

Efficacy and safety of novel polyethersulfone dialyzers: a multicenter, randomized, crossover study

Seong Geun Kim^{1,*}, Semin Cho^{2,*}, Jin Kyung Kwon³, Minsang Kim³, Soojin Lee⁴, Jeong Min Cho², Hyuk Huh⁵, Min Woo Kang⁶, Soie Kwon⁷, Jung-ho Shin⁷, Yun Kyu Oh^{8,9}, Dong Ki Kim^{3,9,10}

¹Department of Internal Medicine, Inje University Sanggye Paik Hospital, Seoul, Republic of Korea

²Department of Internal Medicine, Chung-Ang University Gwangmyeong Hospital, Gwangmyeong, Republic of Korea

³Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

⁴Department of Internal Medicine, Uijeongbu Eulji University Medical Center, Uijeongbu, Republic of Korea

⁵Department of Internal Medicine, Hallym University Kangnam Sacred Heart Hospital, Seoul, Republic of Korea

⁶Department of Internal Medicine, Korea University Guro Hospital, Seoul, Republic of Korea

⁷Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea

⁸Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, Republic of Korea

⁹Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

¹⁰Kidney Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea

Background: The continuous rise in healthcare costs associated with hemodialysis has become a growing concern in South Korea, where hemodialysis is the predominant treatment modality for end-stage kidney disease. Currently, all dialyzers are imported, underscoring the need for domestically manufactured alternatives. This study aims to evaluate the clinical efficacy and safety of a domestically produced novel polyethersulfone dialyzer.

Methods: This multicenter, randomized, crossover clinical trial evaluated the non-inferiority of the Synoflux series dialyzer (Synopex Inc.) compared to the commercially available FX Classix dialyzer (Fresenius Medical Care) in maintenance hemodialysis patients. Each patient was randomly assigned to one of two treatment sequences, receiving each dialyzer for 4 weeks in a crossover design. The primary endpoints were the urea reduction ratio (URR) and single-pool Kt/V (spKt/V). Secondary endpoints included the clearance of middle molecules and safety outcomes.

Results: The Synoflux series dialyzer met the non-inferiority criteria for both URR (mean difference, -1.29% ; 95% confidence interval [CI], -2.01 to -0.58) and spKt/V (mean difference, -0.06 ; 95% CI, -0.10 to -0.02). It demonstrated superior clearance of middle-molecule solutes, including cystatin C, β 2-microglobulin, and prolactin. No serious adverse events related to the dialyzer were reported, and the frequency of hypotension or clotting events was comparable between the dialyzers.

Conclusion: The Synoflux series dialyzer demonstrated non-inferior efficacy and acceptable safety compared to the widely used FX Classix dialyzer, thereby supporting its clinical applicability as a domestically produced alternative for maintenance hemodialysis.

Keywords: Artificial kidneys, Chronic renal insufficiency, Renal dialysis, Uremic toxins

Received: April 25, 2025; **Revised:** May 13, 2025; **Accepted:** May 18, 2025

Correspondence: Dong Ki Kim

Department of Internal Medicine, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Republic of Korea. E-mail: dkkim73@gmail.com

ORCID: <https://orcid.org/0000-0002-5342-1197>

*Seong Geun Kim and Semin Cho contributed equally to this study as co-first authors.

© 2025 by The Korean Society of Nephrology

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial and No Derivatives License (<https://creativecommons.org/licenses/by-nc-nd/4.0/>) which permits unrestricted non-commercial use, distribution of the material without any modifications, and reproduction in any medium, provided the original works properly cited.

Introduction

The incidence of end-stage kidney disease (ESKD) in South Korea has more than doubled over the past 12 years, rising from 9,335 cases in 2010 to 18,598 cases in 2022. Additionally, the overall prevalence has increased by 90% over the past decade, from 70,211 cases in 2012 to 134,826 cases in 2022 [1,2]. This significant rise ranks among the highest globally, placing South Korea second in the incidence rate of ESKD among the member countries of the Organization for Economic Cooperation and Development [3]. Hemodialysis remains the most widely utilized modality for kidney replacement therapy. While advancements in dialysis care and management have contributed to improved clinical outcomes [1,4,5], the rising prevalence of ESKD and the growing reliance on hemodialysis have resulted in substantial economic burdens [6]. Consequently, there is an increasing need to alleviate these burdens by implementing cost-effective strategies, including the domestic production of essential medical devices such as hemodialysis dialyzers.

Recently, the Synoflux series high-flux dialyzer (Synopex Inc.) received regulatory approval from the Korean Ministry of Food and Drug Safety as a class III medical device following a non-inferiority evaluation against commercially available dialyzers. The membrane is manufactured using a modified polyethersulfone (PES) membrane, which is known for its high biocompatibility, efficient toxin removal, and robust structural stability [7,8]. However, there is currently no clinical evidence available to verify its safety and efficacy in real-world patient settings. Therefore, this clinical trial aims to evaluate the non-inferiority of the domestically developed Synoflux series hemodialysis dialyzers compared to commercially available alternatives in Korean patients with ESKD. Additionally, this study seeks to collect and analyze safety data to ensure clinical applicability and regulatory compliance in routine hemodialysis practice.

Methods

Ethical considerations

This study received approval from the Institutional Review Boards of the participating clinical centers (see [Additional information](#)). All procedures conformed to the principles outlined in the Declaration of Helsinki and were conducted

in accordance with the International Conference on Harmonization Good Clinical Practice guidelines. Written informed consent was obtained from all participants prior to enrollment, with additional safeguards implemented for elderly individuals as appropriate. Participant confidentiality was strictly maintained through the use of coded data and secure storage. Provisions for compensation and prompt management of adverse events were also established.

