

# Evaluation of Different Dialyzers and the Impact of Predialysis Albumin Priming in Intermittent Hemodialysis With Reduced Anticoagulation



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**Introduction:** Systemic anticoagulation is widely used in routine clinical hemodialysis, but can be contraindicated in specific settings. Anticoagulant-free treatment regimens are prone to failure even in chronic intermittent hemodialysis. We quantified fiber blocking in settings of reduced anticoagulation to assess performance of different dialyzers and the potential benefit of albumin priming.

**Methods:** This crossover study included 10 patients performing 4 hours of hemodialysis at midweek in 7 different settings: that is, using Solacea 19H and FX800, both with regular and half dose of anticoagulation, Evodial 1.3 without systemic anticoagulation, and FX800 (half dose) and Evodial (no anticoagulation) when primed with a human albumin solution. Dialyzer fiber blocking was visualized in the dialyzer outlet potting using a 3-dimensional computed tomography (CT) scanning technique on micrometer resolution.

**Results:** No sessions had to be prematurely interrupted because of circuit clotting. The relative number of open fibers post dialysis was not influenced by the reduction of anticoagulation in the Solacea making this dialyzer superior in fiber patency in this setting above both the FX800 with reduced anticoagulation and the Evodial with no anticoagulation. Furthermore, no differences in relative number of open fibers were found in the FX800 and Evodial dialyzers with versus without albumin priming.

**Conclusion:** In situations in which reduced anticoagulation is indicated, the asymmetric triacetate ATA Solacea dialyzer outperforms a dialyzer with a conventional polysulfone membrane (FX800) or with the heparin-coated polyacrylonitrile membrane (Evodial). The use of human albumin to prime the dialysis circuit did not improve dialyzer patency.

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**KEYWORDS:** albumin priming; clotting; coagulation; dialyzer; fiber patency; zero anticoagulation

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Exposure of blood to the extracorporeal circuit activates coagulation pathways, such that systemic anticoagulation is routinely required to provide operative intermittent hemodialysis. Dialysis without anticoagulation might, however, be indicated in patients with acute bleeding disorders, trauma, scheduled surgery, or a high bleeding risk. Citrate-based regional anticoagulation gained popularity, but its use in the setting of chronic dialysis is cumbersome because of the need of continuing vigilance and stringent follow-up during

treatment. Several methods to decrease or even abolish the need for systemic anticoagulation have been proposed, such as predilution, periodic saline flushing, or the use of heparin-coated membranes. However, these techniques face high failure rates if not combined with (reduced dose) anticoagulation.<sup>1</sup>

Exposure of blood to artificial surfaces almost immediately leads to the adsorption of plasma proteins. Mainly high molecular weight proteins, such as albumin, fibrinogen, fibronectin, and globulins, are adsorbed at the membrane surface. The nature of the initial protein layer influences hemocompatibility. Albumin adsorption, in opposition to fibrinogen or gamma-globulin adsorption, tends to decrease platelet adsorption to the material.<sup>2</sup> Adding albumin to the priming solution of the cardiopulmonary bypass circuit is part

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of the standard protocol in many cardiac surgery centers, supposedly causing delayed adsorption of fibrinogen and reduced activation and adhesion of platelets.<sup>3</sup> A meta-analysis linked the use of albumin priming with smaller on-bypass drop in platelet count,<sup>4</sup> suggesting improved biocompatibility. However, other studies (not included in this meta-analysis) did not confirm this finding.<sup>3</sup> Also, when used in the setting of hemodialysis, conflicting results are reported.<sup>5,6</sup>

Multiple surrogate markers can be measured during or after hemodialysis to estimate the activation of coagulation, such as biochemical markers, visual scoring of the filter, and/or venous drip chamber,<sup>7,8</sup> and the possibility to finalize the dialysis session as planned.<sup>9</sup> However, none of these tools is able to objectively quantify coagulation at the level of fiber patency. Recently, a micro-CT protocol was developed that allows the assessment of fiber blocking at single fiber level.<sup>10</sup> This knowledge is of importance, as dialysis efficiency becomes progressively impaired as the total exchange surface of the dialyzer goes down by unnoticed fiber clotting.

The aim of the present crossover study was to evaluate different dialyzers using different membranes when using reduced anticoagulation doses, as well as the potential benefit of predialysis albumin priming. Fiber patency, as assessed by micro-CT scanning, was considered as outcome parameter.

