



# THE BENEFITS OF CITRASATE™

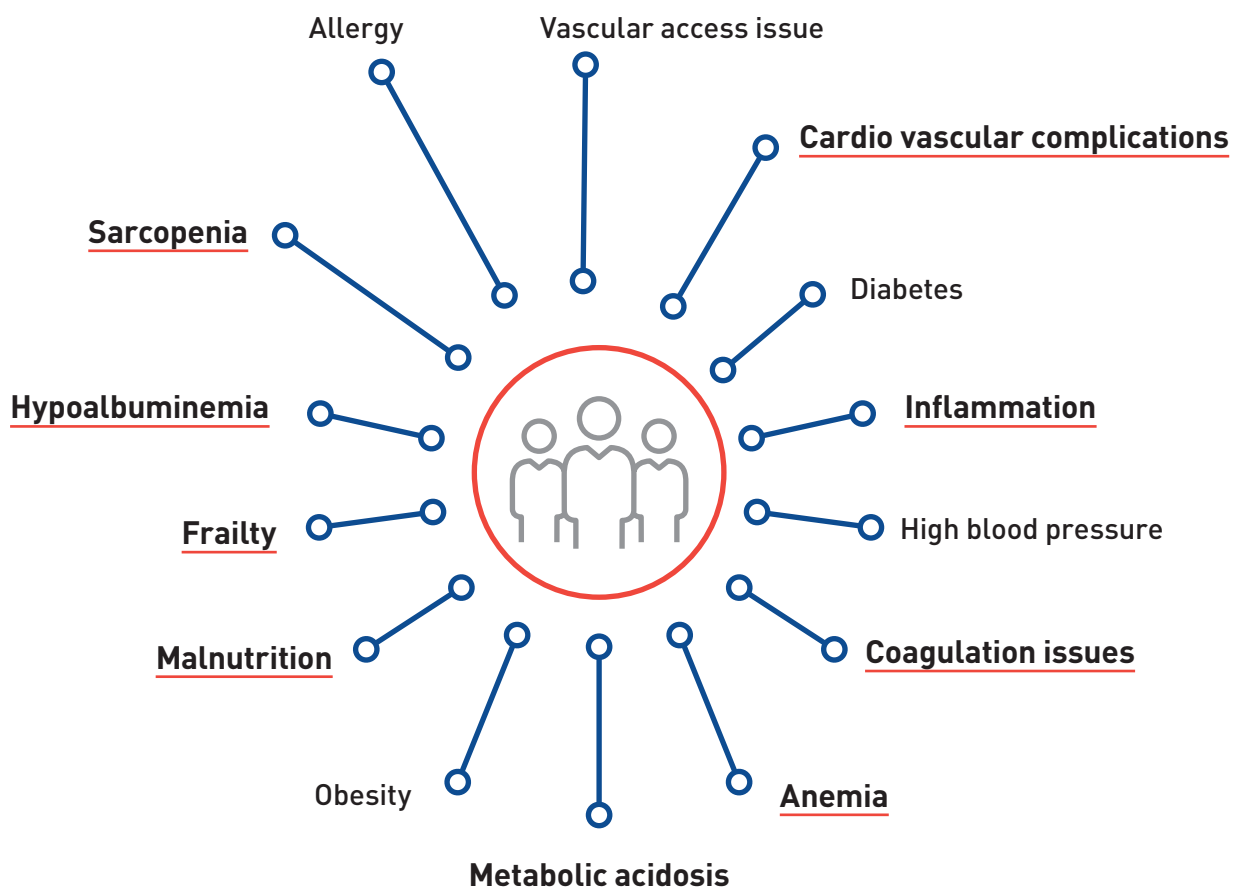
CITRATE-BASED DIALYSATE IN DIALYSIS TREATMENT



# Is dialysate going to be the next focus of dialysis treatment?

For patients with end stage renal disease, the aim of dialysis treatment is removing the uremic toxins on the one hand and **correcting the levels of the blood electrolytes** on the other. <sup>1</sup>

## Which patients would benefit from Citrasate?



The **dialysis fluid** plays a key role since it is composed of the elements (bicarbonate and acid concentrate) that **normalize the electrolyte constitution** of the blood.<sup>2</sup> Despite such an important role, the effect of the dialysis fluid on the patient is often underestimated.