Study design

This study is a multicenter, randomized, crossover clinical trial designed to evaluate the non-inferiority of the Synoflux series dialyzer compared to the commercially available FX Classix dialyzer (Fresenius Medical Care AG & Co. KGaA) in patients with ESKD undergoing maintenance hemodialysis. After obtaining written informed consent (Visit 1), eligible participants underwent a screening period of up to 2 weeks to confirm their eligibility based on the inclusion and exclusion criteria. Qualified participants were then randomized in a 1:1 ratio into one of two groups: Group 1 (Synoflux dialyzer first) or Group 2 (control dialyzer first) at Visit 2. Randomization was performed using a block randomization method, with the allocation sequence generated by a central computer. This process was conducted by an independent statistician who was not involved in the clinical trial to ensure allocation concealment.

Patients underwent hemodialysis three times per week, with each session lasting 4 hours. The study comprised two consecutive 4-week treatment periods. In Period 1 (Visit 2 to Visit 3), Group 1 received the Synoflux dialyzer, while Group 2 received the control dialyzer. In Period 2 (Visit 4 to Visit 5), participants switched to the alternative dialyzer type, ensuring that all subjects were exposed to both devices. All dialyzers used in the study had a membrane surface area of either 1.4 or 1.8 m², and this surface area was consistently maintained after crossover to ensure comparability between treatment periods. The dialysis schedule and duration remained consistent across both groups. To ensure consistency in efficacy assessment, key dialysis parameters—including blood flow rate, dialysate flow rate, and session duration—were strictly standardized at 4 hours on the days of efficacy evaluation (Visit 3 and Visit 5). While ultrafiltration volume was individualized based

on clinical needs, we ensured during study planning and execution that the variation in ultrafiltration between these visits would remain within 0.5 kg per participant to minimize confounding. The overall study design is summarized in Fig. 1.

Eligibility criteria

Participants were eligible for inclusion if they met the following criteria: age ≥ 19 years; undergoing stable thrice-weekly maintenance hemodialysis for a minimum of 3 months prior to enrollment; provided written informed consent after receiving a comprehensive explanation of the study; and were deemed suitable for study participation through to completion at the discretion of the investigator.

Exclusion criteria included patients undergoing hemodialysis on a schedule other than three times per week; those receiving concomitant peritoneal dialysis; individuals planning to transition to peritoneal dialysis or undergo kidney transplantation during the study period; and those with residual renal function, defined as a daily urine output of ≥ 500 mL despite three-times-weekly dialysis. Patients were also excluded if they had a history of acute infection within 4 weeks prior to screening or were diagnosed with active malignancy, liver cirrhosis, HIV infection, bleeding disorders, severe congestive heart failure, recent myocardial infarction, stroke, seizure, thrombosis, or uncontrolled arrhythmia. Additionally, women who were pregnant,

breastfeeding, or unwilling to use appropriate contraception were deemed ineligible for participation.

Efficacy endpoints

The primary efficacy endpoint was the urea reduction ratio (URR, %) at the 4th week of each dialysis period, calculated using the following formula: $URR (\%) = [(C_{pre} - C_{post}) / C_{pre}] \times 100$, where C_{pre} and C_{post} represent the pre- and post-dialysis blood urea nitrogen (BUN) concentrations, respectively. Single-pool Kt/V (spKt/V) was also assessed as an index of dialysis adequacy, calculated as follows: $spKt/V = -\ln(R - 0.008 \times t) + [(4 - 3.5R) \times UF/W]$, where R is the post-/pre-dialysis BUN ratio, t is the dialysis duration (hours), UF is the ultrafiltration volume (L), and W is the post-dialysis body weight (kg). Secondary efficacy endpoints included the reduction ratio (%) of middle-molecule solutes such as cystatin C, $\beta 2$ -microglobulin, myoglobin, prolactin, and interleukin-6 (IL-6).

Safety endpoints

The primary safety endpoint was the preservation of albumin, measured by tracking serum albumin levels, at three predefined time points: baseline (Visit 2), the crossover point (Visit 3), and the end of the study (Visit 5). Secondary safety assessments included the monitoring of adverse events during each dialysis session. Intradialytic hypoten-

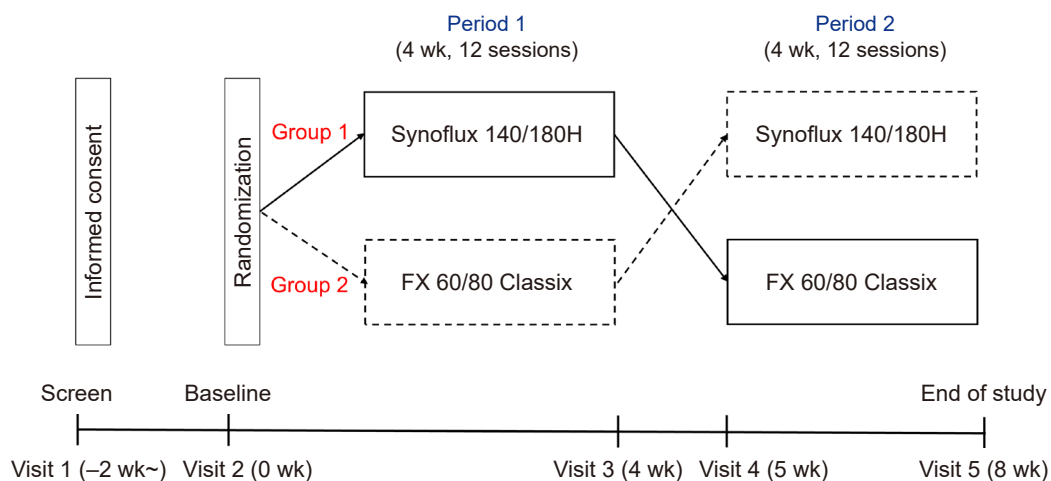


Figure 1. Study protocol.

