SU COSA BASIAMO OGGI LA SCELTA DELLA MEMBRANA DIALITICA?

Dr. Massimiliano Migliori

Versilia

Non temere, o uomo dagli occhi glauchi! Erompo dalla corteccia fragile io ninfa boschereccia Versilia, perché tu mi tocchi.

The quality of treatment is strongly dependent on the performance of the dialyzer

↓ natural polymers

↓ synthetic polymers

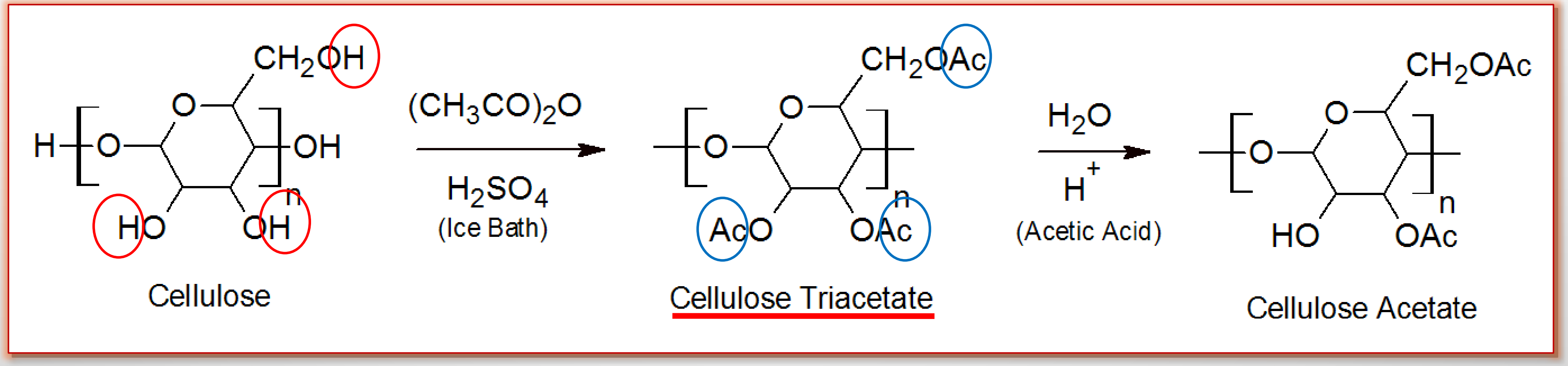
natural polymers

Cuprophan®: cellulose dissolved in cuprammonium solution

Another cuprammonium rayon membrane with nearly the same chemical and physical structures was developed in Japan

These membranes were also called **regenerated cellulosic (RC)** membrane since they were cast from cellulose or cotton fibers.

Chemical modifications were made for RC membranes mostly because of improving their biocompatibility by replacing their hydroxyl group(s) with acetate group(s).



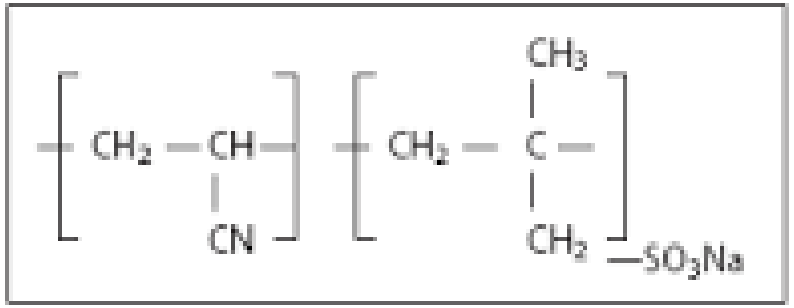
They are called cellulose acetate (CA), cellulose diacetate (CDA), and cellulose triacetate (CTA) in accordance with the number of introduction of acetate groups to the cellulose backbone

They have much higher solute and hydraulic permeabilities as well as better biocompatibility than original RC membranes

The first **synthetic polymeric** membrane was developed in **1969** by Rhône-Poulenc (France) and was named **AN-69®**, since the main material of the membrane was **acrylonitrile (AN**).

It was also the first dialyzer sterilized by the gamma-ray irradiation.

Fig. 1. Chemical formula for AN69 copolymer, consisting of acrylonitrile and sodium methallylsulfonate.

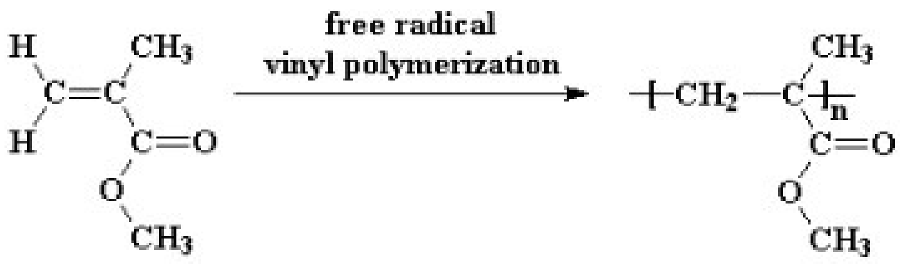


The first dialyzer with a synthetic polymeric hollow fiber membrane sterilized by gamma-ray was introduced by Toray Co. (Tokyo, Japan), in which **polymethylmethacrylate (PMMA)** was used as a main material of the membrane

Preparation:

Suspension polymerisation

Radical polymerisation



methyl methacrylate

poly(methyl methacrylate)

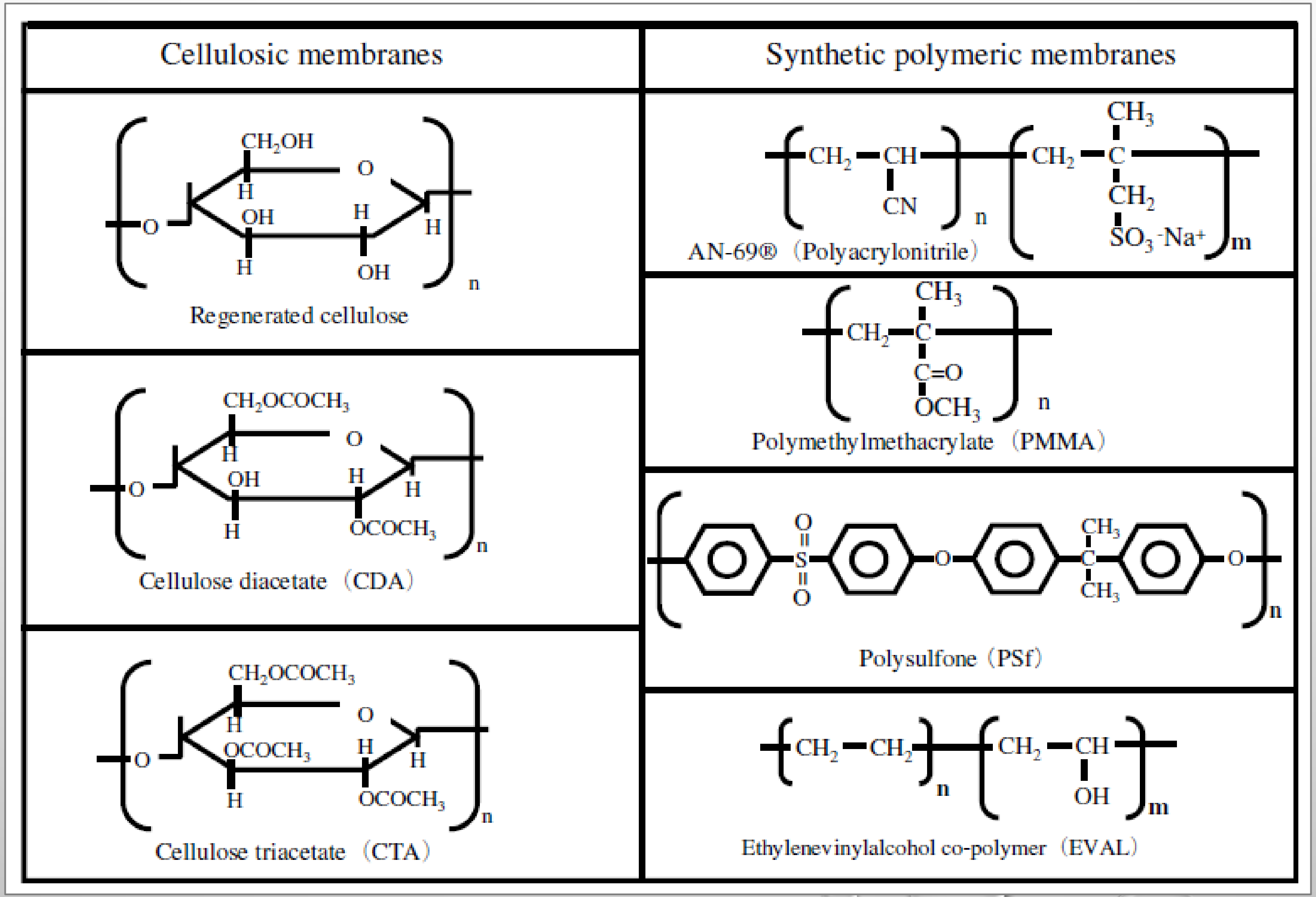
Synthetic Polymeric Membranes

Among them, **polysulfone** (PSF) and the like (including **polyethersulfone** (PES), **polyarylethersulfone** (PAES), etc.) have the highest market share over the world.

Since these membranes are made from petroleum, they are **hydrophobic** in nature.

Then most of these membranes include so-called **hydrophilic** agent that also plays a role of **pore-forming agent** when cast.

