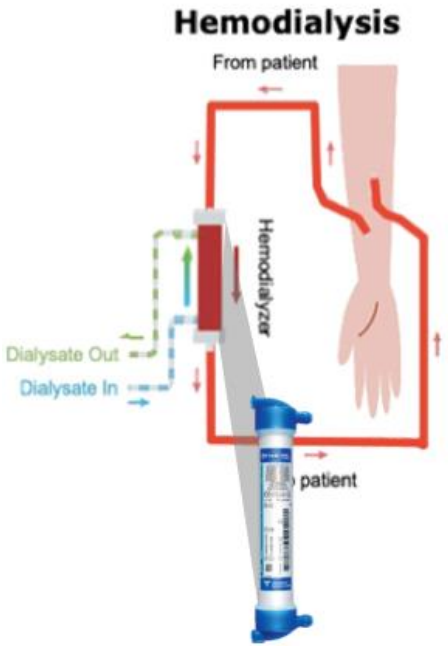


How Can Membrane Innovation Improve Outcomes?

Prof. Bernard Canaud

Montpellier University, School of Medicine, Montpellier-F

& Senior Medical Scientist, Global Medical Office FMC, Bad Homburg-G

FRESENIUS MEDICAL CARE

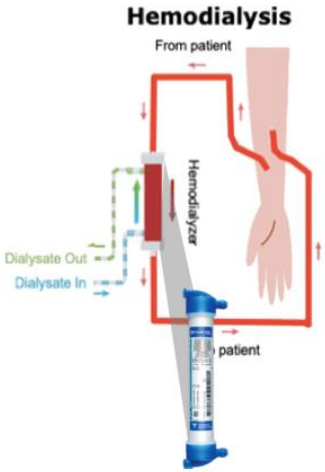
HYBRID CONGRESS ESNT 2022 www.esntcongress.org

40 CONGRESS OF THE EGYPTIAN SOCIETY OF NEPHROLOGY & TRANSPLANTATION

15-18 2022 FEBRUARY INTERCONTINENTAL CAIRO CITY STARS HOTEL,EGYPT

Scientific Industry Symposium

Outline



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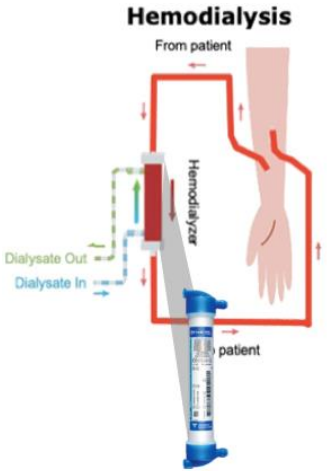
3 What are the Objectives of an Innovative Membrane and Dialyzer?

4 What Are the Clinical Facts and Evidences?

5 What is the Take Home Message?

Outline



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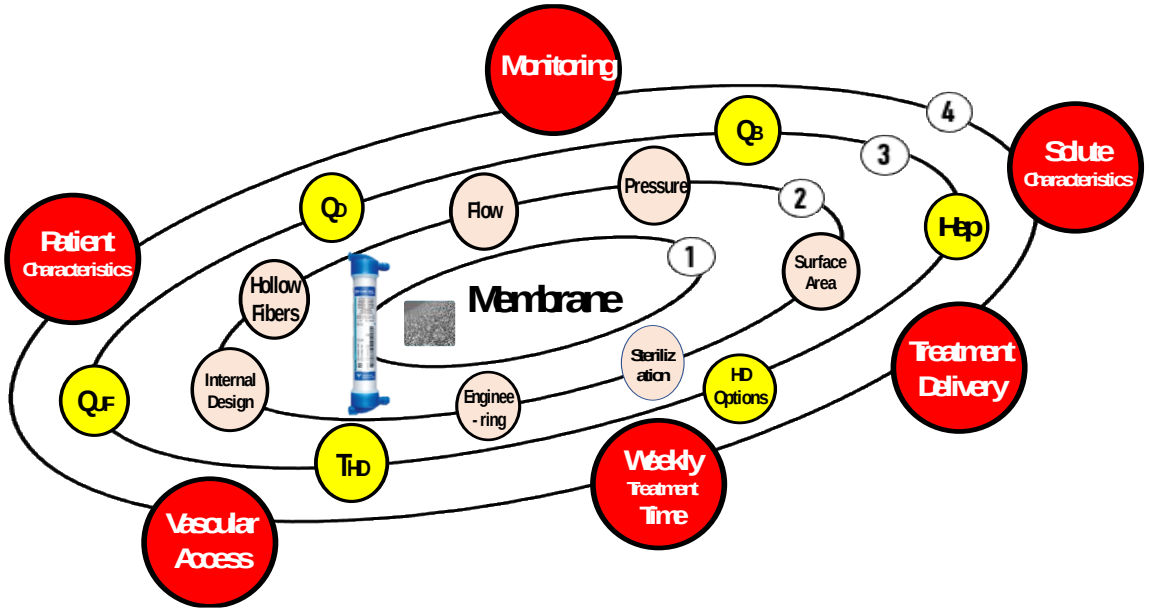
Membrane and Hemodialyzer are Stars in a Constellation

System – Dialyzer Performances Result from Multiple Factors



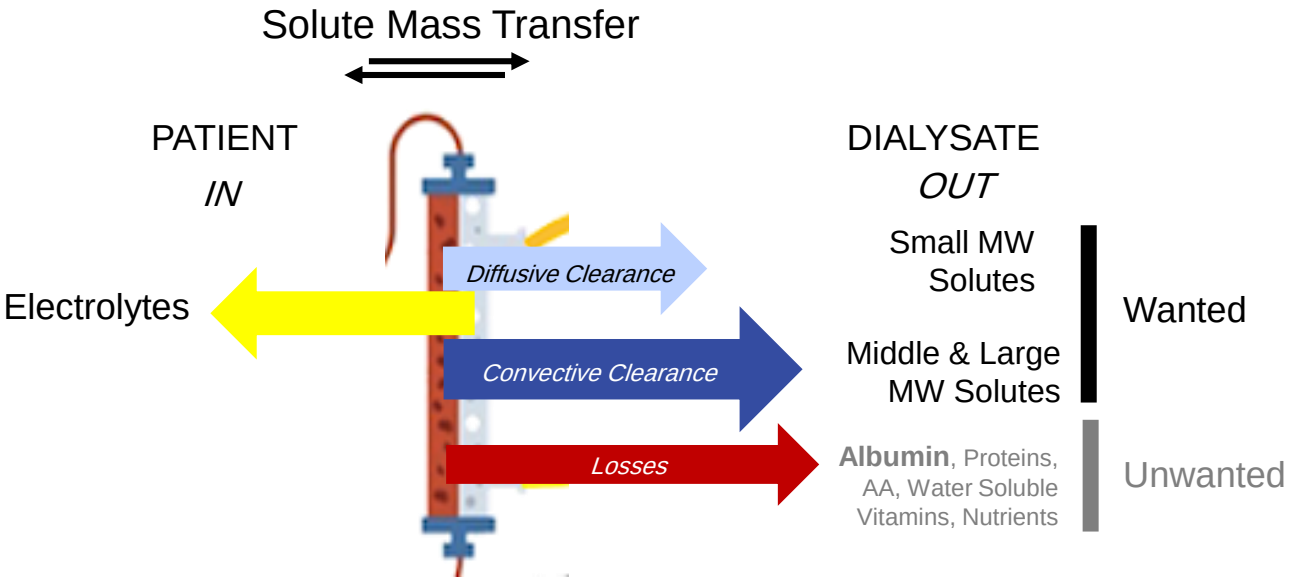
1 Membrane

2 Hemodialyzer

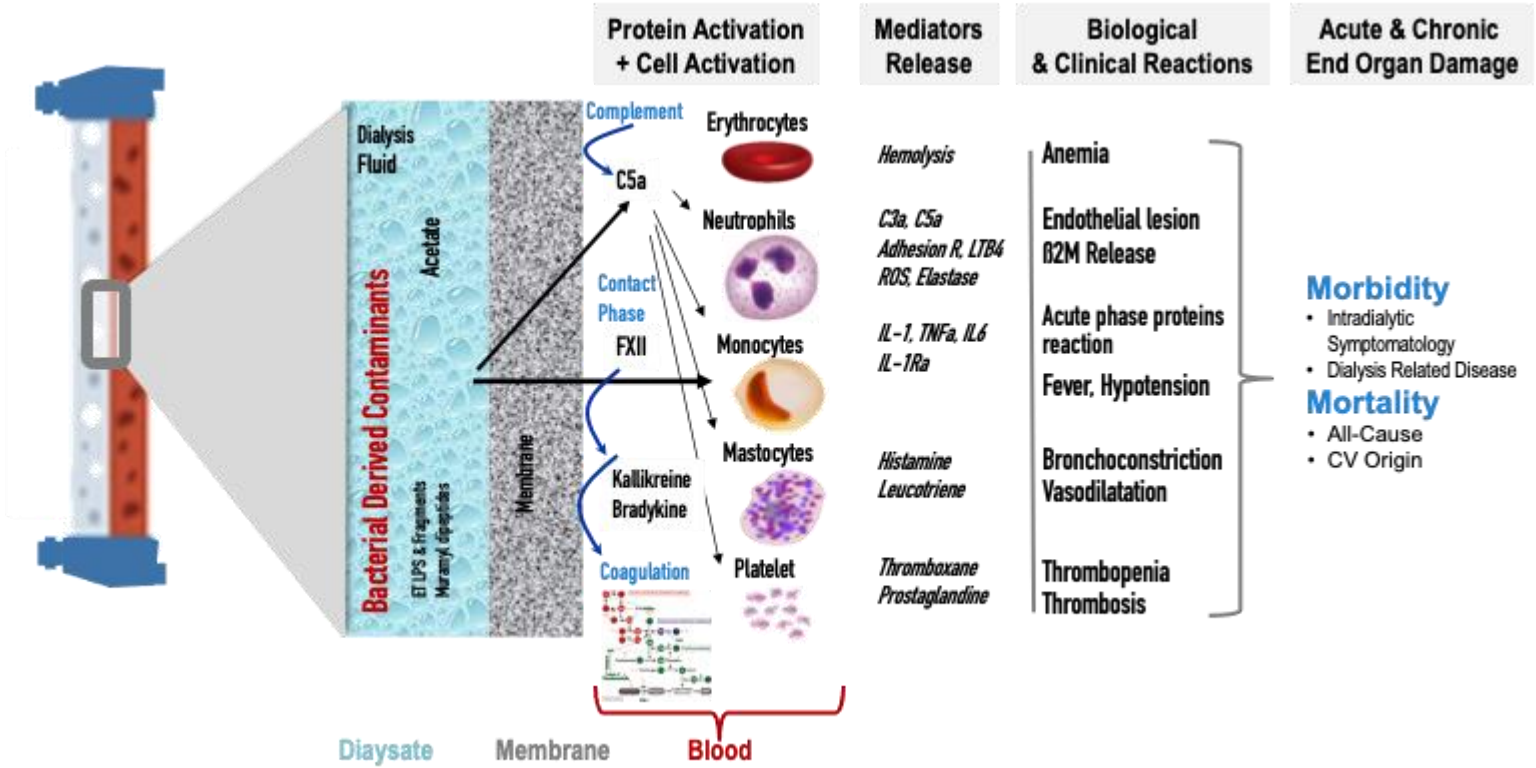
3 Operating Conditions

4 Treatment Implementation & Patient Interaction

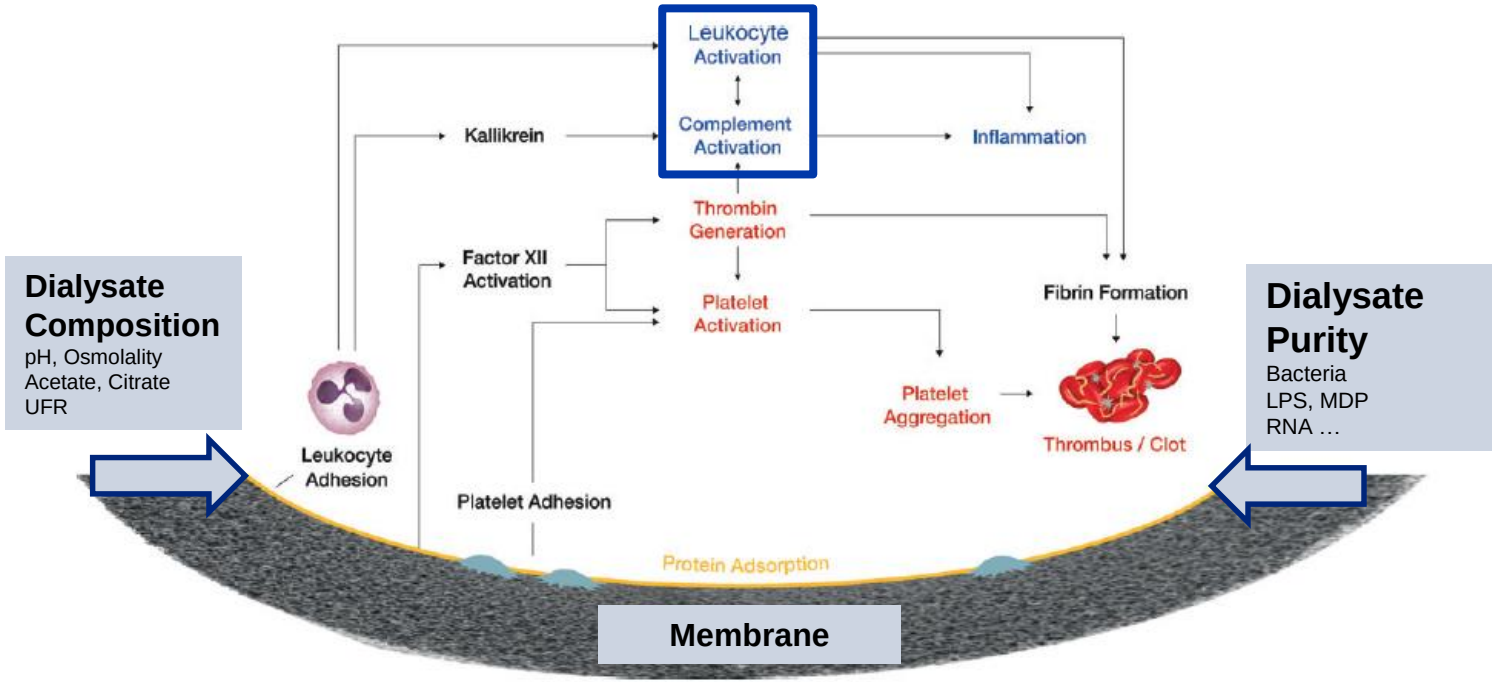
Hemodialyzer is a BIOEXCHANGER with Limited Sieving Selectivity (Molecular Size/MW)