Synoflux dialyzer, Synopex Inc.; FX Classix dialyzer, Fresenius Medical Care AG & Co. KGaA.

sion (IDH) was defined as a nadir systolic blood pressure <90 mmHg following dialysis initiation. Dialyzer clotting was defined as the premature termination of dialysis due to circuit coagulation or the need for increased heparin dosing, and it was evaluated on a per-session basis. In addition to IDH, patient-reported symptoms, including dizziness, nausea, muscle cramps, and chest discomfort, were systematically collected during each dialysis session.

Statistical analysis

Between-group comparisons of continuous variables were conducted using either an independent t test or a Wilcoxon rank-sum test. Categorical variables were compared using the chi-square test or Fisher exact test, as appropriate. For paired comparisons of continuous variables between test and control dialyzers (e.g., spKt/V, URR, and reduction ratios of middle-molecule solutes), a paired t test or Wilcoxon signed-rank test was utilized based on the data distribution. Differences in outcomes were reported as mean differences with corresponding 95% CIs.

The primary efficacy endpoints were analyzed using a non-inferiority framework. Non-inferiority was assessed utilizing the two one-sided test procedures. The non-inferiority margin was predefined as 10% of the mean value of the control dialyzer for spKt/V and 5% for URR. For serum albumin, which served as the primary safety endpoint, a non-inferiority margin of 5% was applied to evaluate albumin preservation. Adverse events were summarized descriptively. IDH and dialyzer clotting events were assessed on a per-session basis, and formal hypothesis testing for adverse events was not the primary focus.

A priori sample size was calculated assuming a non-inferiority margin (δ) of 5%, within-subject standard deviation of 8.07%, and no true difference ($\epsilon = 0$), based on parameters reported in a previous randomized controlled trial comparing a medium cut-off (MCO) dialyzer and a high-flux dialyzer [9]. This yielded 21 patients per sequence for 80% power at a one-sided α of 2.5%. Accounting for a 15% dropout rate, the target enrollment was set at 50 patients.

All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc.). A two-sided p-value of <0.05 was considered statistically significant unless otherwise specified.

Results

Study population

A total of 50 patients with ESKD undergoing maintenance hemodialysis were initially enrolled in the study. Among the participants, one patient voluntarily withdrew consent, and another was excluded due to an acute cerebral infarction that occurred prior to the completion of the first treatment period. Consequently, 48 patients completed the study and were included in the final analysis. Of these, 25 patients were assigned to Group 1 and 23 to Group 2. The mean age of the participants was 62.5 ± 9.8 years, with 50% being male. The proportion of patients with diabetes was 58%, and the median duration of dialysis was 63 months. There were no significant between-group differences in dry weight, body mass index, type of vascular access, or anticoagulation use. The distribution of the dialyzer membrane surface area (1.4 m^2 vs. 1.8 m^2) was also comparable. Baseline demographic and clinical characteristics are summarized in [Table 1](#).

Parameters during the study period

Clinical and biochemical parameters were monitored throughout the study to assess overall patient stability ([Table 2](#)). No clinically significant changes were observed in systolic or diastolic blood pressure, pulse rate, or hemoglobin levels from baseline (Visit 2) to the crossover (Visit 3) and end-of-study (Visit 5) visits in either group. Similarly, serum electrolytes—including sodium, potassium, calcium, and phosphate—as well as liver enzymes and total cholesterol levels remained within stable ranges over time without significant between-group differences. These findings indicate that hemodynamic and metabolic profiles were well maintained throughout the crossover periods.

Primary efficacy outcomes

Non-inferiority analyses were performed for the primary efficacy endpoints, including Kt/V and URR. In the overall analysis, the mean URR was $72.47\% \pm 6.25\%$ for Synoflux and $73.77\% \pm 6.61\%$ for the control, resulting in a mean difference of -1.29% (95% confidence interval [CI], -2.01 to -0.58). This result fell within the predefined non-infe-

Table 1. Baseline characteristics

Characteristic	Total	Group 1	Group 2	p-value
No. of patients	48	25	23	
Age (yr)	62.5 ± 9.8	60 ± 11.0	65.2 ± 7.8	0.07
Male sex	24 (50.0)	12 (48.0)	12 (52.2)	0.77
Dry weight (kg)	60.8 ± 13.9	63.1 ± 14.2	58.3 ± 13.4	0.24
Body mass index (kg/m ²)	23.2 ± 4.0	23.8 ± 4.5	22.6 ± 3.3	0.31
Diabetes mellitus	28 (58.3)	16 (64.0)	12 (52.2)	0.41
Hypertension	28 (58.3)	15 (60.0)	13 (56.5)	0.81
Dialysis vintage (mo)	63 (23.7–111.5)	52 (19.0–105.0)	68 (33.0–149.5)	0.14
Surface area of hemodialysis membrane (m ²)				0.25
1.4	23 (47.9)	10 (40.0)	10 (43.5)	
1.8	25 (52.1)	15 (60.0)	13 (56.5)	
Vascular access				0.37
Fistula	40 (83.3)	22 (89.0)	18 (78.3)	
Graft	8 (16.7)	3 (11.0)	5 (21.7)	
Anticoagulation				0.50
Yes	45 (93.8)	24 (96.0)	21 (91.3)	
No	3 (6.3)	1 (4.0)	2 (8.7)	

Data are expressed as number only, mean ± standard deviation, number (%), or median (interquartile range).

