Performance and Hemocompatibility of a Novel Polysulfone Dialyzer: A Randomized Controlled Trial

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Key Points

- We investigated the performance and hemocompatibility of a new polysulfone hemodialyzer with enhanced membrane properties.
- β2-Microglobulin removal rate was noninferior to both comparator dialyzers and superior to a cellulose-acetate–based dialyzer.
- The dialyzer showed a favorable hemocompatibility profile on the basis of markers for complement, cell and contact activation, and coagulation.

Abstract

Background High-flux dialyzers effectively remove uremic toxins, are hemocompatible to minimize intradialytic humoral and cellular stimulation, and have long-term effects on patient outcomes. A new dialyzer with a modified membrane surface has been tested for performance and hemocompatibility.

Methods This multicenter, prospective, randomized, crossover study involved the application of the new polysulfone-based FX CorAL 600 (Fresenius Medical Care, Bad Homburg, Germany), the polyarylethersulfone-based Polyflux 170H (Baxter Healthcare Corporation, Deerfield, IL), and the cellulose triacetate–based SureFlux 17UX (Nipro Medical Europe, Mechelen, Belgium), for 1 week each, to assess the noninferiority of the FX CorAL 600’s removal rate of β2-microglobulin. Performance was assessed by removal rate and clearance of small- and medium-sized molecules. Hemocompatibility was assessed through markers of complement, cell activation, contact activation, and coagulation.

Results Of 70 patients, 58 composed the intention-to-treat population. The FX CorAL 600’s removal rate of β2-microglobulin was noninferior to both comparators (P<0.001 versus SureFlux 17UX; P=0.0006 versus Polyflux 170H), and superior to the SureFlux 17UX. The activation of C3a and C5a with FX CorAL 600 was significantly lower 15 minutes after treatment start than with SureFlux 17UX. The activation of sC5b-9 with FX CorAL 600 was significantly lower over the whole treatment than with SureFlux 17UX, and lower after 60 minutes than with the Polyflux 170H. The treatments with FX CorAL 600 were well tolerated.

Conclusions FX CorAL 600 efficiently removed small- and medium-sized molecules, showed a favorable hemocompatibility profile, and was associated with a low frequency of adverse events in this study, with a limited patient number and follow-up time. Further studies, with longer observation times, are warranted to provide further evidence supporting the use of the new dialyzer in a wide range of therapeutic options, and for long-term treatment of patients on hemodialysis, to minimize the potential effects on inflammatory processes.

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Introduction
The majority of patients who receive RRT rely on extracorporeal treatments (1). Here, the dialyzer is the cornerstone for adequate dialysis performance and a central element on which efforts are focused to provide the most hemocompatible extracorporeal circuit.

High-flux dialyzers, applied either in hemodialysis (HD) or in online hemodiafiltration (HDF), deliver the most efficient elimination of uremic retention solutes over the relevant mol wt range. High-flux dialyzers aim at approaching the elimination characteristics of the kidney, and a sharp mol wt cutoff prevents excessive albumin loss. The importance of removing both small- and medium-sized mol wt uremic solutes (2) has been underscored by studies identifying β2-microglobulin as an independent risk factor for mortality among patients on dialysis (3,4). Moreover, the hydraulic characteristics of high-flux dialyzers allow for online HDF, which has gained wide clinical acceptance on the basis of evidence of further improved elimination of uremic solutes (5) and improved survival (6), particularly when treated with high convection volumes (7–9).

The role of dialyzer hemocompatibility for different patient outcomes has been widely investigated. Upon contact of blood with foreign surfaces, cell reactions and release of humoral factors may be triggered. The latter includes the activation of the complement system, with a release of complement factors and the induction of cytokines and coagulation factors (10). Release of humoral factors may contribute to various pathophysiologic processes in patients on HD (11). This hypothesis is supported by recent findings from a population-based cohort of people without CKD, where the complement factors C5a and sC5b-9 were associated with markers of acute and chronic inflammation processes and of endothelial dysfunction (12). Complement activation during dialysis treatments is most prominent with cellulose-based membranes; however, synthetic membranes also induce transient complement activation (13). Besides this transient reaction, complement activation has been reported to have a long-term effect on the outcomes of patients on dialysis, such as increased infection risk, fibrosis, and cardiovascular events (14–16). Complement activation has also been discussed as a factor contributing to the higher mortality risk that has been associated with cellulose-based membranes, as compared with synthetic membranes (17).

