

# HDx: A WORLD OF DIFFERENCE

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# HDx: A WORLD OF DIFFERENCE

## The Rise of Expanded Hemodialysis Therapy and the Medium Cut-Off Membrane

Expanded Hemodialysis (HDx) is a dialysis treatment where diffusion and convection are conveniently combined inside a hollow fiber dialyzer equipped with a High Retention Onset (HRO) membrane defined as Medium Cut-Off (MCO), with no special requirement of a particular hardware, preparation of replacement fluid, or additional nursing skill, versus the necessary ones required to perform conventional hemodialysis (HD) in standard mode<sup>1,2</sup>



-  **Ronco, C**  
**The Rise of Expanded Hemodialysis.** *Blood Purif.* 2017;44:I-VIII.
-  **Hutchison CA and Wolley M**  
**The Rationale for Expanded Hemodialysis Therapy (HDx).** *Contrib Nephrol.* 2017; 191:142-152.
-  **Ronco C and Clark WR**  
**Hemodialysis Membranes.** *Nat Rev Nephrol* 2018;14(6):394-410.
-  **Lorenzin A, Golino G, de Cal M, et al.**  
**Flow Dynamic Analysis by Contrast-Enhanced Imaging Techniques of Medium Cutoff Dialyzer.** *Blood Purif.* 2022;51:138-146.
-  **Boschetti-de-Fierro A, Voigt M, Storr M, et al.**  
**MCO Membranes: Enhanced Selectivity in High-Flux Class.** *Nature/Sci Rep.* 2015; 5:18448.





# The Rise of Expanded Hemodialysis

Ronco, C. The Rise of Expanded Hemodialysis. *Blood Purif.* 2017;44:I-VIII. doi: 10.1159/000476012.

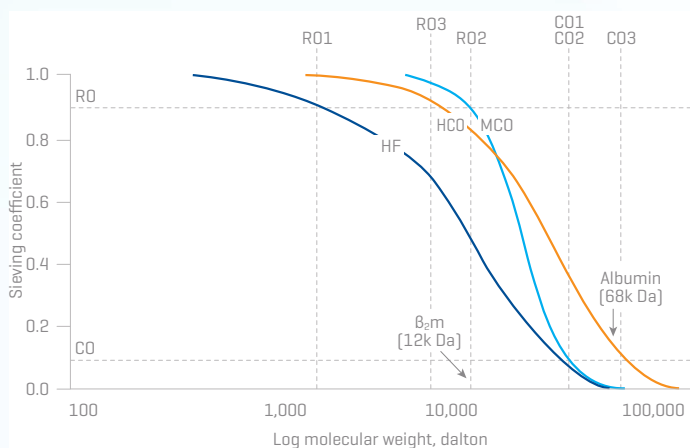
## BACKGROUND

Significant improvements have been made to hemodialysis over the years leading to longer survival and improved quality of life in patients with end-stage kidney disease (ESKD). However, despite technological advances and improved patient care, long-term outcomes are still suboptimal with a high rate of hospitalization and mortality. Important limitations of current dialysis techniques emerge clearly with several uremic solutes inadequately removed.

The most recent evolution in the field of membranes is the development of a new class defined as “high retention onset” (HRO) due to the peculiar high sieving value in the middle to high molecular weight range. The introduction of HRO membranes in the clinical routine has enabled the development of a new concept therapy called “expanded hemodialysis (HDx)”. This new therapy is likely to modify the outcome of ESKD patients with the enhanced removal of molecules traditionally retained by current dialysis techniques. A careful analysis of the history of dialysis may help to avoid repeating mistakes of the past and project patient care toward more effective forms of treatments.

## EVOLUTION OF DIALYSIS

Pore density and size distribution are the two main factors affecting the quantity and the spectrum of molecules that are removed by a dialysis membrane. The sieving coefficient curve is an empirically derived function that depends on these variables. However, the cutoff value is insufficient to fully characterize the shape of the sieving curve. A further parameter termed “retention onset” (RO) should also be determined for this purpose. This parameter describes the molecular weight/radius where the sieving value is 0.9. In an integrated transport model, a membrane with a tight pore size distribution will have a very steep sieving curve, while a membrane with a wide pore size distribution will have a flatter sieving curve possibly with a cutoff value beyond the molecular weight of albumin. This new approach helps the characterization of new classes of membranes. See Figure 1.



New membranes with a relatively high cutoff value (HCO) have been recently introduced in clinical practice with the potential to remove toxins in the high molecular weight range that are increased in blood during sepsis, rhabdomyolysis, and hematological disorders. In such circumstances, high molecular weight solutes such as cytokines, myoglobin, or free light chains are the main targets for removal. The limit of these membranes, however, is the possibility of albumin leak due to the pore size opening and therefore their use is limited to a few sessions in diffusive mode until more information is available on clinical benefits and/or threats.

More recently, a great deal of effort has been made to produce membranes with a tight pore size distribution resulting in a steep sieving curve. The attempt is to keep molecular weight retention onset (MWRO) and molecular weight cutoff (MWCO) very close to each other, with a cutoff value close but lower than that of albumin. The result should be an improved removal of uremia retention molecules in the middle-to-high weight range with marginal or no albumin leak. See Table 1.

Solute	MW, Da	Class	Action/effect
B-2 M	12,000		Amiloidosis CTS
Leptin	16,000	Middle*	Malnutrition
Myoglobin	17,000		Organ damage
κ-FLC	23,000		Toxicity
Prolactin	23,000		Infertility
Interleukin-6	25,000		Inflammation
Hepcidin	27,000	Large*	Anemia
Bound P-cresol	33,500		CV toxicity
Pentraxin-3	43,000		Acute phase protein
λ-FLC	45,000		CV toxicity
TNF-α (trim)	51,000		Inflammation

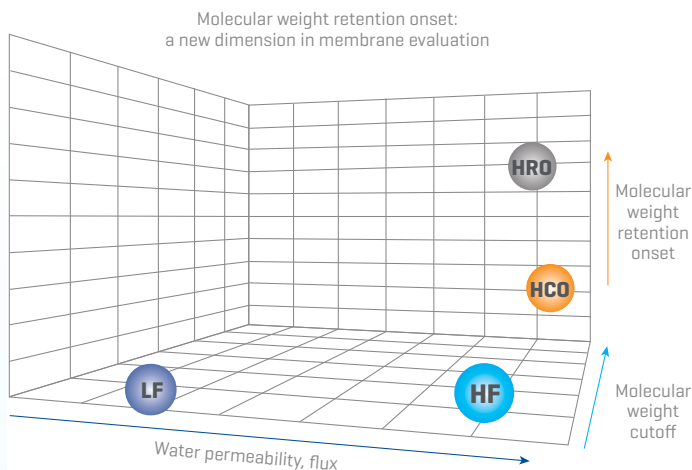
**TABLE 1.** Uremia Retention Solute Inadequately Removed by Current Hemodialysis Techniques. \*Value referred to the molecular weight interval between urea and albumin. MW: molecular weight; Da: daltons; β-2 M: beta-2 microglobulin; κ-FLC: kappa free light chain; λ-FLC: lambda free light chain; TNF-α: tumor necrosis factor-alpha; CTS: carpal tunnel syndrome; CV: cardiovascular. Table adapted from Ronco C.

**FIGURE 1.** Theoretical sieving curves for 3 different classes of membranes; high flux (HF), high retention onset (HRO) and high cutoff (HCO). The point in the curve where sieving coefficient is 0.1 determines the molecular weight cutoff (MWCO) value. The point in the curve where the sieving coefficient is 0.9 determines the molecular weight retention onset (RO) value. While the HRO membrane demonstrates a similar cutoff value of the HF membrane, it demonstrates a completely different behavior. While the RO for the HF membrane is in the range of 1,200 Da (Vitamin B12), the RO for the HRO membrane is in the range of 12,000 Da (β-2 microglobulin). MWCO value can be different in the 2 membranes with small leakage of albumin in the HRO class, but this effect is neutralized after a few minutes from the beginning of the treatment due to protein deposition at the blood membrane interface. HCO membrane has a cut-off value beyond the molecular weight of albumin and determines some albumin loss. HF: high flux; HRO: high retention onset; MWCO: molecular weight cutoff; RO: retention onset. Figure adapted from Ronco C.





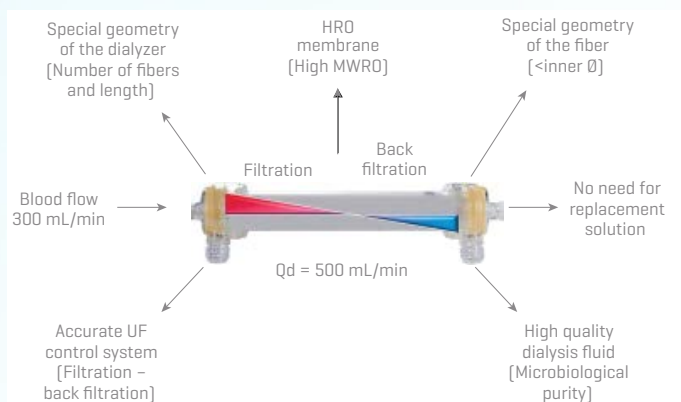
Based on these characteristics and the performance tests, it is proposed to define this new class of membranes as high RO (HRO) being the RO, the new dimension of characterization. Please see Figure 2.



**FIGURE 2.** Molecular Weight Retention Onset: A New Dimension of Membrane Evaluation. The tridimensional graph describes the domain map of hemodialysis membranes. The main parameters describe the nature and performance of the membrane: water permeability or flux (increasing this parameter results in a move from low flux (LF) to high flux (HF) membranes), molecular weight cut off (MWCO) and molecular weight retention onset (MWRO). MWCO and MWRO characterize the steepness of the sieving coefficient curve and its location in terms of molecular weight range. LF: low flux; HF: high flux; HCO: high cutoff; MWCO: molecular weight cutoff; HRO: high retention onset; MWRO: molecular weight retention onset. Figure adapted from Ronco C.

### HDX: A NEW THERAPY FOR A NEW MEMBRANE

The new term “HDX” is the technique terminology for the application of HRO membranes in clinical dialysis. The term defines a treatment where diffusion and convection are conveniently combined inside a hollow fiber dialyzer equipped with an HRO membrane. A dialysis machine with ultrafiltration control is required, but no replacement solution or elevated ultrafiltration rates are needed to perform the therapy. See Figure 3.



**FIGURE 3.** Expanded Hemodialysis and Related Operational Parameters. HRO: High retention onset; MWRO: molecular weight retention onset; UF: ultrafiltration. Figure adapted from Ronco C.

The shape of the sieving curve of the HRO membrane is peculiar and optimized to perform HDx. Using a simple ultrafiltration-controlled hemodialysis technique, solute clearances in the spectrum of molecular weights traditionally retained with other techniques and membranes appear enhanced. Large molecules have low diffusion coefficients, and their removal requires the contribution of convection. An increase in convection can be achieved either with high flux (HF) membranes in hemodiafiltration (HDF) or by HRO membranes in HDx.

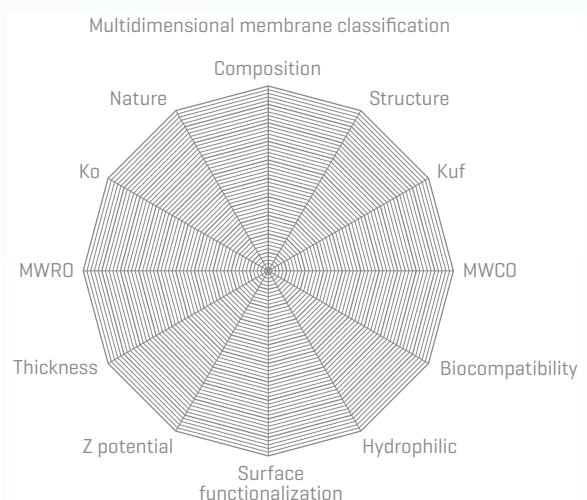
In HDF, the clearance (K) resulting from the product between ultrafiltration rate (Quf) and sieving (S) coefficient, ( $K = Quf \times S$ ), is increased by Quf in the presence of a relatively low molecular S. In HDx, the same clearance is achieved in the presence of a much lower Quf because of higher S. In HDF, large amounts of ultrafiltration require replacement of volume by commercially prepared or fluids produced online. In HDx, this is not needed. A significant amount of internal convection is present, but it is masked and balanced by an adequate amount of internal backfiltration. The mechanism of filtration-backfiltration is further enhanced using fibers with reduced inner diameter leading to a high pressure drop in the blood compartment at a given blood flow.

In the presence of enhanced sieving values for large molecules such as beta-2 microglobulin ( $\beta$ -2 M), (12,000 Da molecular weight) or free light chains, relatively high clearances are achieved even at lower levels of convective flux and without requiring the fluid exchange volumes normally required in HDF. The fiber length and inner diameter are essential elements to optimize internal filtration and the mechanism of filtration-backfiltration. This mechanism, although invisible, makes it possible to achieve a significant amount of convection inside the dialyzer where filtration takes place in the proximal part and backfiltration compensates in the distal part. The ultrafiltration control system of the dialysis machine regulates the process and provides the exact amount of net filtration required for the scheduled weight loss of the patient.

### MULTIDIMENSIONAL MEMBRANE EVALUATION

The evaluation of a membrane should consider many different dimensions. The dimensions could include the composition, the sieving (S) for middle molecules such as  $\beta$ -2 M, the interaction with water molecules, the MWRO for different molecular weight solutes, the biocompatibility, the hydraulic conductance or permeability (Kf), the presence of electrical charges and potential, the molecular weight cut off (MWCO) for different molecular weight solutes, the thickness, and the diffusion coefficient (Ko).

A specific graph should be able to identify a membrane or a class of membranes and thus offer the needed information to clinicians for a correct application of the membrane in a defined technique and therapy. Please see Figure 4.



**FIGURE 4.** Membrane Class Domain Map. Multidimensional approach to membrane classification includes the composition, the sieving (S) for middle molecules such as  $\beta$ -2 M, the interaction with water molecules, the molecular weight retention onset (MWRO) for different molecular weight solutes, the biocompatibility, the hydraulic conductance or permeability (Kf), the presence of electrical charges and Z potential, the molecular weight cutoff (MWCO) for different molecular weight solutes, the thickness, and the diffusion coefficient (Ko). S: sieving;  $\beta$ -2 M: beta-2 microglobulin; MWRO: molecular weight retention onset; Kf: filtration coefficient; MWCO: molecular weight cutoff; Ko: diffusion coefficient. Figure adapted from Ronco C.





## CONCLUSION

The analysis of outcomes in clinical dialysis demonstrates that hemodialysis is still far from effectively replacing the function of the native organ. The case of HRO membranes and HDx is a typical example of progress and innovation in dialysis. It is unlikely that the efficacy of these membranes and this therapy will be proven in a large randomized controlled trial and their application will probably be based on application in clinical routine on criteria different from the classic evidence. It will be probably easier to perform simple pragmatic trials utilizing registries and big data analysis derived from electronic medical records once HDx is sufficiently adopted in clinical routine.

An important question remains to define the best utilization of HDx. Is it going to be a rescue therapy for patients with a high level of uremia retention products, erythropoietin-resistant anemia, malnutrition-inflammation syndrome; or an elective therapy for patients beginning hemodialysis and candidates for an early transplant? HDx could be an ideal transition therapy for patients moving out from peritoneal dialysis and waiting for a transplant. This is an area where the application of precision medicine and treatment personalization will be highly recommended and will be found useful. The interesting features of HRO membranes and the improved possibility to remove middle-high molecular weight solutes will spur new research in the field of hemodialysis and will constitute a new hope for ESKD patients of improved medium- to long-term clinical outcomes. The “rise of HDx” is expected in the next few years, depending on the personal experience of users.



# The Rationale for Expanded Hemodialysis Therapy (HDx)

**Hutchison CA and Wolley M.** The rationale for expanded hemodialysis therapy (HDx). *Contrib Nephrol.* 2017; 191:142-152. doi: [10.1159/000479262](https://doi.org/10.1159/000479262).

## BACKGROUND

To date, the class of uremic toxins known as large middle-molecules has been classified as “difficult to remove” in dialysis membrane technologies. Expanded hemodialysis utilizes a new generation of high-retention-onset hemodialysis membranes; these membranes provide the ability to remove large middle-molecules effectively for the first time, without significant albumin loss. These large middle-molecules appear to be linked to several unsolved clinical complications of end-stage kidney disease (ESKD); their increased removal may potentially lead to improved patient outcomes.

## OBJECTIVE

The purpose of this review was to evaluate the removal of large middle-molecules by the new high-retention-onset membranes, clinical relevance of these molecules, and how expanded hemodialysis can be prescribed.

## DISCUSSION

### High-Retention-Onset Membranes

High-flux dialysis membranes have been designed principally to remove middle-molecules up to the size of  $\beta$ -2-microglobulin (16 kDa). Due to the non-uniformity of membranes' pores, molecules much larger than  $\beta$ -2-microglobulin can be removed, but the absolute clearance rates are limited.

In addition, high flux membranes have a low molecular-weight-retention-onset (MWRO) value of 2-5 kDa. The term “retention onset” refers to the molecular weight at which the sieving value for a membrane reaches 0.9; there is no longer “free clearance” of molecules greater than this size. The term “molecular weight cut off” (MWCO) refers to the other end of the sieving curve of the membrane. This is the point when the sieving coefficient has reached 0.1, which means almost no clearance of a given molecule.

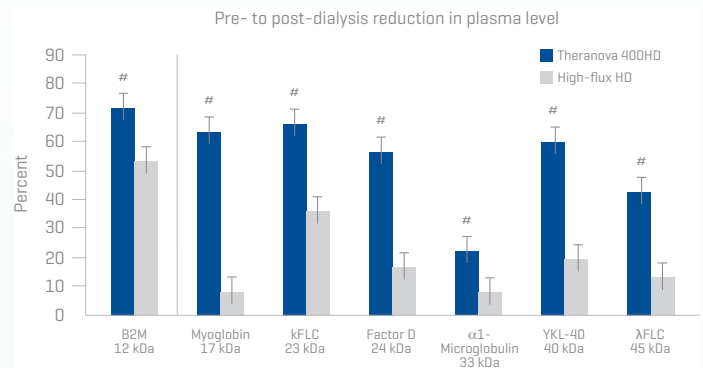
The closer the values of MWRO and MWCO, the steeper is the slope of the sieving coefficient. The ability to provide a steep sieving coefficient curve for a dialysis membrane allows the curve to be moved to the right, closer to basement (glomerular) membrane, enabling the removal of larger molecules without the loss of very clinically important large molecules, such as the protein albumin (65 kDa)<sup>1</sup>.

Technical advances have now allowed the distribution of pore sizes to be narrowed, which in turn has tightened the relationship between the MWRO and MWCO of a membrane. This new generation of dialyzers has been referred to as “mid-cut off membranes” or “high-retention-onset membranes”.

### Large Middle-Molecules

In comparison with high-flux membranes (polysulfone-PVP blend), high-retention-onset membranes (polyarylethersulfone-PVP blend) have significantly higher clearance rates of middle-molecules with molecular weights greater than 15 kDa. See Figure 1.

Currently there are 27 middle molecules with molecular weights greater than 15 kDa described in medical literature (see Table 1).



**FIGURE 1.** Reduction rates of large middle-molecules on high-flux and TheraNova dialyzers. Nineteen patients, blood flow  $301 \pm 22$  mL/min, treatment time 4 hours. High-flux hemodialysis undertaken on FX CorDiax 80 dialyzer (polysulfone-PVP blend membrane). Dialysis with TheraNova dialyzer (polyarylethersulfone PVP blend membrane). Bars indicate mean and standard deviation (SD). Post-dialysis data corrected for hemoconcentration. # $p < 0.001$  vs high-flux dialysis. Adapted from Hutchison and Wolley.

Serum concentrations of middle-molecules in dialysis are principally influenced by renal rates and production rates. As a result of these two variables, serum concentrations of large middle-molecules are highly variable in dialysis patients compared to healthy controls.

The 27 large middle-molecules can be classified into 5 broad groups: cytokines (n-5); adipokines (n-4); growth factors and other hormones (n-4); immune-mediated molecules (n-8), and other molecules (n-6).

The 5 cytokines had molecular weights between 17 and 28 kDa. The interleukins (IL)-1 $\beta$  (17.5 kDa), IL-6 (21-28 kDa), IL-18 (18 kDa), and tumor necrosis factor (TNF)- $\alpha$  (17 kDa) are all widely accepted as pro-inflammatory and are likely to be contributing factors to the chronic inflammation frequently seen in dialysis patients. However, IL-10 (18 kDa) is more clearly described as an anti-inflammatory cytokine.

Adipokines are cytokines but they are produced principally by adipose tissue. For the 4 adipokines described as large middle-molecules, their molecular weights range from 16 to 52 kDa with serum concentrations that are typically 2- to 6-fold of those seen in healthy controls. These adipokines have wide ranging biological functions in health and disease.

Three growth factors are found in this group of uremic toxins: vascular endothelial growth factor (34 kDa), fibroblast growth factor 2 (18 kDa), and fibroblast growth factor 23 (32 kDa). These molecules span from 18 to 34 kDa and have been described to be hundreds of fold higher in dialysis patients compared to healthy controls.

Several immune-mediated proteins are found in this group of large middle-molecules including the free light chains (FLC)  $\kappa$  (22.5 kDa) and FLC  $\lambda$  (45 kDa) and complement factor-D (24 kDa). With molecular weights spanning 17-45 kDa, they represent nearly the entire breadth of larger molecules, which can be removed with expanded hemodialysis.

An additional 6 large middle-molecules can be removed by this new therapy. Of these, potentially the most clinically relevant



are the advanced glycosylation end products (<1-70 kDa) which are up to 20-fold higher in dialysis patients. These large middle-molecules are implicated in multiple pathways of progressive cardiovascular disease. See Table 1.

### Clinical Relevance of Large Middle-Molecules

To be classified as a uremic toxin, in addition to having raised concentrations in end stage kidney disease (ESKD), a molecule must also have adverse biologic effects. These large middle-molecules appear to be linked to unsolved complications of ESKD including chronic inflammation, cardiovascular disease, secondary immunodeficiency, erythropoietin resistance, and symptom burden. In symptom burden, the molecules can directly cause symptoms; for example, the retention of  $\alpha$ -1 microglobulin (33 kDa) is associated with restless leg syndrome and the retention of cytokines is associated with flu-like symptoms. See Table 1.

### Prescription of Expanded Hemodialysis Therapy

The high-retention-onset membranes provide clinicians the opportunity to increase the clearance of large middle-molecules beyond that provided with conventional hemodialysis strategies. Patients with residual renal function may benefit, as well as patients with conditions linked to retention of large middle-molecules, as detailed in the Clinical Relevance section.

As high-retention onset membranes are used to increase the clearance of middle molecules, the factor of time should be

considered. In dialysis settings where time is flexible such as home hemodialysis, the high-retention-onset membranes could be utilized for longer or more frequent dialysis treatments to further increase middle-molecule removal.

## CONCLUSIONS

Expanded hemodialysis utilizes a new generation of hemodialysis membranes, which allows for the first time, the effective clearance of large middle-molecules without significant albumin loss. These middle molecules have circulated in chronic kidney disease patients since the use of the first hemodialysis machine by Dr. Kolff in 1943. Biological pathways have been described for the involvement of these molecules in cardiovascular disease, secondary immunodeficiency, chronic inflammation, and symptom burden. Potentially, increased removal of large middle-molecules (molecular weight >15 kDa) can lead to improved patient outcomes. More studies are needed to further understand these biological pathways; therefore, this hypothesis should now be tested in robust clinical studies.

**HDx utilizes a new generation of high retention onset/medium cut-off membranes that efficiently remove large middle-molecular uremic toxins that have been linked to the development of inflammation, cardiovascular disease and other dialysis related comorbidities.**

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.

	Class	Molecule	Molecular weight, kDa	Relative increase in dialysis	Clinical relevance
1	Cytokines	Interleukin-18	18	~2-fold higher	• Interleukins, 18, 6, 18 and tumor necrosis factor- $\alpha$ (TNF- $\alpha$ ) can provide pathways to chronic inflammation
2		Interleukin-6	21-28	2- to 5-fold higher	
3		Interleukin-18	17.5	~2-fold higher	
4		Interleukin-10	18	~1.5-fold higher	
5		Tumor necrosis factor- $\alpha$	17	4- to 5-fold higher	
6	Adipokines	Adiponectin	30	2- to 3-fold higher	• Adipokines adiponectin and leptin, Interleukins 18, 6, 18 and TNF- $\alpha$ , advanced glycosylation end products, and prolactin provide pathways for atherosclerosis
7		Visfatin	52	3- to 6-fold higher	
8		Leptin	16	3- to 4-fold higher	
9		Retinol-binding protein 4	21.2	3- to 4-fold higher	
10	Growth factors and other hormones	Vascular endothelial growth Factor	34	~2-fold higher	• Fibroblast growth factors 2 and 23 have been linked to left ventricular hypertrophy, and associated pathologies of atrial fibrillation and heart failure
11		Fibroblast growth factor 2	18		
12		Fibroblast growth factor 23	32	>200 fold higher	
13		Prolactin	23	2- to 4-fold higher	
14	Immune-mediated proteins	Complement factor D	24	4- to 17-fold higher	• Polyclonal free light chains (k FLC, $\lambda$ FLC), $\alpha$ 1-acid glycoprotein, and fibroblast factor 23 have been described to impair normal function of neutrophils (Secondary Immunodeficiency)
15		$\kappa$ -Ig light chains	22.5	2-16	
16		$\lambda$ -Ig light chains	45	2-18	
17		$\alpha$ 1-acid glycoprotein	35-44	<1.5 fold higher	
18		Soluble TNF receptor 1	27-30	3- to 10-fold higher	
19		Soluble TNF receptor 2	17	3- to 10-fold higher	
20		Pentraxin-3	40	2- to 7-fold higher	
21		YKL-40	40	2- to 5-fold higher	
22		B-Trace protein	26	>35-fold higher	
23	Other molecules	Myoglobin	17	2- to 7-fold higher	• Advanced glycosylation end products, prolactin, adiponectin and leptin, Interleukins 18, 6, 18 and TNF- $\alpha$ provide pathways for atherosclerosis
24		Hyaluronic acid	Variable	3-fold	
25		Advanced glycosylation endproducts	<1-70	5- to 16-fold higher	
26		Clara cell protein	15.8	~30-fold higher	
27		$\alpha$ 1-Microglobulin	33	~9-fold higher	

**TABLE 1.** Large middle-molecules with molecular weights greater than 15 kDa. Classification, molecular weights, serum concentrations in dialysis patients, and clinical relevance. Table adapted from Hutchison and Wolley.





# Hemodialysis Membranes

**Ronco C and Clark WR.** Hemodialysis membranes. *Nat Rev Nephrol.* 2018; 14:394-410.  
doi: [10.1038/s41581-018-0002-x](https://doi.org/10.1038/s41581-018-0002-x).

## BACKGROUND

Hemodialysis is an extracorporeal process in which the blood is cleansed via removal of uremic retention products by a semipermeable membrane. Traditionally, dialysis membranes have been broadly classified based on their composition (cellulosic or non-cellulosic) and water permeability (low flux or high flux). Incorporation of innovative manufacturing processes have led to consideration of other parameters for classification including new permeability indices, hydrophilic vs hydrophobic balance, adsorption capacity, and electrical potential.

## AIM

To provide clinicians with an updated analysis of dialysis membranes and dialyzers, highlighting online hemodiafiltration and new therapies such as expanded hemodialysis, and considerations governing the clinical acceptable balance between large-solute clearance and albumin loss for extracorporeal therapies.

## OVERVIEW

### History of Dialyzers

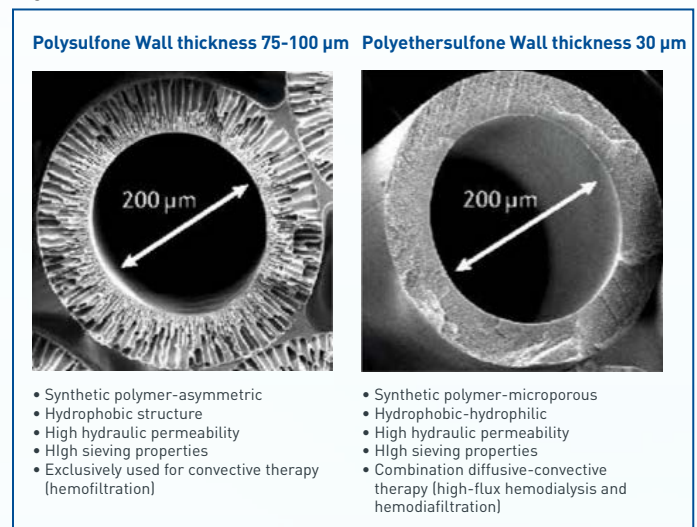
The availability of devices like the rotating drum kidney, coil dialyzer, and Kiil dialyzer allowed the use of dialysis to grow but it had many limitations. Of note were the high blood compartment volumes required and the inefficient mass transfer characteristics. In the late 1960s the hollow-fiber artificial kidney revolutionized dialysis by providing improved geometry in terms of blood rheology and solute mass transfer. Specific advantages included an improved surface-area:volume ratio in the blood compartment and decreased boundary layer effects with acceptable end-to-end pressure drops. These made the hollow-fiber configuration the main choice in dialysis. At present (2018) approximately 300 million hollow-fiber hemodialyzers are utilized worldwide.

### History of Hollow-fiber Membranes

Categorization of dialysis membranes have traditionally been based on their material composition, either cellulosic or synthetic membrane groups. The use of unmodified cellulosic membranes has dropped precipitously over the past decades, to the point of effective absence from the market (i.e. no longer manufactured). Dialyzers with synthetic high-flux membranes now dominate clinical practice.

Synthetic membranes were originally developed for a dialysis application more than 40 years ago to address the relative bio-incompatibility and limited permeability of unmodified cellulosic membranes. The first highly permeable membrane, sulfonated polyacrylonitrile (AN69), was introduced in the late 1960s. Subsequent development included polysulfone membranes, which had very thick walls (75-100  $\mu\text{m}$ ), and despite higher permeability, were not conducive to diffusion-based therapies. Their use was originally limited to convection-based hemofiltration. Modern

synthetic membranes (e.g. polyethersulfone (PES)) have thinner walls (20-50  $\mu\text{m}$ ) and higher permeability, permitting diffusion and convection to be employed simultaneously. Please see Figure 1.



**FIGURE 1.** Physical Characteristics of Synthetic Membranes. Adapted from Ronco and Clark.

The majority of synthetic membranes (e.g. PES) used for contemporary dialysis have an asymmetric structure. In contrast, synthetic membranes similar to cellulosic membranes (e.g. AN69 and poly (methyl methacrylate) (PMMA)) are structurally symmetric.

### New Membrane Classification

#### Focus on Solute Permeability Properties

Conventional membranes that are used in hemodialysis generally provide high clearance for small solutes such as urea (60.055 Da)<sup>1</sup> and creatinine (113.12 Da)<sup>2</sup>. However, membranes in current use provide limited clearance of compounds >10 kDa. Although these membranes have relatively large mean pore sizes (compared to unmodified cellulosic membranes), they still offer mass transfer resistance to the diffusive removal of large solutes. Furthermore, (membrane) fouling has a considerable effect on convective solute clearance, especially for molecules >10 kDa.

In typical hemodialysis operating conditions, the water permeability characteristics for a standard high-flux dialyzer result in a fairly large drop in the blood compartment axial pressure during treatment. The pressure drop is sufficiently large that the blood compartment pressure is less than the dialysate compartment pressure in normal operating conditions.

There is a point at which the ultrafiltrate begins to be driven from the dialysate to the blood as opposed to the 'standard' (blood-dialysate) direction. This combination of filtration and backfiltration, termed internal filtration, is considered to be the predominant mechanism by which larger compounds are



removed during standard high-flux dialysis. Maximizing the extent of internal filtration during high-flux dialysis through a combination of increased membrane permeability (increased pore size) and higher axial blood compartment resistance (decreased hollow fiber inner diameter) can provide clinically meaningful increases in large solute clearance.

Classification schemes that focus even more on solute permeability properties have been proposed. These new classification systems acknowledge the importance of larger molecules and the need to incorporate additional membrane classes that have extended removal spectra. High-flux and 'protein leaking' membranes have been defined based on a combination of water permeability, beta-2 microglobulin ( $\beta_2m$ ) [12 kDa]<sup>3</sup> removal factors (sieving coefficient (SC) or clearance) and albumin [65 kDa]<sup>3</sup> parameters (SC or amount cleared). In this system, the high-flux class is defined by a water permeability of 20–40 m/h/mmHg/m<sup>2</sup>, a  $\beta_2m$  SC of 0.7–0.8 and albumin loss of < 0.5 g (on the basis of a 4 h hemodialysis treatment), whereas the same parameters defining a protein-leaking membrane are >40 m/h/mmHg/m<sup>2</sup>, 0.9–1.0, and 2–6 g, respectively. Although not explicitly stated, these values correspond to 'virgin' membrane performance and do not reflect potential diminutions during treatment as a result of secondary membrane effects.

#### Medium Cut-Off (MCO) and High Cut-Off (HCO) Membranes

Two new membrane classes, medium cut-off (MCO) and high cut-off (HCO), have been proposed, extending the earlier classification scheme.

The HCO class is characterized by a substantial increase in water permeability (relative to both high-flux and the protein-leaking classes) and a virgin  $\beta_2m$  SC of 1.0. However, the high albumin loss rates associated with this membrane class generally preclude their long-term use for patients with end stage renal disease (ESRD). In addition, this membrane has been used for fairly limited time periods in clinical conditions in which the potential risks due to albumin loss are considered reasonable to the potential benefits (e.g. for patients with myeloma-associated acute kidney injury to target augmented removal of free antibody light chains [kappa interleukin light chain [22.5kDa]<sup>3</sup>; lambda interleukin light chain [45 kDa]<sup>3</sup>). The role of HCO membranes in clinical practice remains unclear.

In comparison to HCO membranes, the MCO class is intended to preserve the  $\beta_2m$  sieving characteristics and to improve the clearance of other large-molecular-weight solutes (for example, free antibody light chains) while demonstrating a marked reduction in albumin permeability. MCO membranes represent the basis for a new diffusion-based therapy called 'expanded hemodialysis'.

#### Molecular Weight Retention Onset (MWRO)

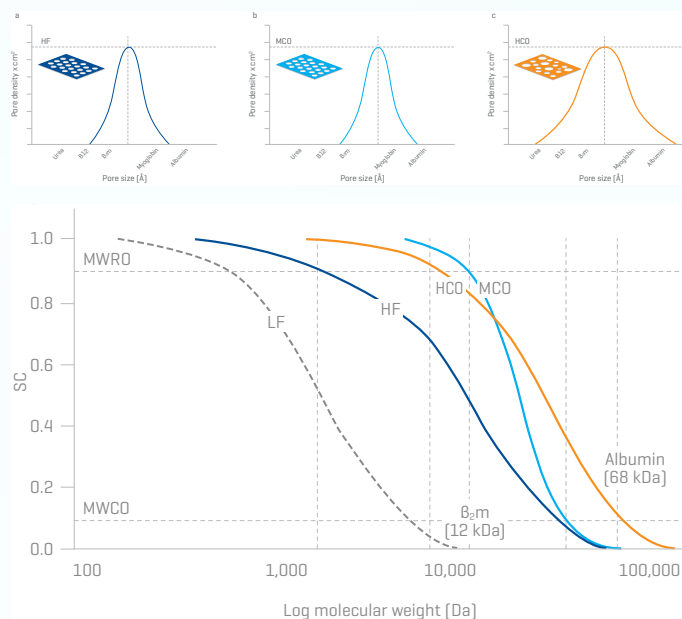
A new solute removal parameter for the characterization of modern highly permeable membranes has been proposed. This new parameter, the 'molecular weight retention onset' (MWRO) index, is generated from a standard solute sieving coefficient versus molecular weight profile, as with the classic molecular weight cut off (MWCO). The MWRO is defined as the molecular weight at which the SC value first reaches 0.9 (whereas the MWCO corresponds to a SC of 0.1). This approach was rationalized by suggesting that the MWRO index, which provides insights about pore size distribution, supplements information provided by the MWCO, which is primarily correlated with mean pore size. The steepness of the sieving coefficient versus molecular weight profile is determined mostly by the proximity of these parameters. A classification scheme has been proposed in which the MWCO and MWRO are utilized in combination to define different dialyzer classes.

#### Insights

Although extending the removal spectrum of modern dialysis membranes beyond the capabilities of standard of high-flux devices is highly desirable, the design challenge is to maximize the removal of large uremic toxins while also maintaining albumin losses for long-term treatment of patients with ESRD. The updated classification system includes the previously mentioned MCO membranes that incorporate high-retention onset (HRO) properties. This membrane class may hold promise in achieving acceptable albumin losses.

Pore size distribution curves (Fig. 2 a–c) and the corresponding sieving coefficient profiles (Figure 2d) and the corresponding sieving coefficient for three classes of membranes (high flux, MCO, and HCO) reveal that as the separation between MWRO and MWCO decreases, the profile of the curve becomes steeper, resulting in increased removal of large uremic toxins and decreased loss of albumin. As shown in Figure 2d, the MCO curve is the steepest of the four curves, stopping before the molecular weight (MW) of albumin, while HCO extends beyond albumin's MW.

By virtue of larger pore sizes, increased membrane diffusivity is one mechanism by which the removal of large solutes is augmented with the MCO class of dialyzers relative to standard high-flux membranes. Although hemodialysis using this type of dialyzer is technically diffusion-based, most large-solute removal still occurs by convection through the mechanism of internal filtration. For MCO and other dialyzers, the effect of this mechanism is intentionally augmented through increases in the mean pore size and reductions in the inner diameter of hollow fibers. Preliminary data suggest that this class of dialyzers has depuration capabilities that approach those of online post-dilution hemodiafiltration without the need for (exogenous) substitution fluid administration.



**FIGURE 2. Performance characteristics of hemodialysis membranes derived from a suggested new classification system.** Pore size distribution curves are schematically depicted for three classes of membranes, high flux (HF; part a), medium cut-off (MCO; part b) and high cut-off (HCO; part c), as well as their sieving coefficient (SC) profiles (part d). As the interval between molecular weight retention onset (MWRO) and molecular weight cut-off (MWCO) decreases, the profile of the curve becomes steeper, increasing the removal of large uremic toxins (such as  $\beta_2$ -microglobulin ( $\beta_2m$ )) while decreasing the loss of albumin (part d). A low-flux (LF) membrane is shown for comparison. Figures adapted from Ronco and Clark.



## CONCLUSIONS

The bidirectional process of mass separation between the blood and the dialysate involves several mechanisms of interaction between the fluid phases and the membrane barrier. The nature of the fluid phases, the characteristics of the solutes and the structure of the membrane represent a combination of elements that are involved in the final process of mass separation and dialysis.

The development of a unifying classification system for dialysis membranes is extremely complex and must be multidimensional. Proposed in the classification system is inclusion of membranes that have substantial differences of potential clinical importance, like MCO membranes. The MCO class is intended to improve the clearance of large molecular-weight solutes, while demonstrating a marked reduction in albumin permeability, influenced primarily by the decreased interval between MWRO and MWCO and resulting steep sieving curve. This membrane class may hold promise in achieving acceptable albumin losses, representing the basis for a new diffusion-based therapy called 'expanded hemodialysis'.

**The MCO membrane features an increased pore density with tight pore-size distribution, enhancing ultra-filtration and permeability via a steep sieving-curve — resulting in clearance of larger uremic toxins, while retaining essential proteins.**

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2. <https://biocyc.org/compound?orgid=META&id=CREATININE> Accessed 6/15/20.
3. 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.



# Flow Dynamic Analysis by Contrast-Enhanced Imaging Techniques of Medium Cutoff Membrane Hemodialyzer

Lorenzin A, Golino G, de Cal M, et al. Flow Dynamic Analysis by Contrast-Enhanced Imaging Techniques of Medium Cutoff Membrane Hemodialyzer. *Blood Purif.* 2021. doi: 10.1159/000516411.

## BACKGROUND

The introduction of new medium cutoff (MCO) membranes has spurred new interest in potential improvements in medium- and long-term outcomes in patients undergoing chronic hemodialysis. MCO membranes present increased solute permeability with improvement of molecular weight retention onset (MWRO) while maintaining cutoff values adequate to limit albumin losses. MCO membranes are utilized in a dialysis technique defined "expanded hemodialysis" (HDx) that provides significant improvement in removal of large (PM > 25 and < 58 kDa) middle molecular weight solutes (LMM) responsible for symptoms and complications. While solute clearances, sieving coefficients, and hydraulic permeability have been extensively studied, flow dynamic characteristics of hollow fiber hemodialyzers utilizing such membranes have not been studied in detail. This information may be required to correctly prescribe HDx and to optimize its operational parameters.

## OBJECTIVE

To evaluate the flow dynamic and cross-filtration characteristics of the new MCO hemodialyzer (Theranova 400; Baxter, Deerfield, IL, USA), and aiming to gather specific information useful for the correct and safe delivery of expanded hemodialysis with the MCO membrane, specifically:

- Define the flow dynamic conditions inside the blood compartment and the flow distribution inside the dialysate compartment
- Define the hydraulic permeability and its sieving properties
- Analyze the segmental cross flow (direct filtration and backfiltration) along the length of the hollow fiber bundle

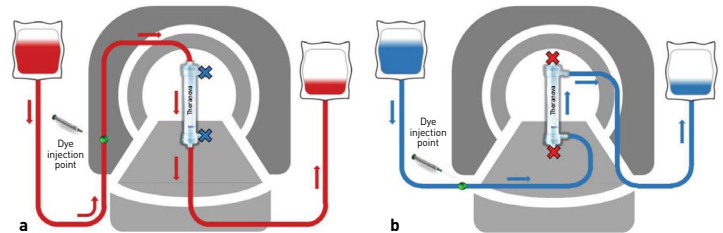
## METHODOLOGY

### Characteristics of Dialyzer Evaluated

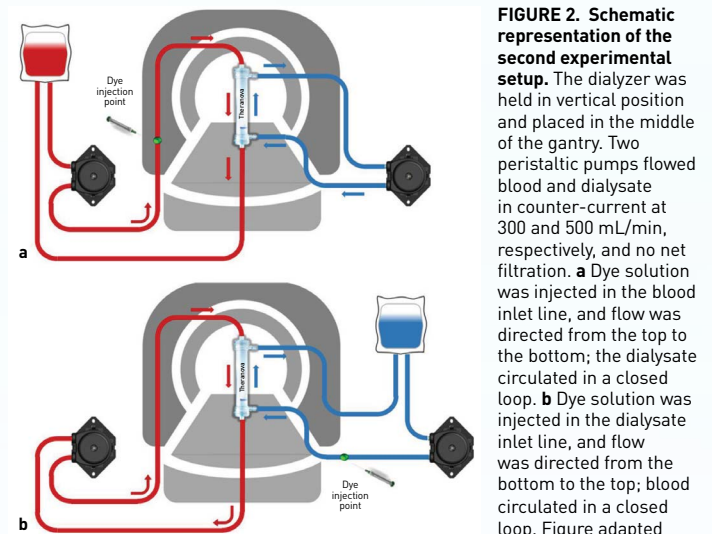
The Theranova 400 dialyzer is a dialyzer designed specifically for HDx with a surface area of 1.7 m<sup>2</sup>. The membrane has an asymmetric 3-layer structure composed of polyarylethersulfone and polyvinylpyrrolidone blend, BPA free. It is characterized by uniform pore distribution and specific sieving properties: high MWRO and molecular weight cutoff (MWCO) value lower than albumin.

### Study Techniques

Blood and dialysate flow distribution and internal transmembrane cross-filtration were studied with two separate imaging techniques: CT helical scanning and sequential and static scintigraphic imaging. Two different experimental setups were used in the CT imaging technique for blood and dialysate flow dynamic analysis. See Figures 1 and 2.

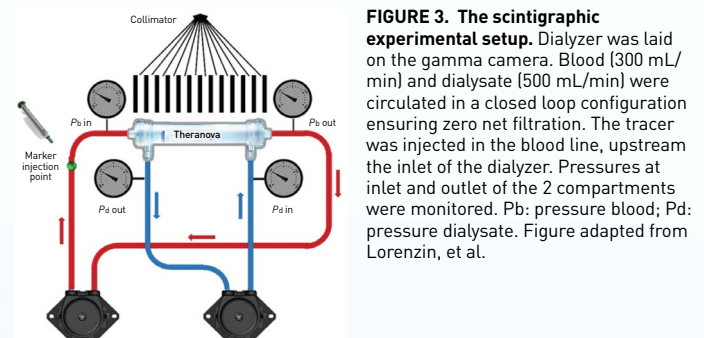


**FIGURE 1. Schematic representation of the first experimental setup.** The dialyzer was held in vertical position and placed in the middle of the gantry. Blood and dialysate compartments were analyzed separately. **a** Dye solution was injected in the blood inlet line, and flow was directed from the top to the bottom; the dialysate compartment was prefilled and sealed. **b** Dye solution was injected in the dialysate inlet line, and flow was directed from the bottom to the top; the blood compartment was prefilled and sealed. Figure adapted from Lorenzin, et al.



**FIGURE 2. Schematic representation of the second experimental setup.** The dialyzer was held in vertical position and placed in the middle of the gantry. Two peristaltic pumps flowed blood and dialysate in counter-current at 300 and 500 mL/min, respectively, and no net filtration. **a** Dye solution was injected in the blood inlet line, and flow was directed from the top to the bottom; the dialysate circulated in a closed loop. **b** Dye solution was injected in the dialysate inlet line, and flow was directed from the bottom to the top; blood circulated in a closed loop. Figure adapted from Lorenzin, et al.

A third analysis was conducted employing a scintigraphic method to assess the internal filtration/backfiltration. See Figure 3.



**FIGURE 3. The scintigraphic experimental setup.** Dialyzer was laid on the gamma camera. Blood (300 mL/min) and dialysate (500 mL/min) were circulated in a closed loop configuration ensuring zero net filtration. The tracer was injected in the blood line, upstream the inlet of the dialyzer. Pressures at inlet and outlet of the 2 compartments were monitored. Pb: pressure blood; Pd: pressure dialysate. Figure adapted from Lorenzin, et al.



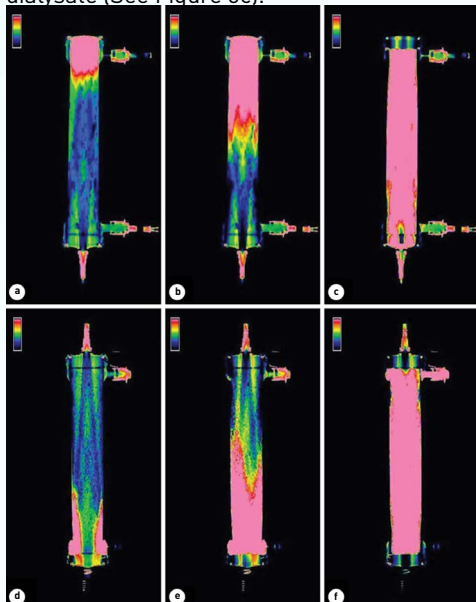
## RESULTS

Figure 4 displays the dye distribution pattern in blood and dialysate compartments during the first experimental setup: blue/green areas are free from dye solution, pink areas point out the presence of the dye solution, and red/yellow areas are transition zones. In the blood compartment (300 mL/min), flow distribution appears homogeneous. Minimal difference in velocity was observed between peripheral and central fibers. In the dialysate compartment (500 mL/min), no dead space or irregularities are noticed from the images of the filled compartments, except for a black spot in the blood one, due to a air bubble artifact (see Figure 4c).

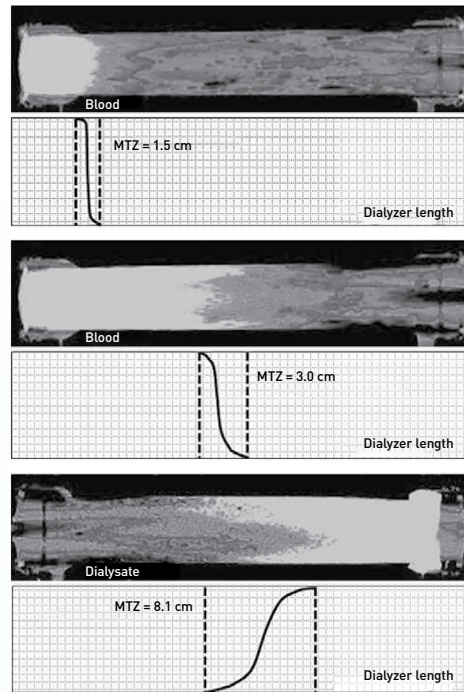
In the blood compartment, the velocity profile changes its shape along the length of the dialyzer. In the inlet blood port, the dye solution displays a homogeneous progression featuring a kind of plug flow configuration with an average velocity of 1.4 cm/s (See Figure 4a). A small increase in differential velocity among the fibers was observed as the dye proceeds toward the outlet port. Peaks of velocity are displayed in the central (1.1 cm/s) and in the extreme peripheral regions (1.5 cm/s) of the dialyzer, while velocities as low as 0.6 cm/s are observed in rare groups of intermediate fibers.

The wall shear rates are 458, 666, and 276 s<sup>-1</sup>, respectively. These differences are absolutely acceptable and compatible with a well-designed blood compartment and a good flow distribution in the fiber bundle. Furthermore, the wall shear rate values are always above the limit where blood viscosity starts to increase significantly. The very short length of the Mass Transfer Zone (MTZ) (1.5 cm) in the proximal part of the dialyzer (See Figure 5a) confirms the plug flow; at half length of the dialyzer, MTZ is slightly longer but still within optimal values (3 cm) confirming the excellent utilization of all fibers of the bundle and a good distribution of flow with optimized flow velocity per single fiber (See Figure 5b).

