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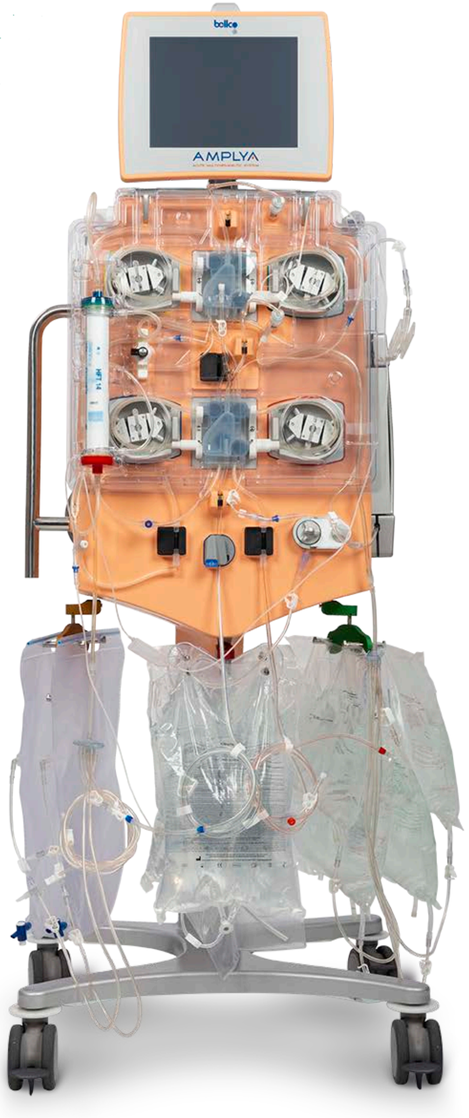
Empowering patients. Enriching lives.

Citrate 20/4 and Amplya

Acute Multitherapeutic System™



Contents

Basic principles

Mozarc Medical proposition

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Anticoagulation in AKI

What is available

- Continuous Renal Replacement Therapy (CRRT) is the most widely used method in Acute Kidney Injury (AKI) in severely compromised patients and in whom prolonged use of anticoagulation is a problem to be considered[3].

- In CRRT the strategies for the anticoagulation of the extracorporeal circuit are based on the use of different substances [1]:

- Heparin (unfractionated);

- Low molecular weight heparin;

- Locoregional circuit: heparin - protamine sulphate;

- Argatroban;

- Regional Citrate Anticoagulation (RCA);

- CRRT are managed also without anticoagulant.

Although bleeding complications have a highly variable incidence in the various cases reported in some metanalysis[2], the risk of bleeding induced using heparin (which has a systemic action) must always be taken into high consideration.

RCA is an attractive anticoagulation mode in CRRT because it restricts the anticoagulatory effect to the extracorporeal circuit. In the last years, several randomized controlled trials have been conducted to investigate its superiority over other anticoagulation modes[3], also considering its action is carried out at a local-regional level (within the dialysis circuit).

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Anticoagulation in AKI

Citrate & guidelines

- The use of RCA in numerous studies (randomized controlled trials, RCT) was an effective and safe method, when compared with other anticoagulation methods, guaranteeing in particular [4]:
- The reduction of bleeding episodes in patients at risk (patients undergoing surgery and/or cardiac surgery, or in subjects with polytrauma);
- The prolonged extracorporeal circuit life;
- Reducing the incidence of hemorrhagic complications;
- Lowering transfusion needs (due to the reduction in bleeding episodes during systemic anticoagulation);
- Its use in case of heparin intolerance

The international KIDGO (Kidney Disease Improving Global Outcomes) guidelines for anticoagulation in CRRT suggests using RCA rather than heparin in patients who do not have contraindications for citrate[1]

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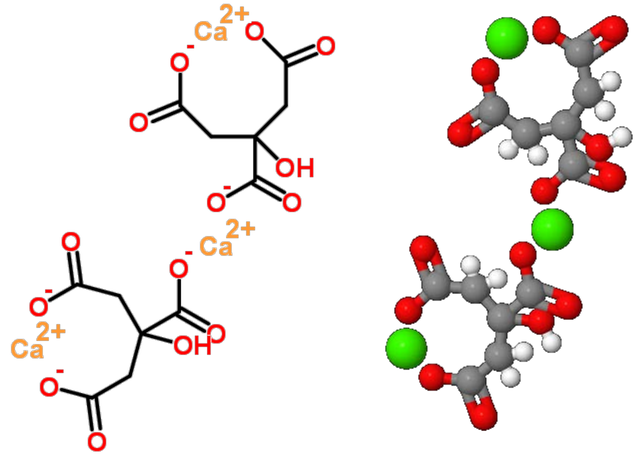
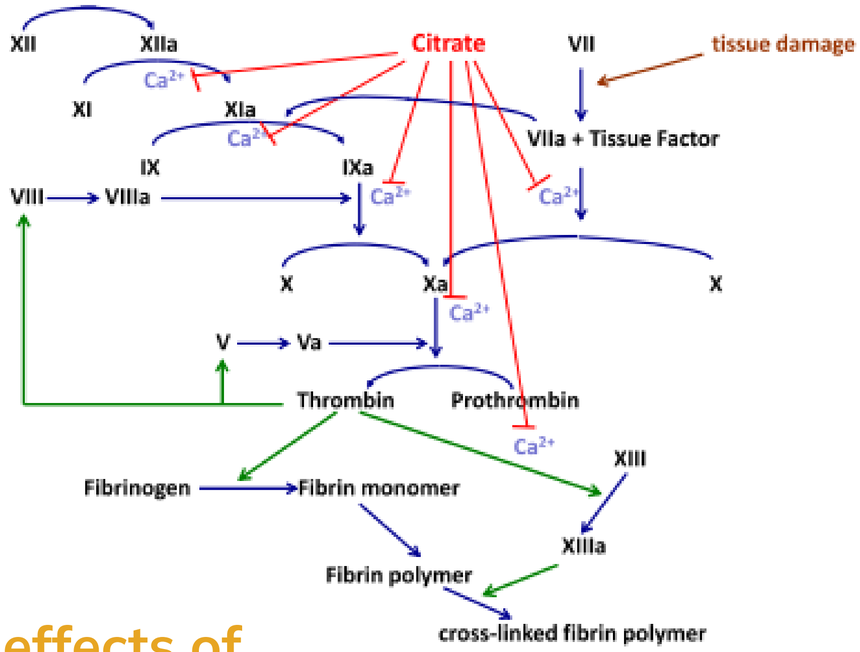
Citrate

What is this

- Citrate is a small (negatively charged) anion (citrate: 191 Dalton; tri-sodium citrate: 258 Dalton) and is dialyzable[5]
- Citrate is essentially a regional extracorporeal anticoagulant, with a short systemic half-life (about 5 minutes), metabolized essentially by the mitochondria of the liver, skeletal muscles and kidneys, with a metabolic half-life of 60 ± 29 minutes[6]
- Citrate chelates calcium[5]
- The removal of calcium from the extracorporeal system inhibits clotting[5]
- When the citrate is metabolized, each molecule yields three molecules of bicarbonate, which will have an impact on the acid-base status[5]





Known effects of citrate on clotting pathways

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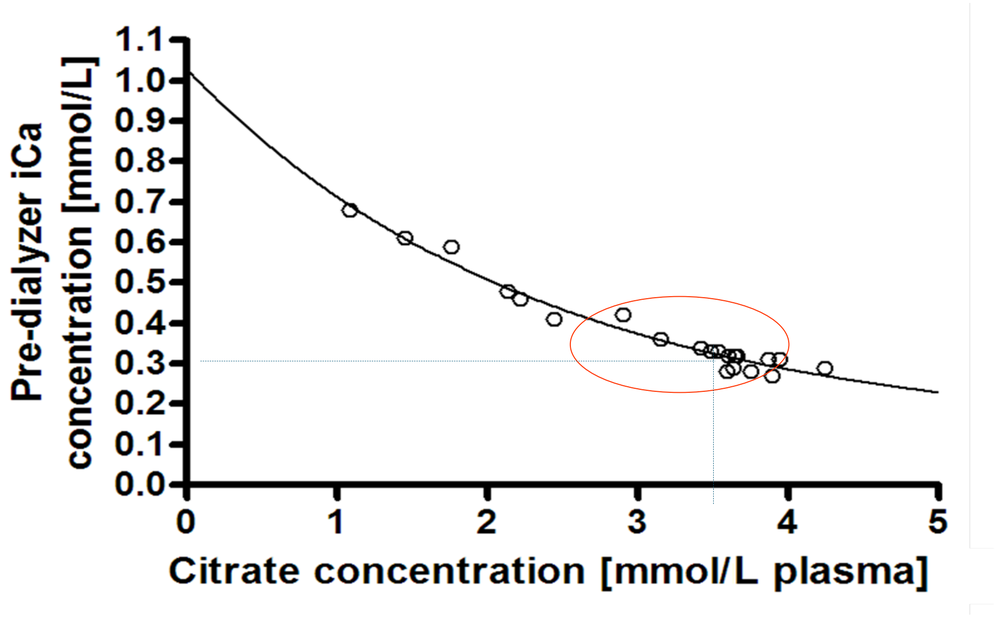
Citrate

How does it work?

