
  - Doubles as buffer
  - Highly effective in studies (> heparin)
  - No thrombocytopenia

- Disadvantages
  - Metabolic complications
  - Complex protocols

Metabolic Consequences

- Metabolic alkalosis
  - Citrate overdose/toxicity
- Metabolic acidosis
  - Citrate toxicity in setting of severe liver disease or hypoperfusion
- Hypernatremia
  - Hyperosmolar citrate solutions
- Hypocalcemia and hypercalcemia
  - Inappropriate calcium supplementation
- Hypomagnesemia

Citrate Toxicity

- Risk Factors
  - Hepatic dysfunction
  - Cardiogenic shock
  - Septic shock
  - Inadvertent overdose
- Detection
  - Worsening metabolic acidosis
  - Elevated total calcium
  - Decreased Ionized calcium → increasing Ca++ infusion requirement
  - Total Calcium: Ionized Calcium ratio >2.5 (if both mmol/L)

Calcium Gap

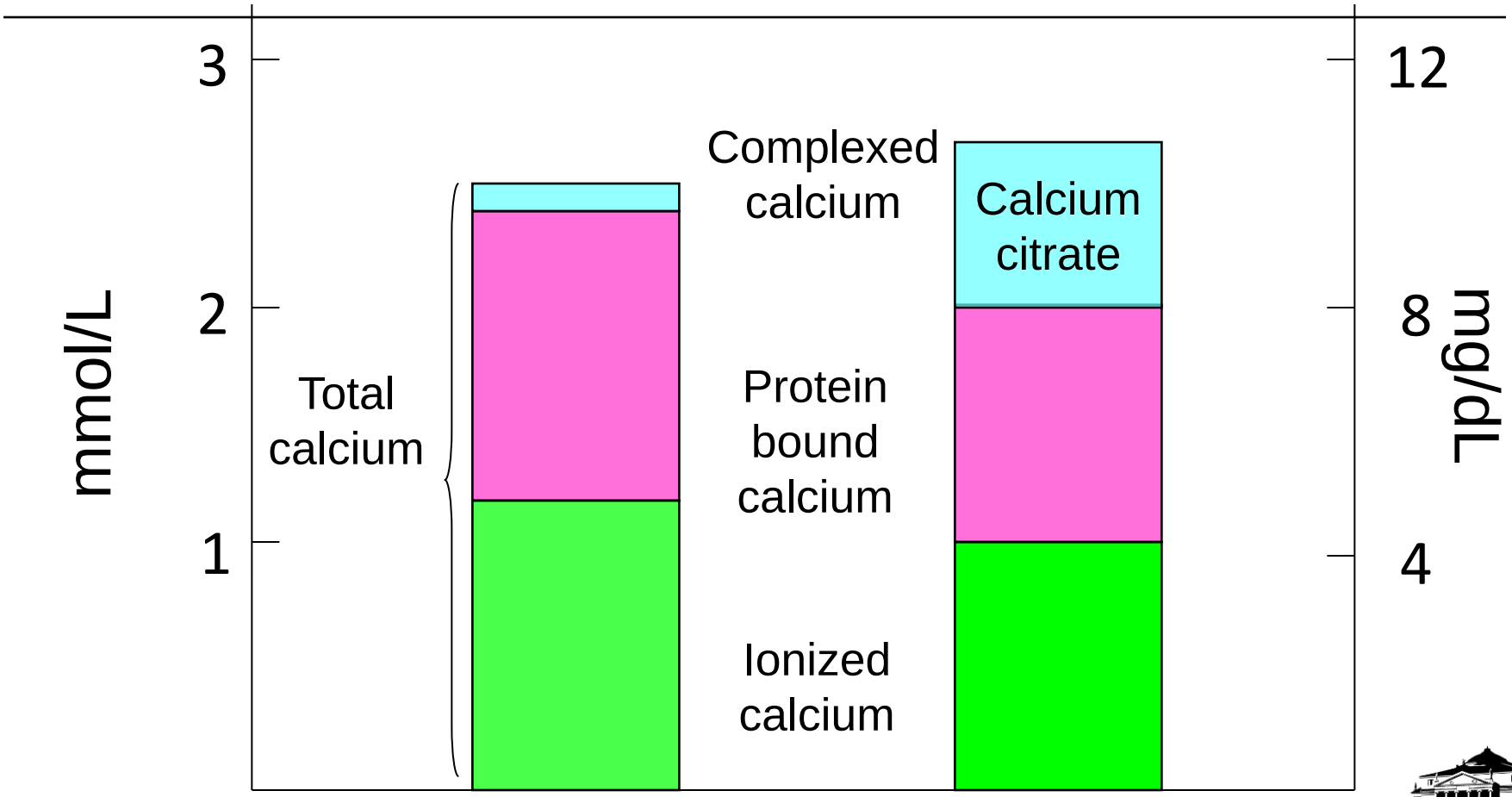

mmol/L
3
2
1
12
8
4
mg/dL
Total calcium
Complexed calcium
Protein bound calcium
Ionized calcium
Calcium citrate