Chemical structures of cellulosic and synthetic polymeric membranes for blood purification



Hydrophilic agent

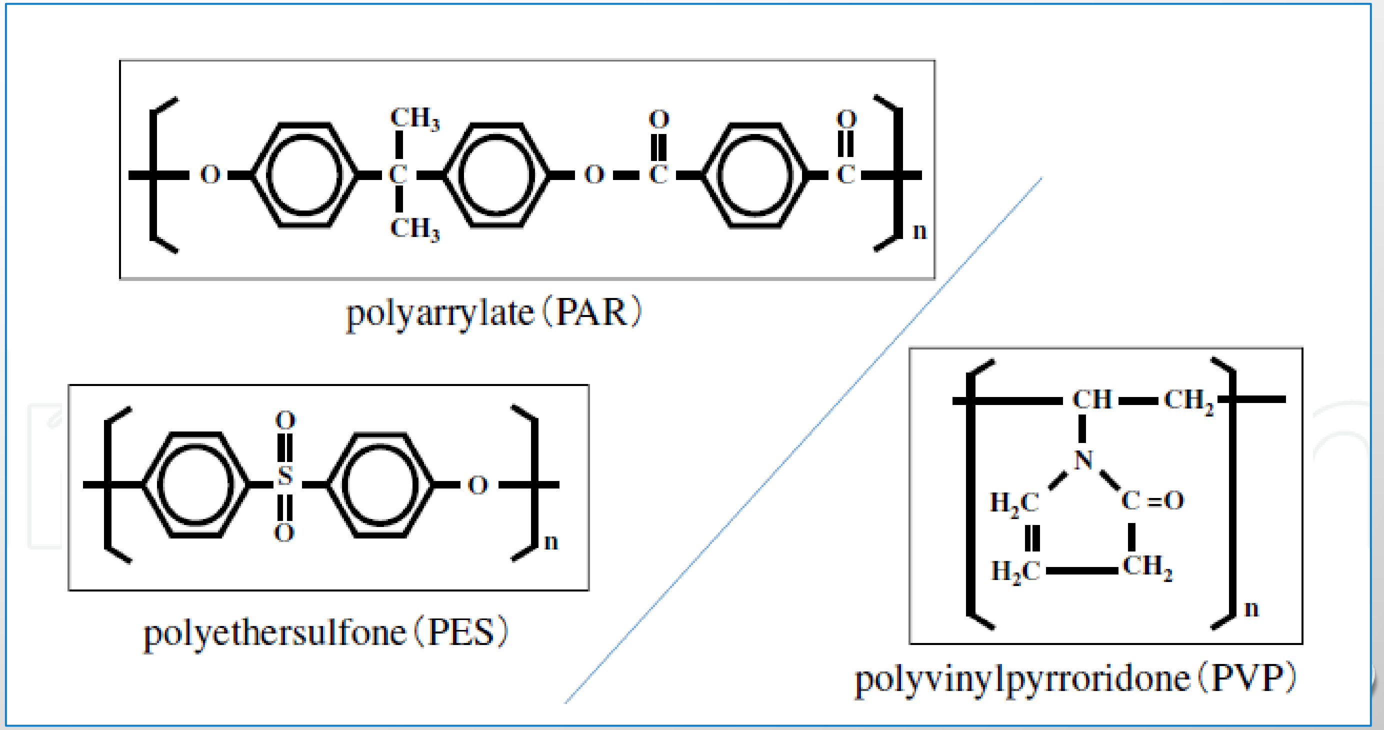
Cellulosic membranes are hydrophilic in nature, including original RC and its derivatives such as CA, CDA, and CTA in which hydroxyl group(s) are replaced by acetate group(s).

On the contrary, since **synthetic polymeric membranes** are originated from petroleum, generally speaking they are **hydrophobic in nature.** Blood coagulation usually occurs soon after blood interacts with hydrophobic materials.

Most synthetic polymeric membranes, therefore, include so-called **hydrophilic agent such as polyvinylpyrrolidone (PVP)** to make membrane hydrophilic. PVP is also known as a **poreforming agent**

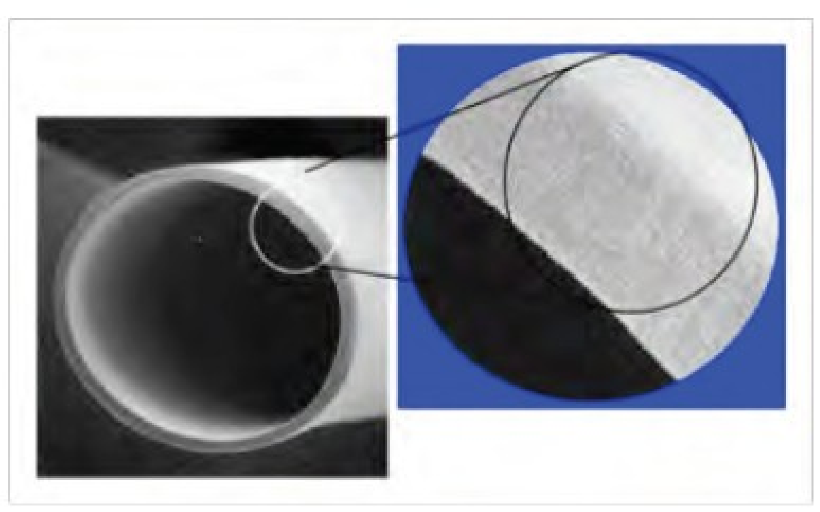
Chemical structures of polyester polymer alloy (PEPA) composed of PES and PAR with polyvinylpyrroridone (PVP).

Chemical structure of PVP together with two other polymers (polyarrylate and polyethersulfone).
PEPA is composed of these two polymers with or without PVP, the former shows strong adsorptive , while the latter has strong adsorptive characteristic to various proteins due to its hydrophobicity

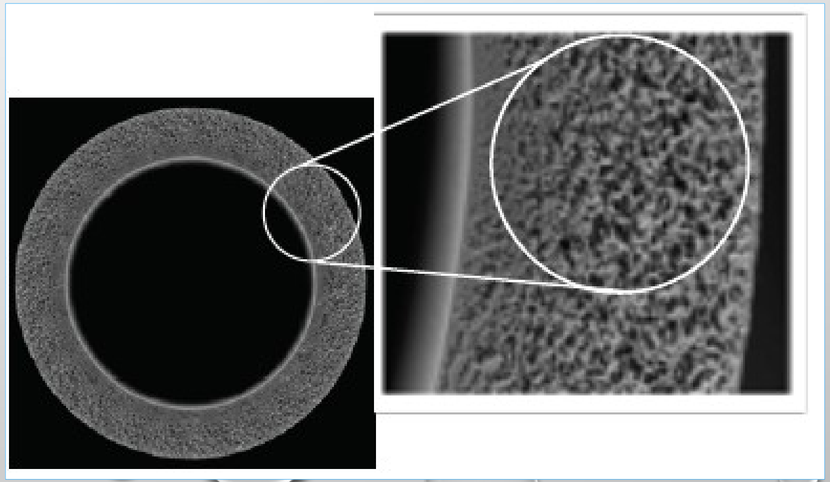


Homogeneous and Asymmetry Membrane

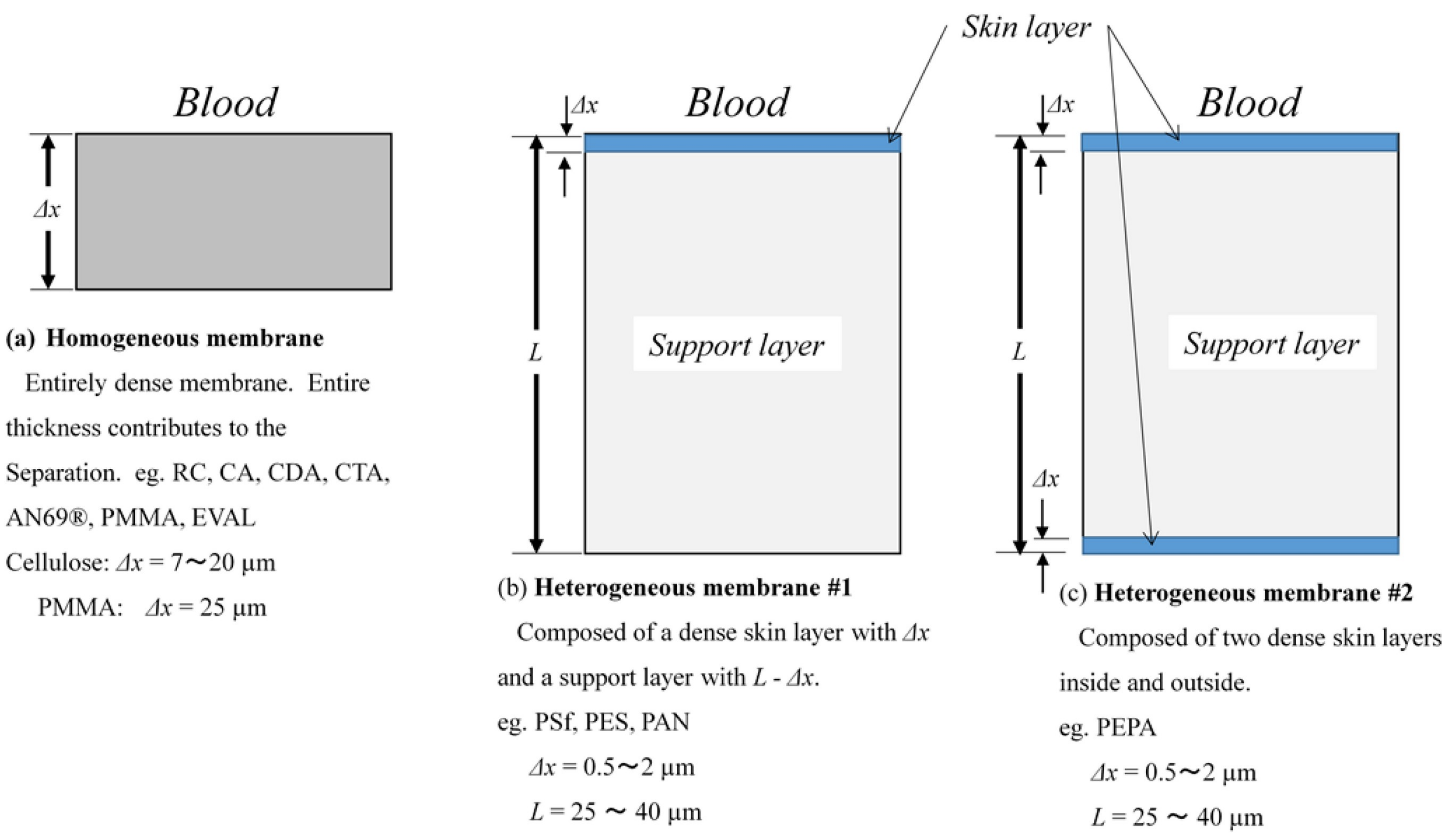
It is **entirely a dense membrane and the entire thickness contributes to the transport resistance for solutes and water.** Membranes of this kind are usually called "homogeneous." Besides EVAL, PMMA, and AN-69®, most cellulosic membranes are homogeneous.



A dense thin layer exists on the inner surface of the membrane, called "**skin layer**" from which the density is gradually decreasing in the radial direction. Since most part excluding the skin layer is known to have **little resistance for solute and water transport, it is called the "support layer".** The support layer, however, has an important role for the membrane to have **enough mechanical strength with little resistance for transport.** Membranes of this kind are called "**asymmetry**."