A plasma citrate concentration of >3.5 mmol/l is typically required to bring ionized Calcium (iCa) levels to below 0.3 mmol/l. **The exact citrate concentration necessary depends mainly on the individual patient's plasma calcium and protein (primarily albumin) concentrations**[7]



During the CRRT treatment, a significant percentage of calcium-citrate complexes (but also citrate – magnesium), which are formed within the extracorporeal circuit, are lost with the effluent (post-filter section). Therefore, the effect of citrate is expressed in its almost totality within the dialyzer[5].

Finally, to restore calcium losses, at the end of the circuit, before the blood returns to the patient, a solution containing calcium chloride (Cl^2 - Ca^{2+}) is infused, so as to bring the plasma concentration of ionized calcium back to a normal range and reactivate the coagulatory cascade at the level of the systemic circulation[5].

The reduced bleeding risk that occurs with the use of citrate derives precisely from the fact that its activity takes place only within the extracorporeal circuit, unlike heparin, which instead has a systemic action[6].

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Citrate

How to use it?

Several protocols use citrate concentrations in the extracorporeal circuit ranging from 3 to 6 mmol/l, in order to keep the ionized calcium concentration before the filter in the range 0.25 - 0.35 mmol/l[8], since the anticoagulant capacity of citrate is ineffective when the ionized calcium levels in the circuit are >0.5 mmol/l[9]

2 possible formulas are[8-10]:

$$\text{Conc. [cit. Blood]} = \frac{\text{Conc. [cit. Bag]} \times \text{QCit}}{\text{QB}}$$

- **Conc. [Cit. Blood]**: concentration of citrate in the blood expressed in mmol/l;
- **Conc. [Cit. Bag]:** concentration of citrate in the bag expressed in mmol/l;
- **QCit:** infusion flow of the citrate-containing solution liquid, expressed in ml/h;
- **QB**: flow of treated blood, or the amount of blood treated in the unit of time expressed in ml/h.

$$\text{Conc. [cit. Blood]} = \frac{\text{Qpre} \times \text{Conc. [cit.Bag]}}{\text{Qpre} + \text{QB}\ (1 - \text{HT}/100)}$$

- **Conc. [Cit. Blood] :** concentration of citrate in the blood expressed in mmol/l
- **Qpre:** infusion flow of the solution containing citrate expressed in ml/h
- **Conc. [Cit. Bag]:** concentration of citrate in the bag expressed in mmol/l
- **QB:** flow of treated blood, or the amount of blood treated in the unit of time expressed in ml/h
- **HT**: hematocrit

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Citrate

Plasma concentration

$$\text{Conc. [cit. Blood]} = \frac{\text{Qpre x Conc. [cit.Bag]}}{\text{Qpre + QB (1 - HT/100)}}$$

- **Conc. [Cit. Blood]:** concentration of citrate in the blood expressed in mmol/l
- **Qpre:** infusion flow of the solution containing citrate expressed in ml/h
- **Conc. [Cit. Bag]:** concentration of citrate in the bag expressed in mmol/l
- **QB:** flow of treated blood, or the amount of blood treated in the unit of time expressed in ml/h
- **HT**: hematocrit

This formula is based on the concept that citrate does not interact with the corpuscular component of the blood[10].

The percentage of corpuscles in the blood is defined hematocrit, a value calculated as the ratio between the corpuscular part, consisting of white blood cells, red blood cells, platelets (red blood cells are the most represented part) and the liquid part (plasma).

Under normal conditions, the corpuscular part in humans is 45%, while the liquid part is 55%; in women this ratio is 40% and 60%. For this reason, the value 1- HT/100 is inserted in the calculation of citrate concentrations in order to consider the diffusion of citrate only in the liquid component, i.e. plasma water.

This formula is based on a study from 1981, which showed that citrate was not permeable to the erythrocyte membrane and therefore had an exclusively plasma-extracellular distribution[11].

In 2012, a study evaluated the efficacy and safety of a CVVH protocol, using solutions with low concentrations of citrate in critically ill patients with acute renal failure after cardio-surgical procedures[3]. In this study, the authors use a mathematical model to estimate the pre-filter citrate concentration in the blood, specifying that plasma water and not whole blood are used in the formula. The same formula was then used in two other studies on the use of RCA [10,12]

Citrate

Complications[5]

Metabolic abnormalities can result from RCA due to the buffering capacity of citrate, the high sodium content of the citrate solutions, and the loss of calcium bound to citrate in the effluent. The electrolyte abnormalities associated with citrate anticoagulation include alkalosis, acidosis, hypernatraemia and hypo- and hypercalcaemia.

Metabolic acidosis

Patients with severe liver failure and lactic acidosis may have difficulty with citrate metabolism and develop citrate toxicity, which is characterized by low systemic iCa^{2+} elevated total serum calcium, metabolic acidosis and an increased anion gap.

The accumulation of citrate causes the systemic iCa^{2+} concentration to fall, whereas the bound fraction of calcium rises. If the calcium infusion is increased to correct the low iCa^{2+}, most of the calcium is bound to citrate. A disproportional rise in total Ca^{2+} occurs, while iCa^{2+} remains low.

Acidosis can occur not only due to failure to metabolize citrate through to bicarbonate, but also due to the continued losses of bicarbonate and calcium citrate complexes in the dialysate effluent/filtrate.

Metabolic alkalosis

Metabolic conversion from accumulated citrate can result in an excessive alkali load. The risk of developing a metabolic acidosis depends upon the amount of citrate infused.

In routine clinical practice, the risk of developing alkalosis is dependent upon the blood flow and citrate load, with some reports of up to 50% of patients developing a metabolic alkalosis.

Alkalosis can be managed by either decreasing the blood flow rate, and so allowing a decrease in the citrate infusion rate into the patient, or by decreasing the infusion of citrate, or additionally by increasing citrate and bicarbonate losses in the dialysate effluent by increasing the dialysate flow.

Citrate toxicity

Why and when?

Citrate is metabolized predominantly in the mitochondria in the liver, skeletal muscle and kidney. Thus, patients with AKI treated by CRRT rely on hepatic and skeletal muscle metabolism. Thus, citrate metabolism may be compromised in patients with cardiogenic shock with reduced hepatic and muscle blood flow.

In addition, patients with acute liver failure, particularly fulminant hepatic failure, cannot adequately metabolize citrate and become acidotic due to continued bicarbonate and citrate losses into the dialysate/filtrate.

Although severe myositis or rhabdomyloysis is unlikely to cause significant citrate toxicity, provided liver function is adequate, muscle injury can cause hypocalcaemia.

Most centres now monitor and regulate citrate anticoagulation by measuring systemic ionized calcium. As the ionized calcium falls in rhabdomyloysis, this can then lead to escalating systemic calcium infusion, which may later result in increased muscle damage in survivors due to calcium deposition, and a reduction in citrate infusion with increased risk of circuit clotting.

Other conditions associated with hypocalcaemia include severe pancreatitis, post-tumour lysis and toxic shock[5]

The cardinal features of citrate toxicity are[13]:

- High anion gap metabolic acidosis *OR* metabolic alkalosis
- Low ionised calcium with a high (or normal) total calcium

The predisposing factors include[13]:

- Liver disease (unable to metabolise the lactate)
- Lactic acidosis
- Coagulopathy (requirement for regional anticoagulation of the extracorporeal circuit)
- Heparin - Induced Thrombocytopenia (HIT) or any other contraindication to the use of heparin
- Hypocalcemia
- Decreased hepatic blood flow (eg. in sepsis or other shock states)

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Citrate toxicity[14]

Which type?

Citrate accumulation is a feared and potentially lethal complication of RCA.

In order to avoid unnecessary therapy interruptions, it is essential for the clinician to distinguish citrate accumulation from other situations resulting in acid-base disturbance during RCA: citrate net overload and insufficient trisodium citrate delivery. The main differences between these entities are summarized in Table 1.

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

Well-designed protocols should aim to minimize citrate delivery to patients. This goal can be achieved by combining several measures.

Limited blood flow should be used. Indeed, since citrate administration is coupled to blood flow, lower blood flow means less need for citrate. This can easily be achieved in diffusion-based modes.

In **diffusive modes**, low blood flows do not translate into low blood purification for two reasons:

1) Dialysate rate remains the limiting factor
2) **High flux membranes** are preferred for RCA, allowing important clearance even with reduced blood flows.