Table 1 Citrate accumulation and alternative diagnoses: summary table

	Citrate accumulation	Citrate net overload	Insufficient trisodium citrate delivery
Mechanism	Incomplete citrate metabolism: persistence of circulating citrate–calcium complexes in the blood	Excess citrate administration relative to buffer requirements	Insufficient alkalotic load administered to the patient to adequately buffer acute kidney injury-associated acidosis
Diagnosis			
Acid-base	Metabolic acidosis	Metabolic alkalosis	Metabolic acidosis
Ca_{tot}/Ca_i ratio	Increased (>2.5)	Normal (< 2.5)	Normal (< 2.5)
Other	Increased need for calcium substitution Trend for a decreased ionized calcium level	None	None
Appreciation	Potentially lethal (via severe hypocalcemia)	Benign and easy to fix	Benign and easy to fix
Incidence	Rare	Common	Rare
Management	Decrease blood flow or increase dialysate flow rate (if mild) Consider alternative anticoagulation strategy	Decrease blood flow or increase dialysate flow rate	Increase blood flow or decrease dialysate flow rate

Schneider et al. Critical Care (2017) 21:281

Which Citrate Protocol?

- Citrate solutions
- Method of citrate delivery
- CRRT circuit options

Commercial Citrate Solutions

Components	4% Sodium citrate	ACD A: 2.2% Sodium citrate	Prismocitrate ™(10/2)	Prismocitrate™ (18/0)	Citra-HF Pre® (Dirinco)
Sodium (mmol/L)	408	225	136	140	139.9
Trisodium Citrate (mmol/L)	136	75	10	18	13.3
Citric Acid (mmol/L)	-	38	2	-	
Dextrose (mmol/L)	-	124	-	-	5
Bag Size (mL)	1000	500 & 1000	5000	5000	5000

Citrate Protocols

	Citric Acid mmol/L	Sodium Citrate mmol/L	Complementary solution	Therapy	BFR mL/min	Citrate dose (mmol/L blood)	Country
Apsner	5	10	-	CVVH	100	**3.7**	Austria
Dorval / Leblanc	5	15	Dia: 0.9% Saline (if needed)	CVVH(DF)	125	**3.7**	Canada
Niles	-	13.3	-	CVVH	180	**2.0**	USA
Gabutti	-	13.3	Dialysate same as citrate	CVVH(DF)	125	**2.66**	Switzerland
Tolwani	-	2%	0.9% Saline	CVVHD	150	**2.0**	USA
Gupta	ACD-A		Calcium in dialysate	CVVHDF	150	**1.9**	USA
Cointault	ACD-A		Calcium in dialysate & pre	CVVHDF	125	**3.9**	France
Kustogiannis / Gibney	-	3.9%	Dia: Na=110, Bicar=variable	CVVHDF	125	**3.6**	Canada
Mehta	-	4%	Dia: Na=117, Bicar=0	CVVHD(F)	100	**3.7 - 5.9**	USA
Hoffmann	-	4%	Pre: 0.9% Saline	CVVH	125	**3.1**	USA
Monchi	-	1000	Post: Na=120 , Bicar=0	CVVH	150	**4.3**	France
Evenepoel	-	1035	Calcium in dialysate	IHD	300	**4.3**	Belgium

Despite the different citrate formulations used, the amount of citrate delivered in the blood for adequate anticoagulation is the same:
2 to 6 mmol/L or ica < 0.35 mmol/L

Citrate Delivery: Fixed

QB (mL/min)	4% TSC (mL/hr)	ACD-A (mL/hr)
100	175	210
125	218	262
150	262	315
200	350	420