In the dialysate compartment, dye solution flows initially along the case and through the outlying fibers with a velocity of 1.8 cm/s. When the solution begins to seep in the center of the fiber bundle, the velocity in the central region rises to 1.7 cm/s. Proceeding to the outlet port, the front of the velocity profile becomes more homogeneous with the optimal utilization of the whole cross-sectional area available for the flow (See Figure 4f). The dialysate MTZ presents a value of 8.1 cm. While a moderate dispersion of local velocities is observed, the value is far below half of the length of the dialyzer confirming optimal flow distribution of the dialysate (See Figure 5c).



**FIGURE 4.** Dye progression in blood (a, b, c) and dialysate (d, e, f) compartments after 4 and 12 seconds and at total filling (33 seconds for blood and 28 seconds for dialysate), for the first experimental setup. Blue/green areas are free from dye solution, pink areas point out the presence of the dye solution, and red/yellow areas are transition zones. Figure adapted from Lorenzin, et al.

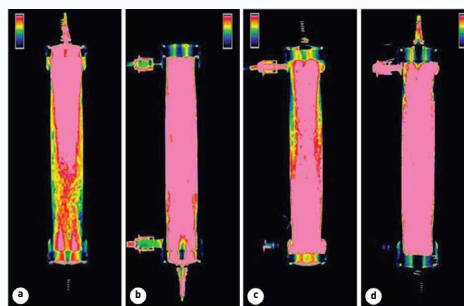


**FIGURE 5.** MTZ in blood (a, b) and dialysate (c) compartments obtained from the first acquisition. MTZ represents the distance between the point of maximal dye saturation and the point of absolute absence of dye. MTZ: mass transfer zone. Figure adapted from Lorenzin, et al.

Figures 6a and 6c report the images obtained from the second experimental setup, in which blood and dialysate circulated counter-current, simultaneously. Compared

with the first experiment (Figures 6b, 6d), images display a perturbation of the dialyzer perfusion likely induced by the local transmembrane cross flow of dialysate and plasma water. The blood flow distribution (blood flows from the top to the bottom) is homogeneous in the proximal half of the dialyzer while in the distal part, yellow areas describe the effect of backfiltration from the dialysate compartment into the hollow fibers. Dialysate compartment describes an analog effect (dialysate flows from bottom to top in counter-current with blood). Dye solution saturates the portion of the dialyzer close to the inlet (pink), while toward the middle of the dialyzer, the flow distribution pattern becomes slightly dishomogeneous due to ultrafiltration (plasma water cross flow from the blood into the dialysate compartment).

This complementary behavior testifies the internal filtration and backfiltration phenomena. Considering the orientation of blood stream, in the proximal part of the dialyzer, plasma water crosses the membrane, and the effect of the internal filtration causes a dilution of the dye solution in the dialysate compartment (See Figure 6c); in the distal part, instead, the reduction in dye intensity in the blood compartment is a consequence of backfiltration, the cross flow of the dialysate through the membrane into the fibers (see Figure 6a).

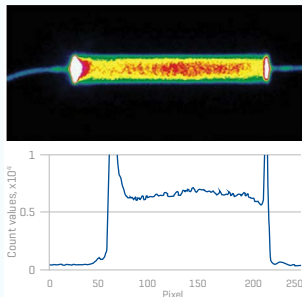


**FIGURE 6.** On the left, CT images acquired after reaching the total filling in the blood (a) and dialysate (c) compartment in the countercurrent flow experiment. Visible differences are noticed if compared with the same images acquired in the first experiment (b, d). The reduction of dye intensity in the images on the left is the consequence of the internal/backfiltration phenomenon that occurs in counter-current flow configuration. Figure adapted from Lorenzin, et al.



### Internal Filtration/Backfiltration

The kinetics of transmembrane cross flow are confirmed in the third experiment. Scintigraphic images (See Figure 7) display significant variation in radioactive count along the length of the dialyzer, due to local transmembrane cross flow of plasma water through the membrane in both directions. The increase in concentration of the marker molecule in the proximal part is ascribed to the direct filtration of plasma water from blood into the dialysate while the dilution in the distal part to backfiltration of the dialysate into blood. The turning point is observed at 53% of the dialyzer length. At steady state, the concentrations at inlet and outlet of the fiber bundle are identical, confirming the condition of zero net filtration. The calculation of relative changes of the marker molecule allows for the cumulative estimation of the amount of filtration and backfiltration inside the dialyzer under the selected experimental conditions.



**FIGURE 7. Scintigraphic image of the dialyzer at the steady state and radioactivity count.** The change in color corresponds to the relative variation in radio labeled marker molecule activity in a numerical scale. Radioactive count is proportional to the marker concentration in blood. In the proximal part, the internal filtration causes the increase in marker counts while the backfiltration in the distal part brings back the radioactive counts to the inlet value, restoring the zero net filtration condition. Figure adapted from Lorenzin, et al.

The concentration of the marker molecule increases reaching a peak value ( $C_{max}$ ) at half length of the filter and then decreases until the end of the fiber bundle reaching the same concentration observed at the inlet. This behavior demonstrates a proximal direct filtration (IF) and a distal backfiltration (BF). Calculated IF was 32.75 mL/min while BF was 32.46 mL/min. The slight difference is compatible with the error of the method. Filtration and backfiltration rates can increase or decrease depending on blood and dialysate flows and dialyzer surface area.

### DISCUSSION

The clinical performance of Theranova as used in HDx is based on a significant convective exchange by enhanced mechanism of internal filtration/backfiltration. This study demonstrated the flow dynamics leading to the dialyser performance. The homogeneous pattern of blood distribution at the inlet port and along the fiber bundle represents a proof of an optimal design of the distributor and the entire blood compartment of the dialyzer. This ensures a good performance of the filter in the diffusion mode and guarantees the optimal utilization of the available surface area. Adequate flow distribution and high wall shear rates contribute to minimize the formation of a protein layer at the blood membrane interface. The occurrence of a significant concentration polarization phenomenon with consequent reduction of membrane permeability is mitigated by the utilization of the dialyzer in the hemodialysis mode (HDx).

Excessive convective rates such as those achieved in the hemodiafiltration (HDF) mode would contribute to impair membrane permeability by the formation of a protein cake onto the internal surface of the fibers. This phenomenon leads to the formation of a new contact surface whose thickness is added to that of the original membrane and interferes with the final permeability of the membrane in vivo. This unwanted effect is prevented by high wall shear rates in all fibers which contribute to reduce the thickness of the protein boundary layer and improve membrane hydraulic and sieving permeability.

The distribution of the dialysate flow outside the fibers is also optimized as demonstrated by the dynamic images where the dye appears to be homogeneously distributed in the entire cross-sectional area of the dialysate compartment. Thus, any blood-to-dialysate flow mismatch is avoided, and the surface area available for the exchange is maximized.

Considering the cross flow kinetic results obtained with the nuclear scintigraphic method, these observations are important. Results confirm a significant amount of filtration and backfiltration inside the dialyzer at zero net filtration > 30 mL/min. This means that in presence of higher blood flows, higher surface areas, and higher net filtration rates (15–20 mL/min), direct fluid cross flow may reach values around 50 mL/minute. This is achieved in presence of a wall shear rate in all fibers sufficiently high to maintain blood viscosity at minimal levels and a significant cleaning effect at the blood membrane interface with negligible concentration polarization of plasma proteins. Such effect results in a maintenance of the sieving properties of the membranes throughout the dialysis session. Internal filtration between 30 and 50 mL/min combined with the sieving characteristics of MCO membranes allows for convective clearance values of medium-large molecules equal or even superior to those achieved in high-volume online HDF, without need of fluid replacement and very high filtration fractions inside the hemodialyzer.

### CONCLUSION

This study demonstrates the basis for the use of MCO membranes in expanded hemodialysis maximizing the benefits of internal filtration while maintaining the simplicity and safety of high-flux dialysis configuration and blood flows in the range of 300 mL/min.





## MCO Membranes: Enhanced Selectivity in High-Flux Class

**Boschetti-de-Fierro A, Voigt M, Storr M, et al.** MCO membranes: enhanced selectivity in high-flux class. *Nature/Sci Rep.* 2015; 5:18448. [doi:10.1038/srep18448](https://doi.org/10.1038/srep18448).

### BACKGROUND

One of the unmet needs in hemodialysis is the adequate removal of uremic toxins over a broad molecular weight range. As synthetic membranes are less selective than the glomerular membrane, current hemodialysis membranes do not remove higher molecular weight toxins appropriately. Consequently, patients on hemodialysis have higher levels of middle and large molecular solutes in plasma.

Membrane innovation is currently directed towards enhanced removal of uremic toxins and increased membrane permeability. During the last decade, some experience has been gathered with high permeability membranes such as high cut-off (HCO) membranes. Pilot trials with HCO membranes indicated that expanded toxin removal might benefit the patient by decreasing the general inflammatory state.

Medium cut-off (MCO) membranes were designed to deliver expanded toxin removal as observed with HCO membranes while retaining albumin (65 kDa)<sup>1</sup> so that they are appropriate for regular use in conventional treatment schedules and treatment mode (i.e. 4-hour treatments, three times weekly in Europe).

### OBJECTIVE

The aim of this study was to present the characterization of four prototypes of novel MCO membranes by dextran filtration<sup>2</sup>. In addition, the sieving properties of the membranes before and after blood contact were reported, and the pore size during operation (i.e. hemodialysis treatment) was compared to the size of uremic toxins and vital proteins.

<sup>2</sup>Fractional clearance studies to measure the size selectivity associated with glomerular filtration have universally employed dextran as a test transport probe. It is neither secreted nor reabsorbed by the renal tubules, so its clearance is easily measured.<sup>2</sup>

### METHODOLOGY

Four different types of prototype devices denoted as MCO 1 to MCO 4, which differ in permeability, were investigated. As reference, a HCO device (Theralite) and a conventional high flux membrane (**Revaclear**) were also tested. All devices were manufactured by Gambro Dialysatoren GmbH, Hechingen, Germany. The membrane material was a polyarylethersulfone/polyvinylpyrrolidone blend.

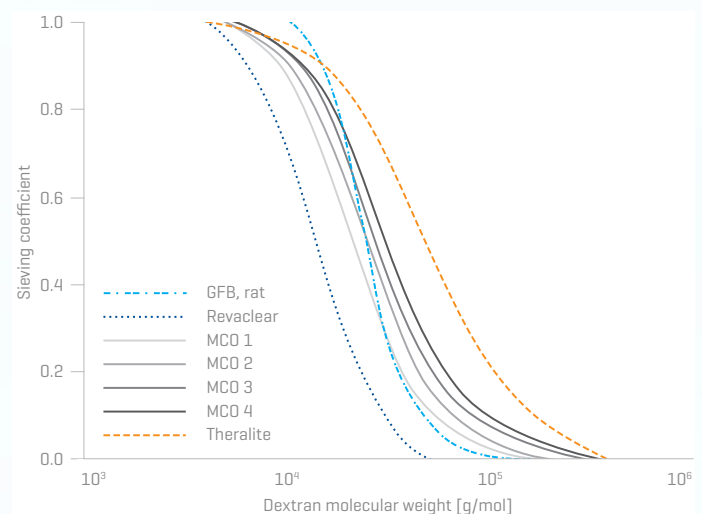
Membranes were characterized in minimodules with the same surface area, nominal length, inner diameter and wall thickness. The minimodules were immersed in water before the filtration experiments. Minimodules intended for characterization after contact with blood for simulating in vivo operation conditions were initially perfused with blood (bovine) for 40 minutes and rinsed afterwards with water.

Dextran solutions were prepared, and filtration experiments were carried out. For experiments run on MCO 4, the dextran solution included one additional fraction of 150 kDa, to allow for sieving coefficient (SC) calculation with similar precision as the other MCO membranes.

### RESULTS

Characterization of the MCO high-flux membranes by dextran sieving profiles in aqueous solution (pristine; before blood exposure).

As shown in Figure 1, the sieving curves for the MCO membranes are located at the molecular weights between that of the conventional high-flux membrane and HCO membrane in aqueous solution (pristine; before blood exposure). The MCO sieving curves are similar to the ficoll sieving curve for the glomerular membrane; blood purification membranes should mimic the filtration spectrum of the natural (glomerular) membrane.



**FIGURE 1. Characteristic in vitro dextran sieving curves measured in aqueous solution (pristine/before blood exposure) for different types of blood purification membranes: high-flux (Revaclear, MCO 1-4), HCO (Theralite).** Data for glomerular membrane added for comparison (rat specimen, ficoll filtration, measured in vivo). Abbreviations: GFB: glomerular filtration barrier; MCO: medium cut-off. Adapted from Boschetti-de-Fierro et al.

The values for Medium Weight Retention Onset (MWRO), Medium Weight Cut Off (MWCO) and pore radius (i.e. effective Stokes-Einstein radius calculated from MWCO) are depicted for the four membranes, as well as the conventional high flux membrane and HCO membrane in Table 1. The differences between the MCO membranes are evident from 1 to 4, showing increased MWRO and MWCO values which indicate increased permeability.



Membrane	Before blood exposure			After blood exposure		
	MWRO [kDa]	MWCO [kDa]	Pore radius [nm]	MWRO [kDa]	MWCO [kDa]	Pore radius [nm]
Revaclear	5.7 ± 0.5	32 ± 3	3.9 ± 0.1	4.4 ± 0.3	14.2 ± 0.2	2.68 ± 0.02
MCO 1	9.4 ± 0.2	56 ± 3	5.0 ± 0.1	5.0 ± 0.4	18.1 ± 0.8	3.0 ± 0.1
MCO 2	10.0 ± 0.6	64 ± 3	5.4 ± 0.1	5.84 ± 0.09	18.2 ± 0.3	3.0 ± 0.1
MCO 3	11.3 ± 0.4	81 ± 9	6.0 ± 0.3	6.32 ± 0.06	22.7 ± 0.8	3.3 ± 0.1
MCO 4 <sup>a</sup>	12.1 ± 0.7	99 ± 7	6.5 ± 0.2	6.77 ± 0.06	25 ± 5	3.5 ± 0.3
Theralite	15 ± 1	300 ± 100	10 ± 2	8.1 ± 0.8	40 ± 8	4.3 ± 0.4

**TABLE 1. Characterization of MCO hemodialysis membranes, conventional high-flux and HCO membranes, based on dextran sieving experiments before and after blood exposure.** Values are + standard deviation for n=3.\*Experiments with MCO 4 included one dextran fraction of 150 kDa. Abbreviations: MWRO: medium weight retention onset; MWCO: medium weight cut off; MCO, medium cut-off. Adapted from Boschetti-de-Fierro et al.

The parameters describing the pore size distribution calculated from the sieving profiles for the same membranes are detailed in Table 2. The presented values assess the mean and broadness of the pore size distribution. The values of the mean of the distribution increase with membrane permeability. The variance of the respective distribution is larger as the pore sizes increase. The pore size distribution for all membranes is narrower after blood contact, indicating that the selectivity of synthetic membranes improves during the operation.

Membrane	Before blood exposure		After blood exposure	
	Mean [nm]	Variance [nm]	Mean [nm]	Variance [nm]
Revaclear	3.0 ± 0.3	2 ± 1	2.42 ± 0.08	0.587 ± 0.003
MCO 1	4.1 ± 0.2	4.7 ± 0.8	2.5 ± 0.1	0.6 ± 0.2
MCO 2	4.0 ± 0.2	4.6 ± 0.4	2.55 ± 0.07	0.7 ± 0.1
MCO 3	4.40 ± 0.03	6.4 ± 0.1	2.9 ± 0.1	1.3 ± 0.4
MCO 4	4.8 ± 0.2	8.8 ± 0.4	3.3 ± 0.6	3 ± 3
Theralite	5.1 ± 0.3	11 ± 2	3.4 ± 0.2	2 ± 1

**TABLE 2. Mean (pore radius) and variance of the log-normal pore size distribution for the 4 MCO prototype membranes, conventional high-flux and HCO membranes before and after blood exposure.** Values are average ± standard deviation for n=3. Adapted from Boschetti-de-Fierro et al.

The challenge in developing novel high-flux membranes with toxin removal capabilities similar to HCO membranes while retaining albumin adequately resides in the membrane manufacturing process. Increasing pore sizes usually leads to an increase in the broadness of the pore size distribution, causing undesirable albumin permeation. Controlled membrane manufacture allows some improvement in this direction. As can be seen, the MCO 4 membrane shows similar mean pore size to Theralite (HCO), while having a 20% smaller variance. The less permeable versions, MCO 1 and MCO 2, show mean pore size around 4 nm with less than half the variance of Theralite. This indicates that the MCO membranes offer enhanced selectivity compared to HCO membranes.

## Membrane Classification After Blood Contact

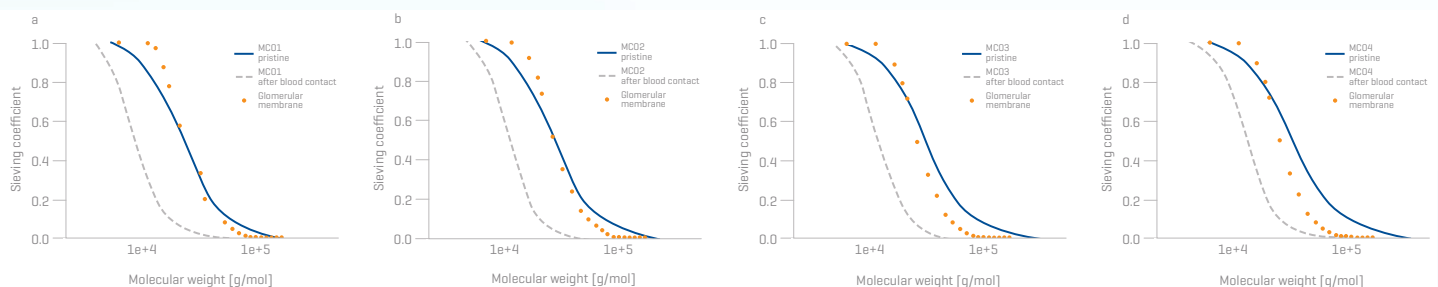
The sieving curves before and after exposing the MCO membranes to blood are shown in Figure 2. After blood exposure, the sieving curves were shifted toward lower molecular weights, and the sieving profiles indicate that the MCO membranes are less permeable than the glomerular membrane.

The natural formation of the protein layer on top of the synthetic membrane during hemodialysis gradually affects the solute removal during the first 40 minutes of treatment. This phenomenon is illustrated by the comparison of the sieving characteristics before and after blood contact. While the pristine MCO membrane allows the passage of molecules above 70 kDa to some extent, the sieving profile of the MCO membranes (as that of every artificial membrane) shifts towards lower molecular weights during operation. This circumstance is a compromise to deliver a tailored removal after the inevitable membrane fouling. As the hemodialysis treatment time is around 4 hours in Europe, this means that during more than 80% of the treatment blood purification is accomplished by a membrane the performance of which is governed by protein fouling. The MCO membranes show sieving profiles close to that of the natural kidney after the formation of the protein layer, thereby maintaining the required performance along the treatment.

The effective pore size is an indication for the biggest molecules that will pass through the membranes. The effective pore size of the MCO membranes is between 3.0 and 3.5 nm after blood contact/formation of the protein layer (see Table 1), indicating that the membranes retain albumin (hydrodynamic radius of 3.51 nm) [65 kDa]<sup>1</sup> during treatment. Additionally, the least permeable MCO membrane has an effective pore radius of 3.0 nm during treatment (Table 1), which should allow adequate removal of large uremic toxins, up to lambda free light chains (λ-FLCs) [45 kDa]<sup>1</sup> with a hydrodynamic radius of 2.8 nm. See Table 3 for hydrodynamic radius (Rh) for albumin and representative middle and large uremic toxins.

Molecule	$R_h$ [nm]	Comments	Ref.
82 microglobulin	1.7	calculated from the diffusion coefficient in free solution	16
Tumor necrosis factor (TNFα)	1.9-2.3	depending on its aggregation state, influenced by concentration and pH	17
Free light chains (FLC) monomeric state (mostly κ-FLC)	2.3	Stokes' radius determined by chromatography	18
Free light chains (FLC) dimeric form (mostly λ-FLC)	2.8	Stokes' radius determined by chromatography	18
Albumin	3.51	calculated from the intrinsic viscosity (agrees with Stokes' radii from diffusion and sedimentation coefficient)	19

**TABLE 3. Hydrodynamic radius (Rh) for albumin and some representative middle and large toxins.** Adapted from Boschetti-de-Fierro et al.



**FIGURE 2. Characteristics of sieving curves for MCO high flux membranes before (solid line) and after blood contact (dashed line), for (a) MCO 1, (b) MCO 2, (c) MCO 3, (d) MCO 4.** The data for the glomerular membrane has been added for comparison [rat specimen, ficoll filtration, measured in vivo]. Abbreviation: MCO; medium cut-off. Adapted from Boschetti-de-Fierro et al.



Based on the data presented, it can be presumed that some albumin permeation takes place even after the formation of the protein layer for the most permeable membrane MCO 4. This effect, if properly controlled, is not necessarily detrimental to the patients. Albumin loss is tolerated to some extent, as demonstrated in peritoneal dialysis patients where weekly albumin losses of 21–42 g/1.73 m<sup>2</sup> are accepted and not linked to outcome detriment.

## CONCLUSION

The novel MCO membranes provide for large pore sizes with appropriate pore size distribution and permeability close to that of the natural kidney. Their MWCO values suggest that, when used in hemodialysis treatments, they allow for removal of an expanded range of uremic toxins compared to conventional high-flux membranes. A formation of a protein layer on top of the synthetic membrane during hemodialysis restricts the removal of molecules above 3.5 nm in radius, ensuring the retention of albumin during a treatment, while still optimizing removal of large uremic toxins.

**Tailored pore sizes of MCO membranes promote removal of an expanded range of uremic toxins, while ensuring retention of albumin. MCO's unique membrane design allows for a filtration profile that's closer to the natural kidney.**

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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.
2. Editorial Review, Change Selectivity in Kidney Ultrafiltration, *Kidney International*. 1995; 47:1242–1251.







# HDx: A WORLD OF DIFFERENCE

## The Unmet Need that HDx Can Address: Large Middle Molecules (LMM) Removal

A new classification links uremic solutes with traditional clinical outcomes and QoL measures including pruritus, RLS, and recovery time. Water soluble protein bound proteins generated by endogenous metabolism can be divided in five uremic classes: Small water-soluble molecules (<500Da), Small-Middle Molecular weight solutes (0.5-15kDa), Medium-middle molecular weight solutes (>15-25 kDa), Large-middle molecular weight solutes (>25kDa-58kDa), and protein bound solutes<sup>1</sup>



-  **Rosner MH, Reis T, Husain-Syed F, et al.**  
**Classification of Uremic Toxins and Their Role in Kidney Failure.** *Clin J Am Soc Nephrol* 2021;161(12):1918-1928.
-  **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.
-  **Kandi M, Brignardello-Petersen R, Couban R, et al.**  
**Effects of Medium Cut-Off Versus High-Flux Hemodialysis Membranes on Biomarkers: A Systematic Review and Meta-Analysis.** *Can J Kid Health Dis.* 2022;9:1-15.
-  **Zweigart C, Boschetti-de-Fierro A, Hulko M, et al.**  
**Medium cut-off membranes - closer to the natural kidney removal function** *Int Artif Organs.* 2017;40(7):328-334.

1. Rosner MH, Reis T, Husain-Syed F, et al. Classification of Uremic Toxins and Their Role in Kidney Failure [published online ahead of print, 2021 Jul 7]. *Clin J Am Soc Nephrol.* 2021;16(12):1918-1928.





# Classification of Uremic Toxins and Their Role in Kidney Failure

Rosner MH, Reis T, Husain-Syed F, et al. Classification of Uremic Toxins and Their Role in Kidney Failure. *CJASN* Dec 2021;16(12):1918-1928. doi:10.2215/CJN.02660221.

## BACKGROUND

Uremia is the build-up of metabolic waste products such as urea that occurs when kidney function is impaired. Along with retention of metabolic waste products, patients with advanced kidney disease typically experience symptoms that may include nausea, vomiting, fatigue, anorexia, muscle cramps, pruritus, mental status changes that lead to a reduced quality of life as well as excess morbidity and mortality.

Dialysis techniques are used to remove these metabolic waste products, with the hope that symptoms and outcomes will also improve. However, this goal has only been partially achieved, and outcomes for patients with kidney dysfunction remain suboptimal. While knowledge of solutes that build-up with uremia has increased, there is a growing recognition that current dialysis prescriptions may not be effective in their removal. Technological advances such as the development of new medium cut-off (MC) hemodialysis membranes, and the ability to perform high efficiency hemodiafiltration enable the removal of molecules up to ~50 kDa.

## OBJECTIVE

An expert conference was convened to identify limitations in the current definition and classification of uremic retention solutes/toxins. Experts in the field of uremia and uremic toxins were tasked with a comprehensive review of the current definition and classification of uremic retention solutes, and posed several critical questions and recommendations to define these toxins better and map future studies for improving outcomes.

## METHODOLOGY

Experts in the field of uremia and uremic toxins were invited to participate in a consensus conference, held virtually November 31 – December 2, 2020. A modified Delphi method was used to achieve consensus.

A pre-conference literature search and appraisal of the scientific evidence was completed. Key themes were identified and workgroups were created to address the following themes: Critical appraisal of limitations in the current definition/classification of uremic retention solutes; Rationale for updating definition and classification of uremic retention solutes and molecules of interest in the field of maintenance hemodialysis and; proposal of a new classification of solutes of interest in uremia and hemodialysis. Individual workgroups presented the output to conference participants for debate, discussion, suggested revisions, and recommendations for research were formulated. The final product was then assessed and aggregated in a videoconference session attended by all attendees, who approved the consensus recommendations.

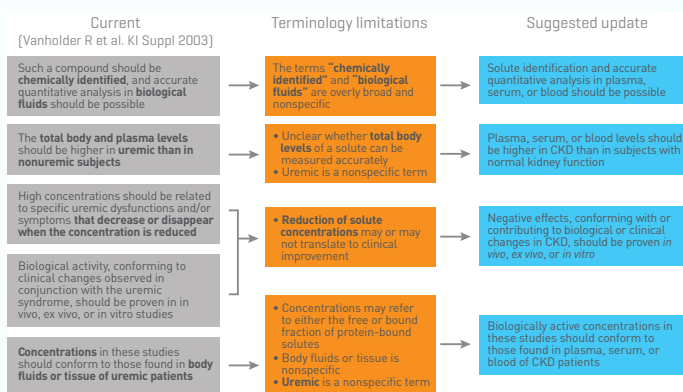
## DISCUSSION

### Redefining uremic toxins

#### Rationale

In 2003, the European Uremic Toxin Work Group (EUTox) proposed five criteria for an organic solute to be classified as a uremic toxin (Figure 1). The panel identified limitations of the current definition and concluded that modifications to the definition are necessary to incorporate new advances in hemodialysis (Figure 1).

FIGURE 1. Definition of uremic toxins



#### Panel Recommendations

1. We suggest that the current definition of uremic toxins should be adapted in terminology to account for the growth in knowledge in the field (Figure 1).
2. We suggest that the scope of the definition should remain limited to organic solutes.

### Physicochemical classification of uremic toxins

#### Rationale

In 2003, EUTox categorized uremic toxins according to their physicochemical characteristics that affect clearance during hemodialysis, which came from the need to simplify and organize uremic toxicity concepts within a framework of therapeutic removal approaches, mainly by hemodialysis.

**Panel Statement 1:** The current physicochemical classification of uremic toxins does not adequately address or reflect how current/modern hemodialysis technologies (mechanisms of adsorption, convection, and diffusion) remove toxins.

There is a continuum in the molecular weight of uremic solutes, and any cut-off based on molecular weight is arbitrary, plus the degree of protein binding for uremic solutes is variable and complicates classification based solely on molecular weight. The most practical classification approach is based upon the principles of removal patterns by standard hemodialysis schedules.



Newer hemodialysis membranes are likely to change the ability to remove higher molecular weight solutes that may be toxic. Currently this can be achieved mainly through convection. The high-flux dialyzer has a molecular weight cut-off of 25 kDa in hemodialysis mode, boosted up to 30 kDa when in hemodiafiltration mode. A new class of membranes is the medium cut-off (MCO) membrane with a cut-off of 56 kDa, a mean pore radius of 5 nm, and a fiber inner diameter of 180  $\mu\text{m}$ . As a comparison, the high-flux membrane has a mean pore radius of 3.9 nm and an inner diameter of  $\sim 200 \mu\text{m}$ . Clearance is more efficient for larger molecules (25–58 kDa) with MCO membranes than high-flux membranes. Clinical trials have consistently demonstrated increased clearance of larger molecular weight molecules such as complement factor D, free  $\kappa$  light chains, TNF- $\alpha$ , and  $\beta 2$ -microglobulin

#### Panel Recommendations

1. We suggest that the current definition of uremic toxins should be based on hemodialysis strategies, membranes, and removal patterns acknowledging that any classification based on cut-off values and/or molecular spatial configuration or charge would be arbitrary and likely will need to be changed as technological development changes solute removal patterns.

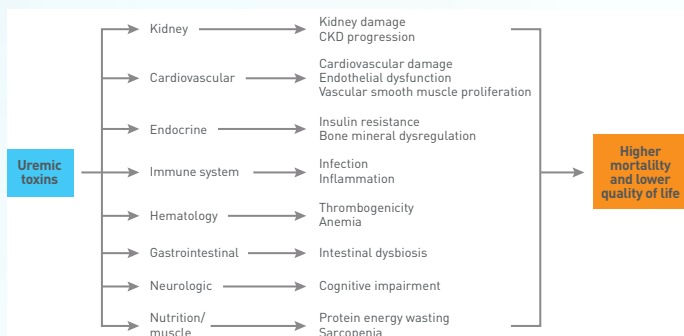
### Classification based on toxicity

#### Rationale

Uremic toxicity negatively affects multiple organ systems and metabolic pathways (Figure 2); cardiovascular damage, increased susceptibility to infection and neurologic manifestations are major factors affecting mortality and quality of life of patients with chronic kidney disease (CKD). The current classification does not link benefits of increased clearance or impact of inadequate clearance of uremic toxins on the body

**Panel Statement 2:** The current physicochemical classification of uremic toxins does not adequately reflect the biological consequences of the toxins and is not able to identify which toxins possess the most clinical relevance.

**FIGURE 2.** Uremic toxins and related systemic disorders



#### Panel Recommendations

1. We suggest using the 2018 classification system (Vanholder et al, *Toxins*) that reflects the degree of known toxicity based upon published peer-reviewed literature to define the pathophysiologic impact of each uremic retention solute. Periodic updates will be required as new evidence of the toxicity of solutes becomes available, and new solutes are identified.
2. We suggest that the pathophysiologic impact of each uremic toxins (e.g., inflammatory, cardiovascular) and solute origin (e.g., intestinal generation, posttranslational modification) should be stated wherever available.

3. We suggest focusing on a limited number of key body system effects that are the most prominent in uremia, such as cardiovascular damage, susceptibility to infection, and neurologic manifestations for pathophysiologic classification.

### Classification based on patient outcomes

#### Rationale

Patients with kidney failure have a high symptom burden and studies have shown that this is more important to patients than survival. The current classification does not guide clinicians in how to prescribe dialysis to improve for instance restless leg syndrome, pruritus or dialysis recovery time. There is a need to consider the role of a range of different solutes including those of larger molecular weight in causing specific clinical scenarios.

**Panel Statement 3:** The current physicochemical classification of uremic toxins does not adequately address patient experience or outcomes and does not reflect personal patient characteristics by which the dialysis prescription should be made (e.g., targeting the prevention of cardiovascular disease, loss of residual kidney function, deterioration of vascular access, or quality of life)

#### Panel Recommendations:

1. Future studies should focus on correlating solute concentrations or the effect of interventions on solute concentrations with clinically relevant outcomes and outcomes of importance to patients.
2. Ideally, dialysis prescriptions would be tailored to improve these symptoms and quality of life based upon removal patterns of uremic solutes linked to symptoms and outcomes.

### Assessment of toxin measurement and removal capacity

#### Rationale

A marker of solute removal should be linked to its toxicity (and improvement of symptoms with removal) and be representative of other toxins with comparable characteristics. Pre-dialysis serum levels after implementation of an intervention are more appropriate measures of the effectiveness of a new technology

#### Panel Recommendations:

1. For assessment of toxin removal by extracorporeal treatment, we recommend measuring the pre-hemodialysis concentration of a toxin after a period of equilibration ( $\geq 4$  weeks).
2. For comparability reasons, we suggest using the same equilibration time (4 weeks) to study any other strategy than extracorporeal removal to decrease toxin concentration (e.g., medication, dietary intervention, xenobiotics, and others).

### Proposal for a new classification system of uremic solutes

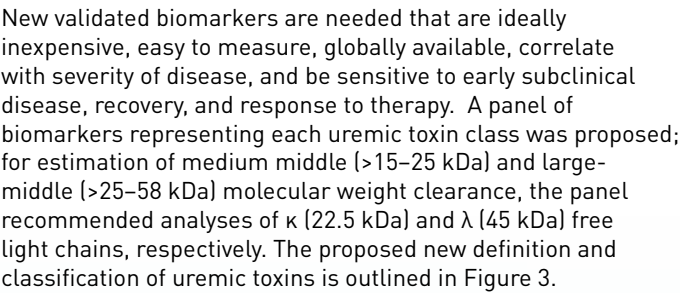
#### Rationale

The panel emphasized that decreased uremic toxin clearance due to low glomerular filtration rate is not the only reason for toxin accumulation; for example, excessive production of cytokines and soluble receptors due to local tissue inflammation is a major contributor to middle molecule accumulation. Therefore a broader view of uremic solutes is needed.

**Panel Statement 4:** New measurement tools for uremic toxins are needed in each class that goes beyond physicochemical classification.

#### Panel Recommendation:

1. The new classification schema must link uremic solutes to traditional clinical outcomes and quality of life measures, including pruritus, restless legs syndrome, and recovery time after dialysis.



**Figure 1: Classification of drug molecules according to their pharmacokinetic properties.**

The diagram illustrates the classification of drug molecules based on their origin and binding properties, leading to their clearance mechanisms.

**Exogenous drug-derived:**

- Protein-bound (>80%):**
  - <0.5 kDa (Small protein-bound molecules):** Cleared by **Hey (G, pG, CML, kynurennines)**.
  - <0.5 kDa (Small molecules):** Cleared by **ADMA, DMA, urea, acid, carbamylated compounds, urea, TMA**.
- Water soluble (Protein-bound <80%):**
  - <0.5 kDa (Small molecules):** Cleared by **ADMA, DMA, urea, acid, carbamylated compounds, urea, TMA**.
  - 0.5-10 kDa (Medium-size molecules):** Cleared by  **$\beta_2$ -microglobulin, G, B**.
  - >15-25 kDa (Medium-middle molecules):** Cleared by **TNF, IL-18, IL-10, IL-6, kappa-ILC, myoglobin, sTNFR2, FGF-2, procatenin, complement factor D**.
  - >25-55 kDa (Large-middle molecules):** Cleared by **Pentastatin-3, sTNFR1, AGEs, FGF-23, lamblin-FIC, CXCL1, CXCL12, IL-2, VEGF-40**.
  - >55-170 kDa (Large molecules):** Cleared by **Modified albumin**.

**Endogenous Generation by endogenous metabolism:**

- Water soluble (Protein-bound <80%):**
  - <0.5 kDa (Small molecules):** Cleared by **ADMA, DMA, urea, acid, carbamylated compounds, urea, TMA**.
  - 0.5-10 kDa (Medium-size molecules):** Cleared by  **$\beta_2$ -microglobulin, G, B**.
  - >15-25 kDa (Medium-middle molecules):** Cleared by **TNF, IL-18, IL-10, IL-6, kappa-ILC, myoglobin, sTNFR2, FGF-2, procatenin, complement factor D**.
  - >25-55 kDa (Large-middle molecules):** Cleared by **Pentastatin-3, sTNFR1, AGEs, FGF-23, lamblin-FIC, CXCL1, CXCL12, IL-2, VEGF-40**.
  - >55-170 kDa (Large molecules):** Cleared by **Modified albumin**.

**Clearance Mechanisms:**

- Renal:**
  - Removed by low-flow HD: **<0.5 kDa**.
  - Removed by high-flow HD: **<0.5 kDa**.
  - Removed by high-flow HDF: **<0.5 kDa**.
  - Removed by MCO HD: **<0.5 kDa**.
  - Removed by HCO HD: **<0.5 kDa**.
- Hepatic:**
  - Removed by low-flow HD: **<0.5 kDa**.
  - Removed by high-flow HD: **<0.5 kDa**.
  - Removed by high-flow HDF: **<0.5 kDa**.
  - Removed by MCO HD: **<0.5 kDa**.
  - Removed by HCO HD: **<0.5 kDa**.

**Marker molecules with known toxicity:** Hey (G, pG, CML, kynurennines), ADMA, DMA, urea, acid, carbamylated compounds, urea, TMA,  $\beta_2$ -microglobulin, G, B, TNF, IL-18, IL-10, IL-6, kappa-ILC, myoglobin, sTNFR2, FGF-2, procatenin, complement factor D, Pentastatin-3, sTNFR1, AGEs, FGF-23, lamblin-FIC, CXCL1, CXCL12, IL-2, VEGF-40, Modified albumin.

**Marker molecules with unknown toxicity:** Hypocretin, HMG, DMA, TMA, PEG, 100-1, various B12, Adiponectin, vitafin, Albumin.

1. Candidate biomarkers representing different types of uremic retention solutes should be identified and used as proxies to study various dialytic and non-dialytic removal strategies.

**Panel Statement 5:** Available and newer dialysis technology (including membranes) must be measured for its effective removal of uremic toxins in each class.

New dialysis methods and new membranes with the ability to clear an extended range of uraemic toxins or with specific characteristics lead to the need of a new classification. Characteristics that should be considered are new permeability indices, the hydrophilic or hydrophobic nature of membranes, adsorption capacity, and electrical potential. Molecular weight retention onset, molecular weight cut-off, and the mass transfer area coefficient should be measured. Clinicians should consider molecular radius, electrical charges, protein binding solute characteristics, high vs. low molecular weight, hydrophilic vs. hydrophobic, endogenous vs. exogenous, secretion by kidney tubules, and different volumes of distribution.

**Panel Statement 6:** The panel stated that prototype uremic biomarkers should be validated as new measurement tools of uremic toxicity.

Identifying prototype biomarkers to optimize patient management is critical. These biomarkers should be linked to improving clinical outcomes and need to predict uremic manifestations, inform about mechanisms and prognosis, improve safety of interventions for uremia, or be a surrogate marker of a uremic toxin or clinical outcome.

Continued research is critical to link biomarkers to improved clinical outcomes and quality of life, and to assess the cost of using novel biomarkers. A multidimensional approach including big data methodologies will be needed to understand the complex pathophysiology of uremia.

Advances in the understanding of uremic toxins and the availability of new hemodialysis membranes (including the MCO membrane) and techniques have led to a reappraisal of the definition and classification of uremic toxins. The consensus panel recommended a more holistic classification of uremic toxins that includes physicochemical characteristics and correlation to clinical symptoms and outcomes. In addition, the identification of representative biomarkers that correlate with removal patterns and are clinically relevant to toxicity may enable more personalized and targeted dialysis prescriptions. Validation of the novel classification will require big data methodologies, validation in external cohorts and experimental evidence of toxicity. Of note, new data on uremic toxins and removal techniques are continuously being published and these recommendations may therefore require modifications as new results become available.





# Exploring the Clinical Relevance of Providing Increased Removal of Large Middle Molecules

**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. doi: [10.2215/CJN.10110917](https://doi.org/10.2215/CJN.10110917).

## BACKGROUND

End stage kidney disease (ESKD) is accompanied by the retention of uremic toxins, molecules that accumulate in kidney impairment and have an adverse biologic effect. Uremic toxins can be broadly classified into three groups: small water-soluble molecules, middle molecules, and protein-bound solutes. Of these three groups, established dialysis technologies most efficiently remove small water-soluble molecules. However, current dialysis strategies lack the ability to provide effective clearance of middle molecules (500-60,000 Da), having been designed to remove  $\beta$ 2-microglobulin (11.8 kDa).

Recent advances in membrane technology have enabled the development of a new generation of membranes, medium-cut off membranes (MCO), which allow for the removal of middle molecules up to 50 kDa, surpassing even the range provided by hemodiafiltration (HDF), the established method for clearing middle molecules.

## OBJECTIVES

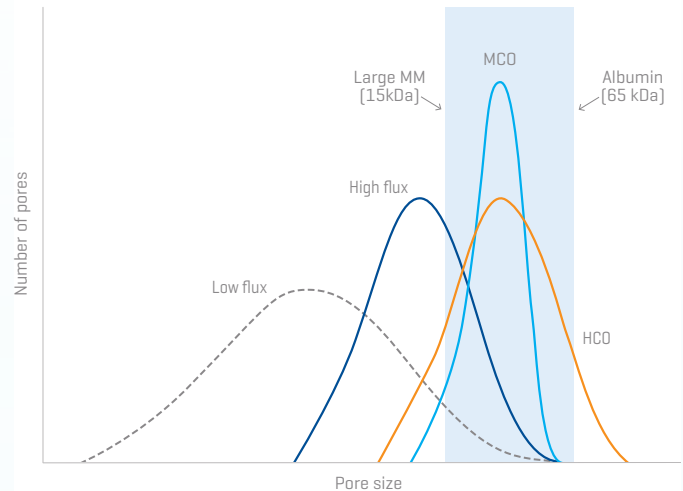
This purpose of the review is three-fold. First, it describes the development of dialysis membranes that allow for removal of large middle molecules without albumin loss. Second, it identifies large middle molecules that can be removed using the MCO membranes, namely those with molecular weight >15 kDa and assesses their clinical relevance. Third, it evaluates clinical experience to date with these membranes and recommended steps to make these membranes widely acceptable as a new therapeutic option for ESKD.

## REVIEW

### Adapting Hemodialysis Membranes to Remove Large Middle Molecules

Hollow fiber hemodialysis membranes have pores which have a bell-shaped distribution of size from small to large. See Figure 1. The pore size distribution of standard high-flux membranes shows low clearance of middle molecules with molecular mass >15 kDa, with the largest of its pores being smaller than albumin (65 kDa) to prevent albumin loss. To increase the size of molecules removed by a membrane, the sizes of the pores needs to be increased by moving the distribution of the pores to the right, which occurred with the high-cut off (HCO) membranes. Although the HCO membranes were able to remove larger molecules, such as the free light chains  $\kappa$ (22.5 kDa) and  $\lambda$ (45 kDa) in myeloma kidney, this resulted in the loss of albumin due to the nonuniformity of the pores.

To enable the clearance of larger middle molecules with molecular mass between 15 and 60 kDa without the loss of albumin, the distribution of the pores within the dialysis membranes had to fundamentally change to a tighter distribution. The MCO dialyzers use this new distribution of pores, which should provide in clinical practice the effective clearance of large molecules without excessive albumin loss.



**FIGURE 1. Medium cut-off membranes provide clearance of large middle molecules without albumin loss.** Schematic of pore size distribution in dialysis membranes. As membranes have been developed to allow the removal of large middle molecules (MMs) without albumin loss, the distribution of the pore sizes has had to be "tightened." The blue bar represents the distribution of large MMs before albumin is lost. The dotted line indicates Low flux, the dark blue line indicates High flux, the orange line indicates high cut-off (HCO) and the light blue line indicates medium cut-off (MCO). Adapted from Wolley M, et al.

### Identification of Large Middle-Molecules

A list of uremic toxins that can be classified as middle molecules was generated from EuTox database, associated publications, and Medline search. The review was limited to middle molecules with molecular mass >15 kDa, above which clearance by high-flux membranes is reduced and clearance is increased by MCO membranes. Protein-bound solutes are clinically relevant but were not assessed because they cannot be removed by MCO membranes.

Fifty-nine (59) middle molecules are summarized in Table 1. Of the 59 middle molecules, 31 middle molecules had molecular mass under 15 kDa, and therefore can be removed by high-flux dialysis. Fourteen middle molecules had molecular mass between 15 and 25 kDa, and therefore can be removed by HDF. Fourteen middle molecules have molecular mass greater than 25 kDa, not currently removed by high-flux or HDF.

### Classification and Biologic Summary of Larger Middle Molecules

The literature review identified 27 middle molecules with molecular mass >15 kDa, the largest of which was 52 kDa. The serum levels of these middle molecules can range from <1.5- to >200-fold higher in patients receiving dialysis or with advanced chronic kidney disease (CKD) than in those with normal kidney function. These molecules were categorized into four broad functional groups: cytokines (n=5), adipokines (n=4), immune-mediated proteins (n=8), growth factors and hormones (n=4), and other molecules (n=6).

In Table 2, the molecular mass, usual biologic role, possible adverse effects in uremia, and relative increase in dialysis or advanced CKD are described for each molecule.



### Clinical Relevance of Large Middle Molecules as Uremic Toxins

#### Accelerated Atherosclerotic Cardiovascular Disease

Patients with CKD and especially those reliant on maintenance dialysis are subject to substantially elevated risk of cardiovascular disease and cardiovascular mortality compared to the general population. Many of the large middle molecules are involved in atherosclerosis. Correlations between serum concentrations of these large middle molecules and the rates of cardiovascular disease and overall survival have also been found.

Elevated levels of proinflammatory cytokines interleukin (IL)-18 (18 kDa), IL-6 (21-28 kDa), IL-1 $\beta$  (17.5 kDa) and tumor necrosis factor (TNF)- $\alpha$  (17 kDa) are all involved with cardiovascular disease. Serum concentrations of IL-18 are associated with plaque burden and instability. IL-6 and IL-1 $\beta$  have been described to be pathologically involved in the progression of atherosclerosis. TNF- $\alpha$  alters endothelial and vascular smooth muscle cell function.

Removed by High Flux (<15 kD)	Molecular Mass, kD	Removed by HDF (15–24.9 kD)	Molecular Mass, kD	Not Currently Removed (>25 kD)	Molecular Mass, kD
Methionine-enkephalin	0.5	Clara-cell protein	15.8	Hyaluronic acid	25
Glutathione	0.6	Leptin	16	B-Trace protein	26
Angiotensin A	0.8	Myoglobin	17	Soluble TNF receptor-1	27
d-Sleep-inducing peptide	0.8	TNF- $\alpha$	17	Adiponectin	30
Dinucleoside polyphosphates	1	Soluble TNF receptor-2	17	FGF-23	32
Substance P	1.3	IL-18	17.5	$\alpha$ 1-Microglobulin	~2.8
Motilin	2.7	FGF-2	18	VEGF	34.2
Orexin B	2.9	IL-10	18	YKL-40	40
Atrial natriuretic peptide	3	Retinol binding protein	21.2	Pentraxin-3	40.2
Desacylgherlin	3.2	Prolactin	22	$\alpha$ 1-Acid glycoprotein	43
Vasoactive intestinal peptide	3.3	$\kappa$ -Ig light chain	22.5	AGEs	45
Calcitonin	3.4	Complement factor D	23.75	$\lambda$ -Ig light chain	45
Gherlin	3.4	IL-18	24	Visfatin	55
b-Endorphin	3.4	IL-6	24.5	AOPPs	>60
Orexin A	3.5				
Calcitonin gene-related peptide	3.7				
Cholecystokinin	3.8				
Endothelin	4.2				
Neuropeptide Y	4.2				
SIAM-1	4.2				
Adrenomedullin	5.7				
Osteocalcin	5.8				
IGF-1	7.6				
IL-8	8				
Parathyroid hormone	9.5				
Guanylin	10.3				
b2-Microglobulin	11.8				
Uroguanylin	12				
Resistin	12.5				
Cystatin C	13.3				
Degranulation inhibiting protein <sup>a</sup>	14.1				

**TABLE 1.** Summary of middle molecules (n=59). <sup>a</sup>Degranulation inhibiting protein corresponds to angiogenin. Abbreviations: HDF, hemodiafiltration; FGF, fibroblast growth factor; VEGF, vascular endothelial growth factor; AGE, advanced glycosylation end product; AOPP, advanced oxidative protein products. Adapted from Wolley et al.

Other middle molecules have also been associated with cardiovascular disease. Immune-mediated protein pentraxin (PTX)-3 (40 kDa) has been linked to unstable plaque in coronary and carotid arteries. B-trace protein (BTP) (26 kDa) is correlated with the severity of coronary disease. The hormone prolactin (23 kDa) levels have been associated with increased risk of

cardiovascular events and all-cause mortality in CKD/dialysis populations. Tissue accumulation of advanced glycosylation end products (AGEs) (<1-70 kDa) can contribute to cardiovascular disease by cross-linking with other molecules, causing structural changes and inducing inflammation in heart and blood vessels.

The adipokine visfatin (52 kDa) is strongly upregulated in atherosclerotic plaque, and serum levels are higher in those with unstable versus stable vascular disease. Additionally, the adipokines adiponectin (30 kDa) and leptin (16 kDa) have been implemented in progressive atherosclerosis by contributing to the recruitment of macrophages and the formation of cells.

#### Contribution to Structural Cardiac Disease

Several growth factors have been linked to cardiac hypertrophy. Experimental animal studies implicated fibroblast growth factor 2 (FGF-2) (18 kDa) and FGF-23 (32 kDa) as having a direct role in this process. Observational studies in humans also revealed a link between FGF-23 and left ventricular hypertrophy.

