The new modality "Expanded Hemodialysis, HDx" for the Home dialysis patients to clear Large Middle Molecules

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Theranova: A New Dimensi
By the end of this session you will
• Understand the evolution of this dialyzer
• Understand how Theranova and HDx are the next step Hemodialys

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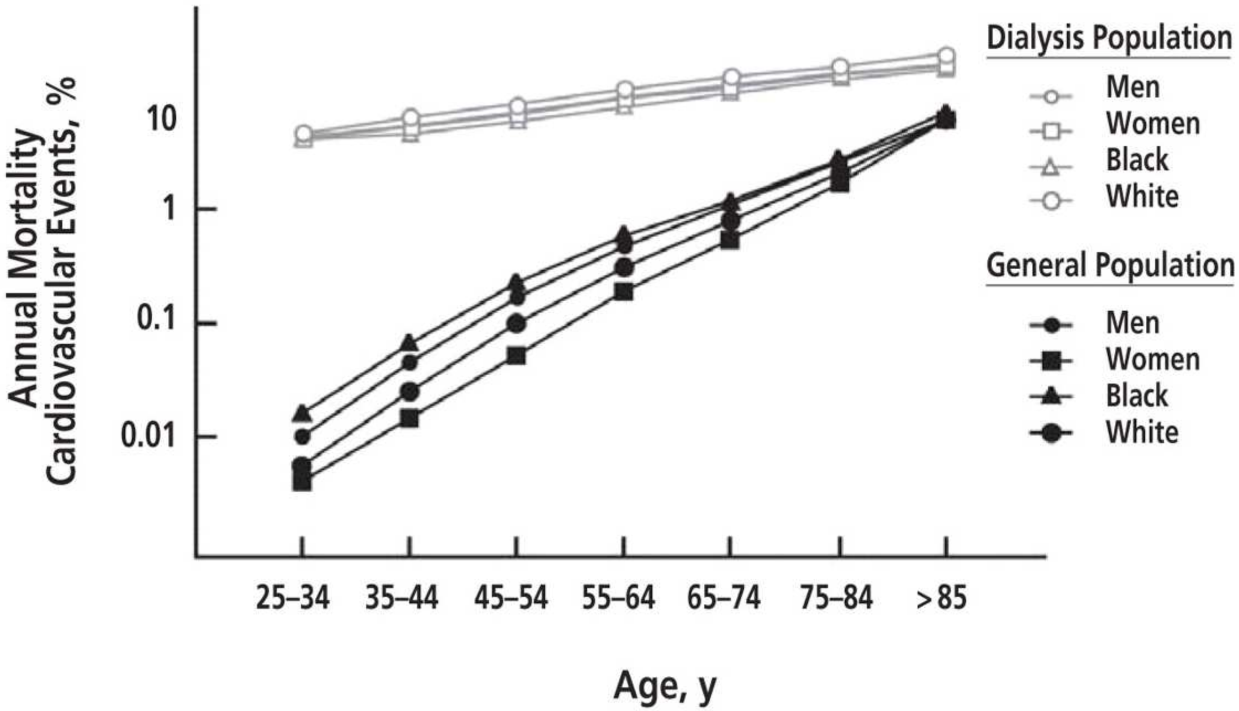
Agenda

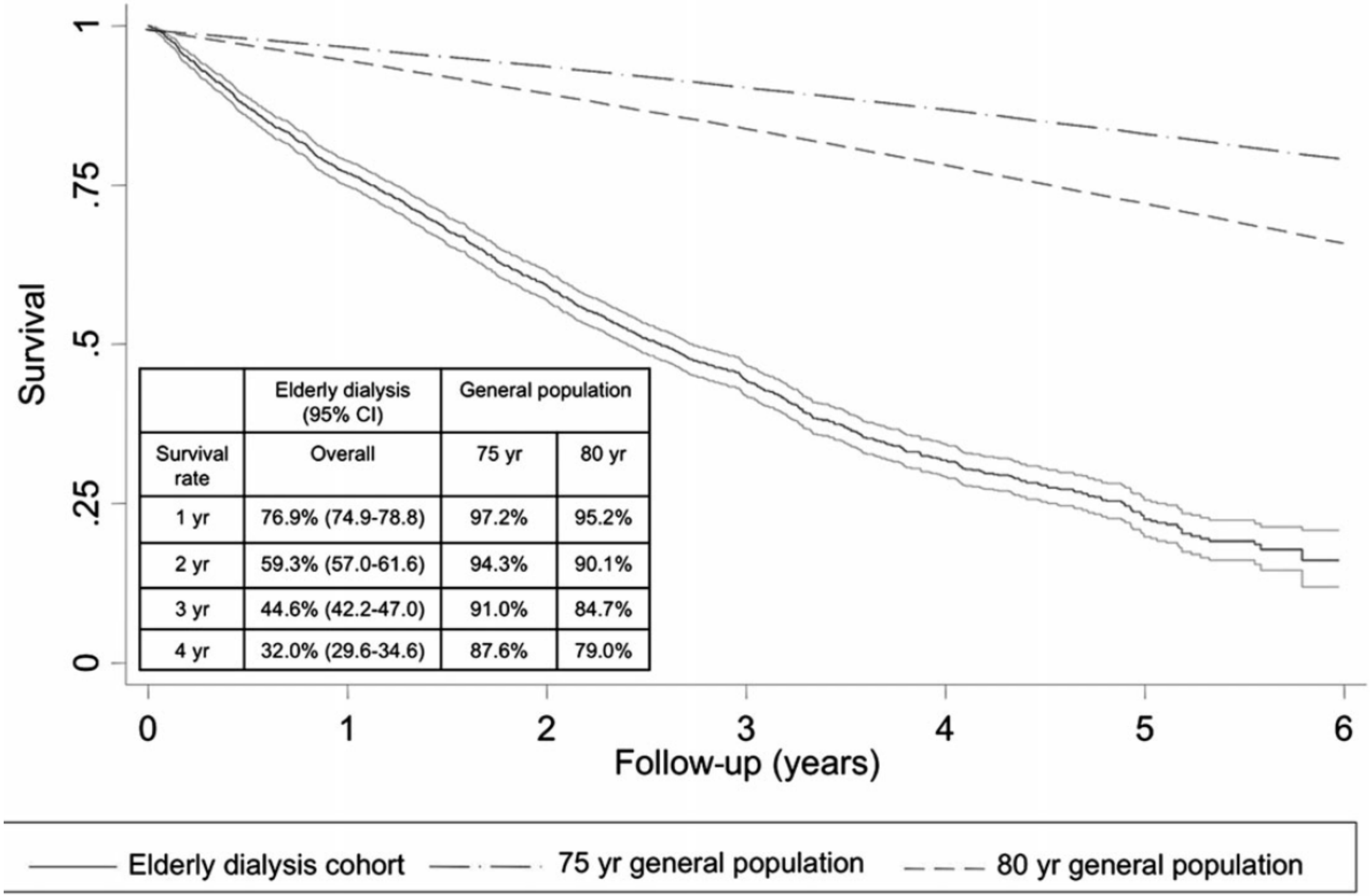
- Renal Transport Middle Molecules
- HDx therapy with the new MCO Theranova membrane
- Summary

