Performance of Hemodialysis with Novel Medium Cut-Off Dialyzers

Kirsch AH Lyko R, Nilsson LG, et al. Performance of hemodialysis with novel medium cut-off dialyzers. *Nephrol Dial Transplant*. 2017; 32:165-172. doi:10.1093/ndt/gfw310.

BACKGROUND

End-stage renal disease (ESRD) results in the retention of uremic toxins, which is associated with high mortality. Uremic toxins are classified into small (< 500 Da) and middle molecular (500 Da–60 kDa) water-soluble solutes and protein-bound substances. While conventional hemodialysis (HD) modalities remove small solutes and smaller-sized middle molecules, clearance of larger middle molecules and protein-bound substances is poor.

Studies have associated middle molecules to pathological features of uremia, such as immune dysfunction and inflammation, as well as adverse outcomes in dialysis patients. Free immunoglobulin light chains (FLCs) have a molecular weight (MW) of ~22.5 kDa for kappa FLC (κFLC) and 45 kDa for lambda FLC (λFLC). Importantly, FLC levels have been associated with mortality in chronic kidney disease (CKD) cohorts.

Efforts have focused on improving the clearance of larger middle molecules in dialysis. The introduction of more water-permeable high-flux membranes allowed the clearance of middle molecules such as β2-microglobulin (12 kDa) and increasing convection with hemodiafiltration (HDF) considerably enhanced middle molecule clearance. However, high flux dialyzers have cut-off values of ~20 kDa and are thus limited in their ability to remove larger middle molecules κFLC and λFLC. Maintenance HD patients who are at high mortality risk seem to benefit from high-flux HD, but large outcome trials comparing HDF to HD have yielded equivocal results.

Medium cut-off dialyzers utilize a novel class of membranes designed to increase the removal of larger middle molecules in HD, and in contrast to more permeable high cut-off membranes, are intended for routine use in maintenance HD patients.

OBJECTIVES

To compare the performance of three prototypes of **MCO** dialyzers with HD and high-volume hemodiafiltration (HDF) using contemporary high-flux dialyzers. Specifically, these studies compared the clearance of larger middle molecules, including κFLC (23 kDa) and λFLC (45 kDa), considered to be uremic toxins.

METHODOLOGY

Study Design

The two studies were prospective, open-label, 4-arm, randomized, active-control, crossover pilot studies comparing **Theranova** 400 dialyzer (**MCO** AA; Gambro Dialysatoren GmbH, Hechingen, Germany, a subsidiary of Vantive Health LLC) and two **MCO** dialyzer prototypes (**MCO** BB and CC) with high-flux dialyzers FX CorDiax 80; Fresenius Medical Care Deutschland, Bad Homburg, Germany in studies 1 and 2 and high-volume HDF (FX CorDiax 800; Fresenius Medical Care Deutschland, Bad Homburg, Germany; study 2.

The membranes of the **MCO** dialyzers had increased permeability (AA < BB < CC). **MCO** membranes AA, BB and CC were polyarylethersulfone-PVP blend membrane polymer; Fx CorDiax 80 and Fx CorDiax 800 were polysufone-PVP blend membrane polymer.

Study 1 compared **MCO** membrane AA (**Theranova** 400 dialyzer), BB, and CC with high-flux dialyzers (FX CorDiax 80), while study 2 compared **MCO** membrane AA (**Theranova** 400 dialyzer) and BB with high-flux dialyzers (FX CorDiax 80) and high-volume HDF (FX CorDiax 800).

Study 1 was conducted in the dialysis units of a medical university and a hospital in Austria. Study 2 was performed in a dialysis center in Germany. The dialysis sessions in study 1 were 4 hours with a dialysate flow (QD) of 500 mL/min and a blood flow (QB) of 300 ± 20 mL/min, while the dialysis sessions in study 2 were 4-5 hours with a QB of 400 + 50 mL/min.

Patients

Patients aged 18 years or above, on either HD or HDF treatment for at least 3 months before enrollment, had a κFLC/λFLC ratio of > 0.37 and < 3.1, and no history of monoclonal gammopathy were enrolled and randomized to each study dialyzer treatment. A total of 39 patients were enrolled: 19 in study 1 and 20 in study 2.