Cross-sectional views of dialysis membranes



Filters

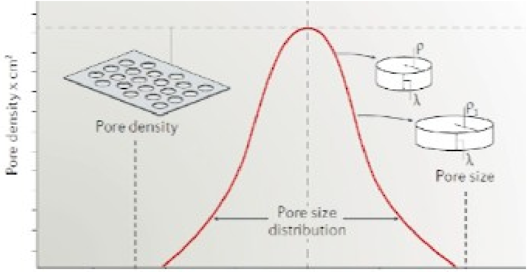
Efficiency and Flux

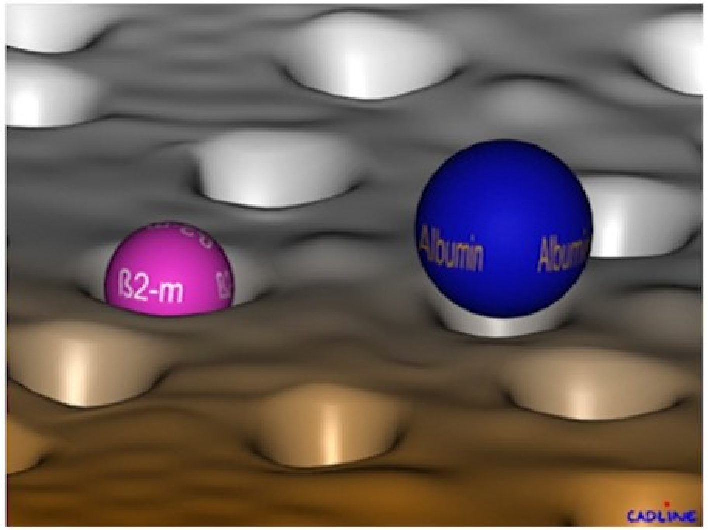
- Efficiency: ability to achieve large small solute clearance with high blood flows (all filters are high efficiency these days)
- Flux: ability to achieve high middle molecule clearance and ultrafiltration rate (determined by the average pore size)

Diffusion and Convection

- Diffusion: solutes move by diffusion between blocks of fluid separated by the membrane
- Convection: solutes move en mass with a block of fluid across the membrane (more effective for moving large molecules

CONVECTIVE TRANSPORT PROPERTIES
...ARE DEFINED BY THE SIEVING COEFFICIENT (SC) PROFILE

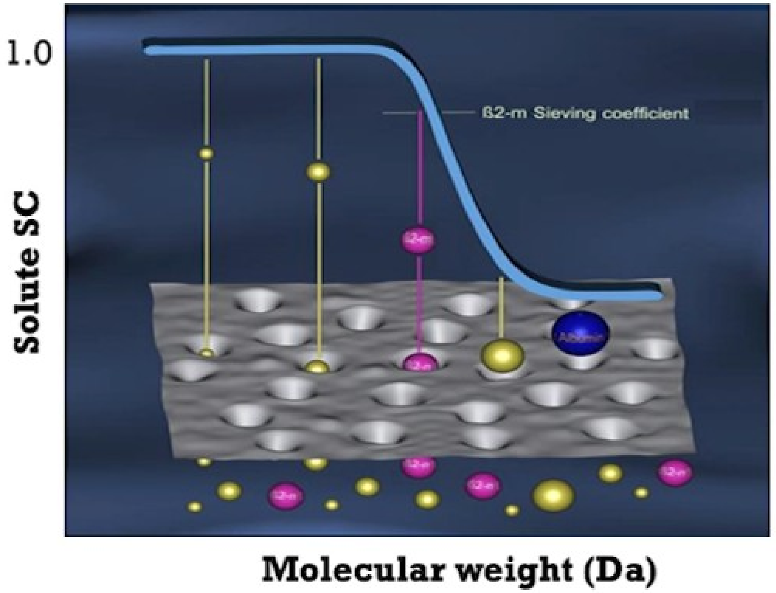




SC = the retention capacity of membrane for a certain solute size

SC = 1 → solute can pass
SC = 0 → complete retention
Cut-off at SC=0.1

Ronco C, Clark WR. Nat Rev Nephrol 2018; 14: 394-410

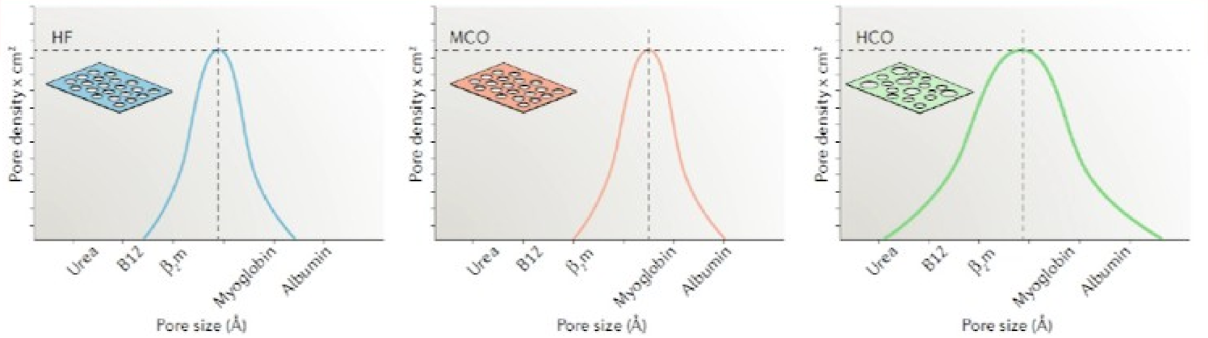


Sieving characteristics of a membrane are given by the sieving coefficient curve

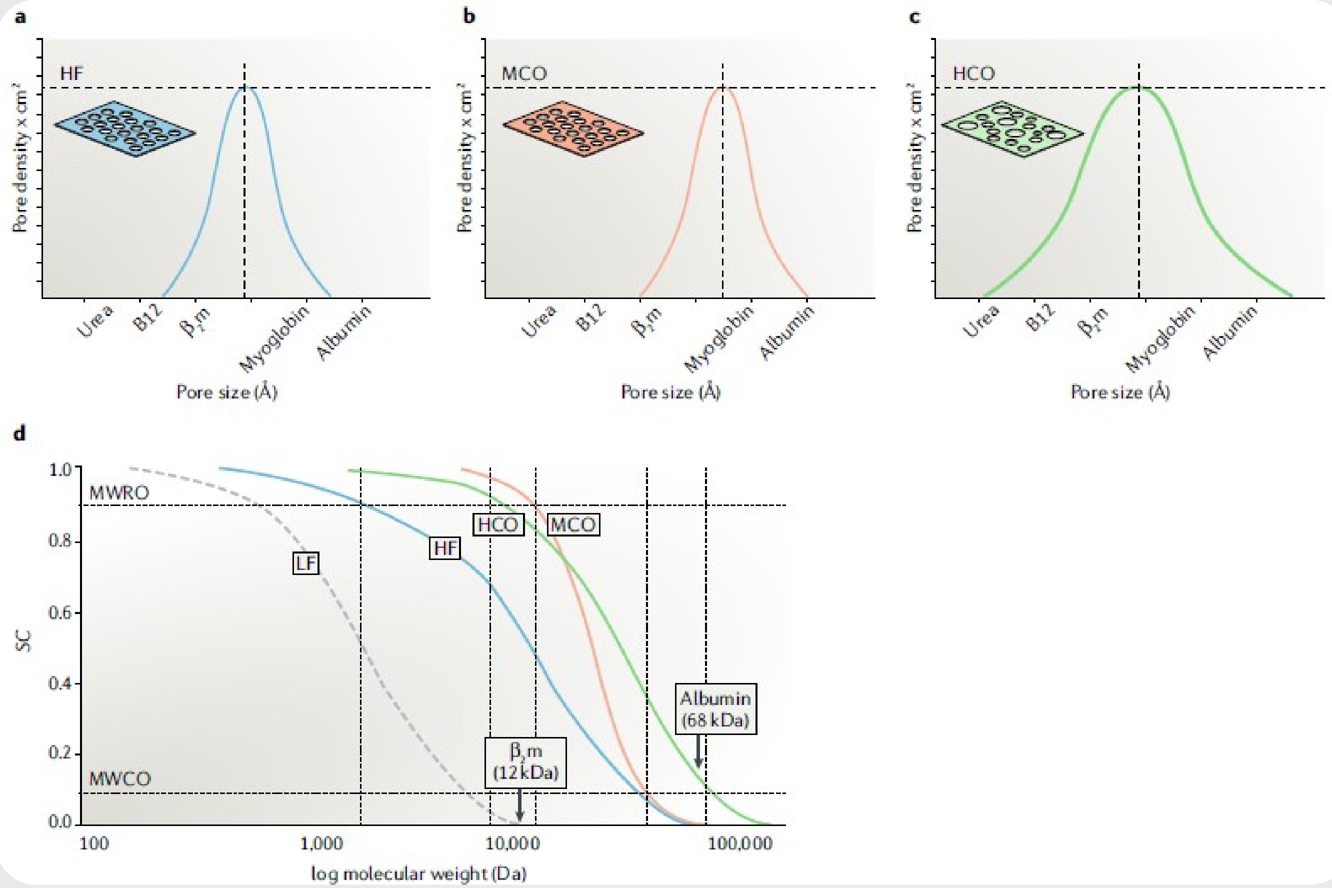
ß2-m is used as a membrane substance

GENERAL CLASSIFICATIONS AND TYPICAL PERFORMANCE OF DIALYSIS MEMBRANES

Dialyzer Type	Water Permeability K_{UF} (ml/h/mmHg´)	Sieving Coefficient for ß2-M	Sieving Coefficient for Albumin
Low-flux	< 10	-	< 0,01
High-flux	> 20	0,7 – 0,8	< 0,01
Protein leaking	5 – 50	0,9 – 1,0	0,02 – 0,03
High cut-off	110	1,0	0,2
Medium cut-off	60 - 85	1,0	0,08



Zweigart C et al. Int J Artif Organs 2017; 40: 328-334



PERFORMANCE CHARACTERISTICS OF HAEMODIALYSIS MEMBRANES DERIVED FROM A SUGGESTED NEW CLASSIFICATION SYSTEM.