Group 1: Synoflux dialyzer (Synopex Inc.) used during weeks 1–4 (Visit 2 to Visit 3), then control dialyzer during weeks 5–8 (Visit 4 to Visit 5). Group 2: FX Classix dialyzer (Fresenius Medical Care AG & Co. KGaA) used during weeks 1–4 (Visit 2 to Visit 3), then Synoflux dialyzer during weeks 5–8 (Visit 4 to Visit 5).

riority margin of 5%. The mean spKt/V was 1.55 ± 0.29 for Synoflux and 1.61 ± 0.32 for the control, with a mean difference of -0.06 (95% CI, -0.10 to -0.02), which satisfied the non-inferiority criterion set at 10%. Group-specific results are presented in [Table 3](#).

Clearance of middle-molecule solutes

[Table 4](#) presents the reduction ratios for middle-molecule solutes, including cystatin C, β 2-microglobulin, myoglobin, prolactin, and IL-6. Synoflux consistently demonstrated superior removal efficiency for these solutes across both groups, with statistically significant differences observed in the overall cohort. Notably, Synoflux resulted in substantial reductions in myoglobin and prolactin concentrations, while the control dialyzer showed little to no removal of these solutes. For IL-6, a slight increase was observed after dialysis with both dialyzers based on the reduction ratio. Nonetheless, there was no statistically significant change between pre- and post-dialysis levels (Synoflux, $p = 0.20$; FX Classix, $p = 0.997$).

Serum albumin changes

In Group 1, albumin levels exhibited a slight decrease during the use of Synoflux, while an increase was noted with the FX Classix dialyzer. Although the lower bound of the 95% CI for Synoflux slightly exceeded the predefined non-inferiority margin of 5%, the overall magnitude of change was minimal ([Table 5](#)).

Adverse events

A total of 48 patients completed the study without experiencing any serious adverse events associated with the dialyzer. IDH was the most frequently reported event and was documented across multiple sessions for both dialyzer types. The overall incidence of IDH events was comparable between the Synoflux and control dialyzers. Dialyzer clotting events were infrequent, occurring in a limited number of sessions, and no consistent pattern of dialyzer-specific clustering was observed. Other minor adverse events, including headache, muscle cramps, and transient symptoms (e.g., nausea, dizziness), were reported at low frequency and were not clinically significant. A total of three

Table 2. Overall patient condition assessed through parameters throughout the observation period

Parameter	Total (n = 48)	Group 1 (n = 25)	Group 2 (n = 23)	p-value
Baseline (Visit 2)				
Systolic BP (mmHg)	150.8 ± 21.3	149.5 ± 18.9	152.2 ± 24.0	0.66
Diastolic BP (mmHg)	74.4 ± 18.2	72.9 ± 16.0	76.0 ± 20.6	0.84
Pulse rate (bpm)	77.0 ± 14.6	77.8 ± 12.3	76.1 ± 17.0	0.69
Hemoglobin (g/dL)	11.0 ± 1.4	10.7 ± 0.7	11.3 ± 1.8	0.11
Sodium (mEq/L)	137 (135–137)	138 (135–139)	138 (135–139)	0.26
Potassium (mEq/L)	4.8 (4.2–5.3)	5.1 (4.4–5.5)	4.5 (4.2–5.2)	0.13
Calcium (mg/dL)	9.1 (8.7–9.6)	9.0 (8.5–9.6)	9.2 (8.9–9.6)	0.25
Phosphate (mg/dL)	4.5 ± 1.3	4.7 ± 1.3	4.2 ± 1.3	0.22
AST (U/L)	18.0 ± 6.9	18.8 ± 6.6	17.1 ± 7.3	0.41
ALT (U/L)	13.0 (10.8–15.0)	13.0 (11.0–15.0)	13.0 (9.5–15.5)	0.41
ALP (U/L)	86.0 (65.8–97.5)	87.0 (77.0–96.0)	84.0 (63.0–99.5)	0.58
Total cholesterol (mg/dL)	138.5 ± 34.7	132.9 ± 39.1	144.6 ± 28.9	0.27
4 weeks (Visit 3)				
Systolic BP (mmHg)	143.4 ± 23.1	150.5 ± 22.9	141.8 ± 22.9	0.20
Diastolic BP (mmHg)	73.5 ± 12.8	74.8 ± 15.3	72.0 ± 9.6	0.46
Pulse rate (bpm)	75.6 ± 12.7	76.5 ± 12.8	74.6 ± 12.8	0.61
Hemoglobin (g/dL)	10.6 (10.0–11.3)	10.5 (9.9–10.8)	10.8 (10.2–11.7)	0.08
Sodium (mEq/L)	136.1 ± 2.9	135.8 ± 3.4	136.4 ± 2.2	0.48
Potassium (mEq/L)	4.8 ± 0.6	4.9 ± 0.5	4.7 ± 0.7	0.28
Calcium (mg/dL)	9.0 ± 0.8	8.9 ± 0.9	9.1 ± 0.6	0.497
Phosphate (mg/dL)	4.7 ± 1.0	4.8 ± 0.9	4.7 ± 1.2	0.51
AST (U/L)	18.5 (13.3–24.0)	20.0 (14.5–23.0)	15.0 (10.0–25.0)	0.41
ALT (U/L)	12.5 (10.0–17.8)	13.0 (10.0–18.0)	12.0 (9.0–17.0)	0.51
ALP (U/L)	80.5 (64.0–113.2)	82.0 (72.5–119.5)	74.0 (61.0–115.0)	0.38
Total cholesterol (mg/dL)	136.5 ± 36.3	130.9 ± 38.8	142.7 ± 33.2	0.27
8 weeks (Visit 5)				
Systolic BP (mmHg)	139.9 ± 21.1	141.5 ± 18.9	138.2 ± 23.2	0.66
Diastolic BP (mmHg)	71.4 ± 15.1	73.2 ± 13.8	69.8 ± 10.3	0.76
Pulse rate (bpm)	76.5 ± 16.6	77.8 ± 12.3	75.1 ± 17.3	0.61
Hemoglobin (g/dL)	10.9 (9.9–11.5)	11.0 (9.9–13.4)	10.7 (9.8–11.6)	0.98
Sodium (mEq/L)	137.0 (135.0–138.8)	137.0 (134.5–139.0)	137.0 (135.0–138.0)	0.63
Potassium (mEq/L)	4.7 (4.4–5.2)	4.6 (4.4–5.2)	4.7 (4.4–5.2)	0.32
Calcium (mg/dL)	8.9 ± 0.8	8.9 ± 0.8	9.0 ± 0.8	0.93
Phosphate (mg/dL)	4.7 (4.1–5.4)	4.7 (4.2–5.4)	4.8 (4.0–5.4)	0.65
AST (U/L)	16.0 (12.3–22.0)	17.0 (13.0–21.0)	16.0 (11.0–24.0)	0.84
ALT (U/L)	11.5 (9.0–15.8)	12.0 (8.0–16.5)	10.0 (9.0–14.0)	0.63
ALP (U/L)	80.0 (63.0–104.3)	85.0 (67.0–107.5)	71.0 (62.0–102.0)	0.44
Total cholesterol (mg/dL)	137.6 ± 40.6	132.7 ± 47.8	142.9 ± 31.2	0.39