Hemodialyzer is also a BIOREACTOR



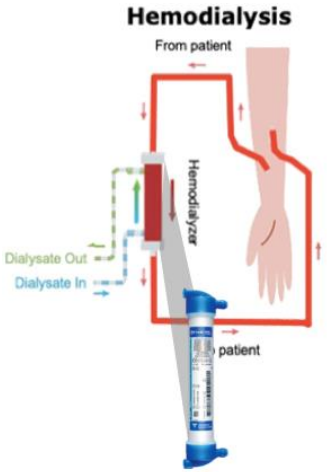
Biological Pathways Involved in Bioincompatibility



Interaction between protein adsorption, coagulation cascade, complement pathways and leukocyte activation

Bowry SK et al., Clinical Kidney Journal, 2021, vol. 14, Suppl 4, i59–i71

Outline



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Challenges in Hemodialysis Therapy and Dialyzer Technology

Patient Dialysis Interaction

- ↑ Solute mass transfer
  - Wanted Compounds
  - Unwanted Compounds

EFFICACY

↑ REMOVAL UREMIC TOXINS

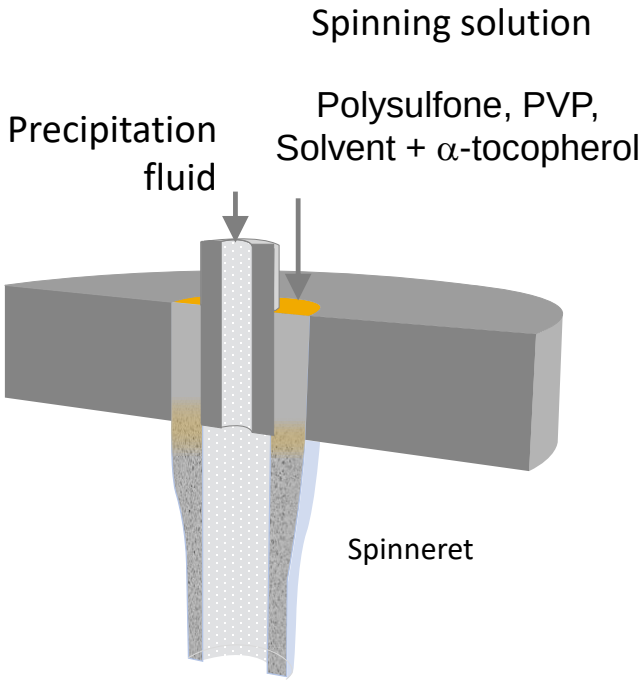
↓ ALBUMIN & ESSENTIAL NUTRIENTS

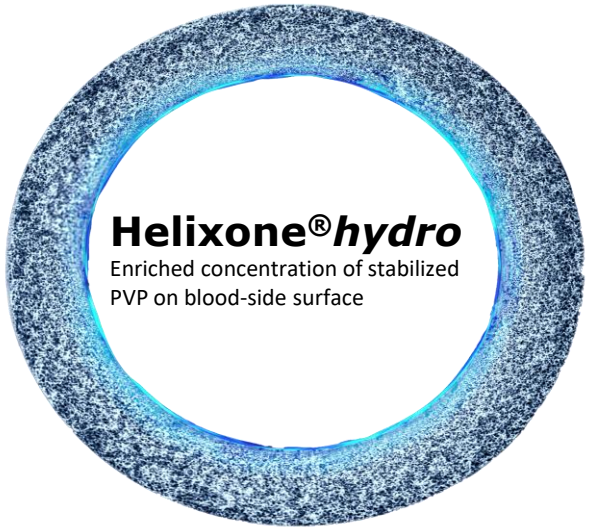
- ↓ Hemoreactivity
- ↓ Thrombogenicity

SAFETY

↓ BIOLOGICAL REACTIONS

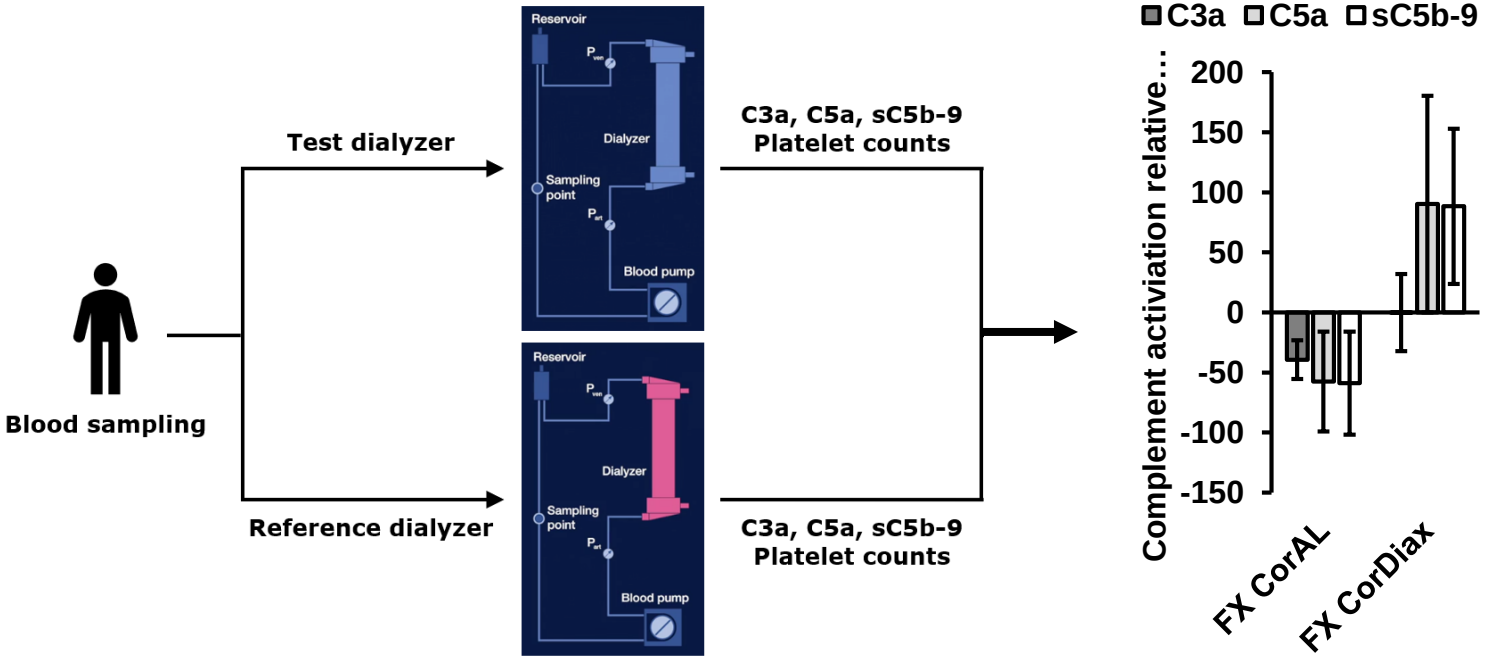
An Example: New Helixone Hydro Membrane FX CorAL Dialyzer (FMC)





FX CorAL Dialyzer (FMC)

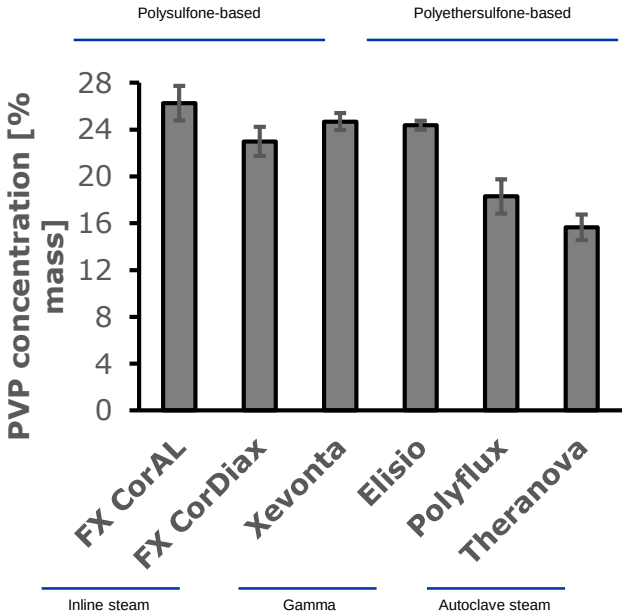
Setup for hemocompatibility measurements



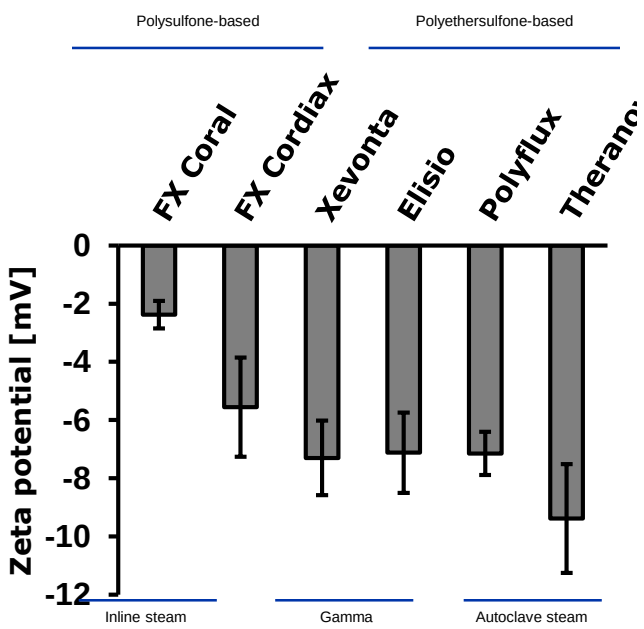
Melchior et al., *Artif Organs* 2021

PVP Surface Coverage

SURFACE CONCENTRATION



SURFACE CHARGE

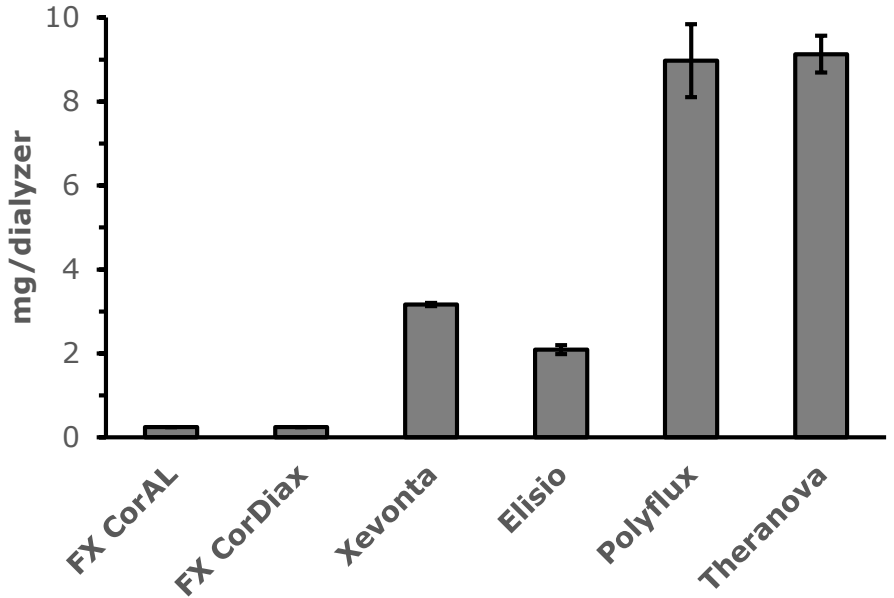


Zawada et al. Hemodialysis International, 2021

Melchior et al. Artifical Organs, 2021

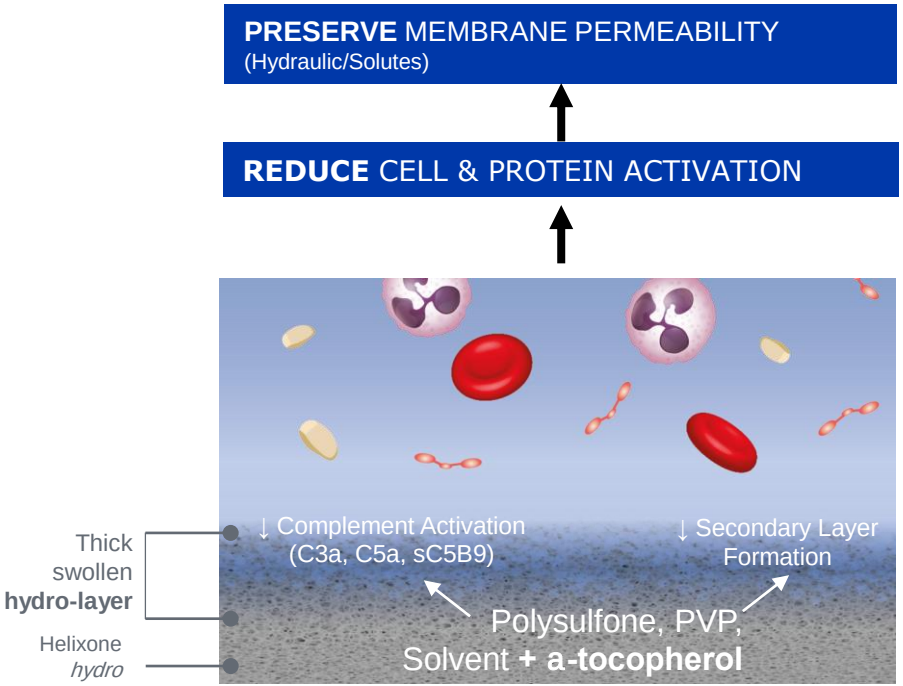
FX CoRal Has Lowest Elutable PVP

- FX CorAL has **high PVP surface coverage**
- FX CorAL has **low levels of eluteable PVP**