Outcomes

The primary outcome was the overall clearance (K_{ovr}) of λFLC using **MCO** dialyzer prototypes in HD mode vs. K_{ovr} using high-flux dialyzers used in HD and HDF. Secondary outcomes were the clearance of other middle molecules and small molecules, as well as safety (albumin removal and treatment tolerance) of **MCO** membrane HD.

RESULTS

Study 1: Free Light Chain Removal During HD Using MCO Dialyzers Compared to a High-Flux Dialyzer

Overall Clearance

In study 1, the λFLC K_{ovr} and the κFLC K_{ovr} with **MCO** membranes AA, BB, and CC were significantly higher than with high-flux HD. See Figure 1A and Table 1A.

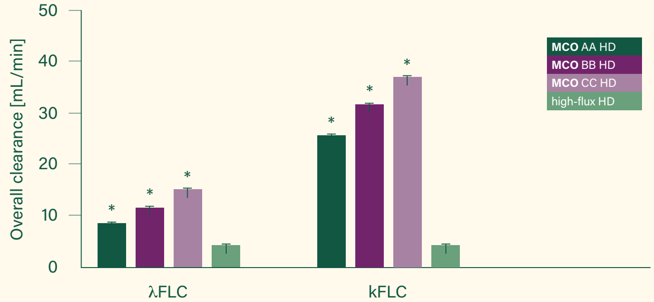

Figure 1A. Overall Clearance. Free immunoglobulin light chain removal during hemodialysis with mediumz cut-off dialyzers and high-flux dialyzer in study 1. Data are least square mean + standard error. *p < 0.001 compared to high-flux dialyzer. Abbreviations: FLC, free light chain; **MCO** membrane, medium cut-off dialyzer; HD, hemodialysis. Adapted from Kirsch et al.

Test Dialyzer	λFLC K_{ovr} Overall Clearance		κFLC K_{ovr} Overall Clearance	
	Least square mean mL/mn (standard error)	*P* value vs high-flux HD	Least square mean mL/mn (standard error)	*P* value vs high-flux HD
MCO AA HD	8.5 (0.54)	P<0.001	26.2 (1.24)	P<0.001
MCO BB HD	11.3 (0.51)	P<0.001	31.8 (1.17)	P<0.001
MCO CC HD	15.0 (0.53)	P<0.001	37.3 (1.24)	P<0.001
High-flux HD	3.6 (0.51)		3.3 (1.17)	

Table 1A. Overall Clearance. Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and high-flux dialyzers in study 1. Data are least square mean + standard error. Abbreviations: FLC, free light chain; **MCO** membrane, medium cut-off dialyzer; HD, hemodialysis. Adapted from Kirsch et al.

Reduction Ratios

The λFLC reduction ratios (RRs) and κFLC RRs of **MCO** membrane AA, BB, and CC were significantly higher than that of high-flux HD. See Figure 1B and Table 1B.

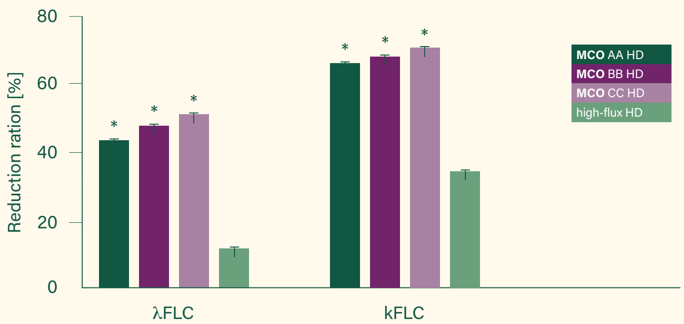

Figure 1B. Reduction Ratio. Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and high-flux dialyzer in study 1. Data are least square mean + standard error. P < 0.001 compared to high-flux dialyzer. Abbreviations: FLC, free light chain; **MCO** membrane, medium cut-off dialyzer; HD, hemodialysis. Adapted from Kirsch et al.