#### Influence on Secondary Immune Deficiency

ESKD is associated with significant immune dysfunction. Patients on dialysis experience high levels of infection-related morbidity and mortality. Immunoglobulin (Ig) free light chains (k-Ig (22.5 kDa),  $\lambda$ -Ig (45 kDa) were shown to reduce glucose uptake by polymorphonuclear leukocytes in vitro and reduce chemotaxis. In addition, serum free light chains were an independent risk factor for death by infectious cause in a CKD population. Adipokine retinol binding protein (RBP) 4 (21.2 kDa) also inhibits the chemotactic movement of polymorphonuclear leukocytes in a concentration-dependent fashion. FGF-23 (32 kDa) has been shown to exert inhibitory effects on leukocytes in a mouse CKD model, which was reversible with a neutralizing antibody toward FGF-23.  $\alpha$ 1 acid glycoprotein (35-44 kDa) inhibits the migration of neutrophils to infectious foci and is associated with the susceptibility to infections in individuals with diabetes.

#### Protein-Energy Wasting in CKD

There is evidence linking cytokines IL-6 (21-28 kDa), TNF- $\alpha$  (17 kDa), IL-18 (17.5 kDa) to anorexia and protein-energy wasting in cancer, AIDS, and geriatric cachexia. Evidence specific to patients with CKD and patients on dialysis is getting stronger. Elevated levels of the adipokine leptin (16 kDa) can contribute to protein-energy wasting by inhibiting food intake and increasing energy expenditure.

In patients on dialysis, IL-6 (21-28 kDa) has a clear inverse relationship with albumin levels in patients on dialysis and have been found to negatively correlate with muscle mass. TNF- $\alpha$  (17 kDa) levels were higher in patients on dialysis with poor appetite, evidence of anorexia, nausea, or vomiting compared with those without. Higher IL-18 (17.5 kDa) levels were associated with lower physical activity scores and faster declines in bioimpedance-derived measure of body cell mass.

#### Contributions to Chronic Inflammation

Retention of inflammatory cytokines, proteins, and other proinflammatory factors can cause chronic inflammation in patients on dialysis. For example, cytokine IL-6 (21-28 kDa) release from both leukocytes and peripheral tissues has been found to be upregulated in uremia, along with the increase of cytokine IL-18 (17.5 kDa).

Similarly, cytokine TNF- $\alpha$  (17 kDa) and immune-mediated proteins TNF receptors 1 (27-30 kDa) and 2 (17 kDa) are also increased in CKD, which further contribute to the chronic inflammation of ESKD.



Molecule (Alternative Names)	Group	Size, kD	Usual Biologic Function	Possible Adverse Effects in Excess or Uremia	Relative Increase in Dialysis or Advanced CKD
IL-18	Cytokine	18	Proinflammatory; induction of TH1 response	Proatherogenic; increased amyloid- $\beta$ production	Approximately 2x higher
IL-6	Cytokine	21–28	Diverse proinflammatory	Proatherogenic; sarcopenia and wasting; anorexia	2–5x higher
IL-18	Cytokine	17.5	Proinflammatory; upregulation of IL-6	Proatherogenic; contributes to systemic inflammation	Approximately 2x higher
IL-10	Cytokine	18	Anti-inflammatory; downregulation of macrophage	Diminished anti-infectious immune function	~1.5x higher
TNF- $\alpha$	Cytokine	17	Upregulation of immune response, induction of fever	Enhanced protein catabolism, anorexia, and muscle protein breakdown	4–5x higher
Adiponectin	Adipokine	30	Modulates glucose	Unknown	2–3x higher
Visfatin (Nicotinamide phosphoribosyl transferase)	Adipokine	52	Intracellularly involved in NAD biosynthesis; extracellularly stimulates angiogenesis and endothelial cell proliferation	Proinflammatory cytokine effects; angiogenic effects, promotion of vascular smooth muscle cell proliferation	3–6x higher
Leptin	Adipokine	16	Regulates appetite and body energy stores	Anorexia and protein-energy wasting	3–4x higher
Retinol binding protein 4	Adipokine	21.2	Delivers retinol from liver to peripheral tissues	Inhibition of leukocyte chemotaxis and function	3–10x higher
Soluble TNF receptor 2	Immune-mediated protein	17	Binds to and limits TNF- $\alpha$ activity	May increase circulating TNF- $\alpha$ <sup>1</sup> / <sub>2</sub>	3–4x higher
$\kappa$ -Ig light chains	Immune-mediated protein	22.5	Unknown	Inhibit leukocyte chemotaxis, apoptosis, and function	2–16x higher
Complement factor D (C3 proactivator convertase)	Immune-mediated protein	24	Component of alternative complement pathway; humoral defense	Overactivity of complement system	4–17x higher
Soluble TNF receptor 1	Immune-mediated protein	27–30	Binds to and limits TNF- $\alpha$ activity	May increase circulating TNF- $\alpha$ <sup>1</sup> / <sub>2</sub> to prolong cytotoxic effects	3–10x higher
$\alpha$ 1-Acid glycoprotein (Orosomucoid)	Immune-mediated protein	35–44	Anti-inflammatory acute-phase protein; suppresses local leukocyte activity and promotes immunosuppressive macrophage differentiation	Inhibition of leukocyte migration, contribution to secondary immunodeficiency	<1.5x higher
Pentraxin-3	Immune-mediated protein	40	Opsonization and complement activation; macrophage activity	Prothrombotic actions in endothelial cells; impaired NO production	2–7x higher
YKL-40 (Chitinase-3-like protein 1)	Immune-mediated protein	40	Regulates local inflammatory markers; other functions unclear	Contribution to upregulation of local tissue inflammation and fibrosis	2–5x higher
$\lambda$ -Ig light chains	Immune-mediated protein	45	Unknown	Inhibit leukocyte chemotaxis, apoptosis, and function	2–18x higher
Vascular endothelial growth factor (Vascular permeability factor)	Growth factor	34	Promotes endothelial cell proliferation, migration, and differentiation; involved in cardiac adaptation to hypoxia and stretch	Involved in cardiomyopathy and left ventricular dysfunction	Approximately 2x higher
Fibroblast growth factor 2	Growth factor	18	Neovascularization; upregulates inflammatory cytokines and chemokines	Cardiac hypertrophy; contribution to local inflammation	
Fibroblast growth factor 23	Growth factor	32	Regulates phosphate homeostasis and kidney hydroxylation of vitamin D	Cardiac hypertrophy	>200x higher
Prolactin	Hormone	23	Primary role in mammary cell proliferation and reproductive function	Amplification of inflammatory cytokine response (IL-12 and TNF- $\alpha$ ); increased CVS events	2–4x higher
Clara cell protein (CC16)	Protein	15.8	Phospholipase-A2-inhibitor; immunosuppressive role in respiratory tract	Unknown	Approximately 30x higher
$\alpha$ 1-Microglobulin	Protein	33	Inhibitor of heme and neutrophil-induced oxidative damage	Inhibition of leukocyte migration, chemotaxis, and IL-2 secretion	Approximately 9x higher
$\beta$ -Trace protein (L-prostaglandin D2 synthase)	Protein	26	Catalyzes isomerization of precursor prostanoids to active forms	Observationally associated with atherosclerotic plaque	>35x higher
Myoglobin	Protein	17	Oxygen carrier in muscle tissue	Increased oxidative stress	3x higher
Hyaluronic acid (Hyaluronan)	Glycosaminoglycan	Variable	Formation of endothelial glycocalyx; structural role in extracellular matrix	Proinflammatory; promotes endothelial dysfunction and damage	5–16x higher
Advanced glycosylation end products	Other	<1–70	Unknown	Adverse structural effects	2–20x higher

**TABLE 2.** Classification, levels in ESKD, and methods of measurement of large middle molecules (n=27). Abbreviations: CVS, cardiovascular system; NO, nitric oxide. Adapted from Wolley et al.

### Clinical Evaluation of MCO Dialyzers

With increasingly porous membranes, such as those in MCO dialyzers, there are two principal safety concerns: back filtration of endotoxins and albumin loss.

An in vitro assessment of the back filtration of endotoxins identified no increased back filtration with MCO dialyzers compared with high-flux dialyzers. Hemodialysis with the MCO membrane is associated with albumin loss of approximately 3 g per session. In a study in which patients were converted from online HDF to MCO dialysis, there was no significant change in serum albumin concentrations, suggesting that this level of albumin loss is tolerable. Additionally, in another study evaluating the efficacy of MCO dialysis for the removal of large middle molecules, MCO dialysis increased clearance of complement factor D (24 kDa), YKL-40 (40 kDa) and  $\alpha$ 1-microglobulin (33 kDa) vs high-flux dialysis.

## CONCLUSIONS

The review identified 27 large middle molecules, many of which have biologic pathways through which they can contribute to cardiovascular disease, secondary immune deficiency, protein energy wasting and chronic inflammation. After reporting of these assessments of safety and efficacy of MCO dialysis, robust clinical trials are now required to determine if increasing their removal by dialysis can improve clinical outcomes.

**MCO membranes improve removal of middle-molecular uremic toxins that have been linked to the development of chronic inflammation, CVD, and other dialysis related comorbidities; this may result in improved patient outcomes.**



# Effects of Medium Cut-Off Versus High-Flux Hemodialysis Membranes on Biomarkers: A Systematic Review and Meta-Analysis

Kandi M, Brignardello-Petersen R, Couban R, et al. Effects of Medium Cut-Off Versus High-Flux Hemodialysis Membranes on Biomarkers: A Systematic Review and Meta-Analysis. *Can J Kidney Health Dis.* 2022;9;1-15. doi: 10.1177/20543581211067090.

## BACKGROUND

Uremic toxins have a range of physiochemical properties associated with diverse effects that contribute to morbidity and mortality in patients with end-stage renal disease. Earlier membrane technologies provide minimal diffusive clearance above 15 kDa. A novel medium cut-off (MCO) membrane (Theranova 400/500, Baxter) removes large middle-molecules while selectively retaining molecules >45kDa.

## OBJECTIVE

Compare the effects of MCO versus high-flux membranes on biomarkers falling within an expanded range of molecular weights through a systematic review and meta-analysis.

## METHODOLOGY

A search was conducted of the MEDLINE, Embase, CINAHL, Cochrane Library, and Web of Science from January 2015 to July 2020, and gray literature sources from 2017. Randomized (RS) and nonrandomized studies (NRS) comparing MCO and high-flux membranes in adults (>18 years) receiving maintenance hemodialysis were included. Study selection, data extraction, and quality appraisals were performed in duplicate and used the Grading of Recommendations Assessment, Development, and Evaluation framework. Outcomes included solute removal (plasma clearance or dialysate quantitation), reduction ratios, and predialysis serum concentrations for albumin, and a range of prespecified large middle molecules and inflammatory markers.

## RESULTS

The search identified 26 eligible studies (10 randomized and 16 nonrandomized; N = 1883 patients; patient-years = 1366.3). All studies used the **Theranova** MCO membrane.

### Albumin

The mean difference (MD) for albumin removal was 2.31 g per session (95% confidence interval [CI], 2.79 to 1.83; high certainty), with a reduction in predialysis albumin of -0.12 g/dl (95% CI, -0.16 to -0.07; I<sup>2</sup> = 0%; high certainty) in the first 24 weeks, returning to normal (MD = -0.02 g/dl, 95% CI, -0.07 to -0.03; I<sup>2</sup> = 56%; high certainty) after 24 weeks. No studies reported hypoalbuminemia that required albumin infusion or discontinuation of treatment with MCO membranes. A summary of albumin results across studies is shown in Table 1.

TABLE 1. Summary of findings - Albumin related measures.

Outcome No. of participants [studies]	Anticipated absolute effects (95% CI)		Certainty	What happens
	Without MCO-HD	Difference		
Albumin loss (g) Follow-up: 2 weeks No. of participants: 230 (5 RS)	The mean albumin loss ranged from 0.2 to 0.56 g	MD 2.31 g higher (2.79 higher to 1.83 higher)	⊕⊕⊕⊕ High	MCO-HD increases albumin loss slightly.
Albumin reduction ratio (%) Follow-up: range, 2-26 weeks No. of participants: 162 (3 RS)	The mean albumin reduction ratio ranged from 7% to 11%	MD 2.39% higher (3.68 higher to 1.11 higher)	⊕⊕⊕⊕ High	MCO-HD increases albumin reduction ratio slightly.
Predialysis serum albumin (g/dl) Subgroup with <24-week follow-up Follow-up: range, 8-13 weeks No. of participants: 305 (5 RS)	The mean predialysis serum albumin ranged from 3.79 to 3.94 g/dl	MD 0.12 g/dl lower (0.17 lower to 0.07 lower)	⊕⊕⊕⊕ High	MCO-HD reduces predialysis serum albumin slightly over the short term (<24 weeks).
Predialysis serum albumin (g/dl) Subgroup with ≥24-week follow-up Follow-up: 24 weeks No. of participants: 129 (1 RS)	The mean predialysis serum albumin was 4.1 g/dl	MD 0 g/dl (0.1 lower to 0.1 higher)	⊕⊕⊕⊕ Moderate <sup>a</sup>	MCO-HD likely results in little to no difference in predialysis serum albumin after 24 weeks of treatment.
Predialysis serum albumin (g/dl) Subgroup with ≥24-week follow-up Follow-up: range, 24-52 weeks No. of participants: 2010 (7 NRS)	The mean predialysis serum albumin (g/dl)—subgroup with ≥4-month follow-up ranged from 3.1 to 4.05 g/dl	MD 0.02 g/dl lower (0.08 lower to 0.04 higher)	⊕⊕⊕⊕ Moderate <sup>a</sup>	MCO-HD likely results in little to no difference in predialysis serum albumin after 24 weeks of treatment.
Predialysis serum albumin (g/dl) Subgroup analysis—RS and NRS with <24-week follow-up Follow-up: range, 8-13 weeks No. of participants: 325 (5 RS, 1 NRS)	The mean predialysis serum albumin ranged from 3.76 to 3.94 g/dl	MD 0.12 g/dl lower (0.16 lower to 0.07 lower)	⊕⊕⊕⊕ High	MCO-HD reduces predialysis serum albumin slightly within the first 24 weeks of follow-up.
Predialysis serum albumin (g/dl) Subgroup analysis—RS and NRS with ≥24-week follow-up Follow-up: range, 24-52 weeks No. of participants: 2139 (1 RS, 7 NRS)	The mean predialysis serum albumin ranged from 3.10 to 4.05 g/dl	MD 0.02 g/dl lower (0.07 lower to 0.03 higher)	⊕⊕⊕⊕ High	MCO-HD results in little to no difference in predialysis serum albumin after 24 weeks of follow-up.

Note. CI = confidence interval; MCO-HD = medium cut-off hemodialysis; MD = mean difference; NRS = nonrandomized study; RS = randomized study.

<sup>a</sup>Estimate prone to risk of bias due to patient attrition.





## Middle Molecules

The review found with high certainty that MCO dialysis resulted in a large increase (standardized mean difference [SMD] > 2.0 for all) in B2-microglobulin,  $\kappa$ - and  $\lambda$ -free light chains, and myoglobin removal, resulting in moderate (SMD > 0.5) to large (SMD > 0.8) reductions in predialysis concentrations for all of these solutes.

**TABLE 2.** Summary of findings - Middle Molecules

Outcome No. of participants (studies)	Anticipated absolute effects (95% CI)				What happens
	Without MCO-HD	Difference	Certainty		
B2M removal (mg) Follow-up: range, 2-8 weeks No. of participants: 152 (4 RS)	-	SMD 1.83 SD higher (0.02 higher to 3.64 higher)	⊕⊕⊕⊕ High <sup>a</sup>		MCO-HD results in a large increase in B2M removal.
B2M removal (mg) No. of participants: 16 (1 NRS)	-	SMD 1.4 SD higher (0.42 higher to 2.38 higher)	⊕⊕⊕⊕ High <sup>b,c</sup>		MCO-HD results in a large increase in B2M removal.
B2M reduction ratio (%) Follow-up: range, 2-26 weeks No. of participants: 323 (7 RS)	The mean B2M reduction ratio (%) ranged from 46% to 77%	MD 8.0% higher (2.8 higher to 13.2 higher)	⊕⊕⊕⊕ High <sup>d</sup>		MCO-HD increases B2M reduction ratio.
Predialysis B2M Subgroup with <12-week follow-up Follow-up: 8 weeks No. of participants: 32 (1 RS)	-	SMD 0.36 SD higher (0.33 lower to 1.06 higher)	⊕⊕⊕○ Low <sup>e</sup>		MCO-HD likely results in little to no difference in predialysis serum albumin after 24 weeks of treatment.
Predialysis B2M Subgroup with ≥12-week follow-up Follow-up: range, 12-26 weeks No. of participants: 403 (5 RS)	-	SMD 0.54 SD lower (1 lower to 0.08 lower)	⊕⊕⊕○ Moderate <sup>f</sup>		MCO-HD likely reduces predialysis B2M after 3 months of treatment.
Predialysis B2M Follow-up: range, 24-52 weeks No. of participants: 438 (6 NRS)	-	SMD 0.43 SD lower (0.84 lower to 0.002 lower)	⊕⊕⊕⊕ High		MCO-HD reduces predialysis B2M slightly.
Myoglobin removal Follow-up: 2 weeks No. of participants: 120 (3 RS)	-	SMD 2.9 SD higher (1.31 higher to 4.49 higher)	⊕⊕⊕⊕ High		MCO-HD likely results in a large increase in myoglobin removal.
Myoglobin reduction ratio (%) Follow-up: range, 2-26 weeks No. of participants: 242 (5 RS)	The mean myoglobin reduction ratio (%) ranged from 8% to 45%	MD 30.26% higher (15.5 higher to 45.03 higher)	⊕⊕⊕⊕ High <sup>g</sup>		MCO-HD results in large increase in myoglobin reduction ratio.
Myoglobin reduction ratio (%) Follow-up: range, 2-52 weeks No. of participants: 118 (6 NRS)	The mean myoglobin reduction ratio (%) ranged from 12% to 44%	MD 27.62% higher (24.29 higher to 30.95 higher)	⊕⊕⊕⊕ High		MCO-HD results in large increase in myoglobin reduction ratio.
Predialysis myoglobin Follow-up: 26 weeks No. of participants: 130 (2 RS)	-	SMD 0.51 SD lower (0.85 lower to 0.16 lower)	⊕⊕⊕○ Moderate <sup>h</sup>		MCO-HD likely reduces predialysis myoglobin.
Predialysis myoglobin Follow-up: 26 weeks No. of participants: 82 (1 NRS)	-	SMD 0.12 SD lower (0.55 lower to 0.31 lower)	⊕⊕⊕○ Moderate <sup>b</sup>		MCO-HD likely reduces myoglobin prehemodialysis slightly.

**TABLE 2.** continued

Outcome No. of participants (studies)	Anticipated absolute effects (95% CI)		Certainty	What happens
	Without MCO-HD	Difference		
Kappa FLC removal Follow-up: 2 weeks No. of participants: 78 (2 RS)	-	SMD 3.89 SD higher (3.45 higher to 4.33 higher)	⊕⊕⊕⊕ High	MCO-HD results in large increase in kappa FLC removal.
Kappa FLC reduction ratio (%) Follow-up: range, 2-26 weeks No. of participants: 249 (5 RS)	The mean kappa FLC reduction ratio (%) ranged from 53% to 72%	MD 14.85% higher (8.27 higher to 21.43 higher)	⊕⊕⊕⊕ High <sup>g</sup>	MCO-HD results in large increase in kappa FLC reduction ratio.
Predialysis kappa-FLC Follow-up: range, 12-26 weeks No. of participants: 403 (5 RS)	-	SMD 0.39 SD lower (0.61 lower to 0.16 lower)	⊕⊕⊕⊕ High	MCO-HD reduces predialysis kappa FLC slightly.
Lambda FLC removal Follow-up: 2 weeks No. of participants: 118 (3 RS)	-	SMD 2.16 SD higher (1.8 higher to 2.52 higher)	⊕⊕⊕⊕ High	MCO-HD results in large increase in lambda FLC removal.
Lambda FLC removal Follow-up: range, 2-3 weeks No. of participants: 130 (2 NRS)	-	SMD 3.71 SD higher (2.97 higher to 4.45 higher)	⊕⊕⊕⊕ High	MCO-HD results in large increase in lambda free light chain removal.
Lambda FLC reduction ratio (%) Follow-up: range, 2-26 weeks No. of participants: 450 (7 RS)	The mean lambda FLC reduction ratio (%) ranged from 13% to 41%	MD 20.85% higher (15.53 higher to 26.16 higher)	⊕⊕⊕⊕ High	MCO-HD increases lambda-FLC reduction ratio.
Predialysis lambda-FLC Follow-up: range, 12-26 weeks No. of participants: 402 (5 RS)	-	SMD 0.53 SD lower (0.9 lower to 0.17 lower)	⊕⊕⊕⊕ High <sup>i</sup>	MCO-HD reduces predialysis lambda-FLC.
Predialysis lambda-FLC Follow-up: range, 24-52 weeks No. of participants: 398 (4 NRS)	-	SMD 0.34 SD lower (0.54 lower to 0.14 lower)	⊕⊕⊕⊕ High	MCO-HD reduces lambda free light chain prehemodialysis slightly.

Note. CI = confidence interval; MCO-HD = medium cut-off hemodialysis; B2M = B2-microglobulin; RS = randomized study; SMD = standardized mean difference; SD = standard deviation; NRS = nonrandomized study; MD = mean difference; FLC = free light chains.

<sup>a</sup>I<sup>2</sup> = 97%, but fully explained by measurement method—removal was higher when measured by plasma clearance versus dialysate quantitation.

<sup>b</sup>Small overall sample size; optimal information size criterion not met.

<sup>c</sup>SMD > 0.8 considered a large treatment effect. Rated up 1 level.

<sup>d</sup>Although I<sup>2</sup> was 99%, heterogeneity was explained by baseline removal ratio (larger effect if removal ratio was <70%), and was further explained by study duration (effect was attenuated with long-term treatment).

<sup>e</sup>Downgraded 2 levels for imprecision with only very small sample size and confidence interval crossing no effect.

<sup>f</sup>I<sup>2</sup> > 50% and confidence intervals do not overlap.

<sup>g</sup>Inconsistency explained by baseline removal ratio such that studies with lower baseline RR had larger effects with MCO-HD.

<sup>h</sup>I<sup>2</sup> = 82% with opposite directions of effect.

<sup>i</sup>Inconsistency explained by duration of follow-up with a larger treatment effect with long-term treatment.



## Cytokines and Inflammatory Markers

Use of the **Theranova** MCO membrane increased the reduction ratio for tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) by 7.7% (95% CI, 4.7 to 10.6; moderate certainty), and reduced predialysis TNF- $\alpha$  by standardized mean difference (SMD)  $-0.48$  (95% CI,  $-0.91$  to  $-0.04$ ; moderate certainty). This review showed with moderate certainty that MCO dialysis had little to no effect on predialysis interleukin-6 (IL-6) plasma concentrations. Medium cut-off dialysis reduced mRNA expression of TNF- $\alpha$  and IL-6 in peripheral leukocytes by mean difference (MD)  $-15\%$  (95% CI,  $-19.6$  to  $-10.4$ ; moderate certainty) and  $-8.8\%$  (95% CI,  $-10.2$  to  $-7.4$ ; moderate certainty), respectively. There was little or no effect on C-reactive protein.

**TABLE 3.** Summary of findings - Inflammatory Markers and Cytokines

Outcome No. of participants [studies]	Anticipated absolute effects (95% CI)		Certainty	What happens
	Without MCO-HD	Difference		
IL-6 reduction ratio (%) Follow-up: 26 weeks No. of participants: 80 (1 RS)	The mean IL-6 reduction ratio (%) was 9.5%	MD 0.2% lower (3.44 lower to 3.04 higher)	⊕⊕⊕○ Moderate <sup>a</sup>	MCO-HD likely results in little to no difference in IL-6 reduction ratio (%).
Predialysis IL-6 Follow-up: range, 12-26 weeks No. of participants: 354 (4 RS)	-	SMD 0.04 SD higher (0.17 lower to 0.25 higher)	⊕⊕⊕○ Moderate <sup>b</sup>	MCO-HD likely results in little to no difference in predialysis IL-6.
IL-6 mRNA expression Follow-up: 26 weeks No. of participants: 46 (1 RS)	The mean IL-6 expression was 100%	MD 8.8 % lower (10.2 lower to 7.4 lower)	⊕⊕⊕○ Moderate <sup>a</sup>	MCO-HD likely reduces IL-6 expression
TNF- $\alpha$ reduction ratio (%) Follow-up: 26 weeks No. of participants: 80 (1 RS)	The mean TNF- $\alpha$ reduction ratio (%) was 26%	MD 7.67% higher (4.7 higher to 10.64 higher)	⊕⊕⊕○ Moderate <sup>a</sup>	MCO-HD likely increases TNF- $\alpha$ reduction ratio.
TNF- $\alpha$ predialysis Follow-up: range, 12-26 weeks No. of participants: 304 (3 RS)	-	SMD 0.48 SD lower (0.91 lower to 0.04 lower)	⊕⊕⊕○ Moderate <sup>a</sup>	MCO-HD likely reduces predialysis TNF- $\alpha$ .
TNF- $\alpha$ mRNA expression Follow-up: 12 weeks No. of participants: 46 (1 RS)	The mean TNF- $\alpha$ expression was 100%	MD 15% lower (19.6 lower to 10.4 lower)	⊕⊕⊕○ Moderate <sup>a</sup>	MCO-HD likely reduces TNF- $\alpha$ expression.
C-reactive protein Follow-up: 12 weeks No. of participants: 145 (2 RS)	-	SMD 0.04 SD higher (0.37 lower to 0.29 higher)	⊕⊕⊕○ Moderate <sup>a</sup>	MCO-HD likely results in little to no difference in C-reactive protein.
C-reactive protein Follow-up: range, 26-52 weeks No. of participants: 1940 (5 NRS)	-	SMD 0 SD (0.23 lower to 0.22 higher)	⊕⊕⊕⊕ High	MCO-HD results in little to no difference in C-reactive protein.

Note. CI = confidence interval; MCO-HD = medium cut-off hemodialysis; IL-6 = interleukin-6; RS = randomized study; MD = mean difference; SMD = standardized mean difference; SD = standard deviation; TNF- $\alpha$  = tumor necrosis factor- $\alpha$ ; NRS = nonrandomized study.

<sup>a</sup>Small overall sample size; optimal information size criterion not met.

<sup>b</sup>Small overall sample size and the confidence interval includes no effect.

## DISCUSSION AND CONCLUSIONS

This review showed with high certainty that dialysis with **Theranova** MCO membrane removes approximately 2 g of albumin per 4-hour conventional hemodialysis session, resulting in a transient decreased serum albumin level of 0.12 g/dl over the short term (<24 weeks), which then returned to baseline. It was shown with moderate to high certainty that compared with high-flux membranes, MCO membranes increase middle-molecule clearance of  $\beta_2$  microglobulin,  $\kappa$ -FLC,  $\lambda$ -FLC, and myoglobin—solutes representing the full spectrum of large middle molecular weights. Little to no effect was seen on IL-6 removal or predialysis levels, while IL-6 mRNA expression was reduced by 8.8% in peripheral leukocytes. Medium cut-off dialysis increased the reduction ratio of TNF- $\alpha$  with a moderate reduction in predialysis levels and reduced peripheral leukocyte mRNA expression by 15%.

Taken together, these findings are consistent with the anticipated effects of the MCO membrane, and may account for improved clinical outcomes that have been associated with MCO membranes including reduced symptom burden, recovery time, infection, hospital length of stay, and quality of life.

### Strengths and Limitations

Strengths of this systematic review and meta-analysis comparing MCO with high-flux membranes include adherence to a rigorous registered protocol, a sensitive search strategy, performing study procedures in duplicate, and the use of GRADE methods. The lack of validation of the included biomarkers as surrogate outcomes is a major limitation in this review. Although they are associated with important physiological processes and clinical outcomes, none of the included biomarkers meet regulatory or statistical criteria for surrogacy.

Therefore, despite their familiarity and frequent use in dialysis trials and guidelines, the authors caution against the sole use of biomarkers in clinical or other decision-making. Further limitations of this review include the exclusion of small solutes and lack of direct comparisons with convective therapies.

### Conclusion

Compared with high-flux membranes, MCO dialyzers increase the elimination of large middle molecules, resulting in decreased predialysis solute concentrations of solutes ranging between 11.8 and 45 kDa. Although MCO dialysis did not normalize serum concentrations of these solutes, the net effect of enhanced clearance within the large middle-molecule spectrum could explain the range of beneficial clinical effects reported to date.

**Evidence generated to date supports that HDx therapy with the Theranova MCO membrane increases the clearance of a wide range of large middle molecules and likely reduces inflammatory mediators, with a minimal transient reduction in serum albumin concentration.**



## Medium cut-off membranes—closer to the natural kidney removal function

Zweigart C, Boschetti-de-Fierro A, Hulko M, et al. Medium cut-off membranes—closer to the natural kidney removal function. *Int J Artif Organs*. 2017;40(7):328-334. doi: 10.5301/ijao.5000603.

### BACKGROUND

Renal replacement therapy uses dialysis membranes that have improved over the decades. Cellulose membranes have been largely replaced by more biocompatible synthetic polymeric membranes. Newer membranes more efficiently remove different sizes of uremic toxins. Membranes with larger pore size have been developed to filter higher-molecular weight substances, although these high cut-off (HCO) membranes unfortunately allow the loss of essential plasma proteins such as albumin.

### SUMMARY

#### Dialysis membranes with different permeabilities have been developed

Hemodialysis (HD) is a process whereby blood is removed from the patient, passed through a dialyzer membrane, then returned to the patient's blood stream. From the 1940s through the 1970s, cellulose membranes were used. Cellulose membranes had several medical disadvantages: they could activate the complement system and induce adverse biological reactions (e.g., leucopenia), inhibit granulocyte metabolism, and release enzymes from granulocytes and monocytes. To mitigate these drawbacks of cellulose membranes, the cellulose' hydroxyl groups were modified in one of the following ways: acetylation (yielding cellulose acetate, diacetate, or triacetate membranes) or substitution using diethylamino groups or benzyl groups. Additionally, surface coating of the membrane with polyethylene glycol (PEG), polyacrylonitrile (PAN-REC) or vitamin E may improve biocompatibility.

Regardless of modifications, cellulose dialyzers are "low-flux" membranes, meaning that they have low permeability to solutes, and they function through diffusion alone rather than convection. As a result, small toxins (up to 5000 Da) may be eliminated, but larger ones (like  $\beta$ 2-microglobulin) are not. For hemofiltration (HF) and hemodiafiltration (HDF), membranes with higher permeability are required, so synthetic polymeric membranes were developed.

Synthetic polymeric membranes are generally hydrophobic (mainly polysulfone or polyethersulfone) or hydrophobic/hydrophilic polymer blends that are considered high flux. High-flux membranes are permeable to  $\beta$ 2-microglobulin and allow passage of "middle molecules" (i.e., up to 20,000 Da) but still prevent significant protein loss; these may be used for HD, HF, HDF.

Additionally, high cut-off (HCO) membranes have been developed for use in specific clinical conditions. These have pore sizes that allow permeability of substances >15,000 Da, including inflammatory cytokines and light chains of immunoglobulins. While these may be used to treat patients with sepsis, severe inflammation, or multiple myeloma, albumin loss may reach 9 to 23 g per treatment, so these membranes are used only for acute applications, not chronic care. Clearing protein-bound uremic toxins without removing excessive amounts of protein has been an unmet need.

The newest generation of highly selective and permeable medium cut-off (MCO) membranes aims to meet this need by removing substances up to 45,000 Da while providing low albumin loss. These membranes offer improved clearance of uremic toxins in the 15,000 to 45,000 Da range as compared with older high-flux membranes used in HD. They may be equivalent to older high-flux membranes set in HDF mode.

#### Different dialysis therapies may affect uremic toxin removal

In patients receiving HD maintenance therapy for endstage kidney disease, insufficient removal of mid-sized and protein-bound uremic toxins has been associated with endothelial injury and chronic inflammation, which contribute to cardiovascular disease, coordination disturbances, or polyneuritis. Uremic toxins are generally considered in three groups, as shown in Table 1: small water-soluble compounds, middle molecules, and protein-bound solutes. Numerous toxins exist; select examples are shown in Table 1.

TABLE 1. Examples of uremic solutes and their molecular weights

Molecule	Molecular Weight	Examples
Small water-soluble compounds	<500 Da	asymmetric dimethylarginine, guanidine, uric acid, oxalate, ethylamine, methylguanidine, neopterin, phenylacetic acid
Middle molecules	>500 Da	$\beta$ 2-microglobulin, adiponectin, $\alpha$ 1-acid glycoprotein, cystatin C, prolactin, osteocalcin, vascular endothelial growth factor
Protein-bound solutes	Variable	p-cresylsulfate, indoxyl sulfate, phenol, indol-3-acetic acid, hippuric acid, homocysteine, carboxymethyllysine, acrolein

Table adapted from Zweigart et al.

Small water-soluble compounds may be easily removed, even across a diffusive membrane using conventional HD. As molecular size and weight increase, however, the diffusion coefficient decreases, which is why middle molecules such as  $\beta$ 2-microglobulin are not easily removed with HD, even when high-flux membranes are used.

In contrast to diffusion methods, convective transport mechanisms are driven by a pressure gradient across the membrane, which leads to ultrafiltration (UF), in which molecules are pulled from the dialysate. Increased UF leads to increased removal of both low- and middle-molecular weight solutes. Treatments such as HF and HDF include convective transport mechanisms and are thus associated with increased removal of low- and middle-molecular weight solutes. Note that the UF rate is limited by the blood flow rate; only 25% to 30% of



the total volume may be filtered before blood cell concentrations may cause cellular damage and dialyzer clotting.

Online HDF post-dilution is generally considered the safest and most effective dialysis treatment because of its superior removal of uremic toxins and because it is associated with a lower incidence of cardiovascular events. Set up for online HDF is complex, and high exchange volume rates (up to 24L/treatment) are required. Automation optimizes the filtration fraction but convection volume is still determined by blood flow rate and treatment time. HDF removes more protein-bound uremic solutes than other dialysis methods. Compared to non-protein-bound solutes of similar weight, however, protein-bound solutes are not removed as efficiently; total removal of protein-bound toxins by HDF depends on how rapidly the toxins may be freed from their protein carrier.

To enhance removal of some protein-bound toxins, adsorptive treatments have been developed, but adsorption of protein-bound toxins is ultimately associated with loss of blood proteins. Protein-leaking membranes for HD offer greater clearance of protein-bound toxins than conventional high-flux membranes, but some albumin loss still occurs.

### Limits of albumin removal are unclear

Low serum albumin is associated with mortality in patients with end-stage renal disease (ESRD). Conventional high-flux membranes are associated with a loss of 0 to 2 g albumin per 4-hour treatment. Albumin loss varies with treatment modality, though, and with treatment parameters. The amount of albumin lost with online HDF treatments varies with dilution mode, degree of flux across a membrane, type of membrane, and other treatment parameters. Reuse of dialyzers after bleaching results in excessive protein removal levels (10 to 12 g), though an albumin removal rate of 4.3 g/session has been reported when bleach reprocessing was limited. Typical albumin loss per online HDF treatment is 1 to 4 g, but it can be > 5 g in some instances. It is unclear how much albumin loss is tolerated in ESRD patients. A summary of middle molecule results across studies is shown in Table 2.

### Dialysis membranes with different permeabilities have been developed

Higher-molecular weight uremic toxins are associated with dialysis comorbidities including chronic inflammation and related cardiovascular disease, immune dysfunction, anemia, and EPO hyper responsiveness. As discussed, HCO membranes remove more of these toxins than high-flux membranes, but also remove more essential proteins, which is why MCO membranes are needed.

For new-generation MCO membranes, manufacturers optimize polymers, spinning, and dialyzer production to make safer, improved products. Improvements such as fiber undulation, high package density, improved flow distribution of dialysate fluid, and decreased fiber diameter have improved dialyzer performance. Removing middle-molecular weight toxins while retaining blood proteins requires an extremely narrow pore-size distribution in the dialysis membrane that can only be made using newer, well-controlled spinning technology. Ideally, MCO membrane properties are intended to be closer to those of the natural kidney than are existing dialyzers.

Table 2 describes the basic categories of membranes described by Boschetti-de-Fierro and colleagues in comparison with MCO membranes. In terms of sieving coefficients, MCO membranes resemble HCO and protein-leaking membranes in their ability to capture  $\beta$ 2-microglobulin but they resemble low-flux and high-flux membranes in terms of protein retention.

**TABLE 2.** General classifications and typical performance of membranes used in dialysis

Dialyzer type	Water permeability <sup>a</sup> (mL/(m <sup>2</sup> *h*mmHg))	Examples	Albumin
Low-flux	10-20	—	<0.01
High-flux	200-400	0.7-0.8	<0.01
Protein-leaking	50-500	0.9-1.0	0.02-0.03
High cut-off	1100	1.0	0.2
Medium cut-off	600-850	1.0	0.008

<sup>a</sup>with 0.9% wt.-% sodium chloride at 37°C  $\pm$  1°C and QB 100-500 mL/min.

<sup>b</sup>according to EN1283. **Adapted from Zweigart et al.**

In vitro data support the use of MCO membranes in conventional treatment schedules and treatment modes, such as 4-hour treatments thrice weekly.

At the time of this review, two clinical trials had compared MCO dialyzers with the recent generation of high-flux dialyzers. In the first trial, two centers in Austria compared three prototype MCO dialyzers (called MCO AA, BB, CC) with the high-flux dialyzer FX CorDiox 80 in 19 patients with ESRD. The primary outcome measure was clearance of  $\lambda$ -free light chains ( $\lambda$ -FLCs) with a molecular weight of ~45,000 Da. Secondary outcomes included removal of other medium-sized solutes ( $\kappa$ -Ig free light chains,  $\alpha$ 1- and  $\beta$ 2-microglobulins, complement factor D) and small solutes. All three prototypes achieved significantly higher clearances of  $\lambda$ -FLCs than did the high-flux membrane (MCO AA, 8.5  $\pm$  0.54; BB, 11.3  $\pm$  0.51; CC, 15.0  $\pm$  0.53 vs. FX CorDiox 80, 3.6  $\pm$  0.51 mL/min). The removal of other medium-sized solutes was significantly greater with MCO membranes (including  $\kappa$ -FLC). The total mass of albumin removed was moderate with MCO (medians [range]: MCO AA, 2.9 g [1.5 – 3.9]; BB, 4.8 g [2.2 – 6.7]; CC, 7.3 g [1.9 – 9.7] vs. FX CorDiox, < 0.3 g [ $<$  0.3 –  $<$  0.3]).

In the second study from Germany, 2 MCO prototype dialyzers (called MCO AA and BB), used in HD mode were compared to two high-flux dialyzers (FX CorDiox 80 and FX CorDiox 800) used in HD and high-volume HDF modes (post-dilution volume-controlled mode with a target convective UF volume of  $\geq$ 23 L). The primary outcome measure was overall clearance of  $\lambda$ -FLC. There was greater overall clearance of  $\lambda$ -FLC by both of the MCO dialyzers in HD mode than by either of the high-flux dialyzers (least squares mean (standard error)): MCO AA, 10.0 (0.57); MCO BB, 12.5 (0.57); vs. high-flux HD 4.4 (0.57) and HDF 6.2 (0.58) mL/min). The clearances of  $\alpha$ 1-microglobulin, complement factor D,  $\kappa$ -FLC, and myoglobin were generally greater for MCO than for high-flux HD and similar or greater than in HDF treatments, whereas the albumin removal was moderate with MCO but greater than that of high-flux HD and HDF (medians [range]: MCO AA, 3.2 g [1.9 – 3.9]; MCO BB, 4.9 g [1.1 – 7.2] vs. FX CorDiox 80, 0.2 g [0.2 – 0.9]; FX CorDiox 800, 0.4 g [0.3-0.8]).

These studies indicate that MCO membranes effectively remove a wide range of middle molecules, substantially better than high-flux HD or even HDF, with moderate removal of albumin. Albumin removal in these studies is similar to what has been reported in the HDF literature. Thus, use of MCO in routine HD mode would be expected to be safe.





## CONCLUSIONS

According to this editorial review, the newest generation of highly selective and permeable MCO membranes:

- Provide efficient removal of large middle-molecules (up to 45,000 Da) while providing moderate or low removal of albumin
- Offer improved clearance of 15,000 to 45,000 Da size molecules compared with high-flux membranes used in HD mode
- Offer equivalent clearance of middle molecules compared with high-flux membranes in high-volume HDF mode
- May potentially offer similar benefits as high-volume HDF without the need for high volumes of fluid and the vascular access required for high blood flow rates
- Offer a simpler means of achieving high-removal therapy for ESRD patients
- Have potential to achieve HDF benefits using the regular HD setup with lesser volume of high-quality fluid






The newer MCO membranes have the potential to raise the standard of care for chronic HD patients, potentially decrease inflammatory responses, and generally improve patient outcomes.

# HDx: A WORLD OF DIFFERENCE

## Performance of HDx: combination of diffusion and convection inside a hollow fiber dialyzer to achieve LMM removal

HDx targets the efficient removal of large-middle molecules, many of which have been linked to the development of inflammation, cardiovascular disease, and other co-morbidities in dialysis patients<sup>1,2</sup>, while maintaining stable serum albumin levels over the long term.<sup>3,4</sup>



-  **Kirsch AH, Lyko R, Nilsson LG, et al.**  
**Performance of Hemodialysis with Novel Medium Cut-Off Dialyzers.** *Nephrol Dial Transplant* 2017;32:165-172.
-  **Krishnasamy R, Hawley CM, Jardine MJ, et al.**  
**A tRIal Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in HemoDialysis Patients (REMOVAL-HD): A Safety Device Study.** *Blood Purif.* 2020;49(4):468-478.
-  **Bunch A, Sanchez R, Nilsson LG, et al.**  
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-  **Weiner DE, Falzon L, Skoufos L, et al.**  
**Efficacy and Safety of Expanded Hemodialysis with the TheraNova 400 Dialyzer: A Randomized Controlled Trial.** *CJASN.* 2020;15(9):1310-1319.
-  **Koball S, Heskamp B, Körtge A, et al.**  
**In Vitro Cytokine Removal: Comparison of Conventional High-Flux Dialyzers and Middle-Cut-Off Dialyzer (TheraNova HDx).** ASN Abstract FR-PO465.

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## 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 (MCO) 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 (HCO) 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 Baxter International Inc.) 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). Membranes MCO AA, BB and CC were polyarylethersulfone-PVP blend membrane polymer; Fx CorDiax 80 and Fx CorDiax 800 were polysulfone-PVP blend membrane polymer.

Study 1 compared MCO AA (**Theranova** 400), BB, and CC with high-flux dialyzers (FX CorDiax 80), while study 2 compared MCO AA (**Theranova** 400) 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 ( $Q_D$ ) of 500 mL/min and a blood flow ( $Q_B$ ) of  $300 \pm 20$  mL/min, while the dialysis sessions in study 2 were 4-5 hours with a  $Q_B$  of  $400 \pm 50$  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

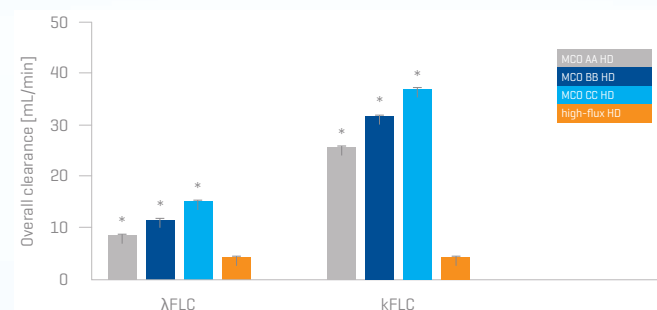
The primary outcome was the overall clearance ( $K_{OVR}$ ) of λFLC using MCO dialyzer prototypes in HD mode vs.  $K_{OVR}$  using high-flux dialyzers used in HD and HDF. Secondary outcomes were the clearance of other middle molecules and small molecules, as well as safety (albumin removal and treatment tolerance) of MCO 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 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 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, medium cut-off dialyzer; HD, hemodialysis. Adapted from Kirsch et al.

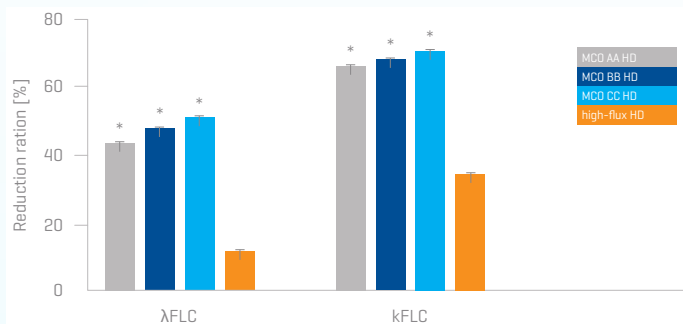


Test Dialyzer	$\lambda$ FLC $K_{ovr}$ Overall Clearance		KFLC $K_{ovr}$ Overall Clearance	
	Least square mean mL/mn (standard error)	P value vs high-flux HD	Least square mean mL/mn (standard error)	P value vs high-flux HD
MCO AA HD	8.5 (0.54)	P<0.001	26.2 (1.24)	P<0.001
MCO BB HD	11.3 (0.51)	P<0.001	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, medium cut-off dialyzer; HD, hemodialysis. Adapted from Kirsch et al.

#### Reduction Ratios

The  $\lambda$ FLC reduction ratios (RRs) and  $\kappa$ FLC RRs of MCO 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, medium cut-off dialyzer; HD, hemodialysis. Adapted from Kirsch et al.

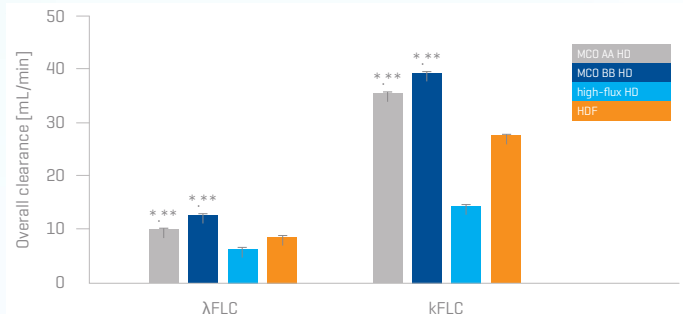
Test Dialyzer	$\lambda$ FLC $K_{ovr}$ Reduction Ratio		KFLC $K_{ovr}$ Reduction Ratio	
	% (standard error %)	P value vs high-flux HD	% (standard error %)	P value vs high-flux HD
MCO AA HD	42.5 (2.06)	P<0.001	66.3 (1.85)	P<0.001
MCO BB HD	47.6 (2.06)	P<0.001	68.4 (1.85)	P<0.001
MCO CC HD	51.5 (2.10)	P<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, 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  $\lambda$ FLC  $K_{ovr}$  and  $\kappa$ FLC  $K_{ovr}$  during HD were again significantly greater (p < 0.001) when using MCO AA or BB compared to high flux HD (see Figure 2A). The  $\lambda$ FLC  $K_{ovr}$  and



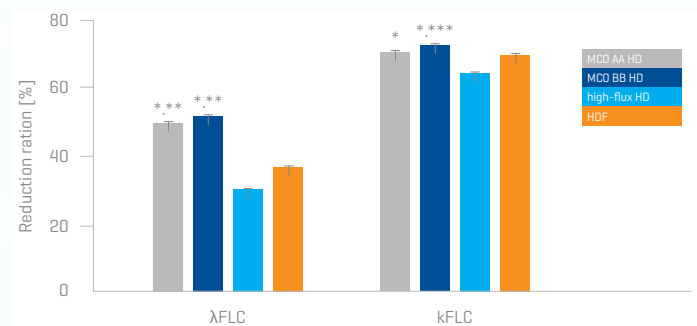
**FIGURE 2A. Overall Clearance.** Free immunoglobulin light chain removal during hemodialysis with medium cut-off dialyzers and high-flux dialyzer and hemodiafiltration in study 2. Data are least square mean + standard error. \*p < 0.001 compared to high-flux HD; \*\*p < 0.001 compared to HDF. Abbreviations: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

Test Dialyzer	$\lambda$ FLC $K_{ovr}$ Overall Clearance		KFLC $K_{ovr}$ Overall Clearance	
	Least square mean mL/mn (standard error)	P value vs HDF	Least square mean mL/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, medium cut-off dialyzer; HDF, hemodiafiltration. Adapted from Kirsch et al.

#### Reduction Ratios

The  $\lambda$ FLC reduction ratios (RR) with MCO AA and BB were superior to that with HDF (p < 0.001). There was no difference between  $\kappa$ FLC RR achieved with MCO AA vs HDF (p=0.3); whereas MCO BB resulted in a statistically significantly higher  $\kappa$ FLC 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 = 0.01, compared to HDF. Abbreviations: FLC, free light chain; MCO, medium cut-off dialyzer; HD, hemodialysis; HDF, hemodiafiltration. Adapted from Kirsch et al.

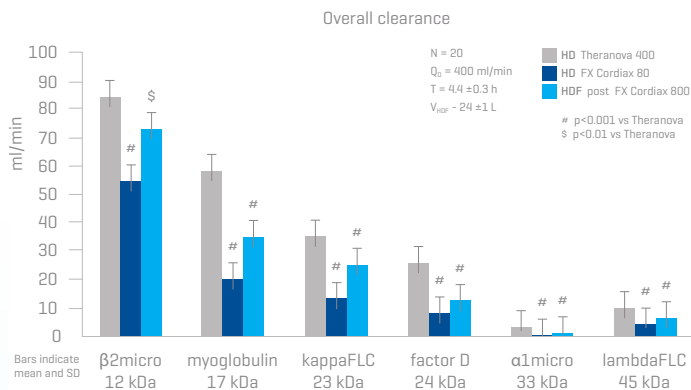
Test Dialyzer	$\lambda$ FLC $K_{ovr}$ Reduction Ratio		KFLC $K_{ovr}$ Reduction Ratio	
	% (standard error %)	P value vs HDF	% (standard error %)	P value vs HDF
MCO AA HD	48.1 (1.72)	P<0.001	72.9 (1.35)	P=0.3
MCO BB HD	52.7 (1.72)	P<0.001	74.8 (1.35)	P=0.01
HDF	37.9 (1.76)		71.6 (1.37)	

**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, medium cut-off dialyzer; HD, hemodialysis; HDF, hemodiafiltration. Adapted from Kirsch et al.

