

ORIGINAL ARTICLE

Comparison of four medium cut-off dialyzers

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ABSTRACT

Background. Recently, several pharmaceutical companies have developed new medium cut-off (MCO) dialyzers for expanded hemodialysis (HDx). This study aimed to compare the safety and efficacy of four MCO dialyzers, against each other and versus high-flux hemodialysis (HD) and post-dilution hemodiafiltration (HDF).

Methods. A prospective study was carried out on 23 patients who underwent six dialysis sessions: two sessions with the FX80 Cordiax in HD and HDF, and four HDx sessions with the Phylther 17-SD, Vie-18X, Elisio HX19 and Theranova 400 dialyzers. The reduction ratios (RRs) of urea, creatinine, β_2 -microglobulin, myoglobin, kappa free immunoglobulin light chain (κ FLC), prolactin, α_1 -microglobulin, α_1 -acid glycoprotein, lambda (λ FLC) and albumin were compared. Dialysate albumin loss was also measured.

Results. The differences in efficacy between the evaluated dialyzers were minimal in small molecules and even up to the size of β_2 -microglobulin. The main differences were found between myoglobin, κ FLC, prolactin, α_1 -microglobulin and λ FLC RRs, in which all four MCO dialyzers, with similar efficacy, were clearly superior to HD and slightly inferior to HDF treatment. Albumin losses in the dialysate with HD dialyzers were <1 g and between 1.5 and 2.5 g in HDx and HDF. The global removal score values were similar in all four HDx treatments, and again significantly higher than those with HD.

Conclusions. The results of the four MCO dialyzers evaluated in this study showed good efficiency, with no significant performance differences between them while being completely safe in terms of albumin loss. Likewise, the study confirms the superiority of HDx over high-flux HD with an efficacy close to that of post-dilution HDF.