Therefore, with potential acute and long-term implications through cellular and humoral activation by artificial surfaces, a good hemocompatibility profile is central to the design of new dialysis membranes (10,18). The FX CorAL 600 dialyzer was recently developed as part of the ongoing effort to improve dialyzer hemocompatibility. This dialyzer contains a membrane comprising a blend of polysulfone and polyvinylpyrrolidone, with small amounts of α-tocopherol added to stabilize the blood-side surface of the membrane (19). The objective of this study was to determine the effect of this modification on performance and hemocompatibility of the new dialyzer, in comparison with two commercially available dialyzers.

Materials and Methods
Study Design and Patients
The objective of the study was to investigate the removal rate and clearance of uremic retention solutes, and determine the hemocompatibility and safety of the new dialyzer, in comparison with two commercially available dialyzers.

This was a prospective, randomized, crossover, and multicenter study. It was performed between August and December, 2018, in six study centers in Germany. We enrolled adult patients with chronic kidney failure, a minimum of 3 months on online HDF, fistula or graft as vascular access, and without major illnesses and known allergies to trial products or related products. Patients were studied during three online HDF sessions in the course of a week, with study dialyzers in a randomized order. Patients were allocated to one of the six possible treatment sequences through central randomization, stratified by study center.

The new dialyzer FX CorAL 600 (Fresenius Medical Care, Bad Homburg, Germany) was compared with two commercially available dialyzers with good performance in small- and medium-sized molecule removal: one with a synthetic membrane material, the polyarylethersulfone-based Polyflux 170H dialyzer (Baxter Healthcare Corporation, Deerfield, IL) (20); and one cellulose triacetate–based dialyzer, the SureFlux 17UX (Nipro Medical Europe, Mechelen, Belgium) (21) (Table 1). A 1 week follow-up for safety surveillance was included at the end of the study, yielding a total study duration of 4 weeks per patient.

Treatments were performed with the 5008 or the 6008 HD system (Fresenius Medical Care) as HDF in online postdilution mode. Treatment parameters (including a blood flow rate of at least 300 ml/min, a dialysate flow rate of ≥500 ml/min, a minimum treatment time of 240 minutes, and a patient-adjusted ultrafiltration rate) remained unchanged between study phases. Substitution flow rate was manually set, and anticoagulation was provided according to center practice.

The study was approved by the ethics committees of the participating centers and the national competent authority. Patients were informed orally and in writing on the purpose, meaning, and risk of the study, and were included in the study after signing and dating the informed consent form. The study was executed in accordance with the Declaration of Helsinki in its current version.

Outcome Variables and Laboratory Methods
Dialyzer performance was assessed using removal rate and clearance of β2-microglobulin, urea, creatinine, phosphate, myoglobin, and α1-microglobulin. To calculate removal rate, plasma samples were taken at the midweek session from the arterial line pre- and postdialysis. To calculate clearance, samples were taken from both the arterial and venous line at 60 minutes after treatment start.

Complement factors, blood cell counts, markers of cell and immune activation, coagulation factors, and contact activation factors were analyzed in samples taken predialysis, 15 and 60 minutes after treatment start, and postdialysis (at 240 minutes). Thrombin-antithrombin (TAT) was measured
predialysis, at 120 minutes, and at 240 minutes after treatment start.
All laboratory analyses were performed following the methods given in Supplemental Table 1.

Statistical Analyses
The primary outcome of this study was noninferiority of the FX CorAL 600 versus the SureFlux 17UX and the Polyflux 170H with respect to the removal rates of β2-microglobulin. The noninferiority margin was set to −2% for the difference between the FX CorAL 600 and either comparator dialyzer.

The sample size estimation was determined on the basis of the hypothesis of noninferiority of the FX CorAL 600 dialyzer compared with the SureFlux 17UX and Polyflux 170H for the outcome measure of β2-microglobulin removal rate. Assuming a lower limit of noninferiority of −2%; an intraclass correlation of 0.4, due to clustering of patients in centers; a one-sided significance level of 1.25%; a drop-out rate of 25%; and a group size divisible by six (the number of study centers), a minimum sample size of 48 patients was estimated.

Removal rates (%) from time=0 minutes (predialysis) to time=240 minutes after start of HDF (postdialysis), and plasma clearances (kb) at 60 minutes after start of HDF, were calculated for β2-microglobulin, myoglobin, α1-microglobulin, phosphate, creatinine, and urea. Laboratory parameters were corrected for hematocrit, as appropriate. All formulas are given in Supplemental Table 1.