Acetate-based dialysates are commonly used in dialysis treatment.<sup>3</sup> For patients susceptible to the side effect of acetate such as **hemodynamic instability, metabolic acidemia and arterial hypotension**,<sup>4</sup> acetate was reduced and replaced with a more biocompatible compound, citrate.<sup>5</sup>

The benefits of citrate-based dialysis is suggested specially for patients with **hemodynamic instability** (cardiovascular diseases such as arrhythmias), with **higher inflammation, and fragile patients** with nutritional problems.<sup>6,7</sup>

Due to the anti-coagulation properties of citrate, citrate-based dialysate is a suitable support for patients with **coagulation issues**.<sup>8</sup>

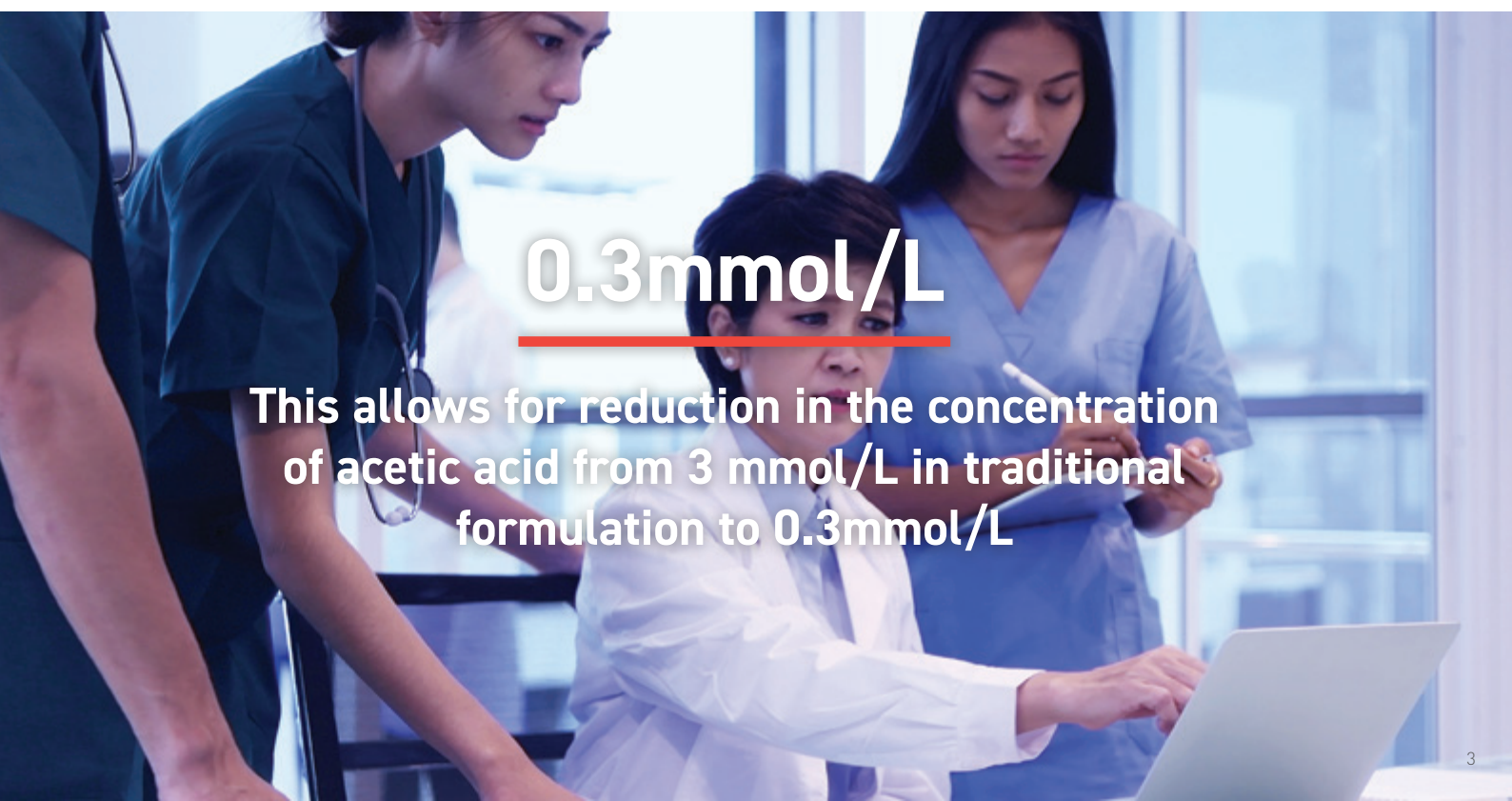
Citrate-based dialysate with high levels of magnesium is beneficial for patients with hypoalbuminemia and nutritional issues.<sup>7,9</sup>