#### Removal of other middle molecules during HD and HDF

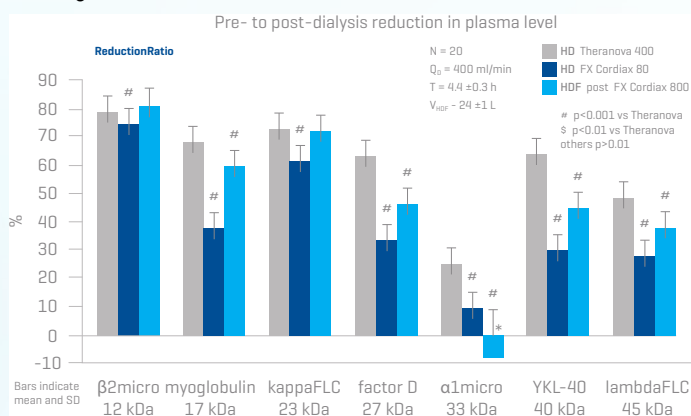
In addition to  $\kappa$ FLC and  $\lambda$ FLC, removal of other larger-sized solutes was greater with MCO HD (MCO AA/Theranova 400) compared to high-flux HD (FX CorDiax 80) and high-volume HDF (FX CorDiax 800). The overall clearance for  $\alpha$ 1-microglobulin (33 kDa), complement factor D (CFD) (24 kDa), myoglobin (17 kDa) and  $\beta$ 2-microglobulin (12 kDa) as well as  $\lambda$ FLC (45 kDa) and  $\kappa$ FLC (23 kDa) were significantly greater for MCO AA HD than HD and HDF (p < 0.001). The exception was the difference for  $\beta$ -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 AA HD (**Theranova** 400) 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 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 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 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)<sup>1</sup>. In both studies, MCO dialyzers resulted in larger albumin removal than high-flux HD and HDF. 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 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 (HCO) 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, 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<sub>ovr</sub> 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 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 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 specifications. Importantly, MCO HD/**Theranova** can be applied to maintenance HD patients, in whom high volume HDF may not be used or is not available.

**MCO (Theranova) membrane provides superior removal of conventional/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.



# A tRial Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in Hemodialysis Patients (REMOVAL-HD): A Safety Device Study

Krishnasamy R, Hawley CM, Jardein MJ, et al. A trial evaluating mid out-off value membrane clearance of albumin and light chains in hemodialysis patients (REMOVAL-HD): a safety device study. *Blood Purif.* 2020; 1-11. doi: 10.1159/000505567.

## BACKGROUND

Patients with end-stage kidney disease (ESKD) are often burdened with a myriad of complications including cardiovascular disease, infection, and malnutrition resulting in high rates of hospitalization, reduced quality of life and increased risk of death. Retention of uremic toxins, especially middle molecules that are not well cleared by current dialysis therapies, may contribute to the disease burden in the ESKD cohort.

The clearance of middle molecules has continued to improve with the evolution of dialysis technology over the last 20 years. With the advent of high-flux dialyzers and hemodiafiltration (HDF), the efficiency of middle molecule clearance by chronic hemodialysis (HD) has continually increased; however, the clearance of almost a third of the larger middle molecules (>25kDa) is yet to be optimized. Pore sizes of dialysis membranes are crucial in determining the clearance of larger middle molecules. However, membranes with larger pore sizes such as the high cut-off dialyzer (HCO) were associated with substantial albumin loss (molecular weight (MW) (65kDa<sup>1</sup>), requiring albumin supplementation following dialysis treatment. This resulted in the view that HCO membranes were unsafe and impractical for maintenance HD.

Advancements have led to the development of a new class of dialysis membranes called the mid cut-off (MCO) dialyzer. This membrane has a pore size between that of a standard high flux and an HCO membrane with narrowly distributed pores to enhance membrane permeability and selectivity. However, the safety and efficiency data for the MCO dialyzer in a clinical setting are limited.

## OBJECTIVE

The primary aim of a tRial Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in Hemodialysis Patients (REMOVAL-HD) study the was to determine the safety of HD using a MCO dialyzer (**Theranova**; Baxter Healthcare, Sydney, Australia) with regard to its effect on change in serum albumin over 6 months in a prevalent HD cohort.

## METHODOLOGY

The study was an investigator initiated, open label, non-randomized, cross over, longitudinal device study conducted across 9 centers in Australia and New Zealand (n=89). Recruitment commenced in January 2017 and the last participant follow-up occurred in April 2018. The criteria for inclusion included >18 years of age, had been on chronic in-center HD for at least 12 weeks.

All visits occurred during participants' mid-week HD session. See Figure 1. Study schema was as follows:

- **Wash-in period (week 0-4)**  
Participants used a 4-week HD wash-in period using a high flux dialyzer (**Revaclear** R400; Baxter Healthcare, Sydney, Australia).
- **Intervention period (week 4-28)**  
Participants then received 24 weeks of treatment with the investigational device, the MCO dialyzer (**Theranova** 400; Baxter Healthcare, Sydney, Australia).
- **Wash-out period (week 28-32)**  
Participants then received a 4-week wash-out period using the **Revaclear** high flux dialyzer again.

Centers were advised to maintain the duration (3.0-5.5 hours/session) and frequency of dialysis (3x/week), target blood flow (> 300 mL/minute) and dialysate flow rate (DFR) (500 mL/minute) throughout the study period.

## Outcome Measures

### Primary Outcomes

The primary outcome was change in centrally measured pre-dialysis serum albumin between baseline (week 4) and 6 months (week 28) during the treatment phase of HD with the MCO dialyzer. Other safety outcomes included change in serum albumin across all study visits during the treatment phase monitoring of any large (> 25%) reductions in serum albumin level at every visit. In addition, serious adverse events (SAE) were recorded regardless of whether they were related to the study intervention using standard criteria for clinical trials.

## Study Procedures

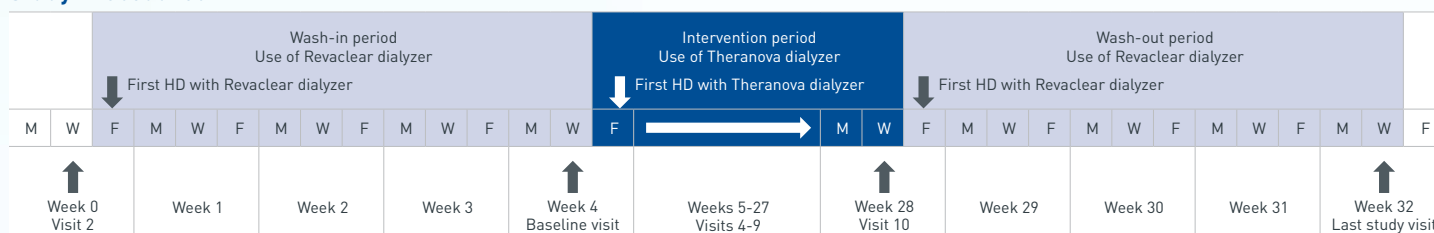


FIGURE 1. REMOVAL-HD study schema. Adapted from Krishnasamy et al. Abbreviations: HD, hemodialysis.



## Secondary Outcomes

Secondary outcomes included change in pre-dialysis serum level of middle molecules (lambda-free light chains [FLC] (45 kDa), kappa-FLC (22.5 kDa) and  $\beta$ 2-microglobulin (11.8 kDa)).

## RESULTS

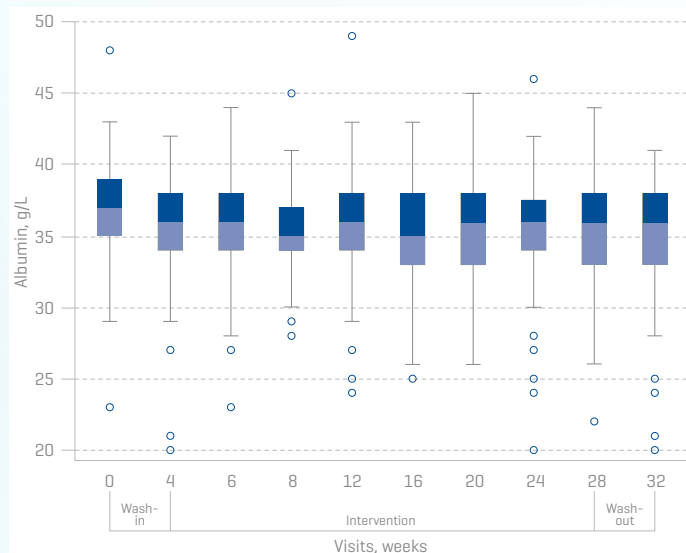
Eighty-nine (89) participants started the MCO HD intervention and provided analyzable data and 87 were sufficiently compliant with the intervention (at least 80% use of MCO dialyzer) to be included in the main analysis of the primary outcome.

### Serum Albumin

Serum albumin 65 kDa<sup>1</sup> levels were stable over 6 months and the overall albumin concentration decline was minimal at 0.7 g/L. See Table 1. In addition, an immediate decline in serum albumin following commencement of the MCO dialyzer was not seen. See Figure 2. A sustained, unexplained reduction in serum albumin of >25% for 2 consecutive visits was not observed in any participant.

Timing	Measurement of Serum Albumin (n=87)	p value
Baseline (Week 4)	35.8 $\pm$ 3.9 g/L	
6 Months (Week 28)	35.1 $\pm$ 4.0 g/L	
Reduction (6 Months-Baseline)	-0.7 g/L (95% CI -1.5 to 0.1)	0.1

**TABLE 1. Measurement of serum albumin and reduction.** Adapted from Krishnasamy, et al. Abbreviations: CI, confidence interval.



**FIGURE 2. Measurement of serum albumin and reduction.** Adapted from Krishnasamy, et al. Abbreviations: CI, confidence interval.

### Middle Molecules

A reduction in FLC was observed 2 weeks into MCO HD (see Table 2), which plateaued and remained unchanged throughout the intervention period. However, levels of both FLC significantly increased following cessation of HD with the MCO dialyzer during the wash-out of high-flux HD phase. (see Table 2). The rebound supports the hypothesis that this dialyzer can result in sustained reduction in middle molecules. The ability to provide sustained removal of large middle molecules such as lambda FLC (45 kDa) suggests that MCO HD is a promising therapy to enhance removal of other large middle molecules such as soluble tumor necrosis factor receptor-1 (27-30 kDa<sup>1</sup>), fibroblast growth factor-23 (32 kDa<sup>1</sup>), advanced glycosylated end products (<1-70 kDa<sup>1</sup>) that are not cleared by current conventional HD therapies, but are strongly implicated in chronic inflammation and accelerated cardiovascular disease in patients with ESKD.

	Average change from week 4-6 (95% CI)	p value	Average change from week 28-32 (95% CI)	p value
Lambda-FLC, mg/L	-9.1 [-14.4 to -3.7]	0.001	7.9 [0.8 to 14.9]	0.03
Kappa-FLC, mg/L	-5.7 [-9.8 to -1.6]	0.007	8.2 [1.3 to 15.1]	0.02

**TABLE 2. Change in lamda- and kappa-FLC following the initial exposure (week 4-6) and cessation of MCO dialyzer (week 28-32) respectively.** Adapted from Krishnasamy et. al. Abbreviations: CI, confidence interval; FLC, free light chains.

No significant change in  $\beta$ -2 microglobulin was observed for the duration of treatment with MCO dialyzer. As standard high-flux HD and HDF provide excellent clearance of  $\beta$ -2 microglobulin, it is not surprising that this study did not find a change in the levels of  $\beta$ -2 microglobulin following conversion to the MCO HD from standard dialysis treatments.

### Adverse Events

There were no reported SAE's related to the MCO dialyzer for the entire duration of the study.

### Study Limitations

The major limitation of the study was the single-arm design. In addition, post-dialysis serum and dialysate concentrations of albumin and middle molecules were not performed and may have provided more in-depth evidence especially regarding the efficacy of this membrane. Participant-level information on the type of dialysate including citrate-based dialysis buffer that may have an impact on middle molecule removal was not collected during the study period. By design, this study excluded major factors that may impact serum albumin measurements and confound the primary outcome in order to assess the independent effect of MCO dialyzer on serum albumin.

## CONCLUSIONS

REMOVAL-HD demonstrated that regular use of MCO dialyzer for 6 months in chronic HD patients was safe and did not result in a significant fall in serum albumin. This study's results support the hypothesis that albumin loss will not be a limitation of the future application of the MCO dialyzer in chronic HD. In addition, the significant rebound of FLC levels following cessation of HD with the MCO dialyzer supports the hypothesis that this dialyzer can result in sustained reduction in middle molecules (up to 45 kDa) and represents a promising therapy to enhance removal of other large middle molecules.

**REMOVAL-HD study demonstrated MCO (Theranova) dialyzer's effective removal of middle molecules up to 45 kDa, such as lambda-FLC, while maintaining stable serum albumin levels, with only 0.7g/L decline in overall serum concentrations.**

**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.



# Medium Cut-Off Dialyzers in a Large Population of Hemodialysis Patients in Colombia: COREXH Registry

**Bunch A, Sanchez R, Nilsson LG, et al.** Medium cut-off dialyzers in a large population of hemodialysis patients in Colombia: COREXH Registry. *Ther Apher Dial.* 2020; 1-11. [doi: 10.1111/1744-9987.13506](https://doi.org/10.1111/1744-9987.13506).

## BACKGROUND

Recent advances in technology have introduced expanded hemodialysis (HDx) utilizing medium cut off (MCO) membranes with high retention onset membranes. MCO membranes easily clear conventional and large middle molecules with acceptable levels of albumin removal (2-4 g/session), which maintains serum albumin levels within the normal range.

Middle molecules, which accumulate during hemodialysis (HD) are considered to be inflammatory mediators. Inflammation also contributes to decreased serum albumin levels. Importantly, a lower serum albumin level is associated with increased mortality. The higher mortality rate associated with low serum albumin levels has been reported to be dependent on inflammation as assessed by high sensitivity C-reactive protein (hsCRP) levels.

**Renal Therapy Services (RTS)** is a nationwide provider in Colombia partially owned by Baxter that serves over 9000 patients who are undergoing HD or peritoneal dialysis. RTS dialysis units provide HD to over 5500 patients, accounting for approximately 29% of patients receiving HD in Colombia.

There is a paucity of longitudinal data regarding the clinical outcomes and safety of MCO membranes, especially in the current practice setting.

## OBJECTIVE

To describe the outcomes and trends in serum albumin levels among a large cohort of patients switched from conventional high-flux HD to HDx utilizing an MCO membrane and document the long-term safety.

## METHODOLOGY

Expanded Hemodialysis Registry Protocol in Colombia (COREXH) is a prospective, observational, multicenter cohort study of patients undergoing HDx in Colombia. Between September 4, 2017 to November 30, 2017 prevalent HD patients (receiving HD therapy for at least 90 days at an RTS renal clinic) were invited to participate in the registry. Patients were required to be at least 18 years of age and receiving HDx for a minimum of 4 hours, 3 times per week using an MCO membrane (Theranova, Baxter, Deerfield, IL). Patients with life expectancy less than 6 months or those with an active infection diagnosed within the previous 4 weeks were not invited to participate. Baseline data were obtained of the last seven days before switching to HDx and represent the initial state of the patient's health, serum albumin levels, and other laboratory parameters. Patients were prospectively followed for one year from enrollment into the registry.

## RESULTS

### Patients

One thousand (1000) patients at 12 clinics across Colombia were invited to participate. A total of 992 patients met the participation criteria and were included in the intention to treat (ITT) group. The majority (62%) of the patients were men, and at enrollment the mean age was 60 years. Over 90% of the patients had a history of hypertension and nearly 50% had a history of diabetes. Two-thirds (67%) of patients had chronic kidney disease (CKD) attributed to hypertension (28%) or diabetes (39%). A total of 638 patients were eligible for the 1-year follow up assessment.

### Albumin Levels

The cumulative change in serum albumin levels in the ITT population during the follow-up was -1.8%. See Table 1. A total of 468 patients in the per protocol (PP) population had all six serum albumin measurements taken during HDx. The changes in serum albumin levels was less pronounced, with an accumulated change of -1.2%. See Table 2.

While a slight decrease in albumin over 12 months of observation was statistically significant in the large cohort study, this should be considered clinically insignificant. At all times, the observed variability of serum levels was within 5% from baseline and the mean serum albumin concentration remained within the normal ranges (3.5-5.5 g/dL).

Follow-up	n	Marginal mean* (g/dL)	Change from baseline (%)	Change from previous <sup>b</sup> (%)	Cumulative change(%)
Baseline	992	4.05 [4.04-4.07]	–	–	–
15 days	938	3.98 [3.97-4.00]	-1.7	-1.7	-1.7
1 month	951	4.00 [3.98-4.01]	-1.2	0.3	-1.4
3 months	883	3.91 [3.90-3.93]	-3.5	-2.0	-3.5
6 months	728	3.94 [3.92-3.96]	-2.7	0.7	-2.8
9 months	735	3.94 [3.92-3.96]	-2.7	0	-2.8
12 months	587	3.98 [3.96-4.00]	-1.7	1.0	-1.8

**TABLE 1.** Change in serum albumin levels over time (ITT population). Abbreviation: ITT, intention to treat. \*Marginal mean is the means estimation based on the fitted model in repeated measures and are presented as 95% confidence interval. <sup>b</sup>The percentual change from the last measurement value Table adapted from Bunch, et al.





Follow-up	n	Marginal mean <sup>a</sup> (g/dL)	Change from baseline (%)	Change from previous <sup>c</sup> (%)	Cumulative change(%)
Baseline	468	4.03 [4.01-4.05]	–	–	–
15 days	468	4.00 [3.98-4.02]	-0.9	-0.9	-0.9
1 month	468	3.98 [3.96-4.00]	-1.3	-0.4	-1.3
3 months	468	3.93 [3.91-3.95]	-2.7	-1.4	-2.7
6 months	468	3.95 [3.93-3.97]	-2.0	0.7	-2.0
9 months	468	3.96 [3.94-3.98]	-1.9	0.0	-2.0
12 months	468	3.99 [3.97-4.01]	-1.2	0.8	-1.2

**TABLE 2.** Change of serum albumin levels over time (PPa). Abbreviation: PP, per-protocol defined as patients who received all treatments with the MCO membrane during the follow-up period or until hospitalization that involved >12 dialysis sessions without MCO or death. <sup>a</sup>Only patients in the PP population who had baseline and all six scheduled serum albumin measurements during HDx were included in the analysis. <sup>b</sup>Marginal mean is the means estimation based on the fitted model in repeated measures and are presented as 95% confidence interval. <sup>c</sup>The percentual change from the last measurement value. Table adapted from Bunch et al.

While a slight decrease in albumin over 12 months of observation was statistically significant in the large cohort study, this should be considered clinically insignificant. At all times, the observed variability of serum levels was within 5% from baseline and the mean serum albumin concentration remained within the normal ranges (3.5-5.5 g/dL).

### Patient Outcomes

Seventy-four (8%) patients died during 866 patient-years (PY) of follow-up; the mortality rate was 8.54 deaths/100 PY (95% confidence interval (CI), 6.8-10.7). There were 673 hospitalization events with a rate of 0.79 events/PY (95% CI, 0.73-0.85) with 6.91 hospital days/PY (95% CI, 6.74-7.09). The observed mortality rate, hospitalization rate, and number of hospital days were lower than previous experiences with the **RTS Network** in Colombia.

### Dialysis Parameters

HDx adequacy, as measured by single-pool Kt/V and serum phosphorus. Single pool Kt/V was 1.68, which is considered a very good level of adequacy for small-molecule reduction and is well above the minimum 1.2 Kt/V per HD session for patients treated 3x weekly, as is recommended by the (US) National Kidney Foundation's Kidney Disease Outcomes Quality Initiative. Serum phosphorus levels remained relatively constant throughout the 12 months, with a mean of 4.55 mg/dL at month 12, which is below the recommended level of 5.5 mg/dL.

### Safety

During the follow-up period, there were 1019 adverse events during 866 person-years of follow-up for a rate of 1.18 adverse events (AE) per PY (95% CI, 1.10-1.25). For comparison, 130,601 sessions were performed with MCO membranes. A total of 667 (66.4%) AEs were serious, and of these, 91 (8.9%) resulted in withdrawal from the study. No AEs during HDx were deemed related to MCO membrane use, according to investigator and techno-surveillance evaluation. AEs numbering 146 were deemed related to the dialytic procedure, which represents 0.17 events per PY (95% CI, 0.14-0.20), equivalent to 1.12 events per 1000 HD sessions (95% CI, 0.90-1.30).

### Strengths and Limitations

Strengths of the present study include the prospective collection of current practice data, an analysis of nearly 1000 patients undergoing HDx, over 130,000 sessions performed, with baseline information and a follow-up for 12 months. Limitations of the study include the absence of a comparison group, which diminishes the strength of adjudging causality to the observed effects. A positive selection bias cannot be excluded, although given the large number of patients and renal clinics involved, it does not appear that the population in this analysis differs much from the general prevalent HD population in the **RTS Network** in Colombia.

### CONCLUSIONS

No adverse events were related to the MCO membrane. HDx using an MCO membrane maintains serum albumin levels within the normal range among patients undergoing expanded hemodialysis with nonoccurrence of dialyzer related adverse effects.

**The MCO (Theranova) membrane is safe and preserves serum albumin levels within the normal range among patients undergoing expanded hemodialysis (HDx).**



# Comparison of Hemodialysis with Medium Cut-Off Dialyzer and On-Line Hemodiafiltration on the Removal of Small and Medium-Sized Molecules

**Belmouaz M, Diolez J, Bauwens M, et al.** Comparison of hemodialysis with medium cut-off dialyzer and on-line hemodiafiltration on the removal of small and medium-sized molecules. *Clin Nephrol.* 2018;1:50-56. [doi: 10.5414/CN109133](https://doi.org/10.5414/CN109133).

## BACKGROUND

Recent data suggest that the use of medium cut-off (MCO) dialyzers in hemodialysis (HD) promotes greater clearance and reduction ratio (RR) for myoglobin (17 kDa) and other large-sized molecules than on-line hemodiafiltration (ol-HDF), but its effects on  $\beta$ 2-microglobulin (11.8 kDa) are not clear.

The association of high serum levels of middle-sized toxins, particularly  $\beta$ 2-microglobulin, with inflammation, immune dysfunction, and patient survival has been established in several studies. The removal of middle-sized toxins such as  $\beta$ 2-microglobulin (11.8 kDa) and myoglobin (17 kDa) depends on both dialyzer permeability and treatment modalities. Ol-HDF, combining the use of a high-flux dialyzer, ultrapure dialysis fluid and extensive convective fluid exchange is currently considered as the new standard for highly efficient renal replacement therapy (RRT), achieving the best extraction of small and middle-sized molecules.

**Theranova** (polyarylethersulfone/polyvinylpyrrolidone, Gambro Dialysatoren GmbH, Hechingen, Germany) is a novel-generation MCO dialyzer designed to remove molecules over 25 kDa. Recent clinical data on the use of MCO dialyzer in HD patients have shown efficient removal of  $\beta$ 2-microglobulin (11.8 kDa), myoglobin (17 kDa), k free light chains (FLC) [22.5 kDa]<sup>1</sup>,  $\lambda$ FLCs [45 kDa]<sup>1</sup> complement factor D [24 kDa]<sup>1</sup>, and  $\alpha$ 1-microglobulin [33kDa]<sup>1</sup>.

## OBJECTIVE

The aim of the study was to compare high-flux ol-HDF with the **Theranova** MCO dialyzer with respect to removal of small (<500 Da) and medium-sized molecules (>500 Da) and nutritional parameters.

## METHODOLOGY

The study was a retrospective analysis of ten stable patients on post-dilution ol-HDF using high-flux dialyzer for at least 6 months. These patients were then switched to HD with the **Theranova**-500™ MCO dialyzer (Gambro Dialysatoren GmbH, Hechingen, Germany) for a 6-month period.

Before switching to MCO-HD, all patients were on ol-HDF using a Polyflux-210H (Gambro Dialysatoren GmbH, Hechingen, Germany) or an Elisio-21H (Nipro Europe, Zaventem, Belgium) dialyzer.

All patients had negligible residual renal function. Pre- and postdialysis serum levels of small molecules (urea [60.055 Da<sup>2</sup>], creatinine [113.12 Da<sup>3</sup>]) and middle-sized molecules ( $\beta$ 2-microglobulin [11.8 kDa] and myoglobin [17 kDa]) measured during the first mid-week session on 2-month intervals, were compared in each patient during treatments with ol-HDF and MCO-HD. A total of 28 sessions for each treatment period were available for analysis.

## Limitations

Limitations of the study included its retrospective design without randomization, small number of analyzed patients, calculation methods without dialysate concentration measures, and the use of slow-flow methods in patients with catheters.

## RESULTS

### Safety

There was no statistical significance for mean number of inter-dialytic hypotensive episodes requiring fluid volume expansion between high-flux ol-HDF and MCO-HD period. There were no clinically relevant adverse events reported with use of MCO-HD.

### Renal Replacement Therapy Characteristics

There was no significant change between the high-flux ol-HDF and the MCO-HD period regarding blood flow rate, ultrafiltration rate, session length, ionic dialysance, or KT/V monitor. See Table 1.

	High-flux ol-HDF	MCO-HD	p
Blood flow rate (mL/min)*	346 ± 27	338 ± 23	.097
Dialysate flow rate (mL/min)	600	500	NA
Ultrafiltration (L)*	1.79 ± 0.66	1.66 ± 0.71	0.58
Session length (min)*	231 ± 6	233 ± 7	0.52
Ionic dialysance* (mL/min)	217 ± 26	218 ± 30	0.52
KT/V monitor*	1.41 ± 0.2	1.40 ± 0.2	0.165
Convection volume (L)*	2.44 ± 0.238	NA	NA

**TABLE 1. RRT characteristics.** \*Data are expressed as mean ± standard deviation (SD). Abbreviations: RRT: renal replacement therapy; ol-HDF, on-line hemodiafiltration; MCO-HD, medium-cut off hemodialysis; NA, not applicable. Adapted from Belmouaz et al.

### Biological, Nutritional and Inflammatory Parameters

Median serum albumin (65 kDa)<sup>1</sup>, serum prealbumin, normalized protein catabolic rate (nPCR), c-reactive protein (CRP) levels did not change significantly between the high-flux ol-HDF and MCO-HD period. Median serum  $\beta$ 2-microglobulin and myoglobin levels before and after dialysis also did not change significantly between the high-flux ol-HDF and the MCO-HD period. See Table 2.

### Biological, Nutritional and Inflammatory Parameters

Median serum albumin (65 kDa)<sup>1</sup>, serum prealbumin, normalized protein catabolic rate (nPCR), c-reactive protein (CRP) levels did not change significantly between the high-flux ol-HDF and MCO-HD period. Median serum  $\beta$ 2-microglobulin and myoglobin levels before and after dialysis also did not change significantly between the high-flux ol-HDF and the MCO-HD period. See Table 2.



	High-flux ol-HDF	MCO-HD	p
Albumin (g/L)*	37.8 (5)	38 (6.4)	.029
Prealbumin (mg/L)*	0.28 (0.08)	0.26 (0.14)	.025
nPCR*	0.9 (0.3)	1 (0.4)	0.95
CRP (mg/L)*	8 (9.0)	7 (6.5)	0.35
<b>β<sub>2</sub>-microglobulin</b>			
Before*	27.5 (4)	28 (3.0)	0.63
After*	5.6 (1.6)	6.2 (0.9)	0.56
<b>Myoglobin (μg/L)</b>			
Before*	164 (81)	184 (151)	0.67
After*	79 (51)	76 (64)	0.72

**TABLE 2. Biological, nutritional, and inflammatory parameters.** \*Data are expressed as median interquartile rate (IQR). Abbreviations: nPCR, normalized protein catabolic rate; CRP, c-reactive protein; ol-HDF, on-line hemodiafiltration; MCO-HD, medium cut-off hemodialysis. Adapted from Belmouaz et al.

### Small and Middle-Sized Molecule Removal

Similar urea and creatinine reduction ratios (RRs) of 79% and 71% respectively, were found using both techniques. Other parameters of removal of these small molecules (KT/V, eKT/V, and ionic dialysance) were similar during the high-flux ol-HDF and MCO-HD periods (see Table 3) despite a difference in dialysis flow rate (600 mL/min for high-flux ol-HDF vs 500 mL/min. for MCO-HD. See Table 1.

There was no significant difference between the high-flux ol-HDF and MCO-HD for mean β<sub>2</sub>-microglobulin and myoglobin RR, as well as mean β<sub>2</sub>-microglobulin and myoglobin Kd. See Table 3. The similar efficacy of MCO-HD for β<sub>2</sub>-microglobulin and myoglobin RR are probably related to diffusive transfer, supplemented by uncontrolled convection arising from the process of internal filtration and backfiltration.

	High-flux ol-HDF	MCO-HD	p
eKTN*	1.49 ± 0.19	1.52 ± 0.19	0.06
<b>Overall reduction ratio (%)</b>			
Urea*	79 ± 4	79 ± 3	0.09
Creatinine*	71 ± 5	71 ± 3	0.26
β <sub>2</sub> -microglobulin	81 ± 5	81 ± 6	0.72
Myoglobin*	60 ± 9	61 ± 7	0.59
<b>Overall clearances (mL/min)</b>			
β <sub>2</sub> -microglobulin	91 ± 11	84 ± 10	0.24
Myoglobin*	51 ± 10	50 ± 10	0.92

**TABLE 3. Small and middle-sized molecule removal.** \*Data are expressed as mean ± standard deviation (SD). Abbreviations: ol-HDF, on-line hemodiafiltration; MCO-HD, medium-cut off hemodialysis. Adapted from Belmouaz et al.

## CONCLUSION

This study is the first evaluating efficacy and safety of MCO-HD with the new-generation **Theranova**-500 dialyzer in HD over a 6-month period, showing similar removal for small molecules, β<sub>2</sub>-microglobulin and myoglobin when compared to ol-HDF, with good tolerance profile and without modification of nutritional status. In addition, median serum albumin levels did not change significantly between the high-flux ol-HDF and MCO-HD period.

Although the study has several limitations, MCO-HD may provide a useful alternative to high-flux ol-HDF for middle-sized molecule removal. MCO-HD has been suggested to more efficiently remove κ and λFLCs than high-flux HD and HDF, which have little impact on the removal of molecules beyond 30 kDa. However, the efficacy of this strategy compared to online high efficiency ol-HDF remains to be assessed by clinical trial.

**The use of MCO (Theranova) dialyzer produced similar removal of urea, creatinine, β<sub>2</sub>-microglobulin and myoglobin as ol-HDF with good tolerance profile and without modification of nutritional status.**

### 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.
2. <https://biocyc.org/compound?orgid=META&id=UREA> Accessed 6/15/20.
3. <https://biocyc.org/compound?orgid=META&id=CREATININE> Accessed 6/15/20.



# Efficacy and Safety of Expanded Hemodialysis with the TheraNova 400 Dialyzer: A Randomized Controlled Trial

Weiner DE, Falzon L, Skoufos L, et al. Efficacy and safety of expanded hemodialysis with the TheraNova 400 dialyzer: A randomized controlled trial. *CJASN ePress* 2020. [doi:10.2215/CJN.01210120](https://doi.org/10.2215/CJN.01210120).

## BACKGROUND

The loss of kidney function in patients with kidney failure causes accumulation of solutes termed uremic toxins due to their negative impact on patient health. These toxins can be grouped into small molecular weight water-soluble molecules, middle molecules, and protein-bound solutes. While the smaller molecules with a molecular mass < 0.5 kilodaltons (kDa) are effectively removed by dialysis, conventional dialysis has more difficulty in clearing middle molecules ranging from 0.5 to 60 kDa. Middle molecules can be further subdivided into two groups based on their molecular weight: conventional middle molecules of 0.5-25 kDa and larger middle molecules of >25 kDa. The former group includes  $\beta$ 2-microglobulin (11.8 kDa), historically considered the standard representative of a middle molecule, while the latter includes free immunoglobulin light chains including  $\lambda$  free light chains (FLCs) (45 kDa). Larger middle molecules are associated with inflammation, cardiovascular events, and other dialysis-related comorbidities in patients with comorbid cardiovascular disease, mineral and bone disorders, and infectious diseases.

Hemodialysis (HD) removes solutes, including small molecules (< 0.5 kDa) and conventional middle molecules (0.5-25 kDa), primarily by diffusion, with very limited convection. Highly porous membranes, such as those featured in high-flux dialyzers, allow some middle molecules like  $\beta$ 2-microglobulin to pass through the membrane, but these membranes do not readily clear larger solutes. Larger middle molecules (> 25 kDa) need to be removed either by convection or by highly permeable membranes.

The term expanded HD (HDx) has been proposed to define a treatment where diffusion and convection are technically integrated inside a hollow-fiber dialyzer equipped with a medium cut-off membrane, enabling removal of small, conventional middle molecules and large middle molecular uremic toxins. TheraNova provides expanded hemodialysis using a hollow-fiber single-use dialyzer, with improved removal of large proteins > 25 kDa while selectively maintaining essential proteins such as albumin.

Existing data on the performance of medium cut-off dialyzers are based on short-term, non-randomized clinical trials. In contrast, this study was a randomized, longer-term (6 months) study.

## OBJECTIVE

To evaluate the efficacy of HDx with the TheraNova 400 membrane for larger middle molecule removal with acceptable serum albumin loss and safety profile over a 6-month period.

## METHODOLOGY

The multicenter open-label, randomized controlled trial was conducted in 21 centers in the US between September 2017 and October 2018.

## Participants

Patients receiving 3X/week in-center maintenance hemodialysis, ages 22 years and older, who met the following criteria were included in the study:

- Clinically stable without acute medical events in the past 30 days
- Receiving HD with a high-flux dialyzer for at least 3 months prior
- Expected to maintain an acceptable urea clearance (Kt/V) with a dialyzer of an approximate surface area of 1.7 m<sup>2</sup>
- Stable functioning vascular access

Key exclusion criteria included: history of acute infection  $\leq$  4 weeks prior to randomization and patients with chronic liver disease, paraprotein-associated disease, hepatitis, HIV, bleeding disorders, active cancer, monoclonal or polyclonal gammopathy. Patients with known serum  $\kappa/\lambda$  FLC ratio less than 0.37 or greater than 3.1 suggestive of monoclonal plasma diseases were also excluded.

Of 282 patients meeting the inclusion criteria, 172 participants were randomized with 86 in each group.

## Methods

The study was an open-label study without concealment of the dialyzer used; the allocation was concealed to the central laboratory and study sponsor. Patients were randomized to receive treatment with either TheraNova 400 (Baxter Healthcare International) or Elisio-17H (Nipro Corporation). Randomization to TheraNova 400 or Elisio-17H, a similar surface area high-flux dialyzer (1.7 m<sup>2</sup>), was stratified by site with dynamic allocation. Dialysis prescription and management were performed per institutional practice. Monthly microbiological water/dialysate quality testing according to current Centers for Medicare and Medicaid Services regulations for dialysis water and conventional dialysate were required. Hemodialysis treatment duration per session for each individual varied based on clinical requirements determined by the clinician, based on the participants' needs. Medications were administered according to each center's standard practice.

## Outcomes

### Primary Safety and Efficacy Outcomes

The primary safety endpoint was the level of pre-dialysis serum albumin (65 kDa)<sup>1</sup> measured after 24 weeks of treatment, and the primary efficacy endpoint was the removal of  $\lambda$ FLCs (45 kDa) measured at 24 weeks of treatment expressed as a reduction ratio (RR).

### Secondary Safety and Efficacy Outcomes

Secondary safety endpoints were change in serum albumin from baseline at weeks 4 and 8.

Secondary efficacy endpoints included the RRs of  $\lambda$  FLCs at 4 weeks and other middle to large molecules: complement factor D (24 kDa);  $\kappa$  FLC (23 kDa); interleukin 6 (IL-6) (25 kDa); tumor necrosis factor alpha (TNF $\alpha$ ) (17 kDa); and  $\beta$ 2-microglobulin





(11.8 kDa) at 4 weeks and at 24 weeks of treatment. Single pool Kt/V was also assessed.

#### Adverse Outcomes

Adverse events were monitored through study completion.

#### Exploratory Outcomes

Exploratory endpoints consisted of patient reported quality of life using the Kidney Disease Quality of Life (KDQoL-36) instrument and the EuroQol (EQ-5D-5L) instrument as well as inflammation assessment by highly sensitive C-reactive protein (hsCRP).

## RESULTS

### Patient Population

Twenty-one centers participated in this clinical study. Of 282 patients meeting the inclusion criteria, 172 participants were randomized, with 86 in each group. A total of 130 participants completed the study; 65 in the **Theranova** 400 group; 65 in the Elisio-17H group. Sensitivity analyses via multiple imputation and last observation carried forward for participants who did not complete the study demonstrated similar results to participants who completed the study.

### Safety Outcomes

#### Primary Safety Outcome

At baseline, the mean pre-dialysis level of serum albumin in the **Theranova** 400 group ( $4.0 \pm 0.3$  g/dL) was comparable to the Elisio-17H group ( $4.0 \pm 0.3$  g/dL). Likewise, after 24 weeks of treatment, the mean pre-dialysis serum albumin level was  $4.0 \pm 0.3$  g/dL in the **Theranova** 400 group and  $4.1 \pm 0.4$  g/dL in the Elisio-17H group, demonstrating non-inferiority of **Theranova** 400\* in maintaining serum albumin levels. See Table 1.

Parameter	Dialyzer	n	Mean (SD)	Median	Min, Max	Two-Sided 95% Confidence Interval*
Pre-dialysis serum albumin after 24 weeks (g/dL)	Theranova 400	64	4.0 [0.3]	4.0	3.5, 4.7	-0.12 to 0.05
	Control	65	4.1 [0.4]	4.0	3.2, 4.9	

**TABLE 1.** Primary Safety Outcome: Pre-dialysis Serum Albumin Assessment after 24 Weeks. Abbreviations: SD: standard deviation. Table adapted from Weiner et al. \*If the lower bound of the two-sided 95% confidence interval around the mean estimated treatment difference between **Theranova** 400 and the control is  $> -0.1765$  then non-inferiority can be claimed. If the lower bound of the two-sided 95% confidence interval is  $> 0$ , then superiority may be concluded.

#### Secondary Safety Outcomes

The change in serum albumin from baseline was significantly different between the two groups only after weeks 4 and 8. After week 4, the mean level was  $4.0 \pm 0.3$  g/dL with a  $-0.1 \pm 0.2$  mean change from baseline in the **Theranova** 400 group, whereas in the Elisio-17H group, the mean level was  $4.0 \pm 0.3$  with a  $0.0 \pm 0.2$  mean change from baseline ( $p=0.03$ ). After week 8, the mean level was  $3.9 \pm 0.3$  g/dL with a  $-0.1 \pm 0.3$  mean change from baseline in the **Theranova** 400 group, whereas in the Elisio-17H group, the mean level was  $4.0 \pm 0.3$  g/dL with a  $0.0 \pm 0.2$  mean

change from baseline ( $p=0.004$ ). Although the differences in change from baseline between the two groups after weeks 4 and 8 were statistically significant, the observed changes were well below 5%, and the mean levels were still within normal lab ranges. See Table 2.

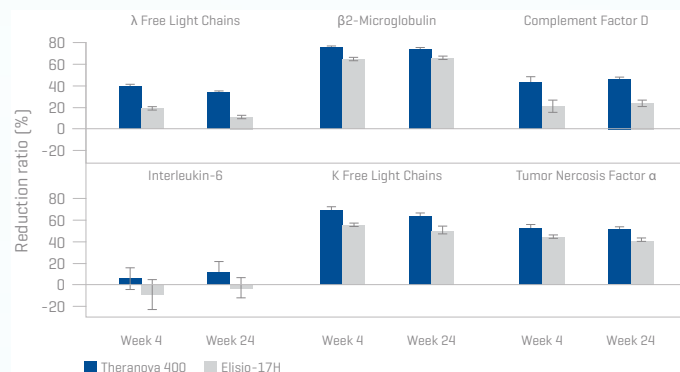
### Efficacy Outcomes

#### Primary Efficacy Outcome

**Theranova** 400 showed significantly larger removal of  $\lambda$  FLCs at 24 weeks of treatment than the Elisio-17H dialyzer (mean RR of  $33\% \pm 11.0\%$  vs  $17\% \pm 13\%$  at 24 weeks [ $p < 0.001$ ]). Significantly larger removal of  $\lambda$  FLC was also observed with **Theranova** at 4 weeks of treatment than with the Elisio-17H dialyzer (mean RR of  $39\% \pm 14\%$  vs  $20\% \pm 11\%$  [ $p < 0.001$ ]). See Table 3, Figure 1.

#### Secondary Efficacy Outcomes

**Theranova** 400 demonstrated superior removal of middle to large molecules as demonstrated by reduction ratios measured at 4 and 24 weeks: complement factor D,  $\kappa$  FLCs, TNF $\alpha$ , and  $\beta$ 2-microglobulin ( $p < 0.001$  for all). The level of IL-6 at the end of the study was lower than at the start of treatment for the **Theranova** 400 group. The RR of IL-6 was negative for the control at both 4 ( $5\% \pm 46\%$  vs  $-9\% \pm 61\%$ ;  $p=0.09$ ) and 24 weeks of treatment ( $11\% \pm 38\%$  vs  $-3\% \pm 39\%$ ;  $p=0.05$ ); these differences were not statistically significant. See Table 3, Figure 1.



**FIGURE 1.** Reduction ratios of middle molecules at 4 weeks and 24 weeks. Adapted from Weiner et al.

Single pool Kt/V was assessed after every 4 weeks of treatment. There were no significant differences in the mean single pool (sp) Kt/V values at all measured time points, except for week 8, where the spKt/V for **Theranova** 400 was  $1.62 \pm 0.29$  and the value for the Elisio-17H was  $1.51 \pm 0.32$  ( $p=0.02$ ). The value of spKt/V was within adequacy standards at all measured time points.

### Adverse Outcomes

No significant differences were observed between the **Theranova** 400 and the Elisio-17H groups in incidence ( $p=0.87$ ) and incidence rate ( $p=0.32$ ) of adverse events (AEs). There were 19 serious adverse events (SAEs) in 15 participants in

Parameter	Timepoint	Theranova 400					Control					
		(n)	Mean (SD)	Median	Min, Max	95% Confidence Interval	(n)	Mean (SD)	Median	Min, Max	95% Confidence Interval	p-value
Pre-dialysis serum albumin (g/dL)	Baseline	86	4.0 [0.3]	4.0	3.4, 4.9	NA	86	4.0 [0.3]	4.0	3.3, 4.7	NA	NA
	4 weeks	80	-0.1 [0.2]	-0.1	-0.8, 0.6	-0.14 to -0.03	77	0.0 [0.2]	0.0	-0.7, 0.5	-0.04 to 0.05	0.03
Change in pre-dialysis serum albumin from baseline (g/dL)	8 weeks	78	-0.1 [0.3]	-0.1	-0.8, 0.5	-0.17 to -0.05	77	0.0 [0.2]	0.0	-0.6, 0.5	-0.05 to 0.05	0.004
	12 weeks	77	-0.1 [0.3]	-0.1	-1.2, 0.6	-0.19 to -0.06	72	-0.0 [0.2]	0.0	-0.8, 0.5	-0.10 to 0.01	0.13
	16 weeks	72	-0.1 [0.3]	-0.1	-1.3, 0.7	-0.21 to -0.05	71	-0.0 [0.3]	0.0	-1.6, 0.5	-0.10 to 0.05	0.11
	20 weeks	66	-0.1 [0.3]	-0.1	-0.7, 0.5	-0.15 to -0.02	69	0.0 [0.3]	0.0	-0.9, 0.5	-0.05, to 0.08	0.07
	24 weeks	64	0.0 [0.3]	0.0	-0.6, 0.4	-0.06 to 0.07	65	0.0 [0.3]	0.1	-0.6, 0.8	-0.02 to 0.11	0.61

**TABLE 2.** Secondary Safety Outcomes: Baseline and Change from Baseline of Pre-dialysis Serum Albumin. Abbreviations: SD: standard deviation. Table adapted from Weiner et al.



Parameter	Dialyzer	Week 4 (n)	Mean (SD)	Median	Min, Max	p-value	Week 24(n)	Mean (SD)	Median	Min, Max	p value
Primary Efficacy Outcome											
RR of λ FLCs* (45 kDa)	Theranova 400	80	39.3 (14.5)	42.4	-46.2, 71.1	<0.001	63	33.3 (11.0)	32.8	8.1, 54.1	<0.001
	Control	75	19.9 (11.4)	18.9	-4.5, 41.6		65	17.2 (12.9)	15.9	-10.7, 74.2	
Secondary Efficacy Outcomes											
RR of complement factor D (24 kDa)	Theranova 400	83	43.0 (23.9)	48.0	-58.1, 78.5	<0.001	62	45.0 (10.4)	46.0	11.0, 68.0	<0.001
	Control	76	20.9 (23.7)	22.5	-110.9, 77.8		65	23.6 (12.1)	23.9	-47.0, 45.5	
RR of κ FLC (23 kDa)	Theranova 400	80	68.8 (17.3)	72.1	-57.9, 94.6	<0.001	63	63.8 (11.8)	65.8	27.8, 87.4	<0.001
	Control	75	54.8 (14.5)	56.0	-29.1, 77.6		65	50.0 (13.2)	49.4	2.3, 74.1	
RR of IL-6 (25 kDa)	Theranova 400	80	5.5 (45.9)	19.6	-155.4, 66.1	0.09	63	11.0 (37.8)	20.8	-128.5, 66.2	0.05
	Control	78	-9.2 (60.6)	3.9	-341.2, 55.6		65	-2.6 (39.4)	7.8	-162.2, 46.2	
RR of TNFα (17 kDa)	Theranova 400	80	52.5 (9.4)	54.3	16.3, 72.4	<0.001	63	50.7 (9.3)	52.2	23.8, 68.5	<0.001
	Control	78	44.1 (9.3)	45.3	11.0, 58.1		65	41.5 (10.2)	41.9	-0.9, 57.9	
RR of β2-microglobulin (11.8 kDa)	Theranova 400	78	75.7 (8.2)	77.2	46.6, 98.9	<0.001	63	73.6 (10.4)	75.9	30.3, 96.7	<0.001
	Control	76	64.9 (8.9)	65.6	24.1, 83.2		65	65.4 (9.4)	65.9	36.8, 90.0	

**TABLE 3. Primary and Secondary Efficacy Outcomes: Reduction Ratios (RR) (%) of Middle Molecules at 4 Weeks and 24 Weeks.**

\*The reduction ratio of  $\lambda$  free light chains at 4 weeks of treatment was a secondary efficacy outcome. Abbreviations. RR: reduction ratio; FLC: free light chain. Table adapted from Weiner et al.

the **Theranova** 400 group, and 39 SAEs in 23 participants in the Elisio-17H group. This difference was not statistically significant. There were no SAEs associated with either device. None of the AEs were unanticipated; all were AEs typically seen in maintenance HD patients. Six patients died during the study, 3 in each group, with 1 death in the Elisio-17H group occurring after participant withdrawal from the study. None of the deaths were assessed as related to either device.

### Exploratory Outcomes

There were no significant differences in the mean hs-CRP at all trial time points. Additionally, no significant differences were observed in the KDQOL-36 survey and EQ-5D-5L questionnaire results between the two groups.

### Strengths & Limitations

Study limitations included conservative exclusion criteria and associated high screening failure rates, study completion rate, insufficient sample size/duration to comment on clinical outcomes such as cardiovascular events and mortality. The trial had multiple strengths, including the randomized design and longer length of study (6 months) vs previous studies, high rates of adherence with minimal loss to follow-up and consistent results across solutes analyzed.

## DISCUSSION AND CONCLUSIONS

Multiple middle molecules are present at higher levels in dialysis patients and have been associated with adverse outcomes. Specifically, larger middle molecules are associated with inflammation, cardiovascular events, and other dialysis-related comorbidities in patients with comorbid cardiovascular disease, mineral and bone disorders, and infectious diseases. In this study, **Theranova** 400 showed significantly greater ( $p < 0.001$ ) removal of conventional and larger middle molecules  $\lambda$ FLC (45 kDa), complement factor D (24 kDa),  $\kappa$  FLC (23 kDa), TNF- $\alpha$  (17 kDa), and  $\beta$ -2 microglobulin (11.8 kDa) than Elisio 17-H at 4 weeks and 24 weeks. In parallel, no sustained reduction was seen in serum albumin levels (65 kDa), an important finding with the association between higher serum albumin concentration and better outcomes in hemodialysis patients. Given the potential role of these uremic toxins in cardiovascular disease and inflammation in kidney failure patients, newer technologies enhancing clearance of middle molecules while limiting loss of important proteins such as albumin may have an important role in improving health of dialysis patients.

Study results suggest that there may be a role for HDx to improve clinical outcomes. In this trial,  $\lambda$  FLCs (45 kDa) were studied as a representative large middle molecule that is easily measured rather than as a presumptive 'uremic toxin', with the current study critically focusing on both clearance of these molecules as well as pre-dialysis levels of large middle molecules. The latter is notable; if there is toxicity associated with retained uremic solutes, therapeutic management will require sustained reduction in the levels of these solutes.