Test Dialyzer	λFLC K_{ovr} Reduction Ratio		κFLC K_{ovr} Reduction Ratio	
	% (standard error %)	*P* value vs high-flux HD	% (standard error %)	*P* value vs high-flux HD
MCO AA HD	42.5 (2.06)	P<0.001	66.3 (1.85)	P<0.001
MCO BB HD	47.6 (2.06)	P<0.001	68.4 (1.85)	P<0.001
MCO CC HD	51.5 (2.10)	P<0.001	70.4 (1.88)	P<0.001
High-flux HD	12.9 (2.10)		36.4 (1.88)	

Table 1B. Reduction Ratio. Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and high-flux dialyzer in study 1. Data are least square mean + standard error. Abbreviations: FLC, free light chain; **MCO** membrane, medium cut-off dialyzer; HD, hemodialysis. Adapted from Kirsch et al.

Study 2: Free Light Chain Removal During HD Using MCO Dialyzers Compared to High-Flux HD and HDF

Overall Clearance

Like study 1, in study 2, the λFLC K_{ovr} and κFLC K_{ovr} during HD were again significantly greater (p < 0.001) when using **MCO** membrane AA or BB compared to high flux HD (see Figure 2A). The λFLC K_{ovr} and κFLC K_{ovr} with **MCO** AA and BB were also significantly higher than that of HDF (p<0.001). See Figure 2A and Table 2A.

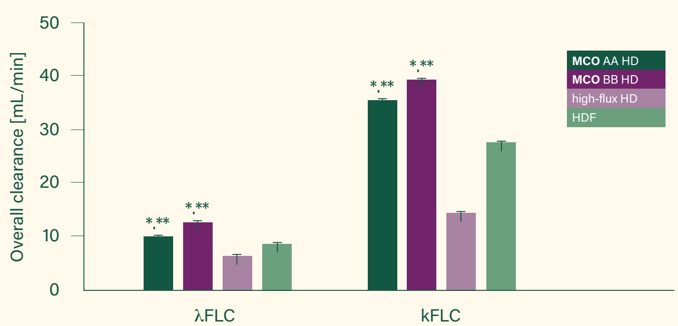

Figure 2A. Overall Clearance. Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and high-flux dialyzer and hemodiafiltration in study 2. Data are least square mean + standard error. *p <0.001 compared to high-flux HD; **p < 0.001 compared to HDF. Abbreviations: FLC, free light chain; **MCO** membrane, medium cut-off dialyzer; HD, hemodialysis, HDF, hemodiafiltration. Adapted from Kirsch et al.

Test Dialyzer	λFLC K_{ovr} Overall Clearance		κFLC K_{ovr} Overall Clearance	
	Least square mean mL/mn (standard error)	*P* value vs HDF	Least square meanmL/mn (standard error)	*P* value vs HDF
MCO AA HD	10.0 (0.58)	P<0.001	35.0 (1.43)	P<0.001
MCO BB HD	12.5 (0.57)	P<0.001	39.4 (1.39)	P<0.001
HDF	6.2 (0.58)		25.4 (1.43)	P<0.001

Table 2A. Overall Clearance. Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and hemodiafiltration in study 2. Data are least square mean + standard error. Abbreviations: FLC, free light chain; **MCO** membrane, medium cut-off dialyzer; HDF, hemodiafiltration. Adapted from Kirsch et al.

Reduction Ratios

The λFLC reduction ratios (RR) with **MCO** membranes AA and BB were superior to that with HDF (p < 0.001). There was no difference between κFLC RR achieved with **MCO** membrane AA vs HDF (p=0.3); whereas **MCO** membrane BB resulted in a statistically significantly higher κFLC RR than HDF (p=0.01). See Figure 2B and Table 2B.

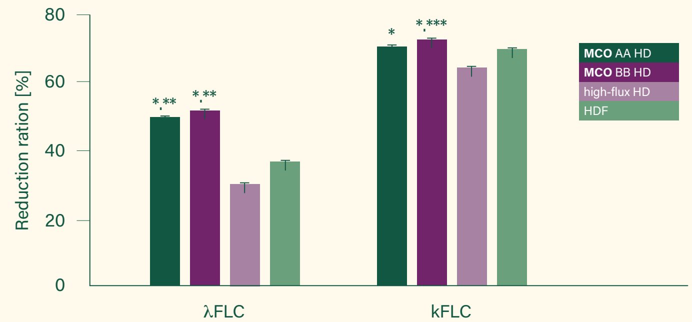

Figure 2B. Reduction Ratio. Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and high-flux dialyzer and hemodiafiltration in study 2. Data are least square mean + standard error*p <0.001 compared to high-flux HD; **p < 0.001 compared to HDF; ***p p=0.01, compared to HDF. Abbreviations: FLC, free light chain; **MCO**, medium cut-off dialyzer; HD, hemodialysis; HDF, hemodiafiltration. Adapted from Kirsch et al.