Dialysis patients are complex and have various clinical needs. A suitable dialysis fluid tailored to the specific needs of the patient is an important aspect of a quality dialysis treatment.

## What is Citrasate™ and what are the benefits of the citrate-based dialysate?

Citrasate contains biocompatible citric acid (0.8 mmol/L), and 0.3 mmol/L acetic acid as an acidifying agent.



**0.3mmol/L**

This allows for reduction in the concentration of acetic acid from 3 mmol/L in traditional formulation to 0.3mmol/L

# Benefits of citrate-based dialysate

## Higher survival

Citrate-based dialysate is safe for the patients and increases the long-term **survival of patients to up to 33%**.<sup>7</sup>

**33%**

**BETTER  
SURVIVAL**

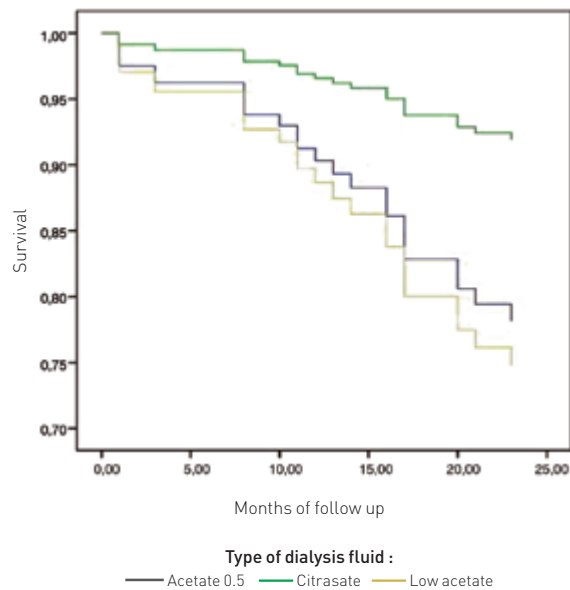


Fig 1: Mortality based on dialysis fluid. Patients treated with citrate-based dialysate have significantly higher survival than patients treated with acetate-based dialysate during a 25-month follow-up ( $p=0.008$ ). Retrospective, single-center study,  $N=137$ .

## Correction of acidosis

**Metabolic acidosis** is a common complication in patients with chronic kidney disease.<sup>10</sup>

As shown in Fig 2, **Citrasate**, has a **significantly lower acidemia** post-dialysis vs. treatment with acetate.<sup>11</sup>

Excess of bicarbonate in dialysis can lead to **post-HD alkalemia** (increase in pH) which is associated with **increased mortality**.<sup>12</sup>

