15-16-17 Aprile 2024 Sala Congressi Hotel CORALLO
Viale Antonio Gramsci, 113, 47838 Riccione

ANTE
Associazione Nazionale Tecnici Emodialisi

XXXI Corso Nazionale ANTE - Dialisi e Tecnologia

"Evoluzione tecnologica nei trattamenti dialitici cronici e acuti: dalla teoria alla pratica"

"Membrane medium cut-off (MCO): una novità o una scelta ormai consolidata?"

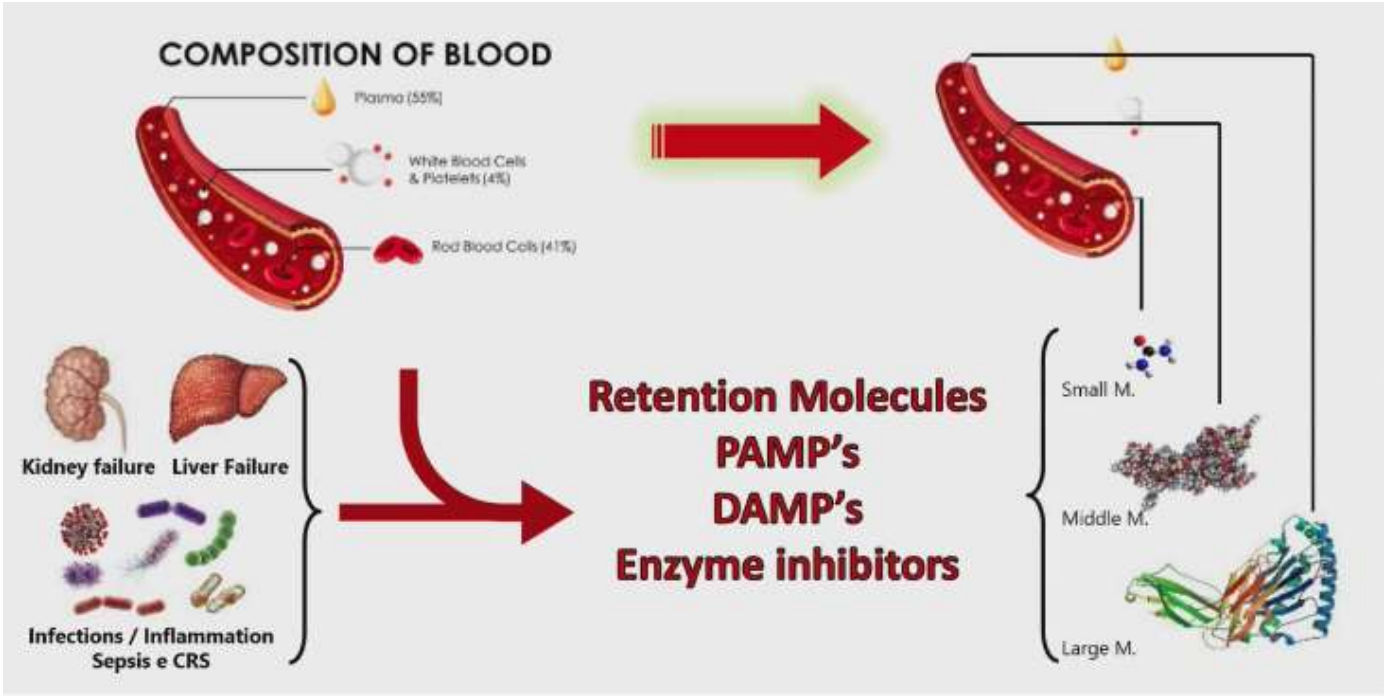
Giuseppe Gernone

ASL Bari
UOSVD di Nefrologia e Dialisi
Ospedali "S. Maria degli Angeli" PUTIGNANO e "S. Giacomo" MONOPOLI

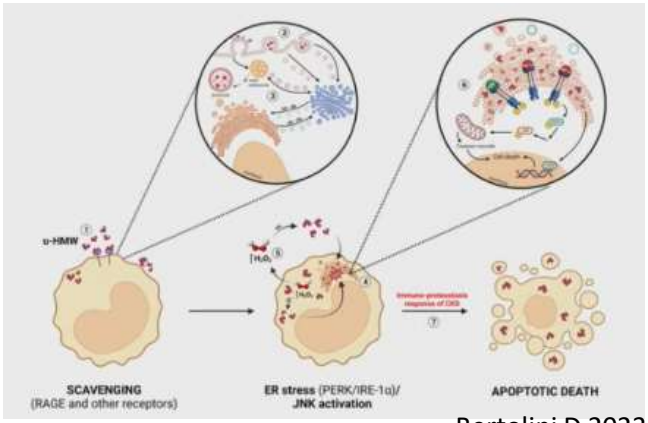
BACKGROUND

- I dializzatori a medio cutoff (MCO) sono ormai da tempo disponibili per l'uso convenzionale in HD.
- Questi dializzatori hanno una dimensione dei pori più grande e più omogenea progettata per migliorare la clearance delle medie molecole senza determinare una sensibile perdita di albumina nel dialisato.
- Tuttavia nonostante una capacità di rimozione di soluti così ampia i benefici di questi dializzatori sono limitati ad un ambito ancora ristretto di situazioni cliniche ed il loro impiego nella pratica clinica rimane tutt'oggi oggetto d'indagine.

UpToDate®



Immuno proteostasis response of CKD in PBL

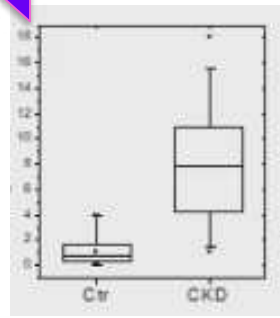


Bertolini D 2023

Microinflammation

- **Biomolecules Damage**
- **Cell Damage & Death**
- **Inflammatory signaling**
- **Premature aging**

Oxidative and carbonyl stress

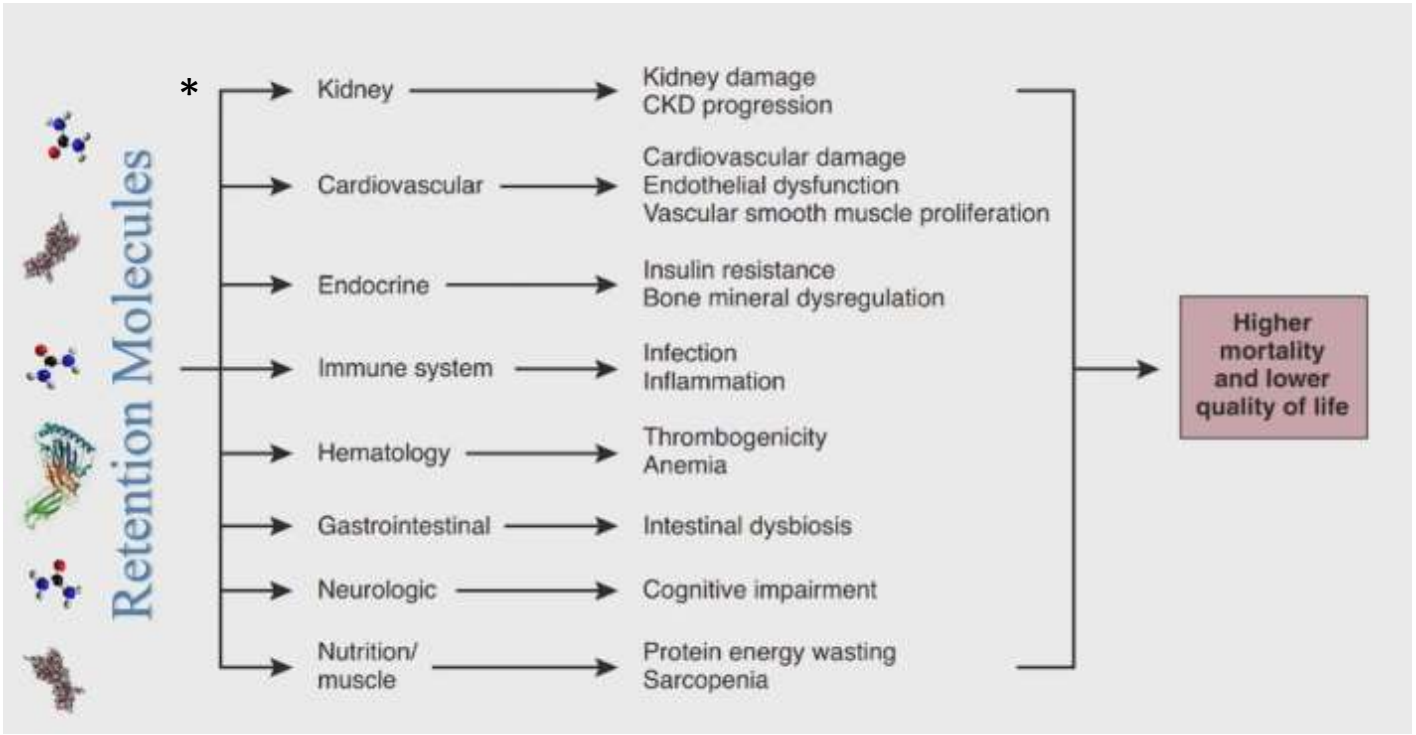


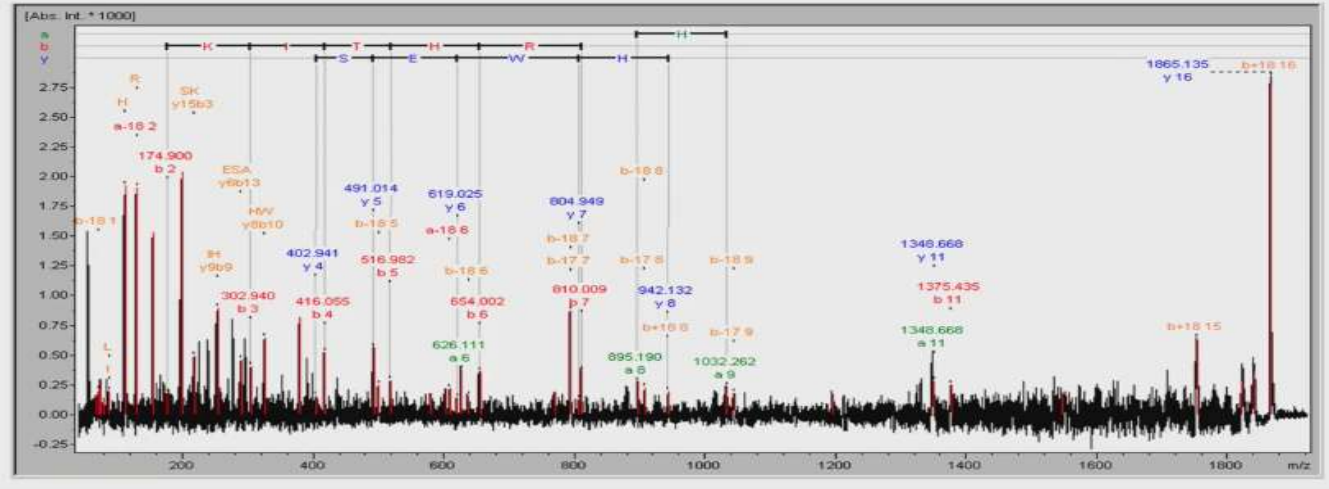
Total Protein Carbonyls

PAMPs *Patterns Molecolari associati ai Patogeni, espressi da patogeni*

DAMPs *Patterns Molecolari associati al Danno, espressi da cellule dell'ospite*

Uraemia Retention Molecule Profile

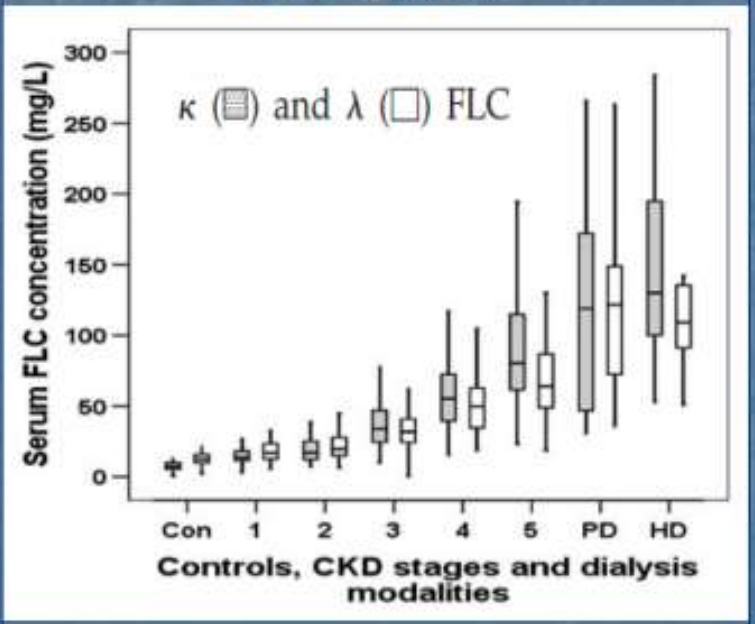




κ- e λ FLC: l'importanza in CKD?

Le FLC aumentano con il peggioramento della MRC

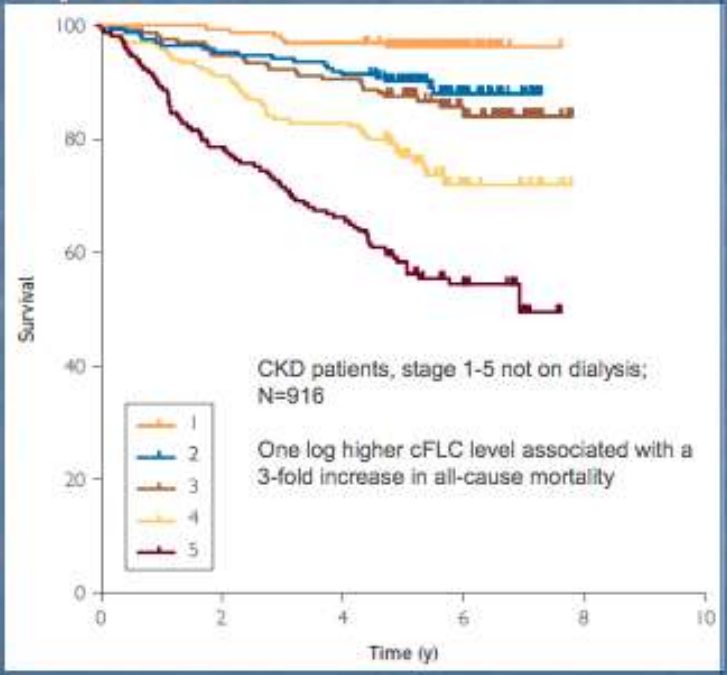
FLC in pz. CKD



Hutchison C et al. Clin J Am Soc Nephrol 2008;3:1684-90

Alti livelli di FLC si associano ad esiti clinici peggiori

Sopravvivenza in CKD e livelli FLC



Ref: Hutchinson et al. Mayo Clinic Proceed 2014;89:615-22

α1-micro globulin (33kDa)
Restless leg syndrome

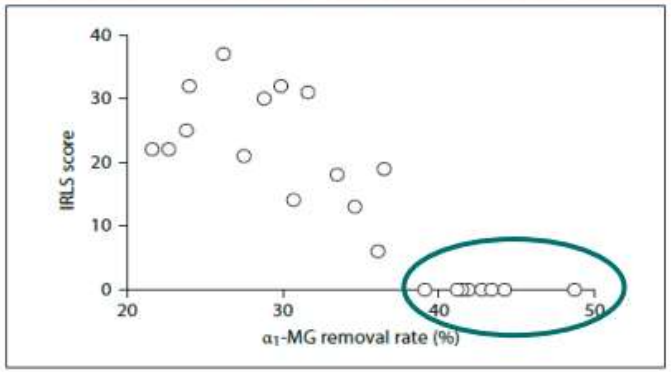


Fig. 1. Relationship between IRLS score and α_1-MG removal rate. The α_1-MG removal rate and IRLS score during the course of treatment of 7 cases of RLS are shown. Although the symptoms were alleviated up to α_1-MG removal rates of 35%, RLS was not cured, and an α_1-MG removal rate of 38% or more was needed to cure RLS.