## PATIENTS AND METHODS

### Patients

This single center, randomized crossover study included 10 stable chronic hemodialysis patients (age

**Table 1.** Properties of the different studied dialyzers

	Membrane	Area m <sup>2</sup>	K <sub>UF</sub> ml/h per mm Hg	D <sub>fiber</sub> μm	d μm	Sterilization technique
Solacea-19H	ATA	1.9	72	200	25	gamma
FX 800	PS	1.80	63	210	35	INLINE steam
Evodial 1.3	PAN	1.35	40	210	42	steam

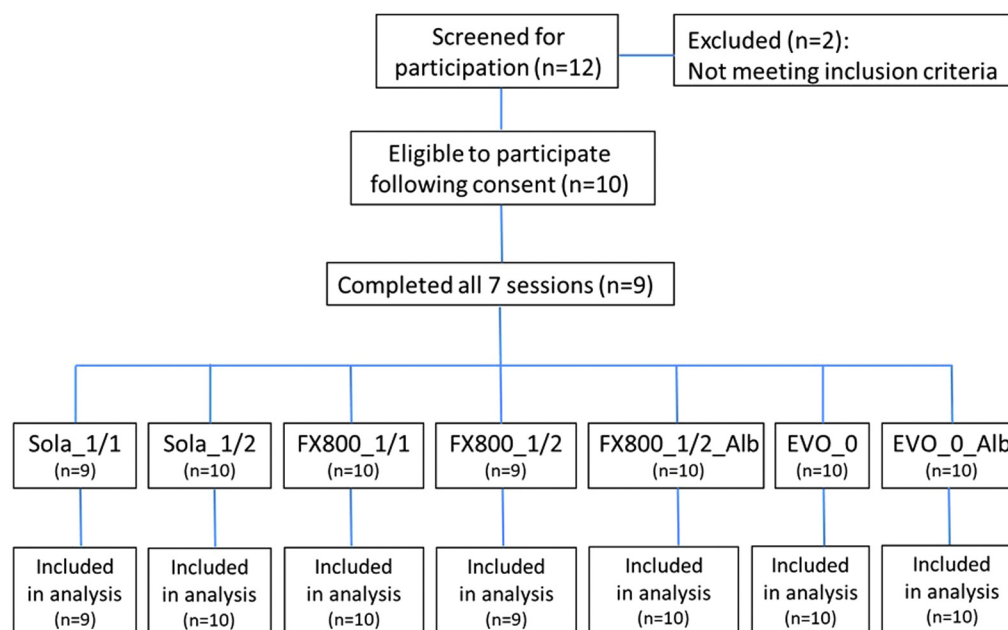
ATA, asymmetric triacetate; d, membrane thickness; D<sub>fiber</sub>, fiber diameter; K<sub>UF</sub>, ultrafiltration coefficient; PAN, polyacrylonitrile; PS, polysulfone.

65.9 ± 16.3, 15.2 [Q1, 9.6; Q3, 25.9] mean months on dialysis, and all male). Patient inclusion is shown in Figure 1. Patients were eligible when they had no known coagulation disorder, active inflammation, or malignancy.

We have opted to use a nonrandomized approach to avoid premature dropout of patients due to loss of circuit because of complete coagulation. As every patient acts as his or her own control, and as there is no reason to presume a legacy effect, order of treatment was deemed to be less important than the risk of dropout.

Double-needle vascular access was achieved through a native arteriovenous fistula (*n* = 7) or a well-functioning double-lumen tunneled central venous catheter, either Hemostar 14.5F (*n* = 2) (Bard, Salt Lake City, UT) or Palindrome 14.5F (*n* = 1) (Medtronic, Minneapolis, MN). Regular treatment of these patients was post dilution hemodiafiltration with high-flux dialyzers FX800 (*n* = 9) (Fresenius Medical Care, Bad Homburg, Germany) or Polyflux 170H (*n* = 1) (Baxter, Deerfield, IL).