The use of citrate **decreases post HD alkalemia vs. acetate**.<sup>2</sup>

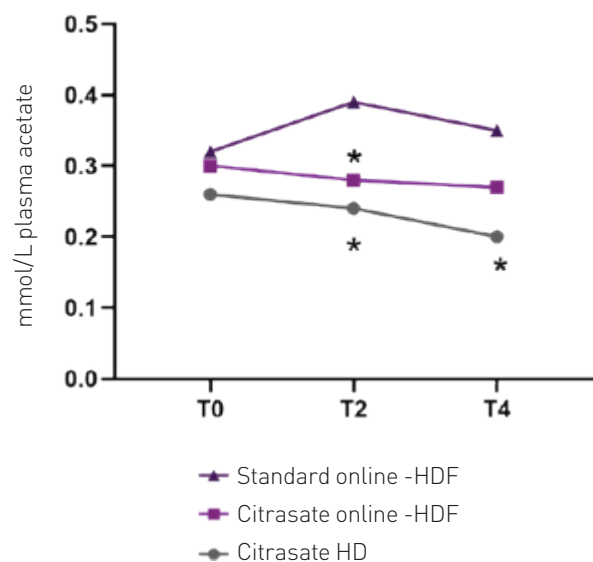


Fig 2. Treatment with Citrasate in 13 patients during 3 dialysis treatments. T0: baseline, T2: 2H and T4: at the end of treatment.

Compared to acetate-based dialysate, the use of Citrasate normalizes the acidemia in patients and decreases the post-HD alkalemia.<sup>2,11</sup>

## Higher biocompatibility and reduction of inflammation

Inflammation and oxidative stress are risk factors for cardiovascular-related mortality in dialysis patients.<sup>13</sup>

Treatment with citrate-based dialysate or Citrasate improves the inflammation by:

- Reducing IL-6 (Fig 3)<sup>14</sup>
- Reducing serum CRP levels (Fig 4)<sup>8</sup>
- Increasing eosinophils (higher biocompatibility)<sup>2</sup>

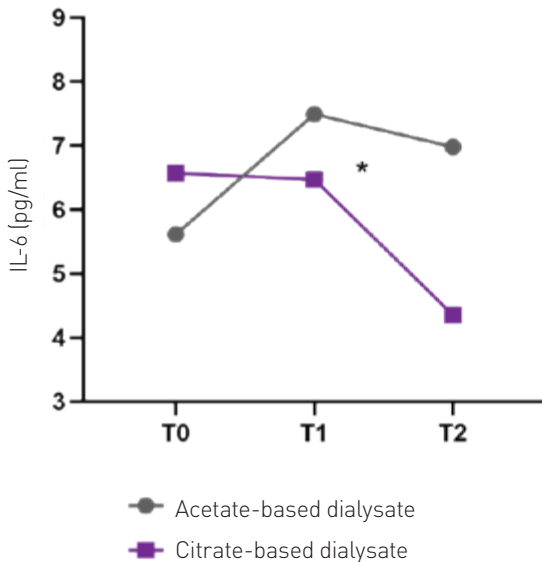


Fig 3. The IL-6 levels at baseline, T1 (1.5 months) and T2 (3 months). The pair-wise differences between T2 and baseline is significantly higher in acetate vs. citrate containing dialysate.  $p = 0.029$ . Multicenter, randomized, controlled study,  $N=47$ .

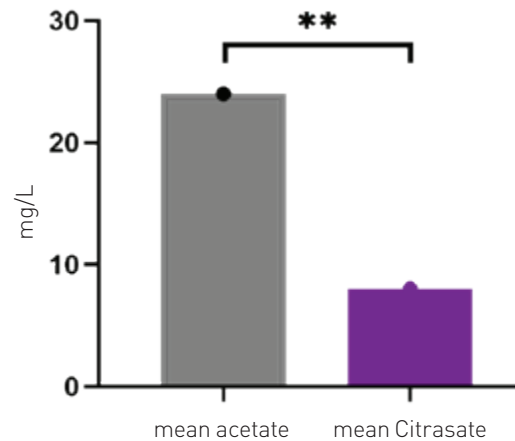


Fig 4. Mean serum CRP levels is significantly reduced in patients treated with Citrasate. Cross-over single center study,  $N=22$ .