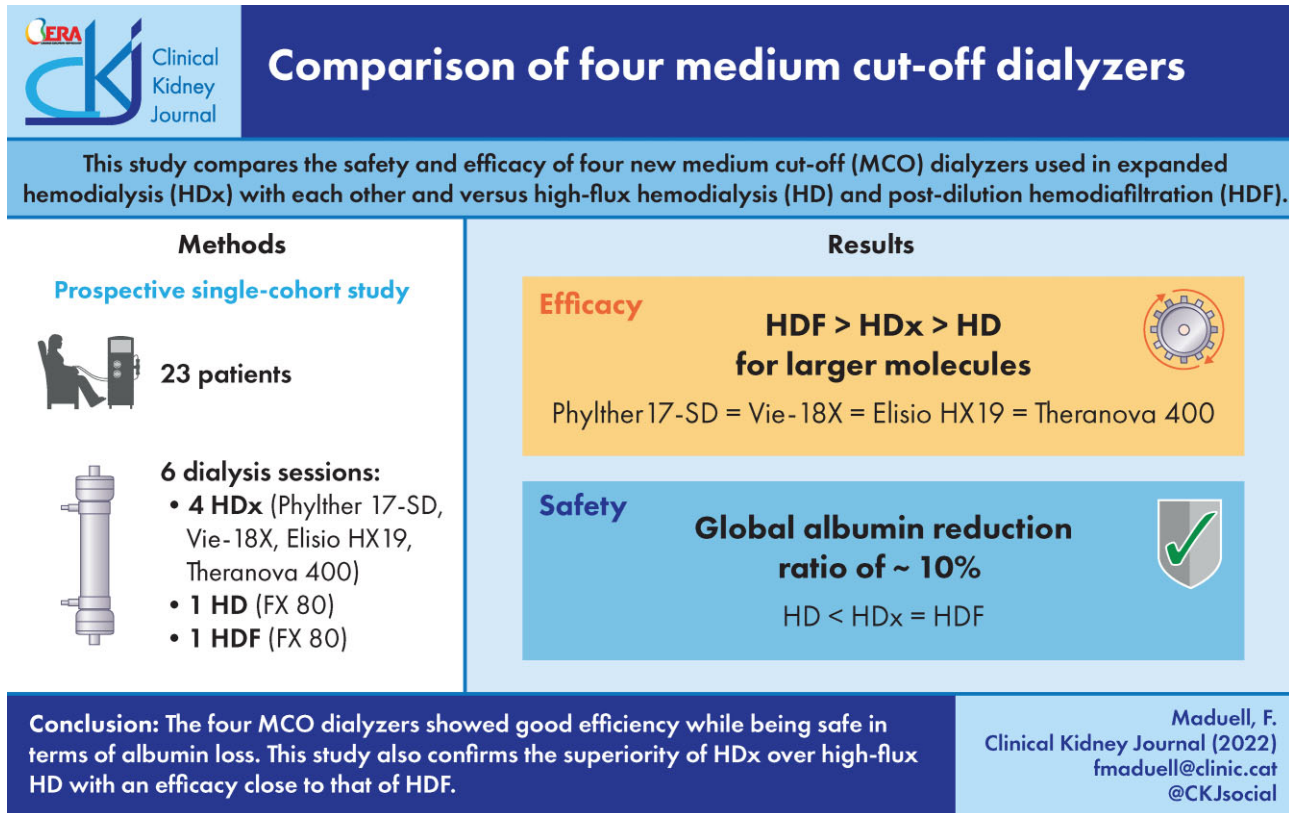
LAY SUMMARY

The pharmaceutical industry has developed new membranes with a bigger and more tailored pore diameter, called medium cut-off dialyzers, the characteristics of which differ from others to the point that they have generated a new dialysis modality, expanded hemodialysis. This study aimed to assess the clinical efficacy and safety of four new medium cut-off dialyzers (Phylther 17-SD, Vie-18X, Elisio HX19 and Theranova 400 dialyzers) compared against each other and with other dialysis modalities—high-flux hemodialysis and post-dilution hemodiafiltration. The reduction ratios of solutes between 60 and 60 000 Da were measured. Safety was evaluated with albumin loss. The results show that all four medium cut-off filters obtained similar results regarding different molecular weight molecules, reduction ratios and albumin loss. And also, expanded hemodialysis has better efficacy than high-flux hemodialysis but is still inferior to hemodiafiltration, without safety concerns.

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GRAPHICAL ABSTRACT



Keywords: dialyzer performance, expanded hemodialysis, hemodiafiltration, medium cut-off, safety

INTRODUCTION

Expanded hemodialysis with medium cut-off (MCO) membranes was designed to improve the permeability of the dialyzers. These can only be used in the hemodialysis (HD) modality and could provide an alternative to hemodiafiltration (HDF) since they achieve similar solute-removal performance to post-dilution HDF [1–3]. This is due to the tailored cut-off of the membrane pores combined with an internal architecture that allows MCO membranes to achieve internal removal capacities for middle molecules and large middle molecules compared with standard HD treatments [2].

Scientific evidence of the superiority of post-dilution HDF versus high-flux HD in overall and cardiovascular survival has been demonstrated [4–7]. Consequently, it can currently be considered the standard conventional HD treatment [8].

Initially, very few alternatives were available for expanded HD (HDx). However, several pharmaceutical companies have recently developed new MCO dialyzers, which have obtained the CE mark, thus increasing their therapeutic possibilities. Unfortunately, few studies have compared their efficacy and their safety issues.

The safety of MCO dialyzers is ensured by restricting pore sizes to limit albumin losses below 5 g per session [9, 10]. In this regard, most published studies report that MCO membranes lead to a higher albumin loss than HD and show inconsistent results compared with HDF [11–16]. However, the albumin loss could be

considered clinically tolerable in all cases, as long as it is used in HD modality.

To evaluate these new MCO dialyzers, this study compared the safety issues and efficacy of four of them and also compared them against high-flux HD and post-dilution HDF treatments. Removal of a wide range of molecular weight molecules was assessed, and safety was evaluated with blood and dialysate albumin loss.

MATERIALS AND METHODS

The study included 23 patients, of whom 15 were male and 8 were female, with a mean age of 68.6 ± 12 years (range 46–90 years) on a regular HD program. Sixteen patients had an autologous arteriovenous fistula as vascular access, six a tunneled catheter and one a prosthetic arteriovenous graft. The causes of end-stage kidney disease were chronic glomerulonephritis (four patients), hypertensive kidney disease (three patients), interstitial nephritis (three patients), systemic disease (two patients), diabetic kidney disease (three patients), autosomal dominant polycystic kidney disease (two patients), urological (one patient) and undiagnosed nephropathy (four patients). The anticoagulants used during dialysis were low molecular-weight heparin (tinzaparin) in 57% of the patients and unfractionated heparin in 26%; the remaining 17% of the patients were dialyzed without heparin. Net fluid removal was prescribed according to the

Table 1. In vitro dialyzer performance

	FX80 Cordiax HD/HDF	Phylther 17SD HDx	Vie-18X HDx	Elisio HX19 HDx	Theranova 400 HDx
Membrane brand	Helixone FMC	Polyphenylene Medtronic	Polysulfone Asahi	Polyethersulfone Nipro	Polyarylethersulfone Baxter
KUF (mL/h/mmHg)	64	53	87.9	75	48
Wall thickness (μm)	35	30	45	40	35
Internal diameter (μm)	185	200	185	200	180
SC B ₂ m	0.90	0.93	0.90	1.0	1.0
SC myoglobin	0.50	0.70	0.80	0.86	0.9
SC albumin	0.001	<0.02	<0.01	0.0024	0.008
Surface (m ²)	1.8	1.7	1.8	1.9	1.7
Sterilization	Steam	Steam	Gamma radiation	Gamma radiation	Steam

KUF, ultrafiltration coefficient; B₂m, β₂-microglobulin; SC, sieving coefficient; NA, not available.

patients' clinical needs. Patients with a urine volume >50 mL per day were excluded. Every included patient provided informed consent. The study was approved by the local Ethics Committee and was conducted according to the Declaration of Helsinki.