Assuming no carry-over effect, a linear mixed model was used for statistical analysis. This model included the fixed effects “period” and “dialyzer,” and the random effects “center” and “patient.” The comparison of the FX CorAL 600 with each of the other two comparator dialyzers was performed by defining contrasts or estimators of the fixed effect “dialyzer.” Noninferiority comparisons were made on the basis of the two contrasts that allow for the estimation of the mean difference in the primary variable removal rate of β2-microglobulin between the FX CorAL 600 and the SureFlux 17UX and between the FX CorAL 600 and the Polyflux 170H, respectively. Further details on the two-step test and adjustments according to Bonferroni and Holm (22) are given in Supplemental Appendix 1.

Because the intention-to-treat (ITT) and per-protocol (PP) populations were identical, no sensitivity analyses were applicable.

Noninferiority comparisons were made on the basis of the two contrasts that allow for the estimation of the mean difference in the primary variable removal rate of β2-microglobulin between the FX CorAL 600 and the SureFlux 17UX and between the FX CorAL 600 and the Polyflux 170H, respectively. Further details on the two-step test and adjustments according to Bonferroni and Holm (22) are given in Supplemental Appendix 1.

Because the intention-to-treat (ITT) and per-protocol (PP) populations were identical, no sensitivity analyses were applicable. Secondary efficacy analyses were conducted on the ITT/PP population. Safety analysis was based on the safety population. Here, all data available from each randomized patient were taken into account.

Sample size estimation and statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Clinical Trial registry name and registration number
Comparative Safety and Clinical Performance of Dialyzers Applied During Post-dilution Online Hemodiafiltration (eMPORA II), NCT03611218

Results

Patients and Treatments
A total of 70 patients from six study centers were recruited. These patients composed the safety population, of which 12 patients were excluded due to dropout before study start (one patient), premature study termination (one patient), and missing or invalid primary efficacy parameter (ten patients). Thus, 58 patients represented the ITT population, which was identical to the PP population because no further criteria to exclude patients from the PP population were applicable.

Patients enrolled in the study were, on average, 68 years old and 74% were male (Table 2). Following the study protocol, treatment parameters during the three study phases were nearly unchanged with blood flow rate of approximately 300 ml/min, dialysate flow rate of 500 ml/min, and treatment time of 4.5 hours; anticoagulation was predominantly performed with unfractionated heparin (Table 3).

| Parameter | Value (N=58) |
|-----------|--------------|
| Age (yr), mean±SD | 67.8±13.4 |
| Sex, % male | 74 |
| Body weight (kg), mean±SD | 80.5±26.2 |
| Female | Male |
| 90.1±19.7 |
| Body mass index (kg/m²), mean±SD | 28.9±6.6 |
| Primary renal disease, N (%)* | Diabetes 21 (36) |
| Hypertension/large vessel disease | 17 (29) |
| Glomerulonephritis | 7 (12) |
| Cystic/hereditary/congenital disease | 6 (10) |
| Others/unknown | 21 (36) |
| Time on RRT (mo), median (range) | 90 (3–212) |

*More than one disease could be documented.
myoglobin was lower than with both comparators. The performance of the FX CorAL 600 was not different for α1-microglobulin and phosphate, and was slightly, but not clinically relevantly, lower for urea and creatinine (Supplemental Table 3).

Complement Activation

With all dialyzers, a peak of C3a and C5a concentrations at 15 minutes after treatment start was observed, which then declined until the end of the treatment (Figure 2, Supplemental Table 4). Moreover, with all dialyzers, sC5b-9 increased within the first 60 minutes and then also declined until the end of the treatment (Figure 2). The increase from predialysis to peak level of C3a and C5a at 15 minutes was significantly less with the FX CorAL 600 than with the SureFlux 17UX, and was comparable with the Polyflux 170H. The increase of sC5b-9 from predialysis to all time points during treatment was significantly less with the FX CorAL 600 than with the SureFlux 17UX, and was also less, but not significantly so, compared with the Polyflux 170H (Supplemental Table 4). When comparing the three dialyzers at the peak concentrations of C3a and C5a (15 minutes), and of sC5b-9 (60 minutes), the FX CorAL 600 showed significantly lower levels of all complement factors than the SureFlux 17UX (P<0.001 for C3a; P=0.02 for C5a; P<0.001 for sC5b-9; Tables 5 and 6). The difference between the FX CorAL 600 and SureFlux 17UX for sC5b-9 persisted until treatment end. The FX CorAL 600 and Polyflux 170H showed comparable peak levels of C3a and C5a (measured at 15 minutes, P=0.68 and P=0.82, respectively). Peak levels of sC5b-9 (measured at 60 minutes) were higher for the Polyflux 170H than for the FX CorAL 600 (P=0.02).