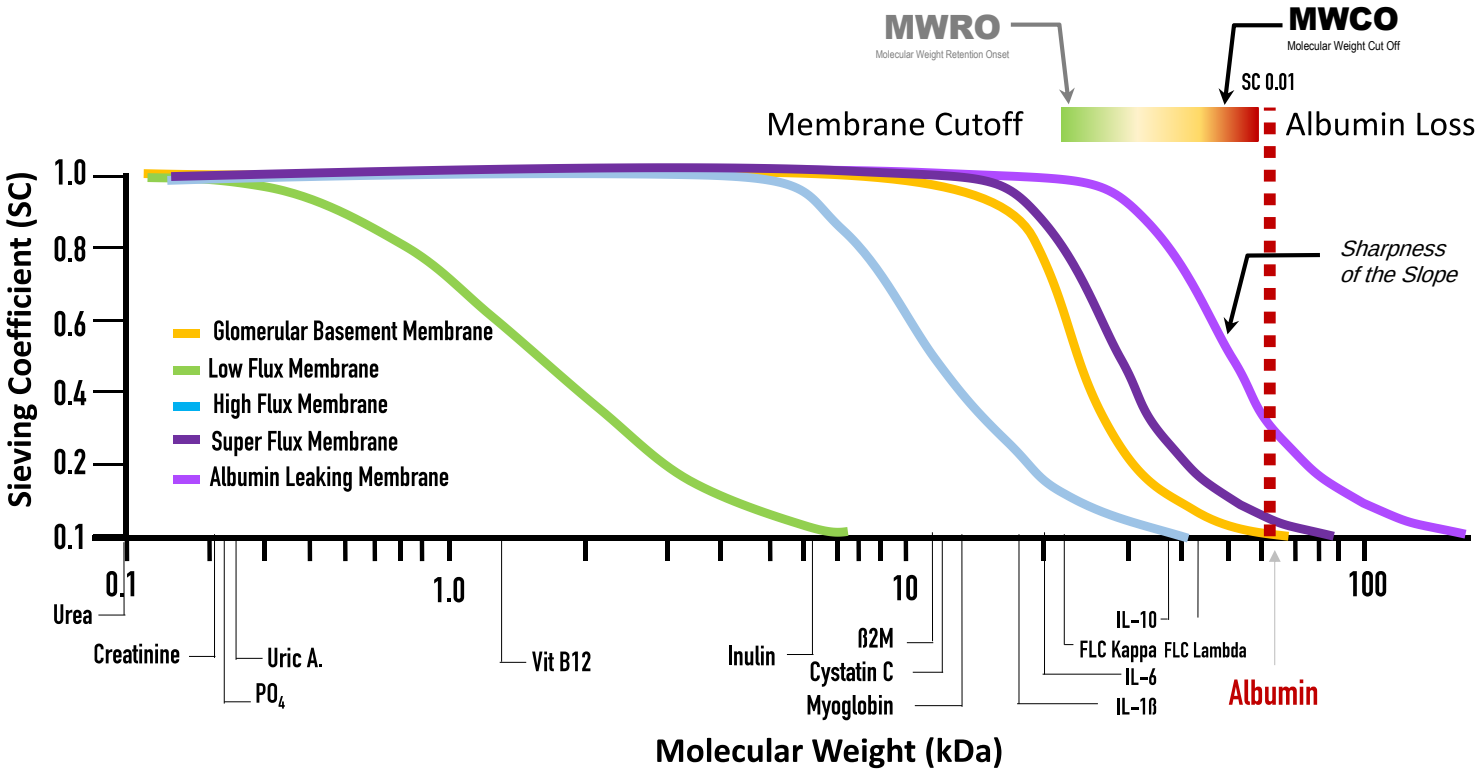
Zawada et al. Hemodialysis International, 2021

Newly Designed PS (FX Coral) Membrane Ensured Reduced Complement Activation and Better Permeability Preservation



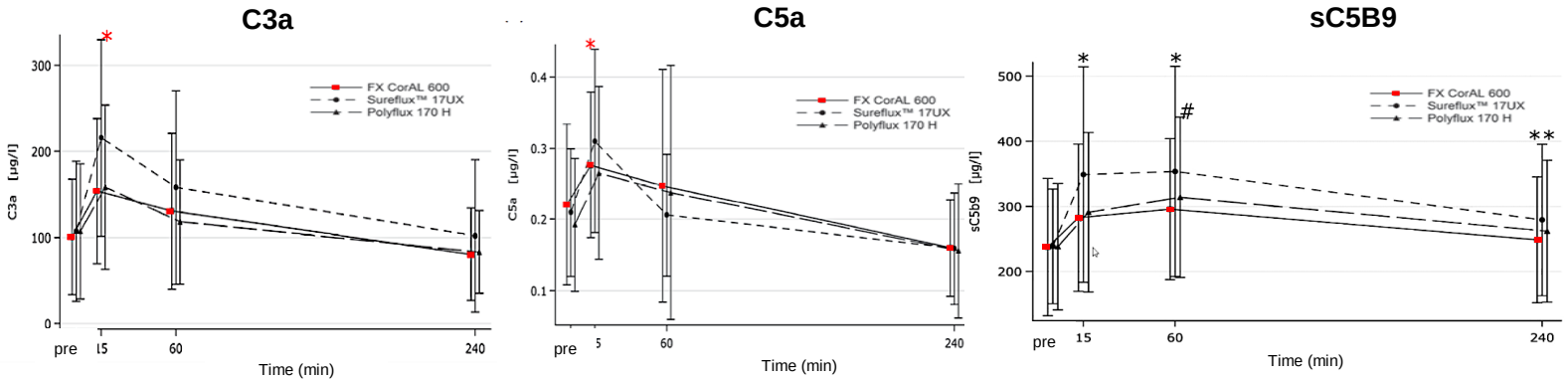
Sieving Capacity or Permeability of a Dialysis Membrane

Discrete Balance Between Retention and Cutoff



Canaud B. C*urr Opin Nephrol Hypertens.*2021;30(6):613-622

Reduced Complement Activation Confirmed an In-Vivo Study



EMPORA II Study - RCT

70 Maintenance HD pats

FX CorAL

- vs. Sureflux 17UX
- vs. Polyflux 170H

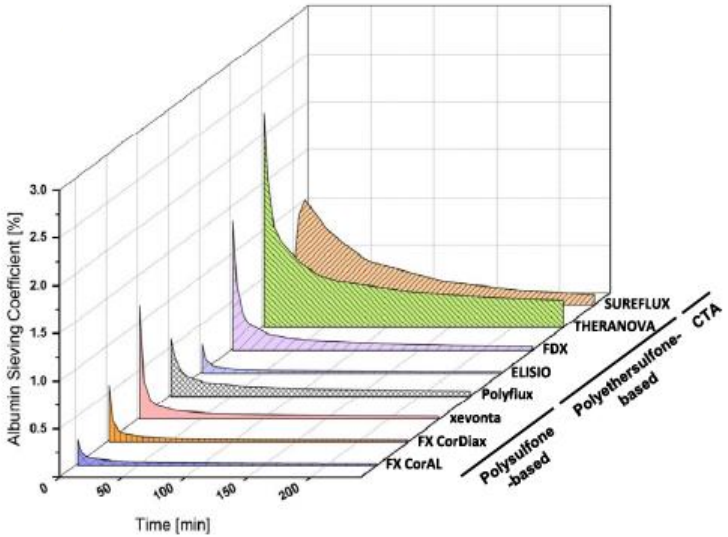
I^{ary} Outcomes

- Complement Activation
- Biocompatibility Markers
- Clinical Performances

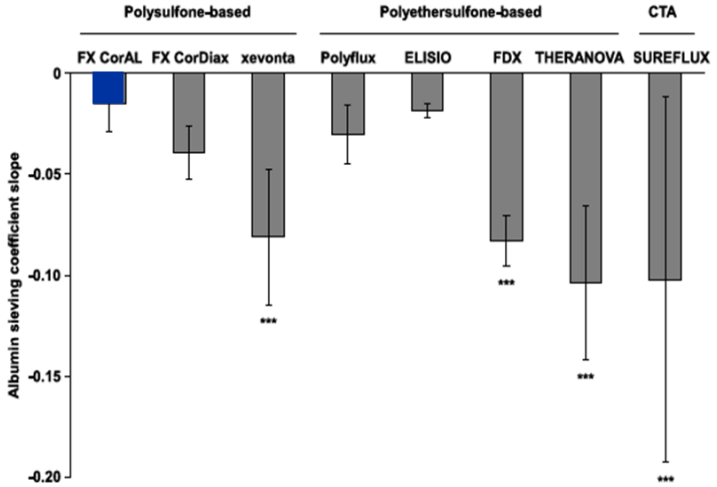
Ehlerding G. et al. *Kidney 360.* 2021.
doi:10.34067/KID.0000302021

Better Preservation of Membrane Permeability and Reduction of Albumin Loss

Time Behavior Changes of Albumin Sieving Coefficient



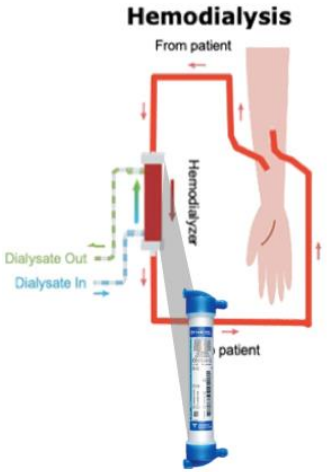
Albumin Sieving Coefficient Slope Over HD Session



Ex vivo Study
Recirculation model
Human blood – 3 hours

Melchior P. *Et al.* Artificial organs. 2021;00:1-9.

Outline



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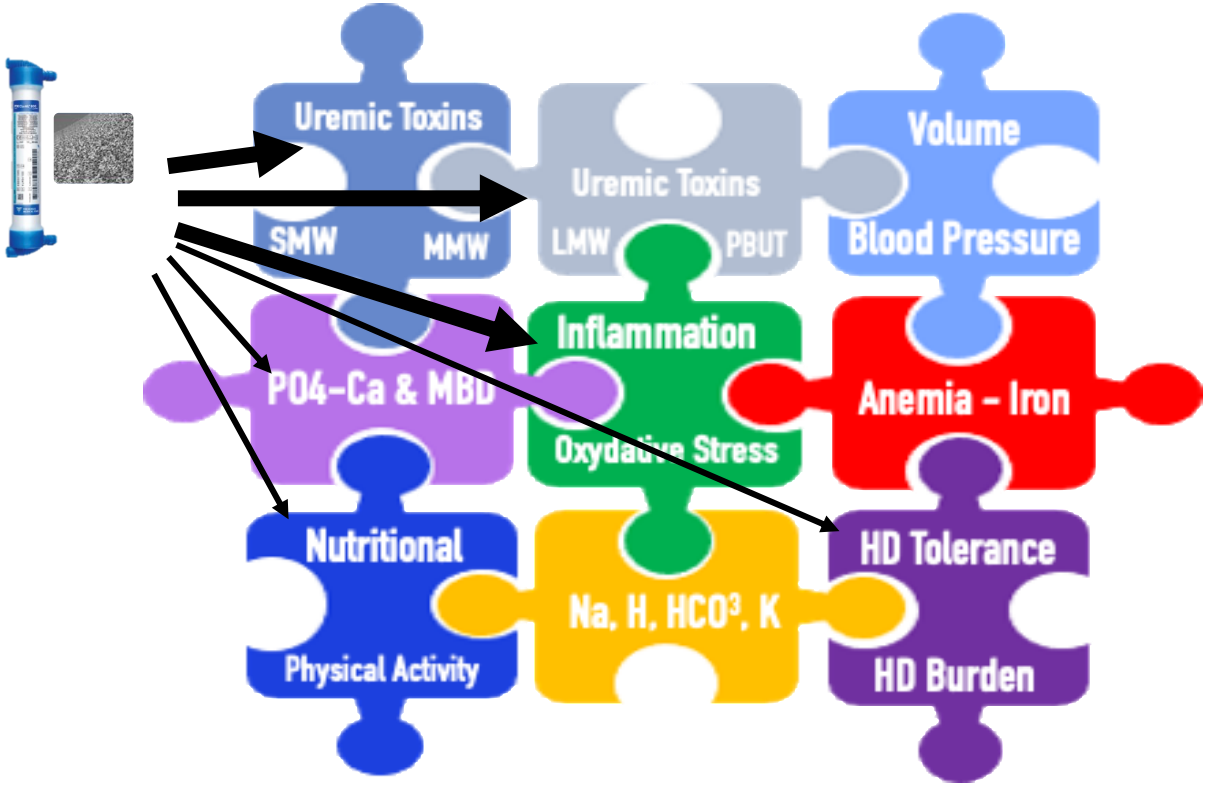
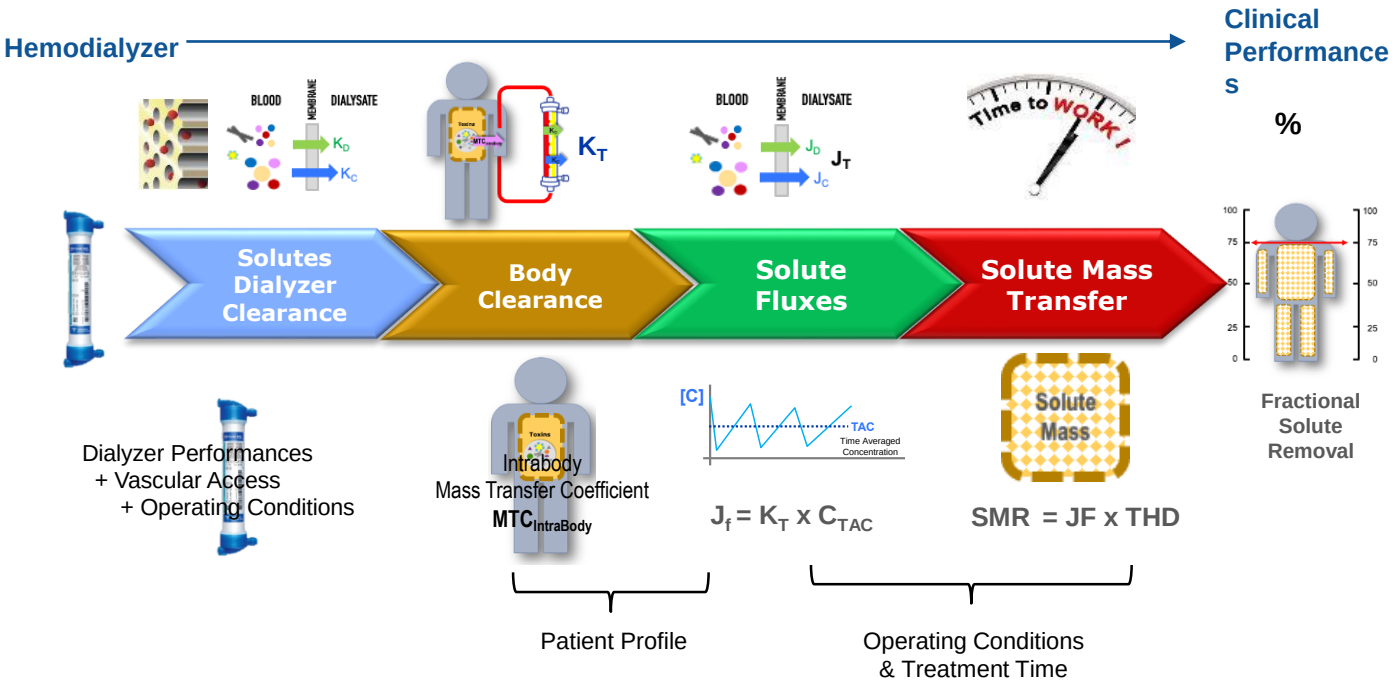
Hemodialysis Adequacy