Citrate-based dialysate leads to 3-fold lower CRP levels benefiting patients with cardiovascular diseases.<sup>8,13-15</sup>

## Improving the nutritional state

Dialysis by citrate improves nutrition by:

- Increasing the **appetite**<sup>6</sup>
- increasing the **lean mass index (LTI)**<sup>2</sup>
- Increasing **serum albumin levels** in patients with hypoalbuminemia<sup>2</sup>

Treatment with Citrasate significantly increases the serum albumin levels by 2.3% even after a short period of 8 months compared with acetate (Fig 5).<sup>8</sup>

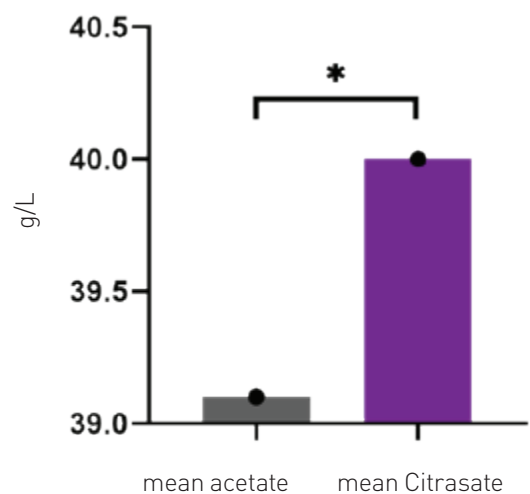


Fig 5. Mean serum albumin levels is significantly increased in patients treated with Citrasate. Cross-over single center study,  $N=22$ .

**7%** HIGHER LTI

## Reducing inter-dialytic hypotension

Interdialytic hypotension occurs in 25% of patients in dialysis<sup>16</sup> and is a significant predictor of mortality.<sup>17</sup>

After more than 4.000 treatments, the use of citrate-based dialysate shows a clear significant reduction of 23% in inter-dialytic hypotension.<sup>2</sup>

### Cost-effectiveness for the dialysis center

Assuming an average time of 15 min for managing a patient with hypotension, this reduction of 23% can save 0.05-0.35 euro per treatment.

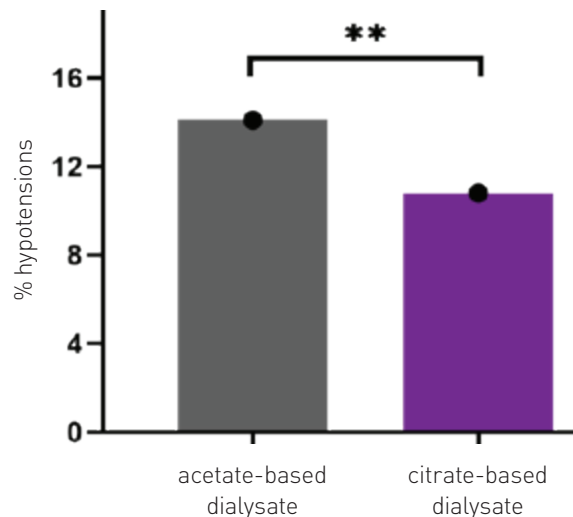


Fig 6. Percentage of arterial hypotension in 4.416 sessions of hemodialysis. Dialysis with acetate-based fluid has a significantly higher % of hypotension compared with citrate-based dialysate. Prospective, multicenter, crossover, randomized study, N=56.

**0.05-0.35 €**  
SAVING PER TREATMENT

## A suitable alternative to heparin

Heparin is widely used as an anti-coagulation strategy for dialysis patients.<sup>18</sup>

However, heparin is associated with **side effects and is contraindicated** for certain patients.<sup>19-21</sup>

For these patients, the reduced dose of heparin can be compensated by citrate thanks to its **anti-coagulation** properties.<sup>22</sup>

### How does citrate inhibit the coagulation cascade?

Citrate ions, due to their negative electric charge, **chelate the positively-charged calcium**. Calcium is an essential component for the coagulation cascade and necessary for the formation of thrombin, an enzyme that catalyzes the formation of fibrin in the clot formation process. Forming a complex with calcium will render it inaccessible for the clotting cascade.<sup>21</sup>

### Clinical evidence

The study by Meijers et al., shows the successful **termination of 94%** of sessions in both hemodialysis and pre-dilution hemodiafiltration with a citrate-based dialysate (in combination with a low-thrombogenic dialyzer, Solacea™).<sup>23</sup>

Other studies have shown reaching **comparable dialysis efficiency with citrate** while gradually lowering the heparin doses.<sup>22</sup>

