УРЕМИЧЕСКИЕ ТОКСИНЫ И ДИАЛИЗНЫЕ МЕМБРАНЫ: ПРОШЛОЕ, НАСТОЯЩЕЕ И БУДУЩЕЕ. ПРАГМАТИЗМ, РОМАНТИЗМ ИЛИ РЕАЛИЗМ?

ВАЛЕРИЙ ШИЛО, МОСКВА
КАФЕДРА НЕФРОЛОГИИ МГМСУ ИМ. ЕВДОКИМОВА; МОСКВА
СЕТЬ КЛИНИК Б. БРАУН АВИТУМ В РФ
АССОЦИАЦИЯ АМОНД

«Декабрьские встречи»

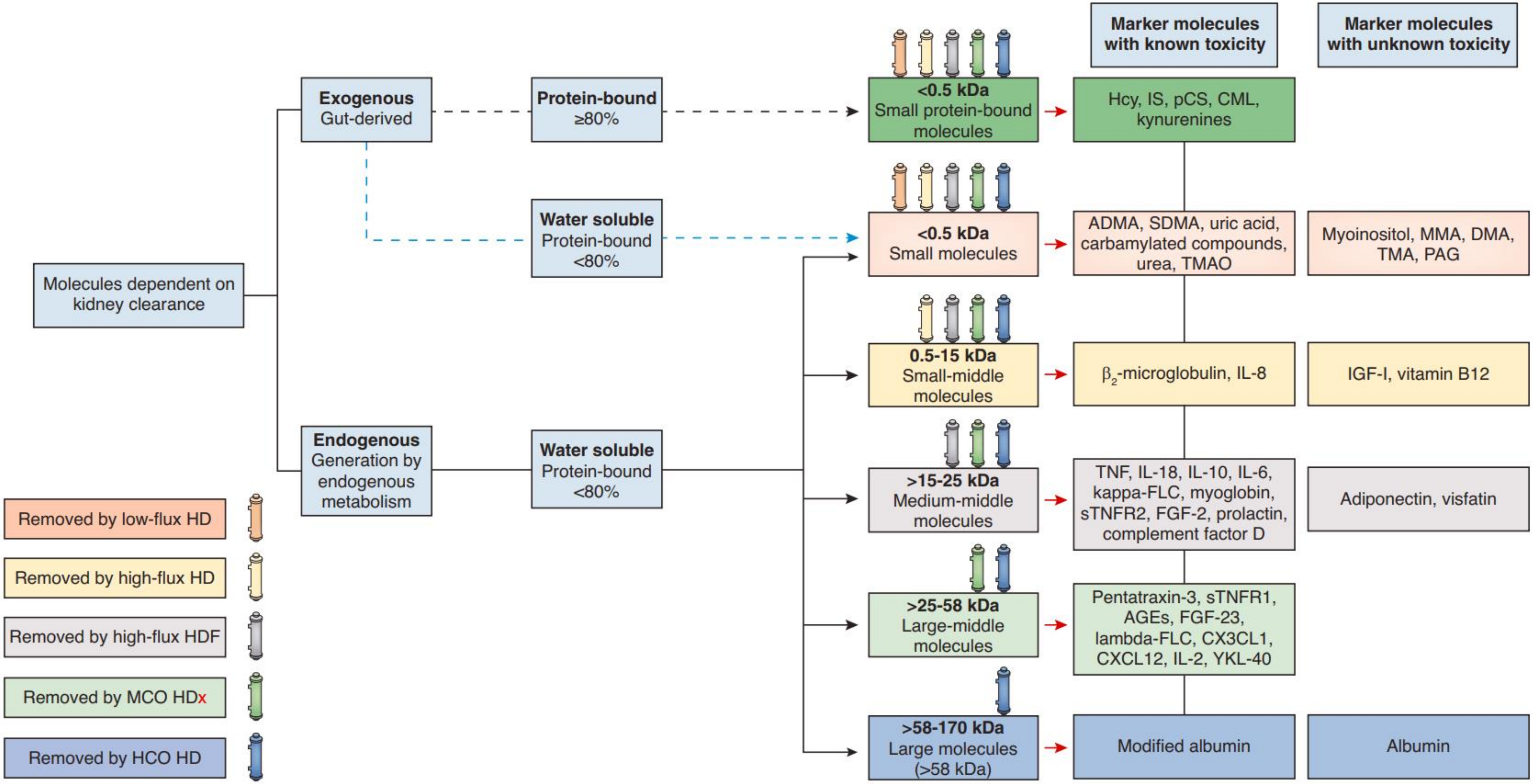
XIV Региональная конференция Санкт-Петербурга и Северо-Западного округа

10-11 декабря 2022 г.