Multitarget Approach to Cover CKD Patient Needs



From Hemodialyzer Clearance to Clinical Performances

Several Factors are Implicated that May Impaired Results



Dialysis Dose (Urea Equivalent) Assessed on Regular Basis (ocmKt) is a Reliable Tool for Quality Control

Medical
Feeling

SUBJECTIVE Assessment

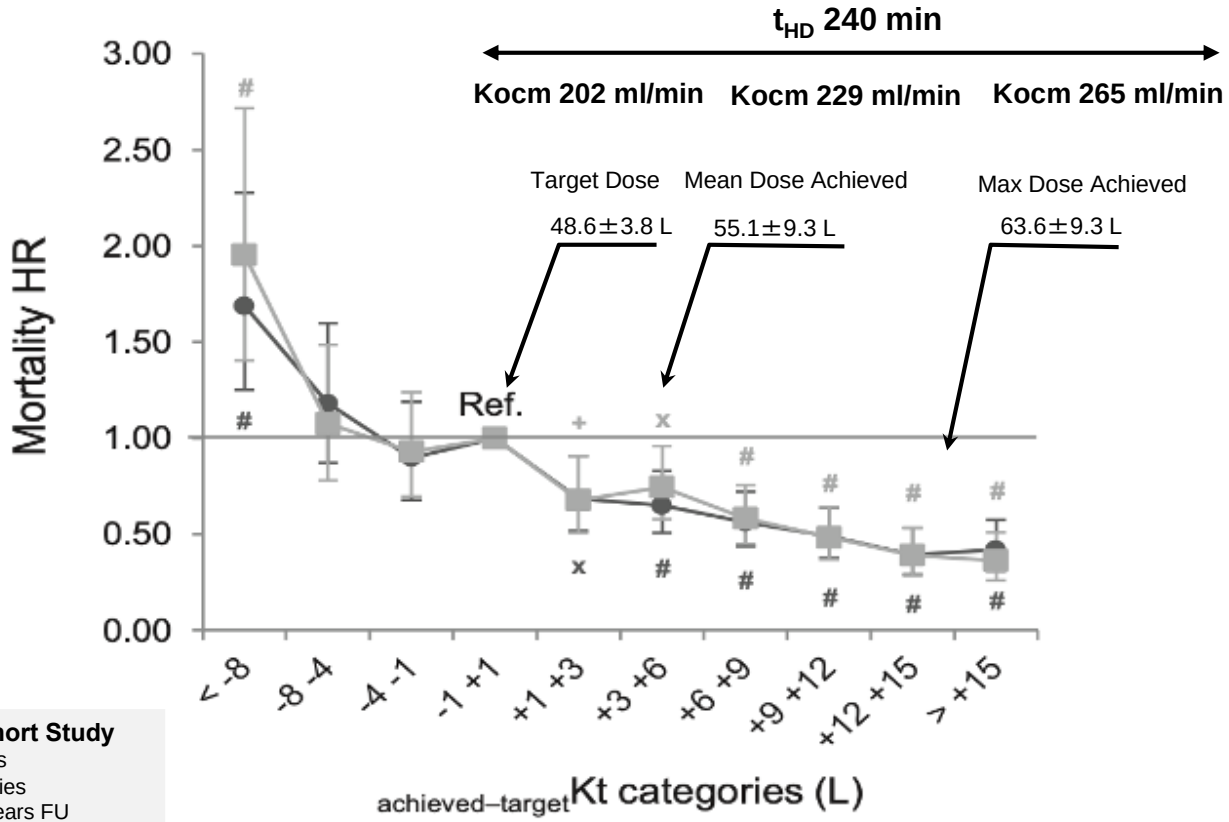
$$\text{ocm}\frac{K \cdot t}{V}$$

OBJECTIVE Assessment

Measurable
Parameter

Dialysis Quantification → **Quality Control Tool**

Dialysis Dose (ocmKt) and Mortality

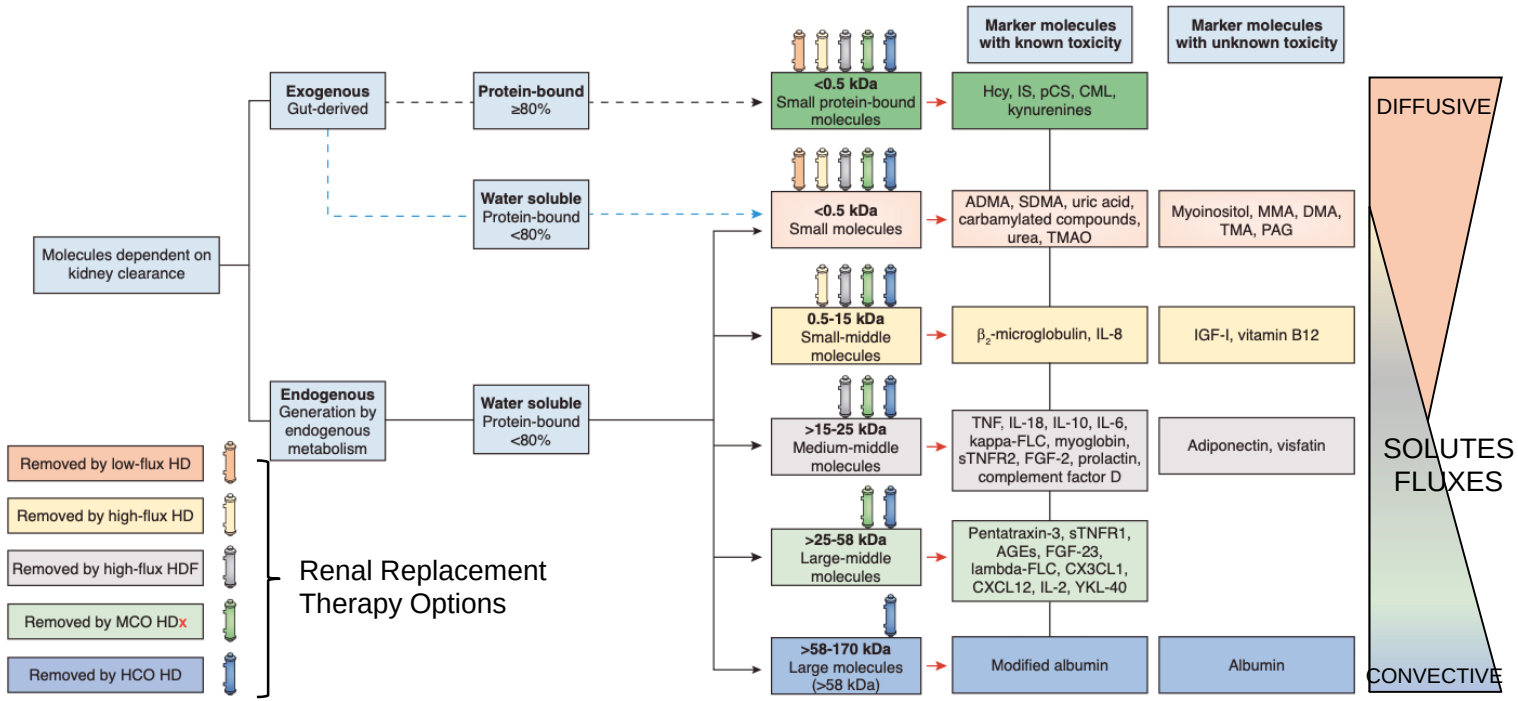


Retrospective Cohort Study
6129 prevalent patients
65 FMC Spanish facilities
45% online HDF – 2 years FU
I^{ary} Outcome: Mortality/Hospitalization

Maduell F et al. *Kidney Int.* 2016;90(6):1332-1341.

Uremic Toxins Classification

Link with Renal Replacement Therapy Options and Fluxes Applied

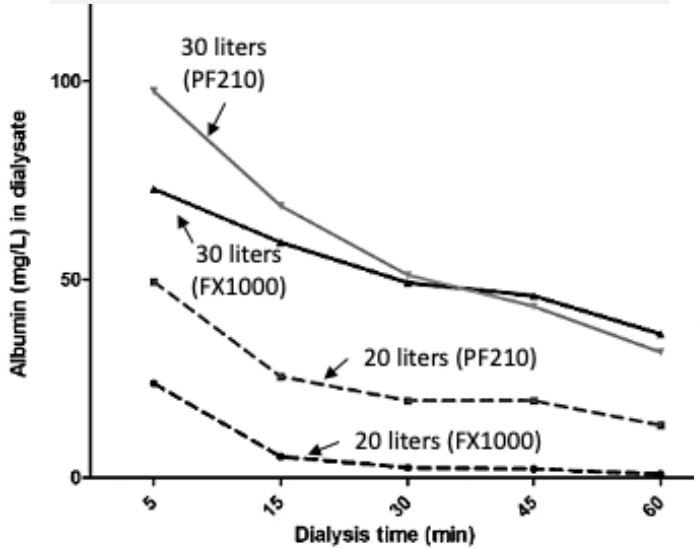


Rosner MH et al, *Clin J Am Soc Nephrol.* 2021 Jul 7. ePub. doi: 10.2215/CJN.02660221.

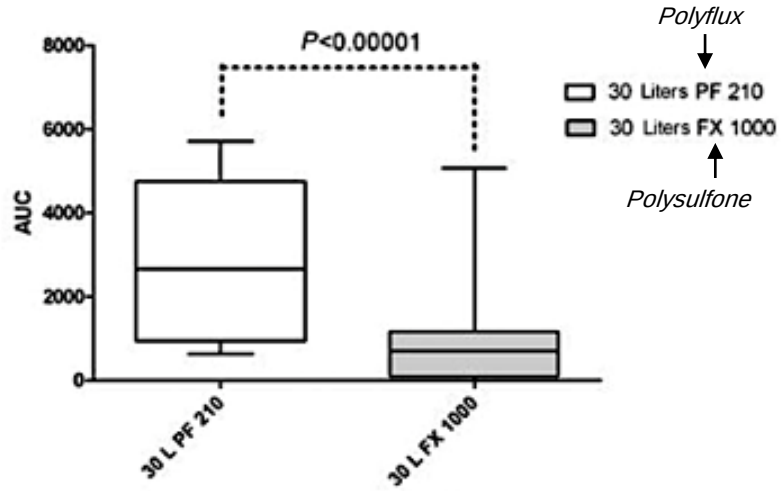
Maximal Membrane Stress is Provided by HDF