We have not solved cardiovascular disease



Adapted from Sarnak MJ et al. Hypertension 2003;42:1050-1065

Survival in Dialysis?



	Elderly dialysis (95% CI)	General population	
Survival rate	Overall	75 yr	80 yr
1 yr	76.9% (74.9-78.8)	97.2%	95.2%
2 yr	59.3% (57.0-61.6)	94.3%	90.1%
3 yr	44.6% (42.2-47.0)	91.0%	84.7%
4 yr	32.0% (29.6-34.6)	87.6%	79.0%

Hutchison C. ERA-EDTA 2016 Presentation

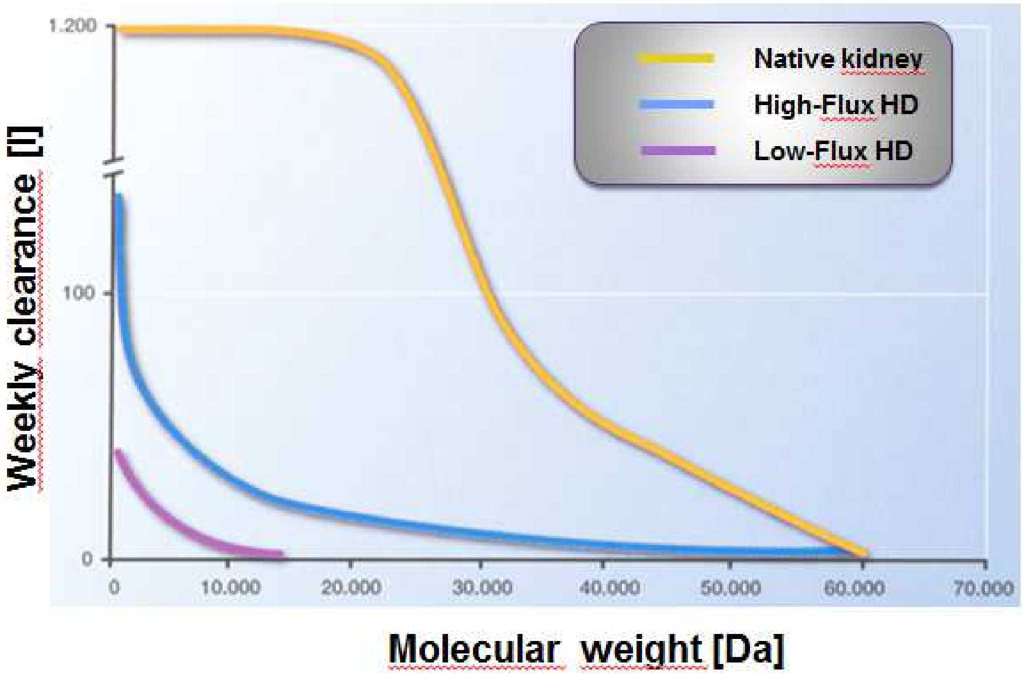
Large Middle Molecules:

- Meet the criteria for an uremic toxin
- Are middle-molecules which currently have limited removal by standard low and high flux HD

Molecular weights >15kDa

Renal transport of middle molecules

Dependence on solute size and molecular weight



Weekly solute clearance as a function of molecular weight

Cheung AK. Blood Purif 1994;12:42-53

Uremic retention solutes of the Middle Molecule group indicating solutes ≥15 kDa and ≥20 kDa in size

α_1-Acid glycoprotein	Desacylghrelin	**Myoglobin**
α_1-Microglobulin	Dinucleoside polyphosphates	Neuropeptide Y
Adiponectin	β-Endorphin	Orexin A
Adrenomedullin	Endothelin-1	Orexin B
AGEs	**Fibroblast growth factor-23**	Osteocalcin
Angiogenin	**κ-Ig light chain**	PTH
Angiotensin A	**λ-Ig light chain**	**Pentraxin-3**
AOPPs	Ghrelin	**Prolactin**
Atrial natriuretic peptide	Glutathion, oxidized	Resistin
Basic fibroblast growth factor	Guanylin	**Retinol binding protein**
β_2-Microglobulin	**Hyaluronic acid**	Soluble intracellular adhesion molecule-1
β-Trace protein	IGF-1	**Soluble TNF receptor 1**
Calcitonin	**IL-1β**	**Soluble TNF receptor 2**
Calcitonin-gene-related peptide	**IL-6**	Substance P
Cholecystokinin	IL-8	**TNF-α**
Clara cell protein (CC16)	**IL-10**	Uroguanylin
Complement factor D	**IL-18**	**Vascular endothelial growth factor**
Cystatin C	**Leptin**	Vasoactive intestinal peptide
Degranulation inhibiting protein I	Methionin-enkephalin	**Visfatin**
Delta-sleep inducing peptide	Motilin	**YKL-40**

Molecular weight 15-20 kDa

Molecular weight 20 kDa or greater

Vanholder et al. Kidney Int 2003;63:1934–43
Duranton et al. J Am Soc Nephrol 2012;23:1258-70
Neirynck et al. Int Urol Nephrol 2013;45:139–50
Chmielewski et al. Sem Nephrol 2014;34:118–34
Hutchison C. ERA-EDTA 2016 Presentation