Purely **convective techniques** can be used but with a higher risk of metabolic complications. Indeed, the combination of low blood flows (to limit citrate administration) and high filtration rates would lead to high filtration fraction, increasing the risk of membrane clogging and decreased Citrate-Calcium complexes clearance. This issue can be minimized if **diluted citrate solutions are used as predilution**.

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Citrate toxicity

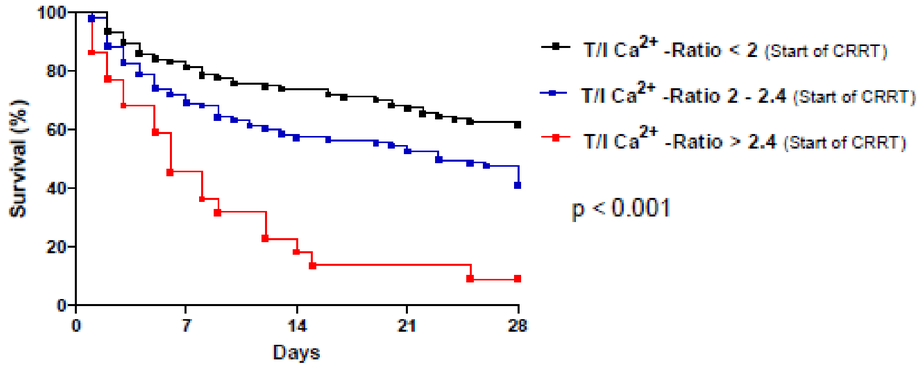
How can you calculate it?

Once a steady-state citrate concentration is achieved, a normal ionized calcium concentration can be achieved by an increased total calcium concentration because a fraction of the ionized calcium is chelated by circulating systemic citrate.

The total-to-ionized calcium ratio (T/I Ca^{2+} ratio) should be directly proportional to the concentration of serum citrate.

Therefore, impaired hepatic citrate metabolism leads to citrate accumulation and increases T/I Ca^{2+} ratio with normal ionized calcium. Thus, citrate accumulation is indicated indirectly by an elevated T/I Ca^{2+} ratio. Patients with hepatic or multi-organ dysfunction (or both) can develop citrate accumulation characterized by low ionized calcium, elevated total calcium, and metabolic acidosis[15].

In critically ill patients undergoing CRRT with RCA, an increased T/I Ca^{2+} ratio in about 33% of patients with severe hepatic impairment was found[16].



In critically ill patients on CRRT-citrate, an elevated T/I Ca^{2+} ratio[15]

- Is an independent predictor for 28-day mortality,
- Is associated with hepatic or multi-organ dysfunction or both,
- Is an indirect marker of systemic citrate accumulation,
- Signals the necessity to decrease the citrate infusion (causing clotting) or increase citrate clearance.

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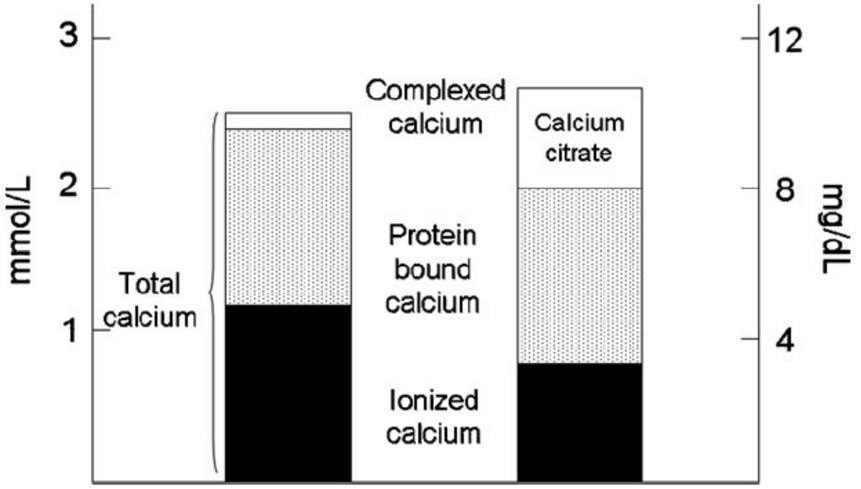
Citrate toxicity

Calcium plasma concentration

Calcium is present in blood plasma in three fractions which are in equilibrium with one another, i.e. the ionized and complex bound calcium which together comprise the diffusible and ultrafiltrable fraction, and the non-diffusible calcium which is bound to the plasma proteins. The ionized calcium is considered to be the physiologically active fraction[17] and must be maintained between 1.0 and 1.25 mmol/l in the patients' blood plasma[5].

With the use of citrate as regional anticoagulant the plasma distribution is influenced in the extracorporeal circuit. Citrate chelates the active, ionized calcium fraction. This results in a decrease of the ionized calcium fraction and an increase of the complex bound calcium in the blood inside the extracorporeal circuit[18].

If citrate cannot be metabolized, then the total serum calcium concentration appears to increase, with a corresponding fall in ionized calcium due to the increase in calcium complexed with citrate, as the calcium–citrate complex is not directly measured it is termed the ‘calcium gap’ as causing an increasing difference between total and ionized calcium[5].



Citrate protocol

Suggestion & monitoring

Although early citrate protocols, adopting a citrate dose of up to 4–6 mmol/l, were characterized by a longer filter survival, it should be underlined that a higher than usual target for ionized calcium (<0.5 mmol/l) in the RRT circuit, obtained by achieving **lower citrate concentration targets in the circuit (2.5–3 mmol/l), is still able to ensure an adequate filter life , and represents a valid strategy in patients at higher risk of citrate accumulation[19].**

Since diffusive and convective transport of citrate is comparable, citrate loss during RCA-CRRT is closely related to total effluent flow rate[19].

An **appropriate setting and subsequent adjustments of the main CRRT parameters are critical to perform a safe RCA** and to modulate buffer supply according to clinical needs, avoiding acid–base and metabolic derangements[19].

RCA requires close monitoring, especially upon initiation of therapy, and management of RCA can prevent some possible side effects[20].

Table 2 Monitoring for early detection of citrate accumulation during RCA

Parameter	Monitoring intensity	Aim and significance
Systemic ionized calcium	Baseline Within 1 h from the start of the treatment and then at least every 4–6 h	To early detect systemic ionized hypocalcemia due to the lack of calcium release from calcium–citrate complexes because of impaired citrate metabolism (after excluding inappropriate calcium replacement)
Systemic total calcium (*simultaneously to systemic ionized calcium*)	Every 12–24 h or more frequently if citrate accumulation is suspected	To calculate the calcium ratio (total to ionized systemic calcium) as an indirect index of citrate accumulation (≥2.5) In the presence of impaired citrate metabolism, a progressively higher calcium infusion rate is required to maintain the systemic ionized calcium concentration within the intended target; the consequent disproportionate rise in total systemic calcium concentration leads to an increase of total-to-ionized calcium ratio
Acid–base parameters (pH, bicarbonate)	Baseline Within 1 h from the start of the treatment and then at least every 4–6 h	To early detect worsening metabolic acidosis due to impaired bicarbonate production related to inadequate citrate metabolism
Serum magnesium	At least every 24 h	To evaluate the need and the amount of magnesium supplementation
Serum sodium	Once daily	To exclude hypernatremia or hyponatremia (rarely observed with a correct matching of RCA solutions) and to prevent sudden increase of serum sodium in chronic liver disease patients with hyponatremia.
Citratemia	Not routinely used for clinical purposes	If available, direct measurement of plasma citrate concentration represents the gold standard to confirm citrate accumulation
Serum lactate	Baseline with subsequent checks scheduled according to clinical	To identify patients at higher risk for citrate accumulation (basal values ≥3.4 mmol/l or upward trend of lactatemia)

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Citrate

Amplya system™ proposition

The choice to administer the low-concentration citrate in predilution is based on some reasoned points which can be summarized as follows[18,21]:

a) The presence of discrete volumes of predilution increases the efficiency of anticoagulation and improves the rheological conditions of the system. In clinical terms, the predilution is reflected in an increased survival of the ongoing CRRT circuit. The slight decrease in creatinine clearance — inherent in the predilution method that dilutes all plasma components, including those exchanged in the dialyzer — does not impact dialysis efficiency in a long, continuous, and low-blood flow method. Furthermore, the increased survival of the circuit and decreased down-time compensate for the potential loss of efficiency.

b) The predilution simplifies the system and allows the use of post-infusion solutions and dialysate at concentrations of electrolytes similar to those in plasma, making them more "physiological." Conversely, the choice of working with citrate supplied with highly hypertonic solutions (trisodium citrate, Na+ 420 mmol/l, citrate 136 mmol/l) requires the use of low-sodium and bicarbonate content solutions for post-infusion and dialysate. This compensation is necessary to prevent hypernatremia and metabolic alkalosis that are generated with the infusion of hypertonic citrate.

Citrate

Amplya system™ proposition - Clinical point of view

- Reasoning in clinical terms, low concentrations of citrate in the extracorporeal circuit seem to be effective in terms of anticoagulation[4].