Test Dialyzer	λFLC K_{ovr} Reduction Ratio		κFLC_{ovr} Reduction Ratio	
	% (standard error %)	*P* value vs HDF	% (standard error %)	*P* value vs HDF
MCO AA HD	48.1 (1.72)	P<0.001	72.9 (1.35)	P=0.3
MCO BB HD	52.7 (1.72)	P<0.001	74.8 (1.35)	P=0.01
HDF	37.9 (1.76)		71.6 (1.37)	

Table 2B. Reduction Ratio. Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and high-flux dialyzers and hemodiafiltration in study 2. Data are least square mean + standard error. Abbreviations: FLC, free light chain; **MCO** membrane, medium cut-off dialyzer; HD, hemodialysis; HDF, hemodiafiltration. Adapted from Kirsch et al.

Removal of other middle molecules during HD and HDF

In addition to κFLC and λFLC, removal of other larger-sized solutes was greater with **MCO** membrane HD (**MCO** AA/ **Theranova** 400 dialyzer) compared to high-flux HD (FX CorDiax 80) and high-volume HDF (FX CorDiax 800). The overall clearance for α1-microglobulin (33 kDa), complement factor D (CFD) (24 kDa), myoglobin (17 kDa) and β2-microglobulin (12 kDa) as well as λFLC (45 kDa) and κFLC (23 kDa) were significantly greater for **MCO** membrane AA HD than HD and HDF (p < 0.001). The exception was the difference for β-2 microglobulin vs HDF in which the significance was p < 0.01. See Figure 3A.

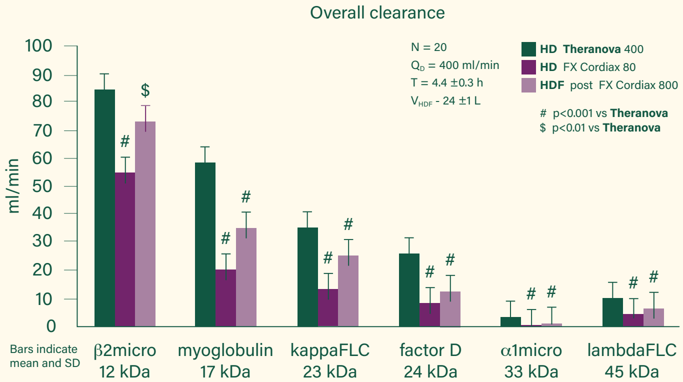

Figure 3A. Overall clearances of medium-sized and small molecules. Comparisons are based on a mixed model with fixed effects of period and study dialyzer type, and the random effect of subject. Abbreviations: HD, hemodialysis; HDF, hemodiafiltration, SD: standard deviation.

The reduction ratios were significantly greater for **MCO** membrane AA HD (**Theranova** 400 dialyzer) than HD and HDF ($p < 0.001$) for λFLC (45 kDa), YKL-40 (40 kDa), Complement Factor D (24 kDa) and myoglobin (17 kDa). **MCO** membrane AA HD also showed a significant difference ($p < 0.001$) vs HD in reduction ratios for κFLC (23 kDa) and β2-microglobulin (12 kDa). A slightly higher reduction ratio for β-microglobulin was achieved with HDF, underlining that **MCO** membrane HD more efficiently removes larger middle molecules. See Figure 3B.