Large Middle Molecule uremic solutes and potential impact on health

α_1-Acid glycoprotein	[43 kDa]	Inflammatory processes (2)
α_1-Microglobulin	[33]	Restless leg syndrome (6)
Adiponectin	[30]	Unclear, low concentration is likely a reflection of abdominal fat/nutritional status (1)
AGEs	[variable]	Inflammatory processes, atherosclerosis progression (1)
Basic fibroblast growth factor	[24]	
β-trace protein	[26]	
Complement factor D	[24]	Chronic inflammation, atherosclerosis progression (1)
Fibroblast growth factor-23 (FGF-23)	[32]	Uremic cardiomyopathy (4)
κ-Ig light chain	[22.5]	Impaired immune defense, nephrotoxicity (1)
λ-Ig light chain	[45]	Impaired immune defense, nephrotoxicity (1)
Hyaluronic acid	[variable]	
Interleukin-1β (IL-1β)	[32]	Inflammation, cognitive dysfunction (5)
Interleukin-6 (IL-6)	[24.5]	Inflammation, atherosclerosis progression, anemia (1); cognitive dysfunction (5)
Interleukin-18 (IL-18)	[20]	
Pentraxin-3	[40]	Endothelial dysfunction (1)
Prolactin	[22]	Sexual abnormalities, anemia, endothelial dysfunction, arterial stiffness (1)
Retinol binding protein	[21]	Oxidative stress, atherosclerosis progression (1)
Soluble TNF receptor 1	[30]	Prolong half-life of TNFα and Increase its cytotoxicity
Soluble TNF receptor 2	[40]	Prolong half-life of TNFα and Increase its cytotoxicity
TNF-α	[26]	Coagulation disorders, insulin resistance, endothelial dysf. wasting (1); cognitive dysf. (5)
Vascular endothelial growth factor	[34]	
Visfatin	[55]	Endothelial damage, inflammation, plaque destabilization (1)
YKL-40	[40]	Associated with standard inflammatory parameters (3)

(1) Chmielewski et al. Sem Nephrol 2014;34:118–34; (2) Lisowska Myjak B. Nephron Clin Pract 2014;128:303-11; (3) Okyay GU et al. Ther Apher Dial. 2013;17:193-201; (4) Grabner A et al. Curr Opin Nephrol Hypertens 2016;25:314-24; (5) Watanabe et al NeuroToxicology 2014;44:184-93; (6) Sakurai K. Blood Purif 2013;35(Suppl1.):64-8;

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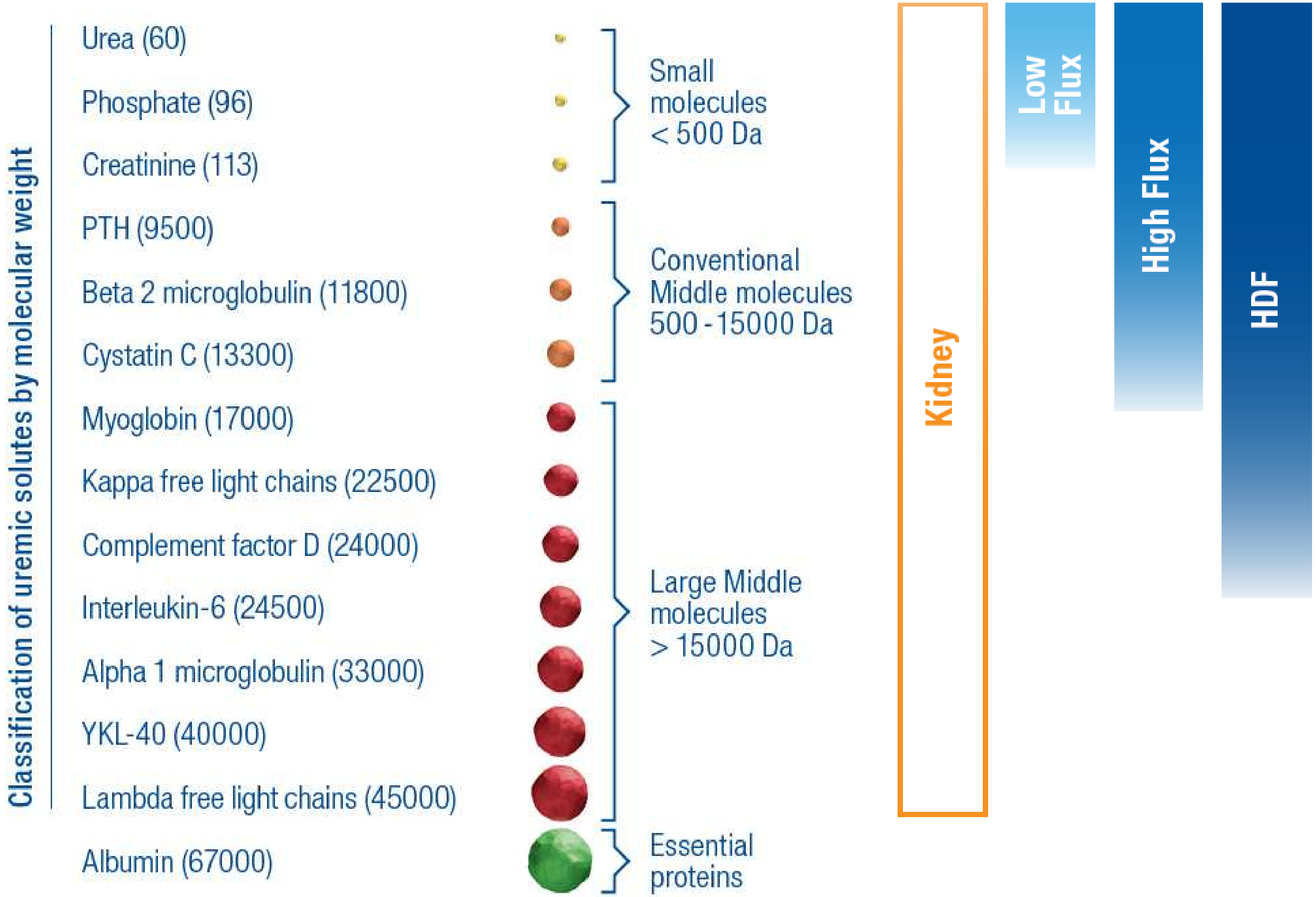
Current therapies have limitations in the clearance of large uremic solutes (large middle molecules)