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee



**Figure 1.** Patient inclusion flowchart.

**Table 2.** Demographic and clinical data of the patient population at baseline

Characteristic	Specification
Gender (M/F)	10 male/0 female
Age (yr)	65.9 ± 16.3
BMI (kg/m <sup>2</sup> )	27.7 ± 7.0
Dialysis vintage (mo)	15.2 [9.6–25.9]
Renal disease	Nephroangiosclerosis ( <i>n</i> = 3); diabetic nephropathy ( <i>n</i> = 2); IgA nephropathy ( <i>n</i> = 1); focal segmental glomerulosclerosis ( <i>n</i> = 1); retroperitoneal fibrosis ( <i>n</i> = 1); renal cell carcinoma ( <i>n</i> = 1); Alport ( <i>n</i> = 1)
CRP (mg/l)	9.3 [6.4–12.0]
Hb (g/dl)	10.7 ± 1.2
Platelet count (10 <sup>9</sup> /μl)	217 ± 46
aPTT (s)	38.7 ± 5.9
INR (–)	1.0 ± 0.1
Regular anticoagulation dose	Tinzaparin 3500 ( <i>n</i> = 3); Tinzaparin 4500 ( <i>n</i> = 7)
Nondialysis anticoagulants	Asaflo 80 mg ( <i>n</i> = 5)

aPTT, activated partial thromboplastin time; BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin; INR, international normalized ratio.

(Ethical Committee, Ghent University Hospital, EC 2017/1459–B670201734230) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study. The trial was registered at [clinicaltrials.gov](http://clinicaltrials.gov) with identifier NCT03820401.

### Dialysis and Anticoagulation

Each patient, serving as his own control, was dialyzed 7 times at midweek for 240 minutes using a 5008 dialysis monitor (Fresenius Medical Care, Bad Homburg, Germany). Blood flow was set at 300 ml/min and dialysate flow at 500 ml/min in hemodialysis mode, and ultrafiltration rates were according to the patient's interdialytic weight gain and clinical status. During the study sessions, patients were dialyzed with 3 different types of dialyzers: the ATA Solacea 19H (Nipro, Osaka, Japan), the Helixone polysulfone FX800 (Fresenius Medical Care, Bad Homburg, Germany), and the Evodial 1.3 (polyacrylonitrile heparin-coated membrane; Baxter) (Table 1), using different anticoagulation doses and the use of albumin priming or not.

For the 5 midweek test sessions with the Solacea and FX800 dialyzers, patients received either their regular dose of anticoagulants (full dose: Sola\_1/1 and FX800\_1/1) (low molecular weight heparin; Tinzaparin, Leo Pharma, Belgium) or only 50% of their regular dose (1 session Sola\_1/2, and 2 test sessions FX800\_1/2); no

anticoagulant was administered in the 2 midweek test sessions with the Evodial (Evo\_0).

We further distinguished between both sessions with equal amount of anticoagulation by either pre-priming the dialyzers with an albumin solution (i.e., FX800\_1/2\_Al and Evo\_0\_Al) or not (i.e., FX800\_1/2 and Evo\_0). After adding 10 ml human albumin 20% (CAF-DCF, Brussels, Belgium) to the dialyzer inlet, 200 ml saline solution was recirculated for 5 minutes to ensure optimal exposure. During this procedure, pump speed was set at 100 ml/min to avoid foaming and bubbles.

Each experimental session was preceded with 2 wash-in sessions with the same type of dialyzer to be used in the experimental dialysis, but always with full regular anticoagulant dose and without dialyzer pre-priming with albumin.

### Micro-CT Scanning and Coagulation Quantification

To quantify the incidence of fiber blocking after 4 hours of hemodialysis, dialyzers were scanned with a reference noninvasive micro-CT scanning technique.<sup>10</sup> In brief, at the end of the dialysis session, a standard rinsing procedure of the hemodialyzer was performed using exact 300 ml rinsing solution. Next, the hemodialyzer was dried using continuous positive pressure ventilation, simultaneously in blood and dialysate compartment. Dialyzer fiber blocking was visualized in the dialyzer outlet potting using a 3-dimensional CT scanning technique on micrometer resolution, as previously described.<sup>10</sup>

For this study, 3 different thresholds were used to define the surface area of an open fiber: 50%, 70%, and 90% of the cross-section of a nonused fiber. Comparing the number of nonblocked fibers in the tested dialyzer with the total number of fibers as measured in 3 non-used dialyzer samples, provided an objective estimate of the percentage of fiber blocking.