- The recent observations of an Australian paper[22] confirm and reinforce these conclusions, in the aspects of an appropriate use of predilution and the consequent clinical advantages.

- In this 2-year prospective study, a protocol with an initial citrate of 3 mmol/l (81 sessions, protocol 1), and a protocol with an initial citrate of 2.5 mmol/l (119 sessions, protocol 2) were compared. The work was performed on CVVHDF patients with citrate infusion in predilution at 18 mmol/l.

- From the comparison, it emerged that the extracorporeal circuit clotting rate was similar in both arms (Protocol 1: 9.9%; Protocol 2: 9.2%; P = 0.881), while with Protocol 1 there was a significant increase in hypo calcemic episodes and widened anion gap (indirect index of tendency to accumulate citrate).

The authors conclude that

The RCA protocol with a lower initial citrate dose of 2.5 mmol/l blood had less citrate-related complications with no loss of efficacy. A more precise RCA prescription at the start of treatment avoids unnecessary citrate exposure and improves safety.

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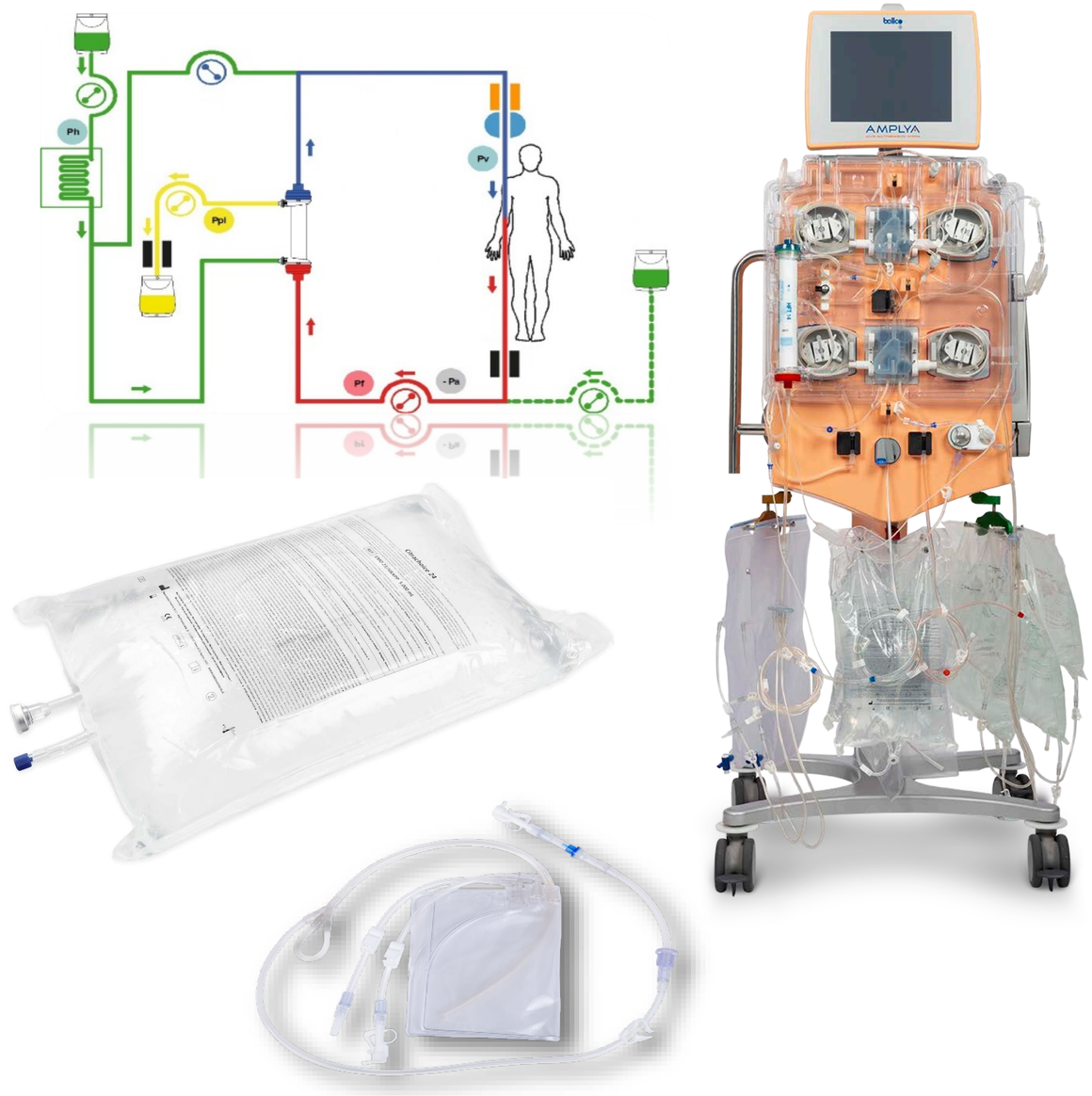
Citrate 20/4 & assisted modality: diluted citrate plasma concentration setting

Amplya system™ proposition[23]

The Amplya system™ offers:

- a **combined plasma assisted citrate modality and 24 mmol/l concentration option** to support to nurse and physician workloads.
- high autonomy of central scale 12 kg (citrate)
- bag changes with running pumps help to maintain the prescribed dose and avoid citrate pump stoppage during the treatment.
- assisted citrate mode that sets all treatment parameters — making it suitable for non-table dependent users
- possibility of using FREE CITRATE mode also referred to as “unassisted" mode
- availability for CVVH, CVVHDF and CPFA treatments



Citrate 20/4 & assisted modality

Amplya system™ proposition - Fluids bags

- RCA requires close monitoring, especially upon initiation of therapy, and management of RCA can prevent some possible side effects, such as metabolic alkalosis (1 mmol of citrate converted to 3 mmol of HCO_3 in the liver), metabolic acidosis (citrate can accumulate if there is liver or skeletal muscle dysfunction), hypocalcemia and hypercalcemia (inadequate control of chelating calcium by citrate or excess infusion of calcium), hypernatremia (when hypertonic trisodium citrate is used), and hypomagnesaemia (from binding to citrate– Ca^{2+} complex)[20].

- The choice to use low-concentration citrate solutions, also known as ‘‘citrate-buffered’’ replacement solutions, can simplify protocols.

- By combining the pre-dilution citrate-buffered solution with a post-dilution replacement fluid, RCA can be performed in pre-post dilution CVVH allowing to separately modulate citrate load and CRRT dose. The ‘‘physiological’’ sodium content and the low citrate concentration of isotonic solutions also avoid the need for customized replacement fluids (lower sodium, lower bicarbonate) specifically formulated for RCA, thus simplifying CRRT handling. In this regard, the adoption of conventional calcium- containing CRRT replacement fluids represents a further simplification that reduces the need for calcium infusion, as well as the risk of errors when calcium-free solutions are handled[19].

Key messages

The use of calcium-containing replacement solutions (CVVH/CVVHDF) does not appear to increase the risk of venous drip chamber clotting during RCA[19]

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Citrate 20/4 & assisted modality

Amplya system™ proposition[23]

In locoregional anticoagulation, the Amplya's **assisted citrate** mode sets treatment data based on patient ideal weight and blood flow:

- Infusion/dialysate flow
- Citrate flow
- Calcium flow

- The machine requires Ca^{2+} value control. It modifies calcium flow relying on value inserted.

- The monitor reminds the operator to select the infusion and citrate bags appropriate for each anticoagulation method.

- In locoregional anticoagulation, the Amplya's **free citrate** mode requires the operator to manually select the appropriate settings for each treatment.

CVVH – STARTING PARAMETERS
TARGET CITRATEMIA 3 mmol/l weight loss 100 ml/h
Hct ~ 35%

Ideal weight (kg)	Qb (range 120-200 ml/min)	Citratemia (mmol/l)	UF flow (ml/h)	CaCl 10% (ml/h)
40	160	3	700	3
50	160	3	900	3
60	160	3	1050	2
70	160	3	1250	2
80	160	3	1400	2
90	160	3	1600	2

	Systemic ionised calcium Ca^{2+}				
	< 0,8 mmol/l	0,8 – 0,99 mmol/l	1,0 – 1,2 mmol/l	1,21 – 1,34 mmol/l	> 1,34 mmol/l
CaCl 10% (ml/h)	+ 2 ml/h	+1 ml/h	No changes	-1 ml/h	-2 ml/h

Usability: With the Amplya system™, the operator can modify treatment parameters by switching from assisted mode to unassisted mode. Operators may then choose to switch back to assisted mode.