Blood Purif 2013;35(suppl 1):64–68

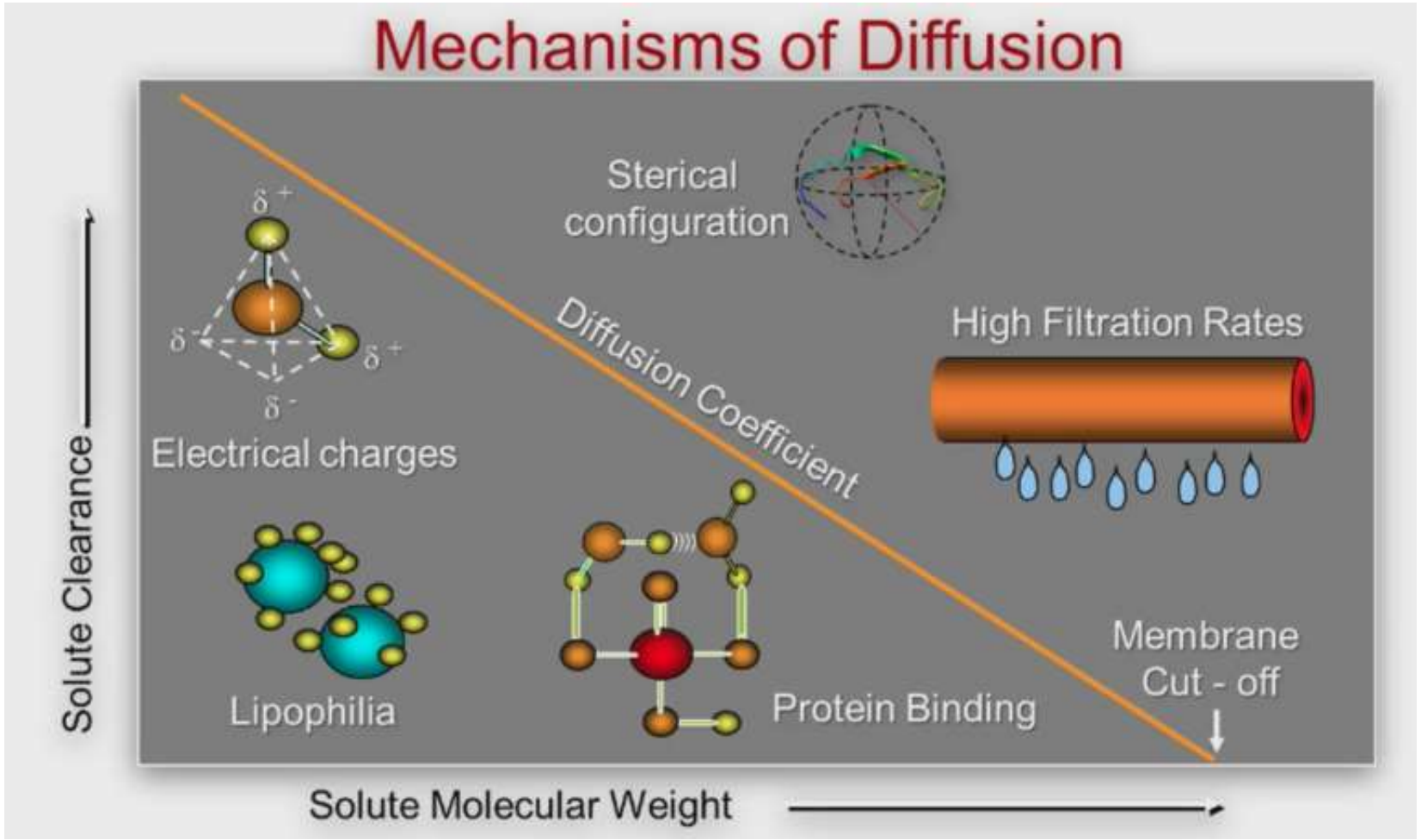
Middle molecules not removed by HDF

Molecule	MW (kDa)
Hyaluronic acid	25
Tumour necrosis factor α	26
β-trace protein	26
Adiponectin	30
FGF-23	32
Interleukin-1β	32
α1-Microglobulin	33
VEGF	34.2
YKL-40	40
Pentraxin-3	40.2
α1-Acid glycoprotein	43
AGEs	45
λ-Ig light chain	45
Visfatin	55
AOPPs	>60

There is a group of larger middle-molecules not currently removed by dialysis strategies

Class	SOLUTE	MW (Da)	Action/Effect
Small	Urea	60	General toxicity
	Creatinine	125	
	Vitamin B12	1250	
Middle	β 2 M	12000	Amiloidosis CTS
	Leptin	16000	Malnutrition
	Myoglobin	17000	Organ damage
Large	κ-FLC	23000	Toxicity
	Prolactin	23000	Infertility
	Interleukin-6	25000	Inflammation
	Hepcidin	27000	Anemia
	Bound P-Cresol	33500	CV Toxicity
	Pentraxin-3	43000	Acute Phase Prot.
	λ-FLC	45000	CV Toxicity
	TNF-α (Trim)	51000	Inflammation
Essential protein	Albumin	68000	Toxin binding capacity

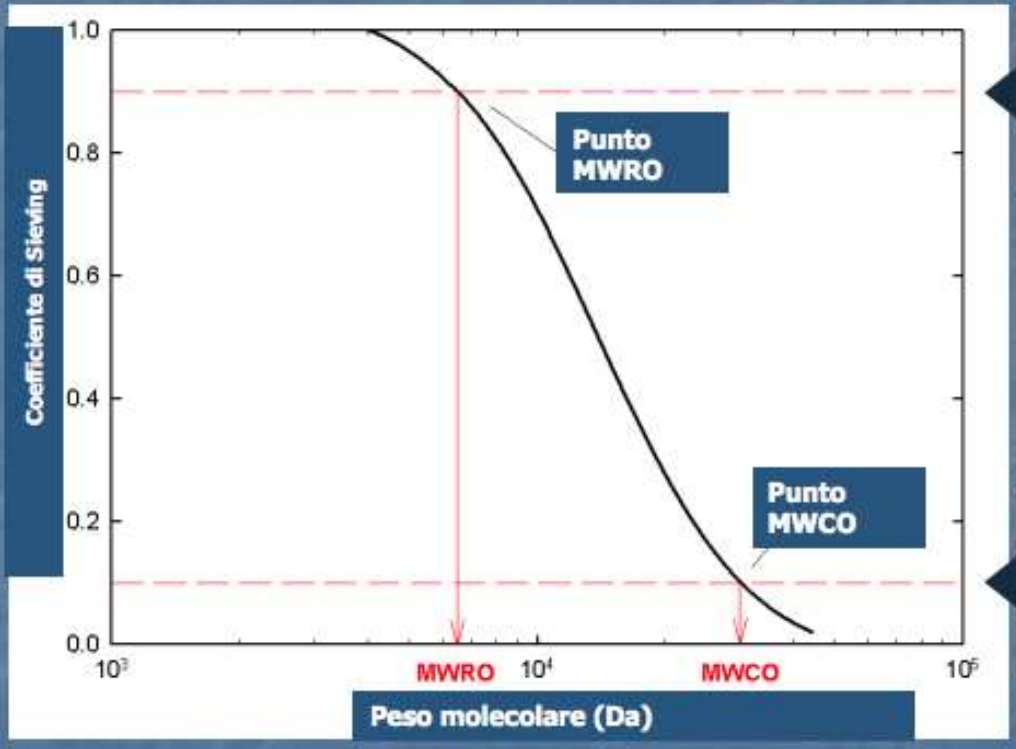
Mechanisms of Diffusion



Il coefficiente di sieving (SC) è il rapporto tra concentrazione di un soluto nell'UF e concentrazione dello stesso nell'acqua plasmatica ingresso filtro: SC = [UF] /[P]. Indica la capacità della membrana di "Ritenere" un determinato soluto

Il SC è determinato dalle caratteristiche del soluto (peso molecolare) e dalle caratteristiche fisiche della membrana (per es. dimensione e morfologia dei pori).

- Se, per una determinata "coppia" membrana-soluto, il SC=1 (100%), il soluto passa liberamente, nessuna ritenzione
- se SC=0 il soluto non passa attraverso la membrana ritenzione completa



MWRO (Retention Onset del peso molecolare):

Peso molecolare al quale il coefficiente di Sieving è 0,9

High Retention Onset

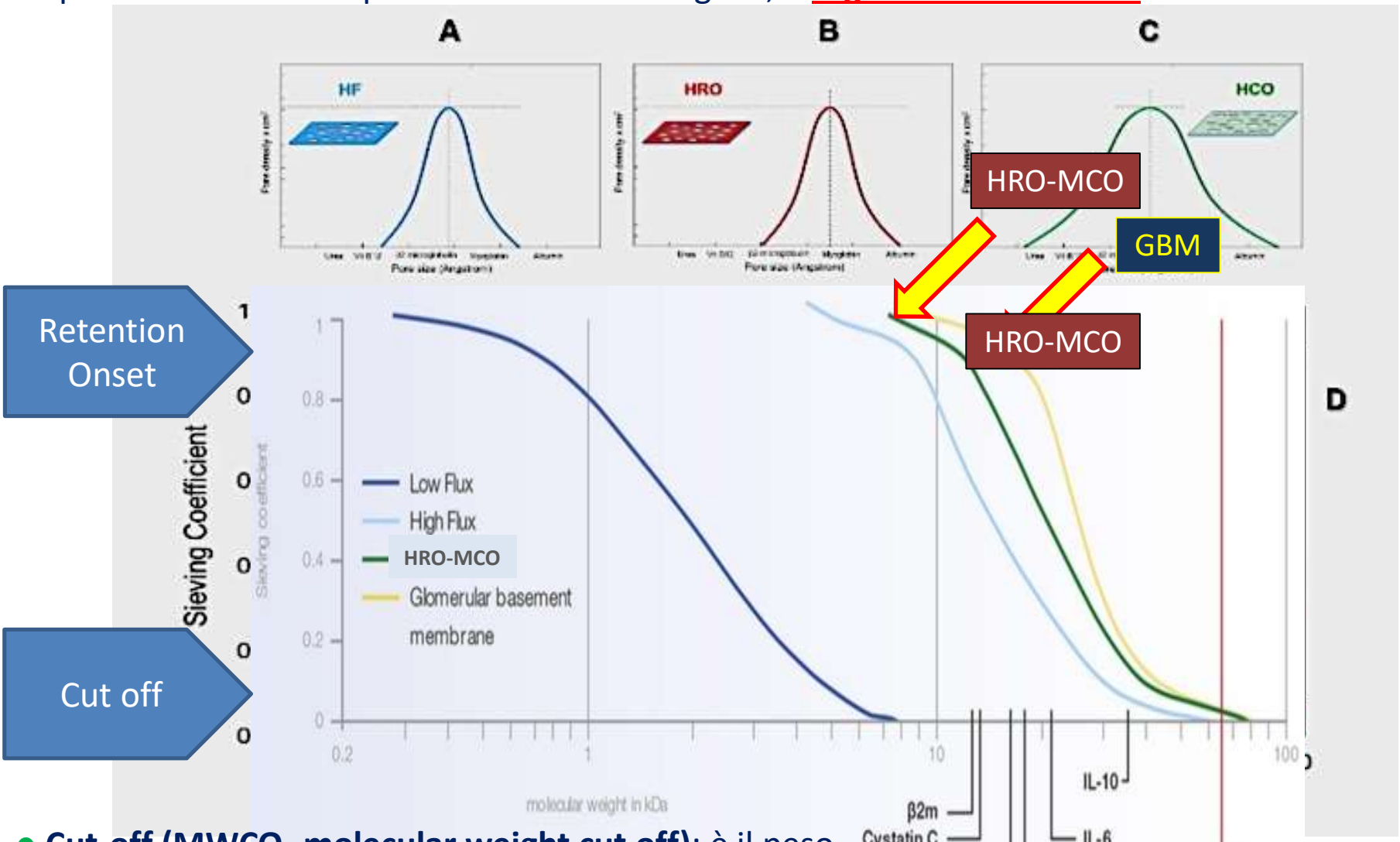
MWCO (Cut-off del peso molecolare):

Peso molecolare al quale il coefficiente di Sieving è 0,1

Panorama delle curve di Sieving

- **Retention onset (MWRO- molecular weight retention onset):**

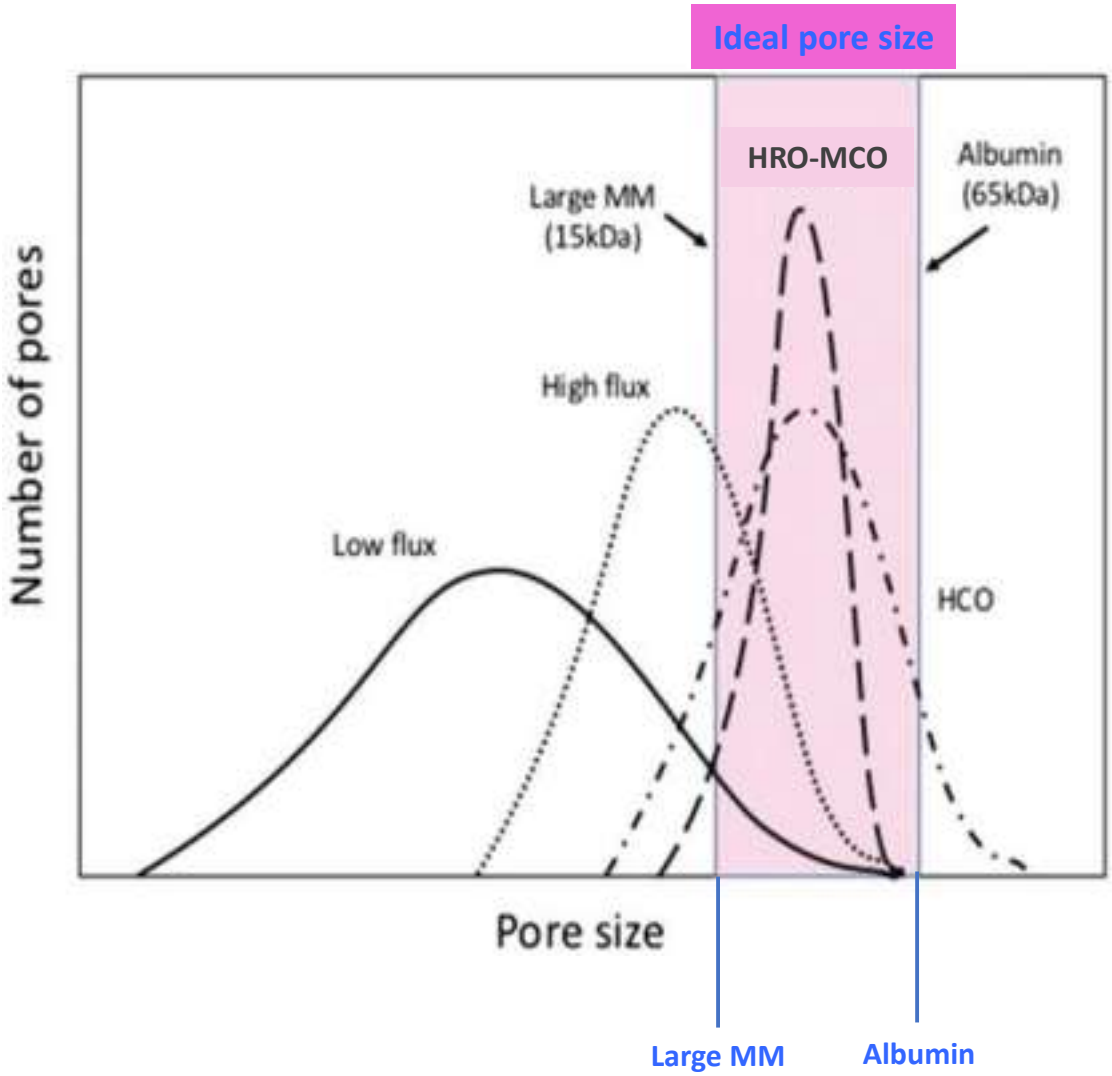
è il peso molecolare al quale il valore di sieving è 0,9 **High Retention Onset**