Cell Activation

Leukocytes showed a typical transient decrease at 15 minutes after treatment start, which recovered at 60 minutes, and decreased again toward the end of the treatment (Figure 3). The mean decrease at 15 minutes was significantly less with the FX CorAL 600 than with both other dialyzers (P<0.001 versus both the SureFlux 17UX and Polyflux 170H; Table 7). Polymorphonuclear elastase increased in the first 60 minutes with all three dialyzers, and then remained stable for the rest of the treatment (Supplemental Figure 1). The increase was highest with the Polyflux 170H and, at

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**Table 3. Treatment parameters applied in study phases using indicated dialyzer**

| Treatment parameter | FX CorAL 600 (N=58) | SureFlux 17UX (N=58) | Polyflux 170H (N=58) |
|---------------------|---------------------|----------------------|----------------------|
| Effective blood flow rate (ml/min) | 306±29 | 303±25 | 305±26 |
| Dialysate flow rate (ml/min) | 500±0.1 | 500±0.3 | 500±0.0 |
| Substitution volume (L) | 17.6±4.5 | 15.3±2.8 | 17.4±4.8 |
| Ultrafiltration volume (L) | 2.2±1.2 | 2.2±1.3 | 2.2±1.3 |
| Effective treatment time (min) | 272±29 | 270±29 | 270±29 |

Dialyzer Performance Measures

The least squares means of the removal rate of β2-microglobulin were 70%, 51%, and 68% for the FX CorAL 600, the SureFlux 17UX, and the Polyflux 170H, respectively (Figure 1). Noninferiority of FX CorAL 600 versus both comparators was statistically significant (P<0.001 versus SureFlux 17UX; P=0.0006 versus Polyflux 170H; Table 4). Further, as derived from the confidence intervals of the difference between the dialyzers, the removal rate of β2-microglobulin was significantly higher with the FX CorAL 600 than with the SureFlux 17UX, and was comparable with the Polyflux 170H (Table 4). The descriptive analysis of further performance parameters is presented in Supplemental Table 3. Clearance of β2-microglobulin with the FX CorAL 600 was significantly higher than with SureFlux 17UX (P<0.001). The clearance and removal rate of 2-microglobulin with the FX CorAL 600 was significantly greater than with the SureFlux 17UX, and was comparable with the Polyflux 170H, and was also less, but not significantly so, compared with the Polyflux 170H (Supplemental Table 4). When comparing the three dialyzers at the peak concentrations of C3a and C5a (15 minutes), and of sC5b-9 (60 minutes), the FX CorAL 600 showed significantly lower levels of all complement factors than the SureFlux 17UX (P<0.001 for C3a; P=0.02 for C5a; P<0.001 for sC5b-9; Tables 5 and 6). The increase of sC5b-9 from predialysis to all time points during treatment was significantly less with the FX CorAL 600 than with the SureFlux 17UX, and was also less, but not significantly so, compared with the Polyflux 170H (Supplemental Table 4). When comparing the three dialyzers at the peak concentrations of C3a and C5a (15 minutes), and of sC5b-9 (60 minutes), the FX CorAL 600 showed significantly lower levels of all complement factors than the SureFlux 17UX (P<0.001 for C3a; P=0.02 for C5a; P<0.001 for sC5b-9; Tables 5 and 6). The difference between the FX CorAL 600 and SureFlux 17UX for sC5b-9 persisted until treatment end. The FX CorAL 600 and Polyflux 170H showed comparable peak levels of C3a and C5a (measured at 15 minutes, P=0.68 and P=0.82, respectively). Peak levels of sC5b-9 (measured at 60 minutes) were higher for the Polyflux 170H than for the FX CorAL 600 (P=0.02).
treatment end, it proved to be significantly higher than with both of the other dialyzers (P<0.001 for comparison with FX CorAL 600; P=0.02 for comparison with the SureFlux 17UX; Table 7).