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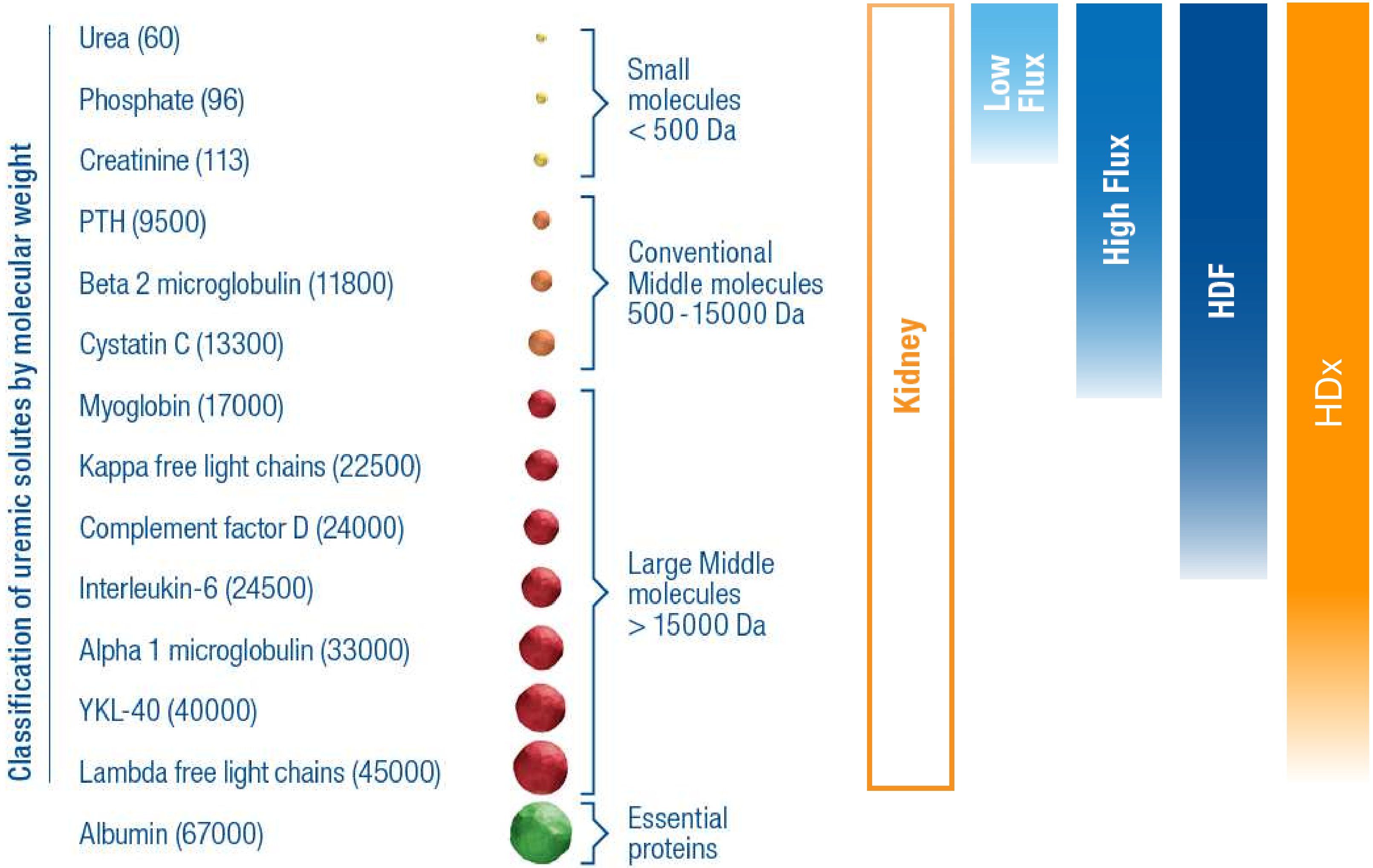
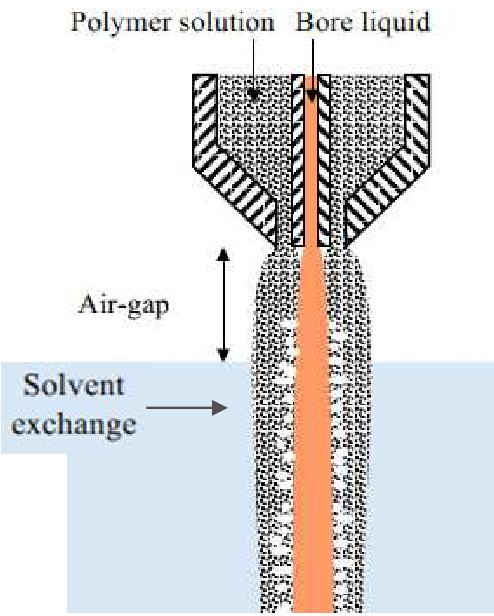
Expanded hemodialysis, HDx: A step closer to the native kidney in which molecules are cleared, simpler than HDF