Albumin Loss according to Membrane Type and Convective Flux

Kinetic of Albumin Leakage



Amount of Albumin Loss

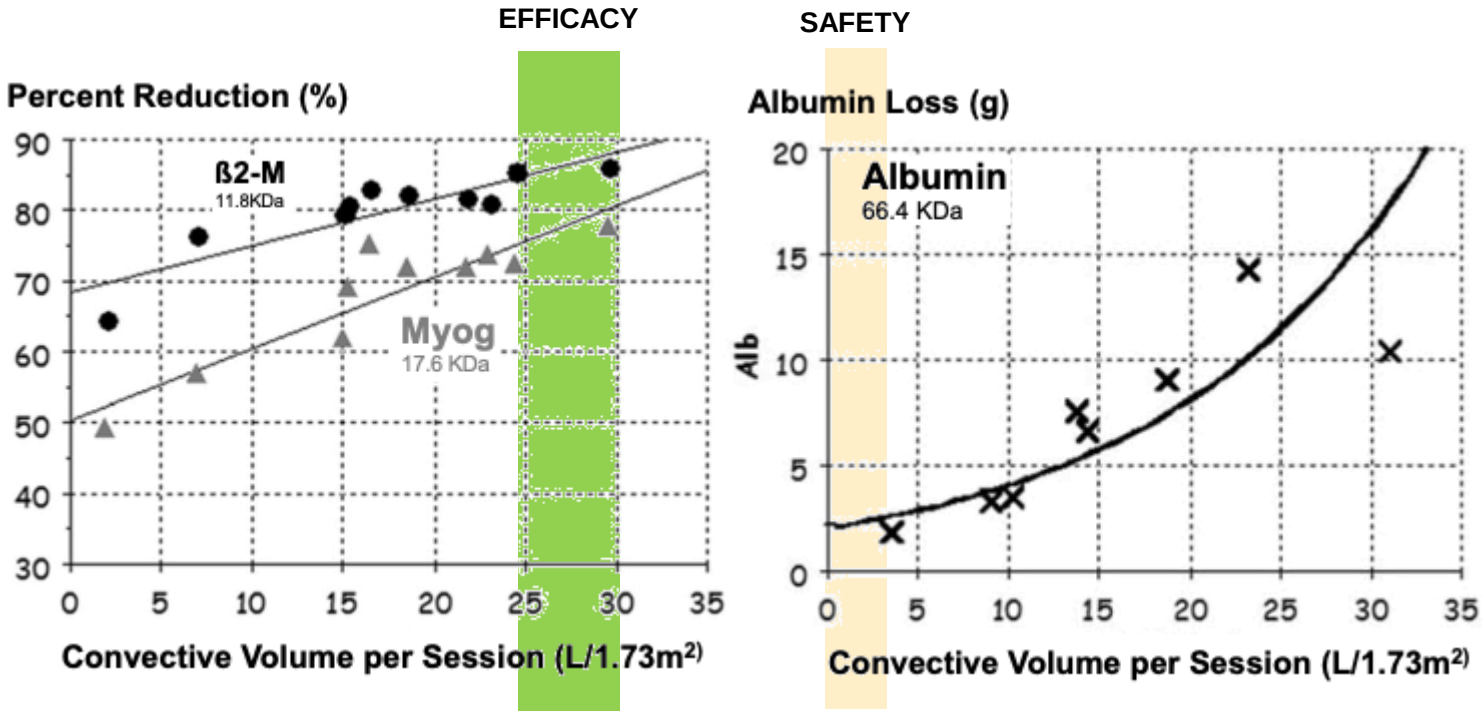


Prospective Cross-Over RCT
20 prevalent HD pts – Post-HDF
2x2 Factorial Design:
- Membrane 2.2m²
- Conv. Volume (20/30)
- UF Controlled

post-HDF	PF210	X	FX1000
	20 L		30 L

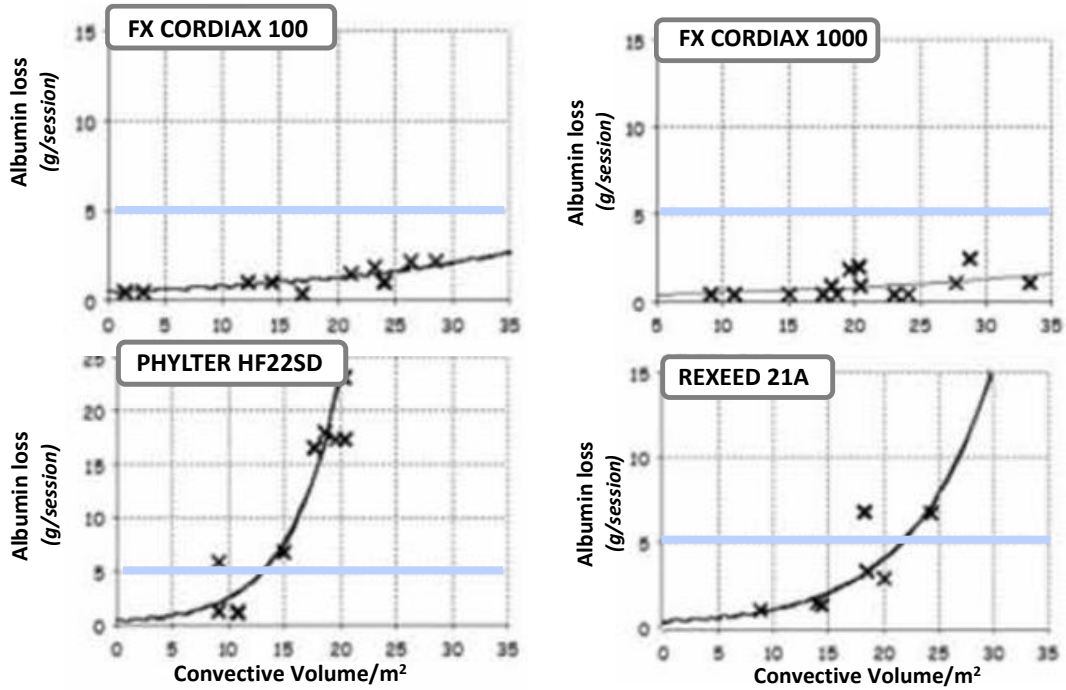
Vega A et al, *Ther Apher Dial.* 2015 Jun;19(3):267-71.

Efficacy (Solute Removal Rate) versus Safety (Albumin Loss) is a Delicate Balance When Membrane Stress is High



Potier J et al, *Int J Artif Organs* 2016;39(9):460-470

Effects of Membrane Type on Albumin Loss in HDF



Potier J et al, *Int J Artif Organs.* 2016;39(9):460-470.

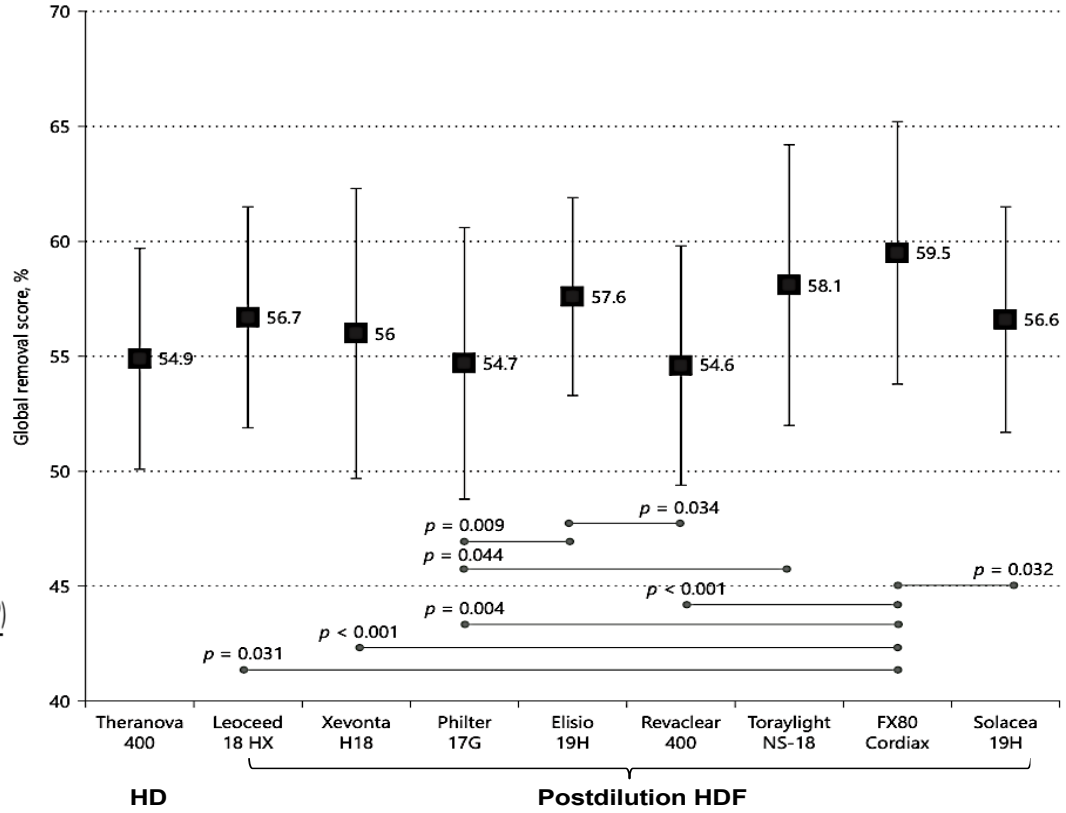
Comparative Efficacy of Various Dialysis Modalities

Overall score for reduction of circulating solutes (60Da-43KDa)

Global Removal Score

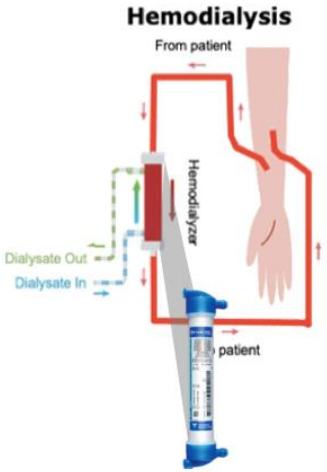
$$\text{Global Removal Score} = \frac{\sum RR\,(\text{Urea} + \text{ß2M} + \text{Myog} + \text{Prol} + \text{A1M} + \text{A1AGP})}{(6 - RR.\text{Alb})}$$

Urea (60Da)
ß2M, Beta 2 Microglobulin (11.8 KDa)
Myog, Myoglobin (17.6 KDa)
Prol, Prolactine (22 KDa)
A1M, Alpha 1 Microglobulin (26KDa)
A1AGP, α1-acid glycoprotein (41-43 Kda)



Maduell F et al. *Blood Purif.* 2019;48(2):167-174.

Outline



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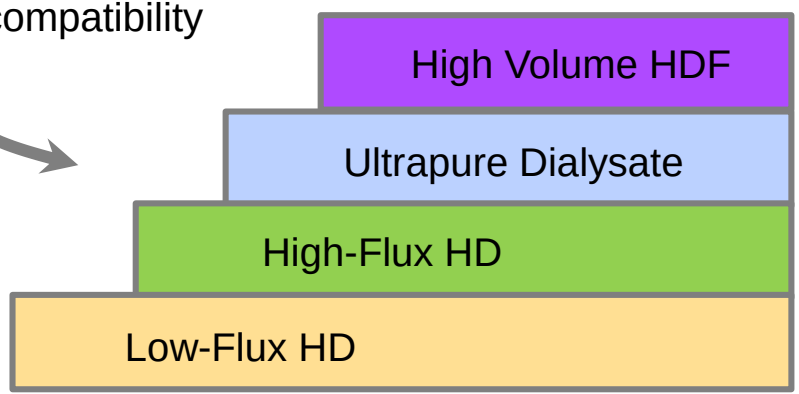
Linking Membrane to Outcomes: Evidence Based Facts

Factors

Membrane Permeability
Solute Mass Transfer
Hemocompatibility

Treatment Modality
& Prescription

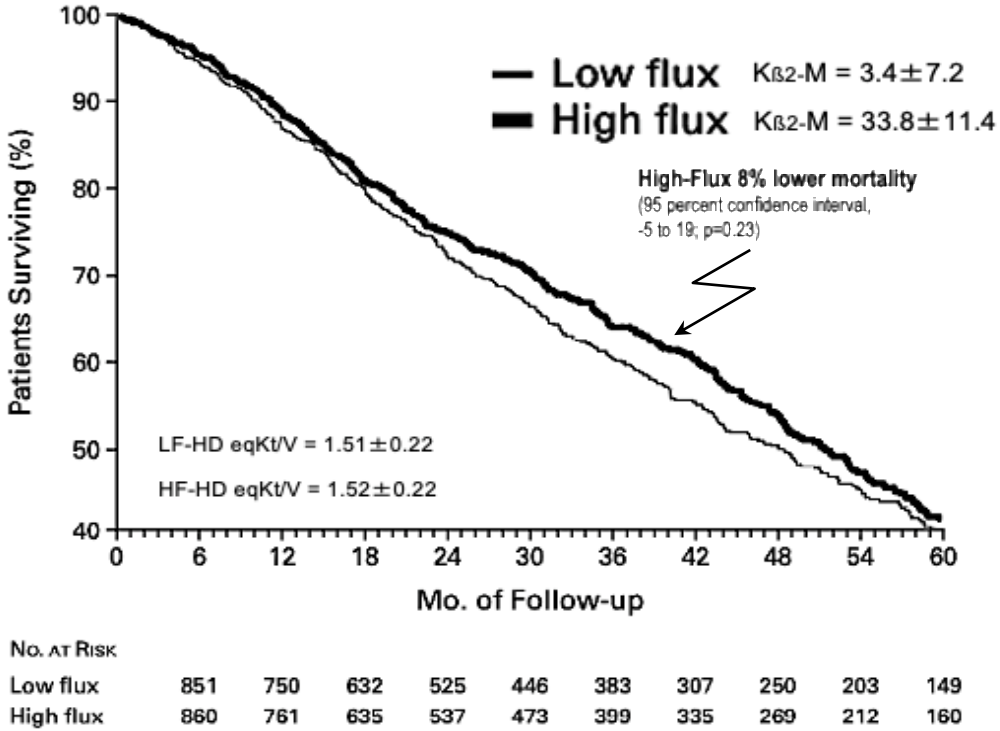


Outcomes

Intermediary		Endpoint
ß2M	Clearance Mass Transfer Concentrations	Mortality Morbidity
Complement Activation	MBL C3d C5b-9	
$_{hs}$CRP	Inflammation	

High-Flux HD is Associated with a Non-Significant Increase in Survival (8% NS) in the HEMO Study