HIGH PERFORMANCE MEMBRANES (HPM)

hollow fiber dialyzers with an advanced level of performance

The criteria to identifie HPM:

- excellent biocompatibility
- effective clearance of target solutes
- pore size larger than conventional hemodialysis (HD) membranes

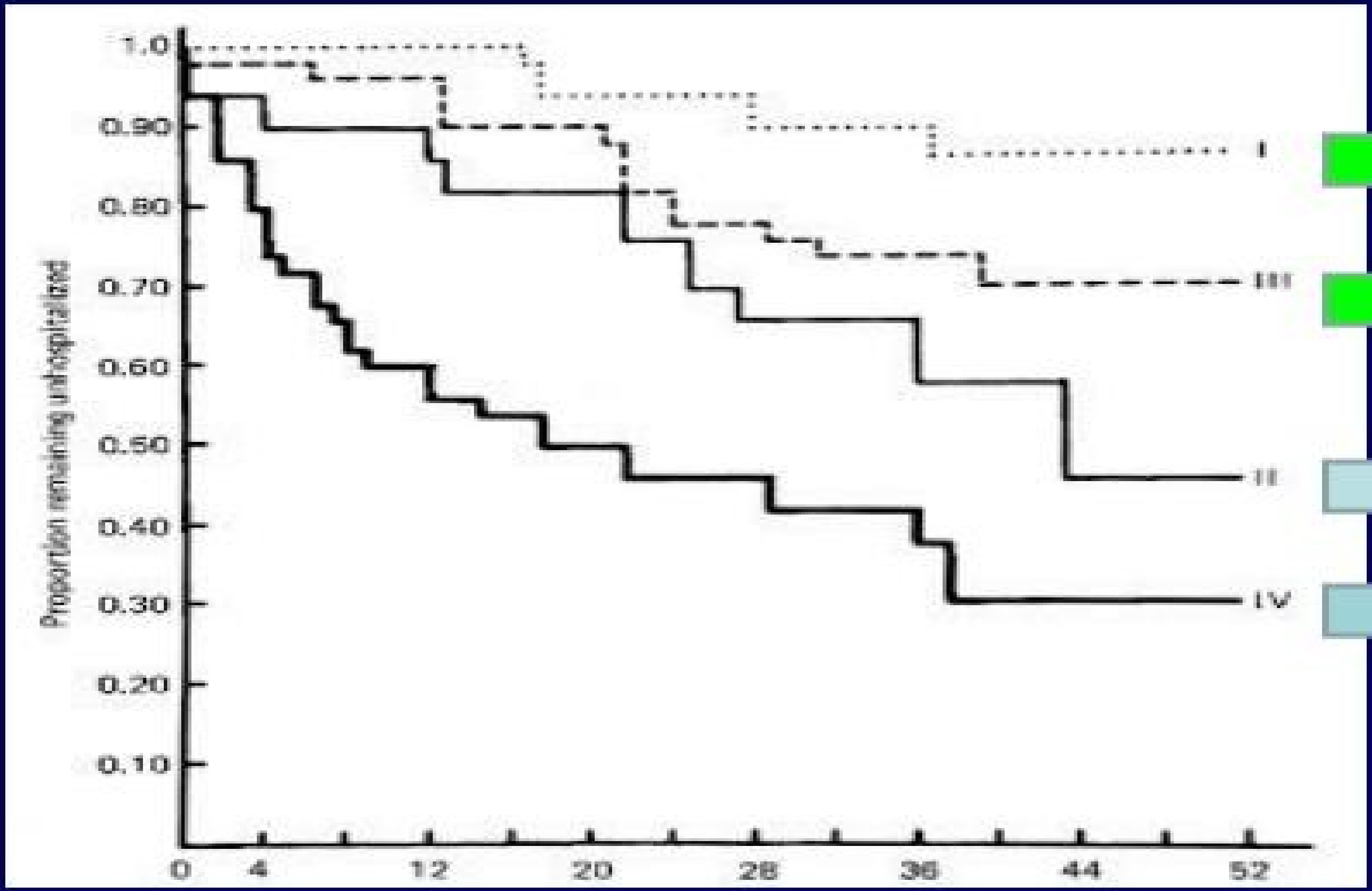
Promoting the removal of protein-bound uremic toxins, and middle to large molecular-weight solutes, including β2-microglobulin (β2-M).

EXAMPLES OF HIGH PERFORMANCE DIALYZERS [6]

MATERIAL	ABBREVIATION	MANUFACTURER	MEMBRANE TYPE
Cellulose triacetate	CTA	Nipro	hollow fiber
Polysulfone	PSf	Asahi Kasei Kuraray Medical Fresenius Toray	hollow fiber hollow fiber hollow fiber
Polyethersulfone	PES	Nipro Membrana	hollow fiber hollow fiber
Polymethylmethacrylate	PMMA	Toray	hollow fiber
Polyester polymer alloy	PEPA	Nikkiso	hollow fiber
Ethylene vinyl alcohol copolymer	EVAL	Asahi Kasei Kuraray Medical	hollow fiber
Polyacrylonitrile	PAN	Gambro	hollow fiber laminated

First Randomised Controlled Trial In Dialysis

Predialysis urea 38 vs 26 mmol. Dialysis 2.5-35h vs 4.5-5 h



high kt/v and long dialysis

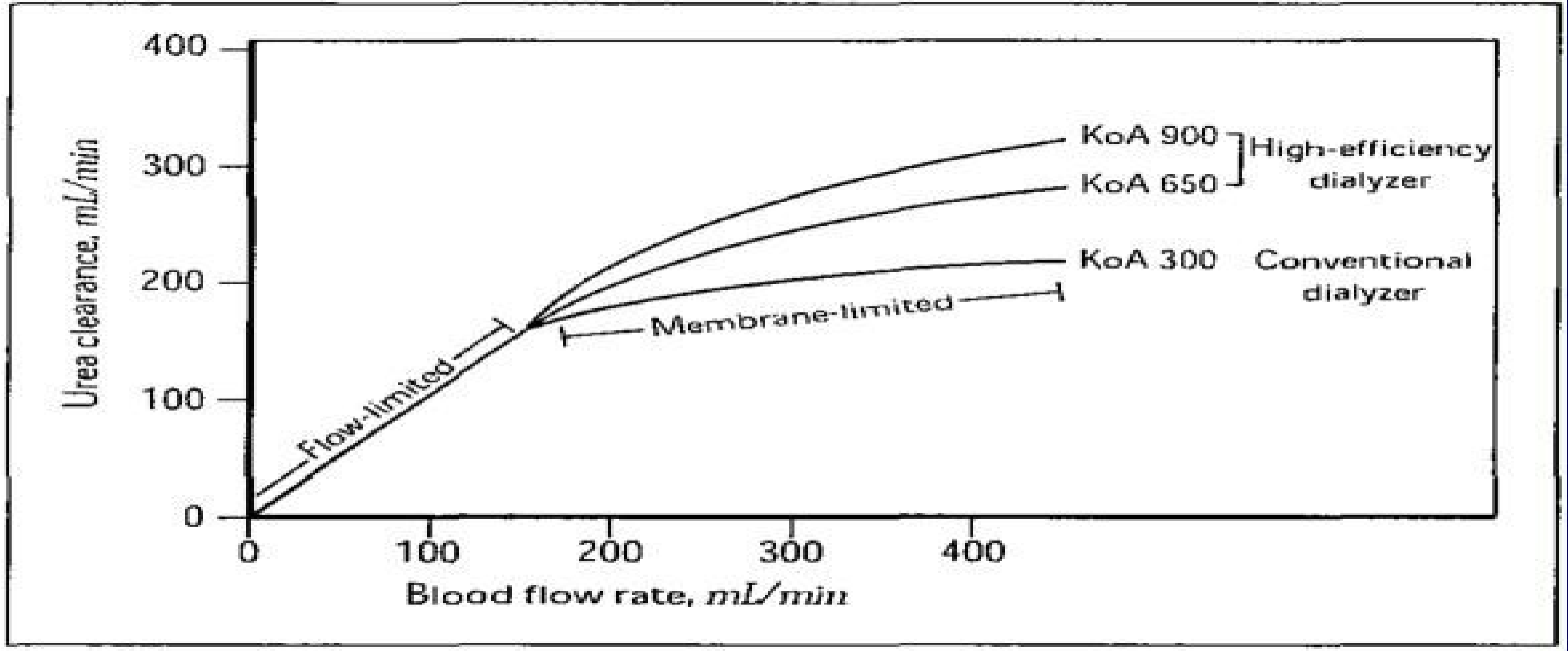
high kt/v and short dialysis

low kt/v and long dialysis

low kt/v and short dialysis

NCDS 1980

Blood flow and Clearance



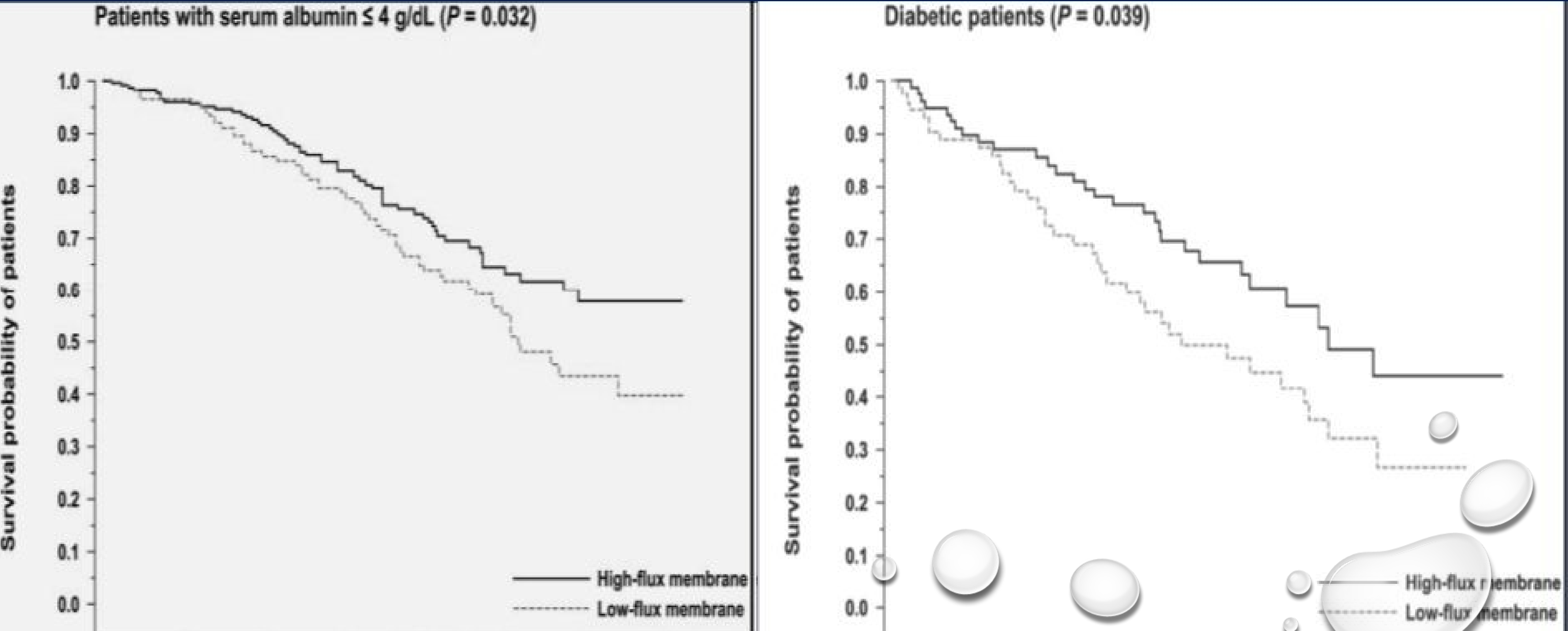
Dialyzer mass transfer-area coefficient (KoA) for area