Data are expressed as mean ± standard deviation or median (interquartile range).

BP, blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Group 1: Synoflux dialyzer (Synopex Inc.) used during weeks 1–4 (Visit 2 to Visit 3), then control dialyzer during weeks 5–8 (Visit 4 to Visit 5). Group 2: FX Classix dialyzer (Fresenius Medical Care AG & Co. KGaA) used during weeks 1–4 (Visit 2 to Visit 3), then Synoflux dialyzer during weeks 5–8 (Visit 4 to Visit 5).

Table 3. Non-inferiority test for primary outcomes

Group	Synoflux	FX Classix	p-value	Mean difference	95% CI
Group 1					
spKt/V	1.53 ± 0.31	1.59 ± 0.35	0.06	-0.053	-0.11 to 0.003
URR (%)	71.94 ± 6.43	73.04 ± 7.04	0.04	-1.092	-2.15 to -0.04
Group 2					
spKt/V	1.56 ± 0.28	1.63 ± 0.29	0.02	-0.07	-0.13 to -0.01
URR (%)	73.05 ± 6.14	74.56 ± 6.16	0.006	-1.50	-2.55 to -0.48
Overall					
spKt/V	1.55 ± 0.29	1.61 ± 0.32	0.002	-0.06	-0.10 to -0.02
URR (%)	72.47 ± 6.25	73.77 ± 6.61	0.001	-1.29	-2.01 to -0.58

Data are expressed as mean ± standard deviation.

CI, confidence interval; spKt/V, single-pool Kt/V; URR, urea reduction ratio.

Group 1: Synoflux dialyzer (Synopex Inc.) used during weeks 1–4 (Visit 2 to Visit 3), then control dialyzer during weeks 5–8 (Visit 4 to Visit 5). Group 2: FX Classix dialyzer (Fresenius Medical Care AG & Co. KGaA) used during weeks 1–4 (Visit 2 to Visit 3), then Synoflux dialyzer during weeks 5–8 (Visit 4 to Visit 5).

Table 4. Comparison of reduction ratios (%) for middle molecules

Parameter	Synoflux	FX Classix	p-value
Group 1			
Cystatin C	55.9 (54.4 to 62.5)	35.9 (30.7 to 45.3)	<0.001
B2-Microglobulin	56.3 (51.7 to 65.7)	49.7 (43.2 to 58.9)	<0.001
Myoglobin	31.9 ± 8.9	-9.5 ± 10.1	<0.001
Prolactin	31.4 (23.0 to 36.2)	-3.4 (-12.9 to 3.4)	<0.001
Interleukin-6	-7.8 (-23.0 to 9.0)	-2.7 (-13.2 to 10.7)	0.22
Group 2			
Cystatin C	59.0 (52.9 to 65.8)	37.4 (34.1 to 43.8)	<0.001
B2-Microglobulin	57.3 (49.7 to 66.1)	50.8 (43.4 to 58.2)	<0.001
Myoglobin	31.8 ± 8.6	-9.5 ± 10.1	<0.001
Prolactin	28.5 (23.9 to 36.9)	0.7 (-14.0 to 3.0)	<0.001
Interleukin-6	-13.7 (-32.1 to 12.6)	-16.8 (-36.1 to 5.1)	0.41
Overall			
Cystatin C	56.6 (53.6 to 62.8)	37.8 (32.9 to 44.8)	<0.001
B2-Microglobulin	56.8 (51.3 to 66.1)	50.8 (43.4 to 58.2)	<0.001
Myoglobin	31.8 ± 8.6	-9.5 ± 10.1	<0.001
Prolactin	28.5 (23.9 to 36.6)	-3.4 (-13.4 to 3.0)	<0.001
Interleukin-6	-10.2 (-26.4 to 9.9)	-9.0 (-20.0 to 9.1)	0.85

Data are expressed as median (interquartile range) or mean ± standard deviation.