Platelets decreased slightly in the first 15 minutes and then remained nearly unchanged over the remainder of the treatment. With the Polyflux 170H, the strongest decrease was observed from baseline to 240 minutes (P=0.002 for comparison with the FX CorAL 600; P<0.001 for comparison with the SureFlux 17UX; Table 7).

TAT concentrations showed a slight increase with all three dialyzers throughout the treatment, with no statistically significant difference at 240 minutes (Table 7).

Kallikrein increased slightly throughout the treatment for all dialyzers. After 240 minutes, the FX CorAL 600 had a lower, but statistically nonsignificant, increase (5.13 U/L) than both the SureFlux 17UX (11.09 U/L, P=0.09) and the Polyflux 170H (10.85 U/L, P=0.11).

### Adverse Events

For each dialyzer, a comparable number of patients experienced at least one adverse event (AE) (Table 8). In total, 22, 20, and 18 AEs occurred with the FX CorAL 600, the SureFlux 17UX, and the Polyflux 170H, respectively. Of these, one, 12, and eight AEs, respectively, have been classified by the investigator as possibly being related to the dialyzer applied in the respective study phase. One serious AE was reported during the phase with the FX CorAL 600 and SureFlux 17UX, and one further serious AE (shunt thrombosis) occurred before any study-related intervention; neither event was related to the medical procedure or the dialyzer. Most AEs resolved without sequelae; four were ongoing at study termination.

### Discussion

This randomized, controlled, multicenter trial investigated performance and hemocompatibility of the novel polysulfone-based, high-flux dialyzer, FX CorAL 600. Non-inferiority of the removal rate of β2-microglobulin, the primary outcome parameter of the study, was confirmed for FX CorAL 600 versus both comparator dialyzers. Moreover, the removal rate of β2-microglobulin was significantly higher with the FX CorAL 600 than with the cellulose triacetate-based dialyzer, and was comparable with the Polyflux 170H dialyzer. This removal rate has been achieved with moderate blood flow rates of approximately 300 ml/min, and substitution flow rates of around 70 ml/min, and can certainly be further enhanced by applying higher blood flow rates and substitution flow rates, as observed in other studies investigating dialyzer performance (23–25).

We compared the FX CorAL 600 with the commercially available, polysulfone-based Polyflux 170H dialyzer and the cellulose triacetate–based SureFlux 17UX, which is often used as an alternative in case of intolerance to synthetic membranes (26,27). All three dialyzers showed the typical pattern of a fast increase of the complement factors C3a and C5a, as measured 15 minutes after treatment start, which was significantly lower with both dialyzers with synthetic membranes compared with the dialyzer containing cellulose triacetate. These differences were more pronounced than previously published comparisons between polysulfone and cellulose triacetate dialyzers; however, the investigated membrane in the FX CorAL 600, and possibly also in the comparator membranes, differ from those studied earlier (28–30). Our *in vivo* data are further supported by *in vitro* investigations confirming less activation of complement factors C3a, C5a, and sC5b-9 with the FX CorAL 600 than with the SureFlux 17UX (19). After the initial increase, C3a and C5a then declined throughout the remainder of the treatment, possibly due to convective elimination, because the molecular mass of C3a and C5a (9–11 kDa) (31,32) is similar to that of β2-microglobulin (11.2 kDa), which is effectively removed by high-flux dialyzers. On the other hand, downregulation within the patient (33) and metabolic processes may also contribute to the decrease over the course of the treatment.

For sC5b-9, the lowest increase, particularly at 60 minutes, was observed with the FX CorAL 600 compared with both the SureFlux 17UX and the Polyflux 170H dialyzer. Because intradialytic elimination likely plays no role, due to sC5b-9’s molecular mass of approximately 1000 kDa, this marker may better reflect the complement activation associated with high-flux dialyzers, such as those used in this study, than small molecules, such as C3a and C5a.