HEMO study: Subgroup analysis

- In high-flux there is significant reduction in RR of death (20%) from cardiac causes and combined outcome of first hospitalization or death from cardiac cause
- Longer dialysis duration
  - High-flux dialysis for > 3.7 year has 32% lower risk of death when compared with low-flux

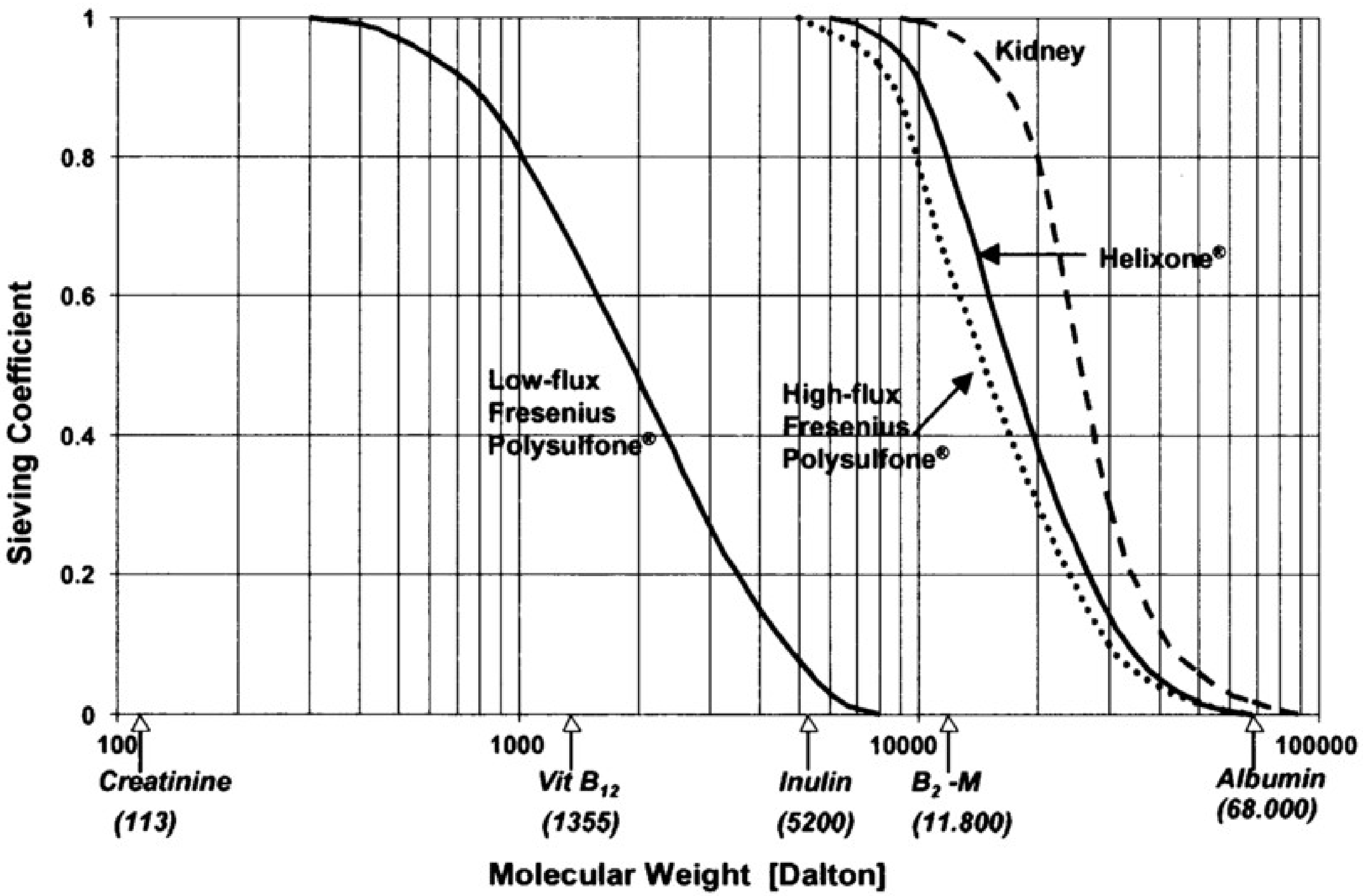
MPO study: Results

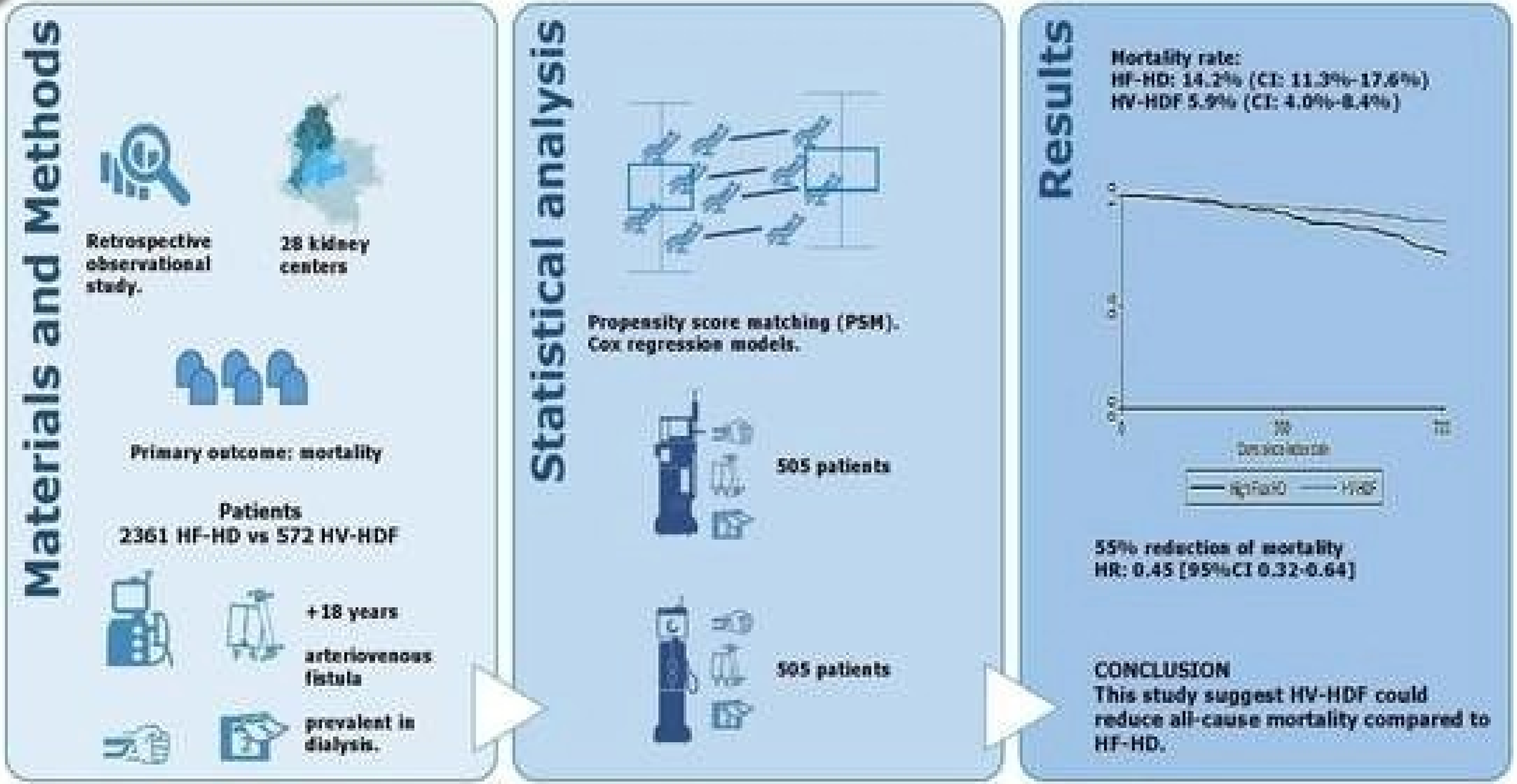
***Locatelli, F. et al. J Am Soc Nephrol* 2009;20:645-654**



Randomized Clinical Trials

FRENCHIE	CONTRAST	TURKISH	ESHOL
420 patients	714 patients	780 patients	906 patients
Age 76 ± 6 years	Age 64 ± 13 years	Age 56 ± 14 years	Age 65 ± 14 years
KIDNEY INT 2017	JASN 2012	NDT 2013	JASN 2013
ON LINE HDF	ON LINE HDF	ON LINE HDF	ON LINE HDF
VS.	VS.	VS.	VS.
HIGH FLUX HD	LOW FLUX HD	LOW FLUX HD	HIGH FLUX HD
Intradialytic tolerance and Survival	Survival	Survival and Cardiovascular events	Survival
Follow-up 2 years	Follow-up 3 years	Follow-up 2 years	Follow-up 2 years


Sieving Coefficient
1
0.8
0.6
0.4
0.2
0
100
1000
10000
100000
Kidney
Helixone®
Low-flux
Fresenius
Polysulfone®
High-flux
Fresenius
Polysulfone®
Creatinine
(113)
Vit B_{12}
(1355)
Inulin
(5200)
B_2 -M
(11.800)
Albumin
(68.000)
Molecular Weight [Dalton]



Kidney Dial. 2022, 2(2), 209-220

See Nefrologia 2014;34(4):520-5 and Nefrologia 2014;34(6):807-8

Hypersensitivity reactions to synthetic haemodialysis membranes — an emerging issue?