Group 1: Synoflux dialyzer (Synopex Inc.) used during weeks 1–4 (Visit 2 to Visit 3), then control dialyzer during weeks 5–8 (Visit 4 to Visit 5). Group 2: FX Classix dialyzer (Fresenius Medical Care AG & Co. KGaA) used during weeks 1–4 (Visit 2 to Visit 3), then Synoflux dialyzer during weeks 5–8 (Visit 4 to Visit 5).

dialysis sessions (0.2%) were prematurely discontinued due to adverse events: one session due to IDH, one due to filter clotting, and one due to headache. No such events occurred during the efficacy assessment visits (Visit 3 and Visit 5), and the overall impact of IDH on treatment continuity was considered negligible. No patients discontinued their participation due to adverse events. A comprehensive

summary of adverse events by dialyzer type is provided in [Supplementary Table 1](#) (available online).

Discussion

This multicenter, randomized, crossover clinical trial evaluated the clinical performance and safety of a domestically

Table 5. Comparison of changes in serum albumin levels

Group 1	Period	Serum albumin (g/dL)		Mean difference	95% CI	p-value
		Before	After			
Group 1	Synoflux	4.0 ± 0.4	3.9 ± 0.3	-0.12	-0.22 to 0.02	0.03
	FX Classix	3.9 ± 0.3	4.0 ± 0.3	0.08	0.01 to 0.15	0.04
Group 2	Synoflux	4.1 ± 0.3	4.1 ± 0.3	-0.01	-0.09 to 0.07	0.83
	FX Classix	4.1 ± 0.3	4.1 ± 0.3	0.01	-0.05 to 0.08	0.69
Overall	Synoflux	4.0 ± 0.3	4.0 ± 0.3	-0.03	-0.12 to 0.01	0.09
	FX Classix	4.0 ± 0.3	4.0 ± 0.3	0.04	-0.02 to 0.09	0.18

Data are expressed as mean ± standard deviation.
CI, confidence interval.
Group 1: Synoflux dialyzer (Synopex Inc.) used during weeks 1–4 (Visit 2 to Visit 3), then control dialyzer during weeks 5–8 (Visit 4 to Visit 5). Group 2: FX Classix dialyzer (Fresenius Medical Care AG & Co. KGaA) used during weeks 1–4 (Visit 2 to Visit 3), then Synoflux dialyzer during weeks 5–8 (Visit 4 to Visit 5).

developed dialyzer compared to a commercially available dialyzer in patients with ESKD. The results demonstrated that Synoflux met the predefined non-inferiority criteria for dialysis adequacy, as measured by URR and spKt/V when compared to the control dialyzer. Additionally, Synoflux exhibited comparable or superior clearance of middle-molecule solutes, particularly β 2-microglobulin, myoglobin, and prolactin, while maintaining acceptable albumin retention within the predefined non-inferiority margin. The safety profile of both dialyzers was similar, with equivalent frequencies of adverse events and no serious dialyzer-related complications observed.

These findings align with previous studies investigating modified PES membranes, which have reported enhanced removal of middle molecules compared to conventional membranes. Specifically, one study demonstrated that as the molecular weight of the solute increased, the clearance advantage of the modified membrane became more pronounced, achieving a 124.8% higher reduction in myoglobin than a reference membrane [10]. These performance improvements are attributed to the incorporation of negatively charged polyelectrolytes into the membrane surface during manufacturing, enhancing solute interaction without altering the base polymer composition. This structural modification results in a steeper sieving profile, facilitating efficient clearance of middle molecules while minimizing albumin loss [7]. In another study, the modified PES membrane exhibited comparable removal of small solutes and low-molecular-weight proteins relative to online post-dilution hemodiafiltration using conventional high-flux membranes while providing superior clearance of myoglobin

compared to a polyacrylonitrile-based membrane [11].

In addition to optimizing sieving performance, membrane development has also concentrated on enhancing fiber geometry to improve solute transport. Reducing the diameter and wall thickness of hollow fibers decreases the diffusion path and facilitates diffusive clearance, while larger molecules necessitate convective transport for effective removal [12]. The membrane evaluated in our study demonstrated advantageous structural characteristics, featuring a mean pore size of approximately 8 nm—double that of its comparator—and a wall thickness of 30 μ m, which is about 10% thinner than that of commonly used comparator membranes. These features enhance diffusive and convective solute transport, particularly improving the clearance of middle molecules. Additionally, the dialyzer incorporates spacer yarns—fine threads strategically positioned between hollow fibers—to maintain consistent inter-fiber spacing and optimize dialysate flow distribution. Previous studies have demonstrated that spacer yarns reduce flow channeling and dead space within the fiber bundle, thereby improving solute clearance. They also promote uniform dialysate flow and minimize surface fouling, which together improve dialyzer performance and biocompatibility [13,14]. The inclusion of this design element in the test dialyzer may have contributed to the favorable clearance outcomes observed in our study.