All investigated complement factors, and their intradialytic behavior, underscore better hemocompatibility of the FX CorAL 600 dialyzer with a polysulfone-based membrane when compared with the cellulose triacetate–based dialyzer.

| Table 4. Removal rate of β2-microglobulin |
|-----------------------------------------|
| **Dialyzer** | **N** | **LSMean Removal Rate (%)** | **SEM** | **97.5% CI** | **P Value** | **95% CI** | **P Value** |
|----------------|-------|-----------------------------|--------|--------------|-------------|------------|-------------|
| FX CorAL 600   | 58    | 70.33                       | 1.35   | 15.82 to 22.17 |             |           |             |
| SureFlux 17UX  | 58    | 51.34                       | 1.35   |              |             |           |             |
| Polyflux 170H  | 58    | 67.68                       | 1.35   |              |             |           |             |
| Difference FX CorAL 600–SureFlux 17UX | 58    | 18.99                       | 1.40   | <0.001       | 16.22 to 21.76 | <0.001   |             |
| Difference FX CorAL 600–Polyflux 170H | 58    | 2.66                        | 1.40   | −0.52 to 5.83 | 0.0006      | −0.11 to 5.42 | 0.0006     |

Least squares mean and test for noninferiority of FX CorAL 600 versus SureFlux 17UX and versus Polyflux 170H. LSMean, least squares mean; SEM, standard error of the mean; 95/97.5% CI, 95/97.5% confidence interval of the differences between investigated dialyzers.

*P value to confirm noninferiority.*
Figure 2. | Course of plasma levels of complement factors (A) C3a, (B) C5a, and (C) sC5b-9 over the treatment by investigated dialyzer. Means±SD are displayed. Pre, predialysis.
Table 5. Least squares mean of differences between dialyzers over time of treatment, comparing the FX CorAL 600 versus SureFlux 17UX

| Parameter | LSMean, µg/L (95% CI) | P Value |
|-----------|-----------------------|---------|
|           | Pre 15 Min 60 Min 240 Min | Pre 15 Min 60 Min 240 Min |
| C3a       | 6.66 (−21.07 to −34.40) 61.96 (34.23 to 55.19) 21.42 (−6.31 to 49.16) | 0.64 <0.001 0.05 0.13 |
| C5a       | −0.011 (−0.039 to 0.017) 0.033 (0.005 to 0.061) (−0.070 to −0.014) | −0.005 0.45 0.02 0.004 |
| sC5b-9    | 1.07 (−18.09 to 20.23) 66.27 (47.12 to 85.43) 30.71 (11.56 to 49.87) | 0.91 <0.001 <0.001 0.002 |

LSMean, least squares mean; 95% CI, 95% confidence interval of LSMean; pre, predialysis; 15 min, 15 minutes after start of HDF; 60 min, 60 minutes after start of HDF; 240 min, at the end of HDF; HDF, hemodiafiltration.

Table 6. Least squares mean of differences between dialyzers over time of treatment, comparing the FX CorAL 600 versus Polyflux 170H

| Parameter | LSMean, µg/L (95% CI) | P Value |
|-----------|-----------------------|---------|
|           | Pre 15 Min 60 Min 240 Min | Pre 15 Min 60 Min 240 Min |
| C3a       | 6.36 (−14.39 to 27.10) 4.33 (−16.58 to 25.24) −12.53 (−33.27 to 8.21) 2.72 (−18.02 to 23.47) | 0.55 0.68 0.24 0.80 |
| C5a       | −0.029 (−0.115 to 0.057) −0.010 (−0.097 to 0.076) 0.068 (−0.017 to 0.154) −0.008 (−0.094 to 0.077) | 0.51 0.82 0.12 0.85 |
| sC5b-9    | 0.54 (−14.97 to 16.04) 11.78 (−3.83 to 27.39) 18.25 (2.75 to 33.75) 13.33 (−2.17 to 28.83) | 0.95 0.14 0.02 0.09 |

LSMean, least squares mean; 95% CI, 95% confidence interval of LSMean; pre, predialysis; 15 min, 15 minutes after start of HDF; 60 min, 60 minutes after start of HDF; 240 min, at the end of HDF; HDF, hemodiafiltration.

Figure 3. Course of leukocyte count over the treatment by investigated dialyzer. Means±SD are displayed. Pre, predialysis.
and, in regards to sC5b-9, to the polyarylethersulfone-based dialyzer. The modification of the polysulfone membrane in the FX CorAL 600 dialyzer, by stabilization of the polyvinylpyrrolidone on the blood-side surface of the membrane, supports the formation of a more robust hydrophilic layer. The hydrophilic layer on the membrane surface enhances hemocompatibility of polysulfone membranes through improved antifouling ability, which yields less protein adsorption and lower coagulation activation (34–36).