Each patient received six different sessions with their usual parameters [dialysis duration 288 ± 17 min, blood flow rate (Q_b) 439 ± 26 mL/min and dialysate flow rate (Q_d) 400 mL/min plus additional dialysate for the replacement volume in HDF]:

- high-flux FX80 Cordiax™, helixone, Fresenius Medical Care, in HD;
- MCO Phylther 17-SD™, polyphenylene, Medtronic, in HD (HDx);
- MCO Vie-18X™, polysulfone, Asahi, in HD (HDx);
- MCO Elisio HX19™, polyethersulfone, Nipro, in HD (HDx);
- MCO TheraNova 400™, polyarylethersulfone, Baxter, in HD (HDx);
- high-flux FX80 Cordiax™, helixone, Fresenius Medical, in post-dilution HDF.

Patients were dialyzed with 5008 Fresenius monitors, and dialyzers were automatically primed. Online HDF was performed with post-dilution infusion and automatic infusion flow. The order of the different treatment sessions was randomly assigned. The dialyzer characteristics are summarized in Table 1. Blood and dialysis fluid samples for analyses were taken from each patient in the same dialysis session of the week.

The dialysis parameters collected in each session were as follows: real duration, dialyzer, Q_b, Q_d, recirculation index measured by the temperature module, arterial pressure, venous pressure, transmembrane pressure, relative hematocrit difference between the start and the end of the dialysis session automatically calculated by the blood volume monitor biosensor, initial and final body weight, the volume of blood processed, and replacement volume.

Laboratory measurements included concentrations of urea (60 Da), creatinine (113 Da), β₂-microglobulin (11 800 Da), myoglobin (17 200 Da), prolactin (23 000 Da), α₁-microglobulin (33 000 Da), α₁-acid glycoprotein (41 000 Da) and albumin (66 000 Da) in serum at the beginning and at the end of each session to calculate the percentage reduction ratio (RR) of these solutes. Free immunoglobulin light chains (FLCs) were also measured, kappa FLC (κFLC) with a molecular weight of 22 500 Da and lambda FLC (λFLC) with a molecular weight of 45 000 Da.

The final concentration of β₂-microglobulin, myoglobin, prolactin, κFLC, α₁-microglobulin, α₁-acid glycoprotein, λFLC and al-

bumin were corrected for the degree of hemoconcentration and the distribution volume (approximate extracellular volume) according to Bergström and Wehle [17]: post-dialysis concentration correction = post-dialysis concentration/[1 + ((pre-dialysis weight – post-dialysis weight)/(0.2 × dry weight))].

Urea and creatinine were measured by molecular absorption spectrometry, albumin and β₂-microglobulin were measured by immunoturbidimetric, and myoglobin and prolactin were measured by indirect enzyme immunoassay; all of them were performed in an Atellica Solution analyzer (Siemens Healthineers, Tarrytown, NY, USA). Finally, α₁-acid glycoprotein, α₁-microglobulin, κFLC and λFLC were measured by immunonephelometry using the BNII analyzer (Siemens Healthineers).

A proportional part of the dialysis fluid was collected throughout the treatment to quantify albumin loss employing a reverse perfusion pump.

A global removal score [14] was also calculated with the following formula: ((urea_{RR} + β₂-m_{RR} + myoglobin_{RR} + prolactin_{RR} + α₁-microglobulin_{RR} + α₁-acid glycoprotein_{RR} – albumin_{RR})/6).

The results are expressed as the arithmetic mean ± standard deviation. Quantitative parameters were analyzed with the Student's t-test for paired data. Parametric data were analyzed with ANOVA for repeated data, followed by Bonferroni's post hoc test. P < .05 was considered statistically significant. Analyses were performed using SPSS software version 23 (SPSS, Chicago, IL, USA).

RESULTS

Assessment of the behavior and tolerance of the dialyzers

We observed proper tolerance to every used filter, with no adverse reactions observed in the connection or disconnection during the HD or HDF sessions in the studied population. Replacement fluid in online post-dilution HDF was 30.4 ± 4.1 L (range 24–37 L) with helixone HDF treatment.

There were no differences in dialysis parameters: Q_b, total blood processed, vascular access recirculation, real session duration, initial weight, final weight, weight gain, initial and final hematocrit measured by the dialysis monitor, arterial pressure, and venous pressure (Table 2). As expected, the transmembrane pressure was significantly higher in HDF sessions than in the other sessions in HD.