Interventional RCT in USA : no significant impact on patient outcomes



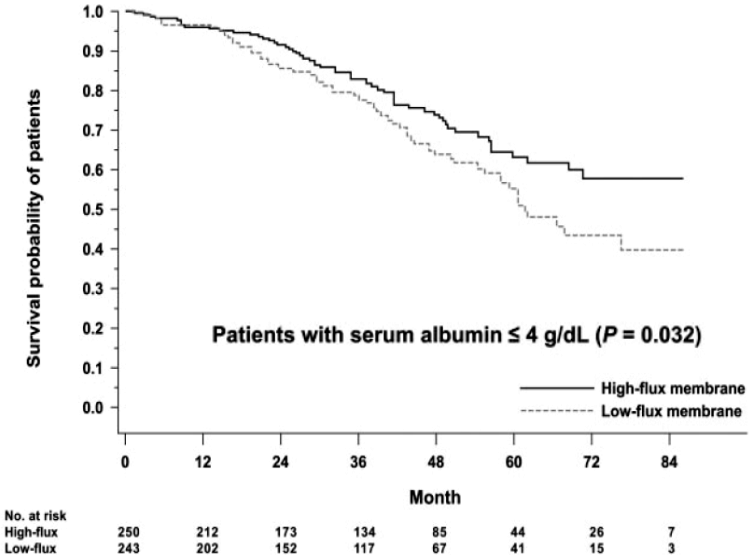
HEMO Study
Prospective RCT
2 x factorial design: Dose/Flux
1846 prevalent HD pts – 5 yrs. FU
- Stand-Dose n=926
- High-Dose n=920
- Low-Flux n=925
- High-Flux n=921

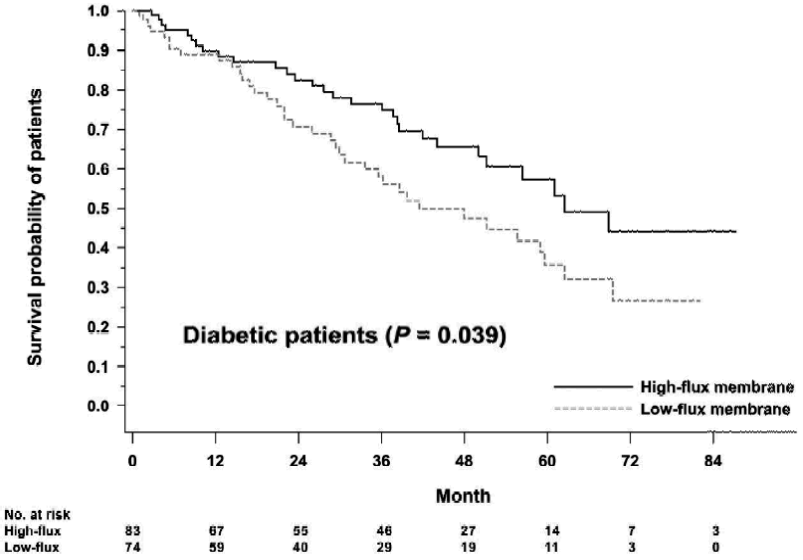
Hemodialyzers were reused up to 12 times

Eknoyan G et al, *N Engl J Med* 2002;347:2010-9.

High-Flux HD Reduces Mortality in Hypoalbuminemic and Diabetic Patients in the MPO Study

Interventional RCT in Europe : positive impact on patient outcomes





CAUTION

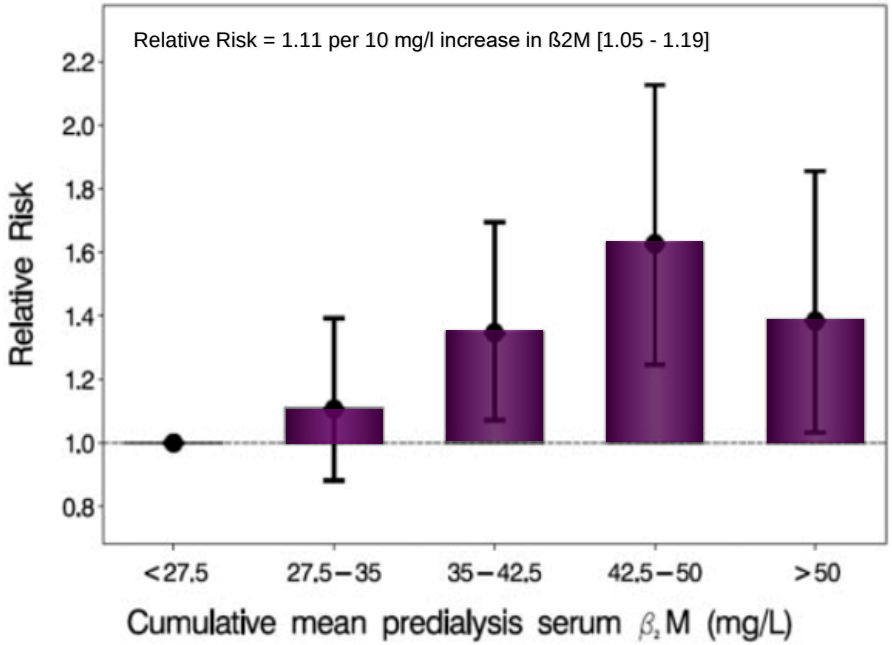
Single-Use Hemodialyzers

MPO Study
Membrane Permeability Outcome Study

Locatelli F et al, *J Am Soc Nephrol.* 2009;20(3):645-54.

ß2-Microglobulin Concentrations Are Associated with Relative Risk of Death in HD Patients

All-Cause Mortality



HEMO Study
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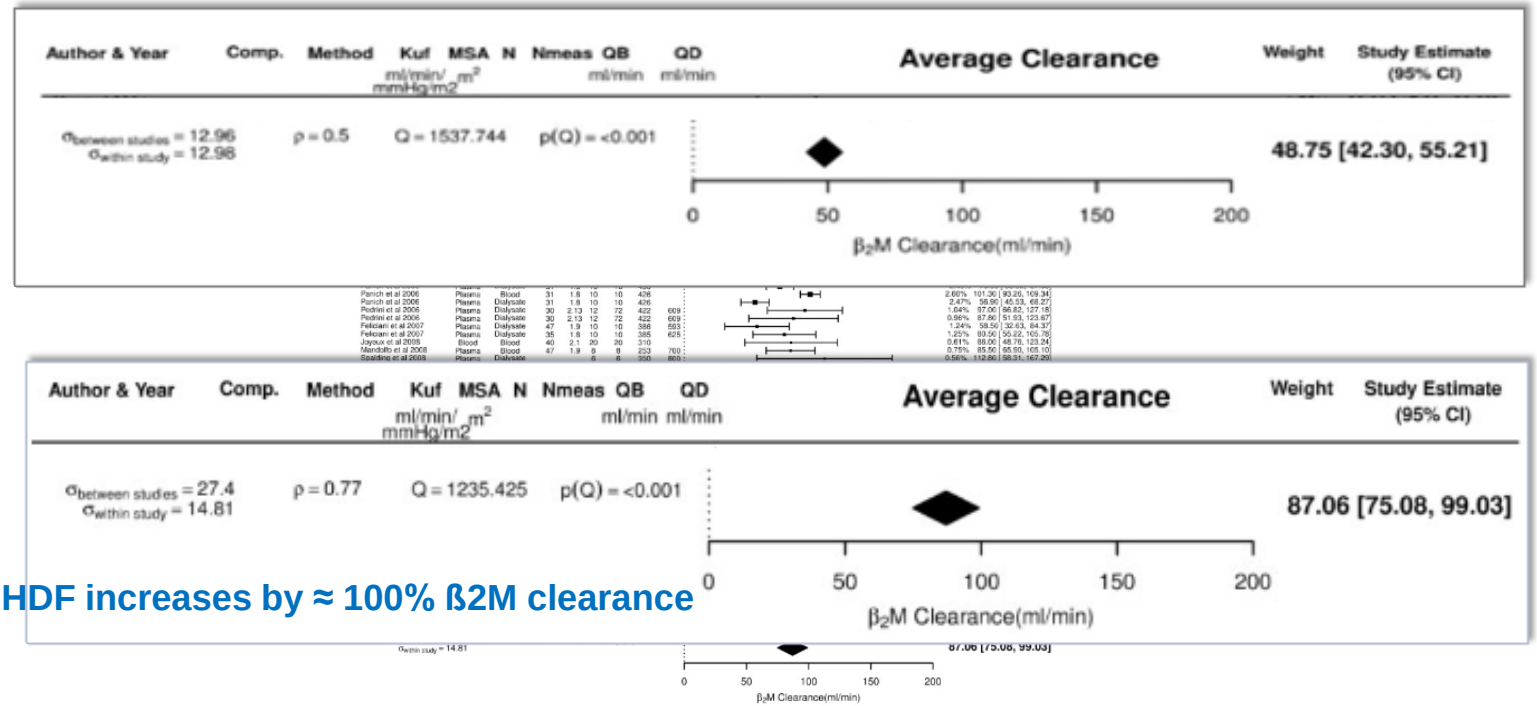
- High-Flux n= 921

Cheung AK et al, *J Am Soc Nephrol* 2006; 17: 546-555

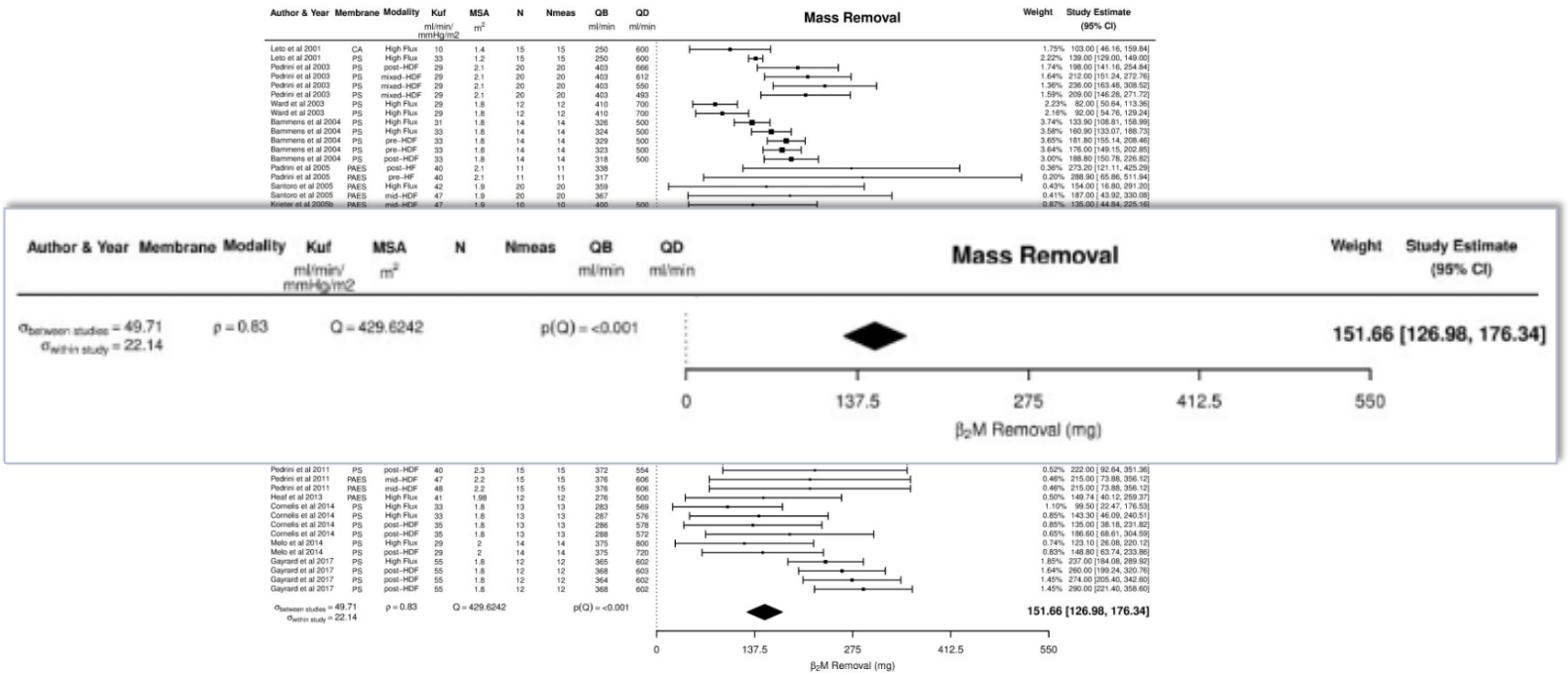
High-Flux HD is Associated with Higher ß2M Clearances



HDF increases by ≈ 100% ß2M clearance

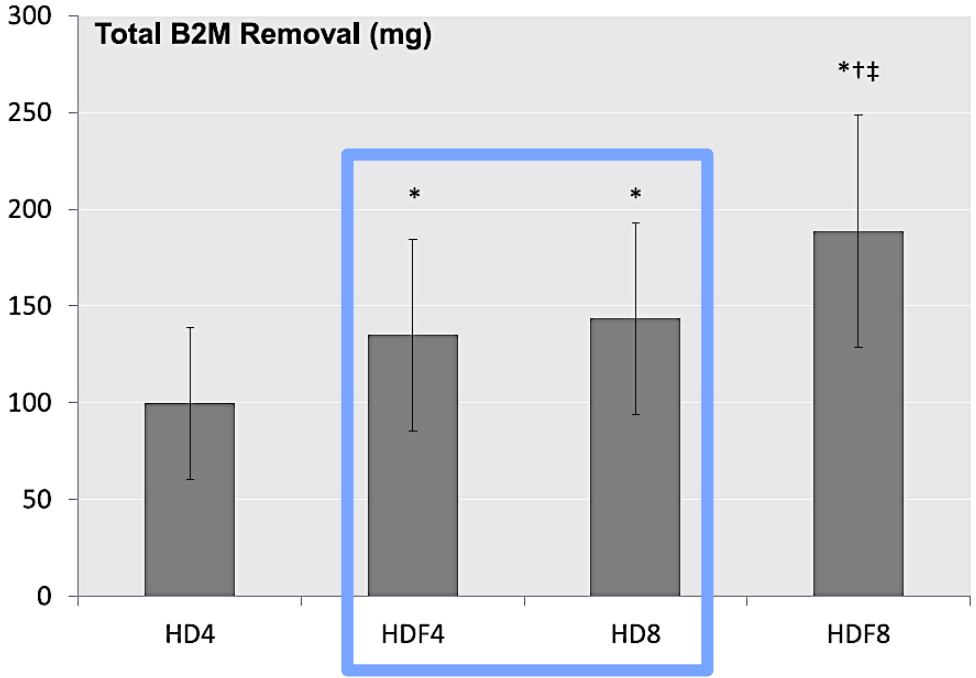
Roumelioti ME et al, *Nephrol Dial Transplant* 2018; 33: 1025–1039

