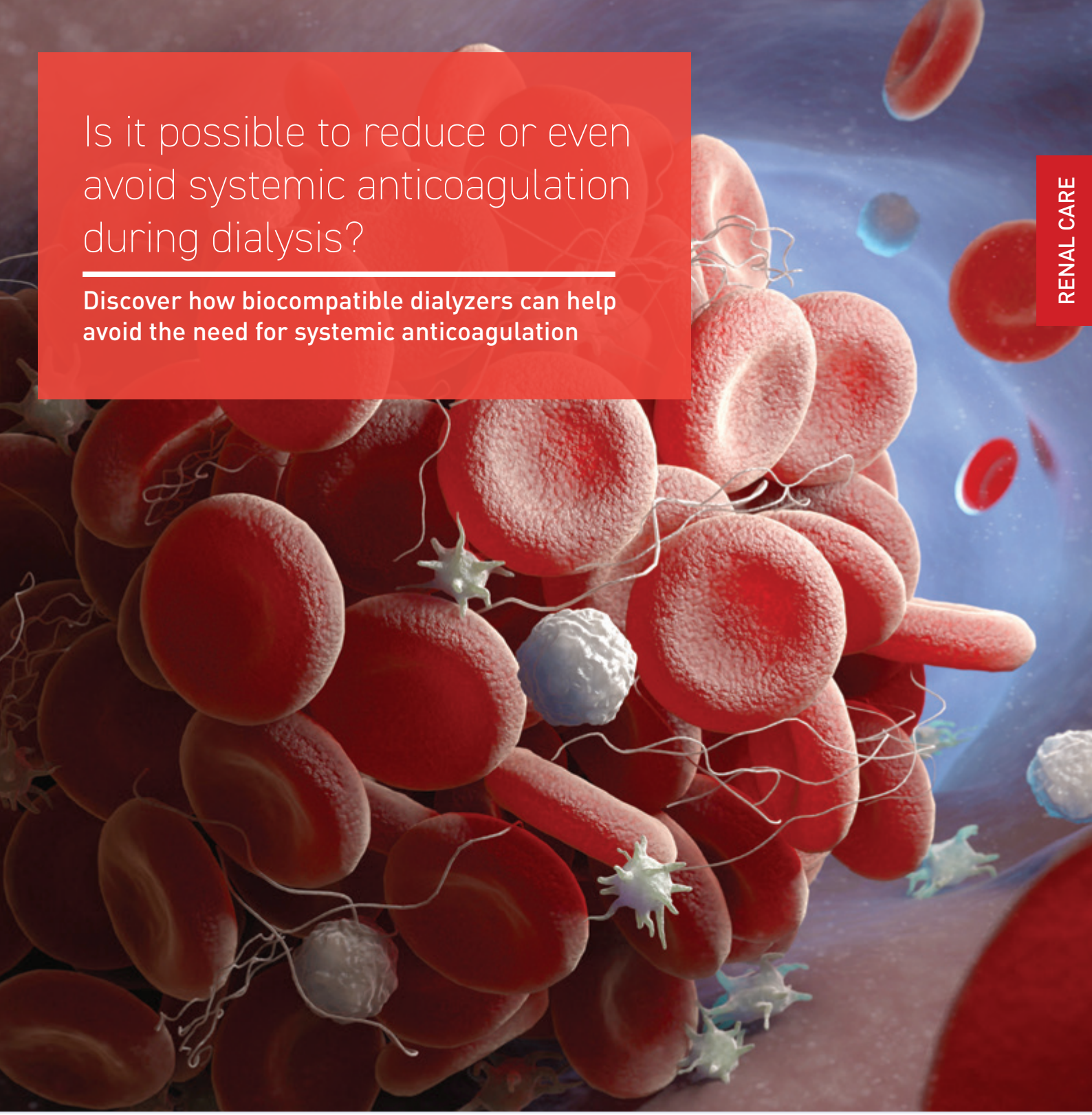


Is it possible to reduce or even avoid systemic anticoagulation during dialysis?

Discover how biocompatible dialyzers can help avoid the need for systemic anticoagulation

RENAL CARE

REDUCING THE NEED FOR HEPARIN DURING DIALYSIS

NIPRO MEDICAL EUROPE

Heparin is the standard approach to prevent clotting - but is it a solution for all patients?

What are the main causes of dialyzer clotting?

Disturbed hemostasis in hemodialysis patients[5,6]

The extracorporeal circuit[1,2,5]

- High shear stress
- Turbulent blood flow
- Interaction of blood with synthetic material

The therapeutic treatment of the patient[1,2]

- Slow blood flow
- Excessive fluid removal
- The administration of thickening agents

Systemic anticoagulation

In order to prevent the clotting of the dialyzer, the majority of dialysis units adopt the strategy of administering significant amounts of systemic anticoagulants during the dialysis session.

However, there are side effects and limitations to systemic anticoagulation.