The enhanced removal of middle molecules is particularly significant due to the established association of these toxins with dialysis-related complications, including amyloidosis, cardiovascular disease, and chronic inflammation. β 2-microglobulin, which has a molecular weight

of 11.8 kDa, is a well-recognized contributor to dialysis-related amyloidosis and is linked to long-term musculoskeletal complications such as carpal tunnel syndrome and destructive arthropathy [15,16]. Enhanced clearance of β 2-microglobulin has been associated with improved functional status, as well as better cardiovascular and overall survival outcomes in dialysis patients [17,18]. Cystatin C (13.3 kDa), traditionally utilized as a biomarker for glomerular filtration rate, also reflects systemic inflammation and has been independently associated with increased arterial stiffness, left ventricular hypertrophy, and adverse cardiovascular events in dialysis patients [19–22]. The effective removal of cystatin C may help reduce the cardiovascular risk burden in this population. Prolactin (23 kDa), often elevated in ESKD due to reduced renal clearance, is linked to multiple pathophysiological consequences, including gonadal dysfunction, menstrual irregularities, sexual dysfunction, and immune dysregulation [23–26]. Its successful clearance may provide therapeutic benefits in addressing these frequently overlooked complications of ESKD.

In this study, IL-6 levels did not significantly decrease following dialysis with either dialyzer, reflecting the known limitations of conventional high-flux membranes in removing cytokines of relatively large molecular weight (~26 kDa) and partial protein-binding characteristics. This observation is consistent with prior evidence suggesting that IL-6 is poorly cleared by diffusion- or convection-based modalities. Notably, IL-6 levels also did not show a significant post-dialysis increase, suggesting that neither membrane provoked a measurable pro-inflammatory response during treatment. While these findings do not allow definitive conclusions regarding biocompatibility, they are reassuring from an immunologic standpoint.

Both dialyzers demonstrated favorable safety profiles, characterized by preserved serum albumin levels and low incidences of IDH, clotting events, and other serious dialysis-related complications. A previous study evaluating the safety of MCO membranes confirmed modest albumin loss; however, these reductions have not been associated with clinically significant consequences or the need for albumin supplementation [27]. In the present study, although a mild decrease in serum albumin was observed in one group, the reduction remained within the predefined non-inferiority margin and did not result in a statistically significant difference across the overall study population.

This study has several limitations. Firstly, the short-term crossover design inherently restricts the assessment of long-term outcomes, such as inflammation, hospitalization, and mortality. Secondly, this study did not include a formal wash-out period between treatment phases. However, in maintenance hemodialysis patients, the physiological and biochemical milieu is effectively reset during the inter-dialytic interval, which may mitigate the need for an extended wash-out period. Thirdly, although a crossover design was employed, statistical correction for potential carry-over effects was not conducted.

However, considering the relatively short duration of each treatment period and the clinical stability of the enrolled patients, the risk of significant carry-over effects is likely minimal. Additionally, Synoflux was compared with a single, widely used imported high-flux dialyzer rather than multiple control membranes. A more comprehensive comparison may be necessary to fully elucidate the clinical versatility of the Synoflux dialyzer. Future studies should incorporate biomarkers of inflammation, oxidative stress, and patient-reported outcomes to better characterize the biological impact and patient-centered effects of this novel PES membrane technology.

In conclusion, the Synoflux dialyzer demonstrated clinical non-inferiority in terms of dialysis adequacy and safety when compared to an imported standard, with potential advantages in middle-molecule clearance. These findings, combined with the structural and mechanical benefits of yarn-based hollow fiber membranes, support the feasibility of domestic production and broader utilization of next-generation dialyzers in Korea. Ongoing clinical evaluations and further industrial optimization are essential to fully realize the clinical and economic potential of this technology.

Additional information

This study was approved by the Institutional Review Board at each participating center: Seoul National University Hospital (No. 2408-176-1567), Inje University Sanggye Paik Hospital (No. 2024-08-011), Chung-Ang University Hospital (No. 2409-003-613), Chung-Ang University Gwangmyeong Hospital (No. 2408-181-102), and SMG-SNU Boramae Medical Center (No. 30-2024-81).

Conflicts of interest

All authors have no conflicts of interest to declare.

Funding

This work was supported by the Korea Medical Device Development Fund grant funded by the Korean government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (project number: 2710000044, RS-2022-00141157).

Data sharing statement

The data presented in this study are available from the corresponding author upon reasonable request.

Authors' contributions

Conceptualization, Methodology: SGK, DKK
Data curation, Investigation: SGK, SL, JMC, MWK, SK
Formal analysis: SC, JS, YKO
Funding acquisition: DKK
Project administration, Supervision: DKK
Writing – Original Draft: SGK, SC
Writing – Review & Editing: HH, JS, YKO
All authors reviewed and approved the final manuscript.

ORCID

Seong Geun Kim, <https://orcid.org/0000-0002-8831-9838>
Semin Cho, <https://orcid.org/0000-0002-6060-9032>
Jin Kyung Kwon, <https://orcid.org/0009-0000-3986-0639>
Minsang Kim, <https://orcid.org/0000-0002-7209-198X>
Soojin Lee, <https://orcid.org/0000-0001-5633-3961>
Jeong Min Cho, <https://orcid.org/0000-0001-7643-994X>
Hyuk Huh, <https://orcid.org/0000-0001-7608-0199>
Min Woo Kang, <https://orcid.org/0000-0002-9411-3481>
Soie Kwon, <https://orcid.org/0000-0002-0878-5469>
Jung-ho Shin, <https://orcid.org/0000-0001-9755-3100>
Yun Kyu Oh, <https://orcid.org/0000-0001-8632-5743>
Dong Ki Kim, <https://orcid.org/0000-0002-5342-1197>