Table 2. Comparison of dialysis parameters in the six study sessions

	FX80 Cordiax HD	Phylther 17SD HDx	Vie-18X HDx	Elisio HX19 HDx	Theranova 400 HDx	FX80 Cordiax HDF
Blood processed (L)	124.6 ± 9.6	123.6 ± 9.9	124.2 ± 9.9	123.8 ± 9.5	124.2 ± 9.8	123.6 ± 9.7
Recirculation (%)	14.3 ± 5.5	14.9 ± 4.1	13.7 ± 4.6	15.4 ± 4.6	15.3 ± 4.8	14.2 ± 4.3
Real dialysis time (min)	283.3 ± 16.7	282.9 ± 17.8	283.0 ± 18.1	282.2 ± 17.3	282.4 ± 17.6	281.2 ± 17.6
Initial weight (kg)	69.7 ± 17.5	70.2 ± 17.6	70.0 ± 17.4	69.8 ± 17.4	70.0 ± 17.6	69.9 ± 17.6
Final weight (kg)	67.3 ± 17.1	67.7 ± 17.2	67.4 ± 17.2	67.2 ± 17.0	67.4 ± 17.3	67.5 ± 17.4
Weight gain (kg)	2.44 ± 1.06	2.59 ± 1.05	2.60 ± 0.81	2.56 ± 0.92	2.63 ± 0.99	2.38 ± 0.96
Initial hematocrit (%)	30.8 ± 4.9	29.7 ± 4.7	30.9 ± 4.7	30.8 ± 4.3	30.6 ± 4.5	30.9 ± 4.8
Final hematocrit (%)	36.2 ± 5.5	35.7 ± 5.8	36.7 ± 5.8	36.5 ± 5.3	36.9 ± 5.6	36.9 ± 6.2
Arterial pressure. (mmHg)	-229 ± 24	-227 ± 22	-230 ± 22	-229 ± 22	-228 ± 25	-228 ± 25
Venous pressure. (mmHg)	199 ± 23	192 ± 24	197 ± 23	202 ± 28	201 ± 21	200 ± 23
TMP (mmHg)	30.0 ± 5.1	31.4 ± 5.0	29.2 ± 3.5	29.0 ± 4.2	28.5 ± 2.6	191.3 ± 32.1 ^a
Substitution volume (L)	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	30.4 ± 4.1

^a P < .001 vs all others dialysis treatments. TMP, transmembrane pressure. Data are presented as mean ± standard deviation.

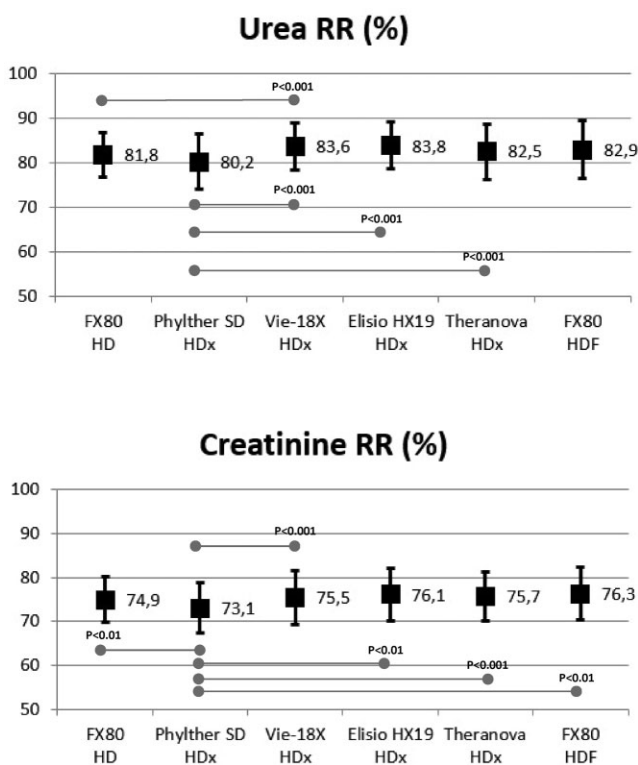


FIGURE 1: Comparison of urea and creatinine reduction ratios in all study situations (ANOVA for repeated data).

Small-sized molecules

The Kt obtained by ionic dialysance was 61.5 ± 5.8 L with FX80 in HD, 58.2 ± 5.4 L with Phylther ($P < .001$ versus all other five study situations), 63.8 ± 5.9 L with Vie 18X, 64.2 ± 6.5 L with Elisio 19HX, 63.4 ± 6.3 L with TheraNova 400 and 68.7 ± 7.6 L with FX80 in HDF ($P < .001$ compared with FX80 in HD, Phylther and TheraNova; $P < .01$ versus VieX and Elisio HX).