Kossmann et al., switched 31 patients from normal dialysate containing acetate (NCD) to Citrasate and gradually reduced the heparin dosage. Even with the reduction of heparin by 55%, all the treatments with Citrasate successfully completed without clotting problems and the episodes of prolonged bleeding were decreased.<sup>24</sup>

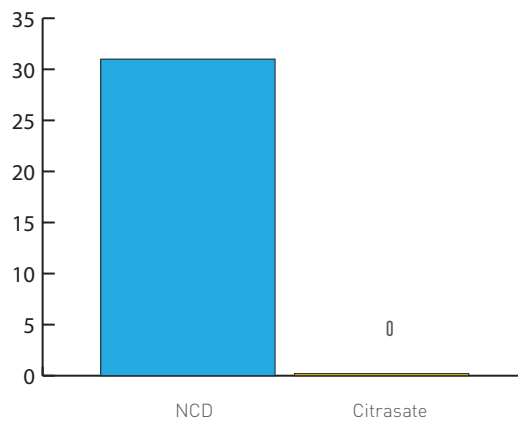
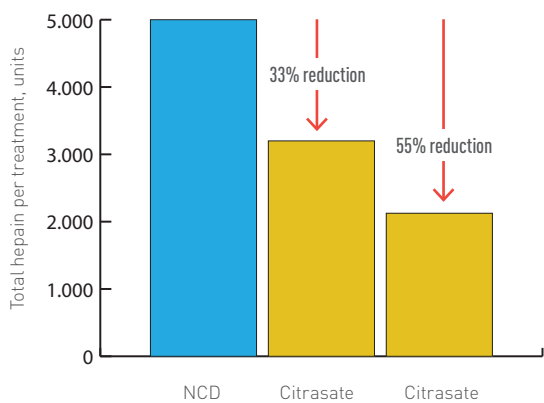


Fig 7a, 7b. Reduction of heparin by 55% decreases the bleeding episodes of >15 minutes. N=31.

## Reduction of heparin cost

By using **Citrasate**, the dose of heparin can be reduced by up to 50%<sup>25</sup> which can result in an estimated **cost reduction of 0.46 and 0.72 euro per treatment** for unfractionated heparin (UFH) and low molecular weight heparin (LMWH), respectively. These prices were calculated based on the UF price of 1.15 euro for the average of 8.000 IU, and the LMWH price of 1.80 euro for the average of 300 IU.

Heparin type	Estimated average reduction cost per treatment for 30%-50% heparin reduction
UFH	0.46 euro
LMWH	0.72 euro

**0.46-0.72 €**  
SAVING PER TREATMENT

## Higher dialysis efficiency

The blood-dialyzer interaction causes the **clotting** of the dialyzer and the reduction of dialysis efficiency. By using citrate-containing dialysis fluid, calcium will be chelated and thus less available for the coagulation cascade.<sup>21</sup>

Clinical studies have shown **increased clearance** of small and middle molecules with **citrate-based** dialysate owing to its superior anti-clotting properties compared to acetate.<sup>26,27</sup>

## Improving anemia

**Anemia** is a common comorbidity in dialysis patients and associated with **cardiovascular mortality** and decreased quality of life.<sup>28</sup>

Treatment with citrate-based dialysate is shown to **increase the hemoglobin levels** in anemic patients with a **1.000-unit reduction in erythropoietin stimulating agent (ESA)**.<sup>9</sup>

## Lower cost of ESA

Based on the average reduction of 1.000 units in ESA when using a citrate-based dialysate, **a range of 0.43-1.70 euro cost reduction** can be estimated depending on the type of ESA used. This reduction is based on the price of ESA ranging from 1.3-5.4 euro for the average dose of 1.000 units of ESA per treatment.