Side effects

Unfractionated (UF) heparin and low molecular weight heparin (LMWH) have both been associated with a number of side effects:[5-8]

- Increased risk of bleeding
- Allergic reactions (e.g. pruritus)
- Heparin-induced Thrombocytopenia (HIT)
- Osteoporotic changes

The use of heparin is contraindicated for certain patient populations

Systemic anticoagulation cannot be used in patients with an allergy to heparin or at risk of bleeding, such as patients experiencing or undergoing:

- Heparin-induced Thrombocytopenia
- Invasive procedure (before and after surgery)
- Gastrointestinal or cerebral haemorrhage
- Low platelet count
- Oral anticoagulant therapy
- Diabetic retinopathy

Clotting of the dialyzer has significant consequences

Lowers the therapeutic quality[1,2]

Reduced membrane surface area

- Less removal of uremic toxins
- Lower exchange of ions

Lower treatment duration

- Interruption of the treatment
- Premature termination of the hemodialysis session

Blood loss[1,3,4]

- The coagulated blood cannot (and should not) be reinfused into the patient
- Loss of up to 200-300 ml per clotting episode

Economic burden[1]

Prolongation of hemodialysis session

- Interruption of the treatment

Increased workload for healthcare professionals

- Nurse intervention is required to solve the problem

Increased costs

- Replacement of the dialyzer
- Saline flushes
- Increased dose of heparin

Alternative strategies to prevent clotting exist, but their efficacy is often limited

Saline flushes[7,9,10]

This calls for intermittent flushing of the extracorporeal circuit with saline.

Disadvantages:

- Requires close one-to-one nursing → additional workload
- Adds increased fluid load to the dialysis patient

60-61,3%

SUCCESS RATE
(without heparin)

Pre-dilution Hemodiafiltration (Pre-HDF)[11,12]

This calls for continuous saline infusion into the arterial line during the entire hemodialysis session.

Disadvantages:

- Requires close one-to-one nursing → additional workload
- Adds increased fluid load to the dialysis patient

40-44,6%

SUCCESS RATE
(without heparin)

Low dose of citrate into the dialysate[13,14]

This calls for dialysate with a low-dose citric acid that replaces (in part or in whole) acetic acid. Citrate chelates ionized calcium and thus inhibits the coagulation cascade.

Disadvantage:

- It only allows for a reduction in heparin dosage by 22-30%[13] or 50%[14] without affecting clotting and dialysis efficacy

SUCCESS RATE
(without heparin)

Not applicable. Requires reduced dosage of heparin or heparin-coated dialyzers

Heparin-coated dialyzer[15,16]

This calls for an AN-69ST dialyzer coated with heparin.

68,5-76,3%

SUCCESS RATE
(without heparin)

Why is the membrane crucial when choosing a biocompatible dialyzer?[16]

The biocompatibility of the dialyzer membrane is not only important for allergic reactions, but also for preventing the activation of the coagulation cascade.

Dialyzers that have large inner surface area (e.g. 2.1 m^2) are optimal for blood clearance, but this also results in an extensive interaction between the blood cells, components, and dialysis membrane during dialysis.

The membrane is essential for the clearance of the blood

- Outflow into the dialysate through the pores
- Adsorption on the membrane

A poorly designed membrane can have important negative consequences

- Damage to blood cells or hemolysis
- Activation of blood cells
- Depletion of functional proteins for homeostasis
- Proteins adsorbed to the membrane surface can trigger the activation of the complement system, the coagulation cascade, and the fibrinolytic system

Is a highly biocompatible dialyzer enough to reduce the need for systemic anticoagulation during dialysis?

What sets SOLACEA™ apart from other dialyzers?

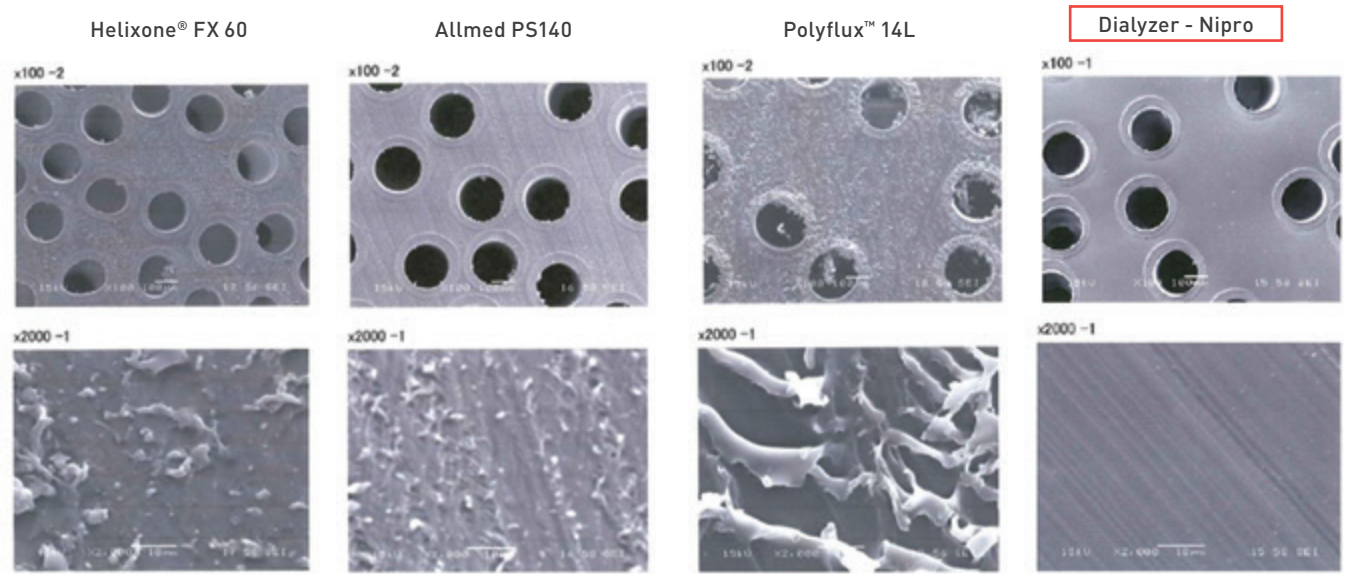
The importance of a smooth entry point

A smooth surface of the potting is essential in preventing damage to blood cells or hemolysis, as well as the activation of platelets and the coagulation cascade.