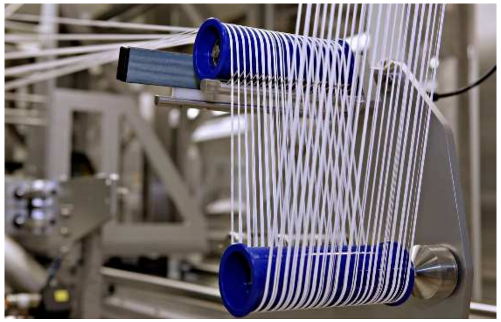


Membrane pore size distribution is determined by the spinning process conditions

Innovation on the spinning process
and speed of porous hollow fibers

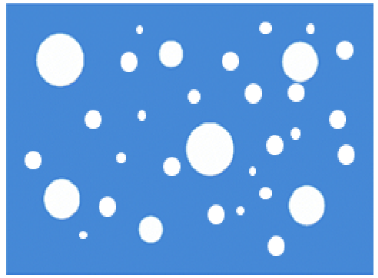


Phase Inversion Process

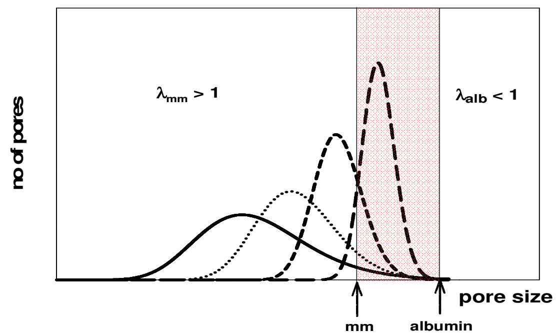


Kim HJ. Jpn J Appl Phys 2016;55 06GH06

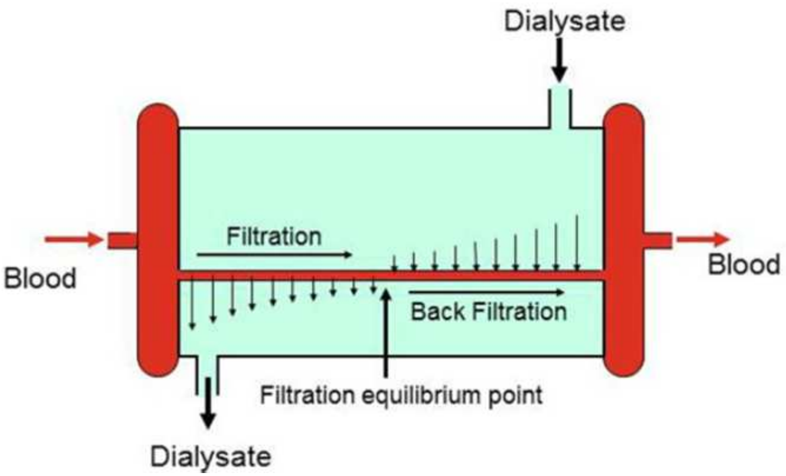
non-uniform pore sizes (highflux)



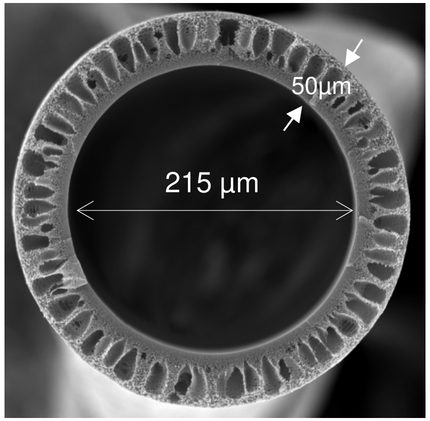
pore size distribution Theranova



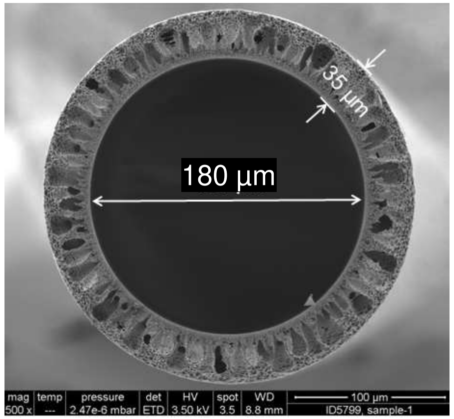
MCO membrane characteristics support internal convection



Inner fiber diameter



Polyflux



Theranova MCO

→ Increased performance as sum of:
- Increase of membrane permeability
- Reduction of inner diameter, more fibers per dialyzer

→ Optimum (Performance, Process Stability): 180 / 35 µm

Blood Purification

Editorial

Blood Purif 2017;44:I–VIII
DOI: 10.1159/000476012

Published online: May 10, 2017

The Rise of Expanded Hemodialysis

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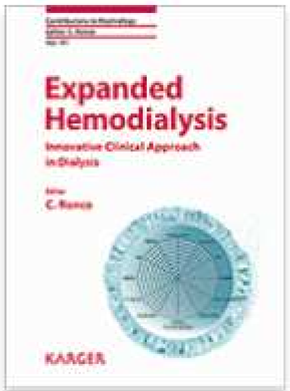
Expanded Hemodialysis

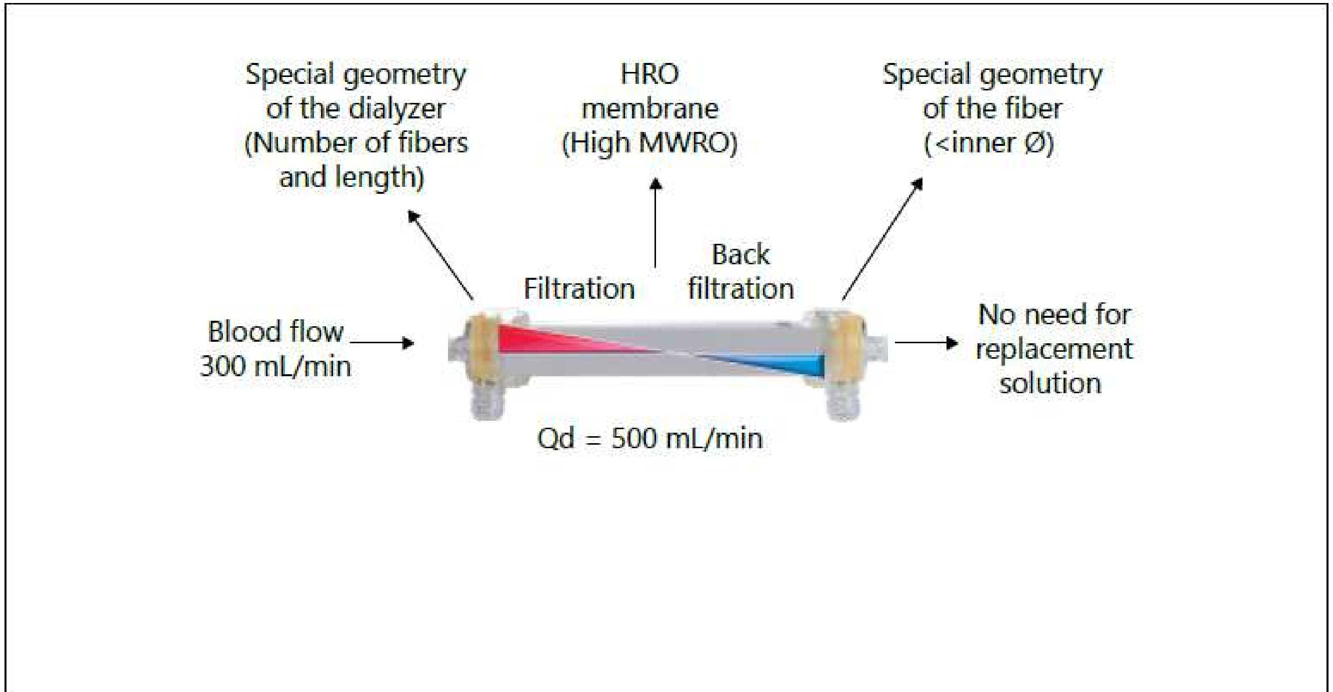
Innovative Clinical Approach in Dialysis