References

1. Kim H, Jeong SA, Kim KM, et al. Trends in clinical outcomes of older hemodialysis patients: data from the 2023 Korean Renal Data System (KORDS). *Kidney Res Clin Pract* 2024;43:263–273.
2. Kim JK, Jung HN, Kim BJ, et al. Burden of end-stage kidney disease by type 2 diabetes mellitus status in South Korea: a nationwide epidemiologic study. *Diabetes Metab J* 2025;49:498–506.
3. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2018 Annual Data Report: epidemiology of kidney disease in the United States. *Am J Kidney Dis* 2019;73(3 Suppl 1):A7–A8.
4. Park HC, Kim DH, Cho A, et al. Remaining life expectancy of Korean hemodialysis patients: how much longer can they live? *Kidney Res Clin Pract* 2024;43:671–679.
5. Ryu JH, Kim H, Kim KH, et al. Improving survival rate of Korean patients initiating dialysis. *Yonsei Med J* 2015;56:666–675.
6. Kim DH, Hyun YY, Cha JJ, et al. Kidney Health Plan 2033 in Korea: bridging the gap between the present and the future. *Kidney Res Clin Pract* 2024;43:8–19.
7. Krieter DH, Lemke HD. Polyethersulfone as a high-performance membrane. *Contrib Nephrol* 2011;173:130–136.
8. Krieter DH, Lemke HD, Wanner C. A new synthetic dialyzer with advanced permselectivity for enhanced low-molecular weight protein removal. *Artif Organs* 2008;32:547–554.
9. Weiner DE, Falzon L, Skoufos L, et al. Efficacy and safety of expanded hemodialysis with the TheraNova 400 Dialyzer: a randomized controlled trial. *Clin J Am Soc Nephrol* 2020;15:1310–1319.
10. Krieter DH, Morgenroth A, Barasinski A, et al. Effects of a poly-electrolyte additive on the selective dialysis membrane permeability for low-molecular-weight proteins. *Nephrol Dial Transplant* 2007;22:491–499.
11. Krieter DH, Hunn E, Morgenroth A, Lemke HD, Wanner C. Matching efficacy of online hemodiafiltration in simple hemodialysis mode. *Artif Organs* 2008;32:903–909.
12. Storr M, Ward RA. Membrane innovation: closer to native kidneys. *Nephrol Dial Transplant* 2018;33(suppl_3):iii22–iii27.
13. Bacal CJ, Munro CJ, Tardy B, et al. Fouling during hemodialysis: influence of module design and membrane surface chemistry. *Adv Membr* 2024;4:100100.
14. Ronco C, Brendolan A, Crepaldi C, Rodighiero M, Scabardi M. Blood and dialysate flow distributions in hollow-fiber hemodialyzers analyzed by computerized helical scanning technique. *J Am Soc Nephrol* 2002;13 Suppl 1:S53–S61.
15. Miyata T, Jadoul M, Kurokawa K, Van Ypersele de Strihou

- C. Beta-2 microglobulin in renal disease. *J Am Soc Nephrol* 1998;9:1723–1735.
16. Assounga AG. Beta 2 microglobulin in kidney failure: a review and an algorithm for renal replacement therapy. *Saudi J Kidney Dis Transpl* 2021;32:1214–1220.
 17. Zhang J, Lu X, Zu Y, Li H, Wang S. Prognostic value of beta-2 microglobulin on mortality in chronic kidney disease patients: a systematic review and meta-analysis. *Ther Apher Dial* 2022;26:267–274.
 18. Shi F, Sun L, Kaptoge S. Association of beta-2-microglobulin and cardiovascular events and mortality: a systematic review and meta-analysis. *Atherosclerosis* 2021;320:70–78.
 19. West M, Kirby A, Stewart RA, et al. Circulating cystatin C is an independent risk marker for cardiovascular outcomes, development of renal impairment, and long-term mortality in patients with stable coronary heart disease: the LIPID Study. *J Am Heart Assoc* 2022;11:e020745.
 20. Ge J, Ji Y, Wang F, Zhou X, Wei J, Qi C. Correlation between cystatin C and the severity of cardiac dysfunction in patients with systolic heart failure. *Risk Manag Healthc Policy* 2023;16:2419–2426.
 21. Pruc M, Swieczkowski D, Cander B, et al. Diagnostic and prognostic value of cystatin C in acute coronary syndrome: an up-to-date meta-analysis. *Cardiol J* 2025;32:142–152.
 22. Song X, Xiong L, Guo T, et al. Cystatin C is a predictor for long-term, all-cause, and cardiovascular mortality in US adults with metabolic syndrome. *J Clin Endocrinol Metab* 2024;109:2905–2919.
 23. Rojhani E, Rahmati M, Firouzi F, et al. Prolactin levels and chronic kidney disease and the subsequent risk of cardiovascular events: a long term population based cohort study. *Sci Rep* 2025;15:7198.
 24. Zhang K, Zhao L, Bin Y, et al. Serum prolactin and gonadal hormones in hemodialysis women: a meta-analysis. *BMC Endocr Disord* 2023;23:203.
 25. Sobolewska J, Żak Z, Monia-Tutur K, Wojciechowska-Luźniak A, Witek P, Niemczyk S. Endocrine disorders in chronic kidney disease. *Paediatr Fam Med* 2022;18:209–218.
 26. Madsen AH, Juul-Sandberg R, Kjær Steffensen G, Grodum E, Schousboe K. The effect of prolactin on sexual dysfunction in uremic men. *SN Compr Clin Med* 2021;3:826–834.
 27. Cozzolino M, Magagnoli L, Ciceri P, Conte F, Galassi A. Effects of a medium cut-off (Theranova®) dialyser on haemodialysis patients: a prospective, cross-over study. *Clin Kidney J* 2019;14:382–389.