Design of the potting

As blood enters the dialyzer, it is pushed into the fibers under high pressure. The potting immobilizes the fibers and prevents the blood from passing into the dialysate compartment.

Microscopic images, measured by scanning electron microscope (SEM):*



* internal data R&D center Nipro Japan

The polyurethane potting of SOLACEA has a very smooth cut.

The importance of a smooth inner surface

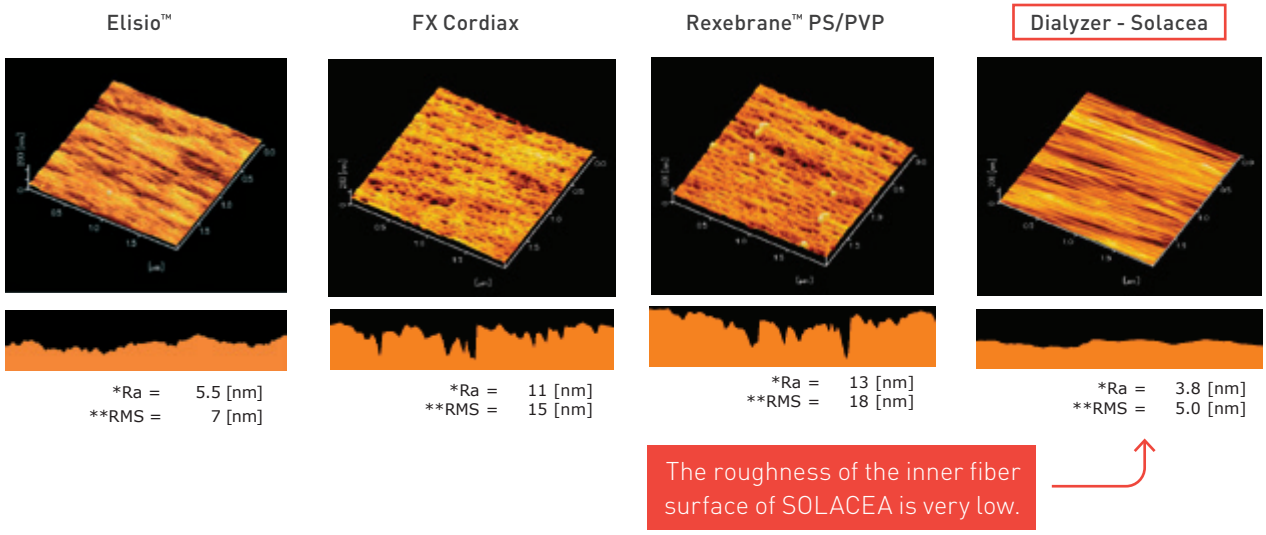
Minimal roughness of the inner surface of the fiber prevents hemolysis and reduces the formation of a protein cake.

Design of the inner fiber surface

This is the contact area between blood and membrane, where the exchange of molecules between the blood and the dialysate takes place.

The fiber spinning process, which takes place during the manufacturing of the dialyzer, ultimately determines the fiber's characteristics.

Microscopic images, measured by scanning electron microscope (AFM):



* Ra : average roughness, ** RMS: square-mean roughness
Nipro internal data; n=3

The importance of a biocompatible chemical composition

The chemical nature of the membrane determines which molecules have higher affinity for the dialyzer fibers, which may then influence the activation of immune cells and platelets.

Choice of the molecular composition of the fibers

Some molecules – such as the pore-forming agent, PVP[17], and the hormonal mimicker, BPA[18] – can leach out of the fiber into the patient's bloodstream.

Adsorption of proteins, measured by proteomic analysis by Peptide Mass-finger printing and MALDI-TOF-MS/MS sequency.

This difference in the type of proteins adsorbed was confirmed by a slightly higher significant platelet activation profile in patients that underwent HD treatment with a polysulfone dialyzer than with a cellulose triacetate dialyzer.[20]

Polysulfone fibers[19]

- Retention of proteins of the **coagulation cascade** and linked to **platelet activation**
- Potentially a higher activation of the coagulation cascade
- Retention of proteins stemming from the blood cells → Potentially a sign of shear stress with consequent partial hemolysis

Cellulose triacetate fibers[19]

- Predominant adsorption of **albumin** → Is thought to reduce the activation of coagulation because albumin has a relative lack of glycosylation, which prevents platelet adhesion