In conclusion, primary and secondary endpoints for safety and efficacy were met. HDx with the **Theranova** 400 dialyzer is safe and efficacious, providing superior removal of larger middle molecules including several putative uremic toxins as compared to a similar size high-flux dialyzer while maintaining serum albumin. While this study demonstrated greater removal of large middle molecules among prevalent hemodialysis patients, larger studies of longer duration are needed to assess long term potential beneficial effects related to more effective removal of these middle molecules, including improvements in cardiovascular disease, inflammation, mortality, and key patient-reported outcomes.

**Theranova provides significant and superior removal of conventional/large middle molecules while retaining stable albumin levels.**

### 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.



## In Vitro Cytokine Removal: Comparison of Conventional High-Flux Dialyzers and Middle-Cut-Off Dialyzer (Theranova HDx)

Koball S, Heskamp B, Andreas K, et al. In Vitro Cytokine Removal: Comparison of conventional high-flux dialyzers and middle-cut-off dialyzer (**Theranova** HDx). ASN 2019. Abstract [FR-P0465](#).

### BACKGROUND

The removal of inflammatory mediators is important for the treatment of acute (ARF) or chronic renal failure (CRF). In ARF and sepsis, attempts are made to achieve removal through the use of high-volume treatments or adsorbers. In CRF, this has so far not been sufficiently addressed, but is important for mortality (MIA syndrome). By using new MCO filters (Baxter **Theranova** HDx), an improvement of cytokine status seems to be possible in both areas. The effectiveness of HDx in the removal of interleukins (interleukin 6, interleukin 10 and TNF $\alpha$ ) in hemodialysis treatments will be assessed.

### METHODS

The efficacy of HDx was compared to a conventional high-flux dialyzer (Fresenius FX80). The measurements were performed in vitro in a 3l pool of fresh frozen plasma (citrate and heparin anticoagulation). IL6 (24.5 kDa) IL10 (18.6 kDa, dimer) and TNF $\alpha$  (17.4 kDa, trimer) were added to plasma (1.5  $\mu$ g/l each). Samples were taken before and after the dialyzer (after 5, 15, 30, 60, 120 and 180 minutes). In addition to cytokines, albumin and total serum protein concentrations were measured (LEGEND MAX Human IL-6/IL-10/TNF- $\alpha$ ; Cobas Mira Plus; Roche LT-AB0103, LT-TP0253). Every test was repeated 5 times.

### RESULTS

**Theranova** HDx showed significantly higher removal rates of all tested cytokines over a period of 180 minutes. A comparison of the concentrations at the beginning and end of the measurements showed:

- IL-6 reduction - HDx about 80% / FX80 about 40%.
- IL-10 reduction - HDx about 50% and FX80 about 10%.
- TNF- $\alpha$  Reduction - HDx about 25%; FX80 no reduction.

The concentration of albumin and total serum protein was not significantly different during the treatment in both groups.

### CONCLUSIONS

Hemodialysis therapy with **Theranova** HDx appears to be a superior therapy option for the removal of cytokines. This opens up new treatment options for both acute and chronic dialysis patients. However, clinical studies are still necessary to assess the significance in patient treatment.

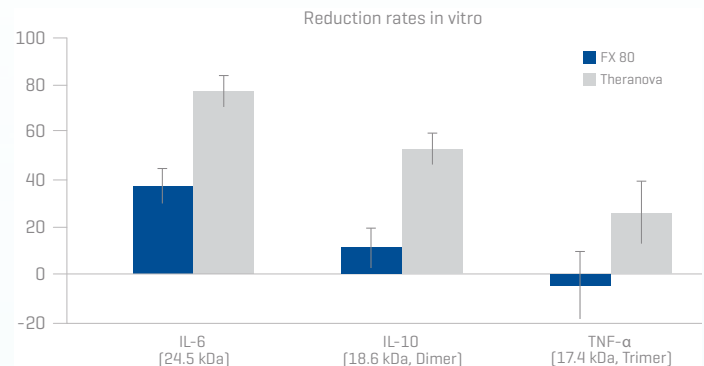


Figure adapted from Koball et al.

# HDx: A WORLD OF DIFFERENCE

## Clinical Effectiveness of the HDx Therapy



HDx may decrease the pro-calcifying effect of uraemic serum compared with HD. Studying pathogenetic processes involved in high Pi-induced calcium deposition found that uraemic serum of HDx-treated patients induced less VSMC necrosis compared with uraemic serum of HD patients.<sup>1</sup>



**Ciceri P, Tettamanti G, Galassi A, et al.**

**Pro-calcifying analysis of uraemic serum from patients treated with medium cut-off membrane in a prospective, cross-over study.** *Clinical Kidney Journal* 2021;14(7):1798-1807.



**Cantaluppi V, Marengo M, Alessandro Q, et al.**

**Removal of Large-Middle Molecules, Inhibition of Neutrophil Activation and Modulation of Inflammation-Related Endothelial Dysfunction During Expanded Hemodialysis (HDx).** *Nephrol Dial Transplant* 2019 Abstract F0048.

1. Ciceri P, Tettamanti G, Galassi A, et al. Pro-calcifying analysis of uraemic serum from patients treated with medium cut-off membrane in a prospective, cross-over study. *Clinical Kidney Journal*. 2021;14(7):1798-1807.





# Pro-calcifying analysis of uraemic serum from patients treated with medium cut-off membrane in a prospective, cross-over study

Ciceri P, Tettamanti G, Galassi A. et al. Pro-calcifying analysis of uraemic serum from patients treated with medium cut-off membrane in a prospective, cross-over study. *Clinical Kidney Journal*. 2020;1-10. doi: 10.1093/ckj/sfaa216.

## BACKGROUND

The retention of a large number of solutes that are normally excreted or metabolized by the kidney is responsible for the symptoms typical in uraemic patients. These molecules are defined as uraemic toxins and can be classified into three groups: small water-soluble molecules, middle molecules and protein-bound toxins. Recently, efforts were put towards developing dialysis membranes that allow the removal of large middle molecules without clinically relevant albumin loss. These membranes are the medium cut-off (MCO) membranes that allow the removal of middle molecules up to ~50,000 Da.

Patients affected by ESRD have an increased morbidity and mortality due to many complications, mainly represented by cardiovascular diseases. In all the causes that induce cardiovascular diseases, an important role is played by vascular calcification (VC), which modifies arterial pulse wave velocity and pressure, leading to hypertension, left ventricular hypertrophy and heart failure. In end stage renal disease (ESRD) patients, VC affects principally the tunica media and vascular smooth muscle cells (VSMCs) and is due to different factors, among which the main ones are high phosphate levels and uraemic toxins.

Phosphate stimulates VSMCs to deposit calcium in the extracellular matrix. In this process, VSMCs lose muscular markers and start to express an osteoblastic phenotype, behaving as simi-osteoblasts. Besides the trans-differentiation, high phosphate promotes calcification by causing apoptosis, with the release of apoptotic bodies loaded with calcium that work as VSMC calcification machinery. Another process that induces calcification exacerbation is necrosis, as the massive release of calcium after rupture of the cellular membrane triggers and participates in calcium deposition.

## OBJECTIVE

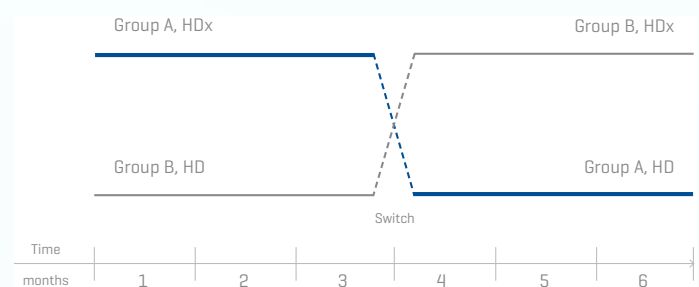
- To investigate whether different dialysis treatments, e.g., MCO or high flux dialysis membranes, could have an impact on calcium deposition
- To characterize uraemic serum composition to find which components are differentially removed by dialysis treatment that could play a role in modulation of the serum pro-calcifying effect.

## METHODOLOGY

### Study Design

Twenty prevalent hemodialysis (HD) patients participated in this prospective, open-label, controlled, cross-over pilot study. The study was undertaken at the dialysis unit at the University of Milan (Italy) from 1 October 2017 to 31 December 2018. Consecutively unselected male and female adult patients with

ESRD on HD were eligible for participation in the study. Patients were divided into two groups (A and B) with similar mean age, male:female ratio and dialytic vintage. As a cross-over design, patients in Group A were treated with TheraNova dialyzer (expanded hemodialysis (HDx)) for the first three months of the study then switched to traditional bicarbonate dialysis for the remaining three months. Patients in Group B were treated with bicarbonate dialysis for the first three months and then switched to HDx for the remaining three months. See Figure 1. Sera samples from both groups were collected at 1, 2, and 3 months. The pro-calcifying effect of uraemic serum in a well-established in vitro model of high-phosphate (Pi)-induced calcification in VSMCs was then analyzed.



**FIGURE 1.** Study Design. HDx: expanded hemodialysis. HD: hemodialysis. Figure adapted from Ciceri, et al.

### Induction of Calcification/Quantification of Calcium Deposition

Rat VSMCs were obtained by enzymatic digestion, and were routinely subcultured in a growth medium. Quantification of calcium deposition was performed by staining, followed by perchloric acid destaining after high propidium iodide (Pi) treatment. Calcium content was determined colorimetrically at a wavelength of 450 nm. Protein content was assessed by a bicinchoninic acid (BCA) protein assay kit and calcium deposition was normalized to protein content and expressed as absorbance (optical density (OD)) per milligram of protein.

### Detection of Apoptosis and Necrosis

Cytoplasmic histone-associated deoxyribonucleic acid (DNA) fragments were detected with a cell death detection Enzyme-Linked Immunosorbent Assay (ELISA) plus kit as a quantitative index of apoptosis 4 days after high Pi treatment. Necrosis was detected with the same kit.

### VSMC Osteochondrogenic Shift

Seven different molecules, either inducers or inhibitors of calcification, involved in VSMC simi-osteoblast transformation were tested.



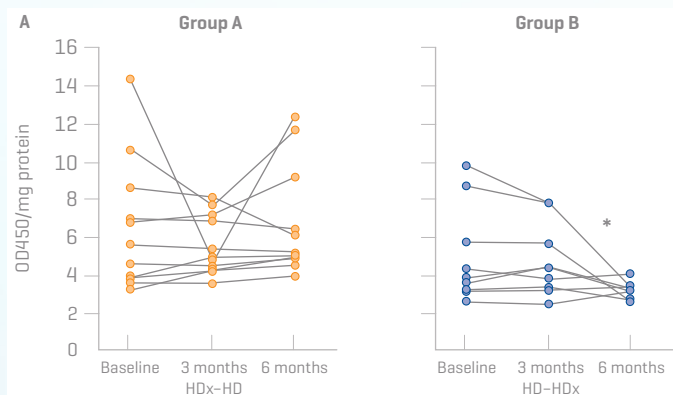
## Uraemic Serum Characterization

- **Uraemic Toxins and Precursors (Protein-Bound Uremic Toxins)**  
– the levels of ten uraemic toxins and three precursors in patients' serum from either the HDx or HD period were measured using a ultra-performance liquid chromatography-tandem mass spectrometer (ULPC-MS/MS)
- **Alpha 1 acid glycoprotein** - alpha-1 acid was detected by ELISA in patients' serum following the kit protocol
- **Micro ribonucleic acid (miRNA)** – content of miRNA was measured in serum-isolated exosomes

## RESULTS

### Effect of HDx on vascular calcification

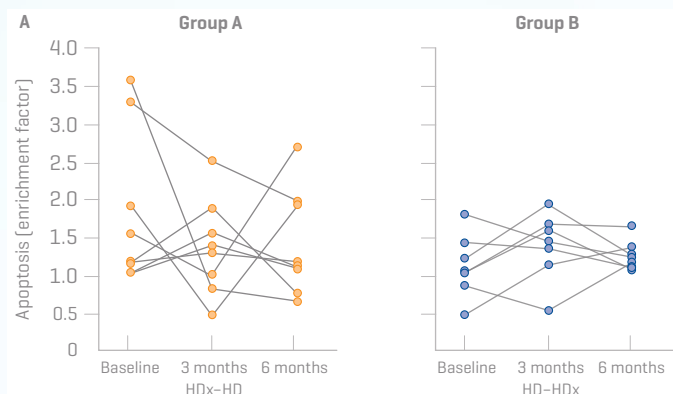
Patients in Group A showed a tendency to a slight reduction of calcium deposition during HDx treatment with a following slight increase after treatment switch [6.6 ± 1.1, 5.6 ± 0.6 and 6.7 ± 1.0 OD/mg protein for baseline, 3 months (HDx) and 6 months (HD), respectively]. Patients in Group B showed no modification in calcification in the first 3 months, whereas after treatment switching to HDx we observed a significant reduction in calcification (4.7 ± 0.6 versus 3.2 ± 0.2 OD/mg protein at 3 versus 6 months, respectively;  $P < 0.05$ ). See Figure 2.



**FIGURE 2.** Effect of HDx on human uraemic serum apoptotic potential in high Pi-simulated VSMCs. Data are presented as mean ± standard error. HDx: expanded hemodialysis. HD: hemodialysis. Pi: propidium iodide; VSMC: vascular smooth muscle cells. Figure adapted from Ciceri, et al.

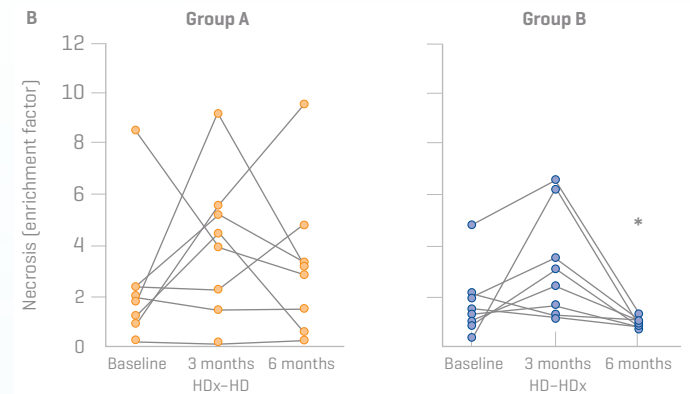
### Effects of HDx on VSMC Apoptosis and Necrosis

In an analysis of apoptosis, no statistically significant modulation by HDx treatment was found in Group A [1.85 ± 0.36 versus 1.38 ± 0.22, enrichment factor, baseline versus 3 months (HDx)] respectively; or in Group B [1.38 ± 0.17 versus 1.27 ± 0.13, enrichment factor, 3 months (HD) versus 6 months (HDx)] respectively. See Figure 3.



**FIGURE 3.** Effect of HDx on human uraemic serum apoptotic potential in high Pi-simulated VSMCs. Data are presented as mean ± standard error. HDx: expanded hemodialysis. HD: hemodialysis. Pi: propidium iodide; VSMC: vascular smooth muscle cells. Figure adapted from Ciceri, et al.

An analysis of necrosis found a decreasing positive effect of HDx on this process. In Group A there were no statistically significant differences between HDx and HD treatment [2.99 ± 0.99, 3.69 ± 0.95 and 5.94 ± 2.85, enrichment factor, baseline, 3 months (HDx) and 6 months (HD), respectively]. In contrast, in Group B, HDx induced a significant amelioration of the necrotic process [4.47 ± 1.52 versus 1.86 ± 1.10, enrichment factor, 3 months (HD) versus 6 months (HDx); respectively;  $P < 0.05$ ]. See Figure 4.



**FIGURE 4.** Effect of HDx on human uraemic serum necrotic potential in high Pi-simulated VSMCs. Data are presented as mean ± standard error. (\* $P < 0.05$ ). HDx: expanded hemodialysis. HD: hemodialysis. Pi: propidium iodide; VSMC: vascular smooth muscle cells. Figure adapted from Ciceri, et al.

### Effect of HDx on Osteochondrogenic Shift

The uraemic serum from the HDx period did not significantly induce a shift to an osteochondrogenic phenotype with high Pi induction or modify the levels of any inducers or inhibitors of calcification compared with the HD period.

### Uraemic Toxin Characterization

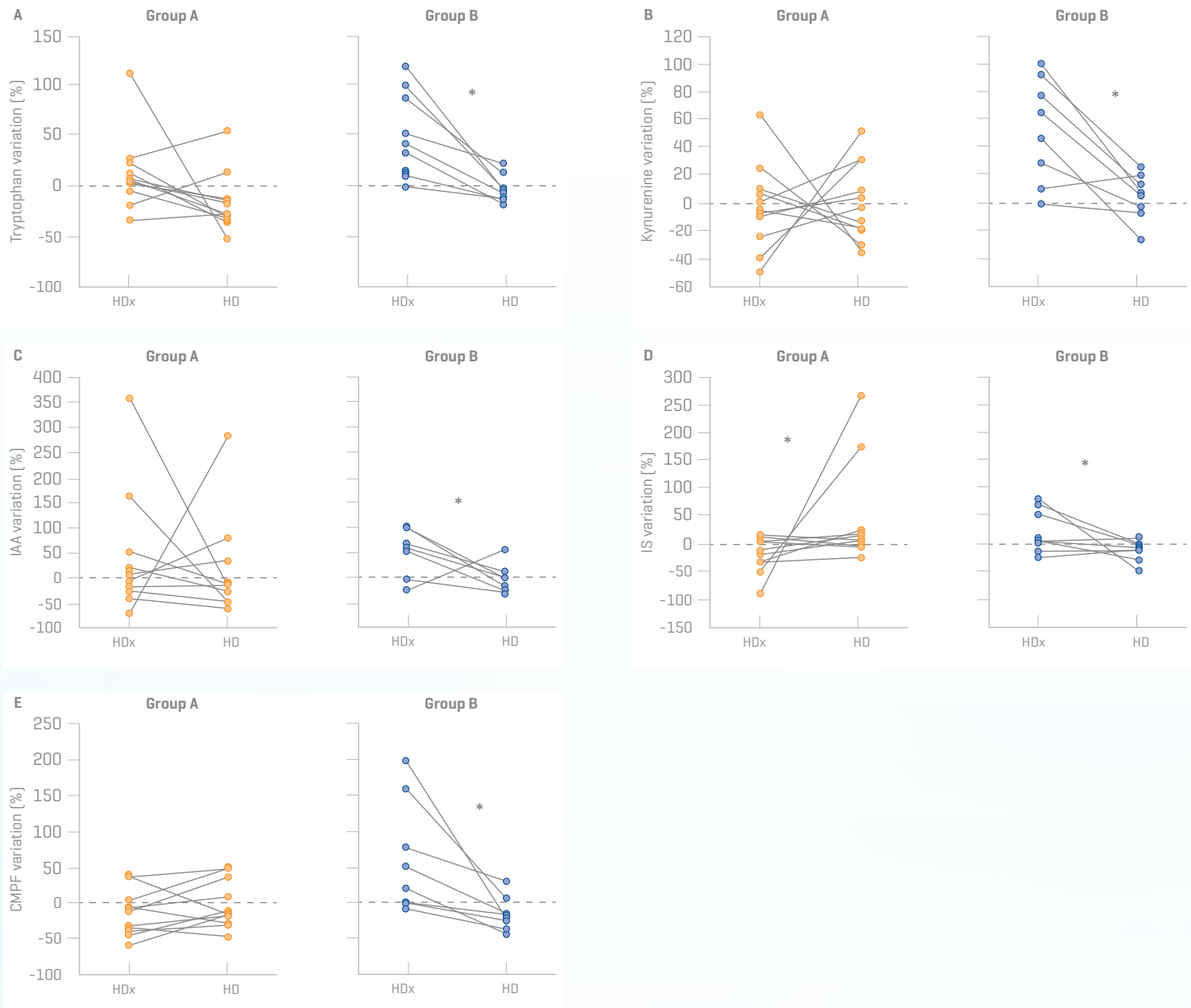
#### Uraemic Toxins and Precursors Profile

Among the 13 protein-bound uraemic toxins tested, a significant decrease was induced during the HDx period in Group B for the following four:

- tryptophan: 51.7 ± 14.2 versus -2.8 ± 5.8 for HD versus HDx;  $P < 0.05$  (Figure 5/A)
- kynurenine: 44.2 ± 13.0 versus -0.1 ± 6.8 for HD versus HDx;  $P < 0.05$  (Figure 5/B)
- indole-3-acetic acid (IAA): 43.1 ± 16.9 versus -2.4 ± 11.0 for HD versus HDx;  $P < 0.05$  (Figure 5/C)
- 3-Carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF): 61.8 ± 27.6 versus -16.1 ± 9.6 for HD versus HDx;  $P < 0.05$  (Figure 5/E)

For 3-idoxyl sulfate (IS) the percentage of variation decreased during the HDx period both in Group A, with a rebound effect after the switch to HD (-21.1 ± 13.0 versus 54.4 ± 33.2 for HDx versus HD;  $P < 0.05$ ), and in Group B (30.6 ± 13.0 versus -17.1 ± 10.2 for HDx versus HD;  $P < 0.05$ ). (Figure 5/D)

No significant variation was found for the other protein-bound uraemic toxins tested.



**FIGURE 5.** Serum concentration of protein-bound uraemic toxins following either HD or HDx. The percentage of variation is intended as the level variation compared with the level in the precedent time point. (A) Tryptophan, (B) kynurenine, (C) indole-3-acetic acid, (D) 3-IS and (E) CMPF. For all five protein-bound uraemic toxins represented, there was a significant decrease following HDx in Group B. 3-IS was significantly decreased by HDx in Group A. Data are presented as mean  $\pm$  standard error. [\*P < 0.05]. HDx: expanded hemodialysis; HD: hemodialysis; 3-IS: 3-indoxyl sulfate; CMPF: 3-Carboxy-4-methyl-5-propyl-2-furanpropionate. Figure adapted from Ciceri et al.

#### *Alpha 1 Acid Glycoprotein Levels*

In Group A, HDx and HD had almost the same effect, with a dispersion of data that resulted in no difference between the two dialysis treatments. In Group B, there was a non-significant tendency towards a decrease from HD to HDx.

#### *miRNA Levels*

Due to the high variability between patients, no statistically significant results could be obtained.

## CONCLUSIONS

This pilot study indicates that HDx may decrease the pro-calcifying effect of uraemic serum. This reduction is important from a clinical point of view since necrosis is one of the driving mechanisms in calcium deposition. In this study HDx reduction of uraemic serum toxicity is potentially one of the main mechanisms. This beneficial effect is due in part to a partial removal of tryptophan, some of its metabolites, such as IS,

and CMPF. The effect of MCO on the removal of protein-bound uraemic toxins is probably related to albumin loss, the main carrier of these toxins. The partial albumin loss during HDx might be beneficial, allowing a decrease in protein-bound uraemic toxin levels that have been difficult to eliminate with extracorporeal strategies until now. MCO might thus decrease uraemic serum pro-calcifying and necrotic effects through albumin loss without any clinical signs of hypoalbuminaemia. This hypothesis deserves deep investigation in larger clinical trials.



# Removal of Large-Middle Molecules, Inhibition of Neutrophil Activation and Modulation of Inflammation-Related Endothelial Dysfunction During Expanded Hemodialysis (HDx)

**Cantaluppi V, Marengo M, Alessandro Q, et al.** Removal of large-middle molecules, inhibition of neutrophil activation and modulation of inflammation-related endothelial dysfunction during expanded hemodialysis (HDx). *Nephrol Dial Transplant* 2019. Abstract [FO-048](#).

## BACKGROUND

HemoDialysis expanded (HDx) represents an innovative strategy to remove uremic toxins of Large-Medium Molecular weight (LMMs,  $\leq$  equal 45 kDa) thanks to the membrane medium cut-off (MCO) and internal convection. LMMs (in particular Free Light Chains-FLCs) are involved in the inhibition of neutrophil apoptosis leading to persistent inflammation, endothelial dysfunction and increased cardiovascular risk of hemodialysis patients.

Aims of the study were to evaluate: 1) the efficacy of HDx on LMM removal (in particular kappa and lambda FLCs) and inflammation inhibition during an observational multicentric study of 6 months; 2) the in vitro effects of plasma drawn from HDx-treated patients (T0 and T6 months) on neutrophil activation and endothelial dysfunction.

## METHODS

Forty-one (41) HD patients (age  $67,6 \pm 13,4$ ) in standard high flux HD were shift to HDx using TheraNova® 400 (1.7 m<sup>2</sup>, Baxter). Each patient was studied at baseline HD (T0), 3 months (T3) and 6 months (T6) after HDx. We evaluated the following predialysis parameters: Urea, Creatinine (Creat), Phosphate (P), Beta2-microglobulin ( $\beta$ 2m), Myoglobin (Myo), Free Light Chains (FLC-k, FLC- $\lambda$ ), Hemoglobin (Hb), Albumin and C Reactive Protein (CRP). For in vitro studies, T0 and T6 plasma were used to evaluate neutrophil activation (ROS generation, apoptosis, adhesion) and endothelial dysfunction/senescence.

## RESULTS

HDx therapy was well tolerated without evidence of major adverse side effects. After 3 months of HDx (T3), we observed a significant decrease of urea ( $p=0,008$ ),  $\beta$ 2m ( $p=0,003$ ), FLC-k ( $p=0,026$ ) and FLC- $\lambda$  ( $p=0,001$ ). No significant differences of the other uremic toxins between the periods (T3 vs. T6) were observed. Albumin levels remained stable during all the study period. A significant decrease of CRP was observed at T3 and T6, suggesting a positive effect of HDx on inflammatory parameters correlated with a worse outcome. *In vitro* studies confirmed that LMM removal by HDx associated with a limitation of neutrophil activation (decrease of ROS, TNF-alpha and IL6 production, increase of apoptosis assessed by TUNEL and caspase-3 ELISA) and of endothelial dysfunction (significant decrease of neutrophil adhesion, increased NO bioavailability and angiogenesis, inhibition of vascular senescence with increased expression of the anti-oxidant and anti-aging factor Nrf2). Preliminary data revealed a potential role of HDx in the modulation of the microRNA content of circulating extracellular vesicles isolated from patients' plasma.

## CONCLUSION

HDx therapy provided high removal of different LMMs, leading to a significant reduction of molecules involved in uremia-associated inflammation and organ dysfunction (in particular FLC kappa and lambda). Long-term studies with a larger sample size are needed to evaluate the clinical impact of HDx. However, our preliminary clinical data and in vitro studies suggested that by improving LMM removal, HDx may limit neutrophil activation and endothelial dysfunction, key factors of the increased cardiovascular risk of hemodialysis patients. A new randomized multicenter clinical trial in Italy is currently ongoing to confirm these data and to evaluate the effect of HDx on microRNA content of circulating extracellular vesicles, microparticles involved in cell-to-cell communication and recently identified as new mechanisms of vascular senescence.



# HDx: A WORLD OF DIFFERENCE

## Patient Reported Measures Reported by Switching to HDx Therapy



HDx therapy may improve patient-reported quality of life aspects of kidney disease, including symptom burden, restless legs syndrome criteria, pruritus, and dialysis recovery time.<sup>1-3</sup>



**Lim JH, Park Y, Yook JM, et al.**

**Randomized Controlled Trial of Medium Cut-Off versus High-Flux Dialyzers on Quality of Life Outcomes in Maintenance Hemodialysis Patients.** *Nature/Sci Rep.* 2020;10:7780.



**Alarcon JC, Bunch A, Ardila F, et al.**

**Impact of Medium Cut-Off Dialyzers on Patient-Reported Outcomes (PROs): COREXH Registry.** *Blood Purif* 2021;50:110-118.



**Bolton S, Gair R, Nilsson LG, et al.**

**Clinical Assessment of Dialysis Recovery Time and Symptom Burden: Impact of Switching Hemodialysis Therapy Mode.** *Patient Relat Outcome Meas* 2021;12:315-321.



**Penny JD, Jarosz P, Salerno FR, et al.**

**Impact of Expanded Hemodialysis Using Medium Cut-off Dialyzer on Quality of Life: Application of Dynamic Patient-Reported Outcome Measurement Tool.** *Kidney Med.* 2021;3(6):992-1002.

1. Lim JH, Park Y, Yook JM, et al. Randomized Controlled Trial of Medium Cut-Off versus High-Flux Dialyzers on Quality of Life Outcomes in Maintenance Hemodialysis Patients. *Nature/Sci Rep.* 2020;10:7780.

2. Alarcon JC, Bunch A, Ardila F, et al: Impact of Medium Cut-Off Dialyzers on Patient-Reported Outcomes (PROs): COREXH Registry. *Blood Purif*, 2020.

3. Bolton S, Gair R, Nilsson LG, et al. Clinical Assessment of Dialysis Recovery Time and Symptom Burden: Impact of Switching Hemodialysis Therapy Mode. *Patient Related Outcome Measures*, 2021:12 315-321.





# Randomized Controlled Trial of Medium Cut-Off versus High-Flux Dialyzers on Quality of Life Outcomes in Maintenance Hemodialysis Patients

Lim JH, Park Y, Yook JM, et al. Randomized controlled trial of medium cut-off versus high-flux dialyzers on quality of life outcomes in maintenance hemodialysis patients. *Nature/Sci Rep.* 2020;10:7780. doi: [10.1038/s41598-020-64622-z](https://doi.org/10.1038/s41598-020-64622-z).

## BACKGROUND

Patients on maintenance hemodialysis suffer from symptoms such as fatigue, generalized weakness, and pruritus. These subjective conditions are assumed to be related to the accumulation of middle molecules that are not cleared by conventional hemodialysis (HD). Middle molecules have molecular weights (MWs) ranging between 500 and 60,000 Daltons, and their size is a barrier to removal with dialyzers. The accumulation of middle molecules is associated with specific complications such as amyloidosis, inflammatory reactions, oxidative stress, and endothelial dysfunction. Consequently, middle molecules contribute to morbidity and mortality and poor quality of life (QOL) in patients with end-stage renal disease (ESRD).

Compared with high-flux dialyzers and hemodiafiltration (HDF), medium cut-off (MCO) dialyzers may improve the removal of middle molecules due to their higher permeability and increased convective transport, but clinical data on the effects of MCO dialyzers on patient-reported outcomes are lacking.

## OBJECTIVE

This study aimed to investigate potential QOL improvement using MCO dialyzers in patients undergoing maintenance HD with a high-flux dialyzer. This study also sought to evaluate the effect of MCO dialyzers on the removal of middle molecules and pre-dialysis plasma concentrations.

## METHODOLOGY

### Study Design

This study was a randomized, prospective, controlled, open-label, phase 4 trial in patients treated with maintenance HD at a national university hospital in South Korea. Patients aged 18 years or older, had been receiving maintenance high-flux membrane HD for more than three months, had vascular access by arteriovenous fistula/graft and adequate dialysis were enrolled.

Patients were randomly assigned into MCO and high-flux groups at 1:1 ratio. Patients and physicians were unblinded to the assignment. The MCO group switched from a high-flux membrane (F<sub>x</sub> CorDiax 60 or 80; Fresenius Medical Care Deutschland, Bad Homburg, Germany) to a **Theranova** 400 dialyzer (Baxter International Inc., Hechingen, Germany) and the high-flux group continued with a high-flux membrane.

### Data Collection and Analysis

Patients completed the Kidney Disease Quality of Life-Short Form (KDQOL-SF) questionnaire. Uremic pruritus was assessed using the modified scoring questionnaire consisting of severity, distribution, and sleep disturbance categories. Questionnaires about QOL and pruritus were completed at baseline and at 12 weeks. Blood samples to identify middle molecule removal were obtained before and at the end of dialysis.

## Study Outcomes

The primary outcomes were the KDQOL-SF and pruritus assessment. For the KDQOL-SF, analysis identified differences between the MCO and high-flux groups, pre- and post-dialysis, in the questionnaire's 26 categories. For pruritus assessment, analysis identified differences in questionnaire responses between the two groups, pre- and post-dialysis, on severity and distribution by time of day (morning, afternoon), sleep disturbance, and scoring of responses to a visual analog scale.

The secondary outcomes were pre-dialysis plasma concentrations and reduction ratios (RRs) of middle molecules at baseline and 12 weeks after randomization. Analysis identified differences between the MCO and high flux groups, pre- and post-dialysis, in levels of three middle molecules:  $\beta$ 2-microglobulin (molecular weight (MW) 11.8 kDa), a small middle molecule, and kappa free light chain [ $\kappa$  FLC] (22.5 kDa) and lambda free light chain [ $\lambda$  FLC] (45 kDa), larger middle molecules.

## Study Limitations

This study has several limitations. The sample size was small, and the study duration was insufficient to evaluate definite effects of the MCO membrane. The **Theranova** 500 dialyzer, which has a greater surface area (2.0 m<sup>2</sup>) than the Theranova 400 dialyzer (1.7 m<sup>2</sup>), was not applied in the MCO group because the **Theranova** 500 has not yet been introduced in South Korea. The actual extent of solute removal could not be estimated, or the exact pathophysiologic correlations proven between middle molecules and the physical components of QOL and uremic pruritus.

## RESULTS

### Patient Characteristics

A total of 50 patients were enrolled and one patient withdrew consent, resulting in 49 patients who completed the study. Twenty-four patients were in the MCO group and 25 were in the high-flux group. No significant between-group differences in age, sex, body mass index, dry weight, daily urine volume, vascular access, baseline dialyzer, and dialysis vintage were observed.

### Comparison of QOL Scores

The baseline perceptions of QOL assessed by the KDQOL-SF were similar in both groups. After 12 weeks, the physical function domain score was better in the MCO group than in the high-flux group and the role-physical function domain score was also higher in the MCO group. See Table 1. The effect of the MCO dialyzer on QOL is likely related to the better removal of middle molecules compared to high flux dialyzers. The improvements in the physical components of the QOL questionnaire over a relatively short exposure period occurred concurrently with the change of the dialyzer.



Reduction ratio (%)	Baseline			12 weeks		
	MCO (n = 24)	High-flux (n = 25)	P	MCO (n = 24)	High-flux (n = 25)	P
Total score	63.7 ± 13.8	57.0 ± 16.4	0.134	63.9 ± 14.4	59.0 ± 17.3	0.283
Kidney disease targeted items	67.9 ± 11.4	62.9 ± 12.3	0.142	66.2 ± 13.3	66.2 ± 12.9	0.995
Symptoms	81.9 ± 13.8	75.4 ± 14.0	0.107	81.3 ± 14.9	78.3 ± 14.6	0.471
Effects of kidney disease	67.6 ± 14.9	60.7 ± 18.9	0.163	65.1 ± 20.3	67.6 ± 18.9	0.654
Burden of kidney disease	40.9 ± 24.4	31.5 ± 26.1	0.200	39.3 ± 27.2	30.8 ± 23.5	0.244
Work status	14.6 ± 27.5	14.0 ± 30.7	0.945	12.5 ± 26.6	18.0 ± 35.0	0.540
Cognitive function	82.5 ± 19.0	83.7 ± 13.6	0.795	78.1 ± 24.1	84.0 ± 17.6	0.328
Quality of social interaction	67.8 ± 18.3	60.5 ± 15.0	0.136	68.1 ± 22.7	67.5 ± 20.3	0.927
Sexual function	57.5 ± 28.8	40.6 ± 42.5	0.500	45.8 ± 35.9	50.0 ± 70.7	0.911
Sleep	64.1 ± 19.3	60.9 ± 17.7	0.553	62.6 ± 15.1	61.6 ± 18.6	0.837
Social support	66.0 ± 22.2	66.0 ± 23.3	0.997	61.8 ± 23.3	73.3 ± 22.1	0.082
Dialysis staff encouragement	87.0 ± 14.0	85.5 ± 16.4	0.736	85.9 ± 15.3	85.5 ± 17.9	0.927
Patient satisfaction	61.8 ± 23.8	60.7 ± 23.0	0.866	61.1 ± 20.1	59.3 ± 22.6	0.773
Short form 36 items	58.9 ± 18.7	50.4 ± 22.6	0.158	61.5 ± 17.7	51.0 ± 24.1	0.088
PCS	61.4 ± 21.7	51.4 ± 25.8	0.150	62.8 ± 20.5	51.7 ± 25.8	0.100
Physical functioning	72.1 ± 23.7	59.4 ± 28.3	0.096	75.2 ± 20.8	59.8 ± 30.1	0.042
Role-physical	56.3 ± 39.2	44.0 ± 40.4	0.287	61.5 ± 37.6	39.0 ± 39.6	0.047
Pain	70.9 ± 22.9	65.0 ± 28.2	0.424	72.2 ± 24.9	69.3 ± 24.1	0.682
General health	37.9 ± 18.7	36.0 ± 26.0	0.768	35.4 ± 20.1	38.4 ± 27.3	0.666
MCS	55.8 ± 18.1	49.2 ± 21.1	0.249	60.2 ± 16.4	50.5 ± 23.8	0.104
Emotional well-being	54.7 ± 16.0	57.9 ± 18.6	0.515	61.7 ± 16.1	53.4 ± 21.8	0.141
Role-emotional	61.1 ± 40.1	38.7 ± 44.8	0.071	62.5 ± 38.5	45.3 ± 45.0	0.159
Social function	70.3 ± 21.1	62.0 ± 28.1	0.249	69.8 ± 23.6	64.0 ± 26.6	0.425
Energy/fatigue	45.8 ± 20.7	39.8 ± 18.6	0.289	51.7 ± 17.9	43.8 ± 21.6	0.173
Health status compared to one year ago	51.0 ± 21.5	46.0 ± 25.7	0.461	53.1 ± 23.7	46.0 ± 24.7	0.308
Overall health rate	57.9 ± 22.1	56.4 ± 25.2	0.824	58.8 ± 22.5	50.0 ± 26.3	0.218

**TABLE 1. Quality of life questionnaire scores at baseline and 12 weeks.** Values are shown as the + standard deviation. Abbreviations: PCS, physical composite summary; MCS, mental composite summary. Adapted from Lim et al.

### Comparison of Pruritus Scores

The morning pruritus intensity was worse in the MCO group than in the high-flux group at baseline, but this difference was not observed at 12 weeks. After 12 weeks, the pruritus distribution in the morning was smaller in the MCO group than in the high-flux group. The MCO group also had less frequent sleep disturbances caused by pruritus-related scratching. See Table 2.

### Comparison of Middle Molecule Concentrations and Reduction Ratios

The serum pre-dialysis and post-dialysis levels of the of three middle molecules ( $\beta$ 2-microglobulin,  $\kappa$ FLC, and  $\lambda$ FLC) did not differ between the MCO and high-flux groups at baseline or at 12 weeks. However, the MCO dialyzer displayed better removal of  $\kappa$ FLC and  $\lambda$ FLC compared with the high-flux dialyzer. The removal of  $\lambda$ FLC was significant,  $p < 0.001$ . See Table 2.

### Comparison of Laboratory Data, Ultrafiltration Volume, and Dialysis Adequacy

No significant differences in biochemical markers including serum albumin (65 kDa<sup>1</sup>), ultrafiltration volume, and dialysis adequacy between the MCO and high-flux groups at baseline and at 12 weeks were found.

Reduction ratio (%)	Baseline			12 weeks		
	MCO (n = 24)	High-flux (n = 25)	P	MCO (n = 24)	High-flux (n = 25)	P
Severity						
Morning	1.92 ± 1.06	1.40 ± 0.50	0.033	1.54 ± 0.72	1.64 ± 0.86	0.667
Afternoon	2.00 ± 1.14	1.72 ± 0.84	0.332	1.88 ± 0.95	1.84 ± 1.07	0.904
Distribution						
Morning	1.42 ± 0.58	1.48 ± 0.71	0.736	1.29 ± 0.46	1.64 ± 0.64	0.034
Afternoon	1.46 ± 0.59	1.56 ± 0.96	0.659	1.38 ± 0.65	1.56 ± 0.71	0.347
Sleep disturbance						
Frequency of waking from sleep	0.83 ± 1.05	0.68 ± 1.28	0.650	0.75 ± 0.85	1.32 ± 1.60	0.126
Frequency of scratching during sleep	0.38 ± 0.92	0.24 ± 0.72	0.571	0.25 ± 0.53	1.00 ± 1.47	0.023
Total score by measuring system	8.58 ± 7.74	7.20 ± 7.58	0.530	6.92 ± 5.98	9.92 ± 8.23	0.152
VAS scoring system						
Morning	2.58 ± 2.24	2.14 ± 2.28	0.496	2.50 ± 1.93	3.34 ± 2.82	0.232
Afternoon	3.04 ± 2.57	2.74 ± 2.53	0.680	3.46 ± 2.32	4.24 ± 3.18	0.333
Average	2.81 ± 2.19	2.44 ± 2.31	0.565	2.98 ± 1.98	3.79 ± 2.91	0.262

**TABLE 2. Assessment of uremic pruritus at baseline and 12 weeks.** Abbreviations: MCO, medium cut-off; VAS, visual analog scale. Adapted from Lim et al.

### Adverse Events

No serious adverse events including cardiovascular events, death, or blood pressure decline that required dialyzer changes were observed.

## CONCLUSION

This is the first randomized controlled prospective trial comparing the effects of MCO and high-flux dialyzers on QOL in patients receiving maintenance HD. The higher physical functioning and role-physical scores with MCO dialyzer than with high-flux membrane found in this study were consistent with prior studies and is likely related to the better removal rate of middle molecules in the MCO group than in the high-flux group. The MCO group also had less frequent sleep disturbances caused by pruritus-related scratching. The new MCO dialyzer may improve self-reported QOL, particularly in the physical domains and uremic pruritus, in patients receiving maintenance HD who use permanent dialysis access. The MCO dialyzer also had a non-significant effect on the serum albumin concentration over 12 weeks of treatment.

**MCO (Theranova) membrane may improve patient-reported outcomes, particularly in the physical domains of QOL and uremic pruritus, through efficient removal of middle molecules, in stable maintenance HD patients.**

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# Impact of Medium Cut-Off Dialyzers on Patient-Reported Outcomes (PROs): COREXH Registry

Alarcon JC, Bunch A, Ardila F, et al. Impact of Medium Cut-Off Dialyzers on Patient-Reported Outcomes (PROs): COREXH Registry. *Blood Purif* 2020. doi: [10.1159/000508803](https://doi.org/10.1159/000508803).

## BACKGROUND

Health-related quality of life (HRQoL) is a patient reported outcome (PRO) that considers the subjective point of view of the patient and supports the evaluation of outcomes and healthcare quality. Patients on dialysis experience poor HRQoL due to the symptoms of end-stage renal disease (ESRD) and the physical and psychosocial burdens of their treatments.

The impact of contemporary renal replacement therapies on a patient's perceived HRQoL is critical to treatment success. While hemodialysis (HD) therapy removes small solutes, the removal of larger molecules >25 kDa (often termed large middle molecules) is limited. Hemodiafiltration (HDF) therapy can remove middle molecules more effectively than HD. However, the effect of an improved uremic environment resulting from the clearance of middle molecules remains unclear based on randomized studies.

Advances in membrane technology have led to the development of novel medium cut-off (MCO) membranes that have enhanced selectivity and increased permeability to conventional and large middle molecules. This results in a steep sieving curve in which the molecular weight retention onset and molecular weight cut-off are very close to each other while remaining lower than that of albumin, mimicking the filtration profile of the native kidney. The application of these membranes in clinical dialysis is known as expanded hemodialysis (HDx) therapy due to the enhanced clearance of large middle molecules, which are associated with cardiovascular disease, immune modulation, and protein-energy wasting. Initial studies have demonstrated that the MCO membrane removes toxins at least as effectively as a hemofilter used in HDF mode. The goal is that this enhanced removal will improve PROs and QoL for dialysis patients.

## OBJECTIVE

The goal of this study was to determine the impact of the MCO membranes on PROs, including HRQoL, presence and severity of symptoms, as well as diagnostic criteria of restless legs syndrome (RLS) in a large multicentric cohort of patients in the Expanded Hemodialysis Registry Protocol in Colombia (COREXH).

## METHODOLOGY

### Study Design and Patients

The study was a prospective, multicenter, observational cohort study of 992 patients undergoing dialysis from 12 renal clinics in Colombia who were switched from high-flux HD to MCO therapy and observed for 12 months. Patients with chronic kidney disease (CKD) aged 18 or older who had been undergoing HD therapy for more than 90 days at a **Renal Therapy Services** network clinic were invited to participate. Patients received HD therapy using the MCO dialyzer (**Theranova**, Baxter, Deerfield, IL, USA) three times a week for a minimum of 4 hours. Patients diagnosed with an active infection within the last 4 weeks or had a life expectancy less than 6 months were excluded. Eligible patients were prospectively followed for 12 months from enrollment.

## Assessments

Baseline (before switching to therapy with the MCO dialyzer) demographic and disease characteristics were collected. HD treatment parameters, including session duration, number of sessions per week, blood flow, dialysate flow, and type of vascular access were recorded. Baseline values of Kidney Disease Quality of Life 36-Item Short Form Survey (KDQoL-SF36), Dialysis Symptom Index (DSI), and diagnostic criteria for RLS were captured and repeated at 6 and 12 months.

## RESULTS

### Patient Profile

A total of 992 patients from 12 clinics were included in the baseline, with 638 remaining at 12-month follow-up. Patients had been receiving high-flux HD for a median of 3.7 years at the time of enrollment.

### Kidney Disease Quality of Life 36-Item Short Form Survey

After 12 months of therapy with the MCO dialyzer, three of five KDQoL domains improved compared with baseline, with the most pronounced improvements found in the kidney disease effects domain. Significant increases in KDQoL-36 mean scores from baseline were also observed for symptoms/problems and burden of kidney disease. No significant changes in scores for mental and physical domains were found (see Table 1). The effect size was modest but consistent across the full 12-month follow up period, suggesting that the expanded clearance of large molecules may be associated with improvements in QoL. In addition, contrary to the expected outcomes for patients receiving chronic dialysis, QoL trended towards improvement over the course of follow-up.

Decreases in the physical and kidney disease components of KDQoL-36 had been associated with increased adjusted mortality risk. The Convective Transport Study (CONTRAST) demonstrated that decreases in physical function, emotional health, and social functioning were significantly associated with mortality over 2 years and were independent of age. Thus, the positive impact of the expanded removal of large middle molecules on QoL measures observed in this study is encouraging.

KDQoL-36 Domain	Statistic	Baseline n = 971	6 months n = 808	12 months n = 642	P value*
Symptoms/problems	Mean	78.6	81.0	81.5	<0.0001
	SD	15.8	15.4	14.9	
Effects of kidney disease	Mean	69.7	72.8	75.1	<0.0001
	SD	22.3	22.0	21.0	
Burden of kidney disease	Mean	46.2	48.9	50.2	<0.0001
	SD	27.5	29.9	32.3	
SF-12 Physical	Mean	41.1	41.0	41.7	0.3
	SD	11.1	11.2	10.5	
SF-Mental	Mean	51.1	51.9	52.3	0.02
	SD	11.6	11.3	11.1	

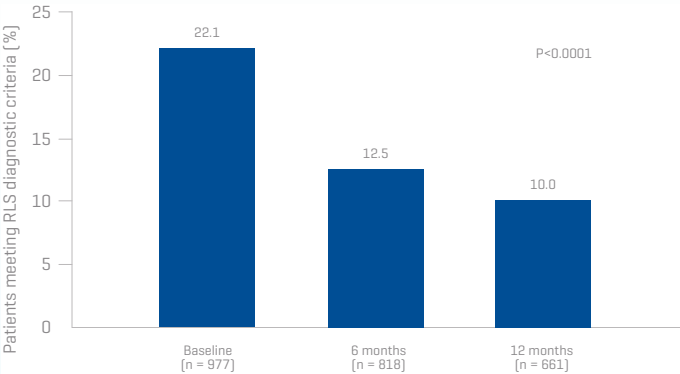
**TABLE 1. Change of Kidney Disease Quality of Life 36-Item Short Form Survey (KDQoL-36) Score Over 12 Months of Follow Up.** \*For hypothesis testing, type-1 error/p value significance was set at p=0.01. Abbreviation: SD, standard deviation. Adapted from Alarcon et al.





### Restless Legs Syndrome Diagnostic Criteria

The proportion of patients meeting RLS diagnostic criteria significantly decreased (54.6%) over the follow-up period. See Figure 1. Combined with the difficulties in correlating uremic toxin removal with RLS occurrence as well as the consistent, yet limited, data indicating HD has minimal impact on RLS, results suggest that the expanded clearance of large middle molecules with the MCO membrane comparable with the natural kidney) may alleviate the development and impact of RLS.



**FIGURE 1. Longitudinal Changes in Patients Meeting Restless Legs Syndrome (RLS) Diagnosis over 12 Months of Follow Up.** Abbreviation: RLS, restless leg syndrome. Adapted from Alarcon et al.

### CONCLUSION

Significant improvements were observed in three of the five HRQoL domains measured by KDQoL: symptoms/problems; effects of kidney disease; and burden of kidney disease. A significant decrease was also shown for the percentage of patients meeting the diagnostic criteria for RLS at 12 months. Expanded clearance of large middle molecules provided by the MCO membrane (closer to the natural kidney) may be associated with improvements in patient’s QoL and may alleviate the development and impact of RLS.

**Expanded clearance of middle molecular uremic toxins with MCO membranes (Theranova) may improve patient reported kidney disease quality of life outcomes including symptom burden, and Restless Leg Syndrome (RLS) criteria.**

### Dialysis Symptom Index

No significant differences in the mean number of symptoms from baseline were observed at 6- and 12-month follow up. However, a significant decrease in mean severity scores from baseline were observed at 6 and 12 months. See Table 2. All 30 DSI items, each of which target a specific physical or emotional symptom, were reported at a lower frequency at 6 and 12 months than at baseline, with marginally significant reductions in shortness of breath, dizziness/light-headedness, and difficulty falling asleep. The decrease in the proportion of patients with difficulties falling asleep, as well as in the presence of dizziness/light headedness was likely related to improvements in RLS and sleep pattern, which has been previously linked to the clearance of middle molecules in literature.