Editor(s): Ronco C. (Vicenza)

Status: available

Publication year: 2017





Membrane as barrier to microbiological contaminants in dialysis fluid – Simulating clinical conditions, a study by the Ghent team

	LPS detection by LAL test (EU/ml) mean ± standard deviation [range] {number of repeats out of 6 above detection limit}		
Product	**Dialysate (natural ET challenge)**	**Blood side at start**	**Blood side after 1 hour**
Low-flux (Polyflux L)	8.6 ± 5.8 [3.5-19.1]	0.004 ± 0.000 [0.004-0.004] {0}	0.005 ± 0.002 [0.004-0.008] {1}
High-flux (Revaclear)	12.2 ± 12.2 [3.6-33.7]	0.005 ± 0.002 [0.004-0.008] {2}	0.005 ± 0.001 [0.004-0.008] {2}
Medium cut-off (Theranova)	8.3 ± 2.4 [6.0-11.8]	0.004 ± 0.000 [0.004-0.004] {0}	0.006 ± 0.004 [0.004-0.014] {3}
High cut-off (Theralite)	8.9 ± 7.4 [3.2-22.5]	0.004 ± 0.001 [0.004-0.006] {1}	0.007 ± 0.005 [0.004-0.016] {5}

bacterial endotoxin (*lipopolysaccharide, LPS*)

detection limit: 0.005 EU/ml

Schepers E et al. ERA-EDTA 2017 Congress Abstract MP537

Endotoxin retention for dialysis membranes of different permeability profile

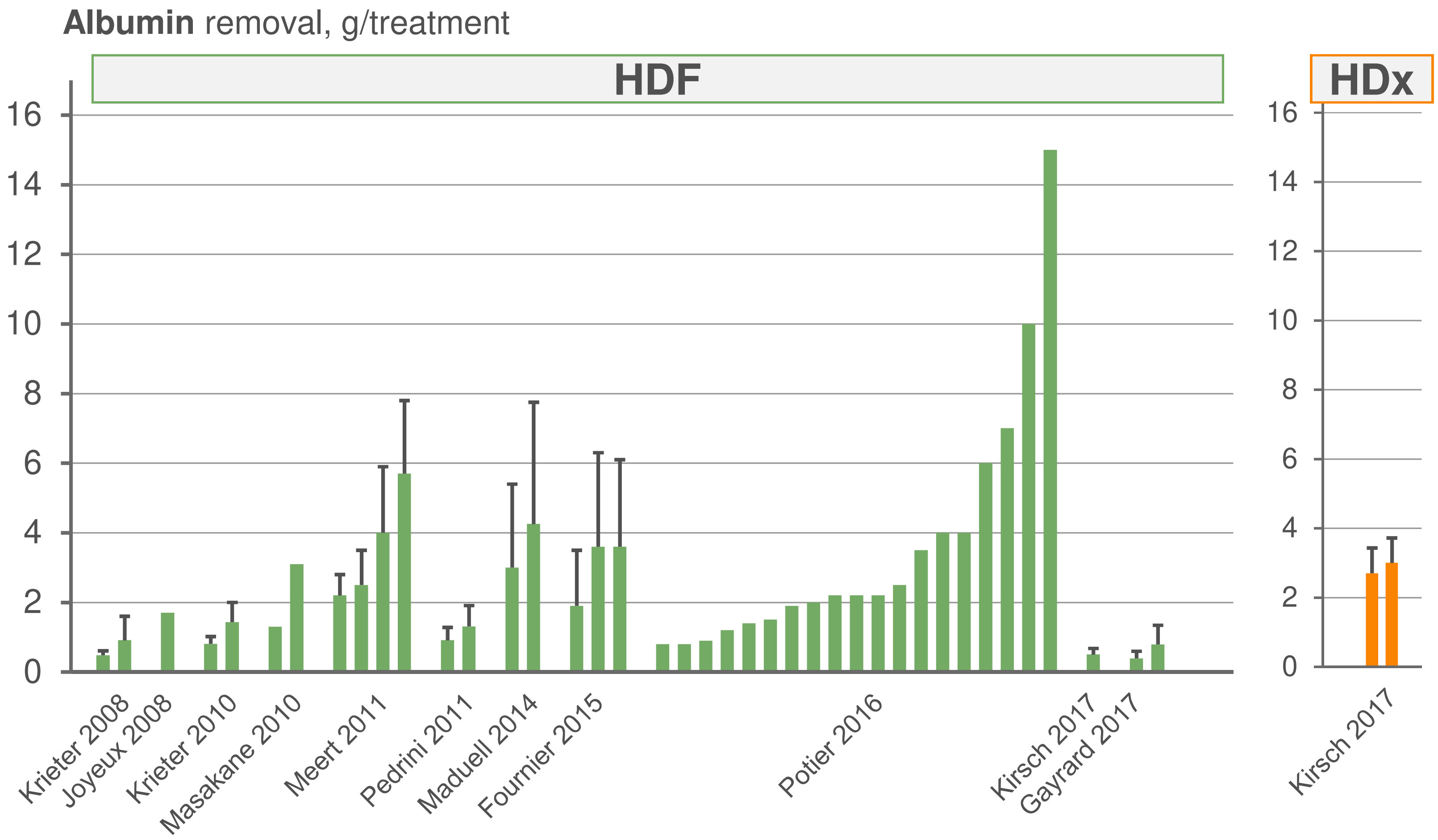
Membrane type[1]	Pore radius [nm] (mean ± SD)	Endotoxin LRV[2] (mean ± SD)
Low-flux	3.1 ± 0.2	2.8 ± 0.2
High-flux	4.5 ± 0.2	3.3 ± 0.3
MCO 4	6.5 ± 0.2	3.5 ± 0.1
HCO	10 ± 2	3.3 ± 0.5