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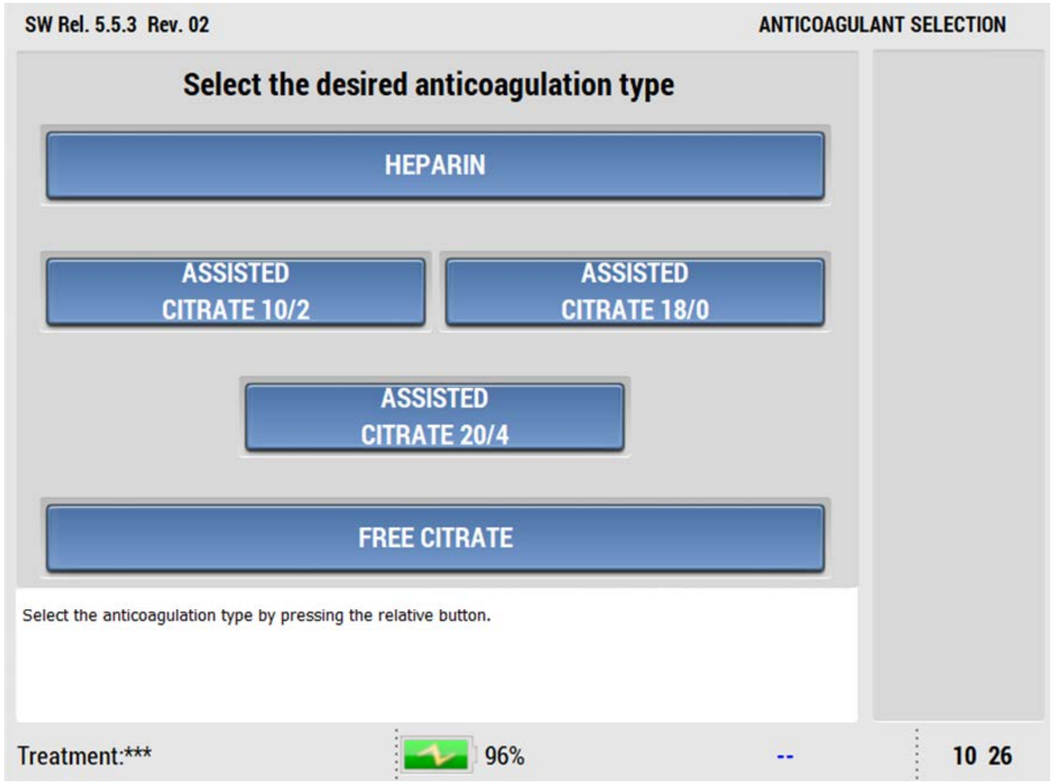
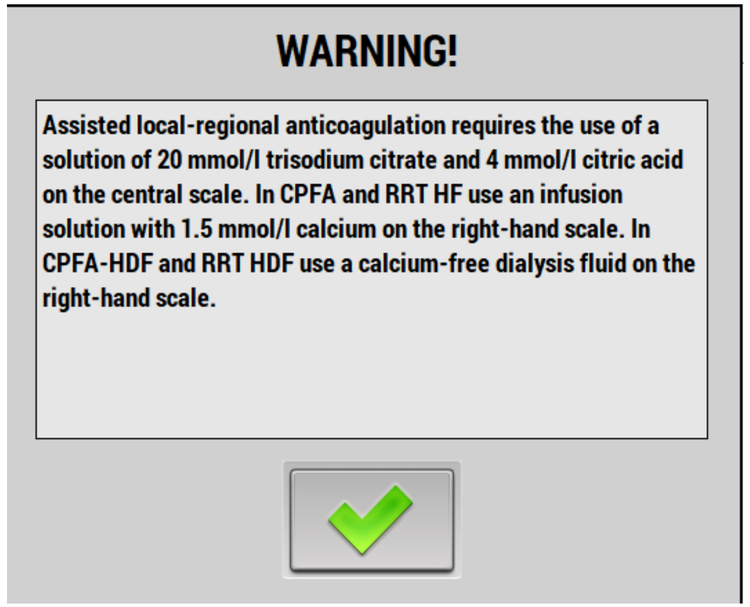
Citrate 20/4 & assisted modality

Amplya system™ proposition – SW[23]

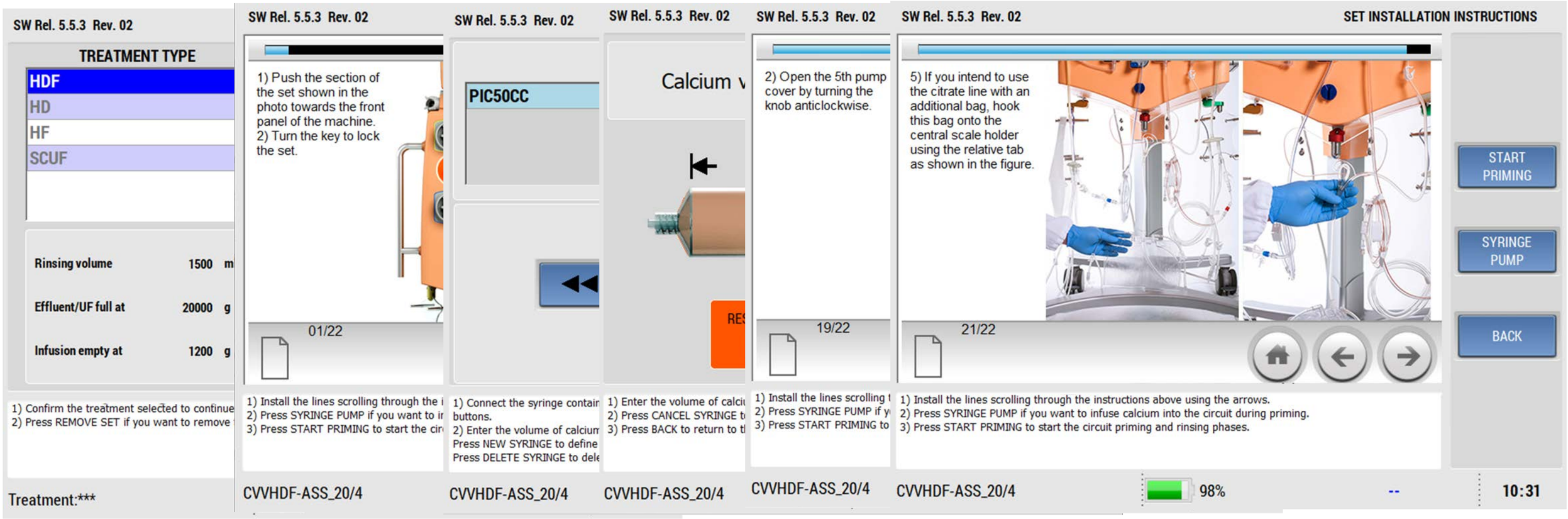




The use of calcium-containing replacement solutions (CVVH/CVVHDF) does not appear to increase the risk of venous drip chamber clotting during RCA[19]

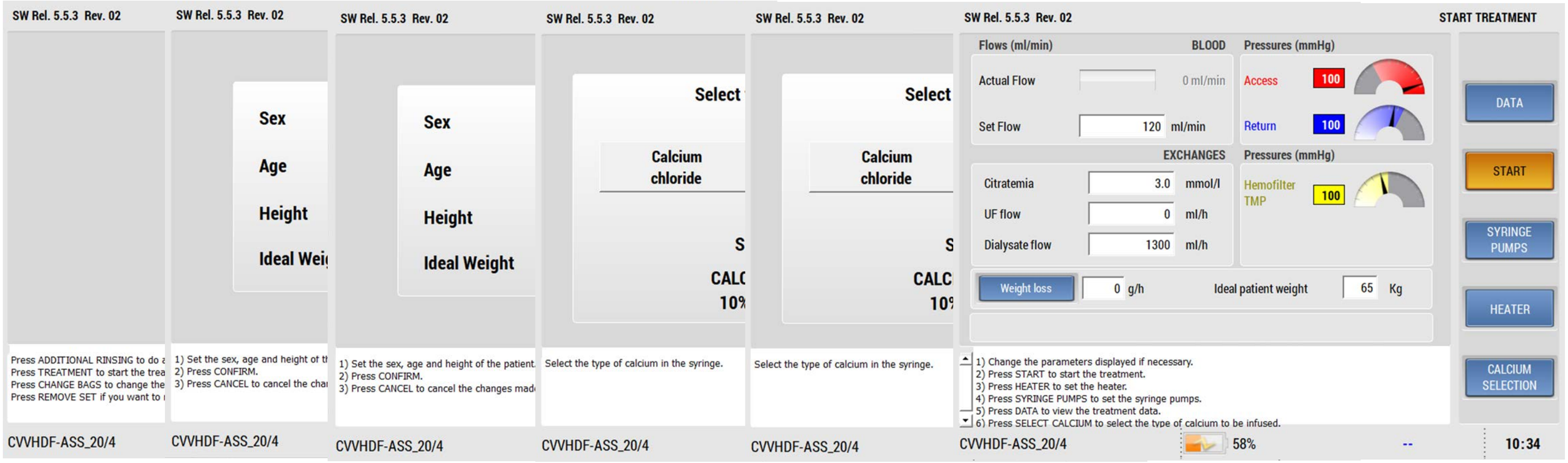
Citrate 20/4 & assisted modality

Amplya system™ proposition – SW[23]