### Strengths and Limitations

The study strengths included its prospective observation, enabling the longitudinal measurement of outcomes and comparison with historical baseline values, and its large cohort of patients (n=992) from multiple clinics. The study limitations included no randomization as a registry, or blinding to the intervention, as well as no comparator group.

DSI Domain	Statistic	Baseline	6 months	12 months	P value
		n = 977	n = 813	n = 642	
Number of symptoms	Mean	10.3	10.3	10.0	0.1 <sup>a</sup>
	SD	6.6	6.7	6.6	
	Mean	9	9	9	NA
	IQR	10	10	9	
Symptom severity score	Mean	30.7	29.9	28.5	0.0009 <sup>b</sup>
	SD	22.3	32.0	21.7	
	Mean	26	26	23	NA
	IQR	32	30	31	

**TABLE 2. Changes in Dialysis Symptom Index (DSI) Over 12 Months of Follow Up.** a. by Friedman’s test. b. by ANOVA. Abbreviations: ANOVA, analysis of variance; DSI: dialysis symptom index; IQR, interquartile range; SD, standard deviation. Adapted from Alarcon et al.



# Clinical Assessment of Dialysis Recovery Time and Symptom Burden: Impact of Switching Hemodialysis Therapy Mode

**Bolton S, Gair R, Nilsson LG, et al.** Clinical Assessment of Dialysis Recovery Time and Symptom Burden: Impact of Switching Hemodialysis Therapy Mode Patient Related Outcome Measures 2021:12 315–321. doi: [10.2147/PROM.S325016](https://doi.org/10.2147/PROM.S325016).

## BACKGROUND

People with end-stage renal disease on hemodialysis (HD) report a high symptom burden that impacts quality of life. Fatigue and lack of energy are common, which interfere with daily life and are associated with poor outcomes. Prolonged recovery time after each dialysis treatment is also common, with patients on conventional HD typically reporting recovery time of 2–4 hours, with approximately 25% reporting recovery time over 6 hours.

It has been proposed that the retention of large middle molecule (MM) uremic toxins in people with chronic kidney disease could influence the symptom burden. A medium cut-off (MCO) membrane was recently introduced, allowing for expanded hemodialysis (HDx) to achieve more effective clearance of large MMs, even when compared to HDF. Further studies are needed to assess the impact of enhanced dialytic removal of large MMs on the dialysis-related symptom burden.

## OBJECTIVE

The aim of this clinical assessment was to evaluate the impact of HDx on patient reported recovery time and symptom burden.

## METHODOLOGY

This pilot retrospective analysis reports on the initial 12-month experience at an in-center renal unit after implementing HDx therapy, focusing on the patient-reported symptom burden during this period.

In 2018 a patient-reported outcome measures (PROM) program was implemented to capture HD patients' symptom burden as part of routine clinical care. At the same time, an evidence-based decision was made to implement HDx, using the MCO membrane (Theranova dialyzer; Baxter Healthcare Ltd), as the preferred in-center hemodialysis therapy to achieve effective MM clearance.

### PROM Data Collection

PROM data collection started in March/April 2018 and was thereafter performed quarterly. PROM assessments were typically administered to people while on dialysis at a mid-week session. Individuals were asked about their post-dialysis recovery time using the question "How long does it take to get back to normal, after dialysis?". Data on symptom prevalence and severity were collected using the 17-item version of the Palliative Care Outcome Scale–Symptom module for renal patients (POS-S Renal), which asks how 17 predefined symptoms had affected patients in the past week using a 5-point scale ("not at all" = 0, "slightly" = 1, "moderately" = 2, "severely" = 3, "overwhelmingly" = 4).

### Dialysis Treatments

At the start of the PROM data collection individuals were on conventional thrice weekly hemodialysis at the in-center dialysis unit and treated with regular high-flux membranes (Revaclear dialyzer in HD and Polyflux H dialyzer in HDF; Baxter Healthcare Ltd). Following the implementation of PROM assessments, the renal team made an evidence-based decision to implement HDx using the MCO membrane (Theranova dialyzer; Baxter Healthcare Ltd). Treatment prescription factors such as frequency, blood flow rate (median 300 mL/min), dialysate flow (500 mL/min), and treatment time (median 4 hours) were not affected by the therapy change.

## RESULTS

### Participants

Overall 90 patients agreed to provide PROM data. Mean age was 73 years, and 62% of participants had received hemodialysis treatments for 3 years or less, and 9% for 10 years or more. Prior to HDx, 25 (28%) of participants received HDF and 65 (72%) received HD.

Participant numbers providing data at 3, 6, 9, and 12 months were 80, 72, 68, and 59 respectively.

### Safety of Transition to HDx therapy

The MCO membrane was introduced without incident over a 2-week period to all individuals on HD at the unit, and it has remained the standard of care. All individuals tolerated the new membrane well. No clinically significant changes in albumin, C-reactive protein, and hemoglobin levels were noted. No signs of increased infection rate were observed.

### Post-dialysis Recovery Time

Overall, the median self-reported recovery time at baseline was 240 min (IQR: 60–720; N = 89). At follow-up, the recovery time was shorter:

- 120 min (22–435) at 3 months,
- 60 min (0–240) at 6 months ( $p < 0.01$ ),
- 60 min (0–240) at 9 months ( $p < 0.01$ ), and
- 105 min (0–180) at 12 months ( $p < 0.01$ ).

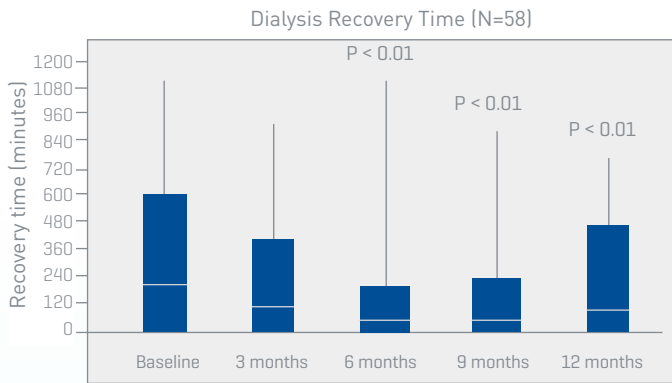
The subgroup of participants who provided recovery time data throughout the 12-month period (N = 58) reported a similarly decreased recovery time (See Figure 1). In this subgroup, the percentage of people reporting a recovery time greater than 360 minutes decreased from 36% at baseline to 26%, 14%, 14%, and 9% at 3, 6, 9, and 12 months, respectively.



## CONCLUSIONS

Sustained improvements in patient-reported post-dialysis recovery time and POS-S Renal fatigue score were observed over a 12-month period after a switch from regular HD/HDF using high-flux membranes to HDx using the MCO membrane. Quarterly application of PROM tools to an in-center HD population was feasible and well accepted by patients. These results provide indications that enhanced clearance of large middle molecules, as achieved by HDx, may have a positive impact on HD individuals' symptom burden.

**Switching to HDx therapy with MCO membrane led to a sustained, clinically relevant decrease in patient-reported recovery time after dialysis and a decrease in fatigue levels.**



**FIGURE 1.** Reported post-dialysis recovery times for individuals who completed the 12-months observation period (N = 58). Notes: Boxes show medians and 25th/75th percentiles and whiskers show 95th percentiles #Denotes  $P < 0.01$  vs baseline.

## Symptom Burden

In the overall population, at baseline the median number of symptoms per participant was 7 (IQR 4–10; N = 90) and the total symptom score varied between individuals from 1 to 42, with a median value of 13 (IQR 7–18.8). At the 3- and 6-month follow-ups, the total symptom score showed a decrease to 11 (5–16) at 3 months ( $p = 0.03$ ) and 10.5 (5–19) at 6 months ( $p = 0.005$ ), while subsequent follow-ups were not different from baseline.

The subgroup of the population who completed the 12-month observation period showed a baseline total score of 12 (7–17.3; N = 56), with a significant decrease at 6 months (See Table 1).

**TABLE 1.** POS-S Renal Total Symptom Scores (Median, IQR for Participants Who Provided Ratings Up to 12 Months (N = 56)

Baseline	3 Months	6 Months	9 Months	12 Months
12 [7-17.3]	10 [4.5-16] P = 0.06	8 [5-19] P = 0.003	11 [5.8-20.3] P = 0.8	12 [5-22] P = 0.8

Notes: P-values are in comparison to baseline.

“Weakness or lack of energy” and “Poor mobility” were reported as the most bothersome symptoms. The percentage of patients reporting that “Weakness or lack of energy” affected them “severely” or “overwhelmingly” in the past week decreased from 28% at baseline to 16%, 15%, 20%, and 16% at 3, 6, 9, and 12 months, respectively.

## Limitations

As this was not a formal study with a control group, we cannot exclude that improvements seen in recovery time and fatigue were unrelated to the membrane and therapy change. It should be considered that PROM data were not returned anonymously so the identification of specific symptoms at the initial assessment could have led to improved symptom management resulting in reduced symptom severity at later stages. These findings reflect a real-life assessment of PROMs in about 80% of the in-center HD population, however, being a single-center experience, these results may not necessarily be applicable to populations in other dialysis centers with other dialysis practices.



# Impact of expanded hemodialysis using medium cut-off dialyzer on quality of life: application of dynamic patient-reported outcome measurement tool

Penny JD, Jarosz P, Salerno FR, et al. Impact of expanded hemodialysis using medium cut-off dialyzer on quality of life: application of dynamic patient-reported outcome measurement tool. *Kidney Med.* 2021; 3(6):992-1002.e1. doi: 10.1016/j.xkme.2021.05.010.

## BACKGROUND

Many patients with chronic kidney disease (CKD) have retained toxins, particularly larger molecular weight toxins, despite maintenance hemodialysis (HD). These toxins have been associated with cardiovascular disease, chronic systemic inflammation, and increased mortality. Not surprisingly, patients receiving maintenance HD often report significant symptom burden and impaired health-related quality of life (HRQoL). To address this need, medium cut-off dialyzers have been developed that offer the opportunity to remove middle-molecular-weight molecules without removing essential proteins such as albumin and without the need for high-flux hemodiafiltration and its added requirements of infrastructure, costs, and patient selection criteria. Patient-reported outcome measures (PROMs) may help guide clinicians in determining when traditional HD has not sufficiently managed patient symptoms and improved their HRQoL. Theoretically, the use of a rapid, relevant, and repeated PROM tool could guide clinical decisions about the most appropriate dialyzer for a specific patient. The London Evaluation of Illness (LEVIL), is such a PROM instrument. Developed with user input, this tool measures well-being, energy level, sleep quality, bodily pain, appetite, and shortness of breath using visual analog scales. LEVIL takes only seconds to complete, provides real-time monitoring, allows a 24-hour recall period, and is intended for repeated use. An initial study has proven that LEVIL is easy to use, acceptable to patients, and sensitive to clinical changes in the short- and long-term.

## OBJECTIVE

This pilot study's main purpose was to establish whether expanded hemodialysis utilizing medium cut-off dialyzers (HDx) may be associated with changes in HRQoL/symptom burden, whether there may be a dose-dependent response, and whether effects were durable over time, as assessed using LEVIL.

## METHODOLOGY

This single-center, unblinded, exploratory pilot study was conducted in the prevalent adult HD population within the London Health Sciences Centre Renal Program in Ontario, Canada. All patients had been receiving thrice-weekly HD for > 3 months. During the 2-week baseline period, patients completed the app-based LEVIL assessment during each of their usual high-flux dialyzer sessions. During the 12-week test period, patients completed LEVIL while receiving HD with a medium cut-off dialyzer that maintained the surface area of the membrane that had been used during the baseline period (i.e., smaller-surface-area dialyzers converted to Theranova 400; larger surface dialyzers to Theranova 500). Blood work included complete blood cell count, electrolytes, C-reactive protein,  $\beta_2$ -microglobulin (B2M),  $\kappa$ - and  $\lambda$ -free light chains (K-FLC, L-FLC), and the free light chain ratio.

A 24-week extension was planned to include a washout phase and a return to high-flux HD for 8 more weeks.

Dialysis treatments were delivered using Fresenius 5008 dialysis monitors, with treatment times between 3.5 and 4 hours. Net ultrafiltration was calculated on an individual basis according to each patient's ideal dry weight. Dialysis prescriptions were unchanged except for the switch between high-flux polysulfone dialyzers and HDx. Patients answered 6-question LEVIL surveys via iPad app during each dialysis session. Each participant's LEVIL scores during the first two weeks (i.e., baseline) were averaged to create a collective baseline score that was used to stratify patients into those with high- or low-HRQoL scores. High HRQoL scores were those with an overall average score  $\geq 70$ ; determination of an "acceptable" HRQoL score was based on a survey of 11 study patients.

Primary outcomes were changes in HRQoL and symptoms when patients were treated with HDx vs baseline conventional high-flux HD. Secondary outcomes included middle-molecule biomarkers and middle-molecule reduction ratios.

## RESULTS

### Study Population

Twenty-eight patients consented to participate. One died before study initiation, another died of overwhelming sepsis during the study, one patient was removed due to poor dialysis attendance, and three patients withdrew consent, leaving 22 patients to be analyzed over 12 weeks. Due to limited patient access during the COVID-19 pandemic, only 6 patients were able to complete the 24-week extension program.

Participants' mean age was  $65.6 \pm 14.6$  years, with a median time on HD of 55 months. Half of the participants were men, 41% had diabetes mellitus type 2, and 41% of patients had some degree of residual kidney function. Half of the population was treated with Theranova 400, half with Theranova 500.

### Stratification

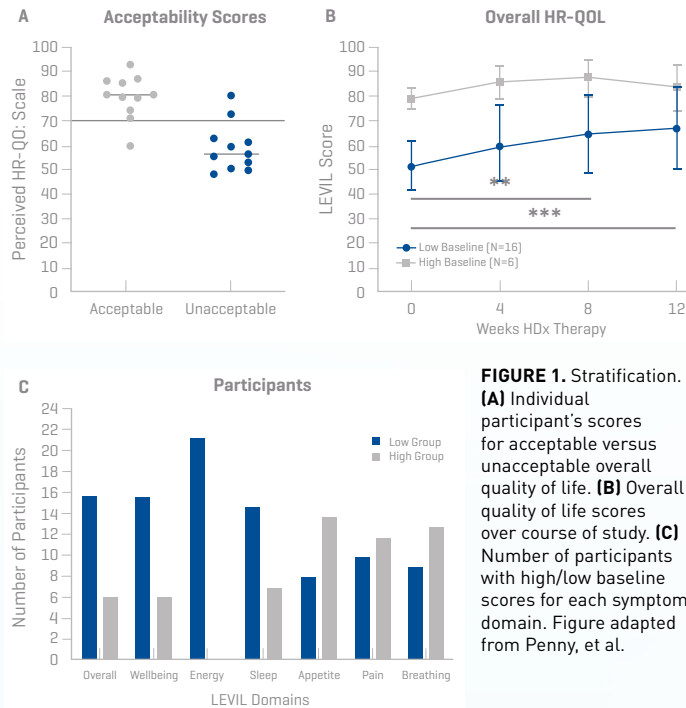
Sixteen of 22 patients (73%) had a low overall HRQoL baseline. Figure 1A shows how individual participants' HRQoL fell on what survey participants deemed "acceptable" or "unacceptable" for HRQoL scores. Figure 1C shows, at baseline, how many participants had "low" vs "high" HRQoL scores for each domain. Note, for example, that none of the participants ranked energy levels as being at a high HRQoL level. When domain sub-analyses are shown, high and low QoL classifications refer to baseline rankings specific to that domain.

### HR-QoL Changes

For the overall HRQoL, the 16 patients with "low" initial overall HRQoL scores and the 6 patients with high initial scores (as shown in Figure 1C) are tracked in Figure 1B and in Table 1 as they received 12 weeks of HDx therapy:

- **Low HRQoL group:** The average HRQoL among those with low initial HRQoL increased significantly from baseline to week 8 ( $P = 0.001$ ) and week 12 ( $P = 0.001$ ).
- **High HRQoL group:** Patients who had high initial HRQoL saw no significant changes in HRQoL throughout the study.





**TABLE 1.** LEVL scores at baseline and 4, 8, and 12 weeks of HDx therapy; Total population and stratified groups. Adapted from Penny, et al.

Total Population								
Initial Study	N	Baseline	4-wk HDx	P	8-wk HDx	P	12-wk HDx	P
Overall HRQoL	22	59.1±14.4	66.8±17.5	0.12	70.9±17.6	<0.001	71.9±16.8	<0.001
Subgroup analysis								
General well-being	22	52.2±19.6	60.9±23	0.28	69±21.1	0.001	71±17.9	0.002
Energy	22	40.3±20.5	53.4±23.3	0.16	59.9±22.8	0.001	64.7±19.6	<0.001
Sleep quality	22	49.4±26.8	62.2±27.9	<0.001	65.6±24.2	<0.001	68.9±24.5	<0.001
Bodily pain	22	67.3±25.5	68±26.8	>0.99	72.5±25.2	>0.99	71.5±22.1	>0.99
Appetite	22	70.3±21.8	77.9±21.6	>0.99	81.1±21.2	0.28	78.0±22.5	>0.99
Breathing	22	78.2±27.5	77.4±25.8	>0.99	75.9±22.9	>0.99	49.6±22.2	>0.99
Scores < 70 at Baseline: Low								
Initial Study	N	Baseline	4-wk HDx	P	8-wk HDx	P	12-wk HDx	P
Overall HRQoL	16	51.5±10.2	59.5±14.4	0.33	64.6±16.2	0.001	67.2±16.9	<0.001
Subgroup analysis								
General well-being	16	43±14.1	52.9±21.4	>0.99	65.2±21.9	<0.001	66.3±17.7	0.002
Energy	22	40.3±20.5	53.4±23.3	0.16	59.9±22.8	0.001	64.7±19.6	<0.001
Sleep quality	16	37.2±20.1	52.8±26.7	0.01	57±22.2	0.002	61.7±24.5	<0.001
Bodily pain	10	43.2±12.3	47.4±24	>0.99	56.2±25.7	0.23	57.3±20.5	>0.99
Appetite	8	46.1±14.8	63.8±28	>0.99	67±30.8	0.05	66.9±31.8	>0.99
Breathing	9	49.6±22.2	53.7±27.3	>0.99	53.7±23.5	>0.99	61.6±24.6	>0.99
Scores ≥ 70 at Baseline: High								
Initial Study	N	Baseline	4-wk HDx	P	8-wk HDx	P	12-wk HDx	P
Overall HRQoL	6	79.2±4.3	86.1±6.8	>0.99	70.9±17.6	0.15	83.6±9.6	>0.99
Subgroup analysis								
General well-being	6	76.6±5.6	82.1±9.7	.71	69±21.1	>0.99	83.5±12.2	>0.99
Energy	0	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sleep quality	6	81.8±8.3	87.3±10.4	.15	65.6±24.2	<0.01	89.2±6.3	0.04
Bodily pain	12	87.4±12.1	85.2±13.8	>0.99	72.5±25.2	>0.99	82.9±16.1	0.68
Appetite	14	84.3±8.8	85.9±11.9	>0.99	81.1±21.2	>0.99	84.4±12.4	>0.99
Breathing	13	92±9	95.2±8.4	>0.99	75.9±22.9	>0.99	85.8±16	>0.99

## Laboratory Values

Table 2 shows laboratory values for the total population and for the two HRQoL subpopulations at baseline and after 12 weeks of HDx therapy:

- **Proteins:** Circulating levels of albumin did not change during therapy ( $P = 0.73$ ); this was also true of the subpopulations (low HRQoL,  $P = 0.096$ ; high HRQoL,  $P = 0.69$ ).

- **B2M:** There was no significant change in serum B2M level, but there was significance in the reduction ratio of B2M between high-flux HD and HDx ( $P < 0.001$ ), and this was true of the subpopulations (low HRQoL,  $P < 0.001$ ; high HRQoL,  $P = 0.03$ ).

- **Free light chains:** A significant reduction in serum levels of K-FLC was noted in the overall population ( $P < 0.001$ ) and the low HRQoL subpopulation ( $P = 0.02$ ) but not the high HRQoL population ( $P = 0.16$ ). For L-FLC, the overall population showed a significant decrease over 12 weeks ( $P = 0.02$ ) even though subpopulations did not reach statistical significance (low HRQoL,  $P = 0.07$ ; high HRQoL,  $P = 0.22$ ). Reduction ratios were consistently significant higher with HDx for K-FLC and L-FLC in the total population and the subpopulations.

**TABLE 2.** Laboratory values at baseline compared with 12-Week HDx. Table adapted from Penny et al.

	Baseline	12-wk HDx	Baseline to 12-wk HDx
Total Population Overall HRQoL (N=22)			
Alb, g/L	41±3.8	40.8±2.8	0.73
Alb RR, %	3.9±6.4	4.3±7.1	0.78
B2M, mg/L	28.8±6.8	28.6±5.9	0.91
B2M RR, %	54.2±9.6	70.6±6.3	<0.001
K-FLC, mg/L	183.6±126.7	164.1±100.4	0.002
K-FLC RR, %	27±22.1	53.3±12.7	<0.001
L-FLC, mg/L	119.2±40.1	111.6±36.8	0.02
L-FLC RR, %	3±9.1	29.5±10	<0.001
FLC-R	1.7±1.3	1.6±1.1	0.15
FLC-R RR, %	24.9±21.1	34.1±13.3	0.05
Low Overall HRQoL Group (N=16)			
Alb, g/L	40.6±2.9	40.6±2.9	0.96
Alb RR, %	3.1±6.3	3.8±8	0.88
B2M, mg/L	29.4±7.4	29±6.4	0.63
B2M RR, %	55.3±10.1	71.5±6.4	<0.001
K-FLC, mg/L	198.9±145.1	178.2±113.3	0.02
K-FLC RR, %	25.8±25.9	54.2±14.1	<0.001
L-FLC, mg/L	118.6±36.5	111.7±36.1	0.07
L-FLC RR, %	3.6±8	32.5±10.1	<0.001
FLC-R	1.8±1.5	1.7±1.2	0.37
FLC-R RR, %	23.5±24.6	32.8±14.9	0.23
High Overall HRQoL Group (N=6)			
Alb, g/L	41.8±4.6	41.2±2.9	0.69
Alb RR, %	6.6±6.7	6±2.3	>0.99
B2M, mg/L	27.3±5.2	27.6±4.4	0.44
B2M RR, %	51.1±8.1	68.3±5.9	0.03
K-FLC, mg/L	142.8±38.5	126.6±38	0.16
K-FLC RR, %	30±8	50.9±9.1	0.03
L-FLC, mg/L	120.8±52.6	111.3±42.2	0.22
L-FLC RR, %	1.7±12.1	22.1±4	0.03
FLC-R	1.3±0.3	1.2±0.2	0.22
FLC-R RR, %	28.4±7.9	37.1±8	0.31

Note: Values are represented as mean ± standard deviation.

## Domain-specific Subgroup Analysis

Both Table 1 and Figure 2 illustrate changes in individual domains over time:

- General well being improved significantly at 8 and 12 weeks ( $P < 0.001$ ,  $P = 0.002$ , respectively) for those in the low HRQoL group at baseline and did not change among those with a high baseline score.

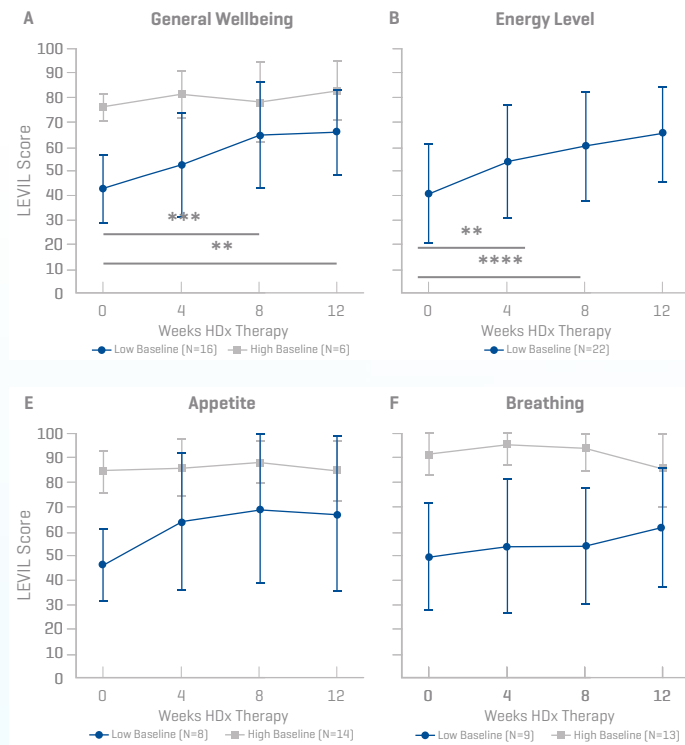
- Energy level was poor for all patients at baseline, but improved significantly at 8 and 12 weeks ( $P = 0.001$ ,  $P < 0.001$ , respectively).

- Sleep quality improved significantly among those with low baseline scores at 4, 8, and 12 weeks ( $P = 0.01$ ,  $P = 0.002$ ,  $P < 0.001$ , respectively). Those with acceptable sleep quality at baseline reported additional benefit after 8 and 12 weeks of HDx ( $P = 0.001$ ,  $P = 0.04$ , respectively).

- Bodily pain, appetite, and difficulty breathing/shortness of breath were not significantly affected by HDx over 12 weeks.



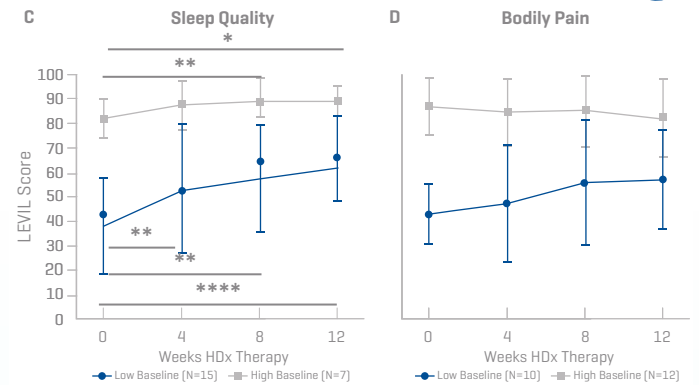
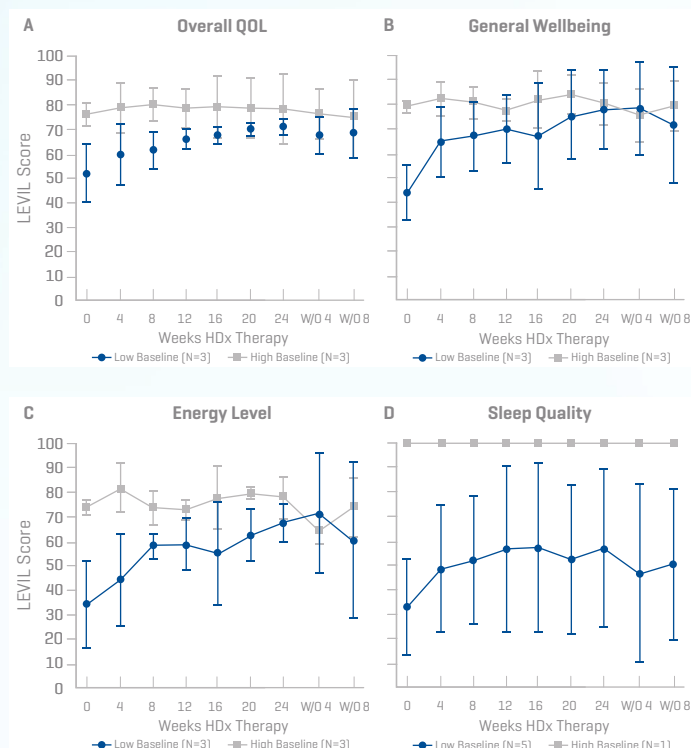
**FIGURE 2.** Subgroup analysis: domain specific analysis. (A) General well-being, (B) energy, (C) sleep, (D) pain, (E) appetite, and (F) breathing. Figure adapted from Penny, et al.



### Extension Evaluation

The COVID-19 pandemic hindered data collection in all but 6 patients, so significance cannot be accurately assessed; Figure 3 is included simply to illustrate that these 6 patient profiles followed a profile consistent with that of the main study. Overall HRQoL, general well-being, and energy level seemed to follow different trends during the 8-week washout period.

**FIGURE 3.** Extension phase; 24 weeks of expanded hemodialysis (HDx) with 8 weeks of washout (W/O). (A) Overall and (B, C, D) domain-specific quality of life. Figure adapted from Penny, et al.



### Study Limitations

Study limitations included small sample size in a single-center setting and nonrandomized unblinded design.

### CONCLUSIONS

In this study, expanded hemodialysis using medium cut-off dialyzers (HDx) over 12 weeks was shown to reduce symptom burden and improve overall HRQoL, particularly among those with poorer HRQoL at baseline. Specific findings include the following:

- Overall HRQoL improved significantly at 8 and 12 weeks among those with low HRQoL at baseline and did not change for those with higher baseline scores.
- Improvements in overall HRQoL seemed to be driven mainly by scores in the domains of general well being, energy level, and sleep quality, which all improved for the group with low scores in those domains at baseline. Interestingly, sleep quality improved with HDx even for those with “acceptable” sleep quality at baseline.
- Laboratory values show no significant change in albumin levels for the total population nor for the subpopulations after 12 weeks of HDx.
- B2M levels in serum were not significantly changed over 12 weeks, but the reduction ratio of B2M was significantly higher in HDx versus high-flux HD.
- A significant reduction in serum levels of  $\kappa$ -FLC was noted in the overall population and the low HRQoL subpopulation but not the high HRQoL population. For L-FLC, the overall population showed a significant decrease over 12 weeks ( $P = 0.02$ ) even though subpopulations did not reach statistical significance. Reduction ratios were consistently significantly higher for K-FLC and L-FLC in HDx versus high flux HD in the total population and the subpopulations.

# HDx: A WORLD OF DIFFERENCE

## Clinical Outcomes Impacted by HDx Therapy



Patients receiving HDx therapy enabled by THERANOVA may have a lower rate of infection and fewer infection-related hospitalization days compared with patients receiving HD.<sup>1-3</sup>



**Molano AP, Hutchison CA, Sanchez R, et al.**

**Medium Cutoff Versus High-Flux Hemodialysis Membranes and Clinical Outcomes: A Cohort Study Using Inverse Probability Treatment Weighting.** *Kidney Med.* 2022;4(4):1-10.



**Kandi M, Brignardello-Petersen R, Couban R, et al.**

**Clinical Outcomes With Medium Cut-Off Versus High-Flux Hemodialysis Membranes: A Systematic Review and Meta-Analysis.** *Can J Kid Health Dis.* 2022;9:1-16.



**Cozzolino M, Magagnoli L, Ciceri P, et al.**

**Medium Cut-Off (Theranova) Dialyzer on Haemodialysis Patients: A Prospective, Cross-over Study.** *Clinical Kidney Journal* 2019:1-8.

1. Molano AP, Hutchison CA, Sanchez R, et al. Medium Cut-Off Versus High-Flux Hemodialysis Membranes and Clinical Outcomes: A Cohort Study Using Inverse Probability Treatment Weighting. *Kidney Med.* 2022;4(4):1-10.
2. Kandi M, Brignardello-Petersen R, Couban R, et al. Clinical Outcomes With Medium Cut-Off Versus High-Flux Hemodialysis Membranes: A Systematic Review and Meta-Analysis. *Can J Kid Health Dis.* 2022;9:1-16.
3. Cozzolino M, Magagnoli L, Ciceri P, et al. Effects of a Medium Cut-Off (Theranova®) Dialyzer on Haemodialysis Patients: A Prospective, Cross-over Study. *Clinical Kidney Journal.* 2019;1-8.





# Medium Cut-Off Versus High-Flux Hemodialysis Membranes and Clinical Outcomes: A Cohort Study Using Inverse Probability Treatment Weighting

**Molano AP, Hutchison CA, Sanchez R, et al.** Medium Cut-Off Versus High-Flux Hemodialysis Membranes and Clinical Outcomes: A Cohort Study Using Inverse Probability Treatment Weighting. *Kidney Medicine*. 2022. In Press. doi: <https://doi.org/10.1016/j.xkme.2022.100431>.

## BACKGROUND

Despite advances in the field of chronic hemodialysis (HD) and improvements in morbidity and mortality, outcomes for chronic HD patients are far from optimal. Improved clearance of uremic toxins may reduce their adverse effects on biological systems and lead to improved outcomes. Recent data suggest that increased removal of large middle molecules may improve clinical outcomes through impact on inflammation and atherosclerosis. Advances in bioengineering have allowed development of a novel medium cut-off (MCO) membrane (Theranova® 400/500, Baxter) that improves clearance of large middle-molecules 25 kDa and above.

## OBJECTIVE

Determine whether there are differences in clinical outcomes when chronic HD patients are treated with MCO membranes compared to high-flux (HF) membranes.

## METHODOLOGY

This was a retrospective, observational, multicenter, cohort study of patients undergoing HD (defined as received HD for 90 days) in Colombia. Patients were included from Baxter Renal Care Services network of renal between September 1, 2017 to November 30, 2017, with follow up to November 30, 2019. Enrollment occurred immediately for patients in the MCO cohort once switched to this new membrane type. Inclusion criteria included: age >18 years; receiving expanded hemodialysis (HDx) using an MCO membrane (Theranova®, Baxter, Deerfield, IL, USA) or conventional HD using HF membrane for a minimum of 4 hours 3 times per week. Patients in both cohorts were included from the same dialysis clinics and membrane allocation was not done by predetermined methods but rather by decisions by each individual clinician. Standard dialyzers available in renal clinics were used. Exclusion criteria were life expectancy of less than six months, active infection, metastatic disease, or a Charlson comorbidity index greater than eight.

Patients were divided into two cohorts according to the membrane used at the time of enrollment: 1) MCO group or 2) HF group. Once a patient had been included in one of the two cohorts, the clinical teams were instructed not to change the membrane type unless determined by a medical decision or patient request.

## OUTCOMES AND ANALYSIS

**Primary outcome:** hospitalization rate from any cause and hospitalization days per patient-year.

**Secondary outcomes:** non-fatal cardiovascular events (any hospitalization event for causes predefined in the International Classification of Diseases 10 as cardiovascular); time to death survival analysis from any cause; changes in serum albumin levels during follow-up.

Inverse Probability of Treatment Weighting (IPTW) using a propensity score was used to control differences between groups. The propensity score for each subject was calculated from a logistic regression model that included clinical and demographic variables as predictors of the exposure status such as age, sex, race, dialysis duration, CKD cause, hypertension history, diabetes history, cardiovascular disease history, Charlson comorbidity index, Karnofsky scale, urine output ml/day, BMI, serum albumin, hemoglobin, parathormone intact, phosphorous, potassium, Kt/V single pool, and normalized protein catabolic rate and the research site location. The IPTW for each individual subject was then calculated and the balance between exposed and unexposed groups in the weighted sample was evaluated based on descriptive methods (standardized differences, with a target value of < 0.1, and variance ratios) and inferential methods (over identification test for covariate balance), and the effect of the exposure on each outcome was estimated using robust standard errors. For the outcome hospitalization rate and days, negative binomial regression models were used for violation of the over dispersion assumption and Akaike and Bayesian Information criteria were used to compare the models; the association was estimated with Incidence Rate Ratio (IRR). Survival time was estimated in the full sample, and the weighed population according to membrane use; the log-rank test was used to compare the equality of the survival functions in the full sample; for comparison in the weighed population, we used Cox regression. To confirm the direction of the effect, negative binomial regression models in full sample were performed.

## RESULTS

### Patients

A total of 1098 patients were enrolled (564 in the MCO group and 534 in the HF group); and 711 completed the total follow-up time (391 in the MCO group and 320 in the HF). Mean age was 60.3 ±14.9 years in the MCO group, and 60.8 ±15.0 years in the HF group, and 65.2% were male in the HF group and 59.6% in the MCO group. The proportion of patients with diabetes mellitus was similar in the two groups, 43.6% for MCO vs. 40.1% for HF,  $p = 0.23$ . Baseline albumin levels were 4.0 g/dl for MCO vs. 4.0 g/dl for HF. After weighting using IPW, no statistically significant difference between groups in baseline characteristics was observed.

### Clinical Outcomes

In the weighted sample, MCO was associated with fewer all-cause hospitalization events rate per patient-year,  $IR = 0.93$  [95% CI 0.82–1.03] versus 1.13 [95% CI 0.96–1.30] for HF, corresponding to a significant IRR MCO/HF of 0.82 [95% CI 0.68–0.99];  $p = 0.04$ .

There was no significant difference in hospital days;  $p = 0.73$ . Across both groups, cardiovascular events were the most frequent cause of hospitalization (28.5% MCO vs 31.1% HF).





The non-fatal cardiovascular event rate per patient-year was lower in the MCO group, IR = 0.18 [95% CI 0.14-0.22] versus IR = 0.28 [95% CI 0.19-0.36] for HF, corresponding to a significant IRR MCO/HF of 0.66 [95% CI 0.46-0.96];  $p = 0.03$ .

There was no significant difference in survival between MCO vs HF dialyzers, HR = 0.88 [95% CI 0.64 to 1.23];  $p = 0.48$ .

Table 1 shows clinical outcomes, and Figures 1 and 2 show survival curves.

**TABLE 1.** Clinical outcomesw in full simple and weighted samples.

Clinical Outcomes	Crude Estimate (95% CI)	P value	Adjusted Estimate With IPTW (95% CI)	P value
<b>Hospitalization events<sup>a</sup></b>				
HF membrane	1.07 [0.99-1.14]	—	1.13 [0.96-1.30]	—
MCO membrane	0.79 [0.73-0.84]	—	0.93 [0.82-1.03]	—
IRR	0.74 [0.67-0.82]	<0.01	0.82 [0.68-0.99]	0.04
<b>Hospital days<sup>a</sup></b>				
HF membrane	10.18 [9.96-10.4]	—	13.21 [10.47-15.95]	—
MCO membrane	6.45 [6.29-6.62]	—	12.47 [9.36-15.59]	—
IRR	0.63 [0.61-0.66]	<0.01	0.94 [0.68-1.30]	0.73
<b>Nonfatal cardiovascular events<sup>a</sup></b>				
HF membrane	0.25 [0.21-0.28]	—	0.28 [0.19-0.36]	—
MCO membrane	0.16 [0.13-0.18]	—	0.18 [0.14-0.22]	—
IRR	0.64 [0.52-0.80]	<0.01	0.66 [0.46-0.96]	0.03
<b>Time to death<sup>b</sup></b>				
HR MCO/HF membrane	0.66 [0.50-0.89]	0.01	0.88 [0.64-1.23]	0.48

Note: The IRR was defined as MCO/HF.

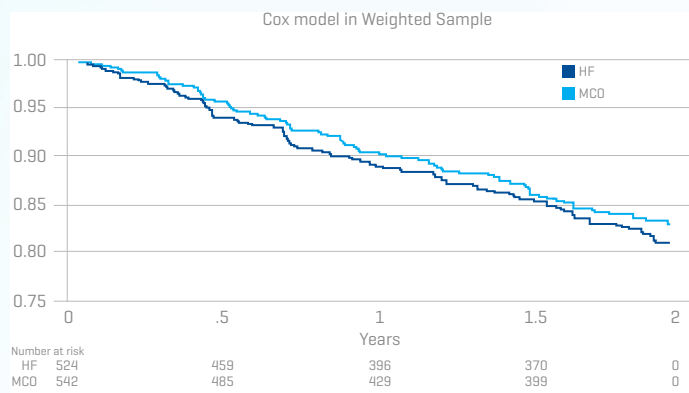
Abbreviations: CI, confidence interval; HF, high-flux; HR, hazard ratio; IPTW, inverse probability of treated weighting; IRR, incidence rate ratio; MCO, medium cutoff.

<sup>a</sup>Negative binomial regression and expressed as hospital days per patient-years.

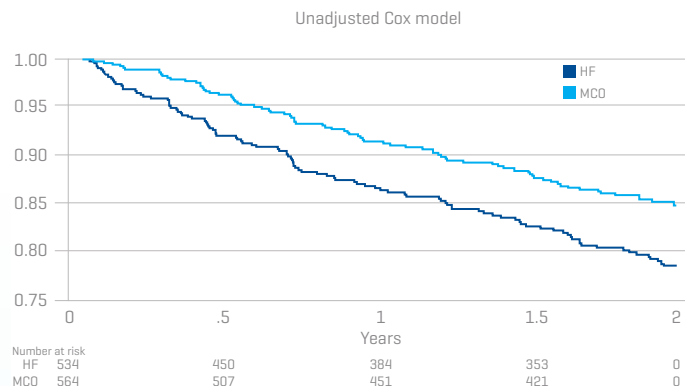
<sup>b</sup>Cox proportional regression.

**FIGURES 1 and 2.** Survival curves according to the type of dialyzer membrane. Figure 1 compares the survival functions in the full sample (crude), finding a statistically significant difference in favor of the MCO membrane and Figure 2 compares the survival functions in weighted samples, where no difference is observed statistically significant)

**FIGURE 1**



**FIGURE 2**

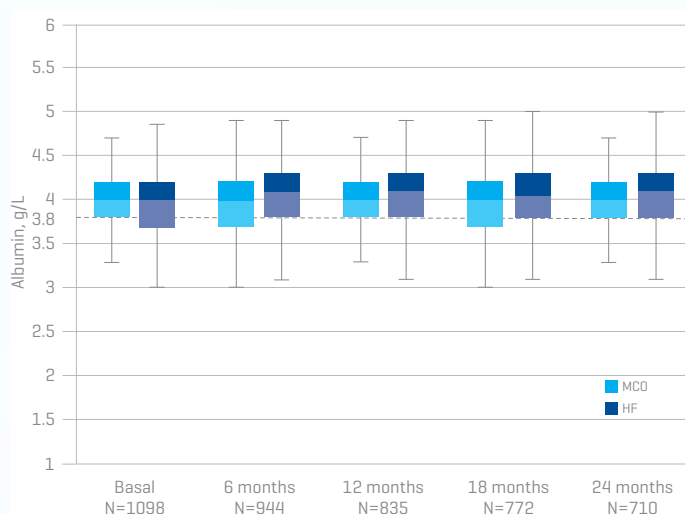


## Laboratory Results

There were no differences between the two groups in albumin, phosphate, potassium, or parathyroid hormone evaluated with the split-plot ANOVA test at baseline or at 6, 12, 18, and 24 months of follow-up. Values for hemoglobin and single-pool Kt/V were higher in the MCO group at baseline, which continued during follow-up ( $p < 0.01$ ).

Serum albumin levels remained stable during the 24-month period, see Figure 3.

**FIGURE 3.** Serum albumin levels



## DISCUSSION AND CONCLUSIONS

This cohort study showed that patients treated with MCO membranes had lower rates of hospitalization and cardiovascular events compared with patients treated with HF membranes. These data support the hypothesis that increased clearance of pro-inflammatory middle-molecules could reduce the occurrence of chronic inflammation, atherosclerosis, structural heart disease and immunodeficiency, thereby reducing the frequency of hospitalization events, particularly for cardiovascular causes.

No difference was found in all-cause mortality or cardiovascular mortality, which could be explained by the short period of follow-up of two years.

There were no differences in serum albumin levels between groups over 2 years of follow-up, demonstrating that stable serum albumin levels are maintained with MCO membranes.



### **Strengths and Limitations**

This study's strength lies in the large number of patients included, standardized data collection with robust quality controls and statistical analysis methods used to deal with the confounding inherent in this type of observational study.

The main weakness of the study is its observational nature. Despite the robust statistical analysis there remains the possibility that unmeasured variables may still generate residual imbalance, skewing the results.

### **Conclusion**

This large cohort study demonstrated that there is a lower incidence of hospitalization events and non-fatal cardiovascular events in chronic HD patients dialyzed with MCO membranes compared to those treated with HF membranes. These results should be corroborated with randomized controlled trials. These results should be corroborated with randomized controlled trials.

**HDx therapy with the *Theranova* MCO membrane is associated with fewer hospitalization events and non-fatal cardiovascular events, and no change in serum albumin compared with HF HD over 2 years follow-up.**



# Clinical Outcomes with Medium Cut-Off Versus High-Flux Hemodialysis: A Systematic Review and Meta-Analysis

**Kandi M, Brignardello-Petersen R, Couban R, et al.** Clinical Outcomes with Medium Cut-Off Versus High-Flux Hemodialysis Membranes: A Systematic Review and Meta-Analysis. *Can J Kidney Health Dis.* 2022;9;1-16. doi: 10.1177/20543581211067087.

## BACKGROUND

Earlier membrane technologies provide minimal diffusive clearance for solutes with molecular weight above 15 kDa. Convective options have been difficult to scale, and high cut-off membranes designed to filter out larger middle molecules unfortunately remove essential blood proteins such as albumin. A novel medium cut-off (MCO) membrane (Theranova 400/500, Baxter) removes large middle-molecules while selectively retaining molecules > 45kDa.

## OBJECTIVE

Compare the effects of MCO versus high-flux membranes used for maintenance hemodialysis (HD) through a systemic review and meta-analysis.

## METHODOLOGY

A search was conducted of the MEDLINE, Embase, CINAHL, Cochrane Library, and Web of Science from January 2015 to

July 2020, with gray literature that included abstracts from pre-specified conferences. Randomized (RS) and non-randomized studies (NRS) comparing MCO and high-flux membranes in adult outpatients receiving maintenance hemodialysis were included. Study selection, data extraction, and quality appraisals were performed in duplicate and used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Outcomes included major clinical events, patient-reported outcomes, safety outcomes, and medication utilization.

## RESULTS

The search identified 22 eligible studies that reported clinical outcomes, including six randomized studies. Among the 16 non-randomized studies, two were cohort studies and the remainder used before-after or crossover designs. Theranova was the only MCO membrane identified in the search. Analysis results are listed by the certainty of evidence per GRADE.

**TABLE 1.** Characteristics of Included Studies, Populations, and Interventions.

Author	Publication type	Country (number of centers)	Number of participants enrolled (number analyzed)	Follow-up (weeks)	Mean age $\pm$ SD (years)	% Male	Interventions	Reported outcomes
<b>Randomized controlled trials</b>								
<b>Parallel arm studies</b>								
Lim et al <sup>20,22</sup>	Full text	Korea (1)	50 (49)	12	I: 62.2 $\pm$ 13.7 C: 63.8 $\pm$ 15.2	66	I: Theranova 400 C: FxCordiax 80 or 60	Survival, QoL (KDQOL), pruritus, adverse events, ERI, iron use, albumin (predialysis), MM
Weiner et al <sup>21</sup>	Full text	USA (21)	172 (130)	24	59 $\pm$ 13	39	I: Theranova 400 C: Elisio-17H	Survival, hospitalization, QoL (KDQOL, EQ-5D-5L), albumin (predialysis), MM
<b>Randomized crossover trials</b>								
Belmouaz et al <sup>23</sup>	Full text	France (1)	40 (40)	26	75.5 $\pm$ 9.9	70	I: Theranova 500 C: Elisio 21H	Survival, ERI, iron utilization, albumin RR, albumin (predialysis), MM
Santos et al <sup>24</sup>	Full text	Spain (1)	13 (13)	2	60.1 $\pm$ 4.6	92	I: Theranova 500 C: FxCordiax 80VR	Bleeding, extracorporeal circuit clotting, aPTT, anti-Xa
Sevinc et al <sup>25</sup>	Full text	Turkey (2)	52 (42)	26	56.4 (median)	58	I: Theranova 500 C: FxCordiax 80	Adverse events, albumin (predialysis), MM, inflammatory marker
Zickler et al <sup>26</sup>	Full text	Germany (2)	50 (47)	4 (+8 week extension study)	I: 58.1 $\pm$ 16.6 C: 59.8 $\pm$ 16	38	I: MCO-Ci400 C: Revaclear 400	Survival, adverse events, CRP, albumin (predialysis), MM, inflammatory mark
<b>Non-randomized studies</b>								
<b>Cohort studies</b>								
Cho et al <sup>27</sup>	Full text	Korea (1)	57 (57)	52	I: 53.7 $\pm$ 10.9 C: 56.4 $\pm$ 10.4	58	I: Theranova 400 C: FxCordiax 80	Survival, ERI, MM, cell-free hemoglobin
Yeter et al <sup>28</sup>	Full text	Turkey (1)	47 (42)	26	52.9 $\pm$ 16	63	I: Theranova 400 C: CorDiax 800	Survival, ERI, iron utilization, CRP, albumin (predialysis)



TABLE 1. continued

Author	Publication type	Country (number of centers)	Number of participants enrolled (number analyzed)	Follow-up (weeks)	Mean age $\pm$ SD (years)	% Male	Interventions	Reported outcomes
<b>Before-after studies</b>								
Alarcon et al <sup>16</sup>	Full text	Colombia [12]	992 (661)	52	60.5 $\pm$ 15.1	62	I: Theranova C: HF	QoL (KDQOL), dialysis symptoms index, restless legs syndrome
Albrizio et al <sup>29</sup>	Abstract	Italy [1]	8 [8]	2	78 $\pm$ 14	25	I: Theranova 400 C: HF	Adverse events, myoglobin
Ariza et al [Sanabria, 2020] <sup>17</sup>	Full text	Colombia [3]	81 [81]	104	61.1 $\pm$ 12.6	52	I: Theranova 400, 500 C: Polyflux 140, Revaclear 300, 400	Hospitalization, hospitalization days, ERI, iron utilization
Baharani, 2017 <sup>a30</sup>	Abstract	England [1]	8 [8]	9	71 $\pm$ 11.8	75	I: Theranova 400 C: FxCordiax 60, 80	Adverse events, MM
Baharani et al <sup>30</sup>	Abstract	England [1]	18 [18]	8	73 $\pm$ 16.7	78	I: Theranova 400 C: Revaclear 300	Adverse events, MM
Bolton et al <sup>31</sup>	Full text (pre-print)	UK [1]	89 [58]	52	73 $\pm$ 12	61	I: Theranova C: Revaclear	Minutes to recover, symptoms (POS-S renal) and symptom severity
Bunch et al <sup>18</sup>	Full text	Colombia [1]	992 (638)	52	60 $\pm$ 15	62	I: Theranova C: HF	Survival, hospitalization, safety, albumin (predialysis)
D'Achiardi et al <sup>32</sup>	Abstract	Colombia (multiple)	52 (41)	24	61 $\pm$ 13	65	I: MCO C: HF	Adverse events, albumin (predialysis), MM inflammatory markers, CRP
García-Prieto et al <sup>33</sup>	Full text	Spain [1]	18 [18]	3	65 $\pm$ 13	50	I: Theranova 500 C: FxCordiax 80VR	Adverse events, albumin loss and RR, MM
Gernone et al <sup>34</sup>	Abstract	Italy [1]	11 [11]	52	70.8 $\pm$ 9	73	I: Theranova C: HF	PCS, MCS, ERI, albumin (predialysis), MM
Kim et al <sup>35</sup>	Full text	Korea [1]	6 [6]	3	66.1 $\pm$ 9.1	100	I: Theranova 400 C: Rexeed-21A	Adverse events, albumin loss, albumin RR, MM
Krishnasamy et al <sup>36</sup>	Full text	Australia and New Zealand [9]	89 [79]	32	66 $\pm$ 14	62	I: Theranova 400 C: Revaclear 400	Adverse events, QoL, RLS, ERI, CRP, albumin (predialysis)
Penny et al <sup>37</sup>	Abstract	Canada [2]	28 [23]	12	65.8 $\pm$ 14.3	52	I: Theranova C: HF	QoL (LEVIL)
<b>Crossover studies</b>								
Cozzolino et al <sup>19</sup>	Full text	Italy [1]	21 [20]	26	71 $\pm$ 13	76	I: Theranova 400 C: FX8, FX10, FX80, FX100, BK1.6, BG2.1	Survival, hospitalization, infection, albumin (predialysis), inflammatory markers

Note. QoL = quality of life; KDQOL = Kidney Disease Quality of Life Instrument; ERI = erythropoiesis resistance index; MM = middle-molecules (removal, reduction ratios, or predialysis serum levels); aPTT = activated partial thromboplastin time; EQ-5D-5L = EuroQol 5-Dimension Questionnaire; RR = risk ratio; MCO = medium cut-off membrane; CRP = C-reactive protein; HF = highflux (not otherwise specified); NR = not reported; PMMA = polymethylmethacrylate; POS-S Renal = Palliative Care Outcome Scale-Symptom module for renal patients; PS = polysulfone.