- **Cut-off (MWCO- molecular weight cut off)**: è il peso molecolare del soluto al quale il valore di sieving è 0,1

Ronco, Blood Purif 2017

La membrana dialitica ideale



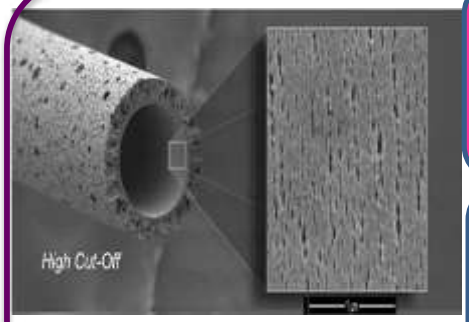
L’evoluzione dell'emodialisi

rimozione molecole ad medio-elevato PM senza perdita di proteine

Filtri HRO-MCO

HDx

Filtri HCO



Vantaggi: rimozione molecole ad elevato PM

Svantaggi: perdita eccessiva di proteine

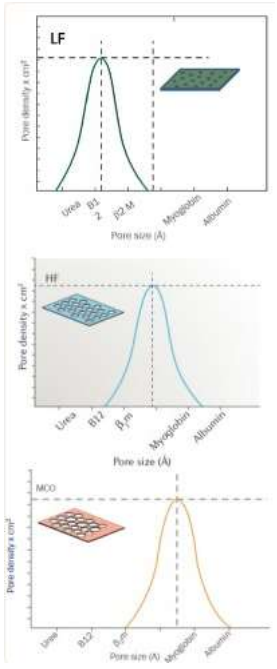
Filtro HF

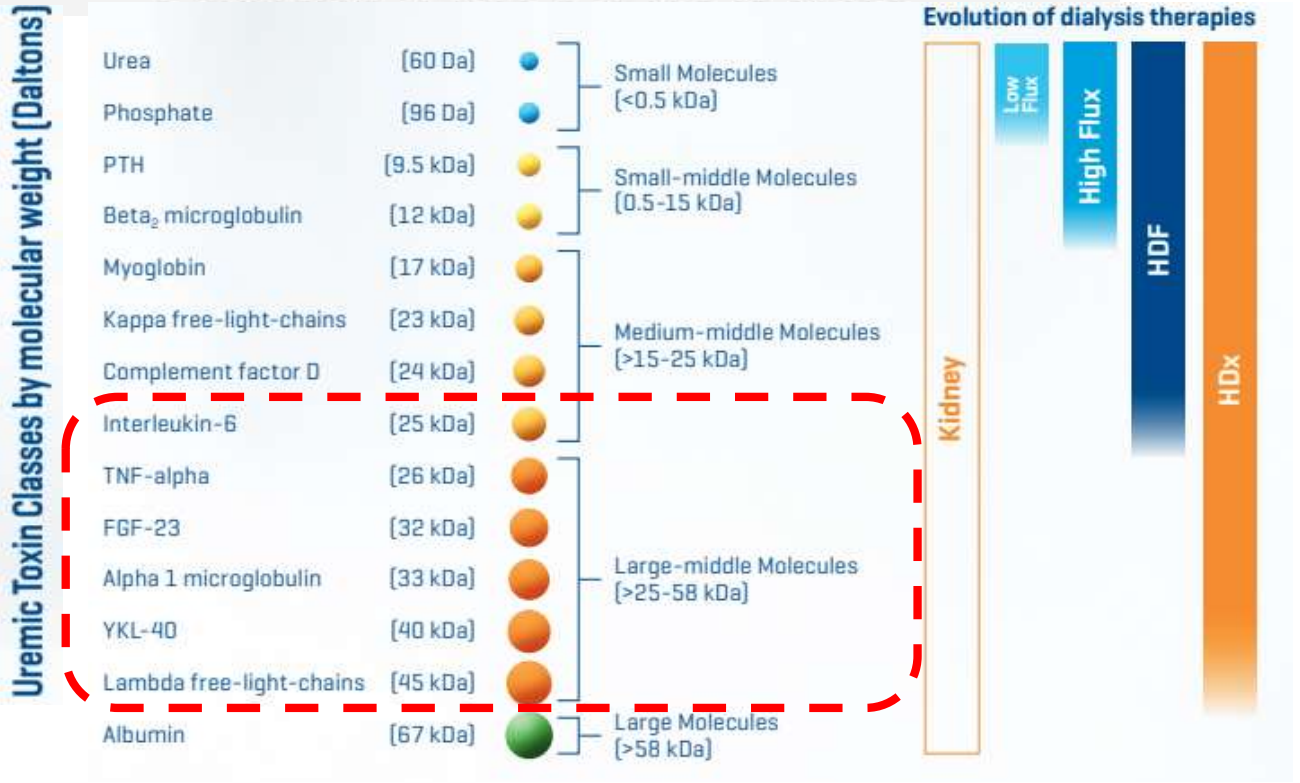
HDF

Filtro LF

Expanded Hemodialysis Therapy (HDx)

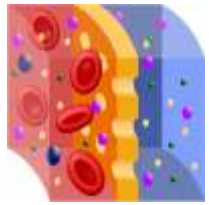
" Dialytic technique removing large middle molecule uremic toxins using standard equipment and standard blood flow rate"





Larger Middle Molecules are efficiently removed by HDx

Expanded Hemodialysis Therapy (HDx)

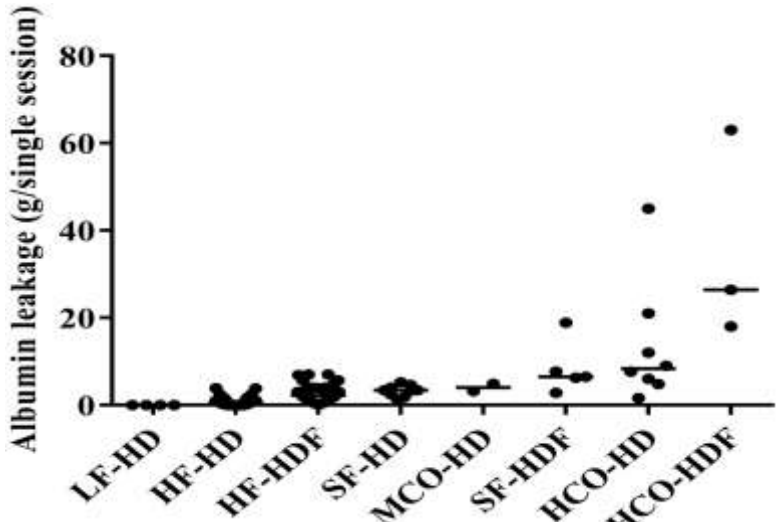


- **HDx** è un trattamento dove **diffusione e convezione sono combinati** mediante una membrana HRO.
- Non richiede monitor specifici, ma solo monitor per HD standard.
- E' possibile utilizzarla in pazienti con **accesso vascolare subottimale e CVC definitivo.**

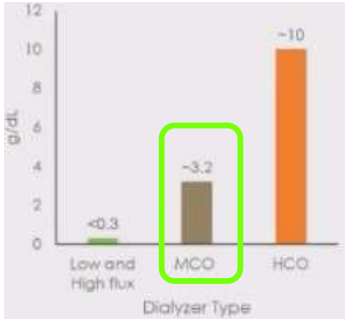
Type of dialyzer and dialysis mode influence albumin loss

Category	Ultrafiltration coefficient[a] (mL/h/mmHg/m^2)	β_2-microglobulin clearance[b] (mL/min)	Albumin loss[c] (g)	Sieving coefficient[a]		Reference
				β_2-microglobulin	Albumin	
Low flux	<12	<10	0	–	0	[16]
High flux	14–40	20–40	<0.5	0.7–0.8	<0.01	[6]
MCO	40–60	>80	2–4	0.99	<0.01	[17, 18]
Protein leaking	>40	>80	2–6	0.9–1.0	0.01–0.03	[19]
HCO	40–60	–	9–23	1.0	<0.2	[20, 21]

Richard A Ward et al.: Nephrology Dialysis Transplantation, Volume 34, Issue 6, June 2019, Pages 901–907, https://doi.org/10.1093/ndt/gfy236



MCO membranes improve middle molecule removal compared with HF membranes, but at the expense of increased albumin loss



'low-flux', 'high-flux' or 'super-flux' (SF) based on the K_{UF} (<10, >20 and >50 mL/h/mmHg, respectively)

The level of albumin loss in g/4 h is (0, <2 and >2 g, respectively)

Nephrol Dial Transplant, Volume 33, Issue 6, June 2018, Pages 906–913, https://doi.org/10.1093/ndt/gfx191

Removal of Large-Middle Molecules on Expanded Hemodialysis (HDx): A Multicentric Observational Study of 6 Months Follow-Up

Vincenzo Cantaluppi,1 Gabriele Donati,2 Antonio Lacquaniti,3 Francesco Cosa,4 Giuseppe Gernone,5 Marita Marengo,6 Ugo Teatini.7,8 *1University of Piemonte Orientale (UPO), Novara, Italy; 2Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; 3Papardo Hospital, Messina, Italy; 4Ospedale Civile Di Legnano, Taranto, Italy; 5ASL BA - "S. Maria degli Angeli" Hospital - Putignano (Bari) – Italy; 6S.C. Nefrologia e Dialisi, ASLCNI, Savigliano, Italy; 7ASST Rhodense, Milano, Italy; 8ASST Rhodense, Milano, Italy*.

41 stable HD pts. 6 months observational multicentric study.
A significant decrease of urea, B2m, FLC-k, FLC-λ and CRP

Albumin levels remained stable.

Conclusions: HDx therapy provided ***high removal of different LMMs*** involved in uremia-associated organ dysfunction and inflammatory parameters correlated with a worse outcome

J Am Soc Nephrol 29, 2018: 208.

LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

11 stable HD patients. 12 months observational study.

HDx therapy (Qb < 300 ml/m') provided:

- a significant ($p < 0.05$) removal of: B2m, Myo, FLC-k and FLC-λ
- a significant decrease of CRP, ERI and EPO dose
- a significant improvement of QoL (indexes of Physical Health-ISF: $p= 0.0001$ and Mental Health-ISM: $p= 0.001$).
- ***Serum Albumin remained stable****

Conclusions: HDx effectively removes uremic toxins up to 45kDa, even with Qb <300 ml/min, in those pts who cannot benefit from convective techniques because of vascular access or intolerance to high volumes of exchange.

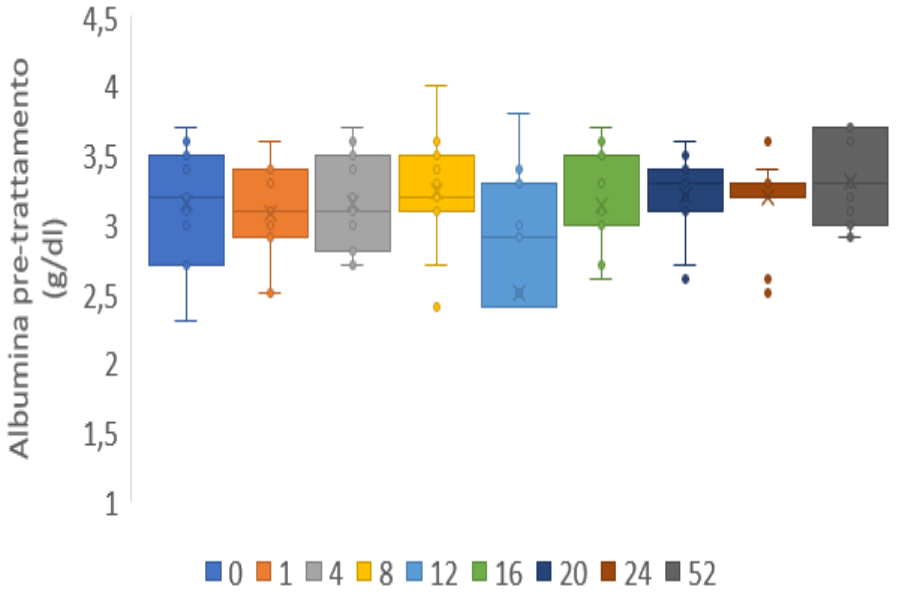
OXFORD UNIVERSITY PRESS

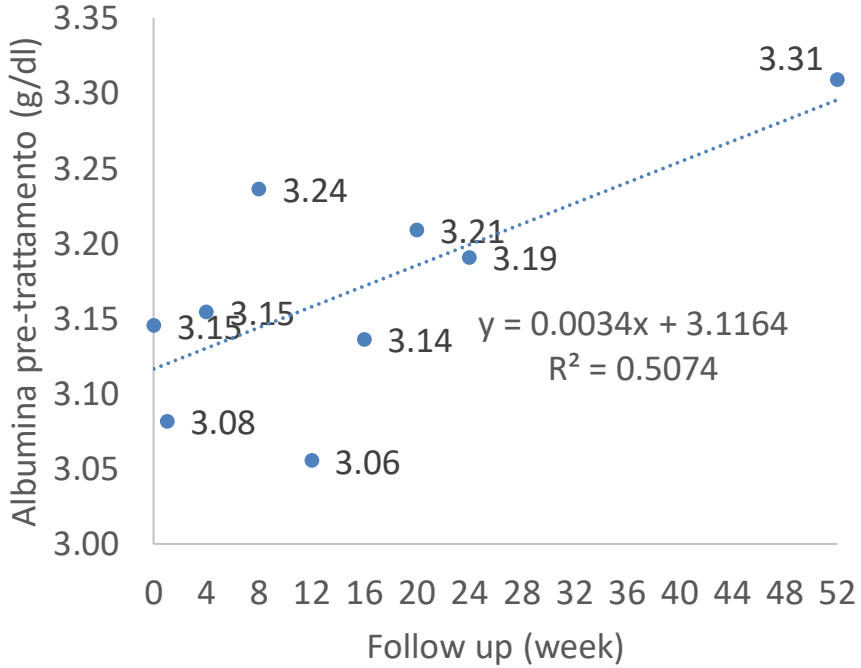
G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant,, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084,
https://doi.org/10.1093/ndt/gfaa142.P1084

LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

HDx preserve albumin levels

N=11



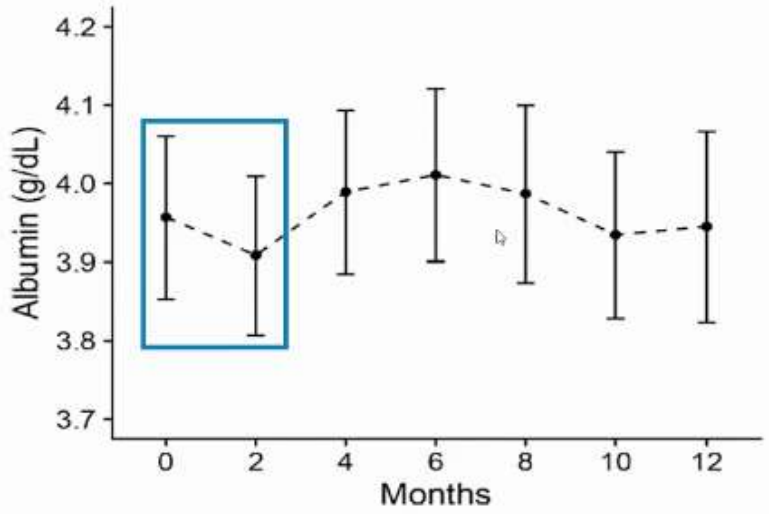


Albumin Baseline 3,15±0,44 g/dl, at 6 mts 3,19±0,33 g/dl, a 12 mts 3,31±0,32 g/dl

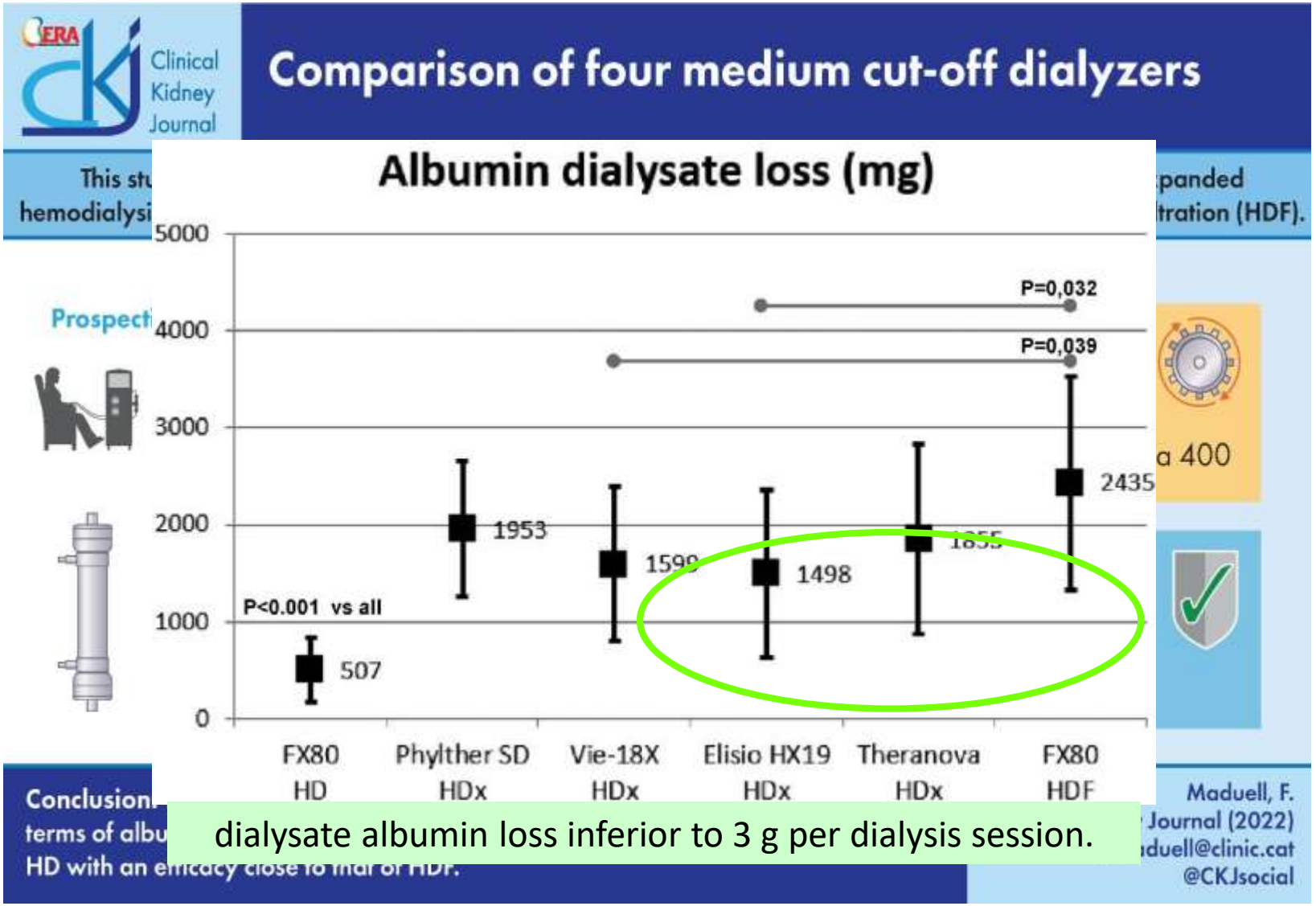
G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant,, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084,
https://doi.org/10.1093/ndt/gfaa142.P1084

Long-term effect of medium cut-off dialyzer on middle uremic toxins and cell-free hemoglobin

Serum albumin concentration during 1-year treatment with medium cut-off dialyzer



Cho N-J et al.: 2019 PLOS ONE



*

Clin Kidney J, Volume 15, Issue 12, December 2022, Pages 2292–2299, https://doi.org/10.1093/ckj/sfac167

LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

11 stable HD patients. 12 months observational study.

HDx therapy (Qb < 300 ml/m') provided:

- a ***significant (p < 0.05) removal of: B2m, Myo, FLC-k and FLC-λ*** *
- a significant decrease of CRP, ERI and EPO dose
- a significant improvement of QoL (indexes of Physical Health-ISF: p= 0.0001 and Mental Health-ISM: p= 0.001).
- Serum Albumin remained stable

Conclusions: HDx effectively removes uremic toxins up to 45kDa, ***even with Qb <300 ml/min***, in those pts who cannot benefit from convective techniques because of vascular access or intolerance to high volumes of exchange.

OXFORD UNIVERSITY PRESS

G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant,, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084,
https://doi.org/10.1093/ndt/gfaa142.P1084

Are Medium Cut-off Membranes the Future, or the Promising Reality for Chronic Hemodialysis Patients?

Effect of the different dialysis modalities on uremic toxins removal

Characteristic	Kirsch et al. 2016[7]	Belmouaz et al. 2020[9]	Weiner et al. 2020[10]	Belmouaz et al. 2022[11]	Maduell et al. 2022[12]	Vega et al. 2023[13]	Kim et al. 2022[15]
Study desing	Prospective, open-label, controlled, randomized, crossover pilot study	Cross-over prospective study	Open label, multicenter RCT	Single center, prospective study	Prospective single-cohort study	Single center, cross-over, RCT	Prospective, randomized, cross-over study
Modalities	MCO versus HF versus OL-HDF	HF versus MCO	HF versus MCO	HF versus SHF versus HDx versus OL-HDF	OL-HDF versus MCO versus HF	HF versus MCO versus OL-HDF	HF versus MCO versus OL-HDF
Time intervention	Single session	12 weeks each modality	24 weeks	Single session	Single session	4 weeks each modality	3 weeks each modality
Patients	39	40	172	8	23	22	22
Age (mean, ± SD)	55 ± 13	75 ± 9	59 ± 13	68	68 ± 12	36	62 ± 11
Residual diuresis 500 mL/day	Not reported	NA 95% < 200 mL	Not reported	NA 100% < 300 mL	NA 100% < 50 mL	NA 100% < 200 mL	NA 100% < 100 mL
β2M RR	HF 73%* MCO 78% OL-HDF 80%+ *p < 0.001 +NS	HF 68% MCO 73% p = 0.04	MCO 73% HF 65% p < 0.001	HF 65% SHF 73% MCO 79% OL-HDF 79% NS	HF 74% MCO 77% OL-HDF 83%* *OL-HDF versus all p < 0.001	HF 27% MCO 73% OL-HDF 62% p < 0.0001	–
κFree light chains	HF 36% MCO 72% OL-HDF 71%+ +p = 0.3 *p < 0.001	–	HF 50% MCO 63% p < 0.001	HF 46% SHF 56% MCO 66% OL-HDF 75%* * OL-HDF versus HF p < 0.001	HF 66% MCO 77%+ OL-HDF 84%* *OL-HDF versus all p < 0.001 +MCO versus HF p < 0.001	–	–
λFree light chains	HF 12%* MCO 42% OL-HDF 37%+ +*p < 0.001	–	HD 17% MCO 33% p < 0.001	HF 17% SHF 33% MCO 46% OL-HDF 60%* *OL-HDF versus HF, SHF, MCO p < 0.01	HF 24% MCO 48%+ OL-HDF 59%* *OL-HDF versus all p < 0.001 +MCO versus HF p < 0.001	–	–
pindoxyl sulfate	–	–	–	–	–	HF -16% MCO -90% OL-HDF -50% p = 0.3	HF 33% MCO 36% OL-HDF 40% NS
p-cresol	–	–	–	–	–	HF -3% MCO -3% OL-HDF -5% p = 0.6	HF 27% MCO 29% OL-HDF 34% NS

Review of the most relevant clinical studies on MCO membranes

Noemí Del Toro-Cisneros. Rev Invest Clin. 2023;75(6):289-99

LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

11 HD patients. 12 months observational study.

HDx therapy (Qb < 300 ml/m') provided:

- a significant ($p < 0.05$) removal of: B2m, Myo, FLC-k and FLC-λ
- a ***significant decrease of CRP, ERI and EPO dose***
- a significant improvement of QoL (indexes of Physical Health-ISF: $p= 0.0001$ and Mental Health-ISM: $p= 0.001$).
- Serum Albumin remained stable

Conclusions: HDx effectively removes uremic toxins up to 45kDa, ***even with Qb <300 ml/min***, in those pts who cannot benefit from convective techniques because of vascular access or intolerance to high volumes of exchange.

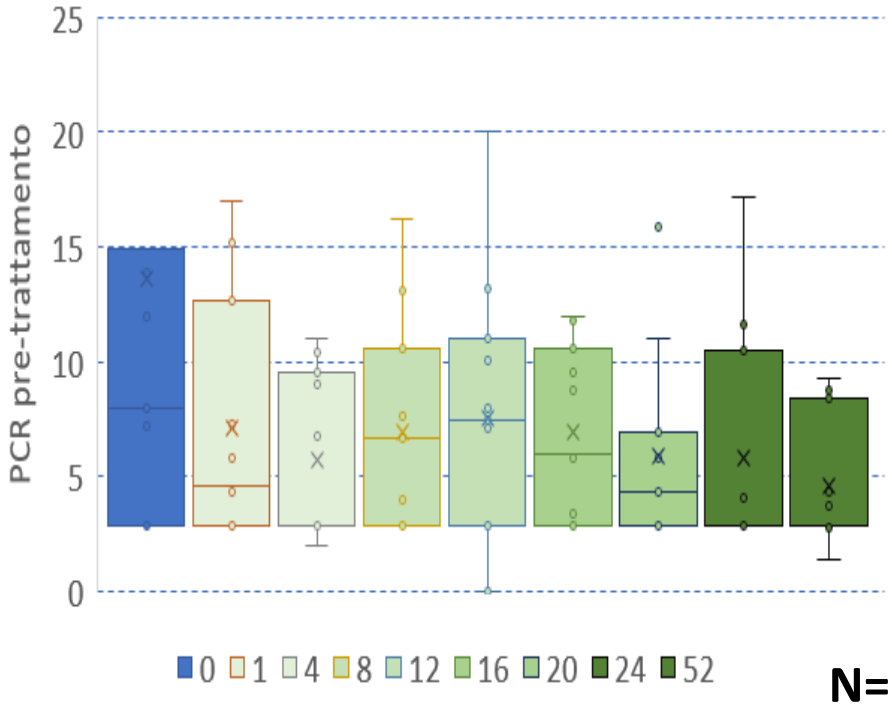
OXFORD UNIVERSITY PRESS

G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant,, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084,
https://doi.org/10.1093/ndt/gfaa142.P1084

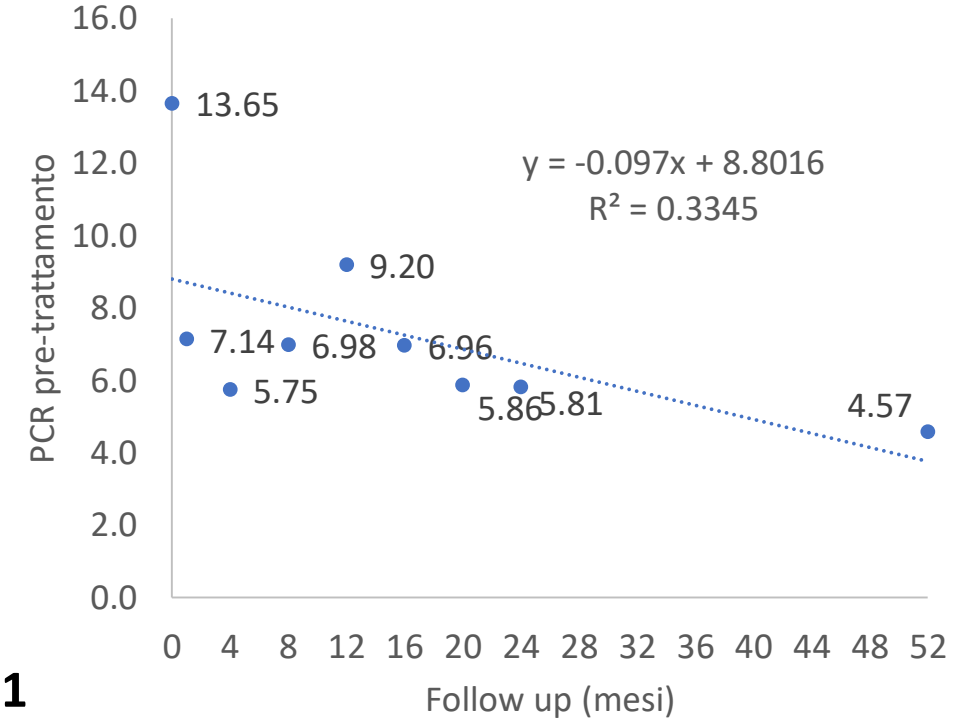
LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

HDx reduce inflammation

CRP Baseline 13,6±14,4, at 6 mts 5,8±4,9, at 12 mts 4,5±2,8 (p<0.05)



N=11



G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant,, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084,
https://doi.org/10.1093/ndt/gfaa142.P1084

REMOVAL OF LARGE-MIDDLE MOLECULES, INHIBITION OF NEUTROPHIL ACTIVATION AND MODULATION OF INFLAMMATION-RELATED ENDOTHELIAL DYSFUNCTION DURING EXPANDED HEMODIALYSIS (HDx)

41 HD patients. 6 months observational multicentric study.

HDx therapy provided high removal of:

- different LMMs involved in uremia-associated inflammation and organ dysfunction in particular FLC-k (p=0,026) and FLC-λ (p=0,001)
- ***a significant decrease of CRP***

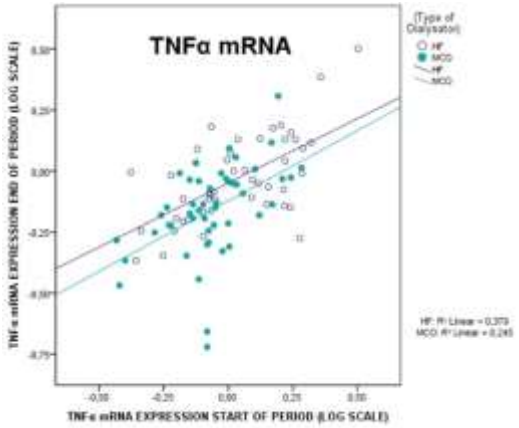
In vitro studies confirmed ***limitation of***

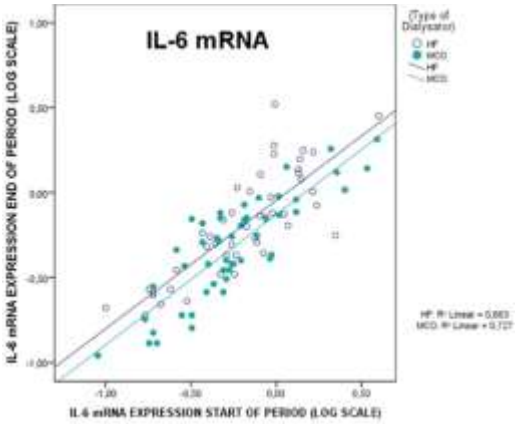
- ***neutrophil activation*** (decrease of ROS, TNF-alpha and IL6 production, ***increase of apoptosis*** .
- ***endothelial dysfunction*** (significant decrease of neutrophil adhesion, increased NO bioavailability and angiogenesis, inhibition of vascular senescence with increased expression of the anti-oxidant and anti-aging factor Nrf2).
- ***potential role in the modulation of the microRNA*** content of circulating ***extracellular vesicles***

V Cantaluppi, M Marengo, A Quercia, M Berto, G Donati, A Lacquaniti, F Cosa, G Gernone, U Teatini, M Migliori et al.
Nephrol Dial Transplant, Volume 34, Issue Supplement_1, June 2019, gfz096.FO048,
https://doi.org/10.1093/ndt/gfz096.FO048.
OXFORD UNIVERSITY PRESS

RESEARCH ARTICLE

Medium Cut-Off (MCO) Membranes Reduce Inflammation in Chronic Dialysis Patients—A *Randomized controlled clinical trial*





Primary endpoints (TNF- α mRNA / IL-6 mRNA) levels before and after 4 weeks treatment.