However, concerning urea and creatinine RR, the only statistically significant difference was observed in urea and creatinine RR between MCO Phylther 17-SD and the other three MCO dialyzers and FX80 Cordiax in HDF treatment (Fig. 1).

Medium-sized molecules

The RR of β_2 -microglobulin with HDF treatments was significantly higher than those obtained with the four MCO dialyzers and high-flux HD treatments. Among MCO dialyzers, the Phylther 17-SD had a slightly lower RR than the other three MCO dialyzers (Fig. 2).

There were no significant differences in the myoglobin and prolactin RR between four HDx treatments, and all of them were significantly higher than those obtained with HD treatments (Fig. 2). In addition, HDF treatments were significantly higher than those obtained with all MCO and HD treatments (Fig. 2).

In the high molecular weight range, there were no significant differences in the α_1 -microglobulin and α_1 -acid glycoprotein RR between the four MCO dialyzers. The α_1 -microglobulin RR with HDF and all HDx treatments were significantly higher than those obtained in helixone HD treatments (Fig. 3). The α_1 -acid glycoprotein RR in HDF was significantly higher than those obtained with FX80 in HD and Elisio HX in HDx treatments (Fig. 3).

Free immunoglobulin light chain removal

The values of κ FLC RRs varied between 60% and 85%, and the values of λ FLC RR varied between 20% and 60%. There were no significant differences in the κ FLC RR between the four HDx treatments. There were similar results in the λ FLC RR between the four HDx treatments; only λ FLC RR obtained with Phylther SD was slightly higher than Elisio HX. All κ FLC and λ FLC RR obtained with the four HDx treatments were significantly higher than those obtained with the HD treatment (Fig. 4). In addition, the κ FLC and λ FLC RR were also significantly higher with HDF than with HD and HDx treatments (Fig. 4).

Albumin loss in blood and dialysate

There were no significant differences in blood albumin RR in all the studied situations: $9.8 \pm 4.7\%$ with helixone in HD, $9.6 \pm 5.2\%$ with Phylther 17-SD in HDx, $9.5 \pm 4.9\%$ with Vie-18X in HDx, $8.7 \pm 4.4\%$ with Elisio HX19 in HDx, $9.0 \pm 6.2\%$ with TheraNova in HDx and $10.4 \pm 5.9\%$ with FX80 in HDF.

The mean amount of dialysate albumin loss was <3 g in all situations, and significant differences were observed between the studied situations (Fig. 5). Albumin losses with HD were <1 g, with HDx were between 1.5 and 2.0 g, and were 2.5 g with HDF treatments (Fig. 5).