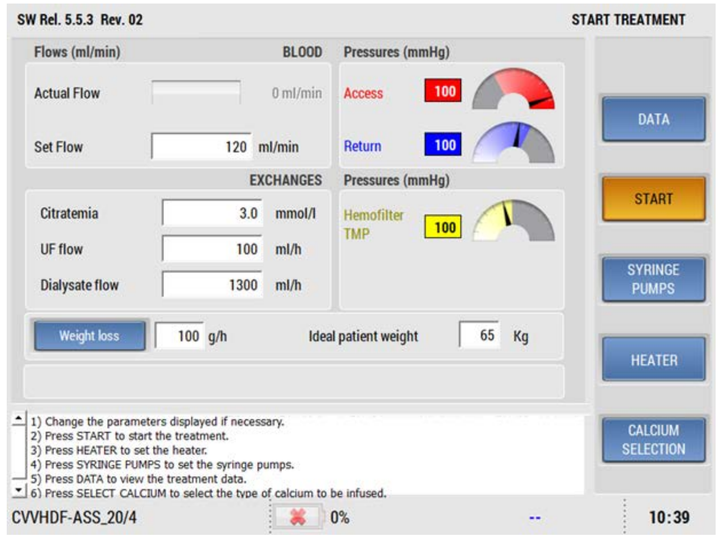
Citrate 20/4 & assisted modality

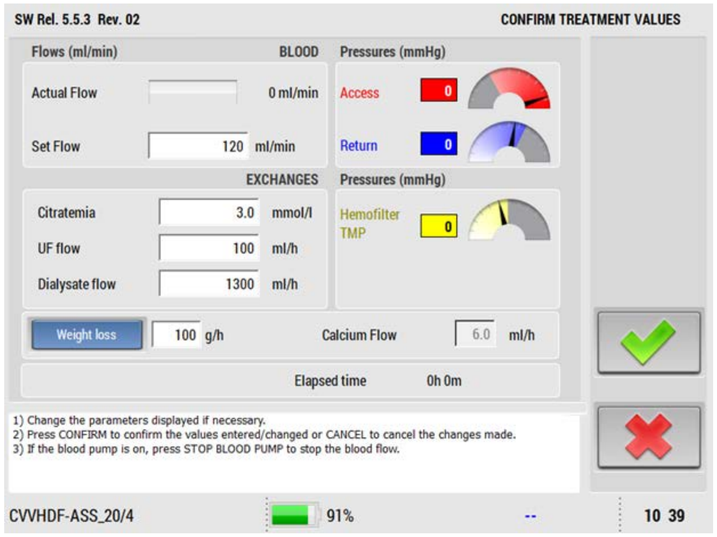
Amplya system™ proposition – SW[23]



Citrate 20/4 & assisted modality

Amplya system™ proposition – SW23



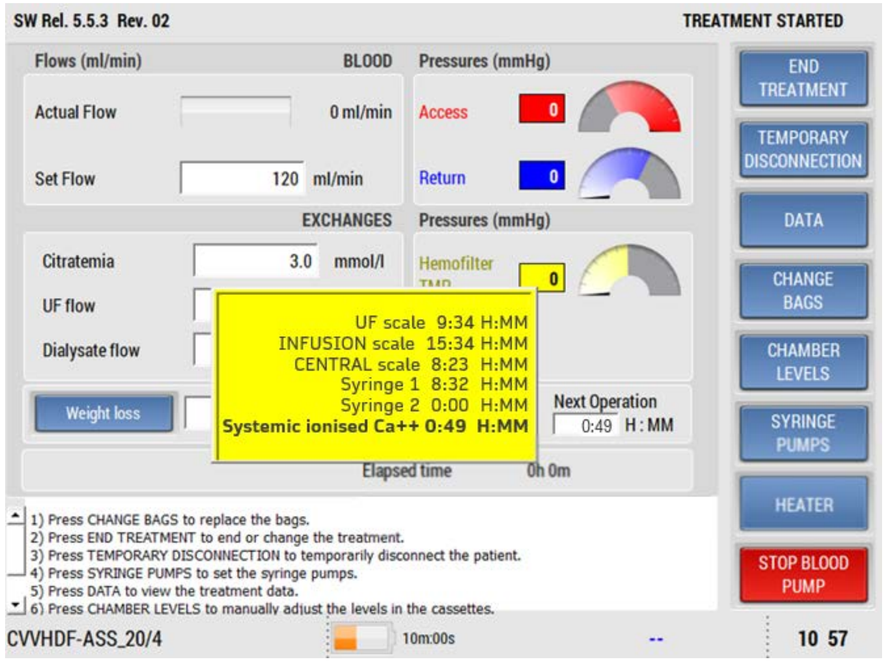


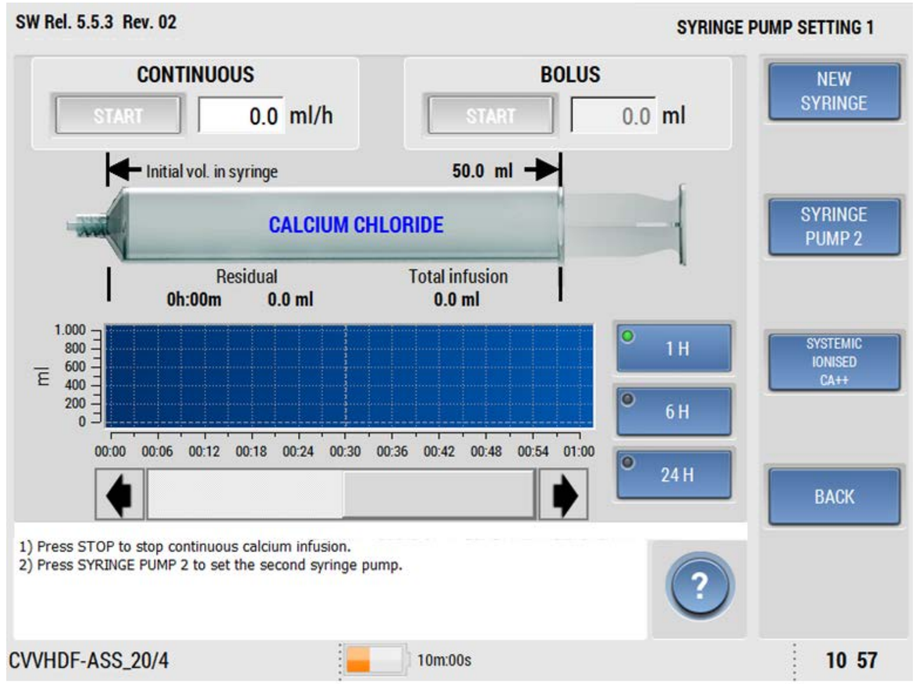
CVVHDF – STARTING PARAMETERS
TARGET CITRATEMIA 3 mmol/l weight loss 100 ml/h
Hct ~ 35%

Ideal weight (kg)	Blood flow (Qb) (range 100-150 ml/min)	Citratemia (mmol/l)	Dialysate flow (ml/h)	CaCl 10% (ml/h)
40	120	3	800	5
50	120	3	1000	5
60	120	3	1200	6
70	120	3	1400	6
80	120	3	1600	6
90	120	3	1800	7

Citrate 20/4 & assisted modality

Amplya system™ proposition – SW[23]