**0.43-1.70 €**  
SAVING PER TREATMENT

# Benefits of Citrasate with higher magnesium (Mg)

In dialysis patients with serum Mg levels above 2.1 mg/dL, a **20% increase in 2-year survival** has been observed (Fig 8).<sup>7</sup>

The increased mortality with **decreased Mg** can be related to the following **consequences** of hypomagnesemia in dialysis patients:

- Development of diabetes<sup>29</sup>
- High blood pressure<sup>29</sup>
- Cardiac arrhythmias<sup>30</sup>
- Vascular stiffness<sup>31</sup>
- Increased vascular calcification<sup>32</sup>
- Increased all-cause and cardiovascular mortality<sup>33</sup>
- Increased metabolic syndrome<sup>34</sup>
- Lower lean mass quality (muscle function)<sup>35</sup>
- Lower response to EPO<sup>36</sup>

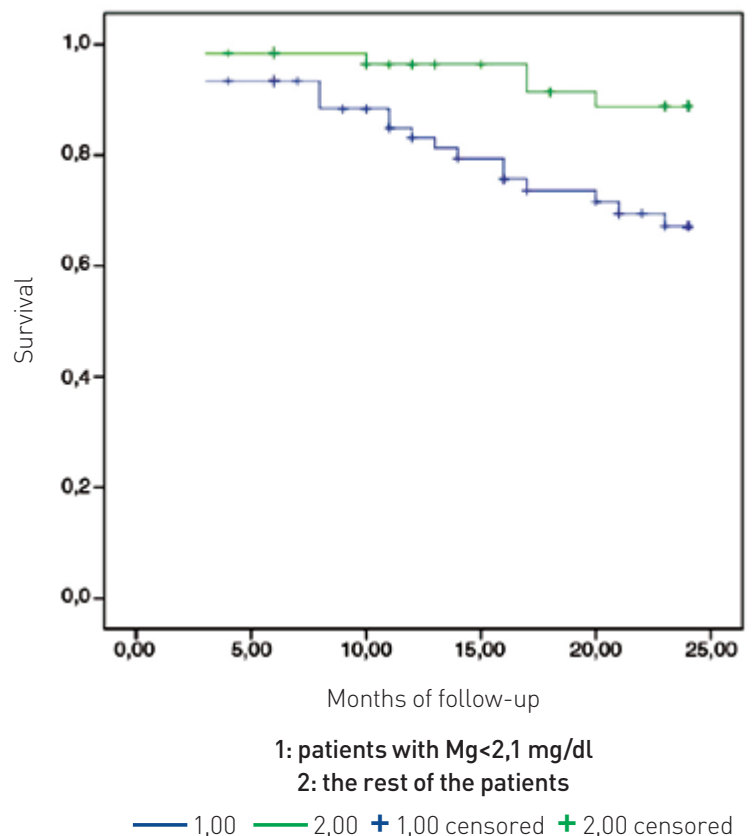


Fig 8. Patients with serum Mg levels > 2.1 mg/dL have a significantly higher survival than patients with < 2.1 mg/dL during a 25-month follow-up ( $p=0.008$ ). Retrospective, single-center study, N= 137.

In patients receiving dialysis, on the one hand, **Mg is cleared** through the dialysis treatment and on the other hand, the **compensation** for Mg through dietary intake is usually limited by the specific recommended diets.<sup>7</sup>

*In vitro*, the higher Mg doses of  $\geq 1$  mmol/L improves the oxidative stress in immune cells of dialysis patients.<sup>37</sup>

The current patterns indicate that higher levels of Mg in the dialysate could potentially improve patients' outcomes.



# Using citrate-based dialysate has several benefits

## For patients

Dialysis patients are complex and have different medical needs. **Individualization of the dialysis fluid** to specific medical needs of the patients has to be considered as an ideal solution.<sup>38</sup> Dialysis with citrate-based dialysate offers several benefits for patients.

## For healthcare staff

- **33% increased survival** of patients<sup>7</sup>
- **23% reduction of hypotensive episodes**, leading to **6 hours saved** for a dialysis unit with 100 patients

## For dialysis centers

- Up to **0.35 euro** cost-saving on reduction of hypotensive episodes
- Up to **0.72 euro** cost-saving on heparin
- Up to **1.70 euro** cost-saving on reduction of ESA



**Total financial advantage of 2.77 euro per treatment**



# Why Citrasate?

Increased clearances



Improvement of inflammation



Improvement of nutrition



Less inter-dialytic hypotension



Acid-base control with less pre-dialysis acidosis

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