	High-flux		MCO		p MCO vs HF
	T = 0	T = 4 weeks	T = 0	T = 4 weeks	
Primary endpoint					
TNF-α mRNA	1.19 ± 0.57	1.02 ± 0.49*	0.92 ± 0.34	0.75 ± 0.31**	< 0.001
IL-6 mRNA	0.86 ± 0.68	0.83 ± 0.67	0.78 ± 0.80	0.60 ± 0.43**	0.001
Clinical chemistry					
Albumin g/l	36.6 ± 3.2	37.5 ± 2.7	37.0 ± 3.6	35.3 ± 3.7**	< 0.001
CRP mg/l	13.4 ± 25.5	9.6 ± 15.7	15.3 ± 30.0	9.3 ± 14.5	n.s.
Urea mg/dl	131± 38	129 ± 35	128 ± 34	115 ± 29**	0.012
Beta2M mg/l	27.0 ± 9.1	26.1 ± 8.6	26.9 ± 8.4	25.7 ± 8.1**	n.s.
TNF-/TNFR-Family					
sTNF-R1 ng/ml	13.3 ± 4.7	12.9 ± 4.7	13.0 ± 4.4	11.0 ± 3.7**	0.01
sTNF-R2 ng/ml					
TNF-α pg/ml	23.4 ± 7.3	22.2 ± 6.0	24.1 ± 8.1	20.6 ± 5.8**	n.s.
sCD40 pg/ml	2238 ± 1705	2044 ± 1382	2403 ± 1980	1867 ± 1297*	n.s.
Main cytokines					
IFN-γ pg/ml	16.0 ± 19.7	14.4 ± 17.8	17.5 ± 19.2	11.8 ± 12.7**	n.s.
IL-17 pg/ml	7.2 ± 7.9	6.5 ± 6.9	8.9 ± 9.5	5.4 ± 5.6**	n.s.
IL-10 pg/ml	59 ± 355	47 ± 280	51 ± 287	65 ± 402**	n.s.
IL-12p40 pg/ml	22.8 ± 16.4	25.4 ± 24.0	26.9 ± 23.1	21.3 ± 17.3*	n.s.
IL-6 pg/ml	9.8 ± 20.5	5.5 ± 4.5*	9.0 ± 13.2	6.0 ± 5.9**	n.s.
Chemotaxis/Adherence					
IL-8 pg/ml	11.7 ± 8.5	10.9 ± 7.9	13.0 ± 9.5	10.8 ± 7.8*	n.s.
MCP-1 pg/ml	480 ± 219	466 ± 152	492 ± 166	444 ± 151*	n.s.
MIP-1b pg/ml	24.8 ± 15.3	22.8 ± 13.6	26.9 ± 15.5	22.1 ± 11.8**	n.s.
sVCAM ng/ml	166 ± 31	150 ± 43**	163 ± 41	149 ± 32*	n.s.
Other					
FLC kappa mg/l	134 ± 65	140 ± 77	137 ± 65	120 ± 54**	0.003
FLC lambda mg/l	91 ± 42	91 ± 44	95 ± 46	79 ± 36**	< 0.001
Fetuin A µg/ml	569 ± 124	543 ± 122	560 ± 131	519 ± 112*	n.s.
Lp-PLA2 ng/ml	180 ± 90	185 ± 108	156 ± 76	189 ± 101**	0.026

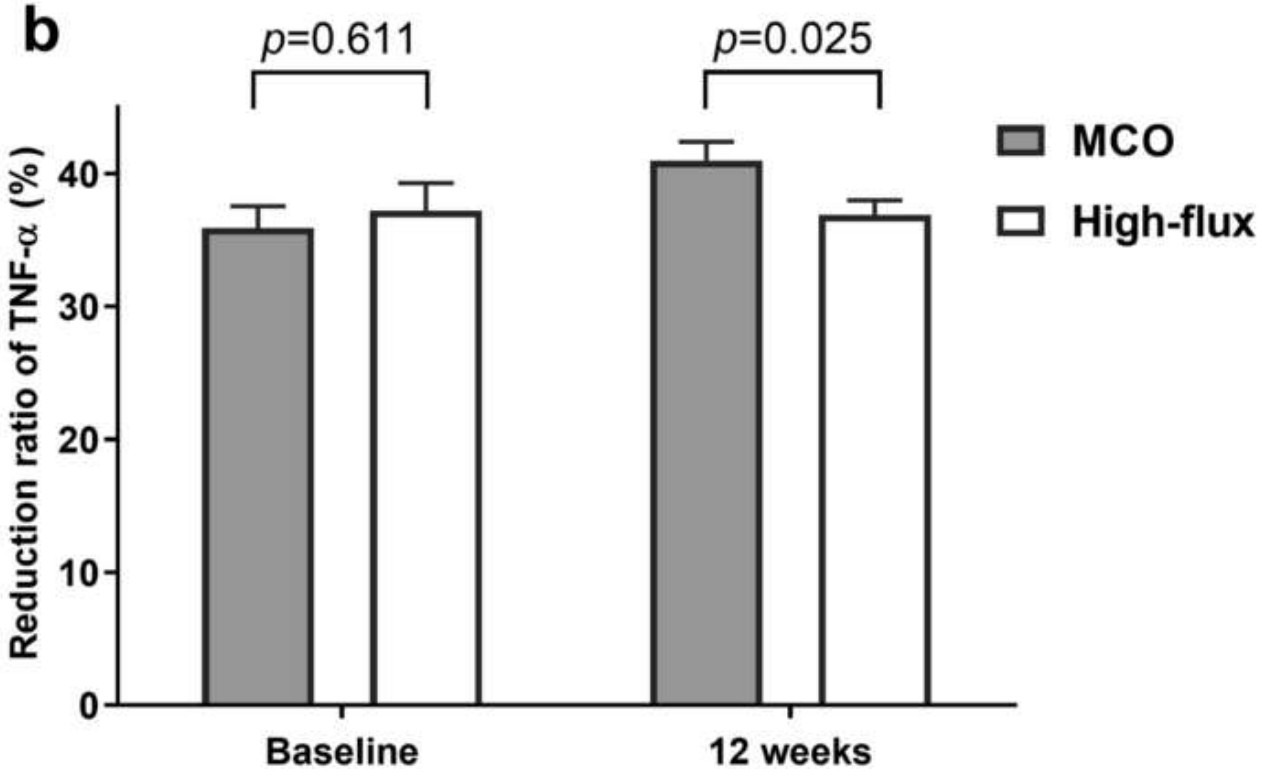
Expression of TNF-mRNA and IL-6-mRNA before and after the cross-over periods using High-flux or MCO dialyzers.

D. Zickler 2017

www.nature.com/scientificreports

SCIENTIFIC REPORTS
nature research

Reduction ratio of serum TNF-α at baseline and at 12 weeks.



TNF-α, tumor necrosis factor-alpha; MCO, medium cut-off.

Lim et al. Sci Rep 2020; 10:16062

AKI DUE TO COVID-19 DISEASE REQUIRING RENAL REPLACEMENT THERAPY: ROLE OF EXPANDED HAEMODIALISYS (HDX) ON INFLAMMATION AND OUTCOME

Retrospective observational study. 12 AKI pts requiring RRT.
Daily HF-HD (FX80, FMC) or HDx therapy (THERANOVA 400, Baxter).
Treatments ranging from 1 to 5 sessions for each pts

Tab. 1

			HDx		HF-HD
			9 pts (average)		3 pts (average)
Urea mg/dl	Baseline		289.5 ± 98.8		292.5 ± 11.5
	After	$p< 0.001$	201.2 ± 67.7*		228 ± 77.5
Creat mg/dl	Baseline		3.5 ± 1		3 ± 0.6
	After		4.3 ± 0.8		3.7 ± 0.9
CRP mg/l	Baseline		181.1 ± 91.1		173.5 ± 33.5
	After	$p < 0.05$	109.8 ± 44*		207.5 ± 100.5
PCT ng/ml	Baseline		12.7 ± 10.9	$p= ns$	5.4 ± 3.1
	After	$p < 0.02$	3.8 ± 1.8*		3.3 ± 2.7
D-Dimer ng/ml	Baseline		5422.7 ± 2597.1		4528 ± 2211
	After		3977.8 ± 2729.7		3253 ± 2085
Noradrenaline mcg/m	Baseline		7.5 ± 3.1		7.2 ± 4.3
	After	$p < 0.002$	13.5 ± 3.8*		12.8 ± 4
BMI kg/cm²			34.9 ± 9.4		35.2 ± 8.6

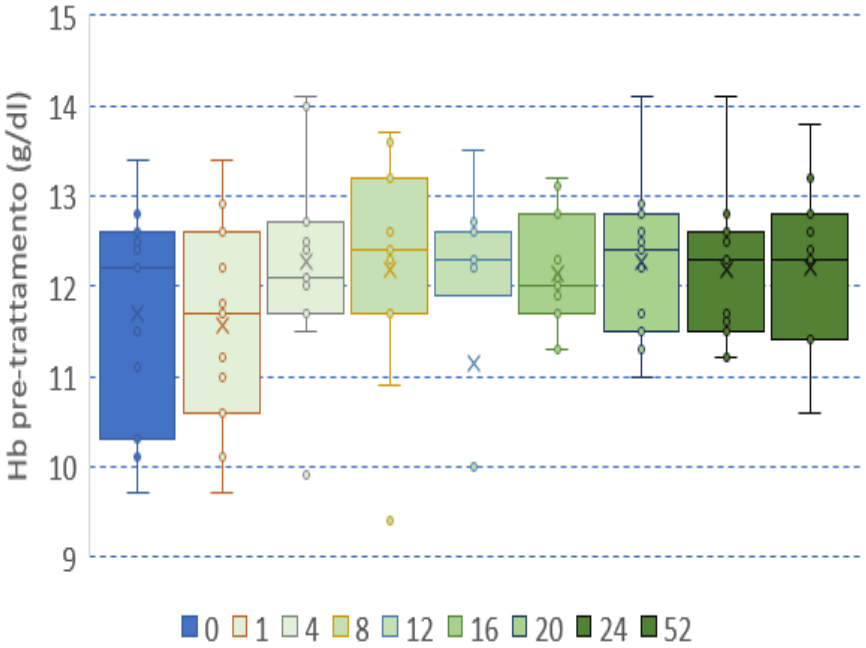
HDx had a better clearance of LMM and significant impact on inflammation and renal markers, compared to HF-HD. Unfortunately, COVID19 pts who received RRT had a poor prognosis, regardless hemodialysis techniques.

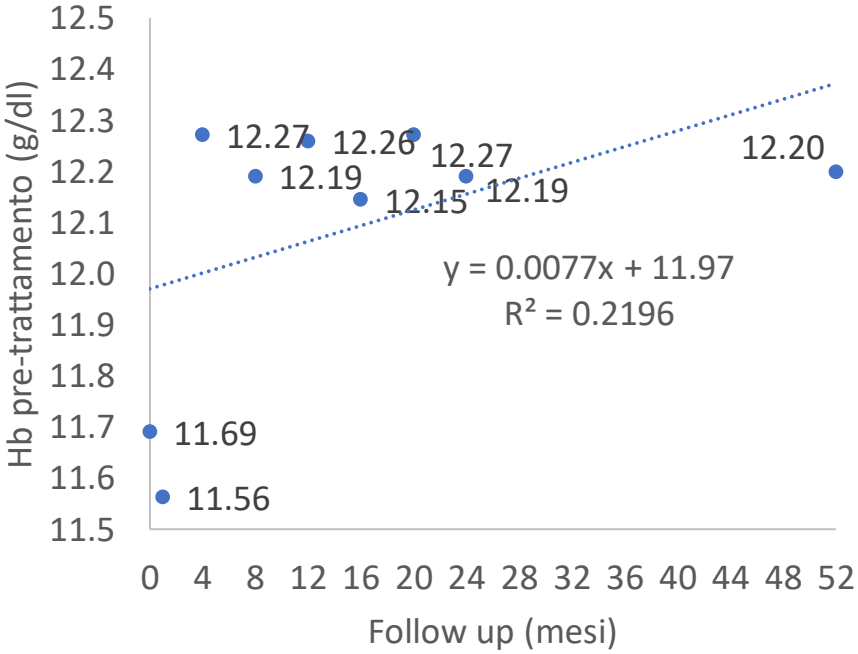
Gernone, G. et al. Kidney International Reports, Volume 7, Issue 2, S368 - S369. February, 2022
https://doi.org/10.1016/j.ekir.2022.01.891

LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

HDx improve anemia

Hemoglobin Baseline 11,7±1,2 g/dl, at 6 mts 12,2±0,9 g/dl, at 12 mts 12,2±0,9 g/dl