Уремические токсины – 2022

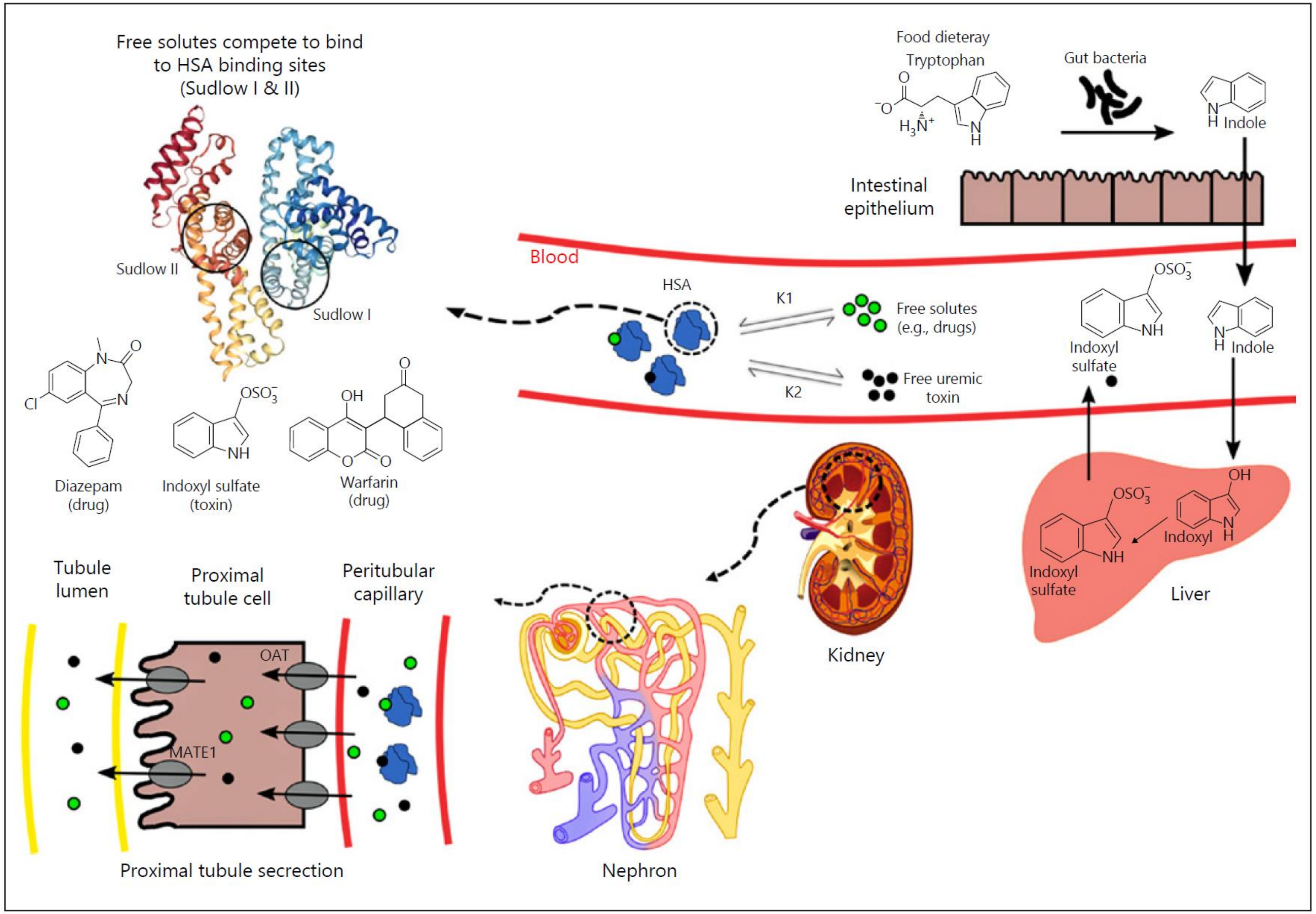
Small (<500 Daltons)	Medium (500–15,000 Daltons)	Large (>15,000 Daltons)	Protein-bound* (Daltons)
Sodium (23) Phosphorus (31) Potassium (35) Urea (60) Creatinine (113) Uric acid (168) Glucose (180)	Vitamin B12 (1355) Vancomycin (1448) ANP (3100) Endothelin (4300) Insulin (5200) PTH (9225) β_2-Microglobulin (11,800) Resistin (12,500) Cholecystokinin (12,700) Cystatin C (13,300)	Cytokines (15,000–30,000) Myoglobin (17,000) Kappa FLC (22,500) Complement factor D (27,000) FGF-23 (32,000) α_1-Microglobulin (33,000) Erythropoietin (34,000) Lambda FLC (45,000) Albumin (68,000) AOP (various) AGEP (various)	Phenol (94) *p*-Cresol (108) Homocysteine (135) Indole-3-acetic acid (175) Hippuric acid (179) Carboxymethyl-lysine (204) Indoxyl sulfate (251) Acrolein (56)