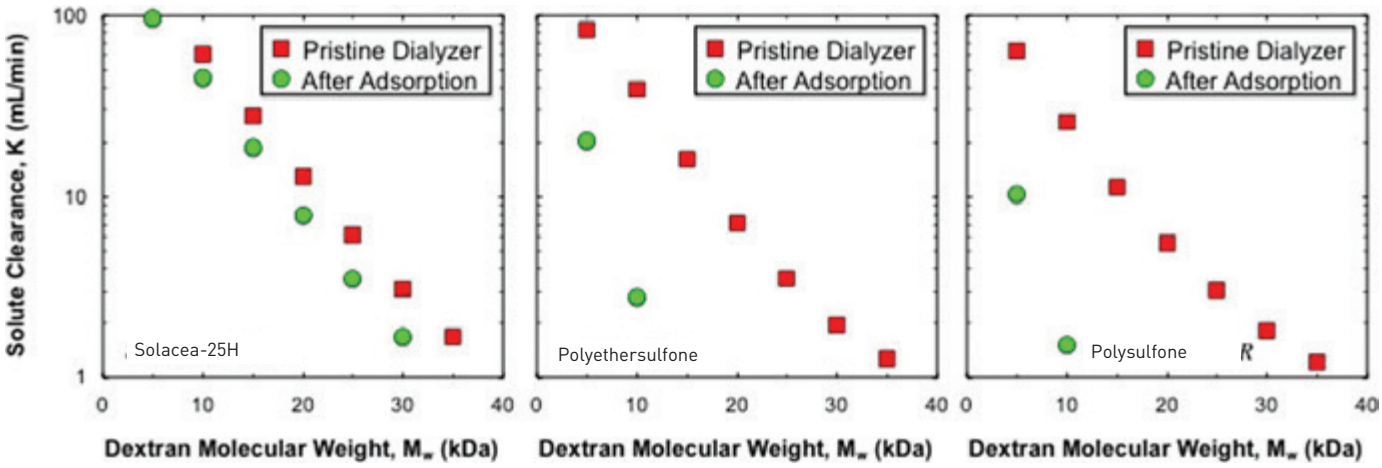
The fibers of SOLACEA are made of cellulose triacetate (without PVP and BPA), which results in the adsorption of proteins that reduces the activation of the coagulation cascade.

What is the scientific evidence supporting SOLACEA?

Adsorption of proteins onto the membrane[19, 21-23]

	Polysfulfone (PS)	Symmetric cellulose triacetate	Asymmetric cellulose triacetate
Amount of proteins	Similar amount		One third of the amount of polysulfone and symmetric cellulose triacetate membranes
Type of proteins	Proteins of the coagulation cascade and those linked to platelet activation	Predominantly albumin	Predominantly albumin
Consequence	Potentially a higher activation of the coagulation cascade	Is thought to reduce the activation of coagulation because albumin has a relative lack of glycosylation, which prevents platelet adhesion	Is thought to reduce the activation of coagulation because albumin has a relative lack of glycosylation, which prevents platelet adhesion

Effect of the adsorption of plasma proteins on performance[23]



Indicates the size of the effect: Polyethersulfone (PES); Polysulfone (PS)

When exposed to blood, the reduced protein adsorption of SOLACEA results in a higher performance.

AUTHORS' CONCLUSION[21]

"The new asymmetric cellulose triacetate membrane has an improved biocompatibility profile as compared to conventional symmetric membrane, the latter being per se characterized by a good biocompatibility." **M. Ronci et al., Proteomics Clinical Applications**

What is the clinical evidence supporting SOLACEA?

STUDY #1

Study performed by BioArtProducts Rostock, 2014, Germany.
Dr. Peter Ahrenholz, Dr. Roland E. Winkler, Dr. Grit Waitz.

STANDARD HEPARIN DOSAGE

Study setup:

- Hemodialysis treatment: post-HDF
- Qb: 350 ml/min., Qd: 600 ml/min., QUF: adapted per patient
- 6 patients in cross-over
- No changes in heparinization

Treatment groups:

- **FX Cordiax:** Polysulfone
- **SOLACEA™:** Asymmetric cellulose triacetate
- **Polyflux™ H:** Polyarylethersulfone
- **FX 80:** Polysulfone

After all of the treatments, HDF post dilution 100ml/min, the clotted capillaries in the patients' dialyzers are estimated after application. The clotted fibers are counted and judged as per the table (right).

Red fibers	Grade
0 ...10	1
11 ... 20	2
21 ... 50	3
51 ... 100	4
>100	5

Results of the visual scoring of clotted fibers:

	FX Cordiax		SOLACEA		Polyflux™ H		FX 80	
Patient	Number of red fibers	Grade	Number of red fibers	Grade	Number of red fibers	Grade	Number of red fibers	Grade
1	>100	5	0-10	1	51-100	4	>100	5
2	0-10	1	11-20	2	>100	5	>100	5
3	>100	5	21-50	3	>100	5	21-50	3
4	51-100	4	21-50	3	>100	5	11-20	2
5	0-10	1	21-50	3	21-50	3	0-10	1
6	51-100	5	0-10	1	21-50	3	21-50	3
Mean		**3,5**		**2,2**		**4,2**		**3,2**

N= 6 patients, crossover study

AUTHORS' CONCLUSION

"Whereas both FMC dialyzers (Cordiax800 and FX80) show, as expected, similar residual blood behavior, SOLACEA-19H is by far the best. The polyflux™ dialyzers had the highest number of clotted fibers." **BioArtProducts Rostock**

STUDY #2

F. Vanommeslaeghe et al. 2019, KIReports.24

REDUCED HEPARIN DOSAGE

93 - 94%

Study setup:

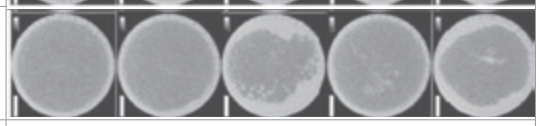
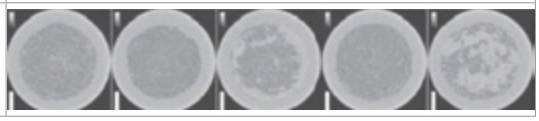
- Hemodialysis treatment: HD
- Qb: 300 ml/min., Qd: 500 ml/min., QUF: adapted per patient

Treatment groups:

SOLACEA: Asymmetric cellulose triacetate	FX800: Polysulfone	Evodial™: Heparin-coated AN-69
Standard dosage of LMWH*	Standard dosage of LMWH*	No LMWH
½ standard dosage of LMWH*	½ standard dosage of LMWH*	