M. Antonia Álvarez-de Lara, Alejandro Martín-Malo

Servicio de Nefrología. Hospital Universitario Reina Sofía. Córdoba (Spain)

Nefrologia 2014;34(6):698-702

Prevalence of a severe reaction:

- 0.25% in the total population on dialysis
- 0.5% in patients treated with synthetic membranes
- 1.1% in patients with AN69
- 4.9% in patients treated with AN69 membranes and ACE inhibitors

Asymmetric Cellulose Triacetate Membrane

A new generation of dialysers with asymmetric CTA membranes have been designed with an increase in hydraulic permeability

Properties:

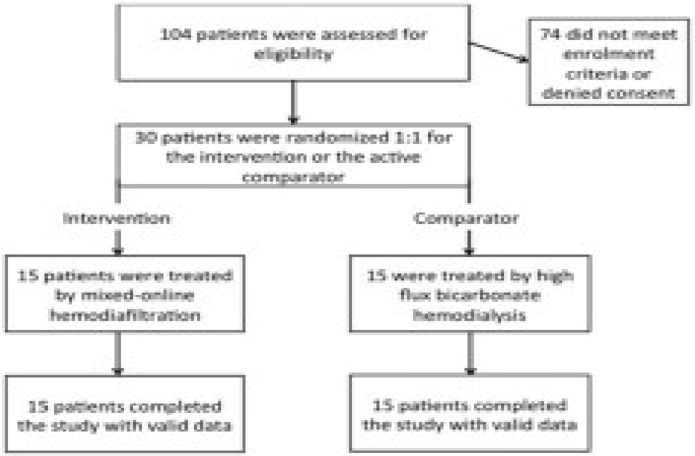
- **Lower risk of hypersensitivity**
- **A lower platelet count decrease**
- **High permeability and filtration performance.**

The ATA membrane dialyzer is a safe polyvinylpyrrolidone-and BPA-free product.

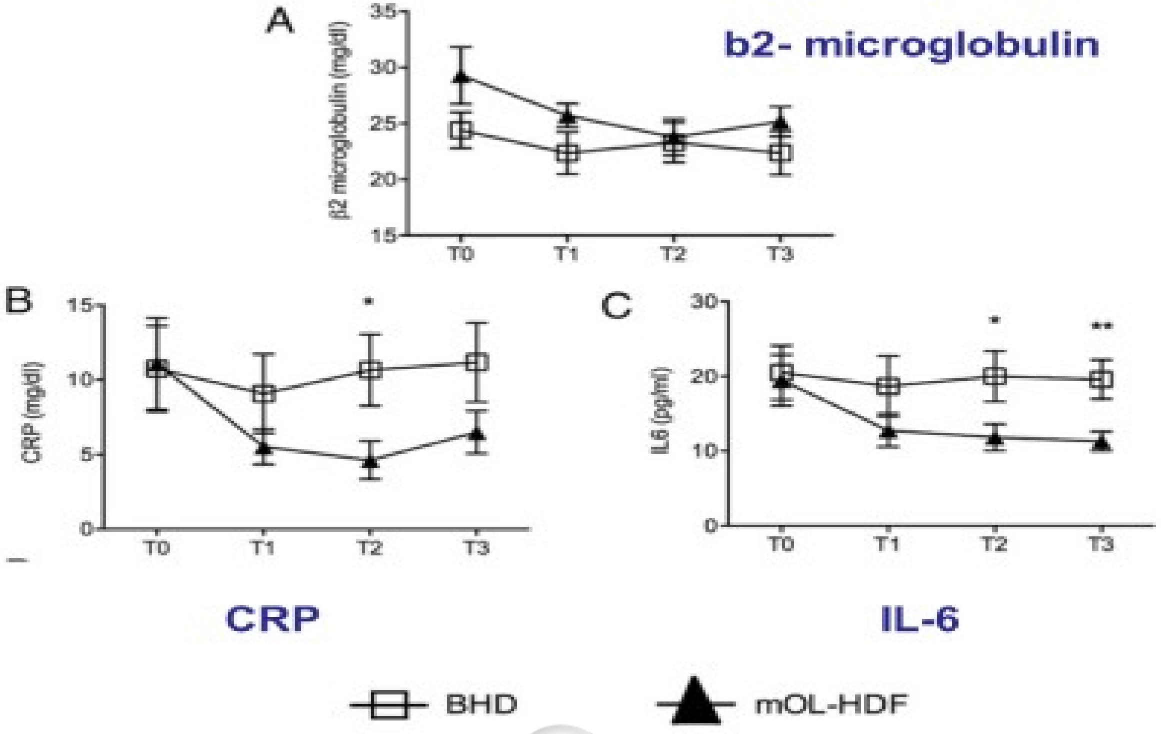
Online Hemodiafiltration Inhibits Inflammation-Related Endothelial Dysfunction and Vascular Calcification of Uremic Patients Modulating miR-223 Expression in Plasma Extracellular Vesicles

The Journal of Immunology

Claudia Cavallari,[*,‡] Sergio Dellepiane,[†,‡] Valentina Fonsato,[*] Davide Medica,[†] Marita Marengo,[‡] Massimiliano Migliori,[§] Alessandro D. Quercia,[¶,‡] Adriana Pitino,[*] Marco Formica,[‡] Vincenzo Panichi,[§] Stefano Maffei,[†] Luigi Biancone,[†] Emanuele Gatti,[#] Ciro Tetta,[**] Giovanni Camussi,[†] and Vincenzo Cantaluppi[¶,‡]



Study flowchart



Online Hemodiafiltration Inhibits Inflammation-Related Endothelial Dysfunction and Vascular Calcification of Uremic Patients Modulating miR-223 Expression in Plasma Extracellular Vesicles

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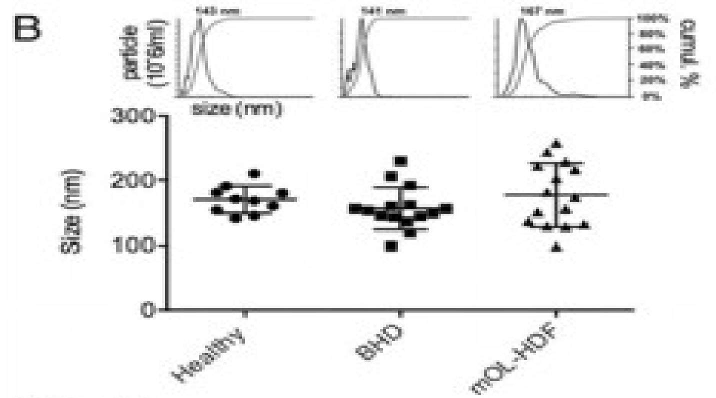
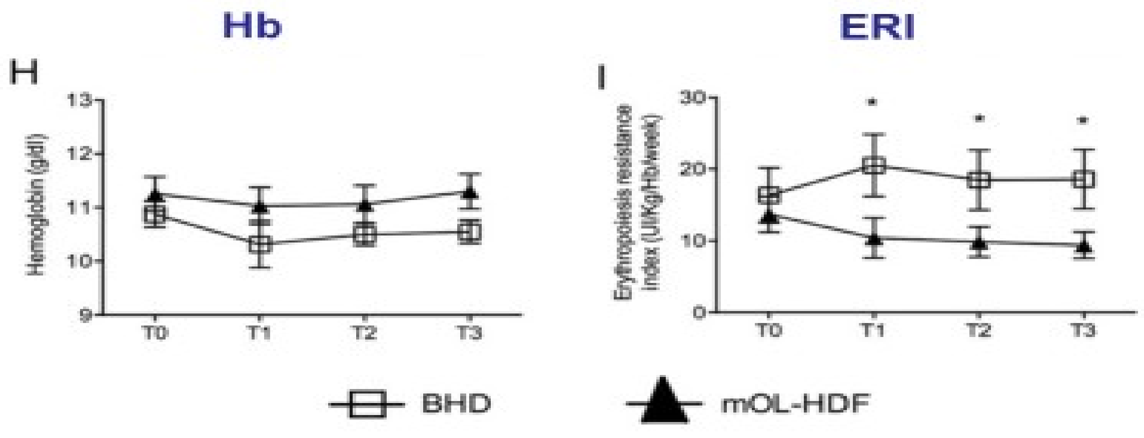
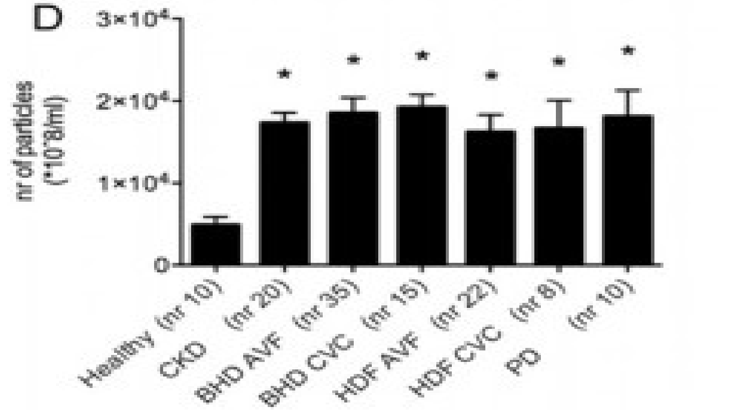
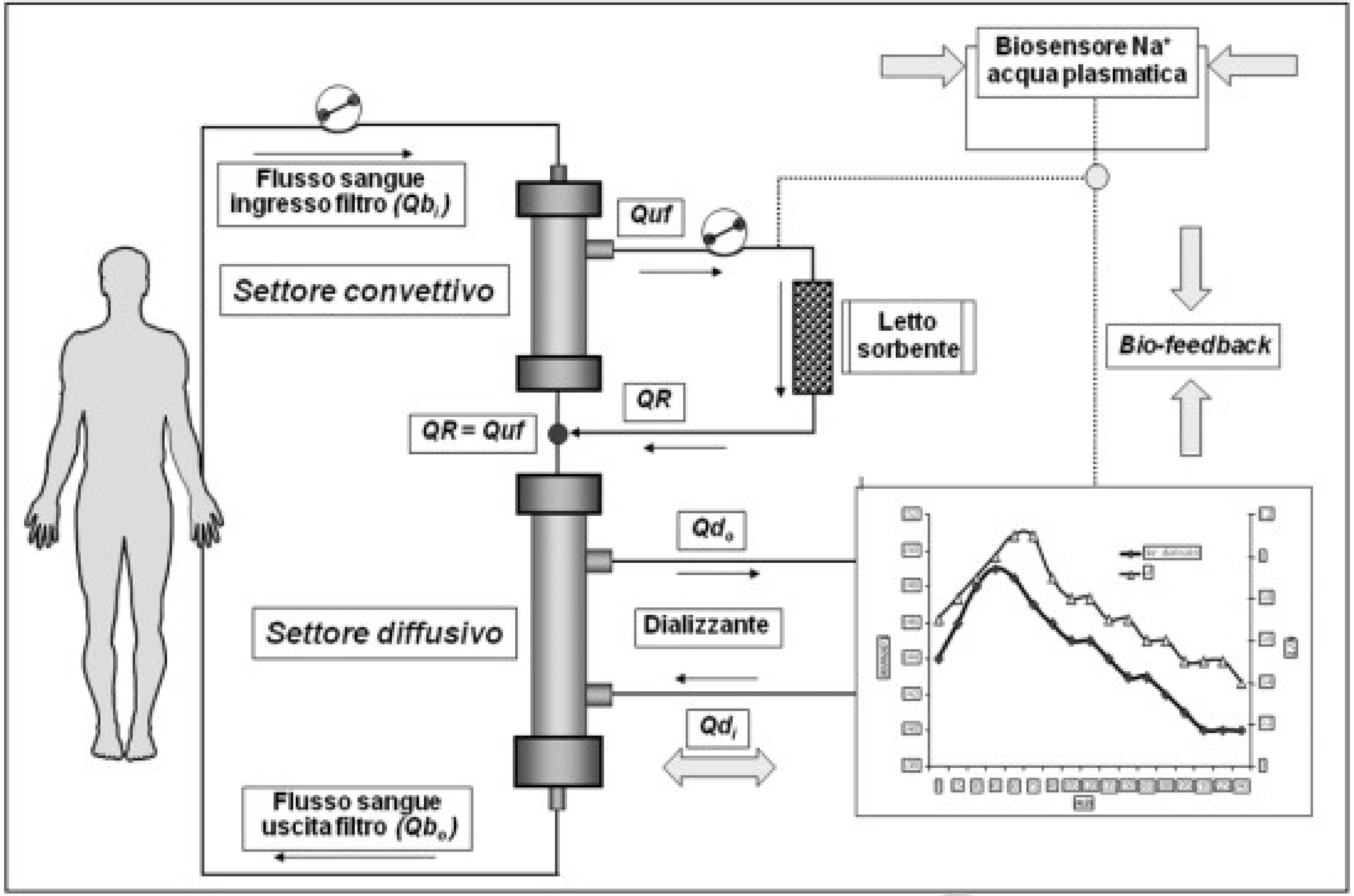
The Journal of Immunology