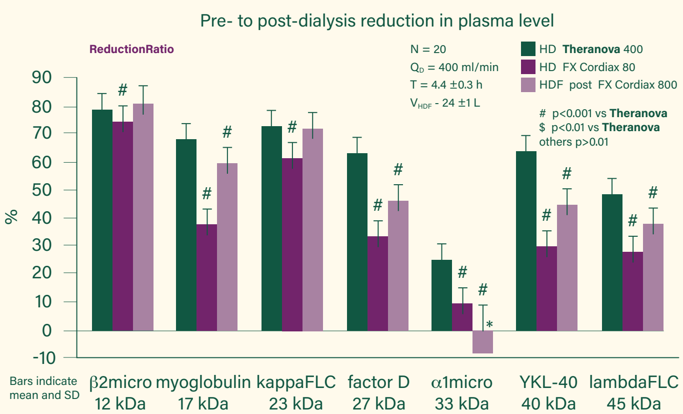

Figure 3B. Reduction ratios of medium-sized and small molecules. Comparisons are based on a mixed model with fixed effects of period and study dialyzer type, and the random effect of subject. Abbreviations: HD, hemodialysis; HDF, hemodiafiltration, SD: standard deviation.

Albumin Removal During MCO membrane HD

Increasing pore sizes, while permitting clearance of larger uremic toxins, bears the trade-off of the leaking of larger molecules such as albumin (65 kDa)[1]. In both studies, **MCO** dialyzers resulted in larger albumin removal than high-flux HD and HDF. However, for **MCO** membrane AA, the tightest of the three membranes, the per treatment albumin loss was about 3 g on average, and the controlled loss was between 1 and 4 g. The albumin loss obtained with the **MCO** AA dialyzer was within range observed in HDF treatment with high flux dialyzers, below transperitoneal albumin losses seen in peritoneal analysis, and less than a third of what has been reported for HD with High Cut-off membranes. See Table 3.

Test Dialyzer	Study 1 – Albumin Removal Median g (range)	Study 2 – Albumin Removal Median g (range)
MCO AA	2.9 g (1.5-3.9)	3.2 g (1.9-3.9)
MCO BB	4.8 g (2.2-6.7)	4.9 g (1.1-7.2)
MCO CC	7.3 g (1.9-9.7)	nv
High-flux HD	0.2g (0.2-0.2)	0.2 g (0.2-0.3)
HDF	nv	0.4 g (0.3-0.8)

Table 3. Albumin removal in studies 1 and 2. Albumin values (median g (range)). Abbreviations: **MCO** membrane, medium cut-off dialyzer; HD, hemodialysis; HDF, hemodiafiltration; nv, no value. Table adapted from Kirsch et al.

Safety

In study 1, the adverse events (AEs) between the study dialyzers were comparable (total = 23) and 11 patients (58%) experienced at least one AE. No serious AEs were recorded and none of the AEs was considered possible or likely to be related to the investigational product.

Similar AEs distribution was observed in study 2 (total = 31) with 11 patients (55%) experienced at least one AE. Two serious AEs occurred, both requiring intradialytic hospitalization but not related to the study treatments. Six AEs were considered possibly or likely to be related to the investigational product: one patient in **MCO** BB dialyzer and one in FX CorDiax 80 dialyzer (each had three events).

Limitations

K_{ovr} only includes transmembrane removal and does not take into account any potential adsorption to the membrane. The study design was confined to a single treatment with each dialyzer for each patient and the study did not examine the long-term effects of such membranes on serum levels of middle molecules and albumin.

CONCLUSION

These studies were the first studies that presented a unique characterization of HD membrane clearance for an extensive size range of middle molecules (11.6 – 45 kDa). **MCO** membrane HD removes a wide range of middle molecules more effectively than high-flux HD, with the trade-off of increased albumin removal, compared to high-flux HD and HDF. **MCO** membrane HD also exceeds the performance of high-volume HDF for removal of larger middle molecules, particularly λFLC. However, for **MCO** AA, the tightest of the three membranes, the per treatment albumin loss was about 3 g on average, and the controlled loss was between 1 and 4 g.

The MCO AA prototype, the most restrictive of the three prototypes tested and the most attractive benefit-risk profile, became the basis for the **Theranova** 400 dialyzer specifications. Importantly, **MCO** membrane HD/**Theranova** dialyzer can be applied to maintenance HD patients, in whom high volume HDF may not be used or is not available.

MCO membrane provides superior removal of large middle molecular uremic toxins (up to 45,000 Da), compared to traditional high flux membranes, with controlled albumin loss between 1 and 4 g, per treatment.

References: 1. Wolley M, Jardine M, Hutchison CA. Exploring the clinical relevance of providing increased removal of large middle molecules. *Clin J Am Soc Nephrol*. 2018; 13:805-814.