<sup>a</sup>Single-arm MCO-HD data without comparator group for survival and hospitalization outcomes; not amenable to meta-analysis

### High Certainty

**Recovery Time:** A non-randomized study (n=89) found that a year of treatment with MCO dialysis reduced recovery time by 420 minutes (95% CI, -540 to -299) shown in Table 1.

### Moderate Certainty

**Infection:** Two non-randomized studies with 68.8 patient years found that MCO dialysis likely reduces infection with a rate ratio of 0.38 (95% CI, 0.17 to 0.85;  $I^2 = 0\%$ ).

**Hospital Length of Stay:** One non-randomized study with 162 patient-years found that MCO dialysis likely reduced mean length of stay by a mean difference of -1.5 days (95% CI, -2.22 to -0.78).

**Quality of Life:** small non-randomized study reported an improvement of 16.7/100 points on a novel instrument (the London Evaluation of Illness [LEVIL] questionnaire).

**Effects of Kidney Disease:** Two randomized studies found little to no difference on KDQOL effects (low certainty). A non-randomized study with 993 subjects demonstrated an improvement of 5.4 points (95% CI, 3.2 to 7.6) after 1 year of treatment with MCO dialysis.

**Pruritus:** A randomized study (n=49) found that MCO dialysis likely reduces pruritus with MD -4.4 points on a 45-point scale (95% CI, -7.1 to -1.66).

**Restless Leg Syndrome:** One large non-randomized study measured a reduction in the prevalence of restless legs syndrome from 22.1% at baseline to 10.0%, 1 year after converting to MCO dialysis with odds ratio 0.39 (95% CI, 0.29 to 0.53).

**Symptom Severity:** One non-randomized study measured the proportion of patients with 1 or more symptom rated as "severe" or "overwhelming" at baseline and 1 year. The odds ratio for a reduction in symptom severity with MCO dialysis was 0.81 (95% CI, 0.76 to 0.86).

**Erythropoiesis Resistance Index (ERI):** In 2 randomized studies the pooled mean difference for ERI was -2.92 U/kg/week/g/L achieved hemoglobin (95% CI, -4.25 to -1.6;  $I^2 = 0\%$ ) with MCO dialysis.





### Low Certainty

KDQOL symptoms/problem list, physical health: The study found that MCO dialysis had little to no effect on KDQOL symptoms/problem list, and physical health.

Mortality: Per existing data, MCO dialysis may have little to no effect on mortality. Four randomized studies and four non-randomized studies treating a total of 597 patients for 12-52 weeks found an all-cause mortality rate of 3.3/100 person-years for the MCO group versus 4.4/100 person-years for the high-flux group, yielding a conclusion that there is little to no difference in mortality.

Hospitalization for any cause: One randomized study with 78.7 person-years provided low certainty evidence that MCO dialysis may result in a reduction in hospitalization, with a rate-ratio of 0.48 [95% CI, 0.27 to 0.84]; two non-randomized studies showed similar effects.

### Safety Concerns

Iron Utilization: In 2 randomized studies (n=90), the pooled mean difference in cumulative intravenous iron use over 12 weeks was -293 mg [95% CI, -368 to -218; I<sup>2</sup>=93%], with MCO dialysis.

Mental Health Composite Score: MCO dialysis had no effect on the KDQOL mental health composite.

Serious adverse events: Four trials that reported SAEs provided low certainty of little to no difference in the rate of fatal or life-threatening adverse events leading to hospitalization, with seven additional non-randomized studies stating that there were no dialysis-related complications related to MCO.

Other safety outcomes: One study of 130,601 hemodialysis sessions reported no Type A or Type B dialyzer reactions with MCO dialysis.

### Strengths and Limitations

Strengths of this systematic review and meta-analysis include adherence to a registered protocol, a sensitive search strategy, independent screening, data extraction and quality appraisal in duplicate. It used GRADE in all aspects of the review and used a rigorous risk of bias assessment tools. Bias in the meta-analysis of PRO measures was ensured by enlisting a blinded collaborator for groupings. Most outcomes were based on a small number of studies, many non-randomized and studies were relatively small resulting in downgrading for imprecision.

### CONCLUSION

The MCO dialyzer improved a range of outcomes with concordant signals of benefit, and in a manner consistent with its anticipated mechanism of effect. While the current available evidence for MCO dialysis is of predominantly moderate certainty, promising innovations in dialysis care are scarce and thus likely to generate interest as the evidence base evolves. The notion that patient-important outcomes can be improved by simply substituting a dialysis membrane is appealing and could by virtue of its scalability, impact patient care, and by its novelty stimulate further innovation. Although larger studies would be needed to further quantify any effects of MCO dialysis on major clinical events, to date, there are no signals in the published literature to suggest risk or harm with this device. Given the very low event rates in trials to date, future studies powered for mortality and other major outcomes could be impractically large; hence, alternate designs such as registry-based cluster randomized trials, prospective cohort studies, and ongoing surveillance might help fill these evidence gaps.

**Evidence generated supports that HDx therapy with the TheraNova MCO membrane may improve patient outcomes.**

# Effects of a Medium Cut-Off [Theranova®] Dialyser on Haemodialysis Patients: A Prospective Cross-Over Study

**Cozzolino M, Magagnoli L, Ciceri P, et al.** Effects of a medium cut-off **Theranova®** dialyzer on haemodialysis patients: a prospective, cross-over study. *Clinical Kidney Journal* 2019; 1-8.  
doi: [10.1093/ckj/sfz155](https://doi.org/10.1093/ckj/sfz155).

## BACKGROUND

Current hemodialysis (HD) techniques have important limitations in adequately removing some of the uremic solutes such as middle molecules and protein-bound uremic toxins. Middle molecules are organic compounds characterized by a molecular weight >500 Da which can accumulate in end stage renal disease (ESRD) and exert many toxic effects. The retention of middle molecules is associated with the development of cardiovascular disease, chronic inflammatory disease, chronic kidney disease-mineral and bone disorder, and other conditions. Better clearance of these toxins would lead to improved long-term outcomes in patients with ESRD.

Online hemodiafiltration provides a good clearance of middle molecules, but the use of this technique is limited by the need for high blood flows and accurate monitoring of devices. Also, high-cut off membranes can be used to remove efficiently middle molecules from the bloodstream, but this treatment is also associated with protein loss, and its chronic use leads to hypoalbuminemia.

The new medium cut-off (MCO) membranes provide diffusive and to some extent convective removal of solutes of molecular weight up to 45 kDa, with only marginal albumin leak. MCO membranes have a tight pore size distribution resulting in a steep sieving curve, with the values of molecular weight retention onset and molecular weight cut-off close to but lower than albumin (65 kDa). Due to these novel membrane characteristics, the treatment with MCO membranes 'expands' the spectrum of uremic toxins that can be removed by HD, therefore called 'expanded HD' (HDx).

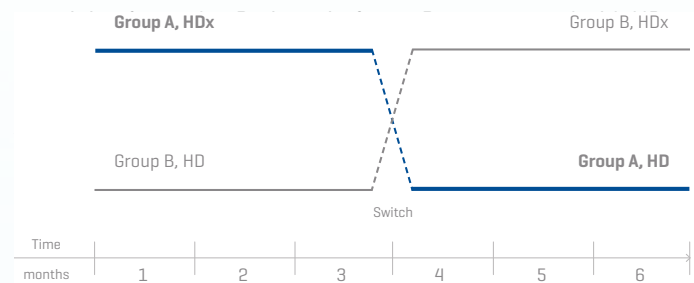
## OBJECTIVE

The aim of this study was to compare HDx using the new MCO membrane **Theranova 400** (Baxter, USA) and bicarbonate dialysis in prevalent HD patients based on hematochemical values, inflammatory markers, parameters of dialysis adequacy, incidence of adverse events, incidence of infections, number and causes of hospitalization.

## METHODOLOGY

Twenty (20) prevalent HD patients participated in this prospective, open-label, controlled, cross-over pilot study. The study was undertaken from October 1, 2017 to December 31, 2018. Consecutively, unselected male and female patients with end stage renal disease (ESRD) on HD were eligible for participation in the study. Participation in the study was voluntary. Patients presenting with cachexia or cancer were excluded.

Patients were discretionally divided into two groups (A and B), with similar mean-age, male-female ratio, and dialytic vintage. In the cross-over design, patients in Group A were treated with Theranova dialyzer (HDx) for the first 3 months of the study, and then switched to conventional bicarbonate dialysis (HD) for the



**FIGURE 1.** Study Design. HDx: expanded hemodialysis. HD: hemodialysis. Figure adapted from Ciceri, et al.

There were four dropouts from the study: one patient was relocated to another dialysis center; one patient was allergic to polysulphone; one patient died; and one patient discontinued treatment with HDx. With incidence and timing of dropouts and enrollment of one replacement patient, biochemical parameters were available at the beginning and end of each study period in 10 patients in Group A. For Group B, biochemical parameters were available for 10 patients for the entire first study period and beginning of the second study period, and for 8 patients during the second study period.

All treatments were provided by Fresenius 5008 (Fresenius 5008, Fresenius Medical Care, Bad Homburg, Germany). A novel membrane, **Theranova 400** (Baxter USA) was used for patients undergoing HDx, while various other membranes (FX8, FX10, FX80, FX100, BK1.6, BG2.1) were used in patients undergoing HD dialysis based on clinical needs.

## RESULTS

### Dialytic Parameters

No significant differences between the two groups were observed during the study, except for higher Kt/V values in Group A which achieved statistical significance only within the third month of the first study period.

### Blood Pressure

A non-significant trend toward higher systolic blood pressure (SBP) was detected in Group B prior to treatment, without further variations throughout the study by both HD and HDx treatments.

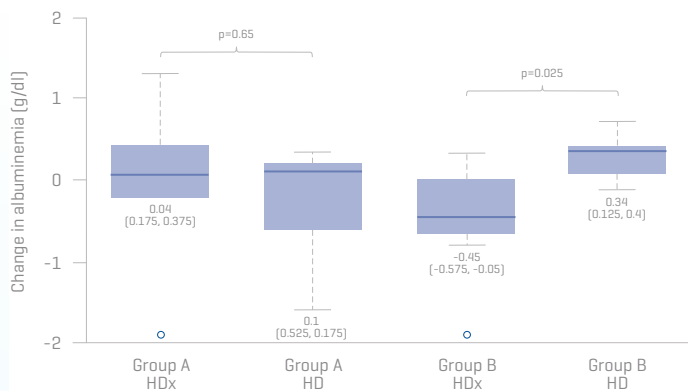
### Hematological Parameters

Hematological parameters did not significantly change during the study and did not differ between the study groups.

### Serum Albumin Levels

Serum albumin levels were maintained in patients in Group A during both treatments, while patients in Group B showed a decrease in albumin concentration following treatment with HDx compared to HD. A median interquartile range (IQR) reduction in circulating albumin of -0.45 g/dl (-0.575 to -0.05) was observed

within Group B during the HDx period compared with an increase of 0.34 g/dL (0.125–0.40) under HD ( $p=0.025$ ) after exclusion of two patients without available albumin levels at the end of the study. See Figure 2. However, median albumin levels were  $\geq 3.5$  g/dL and no patients had clinical symptoms of hypoalbuminemia or needed intravenous albumin administration.



**FIGURE 2.** Change in albuminemia in Groups A and B during treatment with HDx and HD. Values are presented as median (IQR). Abbreviations: HDx, expanded hemodialysis; HD, hemodialysis; IQR, interquartile range. Adapted from Cozzolino et al.

### Inflammatory Cytokines

Levels of two inflammatory cytokines, middle molecules interleukin (IL)-1 $\beta$  (17.5 kDa<sup>1</sup>) and IL-6 (21–28 kDa<sup>1</sup>) were measured. While not statistically significant, levels of sera IL-1 $\beta$  were higher under Group A under HD compared with HDx, and IL-1 $\beta$  levels were reduced under HDx versus HD in Group B. IL-6 levels slightly increased following HD compared with patients under HDx in Group A and reduced in HDx patients versus those under HD in Group B, but this difference did not achieve statistical significance.

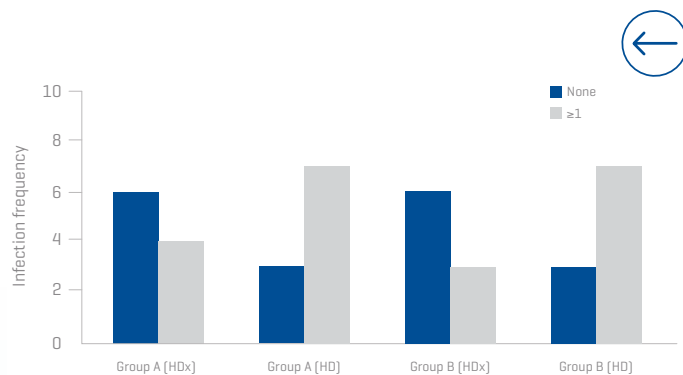
Lower concentrations of inflammatory cytokines induced by treatment with MCO membranes may lead to beneficial effect in patients with ESRD. IL-1 $\beta$  seems to be associated with left ventricular hypertrophy in dialysis patients and with the progression of atherosclerosis in patients with ischemic heart disease, in whom serum concentrations of IL-1 $\beta$  correlate with plaque severity. Elevated levels of IL-6 are also associated with cardiovascular mortality and left ventricular hypertrophy in HD patients.

### Hypotension

Although there was a slightly higher incidence of symptomatic hypotensive events in the HDx group (8 events vs 5 events), the total number of absent/low hypotensive events was 11 in the HD group versus 9 in the HDx group, and both groups had the same number of moderate or high hypotensive events ( $n=9$ ). A larger sample size will be needed to verify whether hypotension rate could be different among dialysis methods.

### Infections

The frequency of infection per patient was categorized into two classes: none and one or more infections per patient. The total number of infections was lower during treatment with HDx than with HD ( $n=7/19$  vs  $n=14/20$ ;  $p=0.03$ ). See Figure 3.



**FIGURE 3.** Frequency of infections in Groups A and B following HD and HDx treatments. Abbreviations: HDx, expanded hemodialysis; HD, hemodialysis. Adapted from Cozzolino et al.

Although difficult to interpret because of small sample size and potential bias, the difference in incidence in of infections during the two treatments is very encouraging since infectious diseases are the most common cause of hospitalization and second most common cause of death among HD patients. These patients are more prone to infections than the general population, mainly because of the high prevalence of an indwelling catheter and a condition of acquired immune dysfunction due to the retention of uremic toxins and chronic inflammation.

### Hospitalization

The frequency of hospitalizations was categorized into two classes: none or one or more episode per patient. Data revealed a non-significant trend toward higher risk of hospitalization with HD; the total number of hospitalizations was higher during treatment with HD than HDx ( $n=11/19$  versus  $n=8/19$ ;  $p=0.53$ ).

### LIMITATIONS

Limitations of this study included small sample size, high number of dropouts, absence of wash-out period prior to switching treatment, and suggested under-treatment for selected conditions based on dialysis adequacy.

### CONCLUSION

This study demonstrates that the chronic use of the novel MCO dialyzer **Theranova** appears to be safe and well-tolerated, without serious side effects or hypoalbuminemia. Importantly, the total number of infections was lower with HDx than with HD ( $p=0.03$ ). Furthermore, it validated the ability of these new membranes to reduce the serum concentration of soluble inflammatory mediators. These results encourage further trials with longer treatment periods and larger sample sizes.






**HDx therapy showed a statistically significant decrease in the rate of infections. Additionally, this study validated MCO (Theranova) membranes' ability to reduce serum concentration of soluble inflammatory mediators, including cytokines.**

# HDx: A WORLD OF DIFFERENCE

## Economic Outcomes Impacted by HDx Therapy



HDx therapy enabled by Theranova in chronic dialysis patients may reduce hospitalization rates and cardiovascular events compared to conventional HD.<sup>1,2</sup>

-  **Blackowicz MJ, Falzon L, Beck W, et al.**  
**Economic evaluation of expanded hemodialysis with the Theranova 400 dialyzer: A post hoc evaluation of a randomized clinical trial in the United States.** [published online ahead of print, 2022 Apr 19]. *Hemodial Int.* 2022;
-  **Ariza JG, Walton SM, Suarez AM, et al.**  
**An initial evaluation of expanded hemodialysis on hospitalizations, drug utilization, costs, and patient utility in Colombia.** *Ther Apher Dial.* 2021;25(5):621-627.
-  **Sanabria R, Hutchison C, Vesga J, et al.**  
**Expanded Hemodialysis and Its Effects on Hospitalizations and Medication Usage: A Cohort Study.** *Nephron* 2021;145:179-187.
-  **Lim JH, Jeon Y, Yook JM, et al.**  
**Medium Cut-Off Dialyzer Improves Erythropoiesis Stimulating Agent Resistance in a Hepcidin-Independent Manner in Maintenance Hemodialysis Patients: Results from a Randomized Controlled Trial.** *Nature/Sci Rep* 2020;10:16062.
-  **Hadad-Arrascue F, Nilsson L-G, Rivera AS, et al.** **Expanded hemodialysis as effective alternative to on-line hemodiafiltration: A randomized mid-term clinical trial.** *Ther Apher Dial.* 2022;26:37-44.

1. Blackowicz MJ, Falzon L, Beck W, et al, Economic evaluation of expanded hemodialysis with the Theranova 400 dialyzer: A post hoc evaluation of a randomized clinical trial in the United States. [published online ahead of print, 2022 Apr 19]. *Hemodial Int.* 2022.  
2. Molano AP, Hutchison CA, Sanchez R, et al. Medium Cut-Off Versus High-Flux Hemodialysis Membranes and Clinical Outcomes: A Cohort Study Using Inverse Probability Treatment Weighting, *Kidney Med.* 2022;4(4):1-10.





# Economic evaluation of expanded hemodialysis with the Theranova 400 dialyzer: A post hoc evaluation of a randomized clinical trial in the United States

**Blackowicz MJ, Falzon L, Beck W, et al.** Economic evaluation of expanded hemodialysis with the **Theranova** 400 dialyzer: A post hoc evaluation of a randomized clinical trial in the United States. *Hemodial Int.* 2022 Online ahead of print. doi: [10.1111/hdi.13015](https://doi.org/10.1111/hdi.13015).

## BACKGROUND

In 2018, approximately 485,000 people in the US received maintenance dialysis for kidney failure, a number that has doubled in the last 20 years. Medicare funds about three fourths of patients requiring dialysis; although dialysis is required by <1% of Medicare enrollees, these patients account for 7.2% of paid Medicare claims.

Despite dialysis, uremic toxins may accumulate over time and increase patient morbidity and mortality. Conventional dialysis modalities such as high-flux hemodialysis (HD) typically remove small molecules (<0.5 kDa) and smaller middle molecules (0.5-25 kDa), but not larger middle molecules (25-60 kDa). To address this unmet need, the **Theranova** 400 dialyzer (Baxter Healthcare Corporation, Deerfield, IL) has been developed and was approved by the FDA in August 2020. The **Theranova** 400 has an expanded solute removal profile up to 45 kDa and may be used in expanded hemodialysis (HDx), a technique that combines diffusion and convection in a hollow-fiber dialyzer with a medium cut-off membrane. In the original analysis, this randomized, controlled trial has shown HDx therapy with **Theranova** to be superior to high-flux HD in terms of the removal of larger middle molecules such as lambda-free light chains, while maintaining adequate serum albumin levels. This secondary analysis aimed to determine if use of HDx therapy could also reduce healthcare costs for this patient population, particularly if, as expected, removal of larger middle molecules is associated with improved clinical outcomes.

## OBJECTIVE

This post-hoc analysis therefore reviewed trial data regarding clinical outcomes in particular hospitalization rates, and healthcare costs of patients treated with either HDx therapy with **Theranova** or high-flux HD.

## METHODOLOGY

This prospective, randomized, open-label, parallel study (NCT03257410) in patients receiving maintenance dialysis treatment compared results of those treated with HDx therapy with the **Theranova** 400 dialyzer to those dialyzed with a high-flux HD dialyzer of the same size, with thrice-weekly sessions over 24 weeks. Patients were clinically stable adults who had received HD with a high-flux dialyzer for ≥3 months; all had stable vascular access and maintained an acceptable urea clearance. Patients were excluded if they had had an acute infection in the previous 4 weeks or if they had certain chronic diseases (i.e., cancer, HIV, hepatitis, chronic liver disease, paraprotein-associated disease, monoclonal/polyclonal gammopathy).

- Hospitalization – any SAE which contained a hospitalization admission date. Hospitalization rate – total number of hospitalizations/total person years of follow up during the trial period.
- Erythropoietic stimulating agents (ESA) use was captured in the study but data were incomplete so use and dose were assumed to be equal between 2 arms.
- Cost of hospitalization – taken from Kaiser Family Foundation USA average in 2018.

This analysis examined hospitalization, hospitalization rate (number of hospitalizations divided by total person-years of follow up), hospital length of stay, total cost of hospitalization, and cost of dialyzers. The cost per high-flux dialyzer was assumed to be \$6.50, and the cost per **Theranova** dialyzer was \$15.00; other costs associated with dialysis were assumed to be equal and were excluded from the model, as were patient medications and medication doses.

## Statistical Analysis

Mean length of hospitalization was estimated using a Poisson (log-count) general linear model. A univariate sensitivity analysis was included to evaluate the impact of observed variability on cost differences between treatments. Itemized and total costs per group were calculated through random sampling of all input parameters based on the closest approximations of their observed distributions; repetition over 10,000 simulations generated the mean and 95% confidence intervals (CI).

## RESULTS

### Study Population

A total of 172 patients were randomized, and 171 were treated at 21 US centers between September 2017 and October 2018; 86 were treated with HDx therapy using **Theranova** (389 patient-months), and 85 with a high-flux dialyzer (366 patient-months). Baseline demographics and clinical characteristics were similar between groups; 39% of patients were female, and the mean age was 59±13 years.

### Clinical outcomes: hospitalization and length of stay

Clinical outcomes are shown in Table 1. Hospitalization was 45% lower in patients treated with HDx therapy with **Theranova** compared with high-flux HD (IRR=0.55; 95% CI: 0.30, 1.00; P=0.042). There was no significant difference in length of hospital stay.

**TABLE 1.** Clinical Outcomes

Health resource utilization	Theranova (n=86)	High-flux HD (n=85)	P-value
Hospitalization events	18	31	--
Total hospital days	74	139	--
Total patient-years (PY)	32.4	30.5	--
Hospitalization rate per PY	0.56 [0.13]	1.02 [0.12]	0.042
Hospital length of stay (mean days [SE])	4.11 [0.57]	4.63 [0.58]	0.406

HD, hemodialysis; PY, patient year; SE, standard error.

**Adapted from Blackowicz et al.**



### Economic evaluation

Table 2 shows the economic evaluation of HDx therapy with **Theranova** compared with high-flux HD. While the trial lasted 6 months, the economic model calculates values over one year of treatment. Although HDx therapy with **Theranova** is associated with a higher dialyzer cost, its lower all-cause hospitalization rate makes it a cost-efficient alternative. Compared with high-flux HD, **Theranova** offered an average annual estimated cost savings of \$4772. Hospitalization rate and length of stay were the main drivers of cumulative cost.

TABLE 2. Economic Evaluation

Item	Unit cost	Per Patient Cost		
		Theranova	High-flux HD	Difference
All-cause hospitalization <sup>a</sup>	\$2518 per day	\$5756	\$11,853	-\$6097
Dialyzer cost <sup>b</sup>	\$15.00 ea/ \$6.50 ea	\$2340	\$1014	\$1326
Cumulative		\$8096	\$12,867	-\$4771

<sup>a</sup>All-cause hospitalization was defined as any serious adverse event that resulted in hospitalization. <sup>b</sup>**Theranova** dialyzer was priced at \$15 in the United States and high-flux dialyzer was assumed to cost \$6.50. HD, hemodialysis.

Adapted from Blackowicz et al.

### Probabilistic sensitivity analysis

A univariate sensitivity analysis (Figure 1) accounted for the observed variability in each model separately. Hospitalization rates were the main drivers of cost difference, particularly in the high-flux HD group. Results favored **Theranova** at the upper and lower thresholds for all inputs.

FIGURE 1. Univariate sensitivity analysis

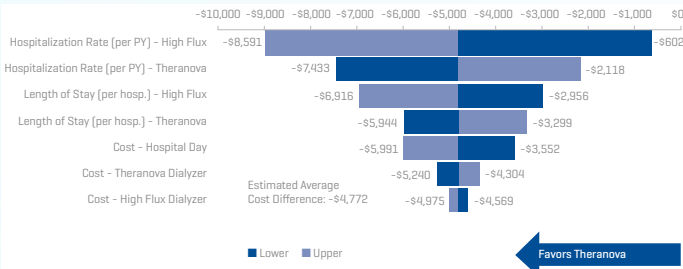


Figure adapted from Blackowicz et al.

Summary estimates were run with >10,000 simulations of costs to verify the mean difference in cost between treatments. Table 4 shows the probabilistic analysis, which determined that HDx therapy with **Theranova** was associated with lower costs in 96% of the simulations.

TABLE 3. Simulated summary of methods of mean cost difference

Item	Per Patient Cost Difference	
	Mean	(95% CI)
All-cause hospitalization (per day)	-\$6103	(-\$11,604 to -\$601)
Dialyzer cost	\$1326	--
Cumulative	-\$4777	(-\$10,278 to \$725)
Proportion of simulations demonstrating Theranova cost-saving over high-flux HD	95.7%	

HD, hemodialysis

Adapted from Blackowicz et al.

### Study Limitations

The 6-month trial had too few hospitalization events to draw sound statistical conclusions between categories (e.g., to eliminate trauma cases or assess infection- or cardiovascular-related events). Cost assumptions had to be made to complete the analysis; assuming that medications would be equivalent between arms was one such assumption. Also, study records on erythropoietin-stimulating agents and iron dosing were incomplete, and authors would have liked to incorporate that variable. Other potential study confounders seem to balance across treatment arms and are unlikely to affect study results.

### DISCUSSION

There are few studies on health economics and patient outcomes regarding HDx therapy with **Theranova**, but this study supports the findings of two other studies, one showing that HDx therapy with **Theranova** was associated with lower hospitalization costs and the second (a retrospective, observational study) that showed that HDx therapy with **Theranova** was associated with a lower risk of hospitalization.

Authors add that the study entry criteria required that dialysis patients be medically stable so the study group tends to be younger than the average dialysis patient age in the USA. Since hospitalization costs drove healthcare costs in this relatively young and healthy population, cost differences could be greater still in a real-world setting, where patients may be older and less medically stable.

Findings are of potential importance in upcoming US payment models in kidney care, particularly the Comprehensive End-Stage Renal Disease Care Model (ESCO) and Kidney Care Choices, which consider hospitalization costs and the number of hospitalizations.

### CONCLUSIONS

In this post-hoc analysis of a randomized clinical trial, the HDx therapy with **Theranova** dialyzer was associated with lower healthcare costs than standard high-flux HD. In addition to its superior removal of large middle molecules, **Theranova** is associated with a reduced hospitalization rate per patient year and is expected to be a cost-saving therapy, based on this significant reduction in hospitalization events.



# An initial evaluation of expanded hemodialysis on hospitalizations, drug utilization, costs, and patient utility in Colombia

Ariza JG, Walton SM, Suarez AM, et al. An initial evaluation of expanded hemodialysis on hospitalizations, drug utilization, costs, and patient utility in Colombia. *Ther Apher Dial*. 2021;25(5):621-627. doi: 10.1111/1744-9987.13620.

## BACKGROUND

An innovation called Expanded Hemodialysis (HDx) with a middle cut-off (MCO) dialyzer membrane allows for superior removal of molecules up to 45 kDa, including conventional/large middle molecule uremic toxins compared with traditional high flux (HF) hemodialysis (HD). Early clinical evidence suggests that HDx enabled by the Theranova (MCO) dialyzer membrane has the potential to improve patient outcomes and Quality of Life (QoL).

## OBJECTIVE

The purpose of this retrospective, before and after study was to provide an initial health economic assessment of the impact of switching patients from HF HD to HDx therapy with MCO dialyzer membrane, on hospitalizations, hospital days, medication use, hospitalization and drug related costs, and patient utilities.

## METHODS

### Study Design

This retrospective study was undertaken in the Renal Therapy Services (RTS)-Colombia network to track and compare outcomes of a subset of patients over the age of 18 prior to, and after switching from HF-HD to HDx with the Theranova (MCO) dialyzer membrane. Patients who had received HF-HD (Polyflux 140; Revaclear 300 or 400, Baxter, Deerfield, IL, USA) three times weekly for 4 hours, for at least 12 months, were switched to receive HDx (Theranova; Baxter, Deerfield, IL, USA). The patient's prescriptions (QD, QB, target Kt/V, duration, and dialysate) were not changed as part of this study. The study included clinical surveillance and periodic survey data related to quality of life between 2017 - 2019. The data for this analysis came from clinics in the RTS database in Colombia that had high-quality electronic medical record data with complete data for every patient. In addition, clinics included had switched all of their patients from HF-HD to MCO-HDx, and had at least a year of data prior to, as well as after the switch to HDx.

Eighty-one (81) patients qualified for inclusion in the study, and data in both the HF-HD phase and the MCO-HDx phase of the study were collected.

### Data Collection and Analysis

The annual count of hospitalizations, hospital length of stay, use of selected medications and QoL as measured by the [Kidney Quality of Life \(KDQoL\)-36](#) were collected during the 1 year prior to initiation of HDx with Theranova (MCO) dialyzer membrane, while patients were receiving HF HD, and during the 1 year after initiation of HDx with Theranova (MCO) dialyzer membrane. Detailed information on comorbidities was used to calculate severity using a [modified Charlson comorbidity index](#) validated in [End Stage Kidney Disease \(ESKD\)](#) patients.

Costs were estimated for hospitalization and medications. Hospital days were monetized based on a recent estimate of cost per day for dialysis-related hospitalizations conducted by RTS. Drug costs were estimated based on published prices,

in Colombia. The hospital and drug-related cost estimates were then converted to US dollars based on an average of the US Colombian exchange rate from March to September 2019 (3,338.27 pesos per US dollar). To examine patient utility associated with the treatment change, a published algorithm based on results from a population in Spain was used to convert the KDQoL results into [EQ-5D](#) utility scores. As a sensitivity analysis, a related method for generating utility scores based solely on the [Short Form \(SF\)-12](#) results of the [KDQoL-36](#) was also used; a patient utility score of 1 signifies perfect health.

A generalized linear multivariable model was conducted to assess the effect of HDx with Theranova (MCO) dialyzer membrane on hospitalization days, which were controlled for some demographic and clinical confounding variables. In addition, annual cost estimates for a patient on HF-HD and MCO-HDx were calculated along with percent changes over time. All analyses were performed using [Stata version 14](#).

### Study Limitations

- With a before and after design, time trends in medication use and hospitalizations may confound the treatment effect. The main analysis controlled for statistically relevant patient characteristics, which helps alleviate the potential for bias related to time-varying factors, but bias may still be present.
- The results are from three clinics from one network in Colombia. Practices may vary to other settings; generalizing results should be performed with care.
- The cost results reflect Colombian rates for hospitalizations and medications that are unlikely to match those in other countries.
- The EQ-5D utilities mapped from the KDQoL are based on a scoring algorithm developed in Spain and may not adequately reflect Colombian preferences.
- This analysis has focused solely on estimating the impact of HDx with Theranova (MCO) dialyzer membrane, in reducing the cost of hospitalizations and medications. The potential cost savings/cost-avoidances of this technology will depend on pricing dynamics and the contracting models for such treatments, over time.

## RESULTS

### Patient Characteristics

Baseline characteristics of the 81 patients enrolled in the study included:

- Average age: 61.1 years
- 64.2% male, 35.8% female
- 98.8% from urban areas
- Primary cause of Chronic Kidney Disease (CKD): 39.5% diabetes, 28.4% hypertension
- Median dialysis vintage: 3.8 years
- 25.9% with a [modified Charlson comorbidity index](#) of 3 or greater



**Hospitalizations**

- Hospitalization rate per patient year: 0.77 with HF-HD and 0.71 in MCO-HDx
- Hospitalization days showed a sizable and statistically significant reduction of ~1.53 days; 5.94 hospital days per patient year on HF-HD to 4.41 on MCO-HDx

**Medication Utilization**

- While the proportion of patients on Erythropoietin Stimulating Agents (ESA), iron, insulin, and hypertension-related medications was roughly the same for patients on HF-HD and MCO-HDx, doses per patient were significantly lower on MCO-HDx (See Table 1)
- Intravenous (IV) In-Center Medications - mean dosage per patient, per year
  - ESA: significantly reduced by 13,194 IU; p<0.01
  - Iron: significantly reduced by 200 mg; p<0.01
- Other Medications
  - Insulin: mean dosage per patient, per year significantly reduced by 1,949 IU; p<0.01
  - Hypertension medications: mean number of tablets, per patient year significantly reduced by 452 tablets; p<0.01

**Patient Utilities**

- The average utility of the patients was estimated, with patient utility remaining stable
- Using a KDQoL-36 based estimate, patient utility was 0.70 on HF-HD and 0.72 on MCO-HDx
- Using the SF-12 based estimate, patient utility was 0.83 during both the HF-HD and MCO-HDx phases

Please see Table 1.

Outcome	HD HF mean (95% CI) N=81	HDx mean (95% CI) N=81
Yearly Hospitalization Rate	0.77 [0.60–0.98]	0.71 [0.55–0.92]
Yearly Hospitalization Days	5.94 [5.41–6.50]	4.41 [3.97–4.90] <sup>a</sup>
Proportion Using ESA	0.85 [0.77–0.93]	0.88 [0.80–0.94]
Dosage Per Patient Per Year of ESA (IU)	181 318 (151 647– 210 988)	168 124 (138 452–197 794) <sup>a</sup>
Proportion of Patients using Iron	0.81 [0.70–0.90]	0.78 [0.69–0.87]
Dosage Per Patient Per Year of Iron (mg)	959 [760–1158]	759 [560–958] <sup>a</sup>
Proportion of Patients Using Insulin	0.35 [0.24–0.45]	0.35 [0.24–0.45]
Dosage Per Patient Per Year of Insulin (IU)	5383 [3274–7490]	3434 [1327–5543] <sup>a</sup>
Proportion using Hypertension Medications	0.78 [0.69–0.87]	0.74 [0.65–0.84]
No. Tablets Patient Per Year of Hypertension Medications	1183 [970–1394]	731 [518–943] <sup>a</sup>
KDQOL-36 based EQ-50 Utility Score	0.70 [0.65–0.75]	0.72 [0.67–0.77]
SF-12 based EQ-50 Utility Score	0.83 [0.80–0.86]	0.83 [0.80–0.86]

**Table 1. Hospitalizations, Medication Utilization, and Patient Utilities with HD or HDx.** Table adapted from Ariza et al. Statistically significant difference found in corresponding univariate GLM analysis of outcome on HDx. <sup>a</sup>All had a P-value <0.01. HD HF: high flux hemodialysis; HDx: expanded hemodialysis; ESA: erythropoietin stimulating agents; KDQOL: Kidney disease quality of life; EQ-5D: EuroQol-5 Dimension; GLM: Generalized linear Poisson.

**Annual Costs**

Estimates for annual average costs of hospitalization were nearly 24% lower with MCO-HDx and sizably lower for many of the medication-related estimates of costs, per patient year.

- Hospitalizations: average annual costs reduced by \$428 with MCO-HDx; 23.9% decrease
- IV in-center Medications – average annual costs:
  - ESA costs reduced by \$28 (7.27%) with MCO-HDx
  - Iron costs reduced by \$0.90 (20.83%) with MCO-HDx
- Other Medications – average annual costs:
  - Insulin: costs reduced by \$79 (32.64%) with MCO-HDx
  - Antihypertensives: costs decreased by \$57 (30.16%) with MCO-HDx

Please see Table 2.

Annual Per Patient Cost Category	Average Annual Costs with HD HF	Average Annual Costs with HDx	Percent change HDx vs. HD HF
Hospitalizations	\$1,822	\$1,394	-23.9%
ESA	\$385	\$357	-7.27%
Iron	\$4.32	\$3.42	-20.83%
Insulin	\$242	\$163	-32.64%
Antihypertensives	\$189	\$132	-30.16%

**Table 2. Annual Costs with HD HF and with HDx.** Adapted from Ariza et al. HD HF: high flux hemodialysis; HDx: expanded hemodialysis; ESA: erythropoietin stimulating agents.

**DISCUSSION AND CONCLUSIONS**

Expanded hemodialysis (HDx) enabled by TheraNova (MCO) dialyzer membrane has shown promise as an important advancement in chronic dialysis-related care, with efficient removal of conventional/large middle molecules and the potential to improve patient outcomes while maintaining QoL. This analysis shows that HDx therapy statistically and significantly reduces hospitalization days and lowers doses of medications (including those used in-center), in a real-world setting over a period of two years. These reductions suggest a potential cost savings of \$593 USD per patient, per year with HDx therapy enabled by the TheraNova (MCO) dialyzer membrane. In addition, the results on utility projections provided initial evidence that HDx was associated with stable EQ-5D utility scores, over time.

**A switch to HDx therapy was associated with a significant reduction in hospital days and medication usage (including ESA and iron), suggesting potential savings of \$593 per patient, per year (or ~\$4/treatment) with HDx/TheraNova.**





# Expanded Hemodialysis and Its Effects on Hospitalizations and Medication Usage: A Cohort Study

Sanabria RM, Hutchison CA, Vesga JI, et al. Expanded hemodialysis and its effects on hospitalizations and medication usage: a cohort study. *Nephron*. 2021;145(2):179-187. doi:10.1159/000513328.

## BACKGROUND

End stage kidney disease (ESKD) places a substantial burden on healthcare systems and patients, due in part to retention of conventional/large middle molecule uremic toxins. Recently, expanded hemodialysis (HDx) with medium cut-off (MCO) dialyzer membrane has been developed, which expands the capacity of hemodialysis (HD) to remove conventional/large middle molecules (upto 45 kDa), while maintaining stable albumin. Clinical trials have shown that clearances of middle molecules during HDx exceeded the clearances provided by high-flux (HF) membranes in HD and hemodiafiltration (HDF) mode. The introduction of HDx with Theranova (MCO) dialyzer membrane to Colombia in 2017 has provided the ability to report real-life comparative data of the effects of HDx therapy on outcomes.

## OBJECTIVE

The purpose was to compare laboratory parameters, hospitalization rates, medication usage and adverse events in a cohort of patients switched from high-flux HD (HF-HD) to MCO-HDx.

## METHODS

### Study Design

This historical, multicenter, observational cohort study of chronic HD patients was undertaken in the Renal Therapy Services (RTS) network in Colombia. Dialysis clinic inclusion was based on standardized processes and electronic medical records, and only centers where 100% of patients switched from HF-HD to MCO-HDx were included.

Patients who had received HF-HD (Polyflux 140; Revaclear 300 or 400, Baxter, Deerfield, IL, USA) three times weekly for 4 hours, for at least 12 months, were switched to receive HDx (Theranova; Baxter, Deerfield, IL, USA). The patient's prescriptions (QD, QB, target Kt/V, duration, and dialysate) were not changed as part of this study.

Eligible ESKD patients aged 18 years or greater treated for chronic HD, received HF HD for at least 1 year prior to conversion to MCO-HDx, and were then maintained on MCO-HDx, for at least 1 year. Patients were required to receive both HF-HD and MCO-HDx treatments at the same center. Patients were excluded if they discontinued therapy, changed provider, underwent kidney transplant, recovered kidney function, went to another renal clinic, or changed to peritoneal dialysis or to another dialyzer.

Eighty-one (81) patients from 3 clinics qualified for inclusion in the study, and data from both the HF-HD phase and the MCO-HDx phase of the study were collected.

### Study Outcomes

Outcomes studied were laboratory parameters, annual hospitalization rates, hospitalization rates by causes, annual hospital stay, 30-day readmission rates, adverse events related to hemodialysis procedures, and medication use. All outcomes were assessed throughout year 1, while on HF-HD and during year 2, after switching to MCO-HDx.

## Data Collection and Analysis:

Data collected included patient demographic characteristics, hemodialysis treatment parameters, laboratory parameters, and monthly data on medication prescriptions of IV (intravenous) ESA/iron. The Wilcoxon signed-rank test was used to evaluate any differences before and after switching to MCO-HDx, to account for the distribution of continuous variables. Rates of hospitalization, hospital days, and hospital readmission were estimated where the numerator constituted the number of events and the denominator was the time contributed by each patient, within the study. These rates were presented with their respective 95% confidence intervals. The incidence rates pre- and post-MCO-HDx were compared using the incidence rate ratio. A hospitalization event was counted if the duration was 1 day or more. A readmission event was counted when a new hospitalization occurred between the fourth and thirtieth day of hospital discharge, immediately before. Stata Statistical Software: Release 14 (StataCorp LP, College Station, TX, USA) was used to perform statistical analyses. Two-tailed tests were used, and a p value of <0.05 was considered significant.

## STUDY LIMITATIONS

While the study was a multicenter study, only 81 patients met full study criteria for analysis. The "before and after" design introduces the potential for bias that is secondary to the changes in dialysis care after switching from HF-HD to MCO-HDx. In addition, this was a single-arm observational study.

## RESULTS

### Patients for Analysis

Of the potential 175 patients receiving HF-HD at the three study clinics, a total of 81 patients were included in the analysis. Twenty-three did not meet eligibility criteria, 48 were lost to follow-up during the HF-HD period, and 23 were lost during the MCO-HDx study period, leaving 81 patients for analysis.

### Laboratory Parameters

Anemia profile after 12 months of MCO-HDx showed a reduction in median erythropoietin resistance, but no significant change in median ferritin levels, hemoglobin levels, and transferrin saturation (TSAT).

- Erythropoietin resistance was reduced significantly on MCO-HDx (3.37 (IQR 7.28)) vs. HF-HD (4.16 (IQR 8.03)),  $p=0.016$
- Ferritin level was 482.70 ng/mL (IQR 934.9) on HF-HD and 530.20 (IQR 825.40) on MCO-HDx ( $p=0.855$ )
- Median TSAT was 27.73% (IQR 14.28) on HF-HD vs. 31.01% (IQR 16.27) on MCO-HDx ( $p=0.454$ )
- Median hemoglobin level was 11.90 g/dL (IQR 2.3) on HF-HD and 11.80 g/dL (IQR 2.2) on MCO-HDx ( $p=0.397$ )

The median levels of the studied markers of inflammation did not change significantly.

- Albumin: 4.01 g/dL (IQR 0.43) during HF-HD vs. 3.99 g/dL (IQR 0.43) after switching to MCO-HDx ( $p=0.82$ )
- High-sensitivity C-reactive protein (hsCRP) (66 measurements in 20 patients): 0.58 mg/dL (IQR 0.92) on HF-HD and 0.43 mg/dL (IQR 0.56) with MCO-HDx ( $p=0.122$ )



### Hospitalization Rates

See Table 1.

- The overall rate of hospitalization events per patient-year was 0.77 on HF-HD vs. 0.71 on MCO-HDx ( $p = 0.698$ ), with no significant differences in hospitalization rate per patient-year due to cardiovascular events, events related to dialysis, or infections
- The rate of hospital days per patient-year reduced significantly by 1.53 days (25.8%) on MCO-HDx (5.94 HF-HD vs 4.41 with HDx;  $p < 0.001$ )
- The 30-days readmission rate per patient-year was 0.15 on HF-HD vs. 0.04 on MCO-HDx ( $p = 0.259$ )

Characteristic	Events	Rate	95%	CI	p value
Global hospitalization rate (events/patient-year)					
Before	61	0.77	0.60	0.98	0.698
After	57	0.71	0.55	0.92	
Hospitalization rate for cardiovascular causes					
Before	17	0.21	0.13	0.34	0.589
After	14	0.18	0.10	0.30	
Hospitalization rate for causes related with dialysis					
Before	17	0.21	0.12	0.34	0.356
After	12	0.15	0.08	0.26	
Hospitalization rate for infectious causes per patient-year					
Before	8	0.10	0.04	0.20	0.653
After	10	0.13	0.06	0.23	
Hospitalization rate for other causes per patient-year					
Before	19	0.24	0.14	0.37	0.764
After	21	0.26	0.16	0.40	
Hospital days per patient-year					
Before	473	5.94	5.41	6.50	<0.001
After	353	4.41	3.97	4.90	
30-day readmission rates per patient-year					
Before	12	0.15	0.09	0.27	0.259
After	7	0.09	0.04	0.18	

Table 1. Hospitalization Rates. CI, confidence interval; rate is defined as events per person year. Person-year is the sum of each person's individual time in the population by one year at risk to the event hospitalization; Events are defined as hospitalization events with a duration longer than 24 hours.

Adapted from Sanabria et al.

### Medication Use

See Table 2.

Significant reductions in medication usage were seen after switching to MCO-HDx.

- In-center IV medication – monthly-median doses:
  - ESA: significantly decreased from 12,000 IU on HF-HD to 10,000 IU on MCO-HDx ( $p = 0.036$ )
  - Iron: significantly decreased from 73.46 mg on HF-HD to 66.36 mg on MCO-HDx ( $p = 0.003$ )
- Phosphate binders - median dose of aluminum hydroxide was not significantly different and change in median dose of calcium carbonate was not clinically important due to variability

### Adverse Events

A reduction in adverse events related to hemodialysis procedures was observed after switching to MCO-HDx (18 events with HF-HD vs 5 events with MCO-HDx). There were no adverse events related to the dialyzer membrane on MCO-HDx. A total of 172 patients were randomized, and 171 were treated at 21 US centers between September 2017 and October 2018; 86 were treated with HDx therapy using Theranova (389 patient-months), and 85 with

Characteristic	Mean	SD	P <sub>25</sub>	Median	P <sub>75</sub>	IQR	<i>p</i> value*
ESA (epoetin α), IU/month							
Before	15,109.82	15,564.73	0.00	12,000.00	24,000.00	24,000.00	0.036
After	14,010.29	15,864.38	0.00	10,000.00	22,000.00	22,000.00	
IV iron, mg/month							
Before	73.46	142.13	0.00	0.00	100.00	100.00	<0.001
After	66.36	167.34	0.00	0.00	100.00	100.00	
Calcium carbonate, mg/month							
Before	749.28	1,001.60	0.00	600.00	1,200.00	1,200.00	<0.001
After	989.51	167.34	0.00	600.00	1,800.00	1,800.00	
Aluminum hydroxide, mg/month							
Before	410.33	1,056.54	0.00	0.00	0.00	0.00	0.471
After	319.17	788.36	0.00	0.00	0.00	0.00	

Table 2. Medication Use. ESA, erythropoiesis-stimulating agents; IU, international unit; IV, intravenous; IQR, interquartile range; SD, standard deviation; P<sub>25</sub>, 25th percentile, P<sub>75</sub>, 75th percentile. \* Wilcoxon signed-rank test. Adapted from Sanabria et al.

a high-flux dialyzer (366 patient-months). Baseline demographics and clinical characteristics were similar between groups; 39% of patients were female, and the mean age was 59±13 years.