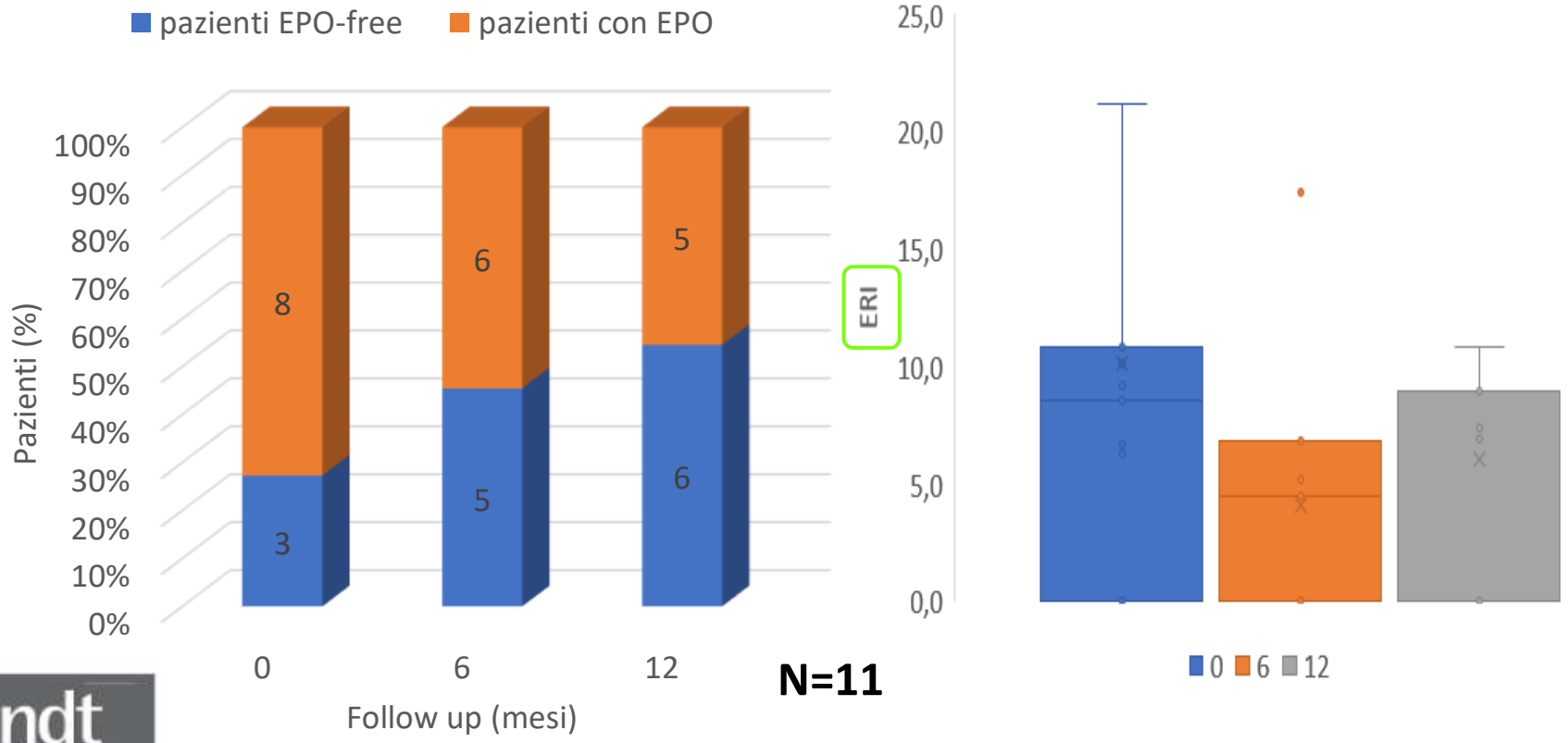
N=11

G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084, https://doi.org/10.1093/ndt/gfaa142.P1084

LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

HDx reduce EPO dose and ERI

EPO dose at Baseline 8.1±9.1 UI, at 6 mts 3.5±4.5 UI (p<0.05), at 12 mts 5.2±6.9 UI



N=11

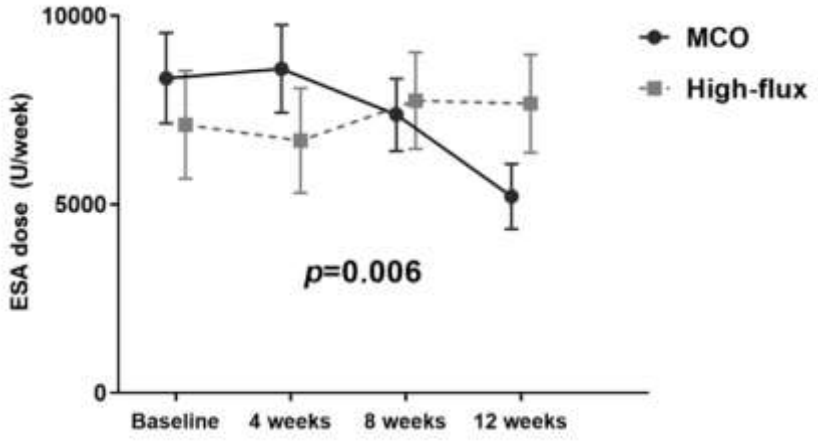
G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084, https://doi.org/10.1093/ndt/gfaa142.P1084

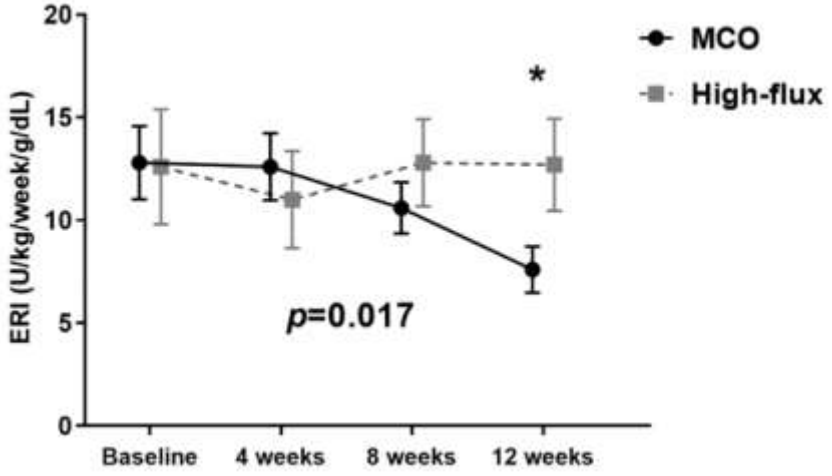
www.nature.com/scientificreports

Medium cut-off dialyzer improves erythropoiesis stimulating agent resistance in a hepcidin-independent manner in maintenance hemodialysis patients: results from a *randomized controlled trial*

SCIENTIFIC REPORTS
nature research

- 49 patients with maintenance HD: MCO (n=24) vs. high-flux HD (n=25).
- Outcome:
  ESA dose, weight-adjusted ESA dose, ERI (erythropoietin resistance index; U/Kg/wk/g/dL) and their changes



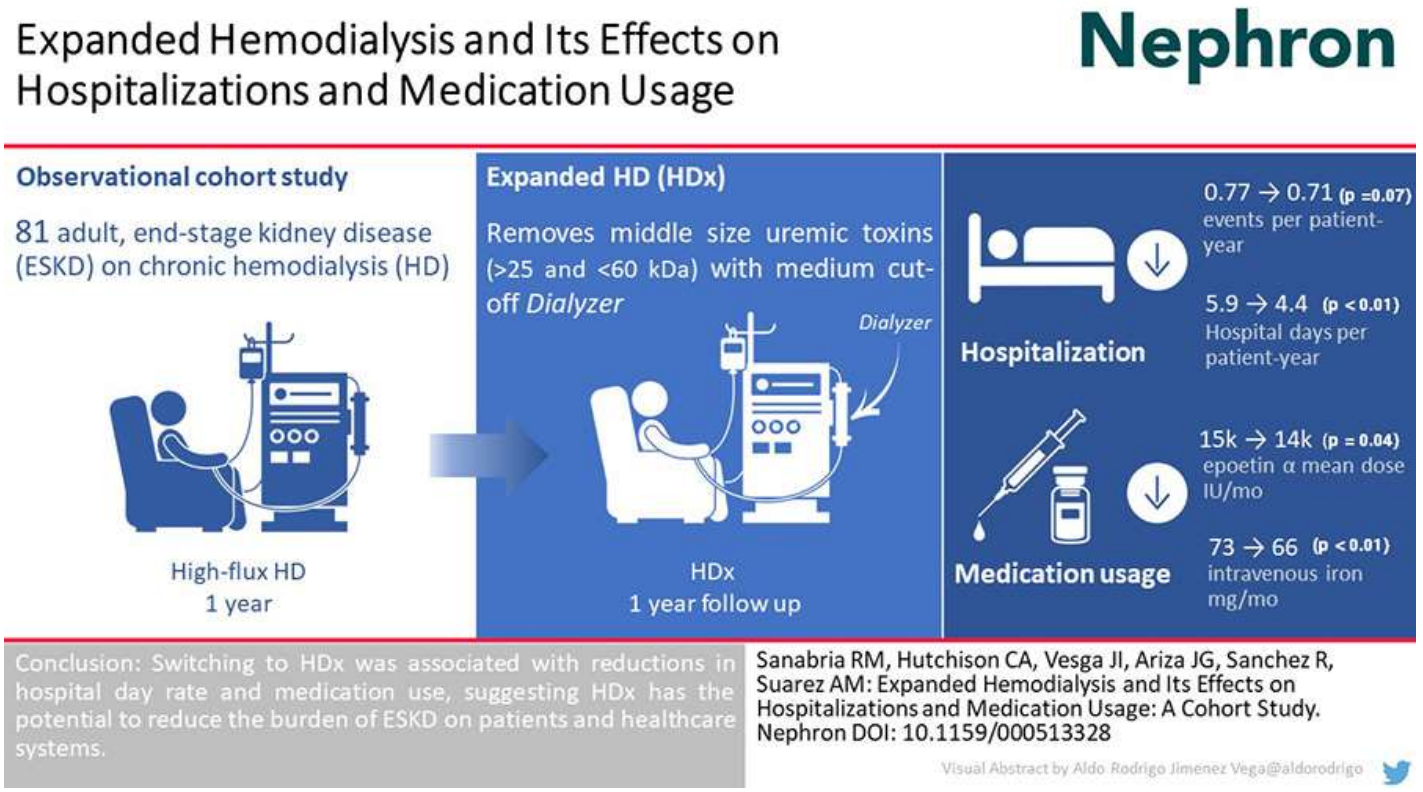


Monthly changes in the ESA dose and ERI levels. ($p = 0.006$ and $p = 0.017$, respectively). The ERI at 12 weeks was significantly lower in the MCO group compared to the high-flux group. **(ERI; U/kg/wk/g/dL)**

Lim et al. Sci Rep 2020; 10:16062

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

Nephron. 2021;145(2):179-187. doi:10.1159/000513328



Parameters	Mean	SD	P_{25}	Median	P_{75}	IQR	*p* value*
Anemia profile							
Hemoglobin, g/dL							
Before	12.10	1.94	10.80	11.90	13.10	2.30	0.397
After	12.09	1.80	10.90	11.80	13.10	2.20	
Erythropoietin resistance							
Before	5.26	5.68	0.00	4.16	8.03	8.03	0.016
After	4.84	5.85	0.00	3.37	7.28	7.28	
Ferritin, ng/mL							
Before	745.96	724.96	194.10	482.70	1,129.00	934.90	0.855
After	727.94	700.82	199.60	530.20	1,025.00	825.40	
TSAT, %							
Before	30.21	14.57	22.33	27.73	36.81	14.28	0.454

Characteristics	Mean	SD	P_{25}	Median	P_{75}	IQR	*p* 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	

LONG TERM EVALUATION OF THE EXPANDED HEMODIALYSIS (HDX) ON DIALYSIS ADEQUACY, ANEMIA AND QUALITY OF LIFE

11 HD patients. 12 months observational study.

HDx therapy (Qb < 300 ml/m') provided:

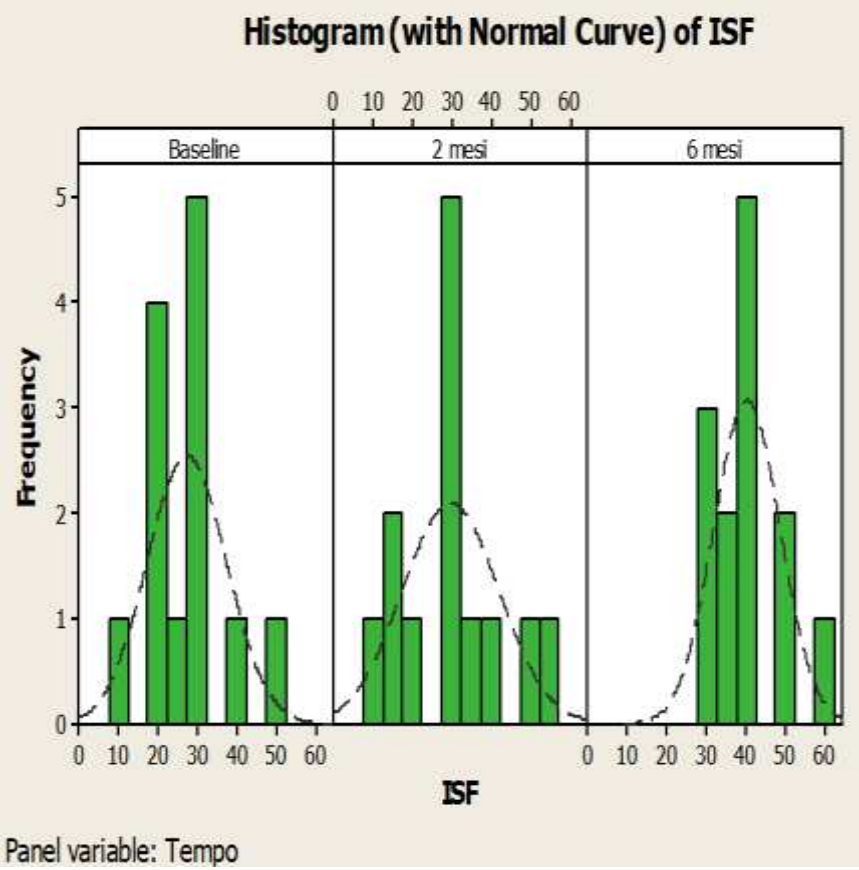
- a significant ($p < 0.05$) removal of: B2m, Myo, FLC-k and FLC-λ
- a significant decrease of CRP, ERI and EPO dose
- ***a significant improvement of QoL**** (indexes of Physical Health-ISF: p= 0.0001 and Mental Health-ISM: p= 0.001).
- Serum Albumin remained stable

Conclusions: HDx effectively removes uremic toxins up to 45kDa, even with Qb <300 ml/min, in those pts who cannot benefit from convective techniques because of vascular access or intolerance to high volumes of exchange.