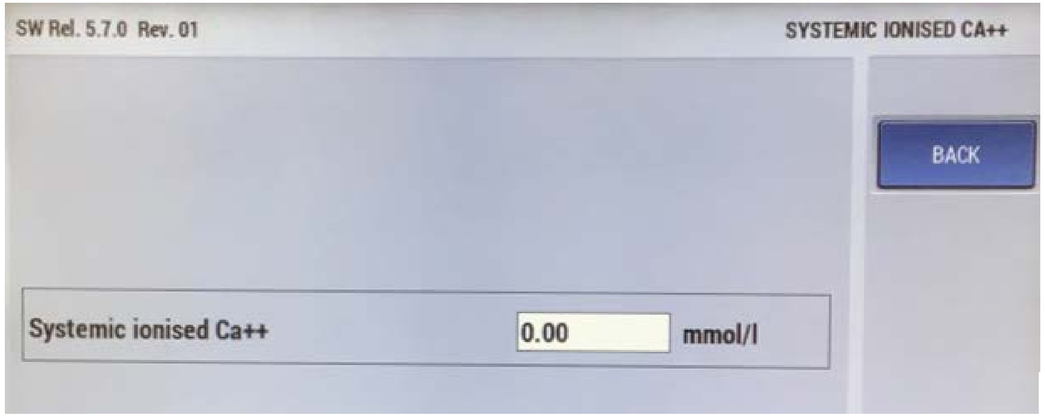


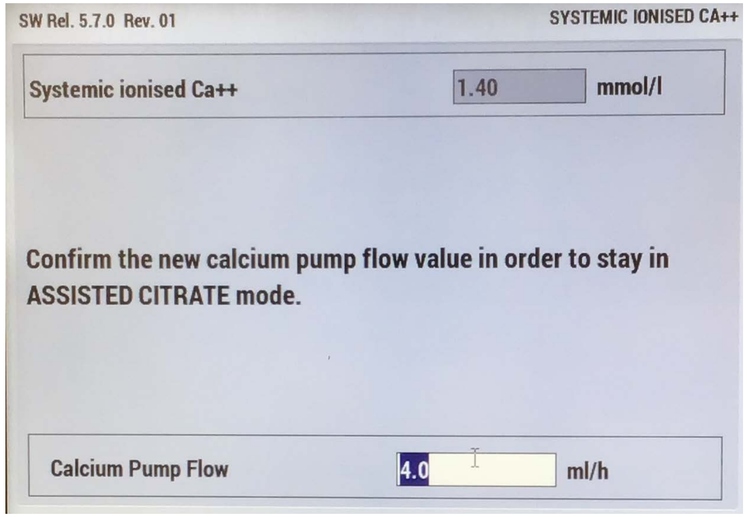
Name: **IONISED CALCIUM**	
Treatments	CPFA, CPFA-HDF and RRT with local-regional anticoagulation
Code: 480	**Description:** ionised calcium
Operator action	1) Measure the systemic ionised calcium of the patient. 2) Press CONFIRM and enter the value measured.
Effects	Yellow warning light, acoustic warning.
Intervention time	Instantaneous
Priority	LOW
Active	Always after treatment start (pressing START), except during temporary disconnection, bag change, blood pump stop, treatment end.

CALCIUM LEVEL MONITORING[24]				
Ionized systemic Ca (range 1,0-1,2 mmol/l)	30’	1 h	2 h	6 h
Ionized post-phylter Ca (range 0,2-0,4 mmol/l)	30’			6 h
Calcemia (range 0,2-0,4 mmol/l)	Daily			

Citrate 20/4 & assisted modality

Amplya system™ proposition – SW23





	Systemic ionised calcium Ca^{2+}				
	< 0,8 mmol/l	0,8 – 0,99 mmol/l	1,0 – 1,2 mmol/l	1,21 – 1,34 mmol/l	> 1,34 mmol/l
CaCl 10% (ml/h)	+ 2 ml/h	+1 ml/h	No changes	-1 ml/h	-2 ml/h

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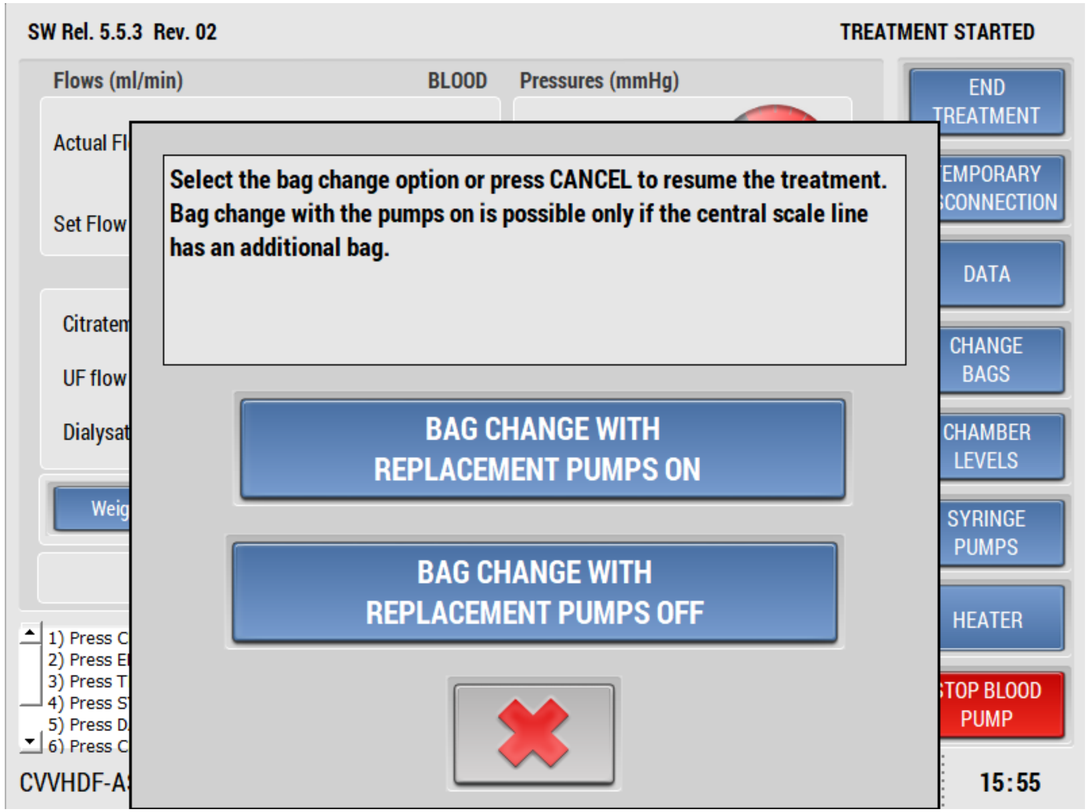
Citrate 20/4 & assisted modality

Amplya system™ proposition – SW[23]



The use of locoregional anticoagulation can be problematic due to the short half-life of the citrate during blood pump stop or citrate infusion stop[6]

Bag change with replacement pumps on[23]

When changing a bag without stopping the pumps, the Amplya system™ sets the pumps speed to maintain the average flows and does not consider the weight variations detected on the scales.

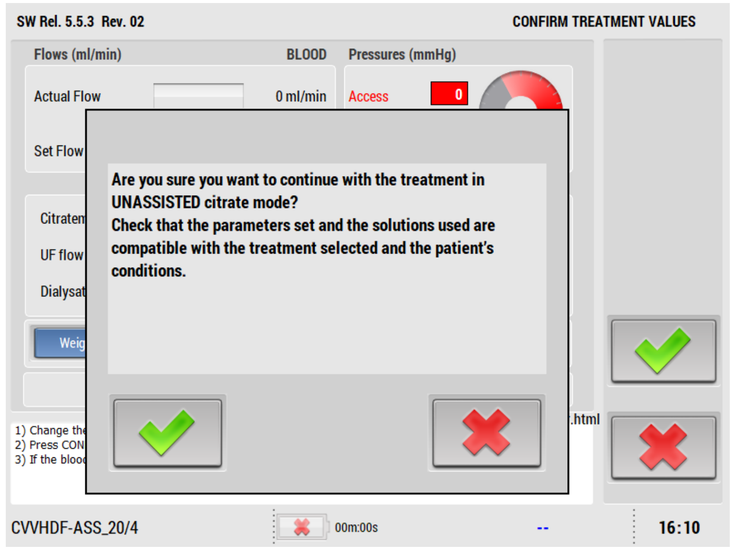
A message is shown on the screen warning the operator to complete the bag change as soon as possible and to check that there is at least one open bag on the side scales (yellow and green).

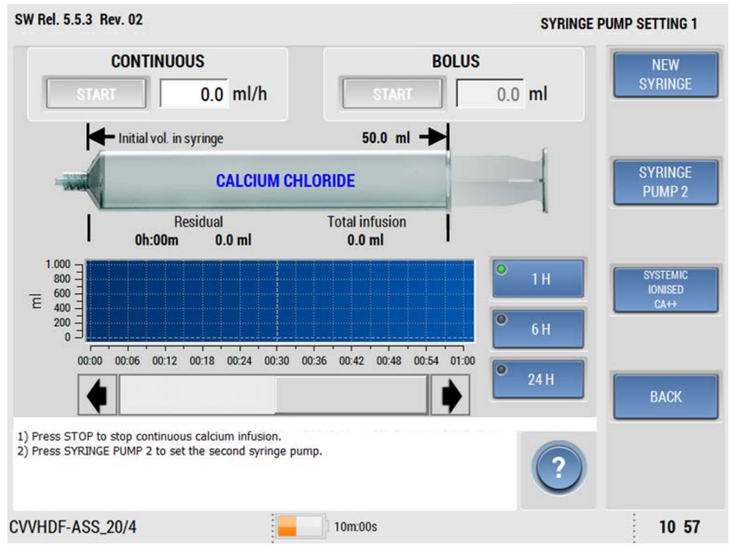
The treatment continues in this way for a maximum of 10 minutes, after which the bag change mode with the pumps off is automatically activated.

This helps to optimize the dose prescribed by the doctor and the real dose administered.