*Regular dosage of LMWH: Tinazaparin 3500 UI (n=3) and Tinazaparin 4500 UI (n=7)

Results of the percentage of open fibers at the end of each dialysis session, measured by micro-CT scanning:

Dialyser	Dose of LMWH	Relative number of open fibers	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Solacea	100%	0,94					
Solacea	50%	0,93					
FX800	100%	0,91					
FX800	50%	0,88[a,b,c]					
Evodial	-	0,32[a,b,c,d]					

N= 10 patients, crossover study

Open fiber = 90% of the fiber surface is open at the end of the treatment

a. p<0,05 vs. SOLACEA 100% LMWH • b. p<0,05 vs. SOLACEA 50% LMWH • c. p<0,05 vs. FX800 100% LMWH • d. p<0,05 vs. FX800 50% LMWH

AUTHORS' CONCLUSION

"In situations in which reduced anticoagulation is indicated, the asymmetric cellulose triacetate (ATA) membrane of SOLACEA dialyzer outperforms a dialyzer with a conventional polysulfone membrane (FX800) or with a heparin-coated polyacrylonitrile membrane (EVODIAL™)." F. Vanommeslaeghe et al. 2019, KIReports.[24]

STUDY #3

F. Vanommeslaeghe et al., 2019, CKJ.

REDUCED HEPARIN DOSAGE

95 - 97%

Study setup:

- Hemodialysis treatment: post- HDF
- Qb: 300 ml/min., Qd: 500 ml/min., Qconv tot: 17,2-17,4L, QUF: adapted per patient

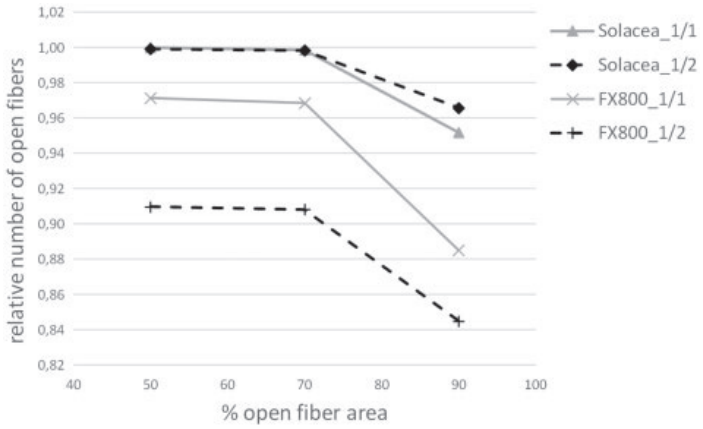
Treatment groups:

SOLACEA: Asymmetric cellulose triacetate	FX Cordiax: Polysulfone
Standard dosage of LMWH*	Standard dosage of LMWH*
½ standard dosage of LMWH*	½ standard dosage of LMWH*

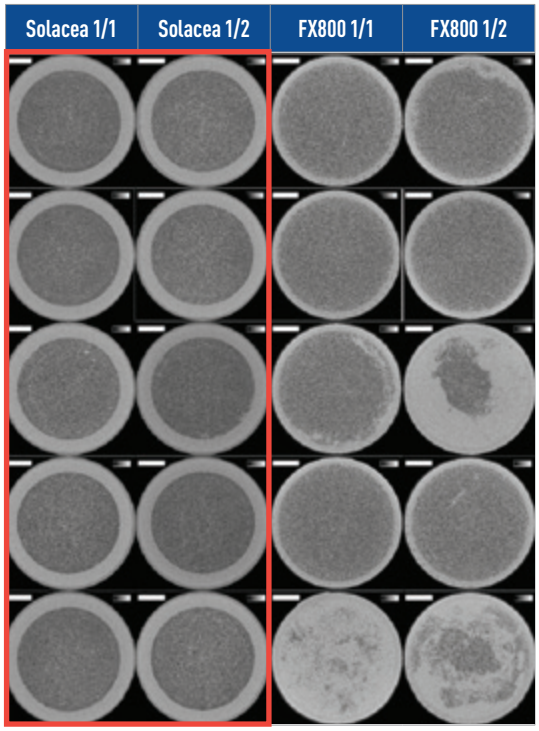
*Regular dosage of LMWH: Tinazaparin 3500 UI (n=3) and Tinazaparin 4500 UI (n=7)

Results of the percentage of open fibers at the end of each dialysis session, measured by micro-CT scanning:

N= 10 patients, crossover study



Fraction of open fibers using different definitions of "open fiber": 50% open area, 70% open area, and 90% open area.



AUTHORS' CONCLUSION

"In conclusion, the SOLACEA membrane seems to be ideal in conditions where systemic anticoagulation is prohibited as it outperforms polysulfone membranes under conditions of low systemic anticoagulation." F. Vanommeslaeghe et al., 2019, CKJ.[25]

STUDY #4

B. Meijers et al., 2020, Poster Presentation ERA-EDTA.26
B. Meijers et al., 2020, CKJ.27

Study setup:

- Hemodialysis treatment: HD or pre-HDF
- Qb: 300-320mL/min., Qd: 700mL/min., QUF: adapted per patient

86 - 94%

Treatment groups:

SOLACEA: Asymmetric cellulose triacetate	
Citrate	**Pre-HDF**
(1 mM) containing dialysate	High volume pre-dilution (Qi/Qd>0,8)

Successful termination of dialysis sessions:

- HD with citrate (1mM) in dialysate: 94%
- Pre-HDF: 86,2%

Results of clearances:

- **HD with citrate** (1mM) in dialysate: better removal of **small water**-soluble molecules
- **Pre-HDF:** better removal of **middle molecular** weight molecules
- No difference in the removal of protein-bound molecules

Molecule	Reduction Rate (HD + citrate)	Reduction Rate (Pre-HDF)	P-value
Blood urea nitrogen	79,4	77,1	0,05
β_2-microglobulin	66	71	0,0009
Myoglobin	61	66	0,0001
Indoxyl sulphate	45,6	46,3	NS
P-cresol sulphate	40,3	39,5	NS

N= 20 patients, crossover study

AUTHORS' CONCLUSION

"Asymmetric cellulose triacetate (ATA) dialyzers have a low clotting propensity. In combination with citrate containing dialysate, asymmetric cellulose triacetate (ATA) may be a suitable alternative to heparin coated membranes for systemic heparin-free hemodialysis."

B. Meijers et al., 2020, Poster Presentation ERA-EDTA.[26]

"A head-to-head comparison study is required to demonstrate that ATA in combination with citrate containing dialysate would be a suitable alternative to heparin-coated membranes for systemic heparin-free hemodialysis."

B. Meijers et al., 2020, CKJ.[27]

STUDY #5

F. Vanommeslaeghe et al., 2020, CKJ.28

Study setup:

- Hemodialysis treatment: HD or pre-HDF or post-HDF
- Qb: 300 ml/min., Qd: 500 ml/min., QUF: adapted per patient
- Pre-HDF: Qs: 50% of Qb; Post-HDF: Qs 25% of Qb

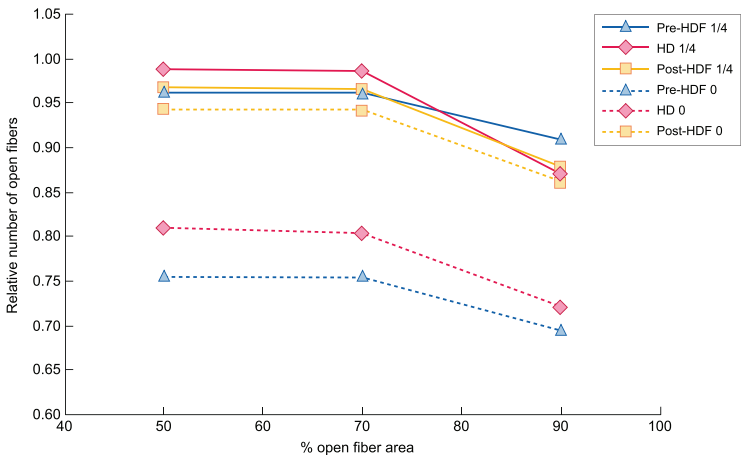
76 - 99%

Treatment groups:

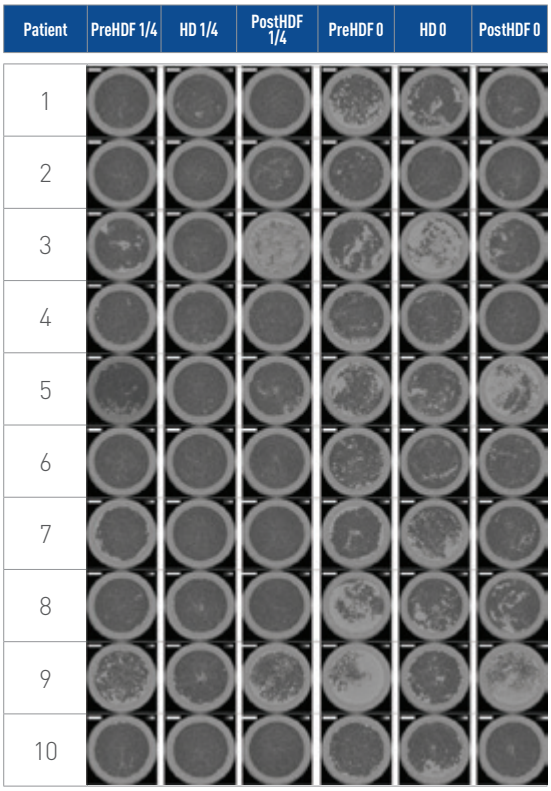
SOLACEA: Asymmetric cellulose triacetate	
¼	pre HDF, HD, post HDF
No LMWH	pre HDF, HD, post HDF

*Regular dosage of LMWH: Tinazaparin 3500 UI (n=5) and Tinazaparin 4500 UI (n=5)

Results of the percentage of open fibers at the end of each dialysis session, measured by micro-CT scanning:



Fraction of open fibers using different definitions of "open fiber": 50% open area, 70% open area, and 90% open area.



AUTHORS' CONCLUSION

"In conclusion, the SOLACEA membrane performs very well even in conditions where systemic anticoagulation is prohibited and thus no single anticoagulant can be applied."

F. Vanommeslaeghe et al., 2020, CKJ.[28]

First impressions: SOLACEA without heparin

Patient history

Age: 72 | **Gender:** Male

Comorbidities:

- Arterial hypertension
- Smoker
- Cerebral infarction in 2009
- Stage 4 CKD (cause: vascular)
- Aortic aneurysm
- Brain aneurysm
- Chronic venous insufficiency
- Parkinson's disease

Case presentation:

The patient was admitted to the ICU after presenting a bilateral renal artery stenosis. An arteriography was performed and a stent was placed in the left renal artery using right femoral access. The patient's stage 4 CKD worsened and hemodialysis was required.