OXFORD UNIVERSITY PRESS

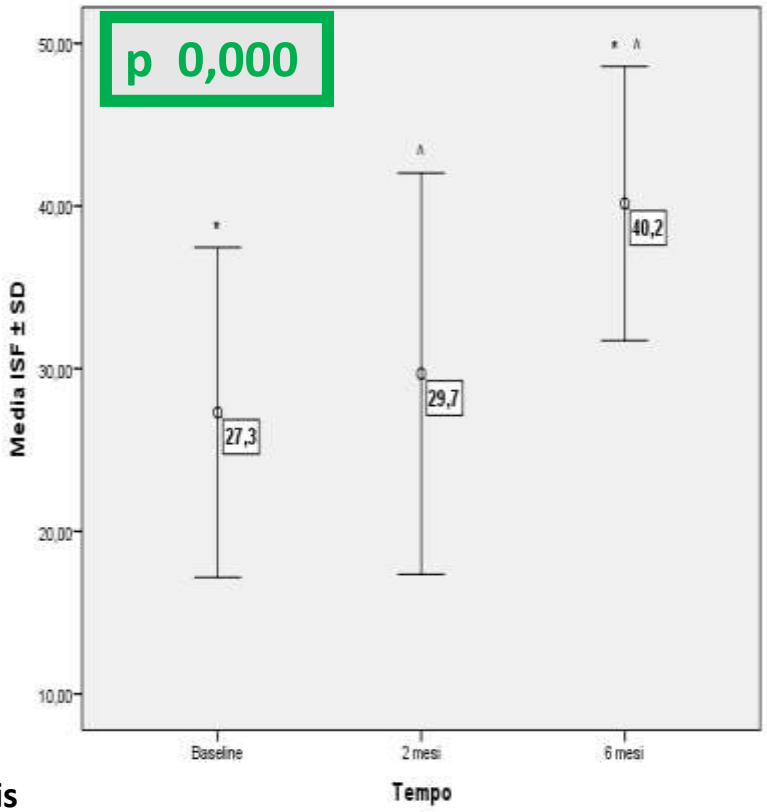
G Gernone, F Partipilo, F Detomaso, V Pepe, S Pietanza, A Mitrotti
Nephrol Dial Transplant, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1084,
https://doi.org/10.1093/ndt/gfaa142.P1084

MID-TERM EVALUATION OF THE NEW MEDIUM CUT-OFF FILTER (THERANOVA) ON REMOVAL EFFICIENCY AND QUALITY OF LIFE



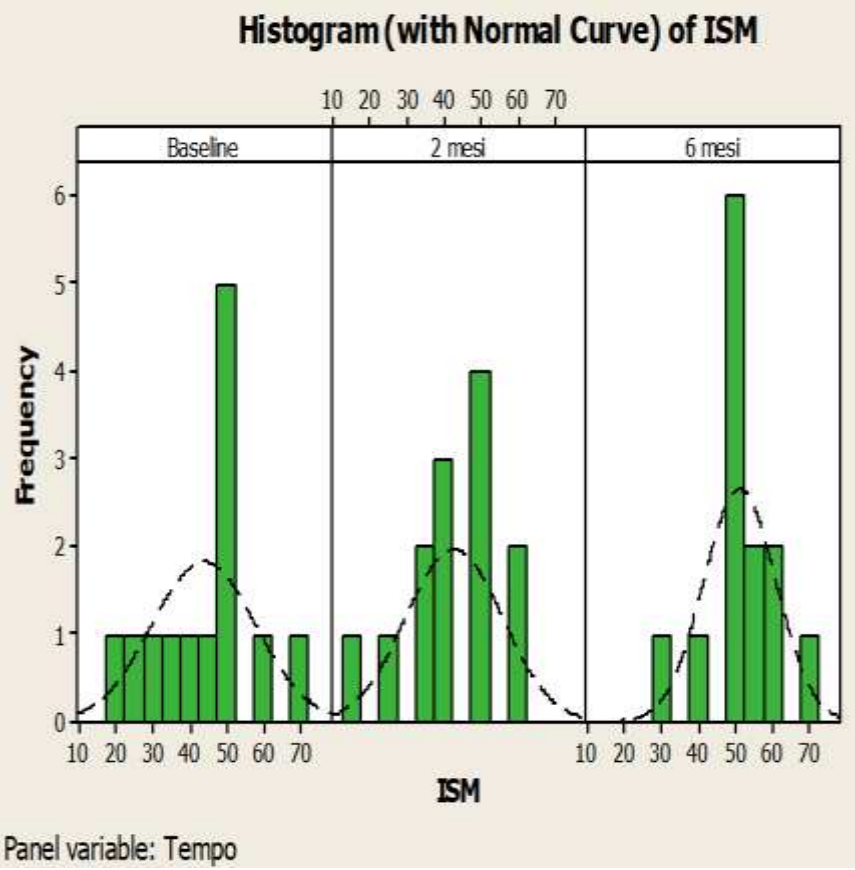
Qualità di vita: ISF

p value < 0,05



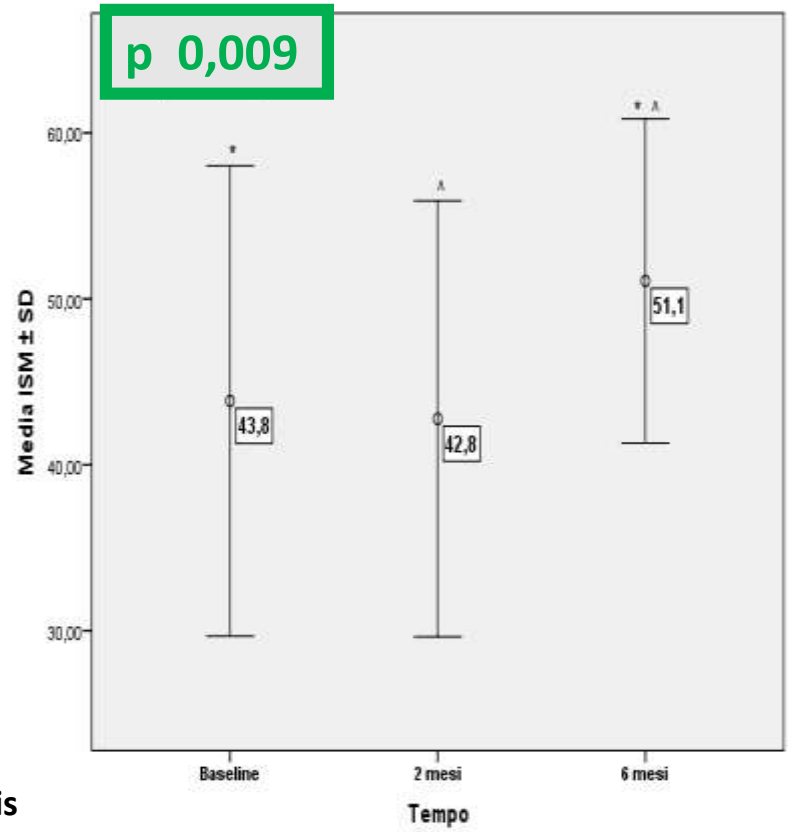
G Gernone, M Montemurro, F Partipilo et al.: **Nephrology Dialysis Transplantation,** Volume 33, Issue suppl_1, May 2018, Pages i513– i514, https://doi.org/10.1093/ndt/gfy104.SP489

MID-TERM EVALUATION OF THE NEW MEDIUM CUT-OFF FILTER (THERANOVA) ON REMOVAL EFFICIENCY AND QUALITY OF LIFE



Qualità di vita: ISM

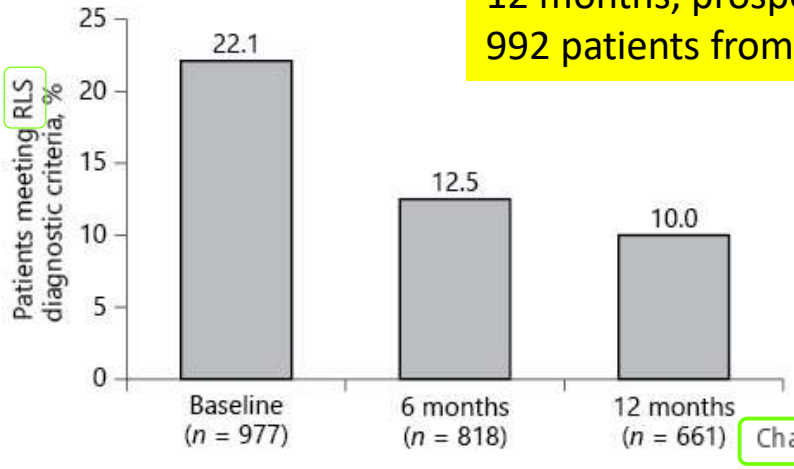
p value < 0,05



G Gernone, M Montemurro, F Partipilo et al.: **Nephrology Dialysis Transplantation,** Volume 33, Issue suppl_1, May 2018, Pages i513– i514, https://doi.org/10.1093/ndt/gfy104.SP489

Impact of Medium Cut-Off Dialyzers on Patient-Reported Outcomes: COREXH Registry

12 months, prospective, multicenter, observational cohort study in Colombia
992 patients from 12 renal clinics ***high-flux HD -> MCO therapy***



Conclusions: HDx was associated with

- higher health-related quality of life scores
- decrease in the prevalence of RLS.

Changes in KDQoL-36 score over 12 months of follow-up

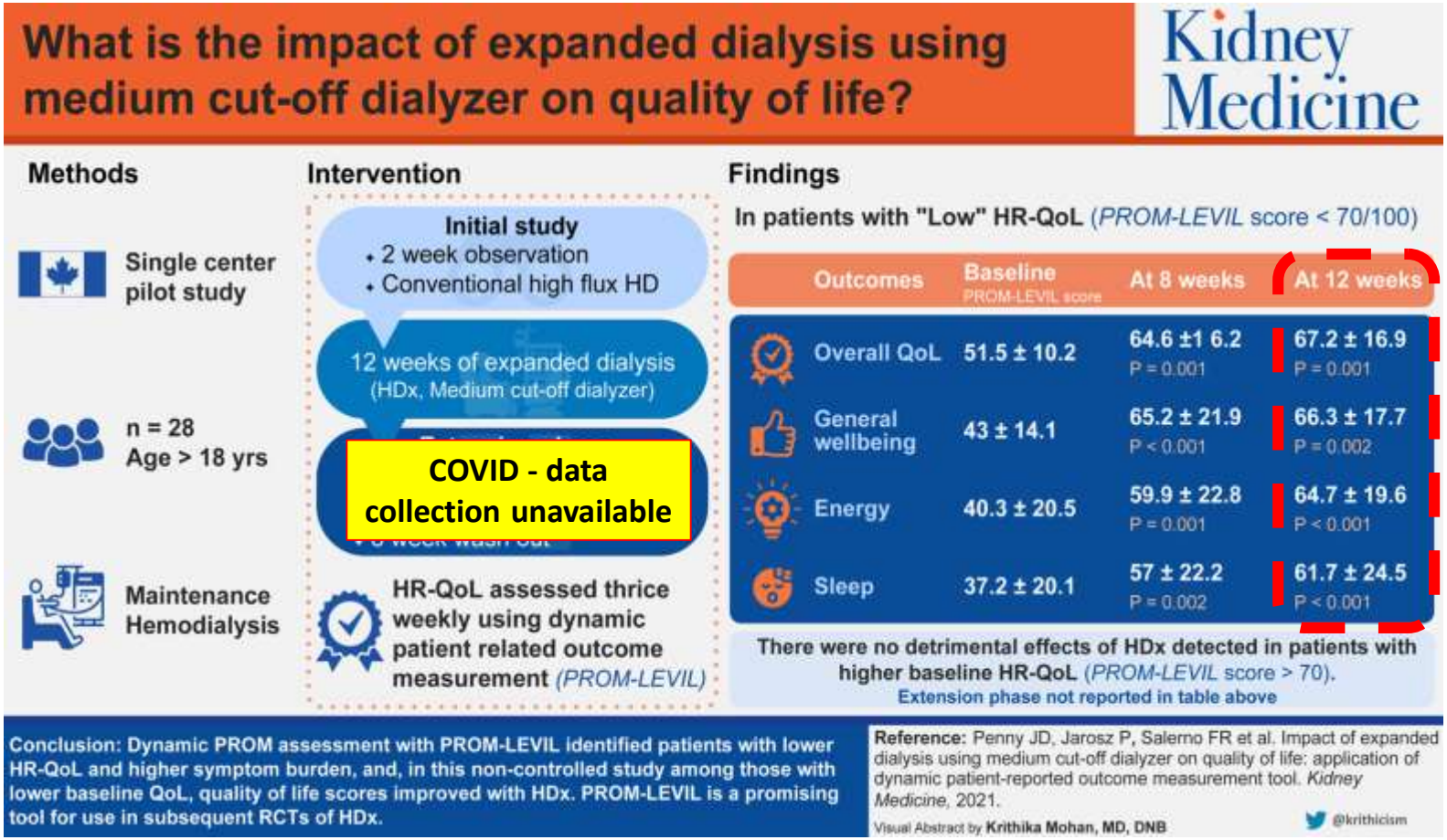
KDQoL-36 domain	Statistic	Baseline, n = 971	6 months, n = 808	12 months, n = 642	p value[a]
Symptoms/problems	Mean SD	78.6 15.8	81.0 15.4	81.5 14.9	<0.0001
Effects of kidney disease	Mean SD	69.7 22.3	72.8 22.0	75.1 21.0	<0.0001
Burden of kidney disease	Mean SD	46.2 27.5	48.9 29.9	50.2 32.3	<0.001
SF-12 physical	Mean SD	41.1 11.1	41.0 11.2	41.7 10.5	0.3
SF-mental	Mean SD	51.1 11.6	51.9 11.3	52.3 11.1	0.02

KDQoL-36, Kidney Disease Quality of Life 36-Item Short Form Survey; SD, standard deviation; SF, short form. [a] For hypothesis testing, type-I error significance was set at $p = 0.01$.

JC Alarcon et al.: Blood Purif. 2020;50(1):110-118. doi:10.1159/000508803

Impact of Expanded Hemodialysis Using Medium Cut-off Dialyzer on Quality of Life: Application of Dynamic Patient-Reported Outcome Measurement Tool

Jarrin D. Penny, Patricia Jarosz, Fabio R. Salerno, Sandrine Lemoine, Christopher W. McIntyre



Kidney Medicine 2021 3 (6) 992-1002.e1DOI: (10.1016/j.xkme.2021.05.010)

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

Are hemodialysis patient outcomes better for medium cutoff membranes than high-flux membranes?

Kidney Medicine

Retrospective

Observational cohort

Multicenter Colombia

Sept. 1, 2017 - Nov. 30, 2017

Dialyzer membrane

Medium cutoff (MCO) N = 564

High-flux (HF) N = 534

IR - incident rate/patient year

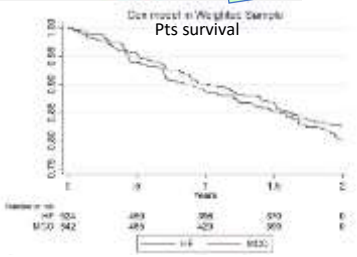
	Hospitalization	Non-fatal cardiovascular events
Medium cutoff (MCO)	IR = 0.93 95% CI: 0.82 - 1.03	IR = 0.18 95% CI: 0.14 - 0.22
	18 % Lower	34 % Lower
	IR ratio MCO/HF = 0.82 95% CI: 0.68 - 0.99, p = 0.04	IR ratio MCO/HF = 0.66 95% CI: 0.46 - 0.96, p = 0.03
High-flux (HF)	IR = 1.13 95% CI: 0.82 - 1.03	IR = 0.28 95% CI: 0.19 - 0.36

No statistical difference in time to death or in serum albumin levels between groups

Conclusion: Hospitalization and cardiovascular events in hemodialysis patients were lower when dialyzed with medium cutoff membranes than with high-flux membranes.

Reference: Molano A, Hutchison C, Sanchez R, et al. Medium cutoff versus high-flux hemodialysis and clinical outcomes: a cohort study using inverse probability treatment weighting. *Kidney Medicine*, 2022.

Visual Abstract by Brian Rifkin, MD



Graphical Abstract

HDx improves mortality compared to HD

Clinical Kidney Journal

Super high-flux membrane dialyzers reduce mortality in patients on hemodialysis: a 3-year nationwide cohort study

In Japan, dialyzers are classified according to their β2-microglobulin clearance: type I dialyzers are classified as low-flux, type II and III as high-flux, and type IV and V as super high-flux dialyzers

Aim

To assess the association of each dialyzer type with 3-year all-cause mortality

Methods

Nationwide prospective cohort study
Dialysis Therapy Renal Data Registry
2008–2011

Low-flux
(< 10 mL/min clearance)

High-flux
(10–30 and 30–50 mL/min clearance)

Super high-flux
(50–70 and ≥ 70 mL/min clearance)

Results

242 467 patients

	Low-flux	High-flux	Super high-flux
	Type I 1.3%	Type II 1.0% Type III 4.2%	Type IV 81.2% Type V 12.3% ← MCO
53 172 (21.9%)	Unadjusted HR **2.43**	Type II HR **1.74** Type III HR **1.21**	Type IV (reference) Type V HR **0.65**

Adjusted HR for (1) basic factors; (2) basic factors + dialysis-related factors; (3) basic factors + dialysis-related factors + nutrition- and inflammation-related factors; type I maintained a higher HR and type V a lower HR

Conclusion: Hemodialysis using super high-flux dialyzers might reduce mortality. Randomized controlled trials are warranted to clarify whether these type V dialyzers can improve prognosis.