### Statistical Analysis

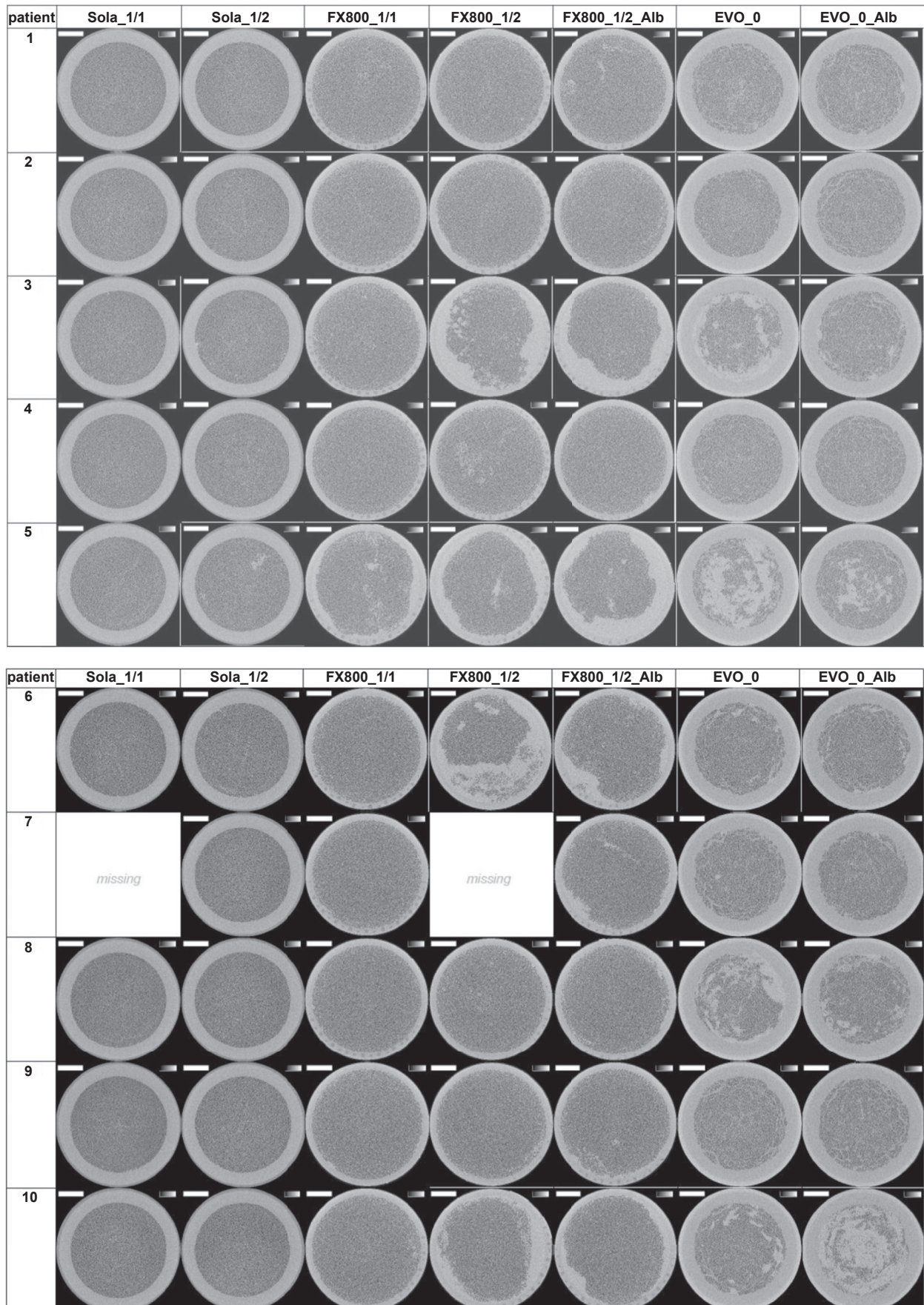
Statistical analyses were performed using SPSS (version 24; SPSS Inc, Chicago, IL). Continuous variables were summarized either as mean ± SD or median value with interquartile range. To compare different related variables, Friedman tests with Wilcoxon *post hoc* tests were performed.

**Table 3.** Characteristics of the dialysis sessions in the different experimental settings

Characteristic	Sola_1/1	Sola_1/2	FX800_1/1	FX800_1/2	FX800_1/2_Al	EVO_0	EVO_0_Al
Dialysis length (min)	241 ± 2	242 ± 2	241 ± 3	240 ± 1	240 ± 1	242 ± 3	241 ± 2
Q <sub>UF</sub> (ml)	2000 [1175; 2500]	2000 [1100; 2798]	2000 [1250; 2600]	2197 [1000; 2800]	2200 [1100; 2800]	2200 [1300; 2550]	1600 [950; 2650]

Mean ± SD, median [25%; 75%].