HDF is Associated With Significant Higher ß2M Mass Removal than High-Flux HD



Roumelioti ME et al, *Nephrol Dial Transplant* 2018; 33: 1025–1039

ß2-M Mass Removed is Significantly Increased by HDF as Function of Treatment Time

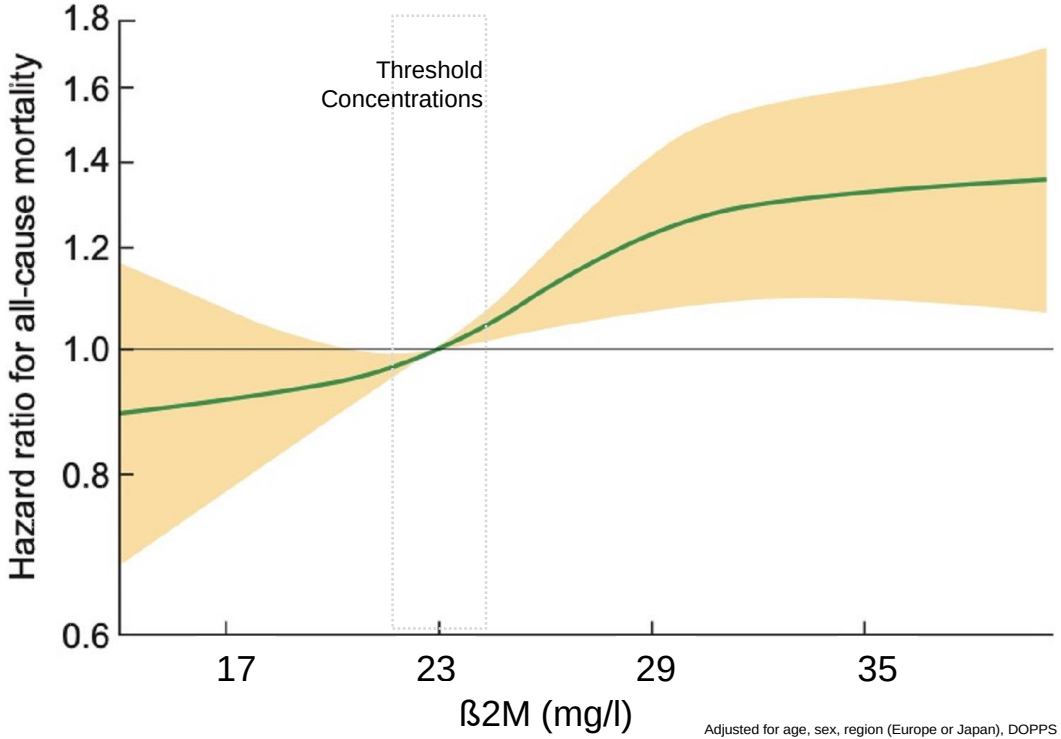


High-Flux HD
4 hours
X
Postdilution HDF
8 hours

Randomized Cross-Over Study
13 prevalent ESKD pats
2X2 : HF-HD vs post-HDF & T4h vs T8h
2 wk. interval between phases
Hemodynamic tolerance
Efficacy, solute removal (IDQ & DDQ)

Cornelis T et al, *Am J Kidney Dis.* 2014;64(2):247-256

Adjusted HR for All-Cause Mortality by ß2M Levels



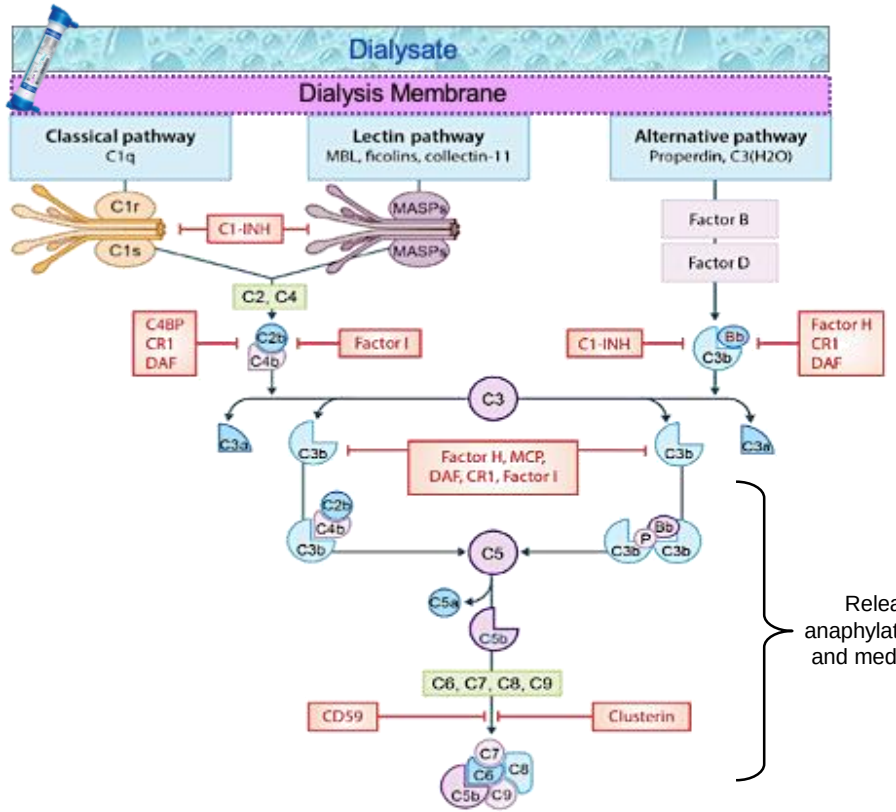
DOPPS
Dialysis Outcomes and Practice Patterns Study

Analysis sample:
- 4 countries
- 5332 participations:
  Japan = 3839
  France = 356
  Italy = 364
  Spain = 773
- 3533 unique patients

Adjusted for age, sex, region (Europe or Japan), DOPPS Phase, dialysis vintage, residual urine volume, serum albumin and five comorbidities (diabetes, coronary heart disease, congestive heart failure, cerebrovascular disease and other cardiovascular diseases).

Kanda E et al, *Clin Kidney J.* 2020;14(5):1436-1442.

Low-Grade Complement Activation May Occur During HD and Contribute to Adverse Reactions and Side Effects

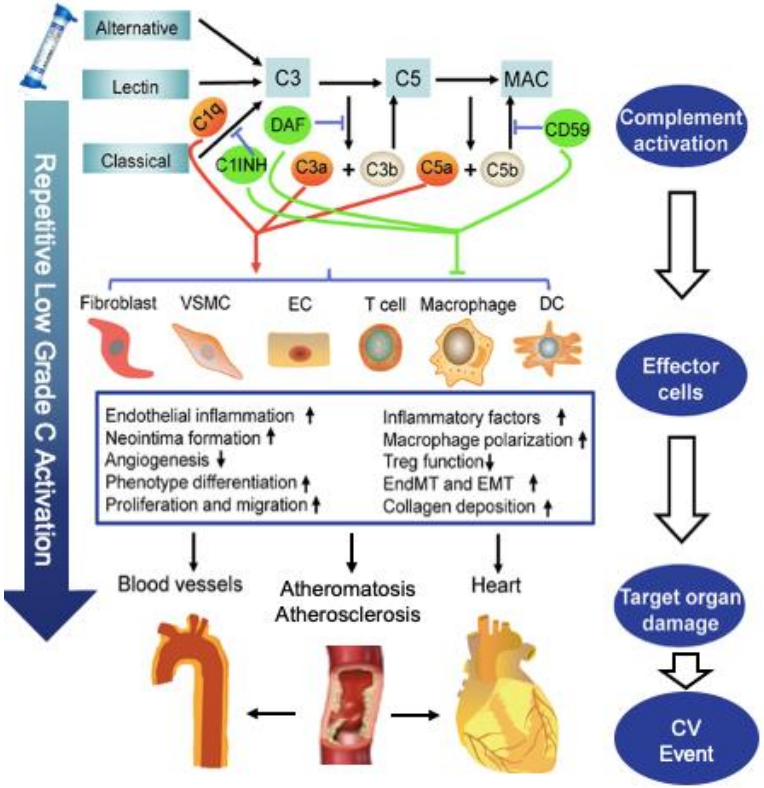


Release of anaphylatoxins and mediators

Inflammation
Oxidative Stress
Thrombosis
End Organ Damage

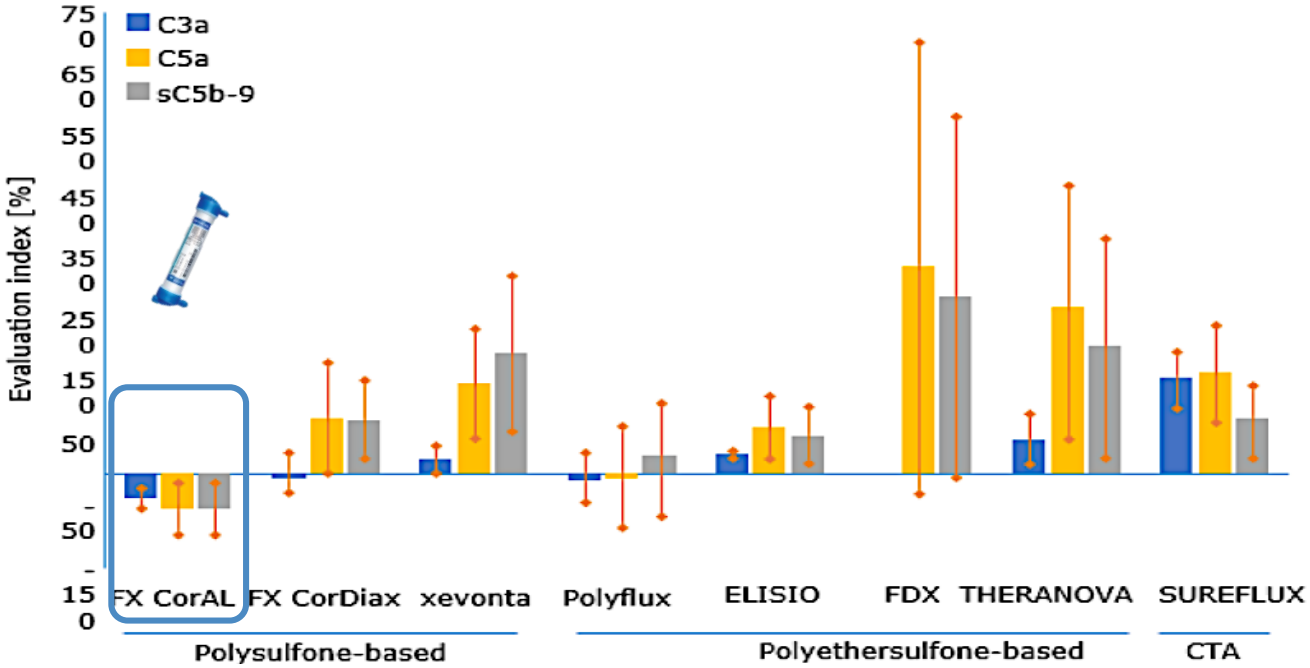
Poppelaars *Front Immun* 2018.09.71

Low Grade Complement Activation is Recognized as Contributing and Enhancing CV Events



Modified from Ruan CC et al, *Hypertension.* 2019;73(5):965-971.