It has been observed that the transiently elevated plasma C3a and C5a levels shortly after treatment start are accompanied by a complementary reduction of peripheral blood leukocyte counts. The three dialyzers showed a similar overall pattern, but there was a significantly lower decrease with the FX CorAL 600 as compared with both other dialyzers, in line with previously published evidence (28). This observation supports an association of complement activation with pulmonary vascular leukocyte sequestration, and also suggests that leukocytes begin to reappear in the peripheral blood only when the complement activation diminishes (37).

The transient increase of complement factors and occurrence of leukopenia has not been reflected by acute symptoms during treatment in our study. However, previous studies showed that complement activation can be associated with various pathophysiologic processes, which may clinically manifest over a longer period of time, and with the development of cardiovascular diseases (38). In a

| Parameter                  | LSMean | P Value   |
|---------------------------|--------|-----------|
| Change after 15 min       |        |           |
| Leukocytes (10^9/L)       | −0.38  | <0.001    |
| PMN elastase (µg/L)       | 16.33  | <0.001    |
| Platelets (10^9/L)        | −15.3  | <0.001    |
| TAT (µg/L)                | 6.90   | 0.81      |
| Kallikrein (U/L)          | 5.13   | 0.16      |
| Change after 240 min      |        |           |
| Leukocytes (10^9/L)       | −0.87  | <0.001    |
| PMN elastase (µg/L)       | 19.34  | 0.26      |
| Platelets (10^9/L)        | −10.5  | <0.001    |
| TAT (µg/L)                | 5.06   | 0.68      |
| Kallikrein (U/L)          | 11.09  | 0.09      |

LSMean, least squares mean; A, FX CorAL 600; B, SureFlux 17UX; C, Polyflux 170H; PMN, polymorphonuclear; TAT, thrombin-antithrombin III.

| Characteristics of Adverse Events | FX CorAL 600 | SureFlux 17UX | Polyflux 170H |
|-----------------------------------|--------------|---------------|--------------|
| Number of patients with AE        | 14           | 13            | 11           |
| Number of AEs in the respective   | 22           | 20            | 18           |
| dialyzer phase                    |              |               |              |
| Relation of AE to medical         | 0/4/18       | 1/13/6        | 0/13/5       |
| procedure, definitively/possibly/ |              |               |              |
| not related                       |              |               |              |
| Relation of AE to medical device, |              |               |              |
| definitively/possibly/not related |              |               |              |
| Serious adverse events            | 1            | 1             | 0            |
|                                   | (road traffic accident) | (cystitis) |
| Symptoms of AEs definitively or     |              |               |              |
| possibly related to medical device |              |               |              |
| Anemia                            | 1            |               |              |
| Palpitations                      | 1            |               |              |
| Flatulence                        | 1            |               |              |
| Asthenia                          | 1            |               |              |
| Feeling hot                       | 1            |               |              |
| Muscle spasms (cramps)            | 1            | 1             |              |
| Myalgia                           | 2            |               |              |
| Dizziness                         | 2            |               |              |
| Headache                          | 1            | 1             | 1            |
| Involuntary muscle contractions    |              |               |              |
| Thrombosis in device (filter      |              |               |              |
| clotting)                         | 1            |               |              |
| Pruritus                          | 1            |               | 4            |

Symptoms of AEs definitively or possibly related to medical device cannot be specifically linked to the dialyzer. Analysis performed in the safety population. One further serious AE (shunt thrombosis) occurred in week −1, before starting treatment with any study dialyzer; patient was withdrawn from study. One patient prematurely terminated the study before being treated with the Polyflux 170H. AE, adverse event.
nondialysis population, C5a and sC5b-9 were suggested to be involved in acute and chronic inflammation and in endothelial dysfunction (12). Similarly, complement C3 and its activation product, the anaphylatoxin C3a, was found to be associated with carotid intima–media thickness, ankle-arm BP index, and may, therefore, have a possibly pathophysiologic role in the development of cardiovascular diseases (39). The role that the dialysis membrane can play in inflammatory processes and possible long-term effects for patients on dialysis could not be assessed in this study with an exposure of only 1 week; however, this potential association warrants further study.

Polymorphonuclear elastase is a marker of cell activation and is released upon degranulation of leukocytes (40). With all investigated dialyzers, it increased in the first hour of the treatment—to the lowest extent with the FX CorAL 600, in line with the lowest leukocyte drop—and remained at the same level until the end of the treatment. The observation of an initial increase when complement factors also transiently rise, and of no further stimulation of leukocyte degranulation when complement levels decrease, would support the hypothesis of an activation by complement, although this is still a matter of debate (41).