### Clinical outcomes: hospitalization and length of stay

Clinical outcomes are shown in Table 1. Hospitalization was 45% lower in patients treated with HDx therapy with Theranova compared with high-flux HD (IRR=0.55; 95% CI: 0.30, 1.00;  $P=0.042$ ). There was no significant difference in length of hospital stay.

## DISCUSSION AND CONCLUSIONS

In this cohort of chronic HD patients, switching from HF-HD to HDx enabled by the THERANOVA MCO dialyzer membrane was associated with a ~26% reduction in number of hospital days per patient-year, and a trend towards reduction in hospitalization rate, which can ease the burden of ESKD on patients and healthcare systems.

During the 12-month period of HDx therapy, in-center IV medication doses of ESA and iron were significantly reduced, in comparison to the 12 months on HF-HD, and were accompanied by a reduction in erythropoietin resistance, while maintaining stable hemoglobin levels. Albumin levels also remained stable with HDx therapy, further supporting THERANOVA's ability to efficiently remove conventional/large middle molecules, while retaining larger (>45 kDa) proteins and essential substances.

Although not significant, a trend toward reduction in an inflammatory marker, hsCRP, was observed after switching to HDx. While the reduction in the rate of hospitalizations related to cardiovascular events with HDx was non-significant, the trend aligns with observations from the general population that show an association of elevated hsCRP levels with cardiac events.

**A switch to HDx therapy enabled by THERANOVA was associated with significant reduction in hospital days, IV ESA/iron doses, and improvement in erythropoietin resistance, which can inform treatment modality decisions and reduce the impact of ESKD on patients and healthcare systems.**



# Medium Cut-Off Dialyzer Improves Erythropoiesis Stimulating Agent Resistance in a Hepcidin-Independent Manner in Maintenance Hemodialysis Patients: Results from a Randomized Controlled Trial

Lim JH, Jeon Y, Yook JM, et al. Medium cut-off dialyzer improves erythropoiesis stimulating agent resistance in a hepcidin-independent manner in maintenance hemodialysis patients: results from a randomized controlled trials *Sci Rep.* 2020;10(1):16062. doi: 10.1038/s41598-020-73124-x.

## BACKGROUND

Anemia is a frequent complication of end-stage kidney disease (ESKD) and is associated with increased morbidity and mortality rates. Anemia in ESKD has multiple causes, including erythropoietin deficiency, uremia-related inhibition of erythropoiesis, and inflammation. Erythropoiesis stimulating agents (ESAs) and iron are used to treat anemia in ESKD patients. However, the responses to ESA vary greatly due to iron deficiency, poor nutritional state, and chronic inflammation. Patients who have been on maintenance hemodialysis regularly exhibit this resistance, which also has a cumulative effect over time.

Uremic toxins are associated with chronic inflammation and are known to affect iron metabolism in ESKD patients by interfering with the response to ESAs. There are uremic substances of various sizes that cause ESA resistance, including hepcidin and inflammatory cytokines. Traditional high-flux hemodialysis (HD) effectively removes small (up to ~15 kDa) molecular uremic toxins but has limited capacity to remove conventional/large middle molecules (up to ~45 kDa), which is believed to improve ESA response.

Newly introduced medium cut-off (MCO) dialyzers have uniformly distributed larger pores and have a greater capacity to remove conventional/large middle molecules and inflammatory cytokines compared to traditional high-flux (HF) dialyzers. However, there is no clear evidence that demonstrates the effect of MCO dialyzer membranes on ESA resistance in maintenance HD patients.

## OBJECTIVE

This study aimed to evaluate whether HDx with MCO dialyzer membrane can improve the ESA resistance in chronic HD patient.

## METHODS

### Study Design

This is a post-hoc analysis of a prospective, randomized, controlled, open-label trial in patients treated with maintenance HD, at a national university hospital in South Korea, for a study period of 12 weeks. The original trial evaluated the impact of HDx with MCO dialyzer membrane on quality of life compared to HD with high flux dialyzer.\* The post-hoc analysis evaluated the impact of HDx with MCO dialyzer membrane on ESA resistance.

\*Lim et al. Randomized Controlled Trial of Medium Cut-Off versus High-Flux Dialyzers on Quality of Life Outcomes in Maintenance Hemodialysis Patients. *Nature/Sci Rep.* 2020; 10:7780. A summary of this study can be found in this compendium.

In the original trial, patients were randomly allocated in a 1:1 ratio to HDx with MCO dialyzer membrane (HDx-MCO group) and high-flux dialyzer (HF HD group). The HDx-MCO group changed their dialysis membrane from a high-flux dialyzer (FX CorDiax 80 or 60; Fresenius Medical Care Deutschland, Bad Homburg, Germany) to a MCO dialyzer (Theranova 400; Baxter International Inc., Hechingen, Germany). The HF HD group continued their treatments with the high-flux dialyzer. There was no change in the dialysis prescription for dialysis time per session, dialysis frequency per week, blood flow rate, and dialysate flow rate during the study period.

## Data Collection and Analysis

Data collected in the original trial was used for this post-hoc analysis. Baseline demographics, comorbid diseases, biochemical data, and dialysis information were collected at the time of enrollment. The erythropoietin resistance index (ERI), calculated as the mean weekly weight-adjusted ESA dose divided by the hemoglobin level, was used to evaluate the ESA resistance; the level was measured every 4 weeks. Blood samples for the measurement of biochemical markers were obtained at the start of a midweek dialysis session. All the baseline samples were collected while patients were being dialyzed with high-flux HD.

## Study Outcomes

The primary outcome was ESA resistance change, defined as the change in ERI after 12 weeks of treatment with either HF HD or MCO-HDx therapy. The secondary outcomes were iron- and anemia-related markers, reduction ratios of the iron regulator (hepcidin), and the inflammatory cytokine tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), after 12 weeks of treatment with either HF HD or MCO-HDx therapy.

## Study Limitations

The number of registered patients was small (n=49), and the study duration (12 weeks) was not long enough to get definite results. Although anemia-related parameters such as iron, transferrin saturation (TSAT), and TNF- $\alpha$ , were significantly different at 12 weeks, the within-group differences were not significant for these parameters. The study was not blinded to clinicians and could have affected the prescription of ESA and iron supplementation. Finally, the detailed mechanism regarding how ESA response was improved by increased removal of conventional/large middle molecules remains unclear.

## RESULTS

### Patient Characteristics

All the enrolled patients (n=49) completed the study except one patient who withdrew consent in the HDx-MCO group. The age, sex, residual renal function, type of dialyzer, dialysis method, comorbidities and ESA treatment were well balanced between the two groups.

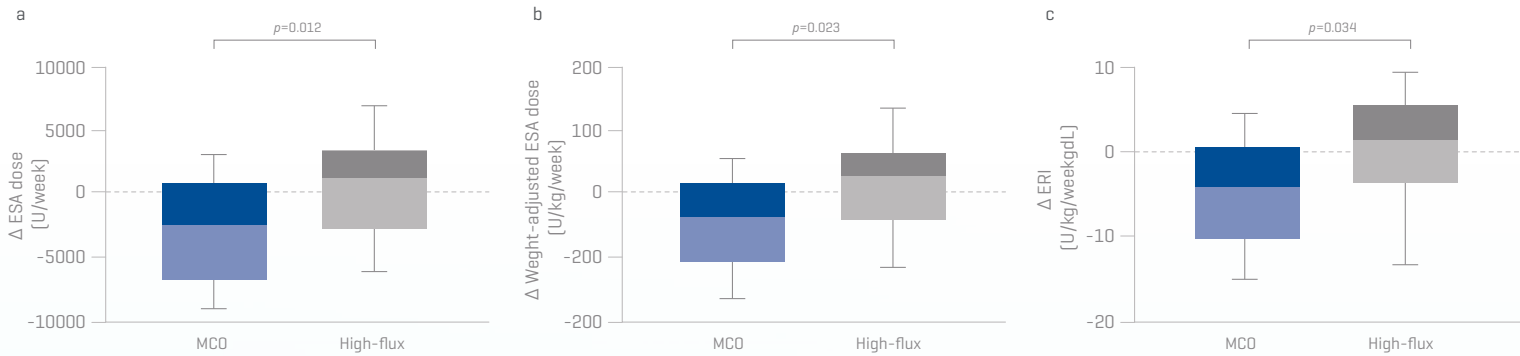
### Primary Outcome: Change in ERI (Reflecting ESA Resistance)

HDx with MCO dialyzer membrane reduced ESA resistance compared to high flux HD. A comparison of differences ( $\Delta$ ) in the baseline and 12 weeks' values of ESA dose and weight-adjusted ESA dose showed significantly lower values in the MCO group, than in the high flux group ( $\Delta$  ESA dose, p=0.012;  $\Delta$  weight-adjusted ESA dose, p=0.023). The difference in ERI was significantly lower in the MCO group than in the high-flux group ( $\Delta$  ERI, p=0.034). See Figure 1.





**Figure 1. Comparison of ESA (a), weight-adjusted ESA (b), and ERI (c) difference. Abbreviations: ESA, erythropoiesis stimulating agent; ERI, erythropoietin index; MCO, medium cut-off. Figure adapted from Lim et al.**

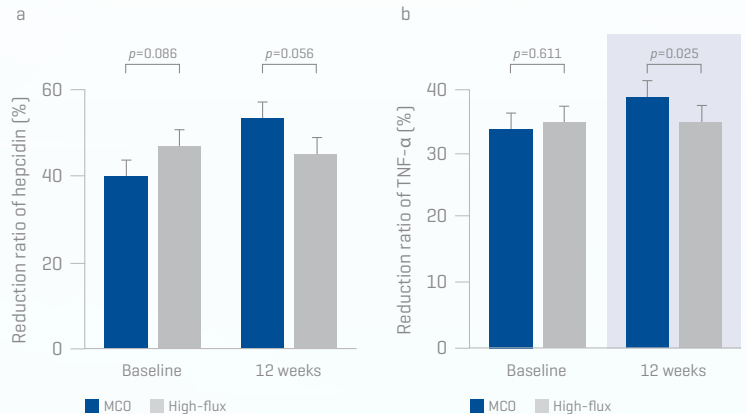


### Secondary Outcome: Iron Metabolism and Anemia-Related Markers

- The serum iron level and TSAT after 12 weeks of therapy were significantly higher in the HDx-MCO group than the HF HD group, despite the comparable use of intravenous (IV) iron (iron,  $p=0.029$ ; TSAT,  $p=0.031$ )
- Other parameters of iron metabolism such as erythroferrone (ERFE), erythropoietin (EPO), and soluble transferrin receptor (sTfR) were not significantly different between the HF HD and the HDx-MCO groups, at baseline or after 12 weeks of therapy
- Serum hepcidin level was not different between groups at baseline or after 12 weeks of therapy
- TNF- $\alpha$  level was significantly lower in the HDx-MCO group compared to the HF HD group, after 12 weeks of therapy
- Biochemical data for serum hemoglobin, albumin, and high-sensitivity C-reactive protein (hsCRP) levels were similar between groups at the start and end of the study, and the changes during the study were not significant. See Table 1.
- The changes in these iron metabolism and biochemical parameters did not show significant differences between groups

### Secondary Outcome: Comparison of the Reduction Ratio (RR) of Serum Hepcidin and TNF- $\alpha$

The RR of serum hepcidin was not significantly different between the HF HD and HDx-MCO groups at baseline or after 12 weeks of therapy. The RR of TNF- $\alpha$  was similar at baseline for the HF HD and HDx-MCO groups; however, after 12 weeks, it was higher in the HDx-MCO group than in the HF HD group ( $p = 0.025$ ). See Figure 2.



**Figure 2. Reduction ratio of serum hepcidin (a) and TNF- $\alpha$  (b) at baseline and 12 weeks. Abbreviation: TNF- $\alpha$ , tumor necrosis factor-alpha; MCO, medium cut-off. Figures adapted from Lim et al.**

## DISCUSSION AND CONCLUSIONS

Changing from HD with high-flux dialyzer to HDx with MCO THERANOVA dialyzer membrane improved the ESA resistance as compared to continuing HD with high-flux dialyzer. The importance of ESA resistance in HD patients has been emphasized in several reports; ESA hyporesponsive HD patients have shown increased all-cause mortality and cardiovascular complications. Although the impact of improved ESA resistance on mortality and cardiovascular events was not evaluated in this study, it might have a positive effect on the prognosis in the long-term.

	Baseline			12 weeks			Difference ( $\Delta$ ) between baseline and 12 weeks		p for difference ( $\Delta$ ) between groups
	MCO	High-flux	p	MCO	High-flux	p	MCO	High-flux	
Hemoglobin (g/dL)	10.6 $\pm$ 0.9	10.7 $\pm$ 1.1	0.859	10.9 $\pm$ 0.9	11.0 $\pm$ 1.0	0.697	0.2 [-0.5, 0.0]	0.0 [-0.3, 0.9]	0.841
Albumin (g/dL)	4.11 $\pm$ 0.38	4.06 $\pm$ 0.33	0.635	3.98 $\pm$ 0.27	4.04 $\pm$ 0.33	0.450	-0.05 [-0.30, 0.00]	-0.10 [-0.20, 0.15]	0.252
hs-CRP (mg/dL)	0.11 [0.03, 0.26]	0.18 [0.05, 0.71]	0.704	0.13 [0.04, 0.46]	0.22 [0.06, 1.30]	0.250	0.00 [-0.10, 0.17]	0.06 [-0.03, 0.78]	0.161
Ferritin (ng/mL)	161.1 [70.1, 305.3]	90.3 [38.6, 205.9]	0.156	123.9 [57.9, 312.2]	158.1 [59.5, 284.2]	0.904	19.2 $\pm$ 173.6	19.1 $\pm$ 151.7	0.998
Iron ( $\mu$ g/dL)	66.1 $\pm$ 25.0	59.6 $\pm$ 29.8	0.410	72.1 $\pm$ 25.4	55.9 $\pm$ 25.0	<b>0.029</b>	2.49 [-5.9, 15.8]	-1.6 [-15.8, 4.0]	0.131
TIBC ( $\mu$ g/dL)	221.4 $\pm$ 37.8	234.8 $\pm$ 51.7	0.309	221.1 $\pm$ 46.3	227.1 $\pm$ 33.9	0.607	-0.3 $\pm$ 36.3	-7.7 $\pm$ 32.2	0.455
TSAT (%)	30.6 $\pm$ 12.3	26.1 $\pm$ 11.9	0.196	34.0 $\pm$ 15.0	25.3 $\pm$ 11.9	<b>0.031</b>	-0.6 [-4.4, 8.1]	0.8 [-8.5, 3.7]	0.325
ERFE (pg/mL)	402.5 $\pm$ 122.3	360.3 $\pm$ 136.0	0.259	483.3 $\pm$ 123.0	386.0 $\pm$ 116.2	0.133	53.0 [-38.3, 95.8]	44.6 [0.8, 73.6]	0.660
EPO (mU/mL)	9.5 [6.7, 16.0]	11.9 [5.0, 18.5]	0.818	10.1 [4.6, 19.9]	7.9 [5.3, 15.3]	0.741	-2.3 [-6.5, 6.2]	0.5 [-9.5, 3.2]	0.889
sTfR (nmol/L)	16.7 [12.8, 23.5]	17.8 [13.6, 23.7]	0.617	16.4 [11.3, 21.9]	18.5 [11.1, 23.6]	0.660	-1.4 $\pm$ 8.3	-1.5 $\pm$ 10.1	0.981
Hepcidin (ng/mL)	46.8 $\pm$ 36.9	32.4 $\pm$ 27.3	0.128	42.1 $\pm$ 23.8	44.9 $\pm$ 26.3	0.688	-3.5 $\pm$ 31.1	12.3 $\pm$ 27.0	0.063
TNF- $\alpha$ (pg/mL)	17.9 $\pm$ 5.0	18.0 $\pm$ 4.7	0.915	16.3 $\pm$ 3.4	19.0 $\pm$ 4.8	<b>0.027</b>	-1.6 $\pm$ 4.3	1.0 $\pm$ 5.7	0.079

**Table 1. Comparisons of the iron metabolism and biochemical parameters. Data are shown as mean  $\pm$  standard deviation or median (interquartile range). Values in bold indicate statistically significant results. Abbreviations: MCO, medium cut-off; HF, high flux; TSAT, transferrin saturation; ERFE, erythroferrone; EPO, erythropoietin; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TNF- $\alpha$ , tumor necrosis factor-alpha; hs-CRP, high sensitivity C-reactive protein. Table adapted from Lim et al.**





The improvement in ESA resistance using HDx with MCO THERANOVA dialyzer membrane may be attributable to the efficient removal of conventional/large middle molecules including TNF- $\alpha$ . Under uremic conditions, chronic inflammation may induce an enhanced state of T-cell activation that leads to ESA resistance. TNF- $\alpha$  (molecular weight (MW) 17.3 kDa) is a representative pro-inflammatory cytokine that is usually elevated with chronic kidney disease. TNF- $\alpha$  causes anemia by inhibiting erythroid-precursor proliferation and promoting hypoferrremia. The study confirmed that switching to the MCO THERANOVA dialyzer membrane resulted in improved TNF- $\alpha$  removal, as shown by lower TNF- $\alpha$  level after 12 weeks of HDx therapy, as compared to patients who continued with HF HD. Changes in erythropoiesis and iron metabolism-related parameters, such as hepcidin, erythroferrone, erythropoietin were analyzed to investigate the association between TNF- $\alpha$  and ESA resistance. TNF- $\alpha$  induces hypoferrremia through both hepcidin-independent and hepcidin-dependent mechanisms. Hepcidin is a relatively small-sized (~27 kDa) large middle molecular uremic toxin that has an effect on ESA resistance. The serum hepcidin level is typically controlled by inflammation and erythropoietin. While the RR and difference in hepcidin at baseline and after 12 weeks of therapy did not vary significantly between groups, after 12 weeks of HDx therapy hepcidin levels decreased by 3.5 ng/mL vs. an increase of 12.3 ng/mL in the HF HD group ( $p=0.063$ ). There was no significant difference between groups in serum level of erythropoietin (30.4 kDa), a regulator of hepcidin, with a decrease of 2.3 mU/mL in the HDx-MCO group, vs. an increase of 0.5 mU/mL in the HF HD group. Erythroferrone (52 kDa), also a regulator of hepcidin, remained unchanged after switching to HDx therapy, which further supports Theranova's ability to retain larger (>45 kDa) proteins and essential substances. Considering these results, it is possible that the hepcidin-independent pathway played a dominant role in improving iron status, in this study.

**In conclusion**, HDx with MCO THERANOVA dialyzer membrane achieved greater improvement in ESA resistance than HD with high-flux dialyzer. HDx with MCO THERANOVA dialyzer membrane efficiently removed the conventional/large middle molecule TNF- $\alpha$ , an inflammatory cytokine, potentially influencing iron metabolism.

**HDx with MCO THERANOVA dialyzer membrane improves ESA resistance over time compared to high-flux HD in maintenance HD patients. HDx therapy enabled by the THERANOVA dialyzer membrane provides superior removal of conventional/large middle molecules, reducing inflammatory cytokines potentially improving iron metabolism.**



# Expanded hemodialysis as effective alternative to on-line hemodiafiltration: A randomized mid-term clinical trial

Hadad-Arrascue F, Nilsson L-G, Rivera AS, et al. Expanded hemodialysis as effective alternative to on-line hemodiafiltration: A randomized mid-term clinical trial. *Ther Apher Dial.* 2022;26:37-44. doi: 10.1111/1744-9987.13700.

## BACKGROUND

Innovation in dialysis membrane design has recently provided a medium cut-off (MCO) membrane that has higher retention onset than conventional high-flux membranes with selectively limited permeability for albumin. This membrane is designed for use in extended hemodialysis (HDx), a therapy option that enhances clearance of middle molecules but does not require external replacement fluid, as does on-line hemodiafiltration (HDF). Short-term studies have found that HDx with this filter provides similar clearance of beta2-microglobulins (β2m) and other large middle molecules as on-line HDF with the potential to outperform HDF in clearing some large molecules. Over a 6-month period, an observational study found noninferiority between the two therapies, but long-term data from a randomized trial are needed.

## OBJECTIVE

To assess long-term utility and safety of HDx relative to HDF, this trial randomized patients already receiving post-dilutional online HDF three times weekly for chronic kidney disease in Spain to receive either HDx or HDF over a 24-week period.

## METHODS

### Study Design

Patients receiving HDF in the Renal Therapy Services dialysis center, Murcia, Spain, were included in an open-label, prospective, 1:1 randomized, parallel-group study over 24 weeks. Patients were clinically stable and between the ages of 18 and 80 years. They were stratified by residual renal function prior to randomization.

HDx treatments used the TheraNova 500 dialyzer, while HDF treatments used the Polyflux 170H dialyzer (2.0 m<sup>2</sup> vs 1.7 m<sup>2</sup> surface area; both from Baxter, Hechingen, Germany). Treatments were delivered via Artis Physio dialysis systems (Baxter, Medolla, Italy). Treatment duration, blood flow rate targets (350 mL/min), dialysis fluid composition, and temperature were maintained as before study initiation. Low-molecular-weight heparin was provided.

The primary outcome measure of this study was the reduction ratio (RR) for middle molecules, calculated by comparing pre-study values with values after 12 weeks of treatment. RR were measured for the following molecules: β2m, fibroblast growth factor 23 (FGF-23), chitinase-3-like protein 1 (YKL-40), and kappa and lambda free light chains (κ and λ FLC).

Secondary outcome measures included change from baseline at 12 and 24 weeks of treatment for various inflammatory markers and middle molecules. Changes in key protein and iron levels were also assessed, as was single pool Kt/v urea and weekly dosing of erythropoiesis-stimulating agents (ESA) and intravenous iron required to manage anemia.

The study was registered as NCT03499691, and its protocol was approved by the ethics committee of Reina Sofia General University Hospital, Murcia.

## Statistical Analysis

A sample size of 40 was possible in the study site and was determined sufficient to assess the primary outcome. Differences between study arms were analyzed using the ANCOVA model. Differences between therapies in change over time were analysed using mixed-effect repeated measurement (MMRM) models. Both models used pre-dialysis concentration and baseline urine output as covariates. Wilcoxon rank-sum test used to analyse change over time for variables with non-normal distribution of data.

## RESULTS

### Patients

In April 2018, 43 patients were enrolled, with the characteristics shown in Table 1. Baseline characteristics were similar between groups. One patient in the HDF arm died during the study. Two were excluded from analysis due to severe adverse events not related to dialysis, one in each arm of the study. Nine patients were excluded from analysis for leaving dialysis for more than 2 weeks; most were in the HDF arm. Only one of these patients left prior to the 12-week analysis.

**TABLE 1.** Patient demographics at study baseline.

	HDx Arm N=21	HDF Arm N=22
Age (years)	60.7 ± 14.3	61.8 ± 9.4
Gender (% males)	57%	73%
Body weight (kg)	76.6 ± 13.1	75.9 ± 16.0
Dialysis vintage (months; median/range)	30 / 6-224	35 / 5-375
Urine production		
Anuric (<100 mL/24 hr)	48%	45%
Oliguric (100-500 mL/24 hr)	29%	32%
Non-oliguric (>500 mL/24 hr)	23%	23%
ESRD comorbidity index	2.5 ± 1.7	1.9 ± 1.8
Malnutrition inflammation score	3.4 ± 2.1	3.5 ± 1.4

ESRD, end-stage renal disease; HDF, hemodiafiltration; HDx, extended hemodialysis. Adapted from Hadad-Arrascue et al.

### Treatments

Treatment characteristics at week 12 are shown in Table 2.

**TABLE 2.** Study treatment characteristics at week 12.

	HDx Arm N=21	HDF Arm N=19
Treatment duration (min)	241 ± 4	239 ± 7
Blood flow rate (mL/min)	400 ± 12	396 ± 8
Dialysis fluid flow rate (mL/min)	500	600
Ultrafiltration volume (L)	2.5 ± 0.8	2.1 ± 3.2
Substitution fluid volume (L)	N/A	24.4 ± 3.2

HDF, hemodiafiltration; HDx, extended hemodialysis; N/A, not applicable. Adapted from Hadad-Arrascue et al.

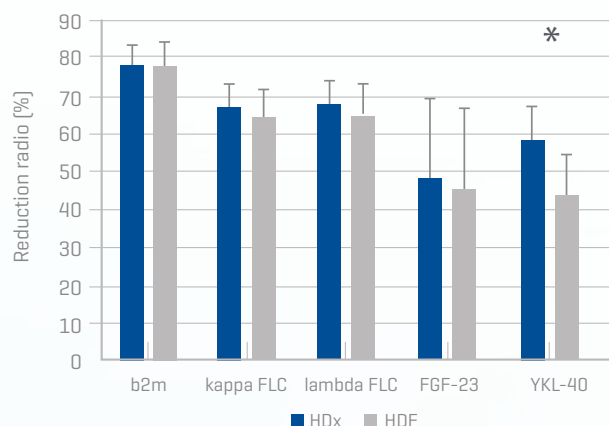


## Primary and Secondary Outcome Measures

Figure 1 shows the primary outcome measure, the 12-week pre- to post-dialysis RR. The RR for YKL-40 was significantly greater for the HDx group compared to the HDF group. RR for the other middle molecules and for key inflammatory markers were comparable for HDx vs HDF:

- Chitinase-3-like protein 1 (YKL-40):  $58.1 \pm 9.5$  vs  $42.4 \pm 12.5\%$ ;  $P=0.0001$
- Beta2 microglobulin (B2M):  $76.6 \pm 5.6$  vs  $77.2 \pm 5.6\%$ ;  $P=0.47$
- Fibroblast growth factor 23 (FGF-23):  $48.1 \pm 21.3$  vs  $45.1 \pm 20.8\%$ ;  $P=0.63$
- Kappa free light chains ( $\kappa$ -FLC):  $67.0 \pm 5.9$  vs  $64.9 \pm 6.9\%$ ;  $P=0.40$
- Lambda free light chains ( $\lambda$ -FLC):  $67.7 \pm 6.2$  vs  $65.9 \pm 8.2\%$ ;  $P=0.31$
- Interleukin-6 (IL-6):  $-13.7 \pm 13.2$  vs  $-16.9 \pm 14.7\%$ ;  $P=0.29$
- C-reactive protein (CRP):  $-7.2 \pm 12.1$  vs  $-8.8 \pm 10.6\%$ ;  $P=0.62$

**FIGURE 1.** Middle molecule pre- to post-dialysis reduction ratios (RR), using week 12 measures.



\* $p<0.0001$

Note: FLC concentrations were measured by the N Latex assay; the lambda FLC RR likely reflect only the removal of lambda monomers. B2m, beta2-microglobulin; FGF-23, fibroblast growth factor 23; FLC, free light chains; HDF, hemodiafiltration; HDx, extended hemodialysis; YKL-40, chitinase-3-like protein 1. Adapted from Hadad-Arrascue et al.

Predialysis biomarkers (both middle molecules and inflammatory markers) were present in similar levels at baseline and showed comparable changes between groups at weeks 12 and 24. This includes FLC, YKL-40, CRP, IL-6, and pentraxin-3 (PTX3). In the same way plasma levels of albumin, fibrinogen, hemoglobin, parathyroid hormone (PTH), and phosphorous did not differ between the study arms.

Table 3 shows data for the only two biomarkers for which there were significant differences between groups for either time point. At week 24, HDx had lower B2m and FGF-23 than did HDF, but this as a "borderline difference." Overall, the two therapies are otherwise comparable in terms of biomarker changes.

**TABLE 3.** Baseline pre-dialysis levels and changes from baseline for the studied biomarkers for those with significant differences between groups at either time point.

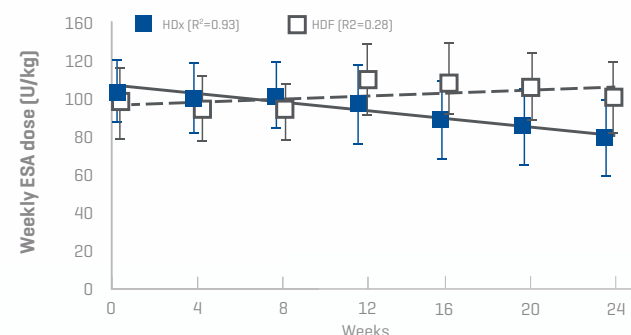
		Baseline	Change, Wk 12	Change, Wk 24
B2m (mg/L)	HDx	25.4 ± 7.6	-0.6 ± 3.6	-0.6 ± 3.9
	HDF	24.3 ± 7.5	-1.0 ± 4.5	+3.3 ± 6.1
	P-value	0.62	0.55	0.046
FGF-23 (pg/mL)	HDx	1153 [402, 1979]	-20 [-597, +512]	-24 [-623, +202]
	HDF	825 [277, 1438]	+208 [-537, +494]	+343 [+44, +1152]
	P-value	0.28	0.45	0.039

B2m, beta2-microglobulin; FGF-23, fibroblast growth factor 23; HDF, hemodiafiltration; HDx, extended hemodialysis. Adapted from Hadad-Arrascue et al

## Exploratory Outcome Measure

Anemia management was analysed all patients in the HDF arm and 20 of 21 patients in the HDx arm received ESA during the study. Those in the HDF study arm received a stable mean weekly dose of ESA over time, while those in the HDx study arm showed a trend toward a decrease in weekly ESA dose from week 8 onward (Figure 2). Erythropoietin resistance index (ERI) in ESA-treated patients showed a similar trend but was not significantly different between groups, and hemoglobin levels were stable over time in both groups.

**FIGURE 2.** Weekly ESA dose per kg body weight



ESA, erythropoiesis-stimulating agent; HDF, hemodiafiltration; HDx, extended hemodialysis. Adapted from Hadad-Arrascue et al.

## Adverse Events

A total of 37 patients (86%) experienced an adverse event (AE) during the study, with 18 subjects reporting 79 AE in the HDx group and 19 subjects reporting 55 AE in the HDF group. Most common AE were hypotension, muscle cramps, and hypertension. Eight patients (HDx, n=3; HDF, n=5) reported serious AE, but none were related to the dialysis procedure.

## DISCUSSION

In the first randomized controlled study comparing HDx to HDF treatment over 24 weeks, HDx provided similar RR as on-line HDF for many middle molecules, with greater reduction for YKL-40. Based on the comparable biomarker levels, a HDx was non-inferior to HDF in clinical effectiveness in this trial.

The online HDF achieved in this study was comparable to recommended HDF therapies with a average HDF convective volume of approximately 26 l/treatment and a convective flow rate close to 28% of blood flow rate.

The large middle molecule clearance data are comparable to previous studies but no significant change over time in pre-dialysis plasma levels. Caution is needed in the interpretation of the B2m and FGF-23 differences that were noted. The stability of pre-dialysis albumin levels is important to note.

There was a trend for reduced ESA dose over time with HDx alongside a steady haemoglobin level indicating an improved ESA response. However the low sample size means firm conclusions cannot be drawn.



## CONCLUSIONS

This randomized, controlled study comparing HDx with online HDF over 24 weeks found the following:

- HDx was noninferior to HDF in terms of middle molecule RR at 12 weeks, and HDx produced a greater RR for YKL-40 over 12 weeks
- HDx was noninferior to HDF in terms of 12- and 24-week effects on middle molecules, markers of inflammation, and plasma proteins. In particular albumin levels were stable
- HDx therapy was associated with a trend for reduced ESA requirement
- Neither HDx nor HDF was judged to have serious AE associated with the dialysis procedure
- HDx may be an attractive option for long-term dialysis, particularly since it is easy to implement and not dependent on on-line HDF equipment



# HDx: A WORLD OF DIFFERENCE

## Safety evidence when creating internal filtration through HDx and MCO

The permeability of the Theranova membrane for endotoxins is not significantly different when comparing low flux, high-flux, medium cut-off, and high cut-off membranes.<sup>1</sup>



 **Schepers E, Glorieux G, Elout S, et al.**  
**Assessment of the Association Between Increasing Membrane Pore Size and Endotoxin Permeability Using a Novel Experimental Dialysis Simulation Set-Up.** *BMC Nephrol.* 2018;19:1.

1. Schepers E, Glorieux G, Elout S, et al. Assessment of the Association Between Increasing Membrane Pore Size and Endotoxin Permeability Using a Novel Experimental Dialysis Simulation Set-Up. *BMC Nephrol.* 2018; 19:1.





# Assessment of the Association Between Increasing Membrane Pore Size and Endotoxin Permeability Using a Novel Experimental Dialysis Set-Up

Schepers E, Glorieux G, Eloit S, et al. Assessment of the association between increasing membrane pore size and endotoxin permeability using a novel experimental dialysis set-up. *BMC Nephrol.* 2018; 19:1. doi: 10.1186/s12882-017-0808-y.

## BACKGROUND

The current trend is to further increase pore size and permeability of dialysis membranes to enhance removal of uremic toxins in the larger molecular weight range even when used in dialysis mode. High-cut off (HCO) dialyzers allow elimination of molecules up to 45 kDa and remove specific middle molecules more effectively than standard high flux membranes. The use of these membranes decreases inflammation and in vitro calcification, but also results in albumin loss.

More recently membranes with a steeper cut-off at a lower molecular weight than HCO membranes, medium cut off (MCO) membranes have been introduced. These membranes can even remove large toxins such as kappa [22.5 kDa]<sup>1</sup> and lambda [45 kDa]<sup>1</sup> free light chains, two compounds associated with inflammatory markers and mortality in chronic kidney disease (CKD).

The question arises whether these membranes with increasing pore size also have higher permeability for endotoxins and other bacterial degradation products potentially present in dialysis fluids. This permeability issue is relevant, since chronic exposure of hemodialysis (HD) patients to low levels of cytokine-inducing microbial components can potentially contribute to the micro-inflammatory status of these patients, thus neutralizing the potential positive effect induced by their capacity of enhanced removal of pro-inflammatory uremic toxins. Therefore, the request for ultrapure dialysate might become a more important concern as membrane pore size becomes larger, even when applied in hemodialysis mode. Standard methods to determine biological contamination are bacterial culture and the Limulus Amebocyte Lysate (LAL) assay. To test true biologic response with more clinical relevance, bio-assays such as the one using the THP-1 cell line can be applied.

In the present study, a realistic dialysis set-up using full-sized dialyzers was developed that simulates the clinical situation in terms of flow rates and viscosity of the medium perfused in the blood compartment.

## OBJECTIVE

To assess commercial dialyzers of comparable composition but with different pore size for their permeability for bacterial degradation products by means of a biological assay sensitive to several bacterial components (THP-1) as read-out in addition to the LAL assay.

## METHODOLOGY

### Dialysis Membranes

The dialysis membranes evaluated for their endotoxin permeability provided by the manufacturer were composed of comparable polymers but with a different pore size: **Polyflux** 17 L (low flux); **Revaclear** 400 (high flux); **Theranova** 400 (MCO); and **Theralite** 2100 (HCO); Baxter, Hechingen, Germany. See Table 1.

Dialyzer	Type	Membrane Polymer	Pore radius* (nm)
Polyflux 17 L	Low flux	PAES/PVP/PA	3.1 ± 0.2
Revaclear 400	High flux	PAES/PVP	3.9 ± 0.1
Theranova 400	Medium cut off	PAES/PVP	5.0 ± 0.1
Theralite 2100	High cut off	PAES/PVP	10 ± 2

**TABLE 1.** Characteristics of dialyzers. \* effective Stokes-Einstein radius; calculated from molecular weight cut-off measured with polydisperse Dextran. Abbreviations: PAES: polyarylethersulfone; PVP, polyvinylpyrrolidone; PA, polyamide, UF, ultrafiltration. Adapted from Schepers, et al.

### Dialysate and blood substitution fluids

Ultrapure dialysis fluid was prepared on-line with an AK200 dialysis machine (Gambro, Lund, Sweden) using a smartbag (Fresenius Medical Care, Willebroek, Belgium) acid concentrate and a BiCart cartridge (Gambro) resulting in a dialysate containing 3 mM K<sup>+</sup>, 140 mM Na<sup>+</sup>, 1.25 mM Ca<sup>2+</sup>, 0.50 mM Mg<sup>2+</sup> and 34 mM bicarbonate. A 1.25% polyvinylpyrrolidone (PVP) (Luvitec® K85 powder, BASF, New Jersey, USA) solution was prepared in sterile phosphate buffered saline (PBS) 10x, pH 7.2 (Gibco, Life Technologies, Paisley, UK) and diluted 1:10 in sterile water (Braun, Melsungen, Germany) to achieve a solution with a kinematic viscosity of 4 mm<sup>2</sup>/s, to mimic the viscosity of whole blood. Compatibility of PVP dissolved in PBS (PVP<sub>PBS</sub>) with both the LAL and THP-1 assay was evaluated per se and in combination with lipopolysaccharide (LPS) in comparison to PBS. No interference of the PVP dissolved in PBS could be observed in both assays.

### Challenge Solution

The ISO11663:2014 standard for LPS allows less than 0.5 endotoxin units (EU)/mL in dialysis fluid. In the *in vitro* experimental set up, the duration of a dialysis session was set to 1 hour. Corresponding to the total exposure during a regular dialysis session of 4 hours, a minimum load of 2 EU/mL should be aimed for. However, to create a worst-case scenario, this load was increased, aiming at a dialysis fluid containing at least 4 EU/mL. To obtain this, a concentrated solution (200 EU/mL) of two clinically relevant water borne bacterial species *Pseudomonas aeruginosa* and *Pelomonas saccharophila* was prepared.

### Dialysis Machine Set Up

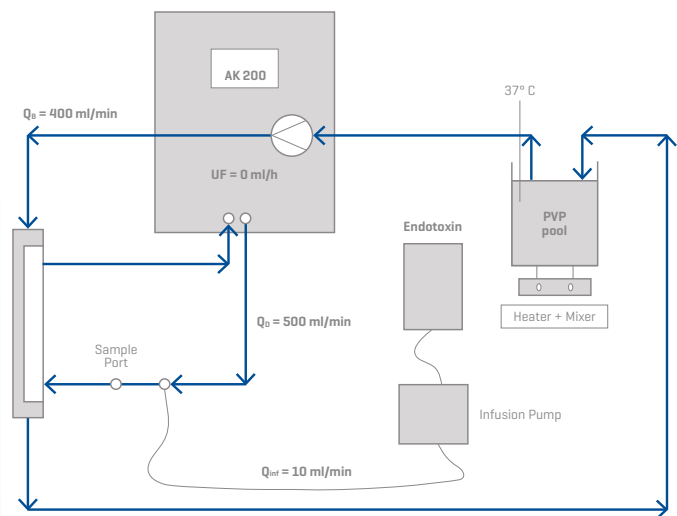
The AK200 dialysis machine was set in double needle treatment and the tubings for hemodialysis (Gambro) and the dialyzers were connected. The four different membranes were tested in random order; for each membrane type, 6 different dialyzers were tested.

During the actual experiment 3 liters of the PVP solution at 37°C was recirculated during 60 min at a blood flow rate (QB) of 400 mL/min while the PVP pool was continuously mixed.

The dialysate flow (QD) was set at 500 mL/min and the challenge solution was continuously infused from the sterile bag into the dialysate line before inlet of the dialyzer at a rate of 10 mL/min with a droplet pump aiming at a contamination level of the dialysate above 4 EU/mL. A sampling port was placed between



the contamination inlet port and the inlet of the dialyzer to assess the level of contamination. A schematic figure of the experimental set-up is shown in Fig.1.



**FIGURE 1.** Schematic overview of the dialysis set-up. After priming both blood and dialysate circuit and after coating the test membrane with plasma, 3 L of PVP solution, continuously mixed, was recirculated at 37° C at the blood side at a blood flow rate ( $Q_b$ ) of 400 mL/min. Samples of the PVP were taken from the pool before and after the experiment. The dialysate was prepared by the AK200 and circulated at a dialysis flow rate ( $Q_d$ ) of 500 mL/min. Before entering the membrane, contaminant was infused at a flow  $Q_{in}$  of 10 mL/min by means of a pump. Samples from the dialysate were taken just before the membrane at 5 and 55 minutes. Ultrafiltration QF was set at 0 mL/min. Figure adapted from Schepers, et al.

RESULTS

Permeability of Dialysis

For the tested membranes, there was a nonsignificant difference in number of the PVP solutions which contained a detectable amount of endotoxin after repetitive circulation through the dialyzer, be it close to the detection limit in the majority of cases.

Table 2 shows the individual and the mean LAL assay responses for the dialysate and PVP solutions per individual experiment, categorized per membrane. Although dialysate-endotoxin concentration varied between 3.2 and 33.7 EU/mL in the individual experiments, mainly due to the difficulty of filtrate preparation and complexity of the experimental set-up, the mean exposure to endotoxins through the contaminated dialysate was above the intended minimum 4 EU/mL for each of the different experiments and did not differ between the different membranes. There was no dose-response correlation between the level of contamination within the tested range of dialysate endotoxin concentration and the detectable concentration of endotoxin in the PVP<sub>post</sub> solutions.

LAL activity in the PVP solution at the blood side of the dialyzer was below the limit of detection (limit of detection (LOD)=0.005 EU/mL) both before (PVP<sub>pre</sub>) and after the experiment (PVP<sub>post</sub>) for 12 out of 24 tested dialyzers. Endotoxin levels were below LOD in all but three (High-flux 2, high cut-off 1) PVP<sub>pre</sub> solutions. This potentially indicates contamination occurred already before the start of the experiment in these three experiments. Positive PVP<sub>post</sub> reading higher than the corresponding PVP<sub>pre</sub> reading, indicating possible contamination from endotoxin in the dialysate, was found in 9 out of 24 experiments (low-flux: 1/6; high-flux: 1/6; MCO 3/6; HCO: 4/6). While more open membranes (MCO and HCO) had a detectable amount of endotoxin, the permeability of endotoxin was not significantly different.

Membrane	Dialysate (EU/mL)	PVP <sub>pre</sub> (EU/mL)	PVP <sub>post</sub> (EU/mL)		Statistics PVP <sub>pre</sub> vs PVP <sub>post</sub>
			Duplicate 1	Duplicate 2	
Low-flux	3.5	< LOD	< LOD	< LOD	n.s.
	3.9	< LOD	< LOD	< LOD	
	5.5	< LOD	< LOD	< LOD	
	9.4	< LOD	< LOD	< LOD	
	10.3	< LOD	<u>0.011</u>	< LOD	
	19.1	< LOD	< LOD	< LOD	
Mean ± SD	8.6 ± 5.8				
High-flux	3.6	< LOD	< LOD	< LOD	n.s.
	4.1	0.008	0.007	0.008	
	5.9	< LOD	<u>0.005</u>	< LOD	
	6.1	< LOD	< LOD	< LOD	
	20.0	0.007	< LOD	< LOD	
	33.7	< LOD	< LOD	< LOD	
Mean ± SD	12.2 ± 12.2				
Medium cut-off	6.0	< LOD	<u>0.023</u>	<u>0.005</u>	n.s.
	6.3	< LOD	< LOD	< LOD	
	6.8	< LOD	< LOD	< LOD	
	8.0	< LOD	<u>0.006</u>	<u>0.005</u>	
	10.6	< LOD	<u>0.005</u>	<u>0.005</u>	
	11.8	< LOD	< LOD	< LOD	
Mean ± SD	8.3 ± 2.4				
High cut-off	3.2	< LOD	<u>0.019</u>	<u>0.013</u>	n.s.
	4.1	< LOD	0.005	0.005	
	5.4	< LOD	<u>0.005</u>	<u>0.005</u>	
	5.8	< LOD	<u>0.005</u>	< LOD	
	12.1	< LOD	< LOD	< LOD	
	22.5	0.006	0.005	0.005	
Mean ± SD	8.9 ± 7.4				

**TABLE 2.** Endotoxin levels in the dialysate and the PVP solution per membrane measured by the LAL-assay (n=6 for each membrane). LOD was 0.005 EU/mL. Data with measurable endotoxin levels were written in *italic* and when they were higher than the PVP<sub>pre</sub> value they were additionally put in **bold** and underlined. Abbreviations: PVP, polyvinylpyrrolidone; LAL, limulus amoebocyte lysate; LOD; limit of detection; EU, endotoxin units; PVP<sub>pre</sub>, PVP before the experiment; PVP<sub>post</sub>, PVP after the experiment; SD, standard deviation. Adapted from Schepers, et al.

Cytokine Induction Assay

In none of the experiments, biological activation of the inflammatory system was observed as measured by a IL-1β (17.5 kDa)<sup>1</sup> production by the THP-1 assay, sensitive for several bacterial components such as intact LPS, LPS fragments, peptidoglycan and short bacterial DNA fragments. As shown in Table 3, 25 EU/mL LPS and the contaminated dialysate significantly induced IL-1β expression, whereas none of the PVP solutions used in the different experiments induced IL-1β expression neither before or at the end of the experiments. Moreover, no significant difference in induction of IL-1β expression was found between the PVP solutions treated with the different membranes.

Despite the fact that in some of the PVP samples endotoxin was detectable, none of the PVP solutions induced a biologic response as assessed by activity of human THP-1 monocytes higher than that of the background culture medium.

The highest measured level of endotoxin in a duplicate sample from the ‘patient side’ was 0.023 EU/mL. This corresponds to a total amount of about 70 EU transferred during the 1 hour dialysis session, and thus a transfer rate of about 1 EU/kg/h (mean patient of 70 kg), which is still well below the pyrogenicity limit of 5 EU/h/kg body weight (the minimum dose that induces fever) for injectable medications and devices.



	Medium	LPS 25 EU/ mL	Dialysate	PVP <sub>pre</sub>	PVP <sub>post</sub>	Statistics <sup>o</sup>
Low-flux	11.44 ± 4.05	53.78 ± 21.11*	51.69 ± 57.07	10.87 ± 4.02	10.53 ± 4.22	n.s.
High-flux	12.86 ± 3.43	62.03 ± 22.91*	88.4 ± 122.13	11.87 ± 3.09	11.09 ± 2.82	n.s.
Medium cut-off	11.93 ± 3.54	54.71 ± 20.85*	40.99 ± 60.49	12.11 ± 3.55	11.13 ± 2.87	n.s.
High cut-off	12.25 ± 3.69	59.97 ± 17.22*	22.78 ± 21.88	11.55 ± 3.69	11.30 ± 3.18	n.s.

**TABLE 3.** Overview of IL-1 $\beta$  expression in pg/mL in the THP-1 cytokine induction assay by the dialysate and PVP solutions. \*p < 0.05 vs Medium; <sup>o</sup>PVP<sub>pre</sub> vs PVP<sub>post</sub>. Abbreviations: PVP, polyvinylpyrrolidone; LPS, lipopolysaccharide; EU, endotoxin units; PVP<sub>pre</sub>, PVP before the experiment; PVP<sub>post</sub>, PVP after the experiment. Adapted from Schepers, et al.

### Strengths of Study

The experimental set-up was a worst-case scenario in which endotoxin exposure was 4x greater than permitted in standard dialysate, spread over a 4-hour dialysis session. In contrast with the clinical setting, most modern dialysis monitors have an additional ultrafilter between permeate and dialysate, providing an extra safeguard for contamination that was bypassed in the set-up infusing the contaminant at the dialyzer inlet.

The four different membranes were tested in random order; for each membrane type, six different dialyzers were tested. The PVP pool was sampled in duplicate before the start (PVP<sub>start</sub>) and the end of the (PVP<sub>post</sub>) of the experiment. Individual data from all experiments was provided as the most exact way to present the data and provide full visibility. The PVP solutions in many cases had a measured LAL activity below the LOD and the individual numbers give a better impression of the limited degree of contamination in case values were above LOD in the blood compartment.

Special emphasis was made in the present study to develop an experimental model mimicking the clinical reality as close as possible.

- The dialysate and blood flows were comparable to the ones applied in the clinic, and in the same context, viscosity of the fluid circulating in the blood compartment was comparable to that of blood, mimicking clinical pressure distributions in the dialyzer and with it, realistic filtration profiles.
- Full size dialyzers were used rather than down-sized models to reflect the migration of endotoxin from the dialysate to the blood side by diffusion and backfiltration. To augment the worst-case scenario, ultrafiltration was set at 0 mL/mn, resulting in maximal backfiltration.
- A protein coating was applied to the tested membranes by circulating a human plasma solution before the beginning of the experiments to mimic the properties of the synthetic membrane during dialysis.

### Limitations Study

Dialyzers of comparable membrane composition from a single manufacturer were chosen to focus the investigation in pore size. Subsequently, the results can not likely be generalized to membranes of different compositions or structure.

Whole blood was not used in the experiments based on cost and difficulty of use. However, use of whole blood in this type of experiment might abrogate activity of endotoxins as several components of blood have the capacity to neutralize endotoxins.

Two water borne bacterial species *Pseudomonas aeruginosa* and *Pelomonas saccharophila* were used as the source of endotoxins. Preparations of bacteria can contain a wide range of contaminants and endotoxins with different molecular weights and transmembrane transport properties. While not all these bacterial products may test positive in the LAL test, they all have a cytokine-inducing capacity as assessed by the production of IL-1 $\beta$  by the THP-1 cell line in the bio-assay.

## CONCLUSIONS

A realistic and feasible model to assess dialysis membrane translocation of bacterial degradation products present in the dialysate was developed and applied to test the retention capacity of 4 different membranes with similar chemical composition but different pore sizes. Although more blood side PVP solutions had a detectable amount of endotoxin using a highly sensitive LAL assay in the more open vs traditional membranes the permeability for endotoxins of the 4 tested dialysis membranes was not significantly different. Moreover, none of these PVP<sub>post</sub> solutions induced IL-1 $\beta$  expression in the THP-1 based bio-assay that is sensitive also to other bacterial byproducts.

The present experiments demonstrate that, when using a 4-fold overload of endotoxin, the use of larger pore membranes, MCO and HCO, is likely safe from that regard. Indeed, in none of the experiments, biological activation of the inflammatory system was observed.

**The MCO (Theranova) membrane maintains the same endotoxin retention as other high-flux membranes.**

**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.



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