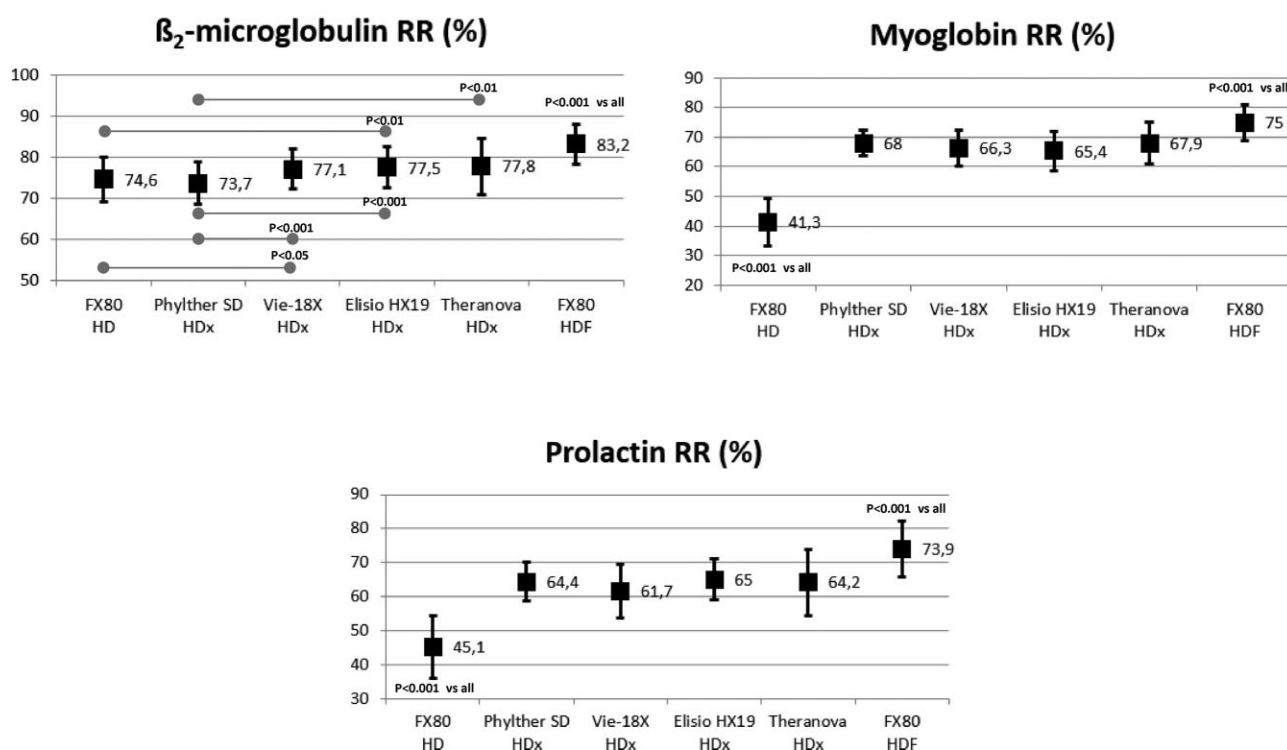


FIGURE 2: Comparison of β_2 -microglobulin, myoglobin and prolactin RRs in all study situations (ANOVA for repeated data).

Global removal score

There were no differences between the four MCO dialyzers. The highest Global Removal Score (GRS) values were obtained in HDF treatment and were statistically superior to HD and HDx treatments. The GRS values with HDx treatments were statistically higher than those obtained with HD (Fig. 6).

DISCUSSION

The present study is, to our knowledge, the first to compare the efficiency and safety issues of four MCO dialyzers in HDx treatments and to confirm that all these dialyzers respond to the MCO membrane classification, with no significant performance differences between them. They all showed similar albumin RR in blood and dialysate albumin loss inferior to 3 g per dialysis session. Likewise, the study confirms the solute removal superiority with HDx over high-flux HD and an efficacy close to post-dilution HDF, showing HDx as the alternative that came closest to post-dilution HDF, as previously published in the literature [16–21], and reinforcing the importance of both the choice of the dialyzer and the treatment modality to obtain optimal performance.

Since 2017, based on the results published by Kirsch et al. [11] on the performance of different medium- and high cut-off membranes, the first MCO membrane (Theranova, Baxter) was marketed and incorporated into clinical practice increasing the therapeutic scenario in hemodialysis. During the following years, several studies were published showing that this MCO dialyzer could provide higher removal performance than that with high-flux HD [13, 18–21], and could be an alternative to HDF, since this specific HD, called expanded HD, could achieve similar efficacy to that achieved by HDF [1, 22–24]. Appreciating the importance that this new class of dialyzers could have in dialysis treat-

ment, several pharmaceutical companies developed new MCO dialyzers, some of them obtaining in 2021 the CE mark (Asahi and Nipro), expanding the range of treatment possibilities. Finally, for more than 10 years, Medtronic already had a generation of polyphenylene dialyzers sterilized with steam, which retains the original size of the pores and therefore behaves like an MCO membrane [15].

The term expanded HD was proposed to define a treatment where diffusion and convection are conveniently combined inside a hollow-fiber dialyzer equipped with an MCO membrane [25]. This is due to the tailored cut-off of the membrane pores with an increased size and an adequate internal diameter that favor internal backfiltration, combined with an internal architecture that allows MCO membranes to achieve increased removal capacities for middle molecules and large middle molecules compared with standard HD treatments [2]. This new type of dialyzer has been called medium cut-off in Europe and super high-flux or sharp cut-off membrane in Japan [25–27]. Interest in this type of dialyzer has grown in recent years due to the efficacy and results obtained without an increase in safety issues, currently placing HDx, along with HDF, as the most effective options for dialysis treatment. This is the main reason why many of the pharmaceutical companies have or are developing them in order to incorporate these dialyzers into their portfolio.

At the current time, there are no clear and concise criteria to define whether a dialyzer pertains to the MCO group; however, they have some common aspects such as the enlarged pore size (something not usually shown in the technical issue) which determines the molecular weight retention onset and molecular weight cut-off sieving curves [9]. The internal architecture of the dialyzer assures a good combination between diffusion and convection. In fact, the optimization of the backfiltration of several dialyzers is not linked to the classic reduction of the