[1] All membranes made of same material, having similar wall structure

[2] Tested with LPS from *E.coli* O55:B5 (N=3); LRV = Logarithmic Retention Value

Ref: Hulko et al. ERA-EDTA 2015 abstract FP516

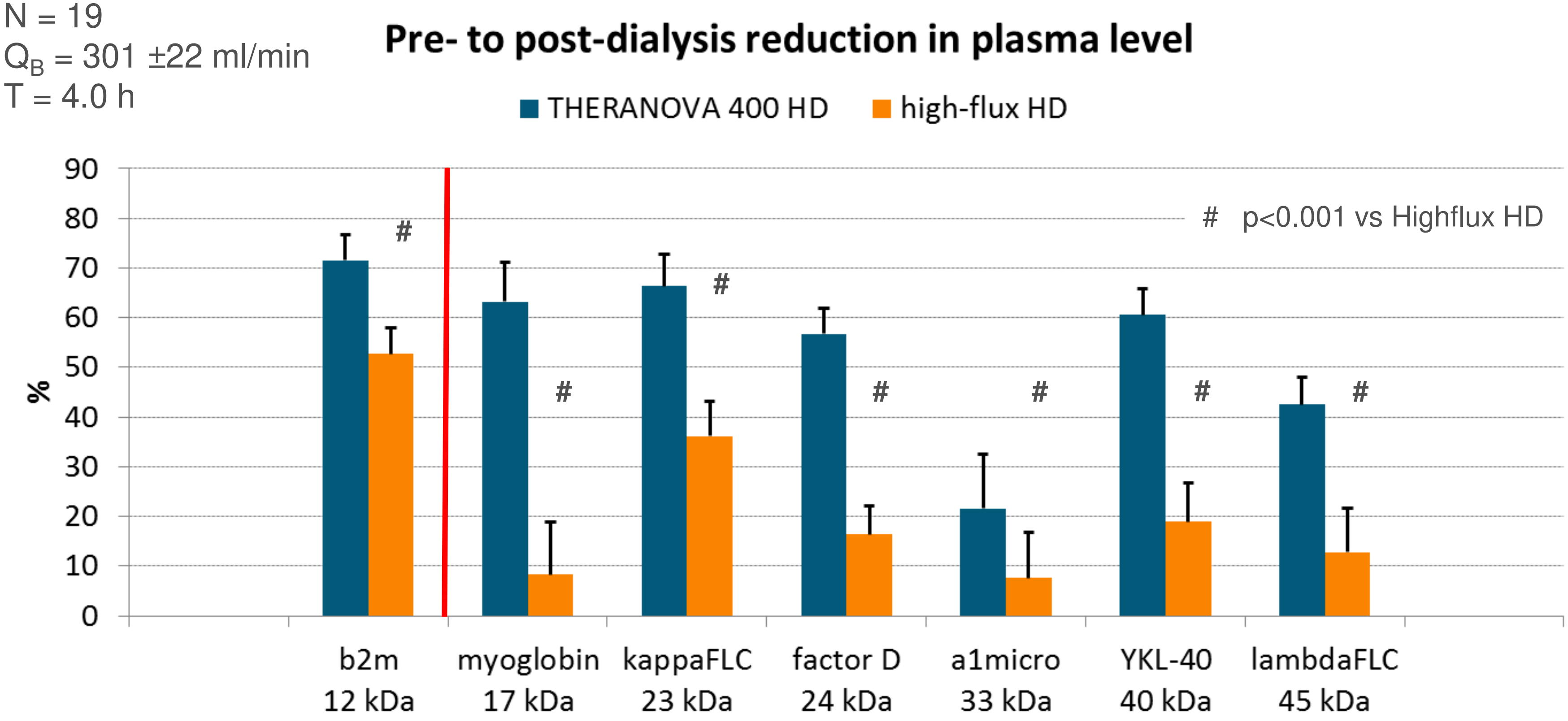
Reported albumin removal in HDF and HDx treatments



HDF data are obtained in different studies using a variety of high-flux dialyzers, different dilution modes (post-, pre-, mid-), and different convective flow rates