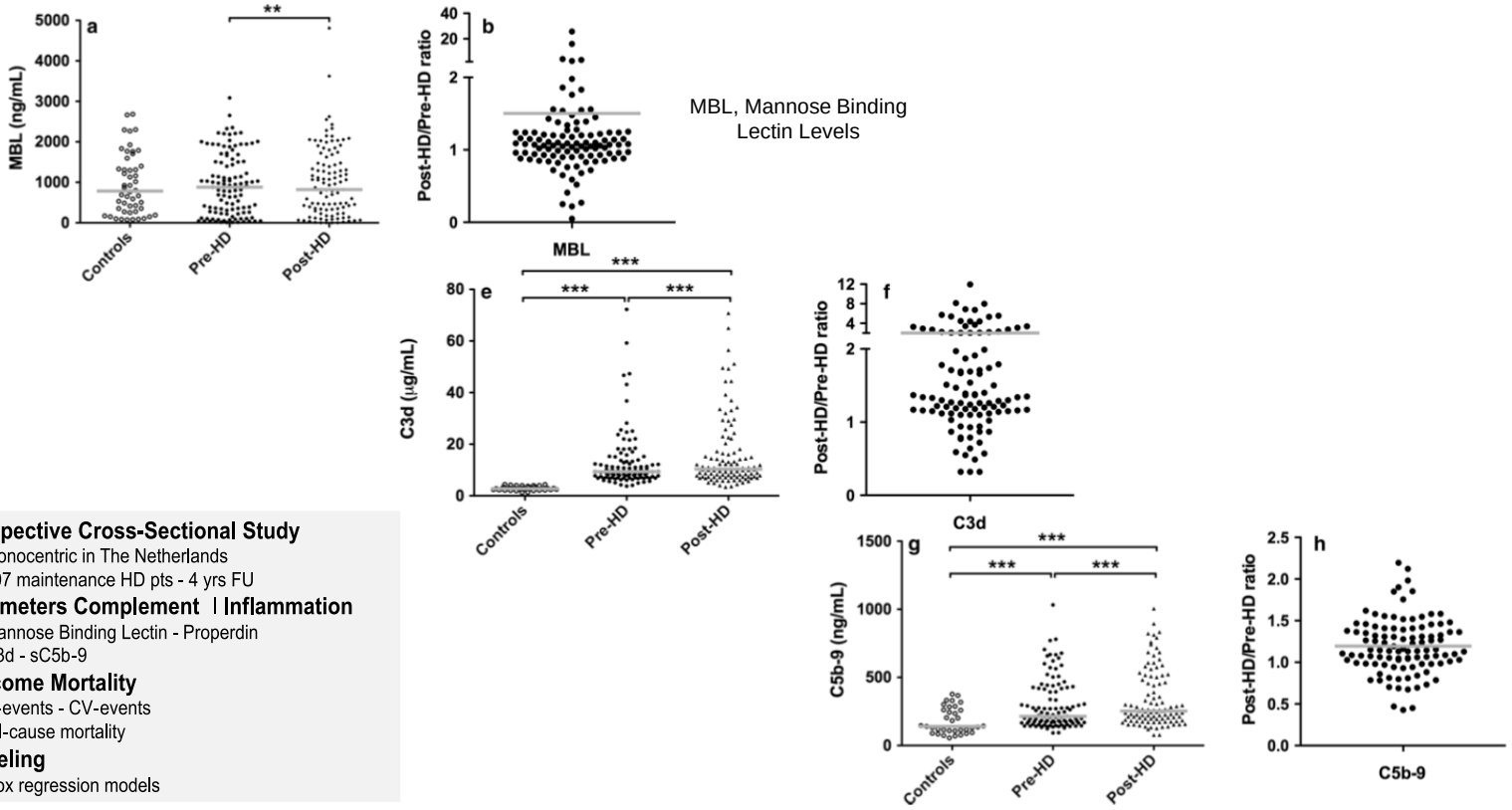
New Membrane Engineering Has Been Shown to Reduce Significantly Complement Activation



Ex vivo Study
Recirculation model
Human blood – 3 hours

Melchior et al., *Artif Organs.* 2021;45(7):770-778

Low Grade Complement Activation Occurs in Regular Maintenance High-Flux Hemodialysis (Polysulfone Dialyzer)



Prospective Cross-Sectional Study
- Monocentric in The Netherlands
- 107 maintenance HD pts - 4 yrs FU

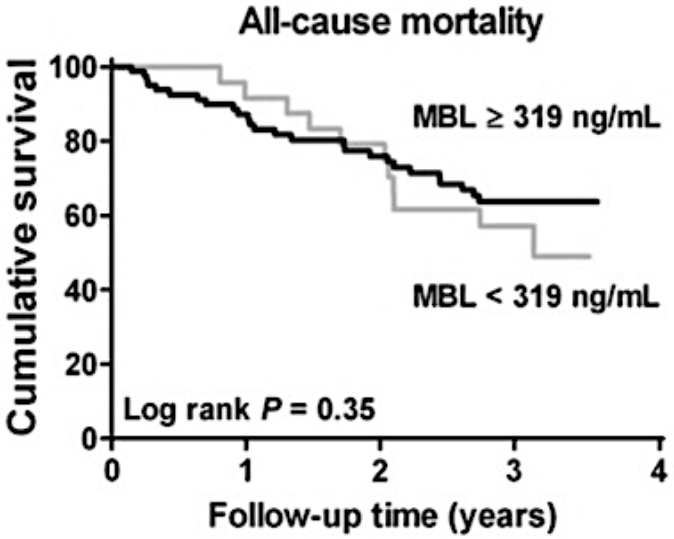
Parameters Complement I Inflammation
- Mannose Binding Lectin - Properdin
- C3d - sC5b-9

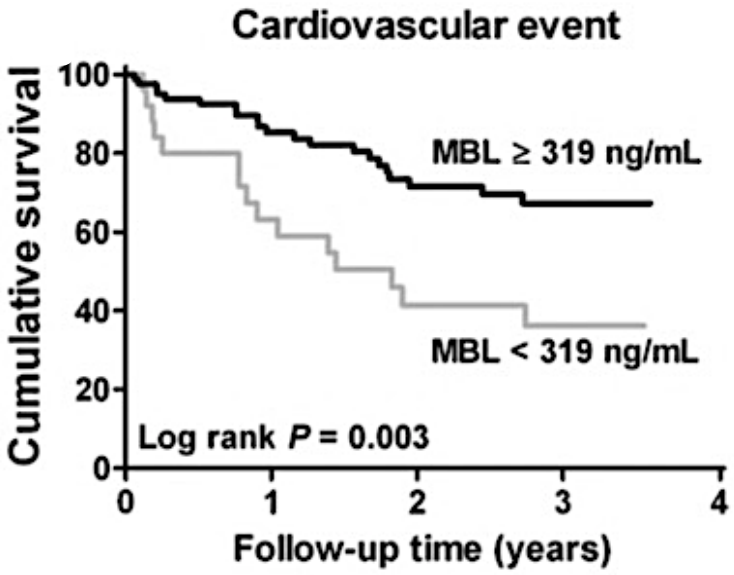
Outcome Mortality
- C-events - CV-events
- All-cause mortality

Modeling
- Cox regression models

Poppelaars et al. *J Transl Med.* 2016;14:236-248

Chronic Complement Activation is Associated with Poor CV Outcome in HD Patients





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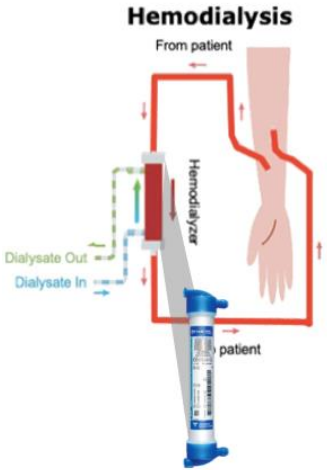
MBL, Mannose Binding Lectin Levels

Poppelaars et al. *J Transl Med.* 2016;14:236-248

Outline



1 What's Role of the Membrane and the Dialyzer in Outcomes?

2 What Does Innovation Mean in Membrane and Dialyzer Technology?

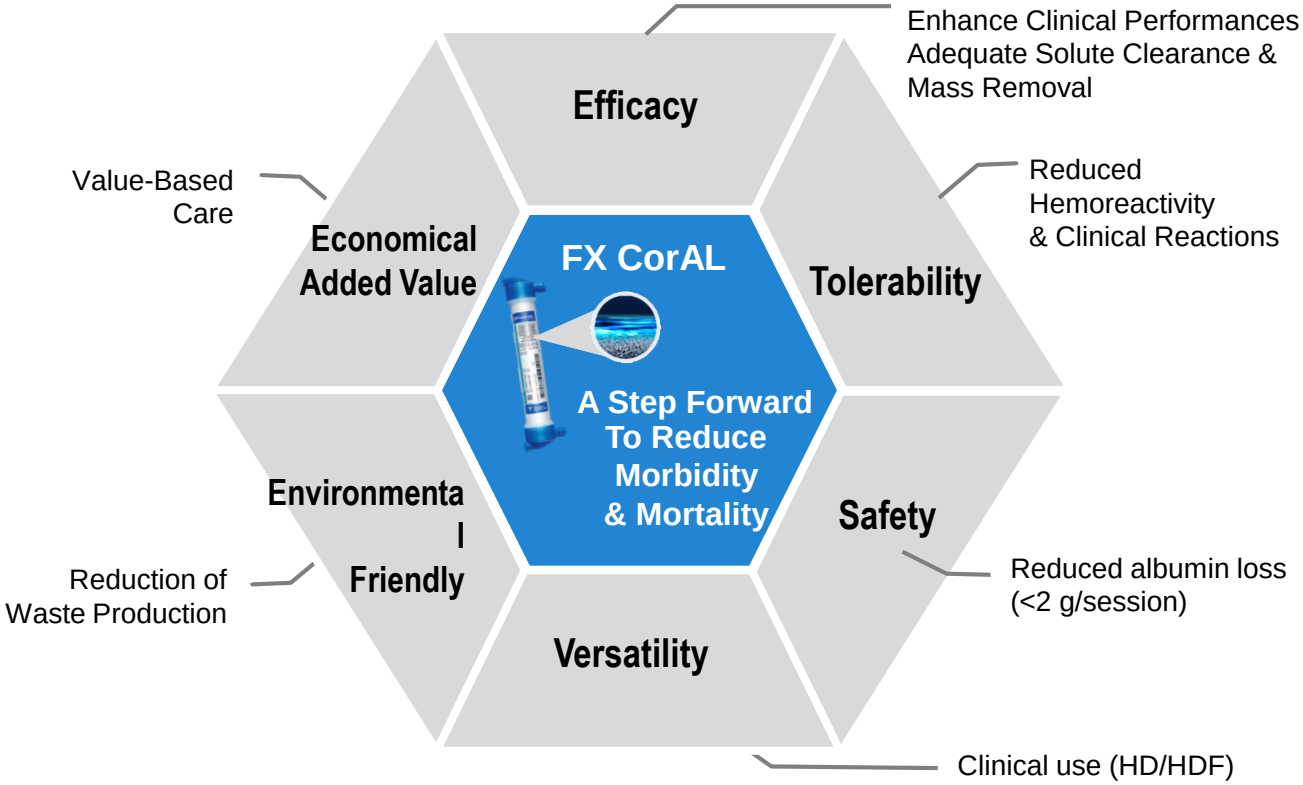
3 What are the Objectives of an Innovative Membrane and Dialyzer?

4 What Are the Clinical Facts and Evidences?

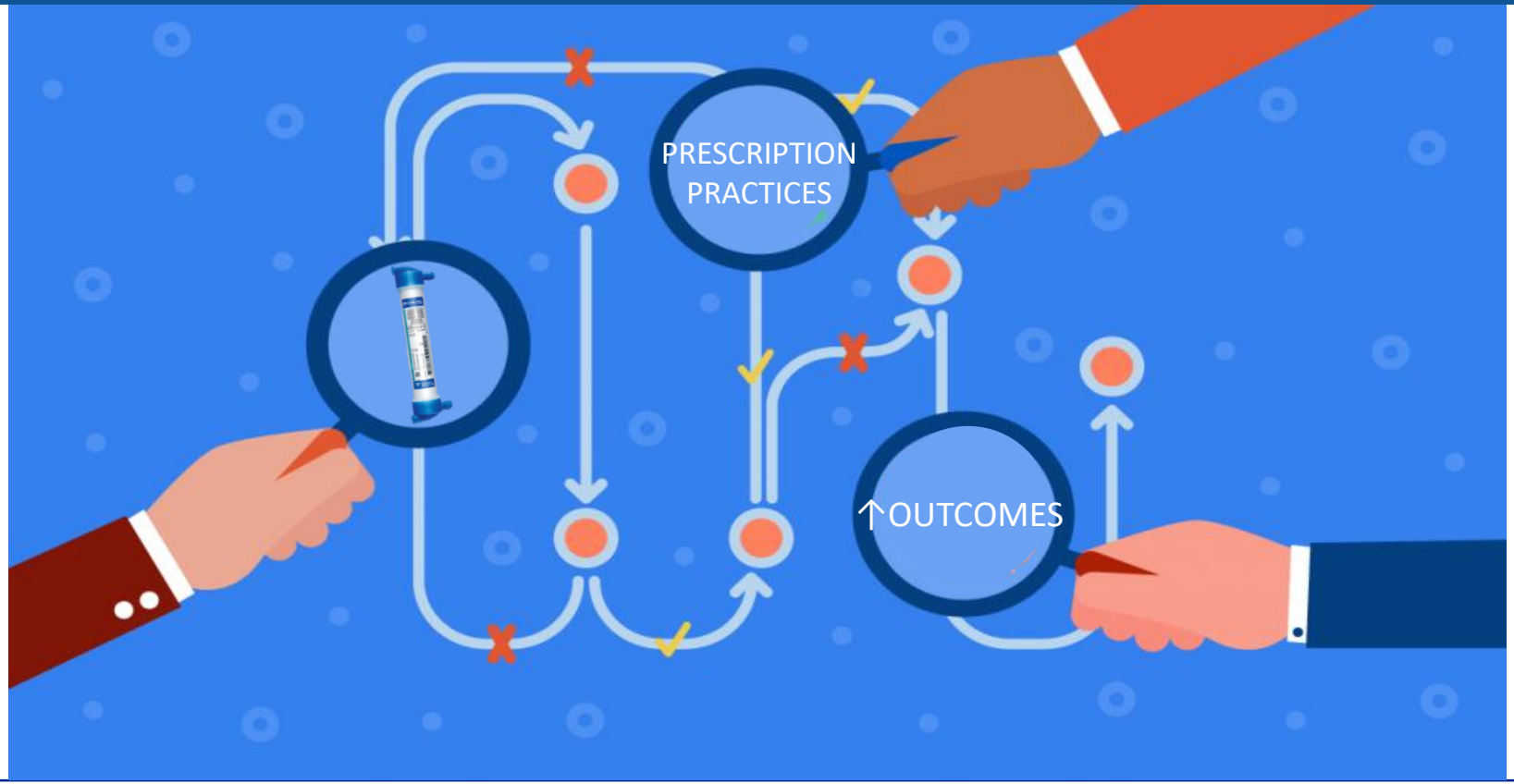
5 **What is the Take Home Message?**

An Innovative Membrane/Dialyzer is on the Way

It Fulfills All Major Criteria To Reduce Morbidity and Mortality



Integrate this Innovative Dialyzer in your Daily Workflow to Improve Patient Outcomes




THANK
YOU!