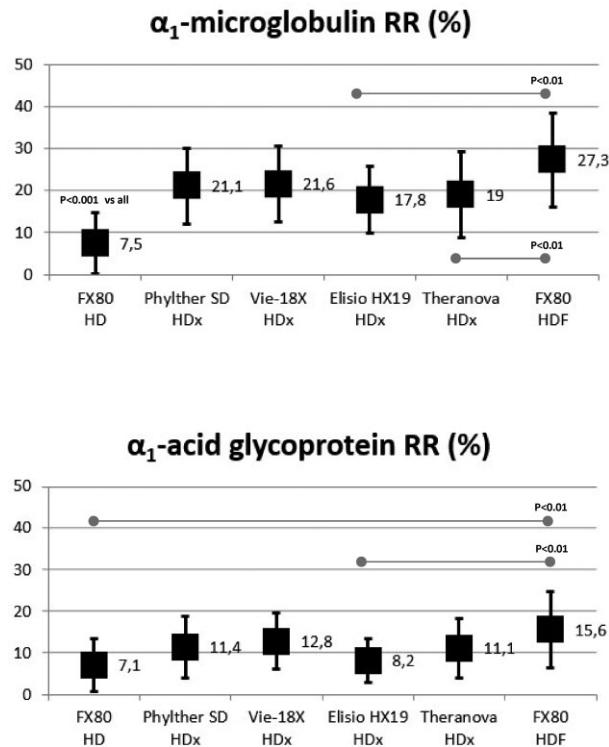


FIGURE 3: Comparison of α_1 -microglobulin and α_1 -acid glycoprotein RRs in all study situations (ANOVA for repeated data).

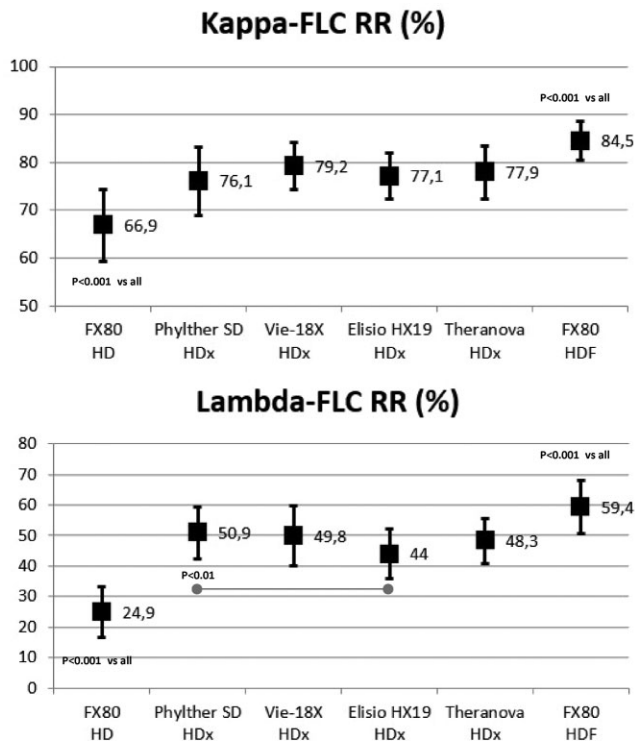


FIGURE 4: Comparison of κ FLC and λ FLC RRs in all study situations (ANOVA for repeated data).

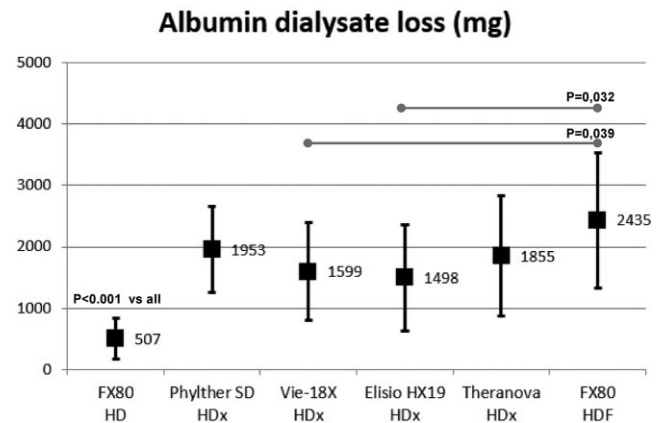


FIGURE 5: Comparison of dialysate albumin loss in all study situations (ANOVA for repeated data).

internal diameter of the fibers as happens in the Theranova one (180 μ m), but through keeping the inner diameter of the fibers and also lengthening the fibers, which particularly compensates backfiltration.

The differences in efficacy between the evaluated dialyzers were minimal in small molecules and even up to the size of β_2 -microglobulin. The differentiating profile was found in the 15 and 30 kDa molecules (myoglobin, prolactin and α_1 -microglobulin). In this study, all MCO dialyzers, with similar efficacy in GRS, were notably superior to high-flux HD treatments by around 60%, though 15% inferior to HDF treatments. These results confirm previously published studies [11–16, 18–21], establishing the current position of HDx as clearly superior to high-flux HD and very close to post-dilution HDF.

Both kappa and lambda light chains, 22 and 45 kDa, respectively, could be considered good differential markers of depurative efficacy, especially in the 40–45 kDa molecular weight range, where there are no clear differentiating markers. The RR of κ FLC with all MCO dialyzers were 12%–15% superior to HD and 10% inferior to HDF treatments. However, the RR of λ FLC with all MCO dialyzers were 90%–100% superior to HD and 10% inferior to HDF treatments. Kirsch et al. [11] found that both FLC RR were superior with MCO treatment than with high-flux HD and post-dilution HDF. Zickler et al. [28] and the a tRial Evaluating Mid cut-Off Value membrane clearance of Albumin and Light chains in HaemoDialysis patients study [29] reported that the MCO dialyzer effectively reduced κ FLC and λ FLC, compared with high-flux HD following 12 and 2 weeks of treatment, respectively.