No use of heparin during the hemodialysis sessions:

This was to avoid interference with the drugs administered during the patient's stay in ICU and avoid bleeding after the procedure. Note that the patient was on antiplatelet therapy with Clopidogrel, but this was stopped prior to catheterization.

Dialysis protocol:

In this type of acute or chronic ICU patient, dialysis is performed in daily sessions lasting 3-4 hours, **without heparin**, and with hourly flushing of the dialysis circuit. Until a few months ago, EVODIAL™ was used, as it is a dialyzer that has lower heparinization needs. However, since several studies exist that indicate **SOLACEA** (asymmetric cellulose triacetate) may have equivalent results, we have started using this dialyzer.

Results:

During the month of October, the patient underwent **21 consecutive dialysis sessions – using SOLACEA and without heparin** – with good results in terms of tolerance and an absence of circuit coagulation problems.

"I would like to describe how we successfully treated a patient using SOLACEA dialyzer for 21 consecutive hemodialysis sessions (4 hours per treatment) without systemic anticoagulation."

Physician testimonial on the use of SOLACEA without heparin

"We consider these results with SOLACEA are at least equivalent to those we obtained with EVODIAL. Therefore, SOLACEA is a good alternative for patients in which no heparin can be used."

Dr. D. Rafael Álvarez Lipe
Head of the Department of Nephrology
Hospital Clínico Universitario Lozano Blesa Zaragoza, Spain

SOLACEA dialyzer: A viable solution for patients at risk of bleeding

Allows for a reduction in the use of heparin[24-28]

- **Patient**: lower risk of bleeding
- **Nurses**: fewer actions required
- **Centers**: reduced heparin costs

Suited for a variety of hemodialysis protocols[24-28]

- HD and high flux HDF
- Pre- and post-HDF
- Combined with acetate and/or citrate containing dialysate

High performance

- Great performance in HDF[29,30]
- Better myoglobin clearance in post-HDF in comparison to polysulfone FX Cordiax[25]
- Better β-2-microglobulin clearance than the symmetric cellulose triacetate membrane[21]

Citrasate™ dialysate concentrate also helps reduce heparin dosage

What is Citrasate?

Citrasate differs from traditional dialysate concentrate formulations because it contains both citric acid (0,8 mmol/L) and acetic acid as an acidifying agent. This allows for a reduction in the concentration of acetic acid from 3 mmol/L in traditional formulations to 0,3 mmol/L.

Higher biocompatibility and anticlotting effect

Citric acid has higher biocompatibility and reduces clotting of the dialysis circuit, thus has the advantage over acetic acid. Moreover, citric acid is a well-known anticoagulant since it chelates ionized calcium, an essential component in the clotting cascade. Although the citrate concentration in Citrasate is not high enough to completely block the activation of the clotting cascade, it does allow for a partial anticlotting effect.

Clinical evidence

Reduction in heparin dosage without effecting dialysis efficacy Ahrenholz and Winkler[10] switched 7 patients from a standard dialysis fluid containing acetate to Citrasate and gradually reduced the heparin dose. Despite the heparin reduction by 50%, all the treatments with Citrasate were successfully finished without clotting problems.

PATIENTS AND METHODS

7 patients treated with a high-flux dialyzer

Weeks 1-2: standard dialysate and heparin (bolus + continuously) as baseline

Weeks 3-6: changed standard dialysate to Citrasate; no change in heparin

Weeks 7-10: dialysis with Citrasate and reduction of heparin in the bolus by 50%

Weeks 11-14: dialysis with Citrasate, bolus of heparin remains at 50%, and reduction of heparin in the continuous dosage by 50%, resulting in a total reduction of 50%

There was no other change in treatment parameters (e.g. session duration, blood flow, dialysate flow, choice of dialyzer).

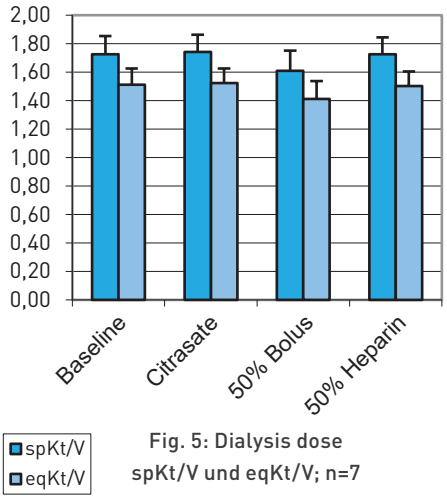


Fig. 5: Dialysis dose
spKt/V und eqKt/V; n=7

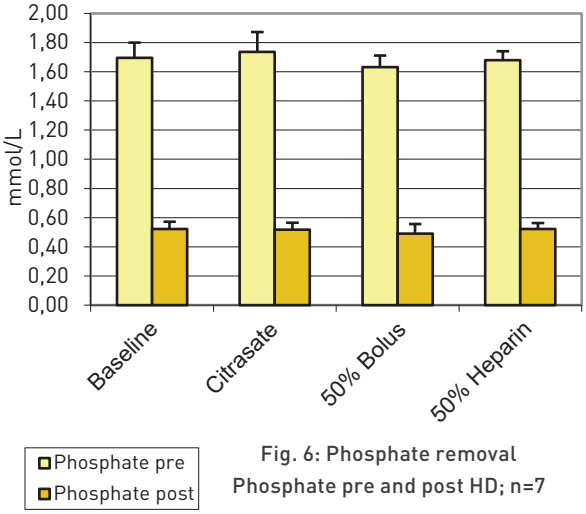


Fig. 6: Phosphate removal
Phosphate pre and post HD; n=7

The results in Fig. 5 show that no significant drop in the dialysis dose or in other clearance values (e.g. phosphate in Fig. 6) takes place despite the reduction of heparin by 50%. In the switch from dialysis fluid containing acetate to Citrasate, without a change in heparin dosage, no increase of dialysis dose (spKt/V) was found in comparison to Kossmann et al.*

*Kossmann RJ et al. Increased efficiency of hemodialysis with citrate dialysate, A prospective controlled study. CJASN 2009; 4:1459-1464

Clinical evidence

Reduction in heparin dosage allows for a shorter bleeding time

Kossmann et al.[9] 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.