Theranova Dialyzer in HD mode

N = 19
Q_B = 301 ±22 ml/min
T = 4.0 h

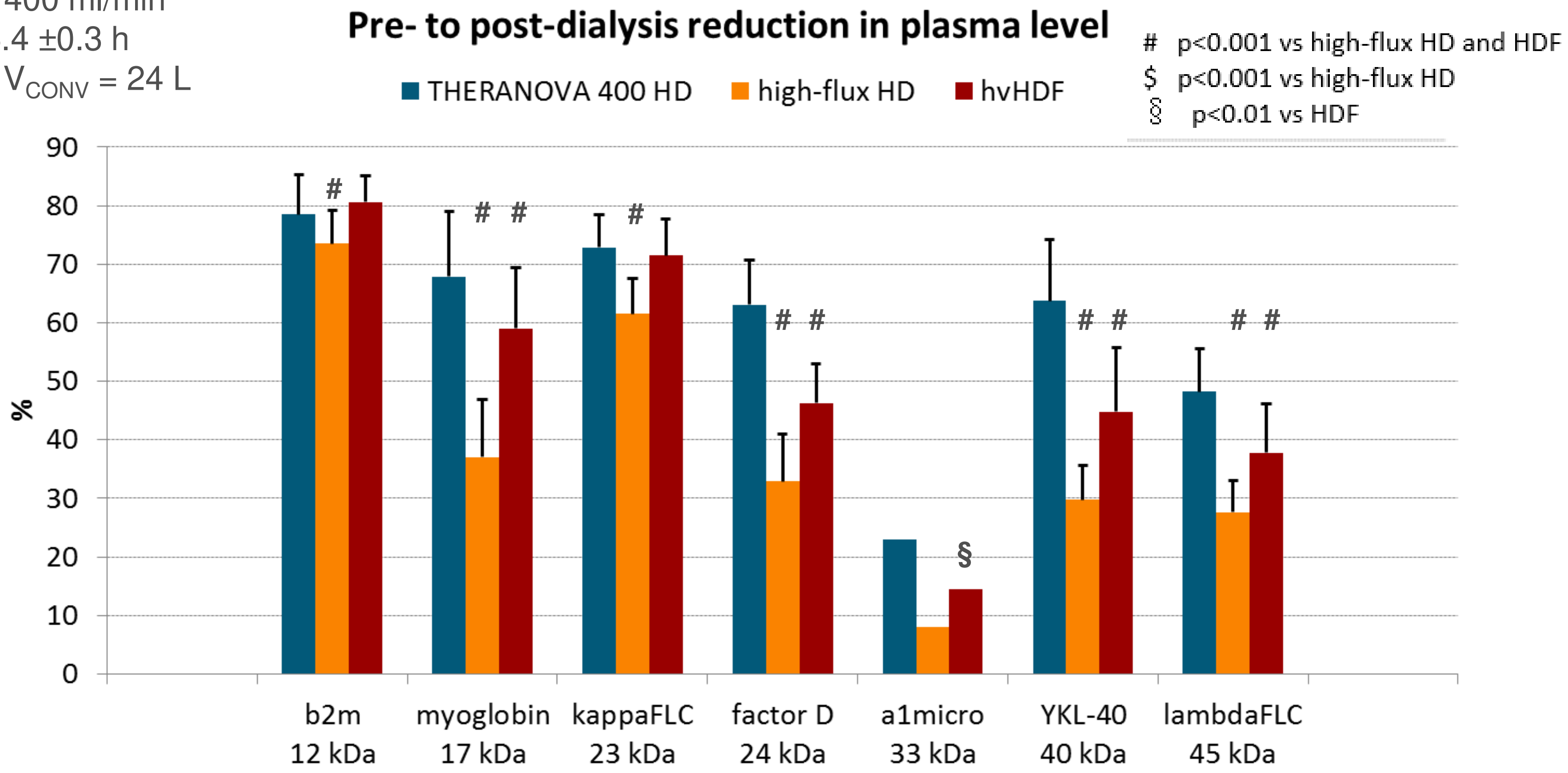


High-flux HD = HD by FX Cordiax 80 dialyzer
Bars indicate mean and SD
Post-dialysis data are corrected for hemoconcentration

Kirsch et al. Nephrol Dial Transplant 2017;32:165-72

HDx performance versus HDFoL and high-flux HD

N = 19
Q_B = 400 ml/min
T = 4.4 ±0.3 h
HDF V_{CONV} = 24 L



hvHDF = high volume HDF by FX Cordiax 800; high-flux HD = HD by FX Cordiax 80

Bars indicate mean and SD (except for alpha1microglobulin data that are presented as medians)

Post-dialysis data are corrected for hemoconcentration

Statistics by a mixed model with fixed effects of period and study dialyzer type, and the random effect of subject.

What could improve with increased removal of large MM?

- Chronic inflammation
- Cardiovascular disease
- Infections (secondary immunodeficiency)

- Quality of life

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- **Summary**

Published clinical studies of MCO Membrane to date

Author	Study	Patients (n)	Abstract	Paper
Kirsch AH	Clearance	39		Neph Dial Trans (2017)
Zickler D	MCO Ci	48		PLOS One 2017
Belmouaz M	HDF to HDx	10		Clin Nephrology 2017
Teatini U	HDF vs HDx	8	ERA-EDTA; 2017	
Schepers E	(*In vitro)*		ERA/EDTA 2017	
Koball S		34	ASN 2017	
Cantaluppi	HF vs HDx	14	EDTA 2018	
Celik L	HF vs HDx	8	EDTA 2018	
Giuseppe G	HF to HDx	14	EDTA 2018	
Santivañez J	HDF vs HDx	8	EDTA 2018	

HDx/MCO Membrane Studies

Study	Key endpoints	Comparator	Study duration per subject	# Subjects
REMOVAL-HD PI: Hutchinson, ANZ multi-center [ACTRN12616000804482]	Changes in S-albumin and FLC levels over 6 months; Several exploratory measures	Standard of care high-flux HD	8 months	85
PI: Koball, Rostock, Germany [DRKS00011638]	Albumin-binding capacity	HDF	4 weeks	30
REMOC PI: Rosenkranz, Graz, Austria [DRKS00012359]	Change in FLCs and S-albumin, various MMs and cytokines, calcification propensity, patient-reported outcomes	HDF	6 months	30
PI: Bridoux, Poitiers, France [NCT03211676]	MMs and inflammatory markers, several secondary measures	HD	6 months	40
ModuVas PI: Zickler, Berlin, Germany [NCT03104166]	Vascular calcification in human cell culture model, PWV and T50 calcification propensity test	HD	7 months	48
PI: Cozzolino, Milan, Italy [NCT03169400]	Vascular calcification and oxidative stress in rat cell culture model	HD	6 months	20
PI: Juillard, Lyon, France [NCT03137056]	I: Proteome of depuration, inflammatory markers II: Effect on albumin isoforms	I:HD II: HD/HDF	I: 16 weeks II: 24 weeks	I: 20 II: 20
MCO-IF PI: Schmaderer, Munich Germany [NCT03270371]	Change in inflammatory score ; calcification biomarkers, calcification propensity	HD	8 months	50
PI: Caldin da Silva, Sao Paolo, Brazil [NCT03274518]	Medium molecule removal; intradialytic hemodynamics; fluid status	HDF	2½ months	16

Key Takeaways

HDx enabled by ***Theranova is***

1) The next step in dialyzer evolution

2) The new MCO membrane with larger pores and increased selectivity that provides in HD mode greater removal of large middle molecules than conventional high-flux membranes

3) A pure HD dialyzer!

Please keep in mind: ~~HDF~~