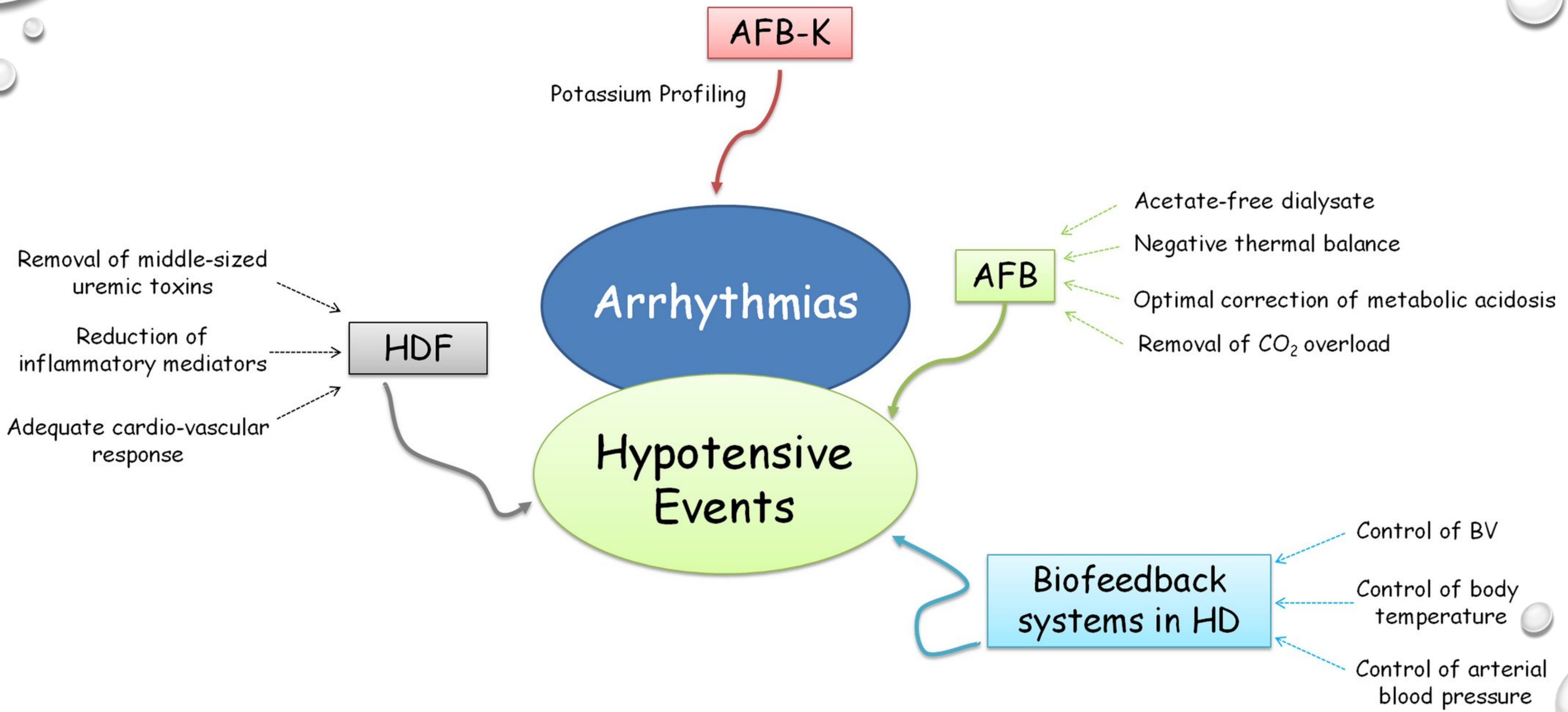






HFR Aequilibrium




AFB-K
Potassium Profiling
Arrhythmias
Hypotensive Events
Removal of middle-sized uremic toxins
Reduction of inflammatory mediators
Adequate cardio-vascular response
HDF
AFB
Acetate-free dialysate
Negative thermal balance
Optimal correction of metabolic acidosis
Removal of CO_2 overload
Biofeedback systems in HD
Control of BV
Control of body temperature
Control of arterial blood pressure

ERI

In-Depth Review

Blood Purification

Blood Purif 2017;43:101–122
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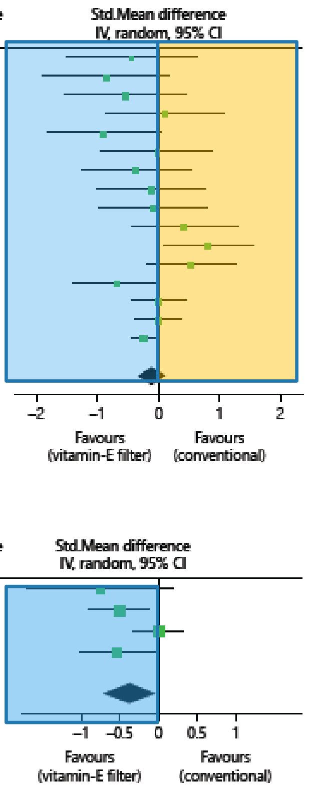
Published online: December 14, 2016

Effects of Vitamin E-Coated versus Conventional Membranes in Chronic Hemodialysis Patients: A Systematic Review and Meta-Analysis

Graziella D'Arrigo[a] Rossella Baggetta[a] Giovanni Tripepi[a] Francesco Galli[b] Davide Bolignano[a]

[a]CNR – Institute of Clinical Physiology, Reggio Calabria, and [b]Nutrition and Clinical Biochemistry Laboratory, Department of Pharmaceutical Sciences, University of Perugia, Perugia, Italy



EPO dose

Study or subgroup	Vitamin-E filter Mean	SD	Total	Conventional filter Mean	SD	Total	Weight	Std.Mean difference IV, random, 95% CI
Aoun, 2010	0.38	0.19	7	0.5	0.3	7	3.2%	−0.45 [−1.51, 0.62]
Baragetti, 2006	3,750	629.1	8	4,250	453.1	8	3.3%	−0.86 [−1.90, 0.18]
Mandolfo, 2012	101	57	8	135	59	8	3.5%	−0.55 [−1.56, 0.45]
Satoh, 2001	111.7	66.3	8	104.4	61.3	8	3.6%	0.11 [−0.87, 1.09]
Huraib, 2000	4,630	2,620	10	7,850	4,069	10	4.0%	−0.90 [−1.83, 0.03]
Takouli, 2010	133.8	93.8	9	136.3	84.8	9	4.0%	−0.03 [−0.95, 0.90]
Huraib, 2000	4,690	1,922	10	5,740	3,341	10	4.3%	−0.37 [−1.25, 0.52]
Satoh, 2001	71.4	31.3	10	75.9	43.3	10	4.4%	−0.11 [−0.99, 0.76]
Triolo, 2003	95.1	26.3	10	97.4	28.3	10	4.4%	−0.08 [−0.96, 0.80]
Westhuyzen, 2003	8,250	3,175.4	11	7,000	2,309.4	11	4.6%	0.43 [−0.41, 1.28]
Clermont, 2001	88	22	16	72	15	16	5.9%	0.83 [0.10, 1.55]
Morimoto, 2005	6,563	2,459	16	5,143	2,596	15	6.0%	0.55 [−0.17, 1.27]
Kobayashi, 2003	4,235	3,103	17	6,118	2,190	17	6.3%	−0.68 [−1.38, 0.01]
Usberti, 2002	104	65	38	104	65	38	10.9%	0.00 [−0.45, 0.45]
Panichi, 2011	6,983	5,679	54	6,983	5,679	54	13.0%	0.00 [−0.38, 0.38]
Cruz, 2008	6,390	5,679	172	7,762	5,865	172	18.6%	−0.24 [−0.45, 0.03]
Total (95% CI)			404			403	100.0%	−0.11 [−0.31, 0.10]

Heterogeneity: Tau² = 0.05; Chi² = 22.15, d.f. = 15 (p = 0.10); I² = 32%
Test for overall effect: Z = 1.01 (p = 0.31)

a

ERI

Study or subgroup	Vitamin-E filter Mean	SD	Total	Conventional filter Mean	SD	Total	Weight	Std.Mean difference IV, random, 95% CI
Andrulli, 2010	5.3	1.78	9	7	2.4	10	10.1%	−0.76 [−1.70, 0.18]
Panichi, 2011	9.3	1.7	54	10.2	1.8	54	30.6%	−0.51 [−0.89, −0.13]
Sanaka, 2013	1.2	1.2	74	1.2	1.1	67	34.1%	0.00 [−0.33, 0.33]
Sanaka, 2013	1	0.7	40	1.4	0.8	32	25.2%	−0.53 [−1.00, −0.06]
Total (95% CI)			177			163	100.0%	−0.37 [−0.70, −0.03]

Heterogeneity: Tau² = 0.06; Chi² = 6.15, d.f. = 3 (p = 0.10); I² = 51%
Test for overall effect: Z = 2.16 (p = 0.03)

b

Fig. 4. a, b Effects of ViE-m vs. conventional membrane on EPO dosage.