No differences among the 7 different sessions (Friedman *P* > 0.05).



**Figure 2.** Cross-sections halfway the outlet potting in 10 patients and 7 tested settings. The grayscale range is 0–0.5 cm<sup>-1</sup>. Bar = 10 mm.

Power analysis was based on data from a previously performed crossover study in patients dialyzed with 2 different types of dialyzer.<sup>10</sup> Using the relative number of patent fibers as primary outcome, we calculated that including 10 patients would yield sufficient power.

## RESULTS

Relevant demographic and clinical data of the patient population at baseline are summarized in [Table 2](#). All flow settings were maintained according to the protocol, and none of the sessions in either arm needed to be terminated prematurely because of clotting. [Table 3](#) shows the dialysis durations and the ultrafiltration rates in the 7 test sessions. One patient missed the session with Solacea with full anticoagulation (Sola\_1/1) and the one with FX800 with half anticoagulation (FX800\_1/2), respectively, because of bloodstream infection and active gastrointestinal bleeding.

The reconstructed images of the cross-sections halfway the outlet potting are presented in [Figure 2](#) for the 10 patients and the 7 experimental dialysis sessions. Open fibers are visualized as black dots.

The number of open fibers in the 3 nonused Solacea, FX800, and Evodial dialyzer samples was  $12,087 \pm 4$ ,  $13,051 \pm 1$ , and  $8640 \pm 4$ , respectively, indicating high consistency in the number of fibers in nonused dialyzers for all studied dialyzer types.

The numbers of open fibers relative to the number in nonused dialyzers are given in [Table 4](#). The patency of the heparin-coated Evodial dialyzer was inferior when applied with no extra anticoagulation, as compared with dialysis with Solacea or FX800 dialyzers with standard anticoagulation. Irrespective of the considered threshold for counting open fibers (i.e., 50%, 70%, or 90% open area), halving anticoagulation dose resulted in relatively fewer open fibers as compared with full anticoagulation in the FX800, whereas no differences were seen in the Solacea dialyzer. With respect to the impact of priming dialyzers with human albumin, no differences were found in fiber patency in the FX800 and Evodial dialyzers.

The lack of impact of an albumin layer is also visualized in [Figure 3](#), showing the relative number of fibers considered as open (*y*-axis) according to 3 different thresholds of surface area that are open (50%, 70%, and 90%, *x*-axis). We observe no differences between the dialyzers whether or not primed with human albumin. Also, there is clearly a more substantial drop in number of open fibers in the Evodial, from 70% to 90% open fiber, indicating that the fibers of FX800, even with only half the standard anticoagulation dose, are more resistant to even small degrees of fiber blocking during dialysis.

## DISCUSSION

The present crossover study investigated the performance with respect to fiber blocking of 3 different dialyzer types, under different anticoagulation strategies, and with the potential impact of priming the dialyzer with a human albumin solution. For this comparison, we quantified fiber patency using an objective and quantitative evaluation technique on a micrometer scale. Our main findings are as follows: first, the Solacea dialyzer is superior in fiber patency when dialyzing with reduced anticoagulation (i.e., half the standard anticoagulation dose) or with the heparin-coated Evodial dialyzer; second, priming the FX800 and Evodial dialyzers with a human albumin solution did not ameliorate resistance to fiber blocking.