Citrate 20/4 & assisted modality

Amplya system™ proposition – SW[23]



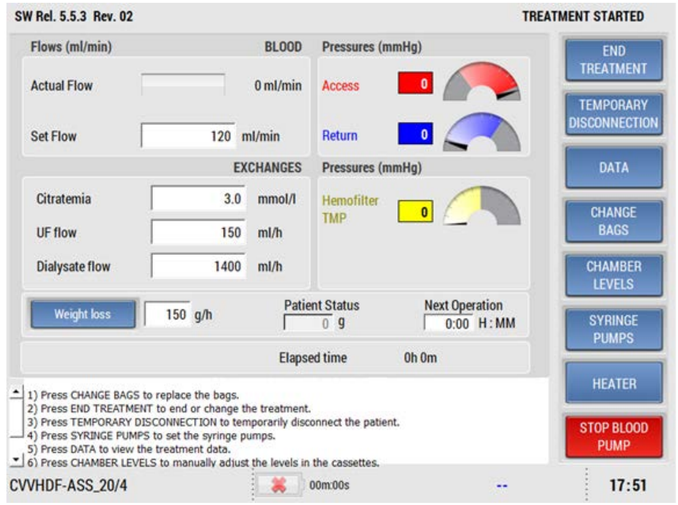


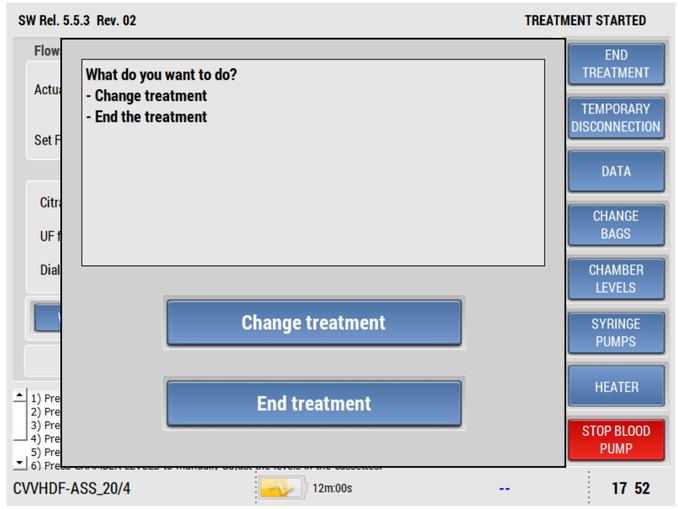
- With the Amplya system™, operators can switch out of assisted citrate mode to modify treatment parameters based on their clinical needs.

- Operators can resume assisted citrate mode only once by pressing the resume assisted citrate button. When you press the button, the CRRT treatment parameters are shown at their default values:
  - Ultrafiltration (UF) flow
  - Dialysate flow
  - Pre-infusion flow
  - Citrate flow

Citrate 20/4 & assisted modality

Amplya system™ proposition – SW[23]





On Amplya equipment while performing Assisted Citrate anticoagulation, you can change treatment between CVVH and CVVHDF (and viceversa) reducing interventions and lost time for nurses

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HOW WE CAN DO EVERYTHING WE SAID?

AMPLYA™

ACUTE MULTITHERAPEUTIC SYSTEM

The Amplya system™ offers a combined assisted citrate modality and 24 mmol/l concentration option to support to nurse and physician workloads[23]

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Clinical benefits

for citrate treatment management

Usability

for nurses’ workload

Economic considerations

for hospitals and warehouses

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Citrate 20/4 & assisted modality

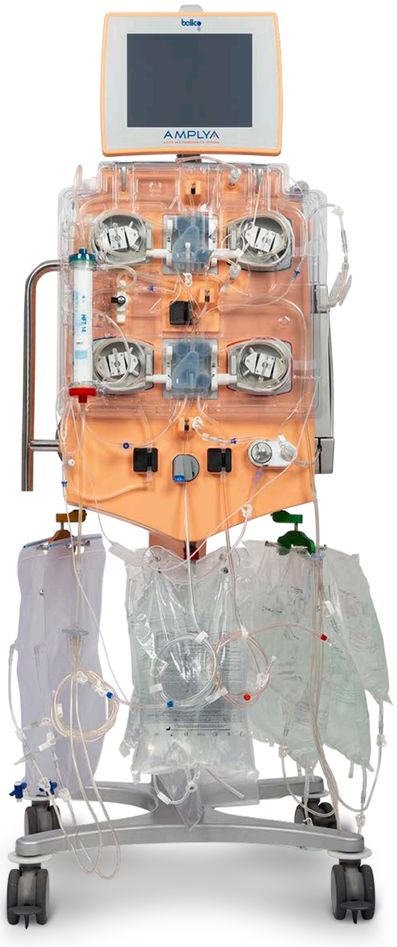
Clinical benefits

- Thanks to assisted diluted citrate with Amplya system™ [5, 25]:
  - Compared to 4% TSC (Tri Sodium Citrate) there is less risk of metabolic alkalosis
  - Compared to 4 % TSC there is less need for citrate thanks to predilution
  - Compared to 4 % TSC there is the possibility of carrying out CVVH as well

- The Amplya system™ allows operators to change bags without stopping the pumps, reducing events of coagulation of circuits with reduced relative blood loss.[26]

- The Amplya system™ is equipped with a reservoir bag[27], which eliminates downtime during bag changes. This helps to optimize the dose prescribed by the doctor and the real dose administered.[23]

- The Amplya's citrate plasma concentration setting reduces the possibility of citrate accumulation and related complications.[2, 10-12]



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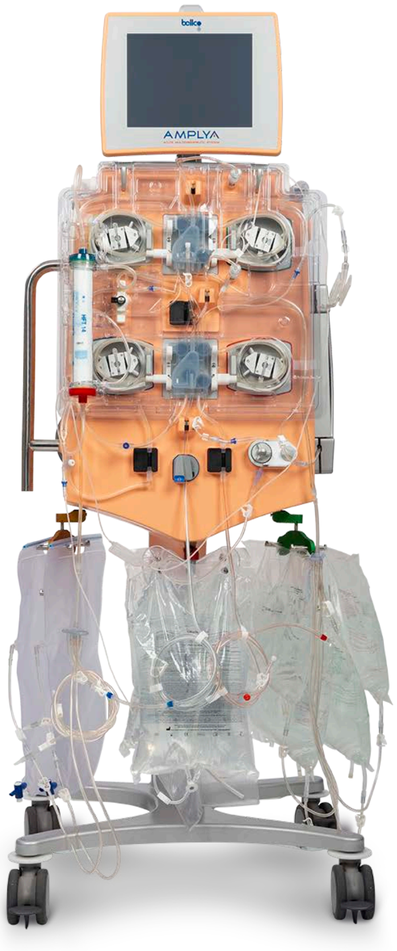
Citrate 20/4 & assisted modality

Usability

- The assisted citrate mode helps nurses to manage the level of systemic ionized calcium — and reminds them to periodically check it[23]

- The Assisted citrate helps operators manage the treatment protocol without tables. The system also provides suggested settings based on treatment type [23]

- Amplya assisted citrate with Citrachoice 24 in the 24 hour period, reduces the number of citrate bag changes by 50% (compared to the use of 10/2 citrate bags) [23]



Citrate 20/4 & assisted modality

Economic considerations

- Assisted Citrate done with Citrachoice 24 provides a number of benefits, including[23]:
  - Compared with 10/2 and 18/0, the amount of anticoagulation solution needed for 24 hours of treatment is reduced, which could lower the economic impact.
  - Compared with 10/2 and 18/0, Citrachoice 24 requires less space in the warehouse
  - Compared with 10/2 and 18/0, decreased cost for RCA due to less use of bags.

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Amplya system™ is an active, non-invasive, class IIb medical device CE0123 manufactured by Bellco Srl.

Pre-assembled device for RRT for Amplya is a non-active, non-invasive, class IIb medical device CE0123 manufactured by Bellco S.r.l.

Pre-assembled device for CPFA for Amplya is a non-active, non-invasive, class IIb medical device CE0123 manufactured by Bellco S.r.l.
The device is included in KABL14P05 – KIT CPFA X AMPLYA Procedure Pack.

Infusion line for Amplya is a non-active, non-invasive, class Is medical device CE0123 manufactured by Bellco Srl.

MD027 Sodium Citrate 10/2 mmol/l is a non-active, invasive, class IIb medical device CE0123 manufactured by Haemopharm Biofluids S.r.l.

Citrachoice 24 is a medical device CE0373 manufactured by Paolo Gobbi Frattini Srl. The composition is 20 mmol/l Na-citrate and 4 mmol/l citric acid, also referred to as 20/4 throughout this document

Please refer to the devices and procedure pack Instructions for Use for complete instructions, contraindications, warnings and precautions.

08/2023 - EMEA-RC-2200039 Rev.01

NOT FOR USE IN US

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