PATIENTS AND METHODS

31 chronic patients were identified as having post-dialysis bleeding times >15 minutes.

Months 1-2: standard heparin dose

Months 3-4: heparin dose lowered by 33%

Months 5-6: heparin dose lowered by another 33%

Thus, heparin dose was reduced by 55% from their initial dose.

There was no other change in treatment parameters (e.g. session duration, blood flow, dialysate flow, choice of dialyzer).

The bleeding time was measured and the dialysis dose was registered as Kt/V (urea).

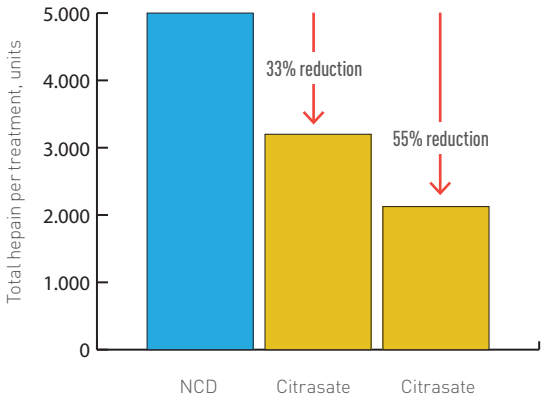


Fig. 3: Heparin dose

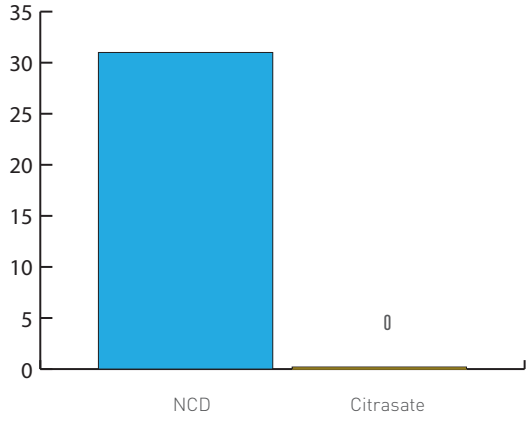


Fig. 4: Patients with bleeding times >15 min

Benefits of Citrasate

The use of Citrasate for high flux hemodialysis:

- Allows for the reduction of heparin by up to 50% without the increased risk of clotting issues in the extracorporeal circuit, and without a reduction of dialysis dose obtained
- Keeps plasma concentrations of calcium and phosphate in a physiologically optimal range
- In combination with reduced heparin dosage, lowers the bleeding times of needle puncture wounds after dialysis
- Increases the hemodynamic stability of hypertensive patients
- Improves biocompatibity, as shown by a decrease in inflammation and oxidative stress

SOLACEA™-H

HIGH FLUX

PERFORMANCE

Clearance (ml/min)[5]	Qb/ Qd (ml/min)	15H	17H	19H	21H	25H
Urea	200/500	196	197	198	199	199
	300/500	266	274	278	283	289
	400/500	312	323	332	340	352
Creatinine	200/500	191	193	195	198	198
	300/500	251	260	267	273	279
	400/500	289	301	311	320	331
Phosphate	200/500	185	188	190	194	196
	300/500	236	246	254	262	271
	400/500	268	282	293	301	318
Vitamin B12	200/500	150	158	164	169	176
	300/500	178	189	199	208	220
	400/500	193	208	219	230	246

Ultrafiltration Coefficient

KUF [mL/hr/mmHg][2]	61	69	72	76	87

Sieving Coefficient[3]

Vitamin B12	1,00
Inulin	1,00
β2-microglobulin	0,85
Myoglobin	0,80
Albumin	0,013

Specifications

Effective surface area (m²)		1,5	1,7	1,9	2,1	2,5
Priming volume (ml)		86	98	108	118	139
Effective length (mm)		227	233	245	254	280
Inner Diameter (µm)		200	200	200	200	200
Membrane thickness (µm)		25	25	25	25	25
Maximum TMP (mmHg)		500	500	500	500	500
Pressure Drop	Qb/Qd [mL/min]	200/500	200/500	200/500	200/500	200/500
	Blood/Dialysate [mmHg]	51/16	47/18	47/16	45/15	43/8
Material	Membrane	ATA™				
	Housing and Header	Polypropylene				
	Potting compound	Polyurethane				
Sterilization method		Dry gamma				
Package		24 pcs/box				

In vitro testing conditions (ISO 8637)

1. Clearance: Qf 0mL/min
2. KUF: bovine blood (Hct 32+- 3%, Protein 60g/L, 37°C), Qb 200mL/min
3. SC: Qb 300 mL/min, Qf 60mL/min

Other compositions are available upon request. For packaging sizes, please contact your local Nipro representative.
Please contact your country representative for product availability and information.

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