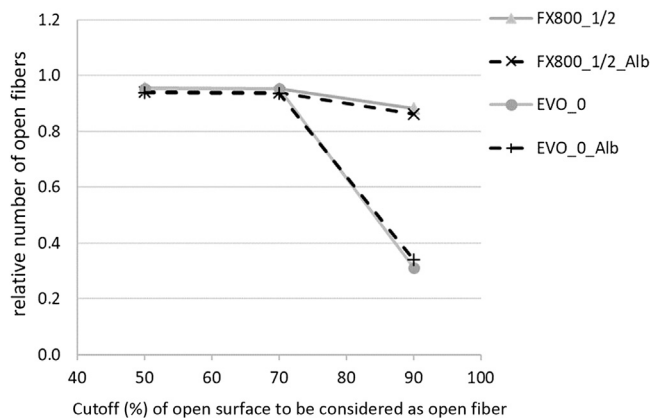
Clotting in the extracorporeal hemodialysis circuit might result in premature termination of the treatment and, in worst case scenario, even blood loss corresponding to the extracorporeal circuit volume. Although this is most often avoided by a liberal use of anticoagulant agents, several patient conditions might necessitate use of reduced or even zero systemic anticoagulation, like in the case of active bleeding or increased risk of bleeding. In such cases, it is important to use a dialyzer that minimally activates the coagulation cascade. Our data indicate that using a Solacea dialyzer allows safe reduction of the regular dose of systemic anticoagulation to half the regular dose. This outperformance might be explained by the improved biocompatibility of the asymmetric triacetate ATA membrane. Because this membrane is manufactured without the need for hydrophilization agents, it is claimed to have a low risk of hypersensitivity and less platelet count decrease.<sup>11</sup> Membranes made from cellulose triacetate have superior biocompatibility, but are not suitable for high-volume on-line hemodiafiltration. The ATA membrane has a dense skin layer on the internal surface at the blood side, and an external support layer with large pores, maintaining high permeability and filtration performance while preserving blood compatibility because of this asymmetric structure and smooth surface. The membrane has lower protein adsorption as compared with conventional membranes.<sup>12</sup>

The use of the heparin-coated Evodial dialyzer, manufactured with polyethyleneimine on the blood-side surface to reduce electronegativity and resulting in capacity to adsorb heparin,<sup>13</sup> could be considered a worthy alternative in cases in which bleeding might be a problem. This should result in less or no clotting even when no systemic anticoagulation is used. We previously showed, using the same accurate quantification technique as described here, that this dialyzer with a heparin-coated membrane is superior to dialyzers with

**Table 4.** Relative number of open fibers in the 7 tested dialyzers for the thresholds of 50%, 70%, and 90% open fiber area

% Open area	Sola_1/1	Sola_1/2	FX800_1/1	FX800_1/2	FX800_1/2_Al	EVO_0	EVO_0_Al	P
50% open area	1.00 [1.00; 1.00] (0.94-1.00)	1.00 [0.99; 1.00] (0.98-1.00)	0.98 <sup>a</sup> [0.97; 0.99] (0.84-1.00)	0.96 <sup>b,c</sup> [0.74; 0.98] (0.61-0.98)	0.95 <sup>b,c</sup> [0.80; 0.97] (0.68-0.97)	0.95 <sup>b,c</sup> [0.66; 0.99] (0.52-1.00)	0.94 <sup>b,c</sup> [0.85; 0.99] (0.39-1.00)	<0.001
70% open area	1.00 [0.99; 1.00] (0.94-1.00)	1.00 [0.99; 1.00] (0.98-1.00)	0.98 <sup>a</sup> [0.96; 0.99] (0.84-1.00)	0.95 <sup>b,c</sup> [0.74; 0.98] (0.60-0.98)	0.95 <sup>b,c</sup> [0.79; 0.97] (0.68-0.97)	0.95 <sup>b,c</sup> [0.65; 0.98] (0.50-0.99)	0.93 <sup>b,c</sup> [0.85; 0.98] (0.38-1.00)	<0.001
90% open area	0.94 [0.93; 0.94] (0.90-0.95)	0.93 [0.91; 0.94] (0.89-0.95)	0.91 <sup>a</sup> [0.88; 0.92] (0.79-0.94)	0.88 <sup>b,c</sup> [0.69; 0.90] (0.52-0.92)	0.86 <sup>b,c</sup> [0.72; 0.89] (0.63-0.90)	0.32 <sup>b,c,d,e</sup> [0.24; 0.49] (0.17-0.57)	0.32 <sup>b,c,d,e</sup> [0.25; 0.50] (0.09-0.62)	<0.001

<sup>a</sup>P < 0.05 vs. Sola\_1/2.  
<sup>b</sup>P < 0.05 vs. Sola\_1/1.  
<sup>c</sup>P < 0.05 vs. FX800\_1/1.  
<sup>d</sup>P < 0.05 vs. FX800\_1/2.  
<sup>e</sup>P < 0.05 vs. FX800\_1/2Alb.  
 Median [25%; 75%] (minimum-maximum).