The activation of coagulation was assessed by platelet count and TAT concentrations. In all cases, the decrease in platelet count was moderate, and less than that found in a study on dialyzers based on similar membrane materials (42). Similar platelet counts before dialysis in all phases hint at both postdialytic recovery of platelet counts and no long-term effect of the intradialytic decrease in platelet counts. TAT increased slightly and steadily during the treatment, as similarly observed in other studies (43), with no significant difference between dialyzers. Thus, some thrombin formation seems to be ongoing, despite systemic anticoagulation, which was applied equally in all three study phases. The absence of macroscopic clotting in the dialyzers (except one case, see Table 8) nevertheless confirms that the applied systemic anticoagulation has been sufficient, despite small increases of TAT, and that the coagulation activation potential of the dialyzers is low.

Kallikrein, a precursor of bradykinin, is generated upon contact activation, i.e., blood contact with negative charges on surfaces (44). There was no evidence of clinically relevant acute contact activation for any of the dialyzers. The FX CorAL 600 had the lowest (but not statistically significant) measured levels of contact activation versus both the SureFlux 17UX and Polyflux 170H. This tendency toward lower contact activation may be related to the lower surface charge observed with the FX CorAL 600 membrane compared with that in the other two dialyzers (19).

AEs were recorded irrespective of being related to the study medical devices or the medical procedure. Given the approximately 200 treatments that were performed with each dialyzer, <10% were affected by an AE. Thus, overall, few AEs occurred during the study; this must also be considered against the background that, in the HD population, intradialytic events that are related to the dialysis procedure, but also to the patients’ pathologic state, are well known and are reported in a wide range of frequencies (45,46). With the new FX CorAL 600, only one AE occurred (headache), which was rated by the investigator to be possibly related to the study dialyzer. No event of hypersensitivity to the new dialyzer was reported; therefore, on the basis of this study, the novel dialyzer can be rated as well tolerated.

The study has been designed to analyze possible acute effects of the membrane material during the dialysis treatment. Therefore, we cannot conclude on long-term effects of performance and hemocompatibility of the new dialyzer on patient outcomes, which requires further studies with longer-term application of this dialyzer.

The FX CorAL 600 dialyzer demonstrated noninferiority in terms of β-microglobulin removal rates compared with two commercially available dialyzers. It efficiently removes small- and medium-molecules during online HDF, shows a favorable hemocompatibility profile, and is associated with a low frequency of AEs in this study of a limited patient number and follow-up time. Clinical studies with longer observation times are warranted to address the effect on hemocompatibility markers associated with inflammatory processes and cardiovascular outcomes. These studies may provide further evidence supporting the use of the new dialyzer in a wide range of therapeutic options and long-term treatments.

Disclosures
A. Erlenkötter, A. Gauly, B. Griesshaber, J. Kennedy, L. Rauber, M. Stauss-Grabo, and A.M. Zawada report being full-time employees of Fresenius Medical Care, and report personal fees from Fresenius Medical Care, outside the submitted work. M. Kempkes-Koch reports receiving grants, personal fees, and nonfinancial support from Fresenius Medical Care, during the conduct of the study. All remaining authors have nothing to disclose.

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Author Contributions
G. Ehlerding, M. Kempkes-Koch, J. Kennedy, L. Rauber, W. Ries, H. Schmidt-Gürtler, S. Wagner, and S. Sätzsch were responsible for investigation; A. Erlenkötter and J. Kennedy were responsible for methodology; A. Erlenkötter and M. Stauss-Grabo conceptualized the study; A. Gauly wrote the original draft; A. Gauly and A. M. Zawada reviewed and edited the manuscript; and B. Griesshaber and M. Stauss-Grabo were responsible for project administration.

Supplemental Material
This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000302021/-/DCSupplemental.
Supplemental Appendix 1: Statistical analysis—Bonferroni

Holm adjustment of linear mixed model.

Supplemental Table 1. Analytical methods of investigated parameters.

Supplemental Table 2. Formula for calculation of removal rates, plasma clearance and correction of laboratory parameters for hematoctrit.

Supplemental Table 3. Least squares mean (LSMean) of removal rates and clearance of performance markers.

Supplemental Table 4. Least squares mean (LSMean) of absolute changes from treatment start to 15 min, 60 min, 240 min for C3a, C5a (A), C5a (B), SC5b9 (C).

Supplemental Figure 1. Course of PMN elastase over the treatment by dialyzer.

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