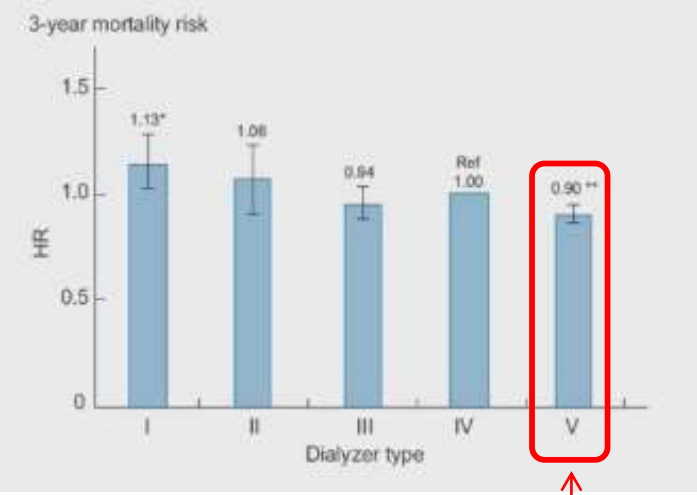
Abe M., et al
Clinical Kidney Journal (2021)
@CKJsocial

Clin Kidney J, Volume 15, Issue 3, March 2022, Pages 473–483, https://doi.org/10.1093/ckj/sfab177

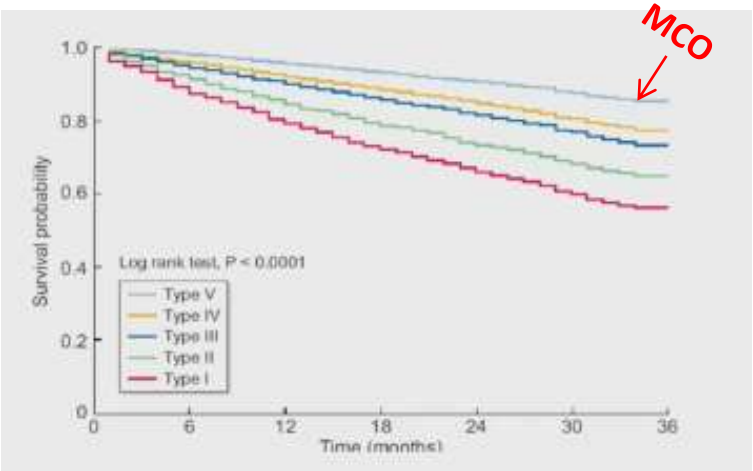
Clinical Kidney Journal, 2022, vol. 15, no. 3, 473–483

Super high-flux membrane dialyzers improve mortality in patients on hemodialysis: a 3-year nationwide cohort study

Masanori Abe[1,2], Ikuto Masakane[1,3], Atsushi Wada[1,4], Shigeru Nakai[1,5], Kosaku Nitta[1,6] and Hidetomo Nakamoto[1,7]



MCO



Middle Molecular Uremic Toxin and Blood Therapy

Journal of Clinical Medicine

A MM is defined as a solute that passes through the glomerulus with a molecular weight in the range of 0.5–58 kDa.

New classifications of "small-middle 0.5–15 kDa,"
"medium-middle 15–25 kDa," and
"large-middle 25–58 kDa"

In Japan has been focused the removal of α1-microglobulin (αMG) in the large MM

Comparison of blood purification modality between Europe and Japan.

Modality		Europe	Japan
HDF		Post-dilution, use non-albumin leakage membered	Pre-dilution, use albumin leakage membrane
	CV	20–25 L/session	48–58 L/session
	Blood flow rate	≥300 mL/min	250–300 mL/min
	Target MMs	Small middle, e.g., β2-microglobulin	Large-middle, e.g., α1-microglobulin
	Evidence	RCT: benefit to survival on higher CV	National cohort: enhanced survival was found to be substitution volume 50.5 L (limitation of CV)
Expanded HD		MCO membrane	Note: This term is not common in Japan. The 2013 functional classification II-b: super high-flux-albumin leaking membrane HD is the equivalent.
	Target MM	Medium middle, e.g., κ free light chain protein	Medium to large-middle

CV: convection volume, MMs: middle molecules, RCT: randomized controlled trial, MCO: medium cutoff.

H Kawanishi. J. Clin. Med. 2024, 13(3), 647;

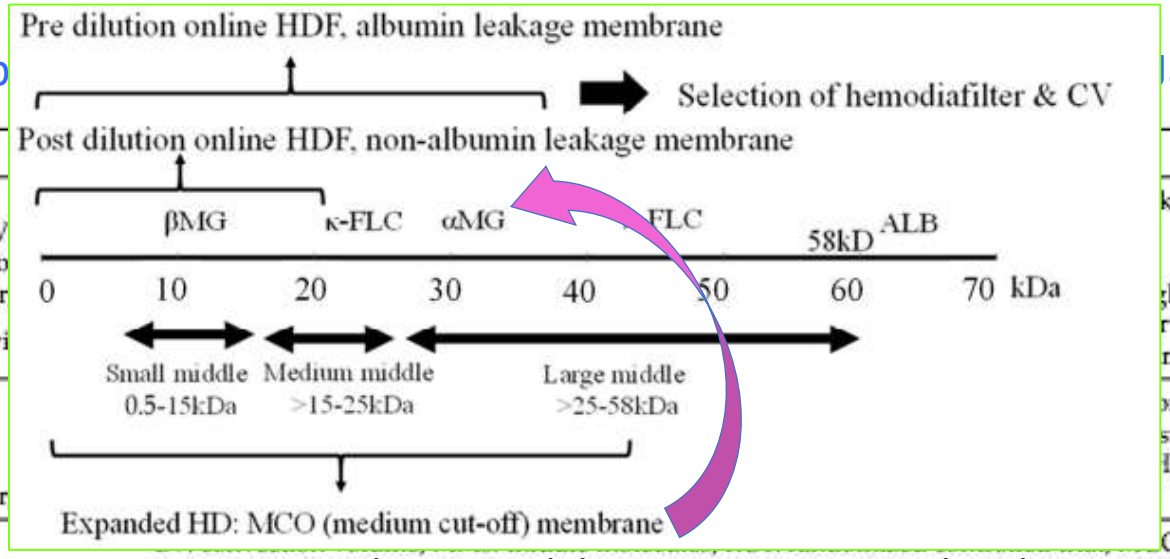
Middle Molecular Uremic Toxin and Blood Therapy

Journal of Clinical Medicine

A MM is defined as a solute that passes through the glomerulus with a molecular weight in the range of 0.5–58 kDa.

New classifications of “small-middle 0.5–15 kDa,”
“medium-middle 15–25 kDa,” and
“large-middle 25–58 kDa”

In Japan has been focused the removal of α1-microglobulin (αMG) in the large MM



Comp ...apan.

Modality	
HDF	...kage membrane
CV ...	...globulin ...rvival was found to be ...mitation of CV)
Expanded HD	...n in Japan. The 2013 super high-flux- ...ID is the equivalent.

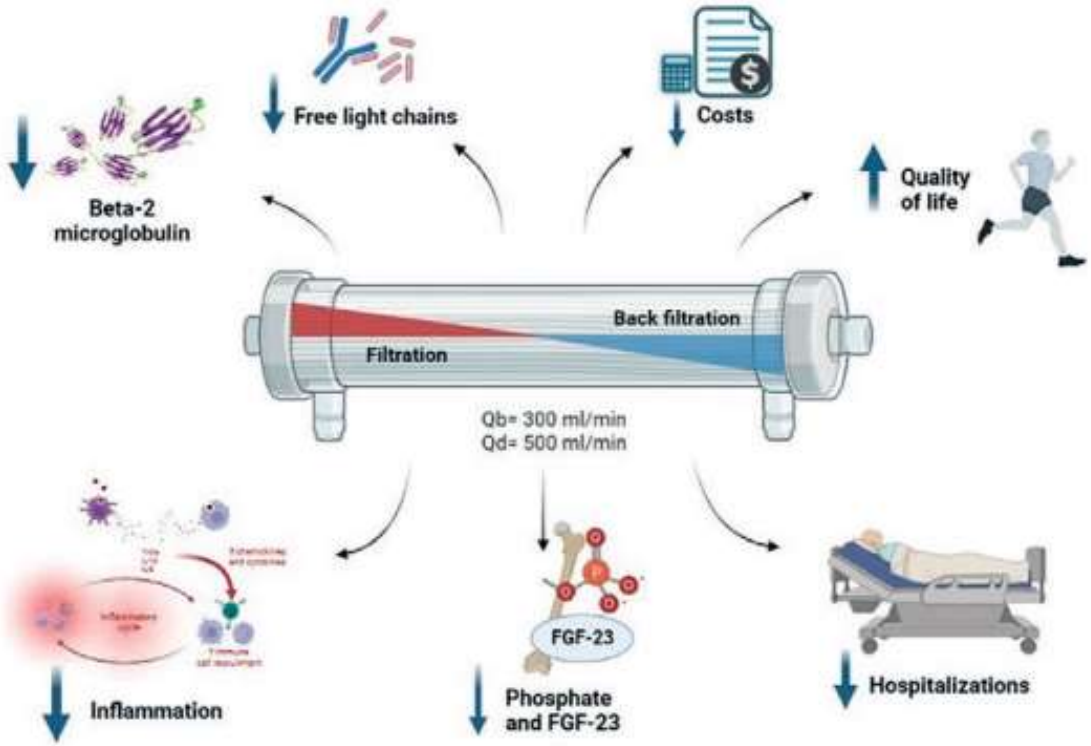
...O: medium cutoff.

CONCLUSION: Uncertainties persist regarding HDF ability to prevent HD- related Hypotension.
A positive impact on survival rate remain tentative. Prescriptions of HDF tend to be specific to the country and facility. αMG removal throug **MM removal will advance therapy to a new level**.

H Kawanishi. J. Clin. Med. 2024, 13(3), 647;

Are Medium Cut-off Membranes the Future, or the Promising Reality for Chronic Hemodialysis Patients?

Summary of beneficial effects obtained with the clinical use of medium cut-off membranes



Noemí Del Toro-Cisneros. Rev Invest Clin. 2023;75(6):289-99

Expanded hemodialysis: what's up, Doc?

Membrane	Brand	Membrane polymer	Inner diameter[a] (μm)	Wall thickness[a] (μm)	Available Surface areas[a] (m^2)	UF coefficient[a] (mL/h/mmHg/m^2)	Myoglobin sieving coefficient	β2-microglobulin sieving coefficient	Albumin sieving coefficient	Sterilization
Phylter	Medtronic	Polyphenylene	200	30	1.7 (Phylter 17 SD)	31.2	0.7	0.93	<0.02	Steam
Vie	Asahi	Polysulfone	185	45	1.8 (Vie 18X) 2.1 (Vie 21X)	49	0.8	0.9	<0.01	Gamma radiation
Elisio	Nipro	Polyethersulfone	200	40	1.9 (Elisio 19HX) 2.1 (Elisio 21HX)	39	0.86	1	0.0024	Gamma radiation
Theranova	Baxter	Polyarylethersulfone	180	35	1.7 (Theranova 400) 2 (Theranova 500)	28.5	0.9	1	0.008	Steam
FDY	Nikkiso	Polyester polymer alloy	210	30	2.1 (FDY 210 GW)	30.5	ND	0.94	ND	Gamma radiation

Ana García-Prieto et al. CKJ, 2023, vol. 16, no. 7, 1071–1080

CONCLUSION:
HOW TO PERFORM HDx

- HDx improve the elimination of higher molecular weight UT compared with HF-HD and similar to OL-HDF
- Any patient on HF-HD could benefit from HDx
- HDx should be considered especially in patients cannot achieve higher convective volumes in OL-HDF (>23 L/session) (vascular access problems)
- A dialysis machine with ultrafiltration control is required: no replacement solution, no specific software or additional complex technology
- HDx to be efficient also with lower blood flows
- OL-HDF with MCO membranes is contraindicated because the loss of albumin may up to 15 g per session.
- Isolated UF with MCO is not recommended due to increased permeability of larger plasma proteins such as free hemoglobin. During isolated ultrafiltration, this causes a reddish coloration of the ultrafiltrate which could activate the internal blood leak detector.
- HDx was associated
  - with reducing dose of ESA and iron
  - Lower hospitalization rate and hospitalization length
  - better perceived QoL (ISF, ISM, RLS) and survival

Ana García-Prieto et al. CKJ, 2023, vol. 16, no. 7, 1071–1080

Expanded hemodialysis: what's up, Doc?

Meta-analysis	Studies included	*N*	Comparison	Primary outcomes	Secondary outcomes	Results
Hung *et al.* [23]	5 RCTs	328	HD with MCO membranes vs HF-HD	RR of β2-microglobulin, κFLC, λFLC and IL-6	Serum albumin levels	Superior clearance of β2-microglobulin ($P < .0001$), κFLC ($P < .0001$) and λFLC ($P = .02$) with MCO dialysers; no differences in serum IL-6 levels Albumin loss was observed in MCO group ($P = .04$) Higher reduction in serum albumin in one study
Yang *et al.* [24]	9 (6 RCTs, 3 non-RCTs)	529	HD with MCO membranes vs HF-HD	RR of β2-microglobulin, κFLC and λFLC Levels of β2-microglobulin, κFLC, λFLC, IL-6, TNF-α and albumin		Superior clearance of β2-microglobulin ($P < .00001$), κFLC ($P < .00001$) and λFLC ($P < .00001$) with MCO dialysers No difference in serum levels of β2-microglobulin, κFLC, λFLC and IL-6 between groups Reduced serum levels of TNF-α ($P = .005$) and albumin ($P = .02$) with MCO dialysers
Kandi *et al.* [25]	26 (10 RCTs, 16 non-RCTs)	1883	HD with MCO membranes vs HF-HD	RR of β2-microglobulin, myoglobin, TNF-α, κFLC and λFLC Levels of β2-microglobulin, κFLC, λFLC, IL-6, TNF-α and albumin Albumin removal		Superior clearance (SMD >2) and reduced serum levels (SMD >0.5) of β2-microglobulin, myoglobin, κFLC and λFLC Increased RR of TNF-α by 7.7% (95% CI 4.7, 10.6) and reduced predialysis TNF-α by SMD −0.48 Albumin removal was 2.31 g per session (95% CI 2.79, 1.83) with a reduction in predialysis albumin of −0.12 g/dL (95% CI −0.16, −0.07) in the first 24 weeks, returning to normal after 24 weeks
Kandi *et al.* [53]	22 (6 RCTs, 16 non-RCTs)	1811	HD with MCO membranes vs HF-HD	QoL, pruritus, RLS and recovery time	All-cause mortality, SAEs, hospitalization, infection and ESA resistance	Improved: - QoL (MD: 16.7/100 points; 6.9, 26.4) - Pruritus (MD = −4.4; −7.1, −1.7) - RLS (odds ratio = 0.39; 0.29, 0.53) - Recovery time (MD = −420 min; −541, −299). Reduced: - Hospitalization (rate ratio = 0.48; 0.27, 0.84) - Hospitalization days (−1.5 days; 95% CI −2.22, −0.78) - Infection (rate ratio = 0.38; 0.17, 0.85) - ESAs resistance (−2.92 U/kg/week/g/L; 95% CI −4.25, −1.6) Little to no difference in mortality (risk difference = −0.4%; −2.8, 2.1) and SAEs (rate ratio = 0.63; 0.38, 1.04)

Clinical Kidney Journal

Ana García-Prieto et al. CKJ, 2023, vol. 16, no. 7, 1071–1080