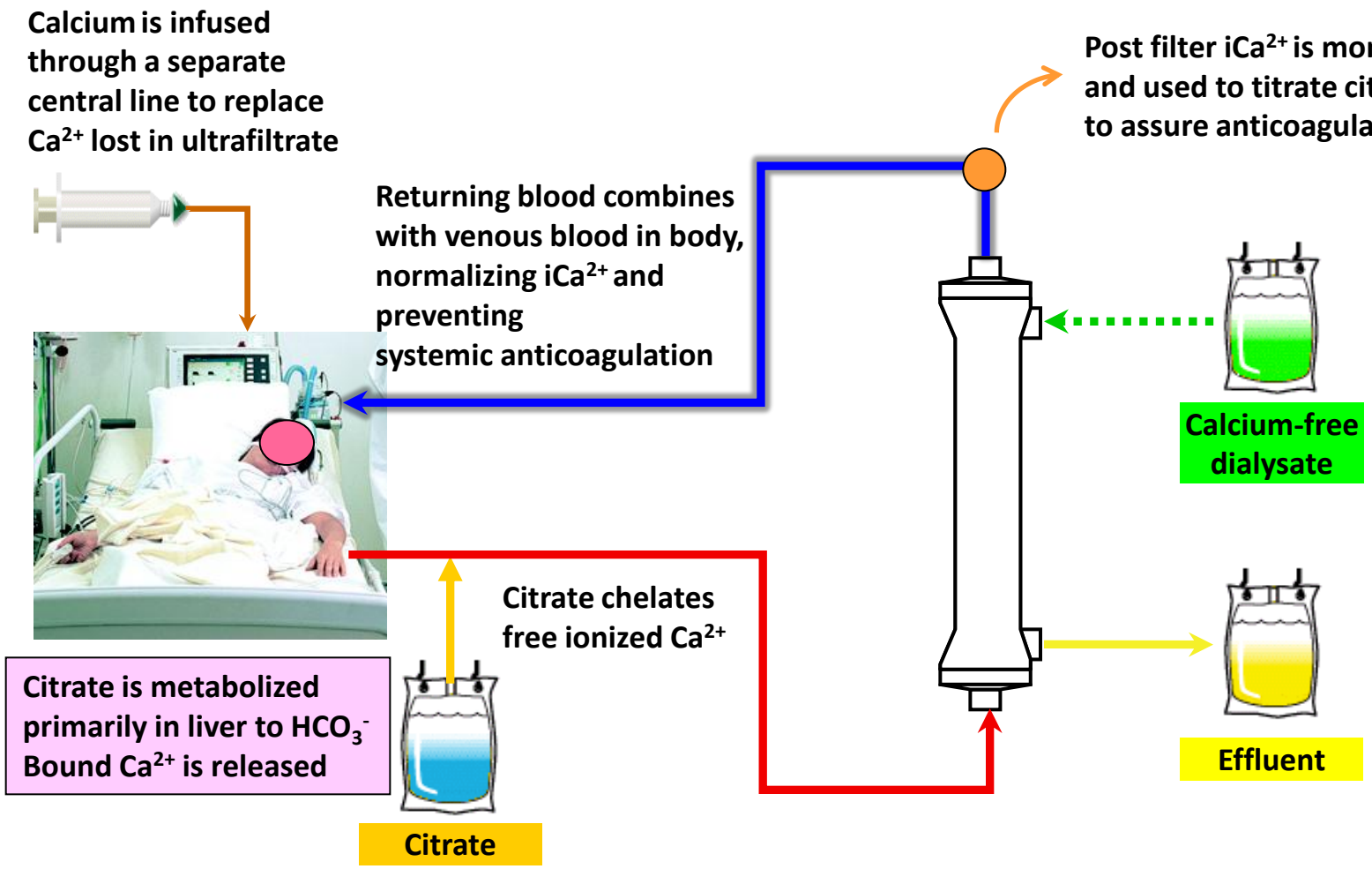
Amount of citrate delivered to achieve blood citrate concentration of 4 mmol/L

QB (mL/min)	4% TSC (mL/hr)	ACD-A (mL/hr)
100	132	159
125	165	200
150	199	239
200	265	319

Amount of citrate delivered to achieve blood citrate concentration of 3 mmol/L

Flanagan MJ et al. AJKD 27: 519-24, 1996

Citrate Anticoagulation in CRRT: Regional Effect in the Circuit



Monitoring

- Circuit serum ionized calcium q 6-8^{H}
  - keep 0.25-0.35 mmol/l (1.0 – 1.4 mg/dL)
- Patient serum ionized calcium q 6-8^{H}
  - keep 1.1-1.3 mmol/l (4.4 – 5.2 mg/dL)
- Serum Total Ca, PO_4 and Mg q 12 -24^{H}

Summary

- Anticoagulation is a requirement for optimal function of CRRT circuit
- NO anticoagulation associated with
  - Decreased filter life
  - Inadequate delivered dose of CRRT
- Advantages of citrate over heparin
  - Increased filter life
  - Decreased bleeding risk
- Disadvantages of citrate
  - Complexity of regimen and monitoring
  - Metabolic abnormalities
  - Citrate toxicity