THIS META-ANALYSIS CONFIRM positive EFFECT OF VITABRANE ON ERI (EPO resistance index) SUPPORTED BY OX STRESS AND INFLAMMATION DATA

ERI CUT-OFF =
8 (IU / wk / kg / g / dL Hb)

EVODIAL

MEMBRANA – HEPRAN, AN96 ST

COPOLIMERO DI ACRILONITRILE E SODIO METIL SULFONATO - POLIETILENEIMINA - EPARINA

Dialyzer Performance During HD Without Systemic Anticoagulation Using a Heparin-Grafted Dialyzer and Citrate-Enriched Dialysate

Setting & Participants

Randomized, crossover, noninferiority study

EVOCIT ARM
Heparin-grafted dialyzer citrate-enriched dialysate NO heparin
4 weeks 3×/wk HD — **13**
4 weeks 3×/wk HD — **13**
307 sessions

EVOHEP ARM
Heparin-grafted dialyzer bicarbonate dialysate unfractionated heparin
13 — 4 weeks 3×/wk HD
13 — 4 weeks 3×/wk HD
310 sessions

Results

	EVOCIT	EVOHEP
Kt/V_{urea}	1.47 ± 0.05	1.5 ± 0.05
	10% noninferiority margin: –0.15 △(95% CI): –0.03 (–0.06 to –0.007)	
Online Kt (L)	47.1 ± 0.6	48.0 ± 0.5
No. of shortened treatments	13/307	0/310
Treatment time (min)	236 ± 5	238 ± 1
Thrombin-antithrombin complex (µg/L)	35 (25-45)	11 (5-20)
Dialyzer blood compartment volume (mL)	77 ± 12	88 ± 8

CONCLUSION: EvoCit is noninferior to EvoHep for solute clearance but results in more shortened treatments, membrane clotting, and thrombin generation.

Karlien François, Dieter De Clerck, Annelies Tonnelier , et al (2021)
@AJKDonline | DOI: 10.1053/j.ajkd.2020.04.004
AJKD AMERICAN JOURNAL OF KIDNEY DISEASES

Nephrol Dial Transplant (2019) 1–10
doi: 10.1093/ndt/gfz005

Global prevalent use, trends and practices in haemodiafiltration

Bernard Canaud[1,2], Katrin Köhler[1], Jan-Michael Sichart[3] and Stefan Möller[3]

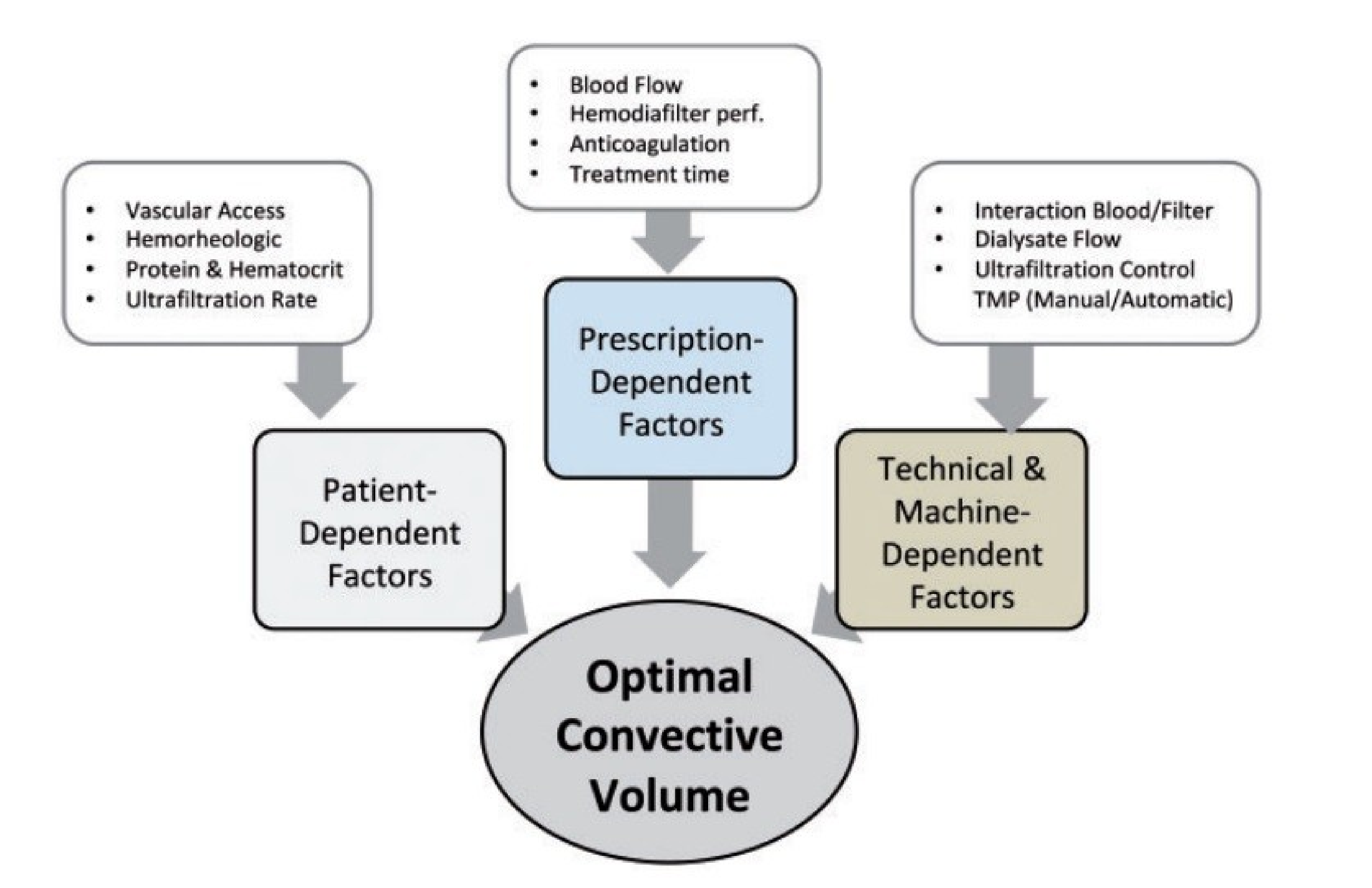
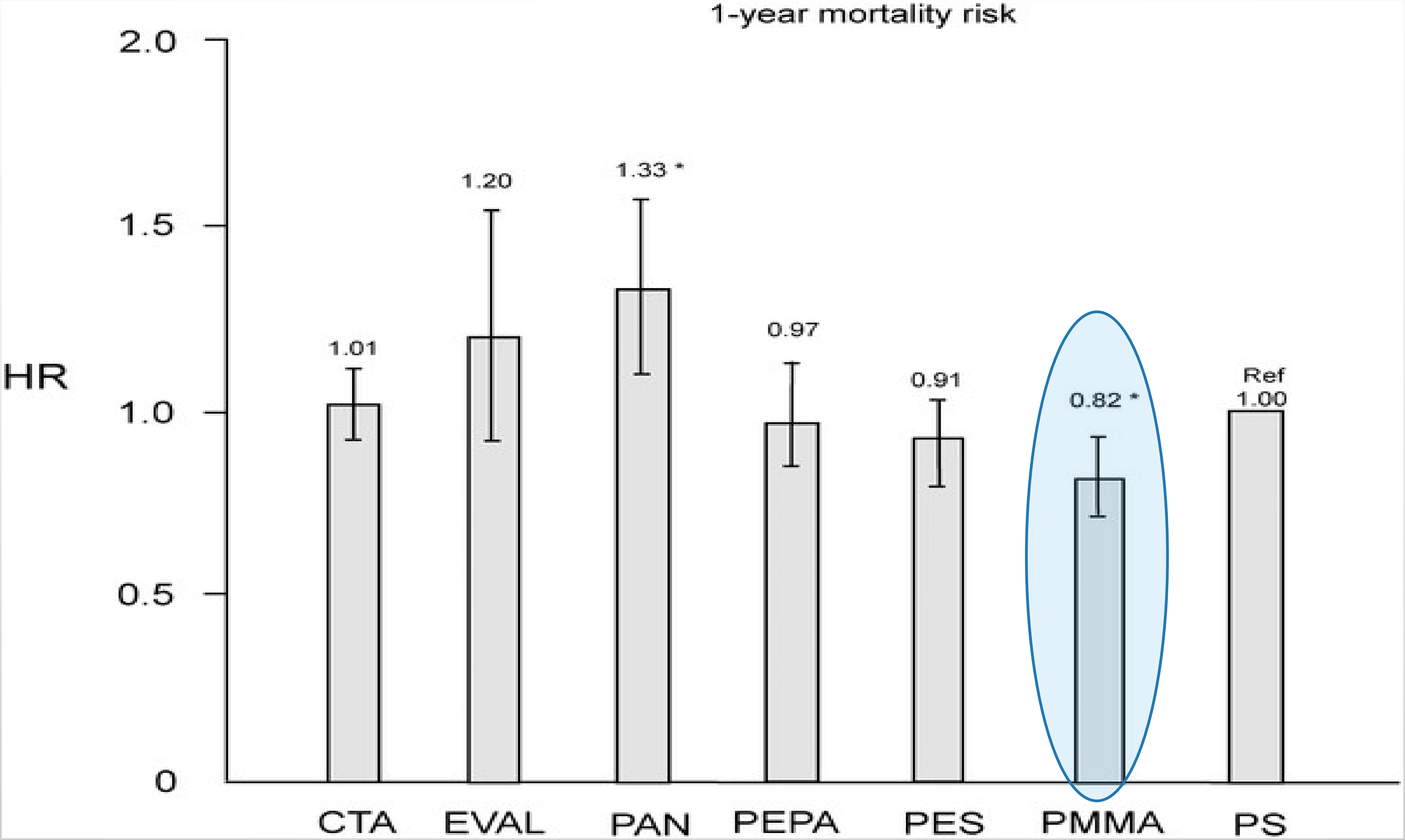


FIG 3. HRS OF ALL-CAUSE MORTALITY AFTER PROPENSITY SCORE MATCHING FOR SIX TYPES OF DIALYZER GROUPS COMPARED TO THE PS GROUP USING COX PROPORTIONAL HAZARDS REGRESSION.



Abe M, Hamano T, Wada A, Nakai S, Masakane I, et al. (2017) Effect of dialyzer membrane materials on survival in chronic hemodialysis patients: Results from the annual survey of the Japanese Nationwide Dialysis Registry. PLOS ONE 12(9): e0184424. https://doi.org/10.1371/journal.pone.0184424
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Approccio qualitativo alla depurazione delle medie molecole: il ruolo di metodiche e di membrane dialitiche