**Figure 3.** Relative number of fibers considered as open (y-axis) according to different cutoff criteria defined by percentage of fiber surface area that needs to be open (50%, 70%, or 90%, x-axis) in the FX800 and Evodial dialyzer with and without priming with albumin.

noncoated membranes during 4 hours of hemodialysis without systemic anticoagulation.<sup>14</sup> The present study revealed, however, that this superiority becomes absent when comparing fiber patency in the Evodial with that in a polysulfone FX800 dialyzer using half the regular dose of anticoagulant. Even more, the heparin-coated Evodial dialyzer becomes inferior when compared with the ATA Solacea dialyzer with reduced anticoagulation.

In line with earlier studies reporting high failure rates,<sup>1,15</sup> this finding questions the evidence supporting the use of dialyzers with heparin-coated membranes in the setting of 4-hour heparin-free hemodialysis. Our present findings add that the Solacea dialyzer seems to be promising for use in conditions in which systemic anticoagulation is contraindicated, as even under conditions of half the regular anticoagulation dose, fiber patency was maintained.

Albumin is the most commonly used colloidal additive to the priming solution of extracorporeal circuits.<sup>5</sup> Low-dose albumin attenuates the rate of fibrinogen binding to polyvinyl chloride.<sup>16</sup> The coating of artificial biomaterials with a protein layer supplied by the albumin priming is supposed to alter its biocompatibility and reduces the rate of clotting. However, albumin is expensive, may put patients at risk for anaphylactic reaction, and clinical trials investigating improvement of coagulant properties yielded conflicting results.<sup>5,17,18</sup> In this study, we evaluated dialyzer patency after albumin priming both for dialyzers with a conventional noncoated polysulfone membrane (FX800) or with a heparin-coated acrylonitrile membrane (Evodial), but could not observe any positive impact. Consequently, neither associated risk of albumin priming nor the costs of albumin can be justified in this setting of chronic dialysis patients.

We can only hypothesize why albumin coating was not beneficial in our study. One cause could be the

difference in structure and binding properties of serum albumin<sup>19</sup> and the presence of fibrinogen fragments in blood of chronic hemodialysis patients.<sup>20</sup> These changes in plasma protein composition may influence adsorption and exchange rate of proteins at the foreign surface. The chemical structure of the membrane is another important factor. Proteomic analysis of polysulfone-based helixone showed significantly higher amounts of fibrinogen and ficolin-2 adsorption, both known to activate intrinsic coagulation versus cellulose triacetate.<sup>2</sup> These data are in agreement with our results that showed a higher patency rate with triacetate. The fact that Evodial did not result in less fiber blocking may be related to the fact that heparin-coated surfaces still adsorb protein, the necessary substrate for platelet adhesion to the material.<sup>21,22</sup> Finally, platelet function is of interest. Advanced renal failure leads to a platelet function defect that will be in part corrected by hemodialysis.<sup>23</sup> As a result, hemodialysis is associated with enhanced platelet aggregation<sup>24</sup> and the formation of micro particles with pro-coagulant activity.<sup>25</sup> The interaction between activated platelets, circulating micro particles and the nature and extent of protein adsorption has not been extensively studied and might be another reason why albumin was not able to improve fiber patency.

A limitation of the present study could be the small number of patients ( $n = 10$ ), but this protocol allowed us to use each patient as his own control over the 7 experimental sessions, powering this study. Also, we used a sensitive reference micro-CT scanning technique to visualize the individual open fibers, such that fiber patency could be determined in the most accurate way as feasible today.

Another limitation is the difference in surface area between the heparin-coated dialyzer and the 2 other dialyzers. This could induce more coagulation by increased shear stress, but on the other hand could also reduce the contact activation. Our current study design does not allow for making any meaningful conclusions on the effect of surface area, however.

In conclusion, a dialyzer with an asymmetric triacetate ATA membrane (Solacea) has superior coagulant properties as reflected in the higher relative number of open fibers at the end of dialysis sessions with reduced anticoagulation. The cost and risks of priming the dialysis circuit with human albumin are not outweighed by improvements of dialyzer patency, both in polysulfone- and heparin-grafted dialyzers. Its use in chronic intermittent hemodialysis is thus not justified.

## DISCLOSURE

All the authors declared no competing interests.

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## AUTHOR CONTRIBUTIONS

FVO, WVB, and SE designed the study; FVO, FDS, and SE carried out the clinical experiments; IJ and MB performed the scanning; IJ performed image reconstructions; MB formatted the images; SE analyzed the data; FVO, FDS, and SE wrote the paper; and all authors thoroughly reviewed the paper.

## SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Consort Statement.

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