The safety of MCO dialyzers is ensured by restricting pore sizes to limit albumin losses below 5 g per session [9, 10]. In this regard, most published studies report that MCO membranes lead to a higher albumin loss than HD and show inconsistent results compared with HDF [1, 2, 9, 13, 16, 24]. The mass of solute collected in the dialysate corresponds only to its elimination by diffusion and convection, obviating the adsorption one, which cannot be quantified routinely; however, to assess the overall loss of albumin (adsorption, diffusion and convection), the albumin RR in the blood was reported. In this study, all four dialyzers in HDx treatment maintained a safe behavior, with a global albumin RR of around 10% and a mean of dialysate albumin loss between 1.5 and 2.0 g per session—higher than HD treatments as has been described, but slightly lower compared with HDF (mean albumin loss 2.4 g). Although albumin loss could be considered clinically tolerable in all study treatments, it is necessary to mention that

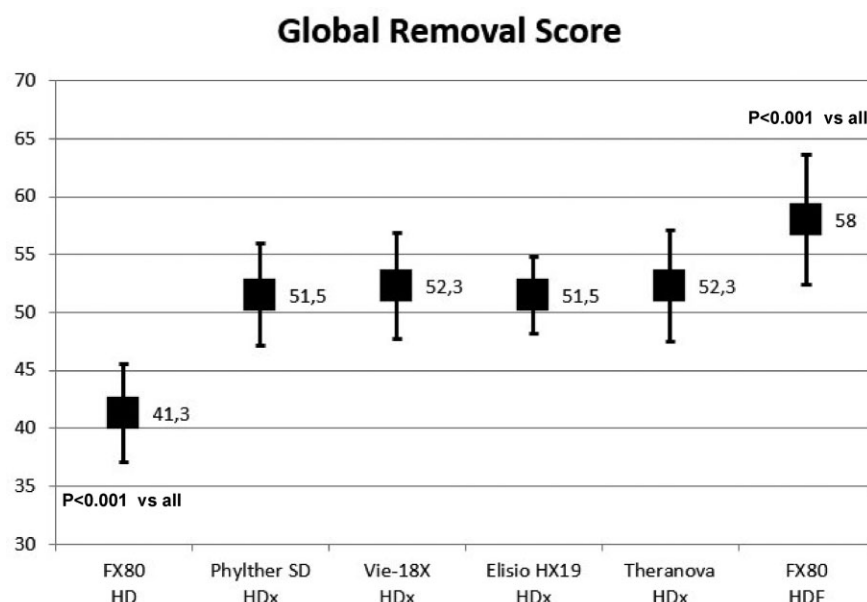


FIGURE 6: Comparison of GRSGRS in all study situations (ANOVA for repeated data).

all MCO membranes should only be used in HD mode to avoid increased albumin losses with a progressive reduction in serum levels [30].

A limitation of the study is that the efficacy was assessed by removal of uremic toxins using RR calculation; however, there was no long-term clinical follow-up with these dialyzers. The advantage of assessing efficacy with the RR allows a final result to be obtained that includes the parameters of each dialyzer. The performance of dialysis therapy is usually evaluated by solute removal, and the quality of dialysis therapies should be assessed by clear outcome studies such as randomized control trials [27]. Other concerns would be that the differences in the surface area, the membrane thickness and the type of membrane influence the purifying efficacy; however, the differences in membrane surface area were $<0.2 \text{ m}^2$; moreover, in a previous study [31] no significant differences were found between Theranova 400 and 500 (1.7 vs 2.0 m^2).

In conclusion, the results of the four MCO dialyzers evaluated in this study showed good efficiency with no significant performance differences between them. All four MCO dialyzers showed similar albumin RR in blood and clinically acceptable dialysate albumin loss. Likewise, the study confirms the superiority of treatment with HDx over high-flux HD and efficacy very close to that of post-dilution HDF. This study helps assess the increase in the availability of MCO dialyzers, which will likely increase even more in the coming years.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj](#) online.

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AUTHORS' CONTRIBUTIONS

F.M. conceived the study. J.J.B., D.R.-E., J.R., L.M.R., M.A.-G., M.V., N.F., M.C.S. and N.R. acquired the data. F.M. and J.J.B. analyzed the data, made the figures and drafted the paper. All authors have revised the drafts and approved the final one.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, F.M., upon reasonable request.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial support for the project. F.M. has received consultancy fees and lecture fees from Baxter, Fresenius Medical Care, Medtronic, Nipro, Toray and Vifor. The other authors declare no conflicts of interest.

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