Новая классификация уремических токсинов 2022



M. Rosner et al CJASN 16, 2021. doi: https://doi.org/10.2215/CJN.02660221

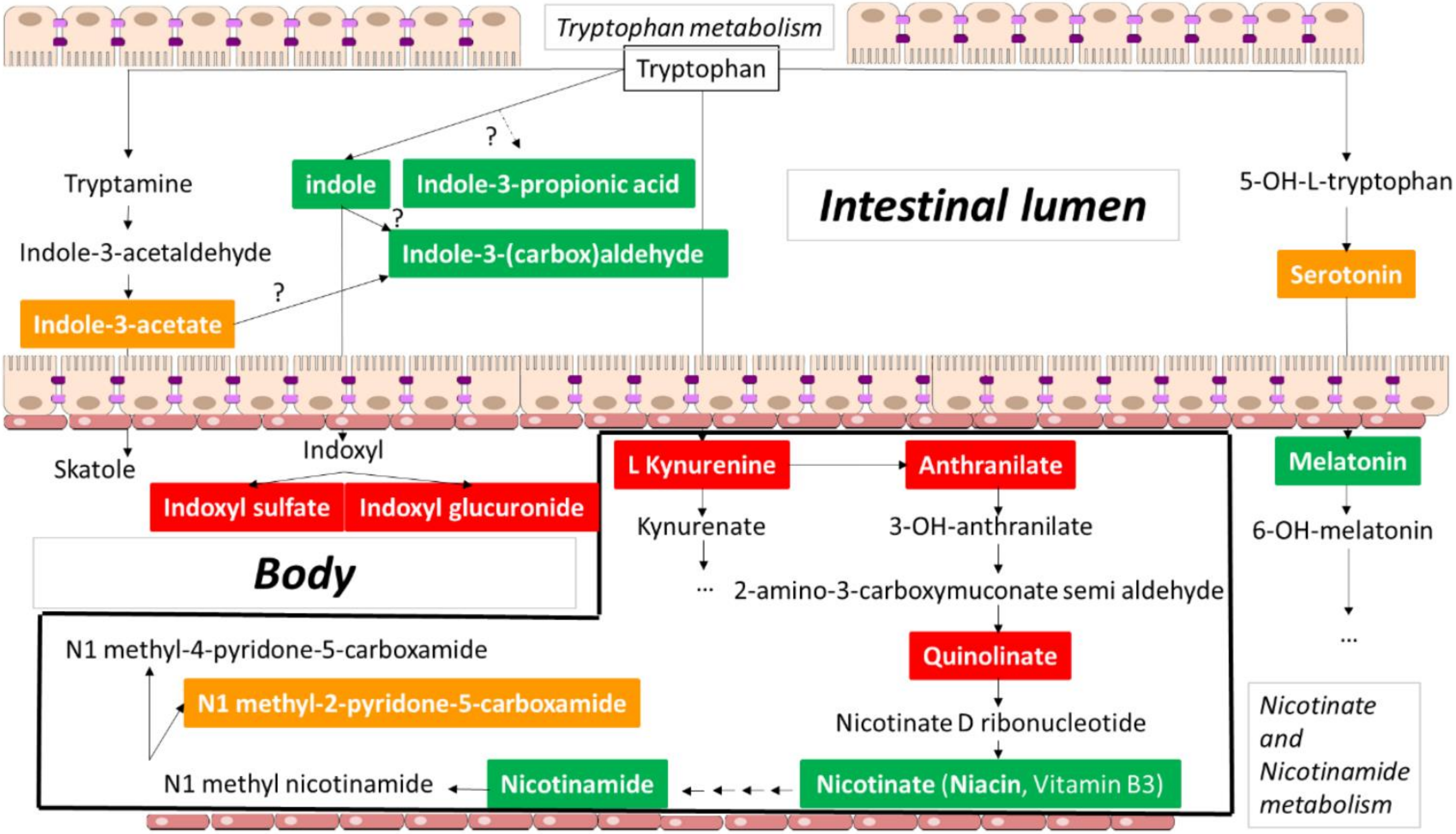
Продукция, транспорт и элиминация индоксил-сульфата



Uremic Toxins and their Relation to Dialysis Efficacy

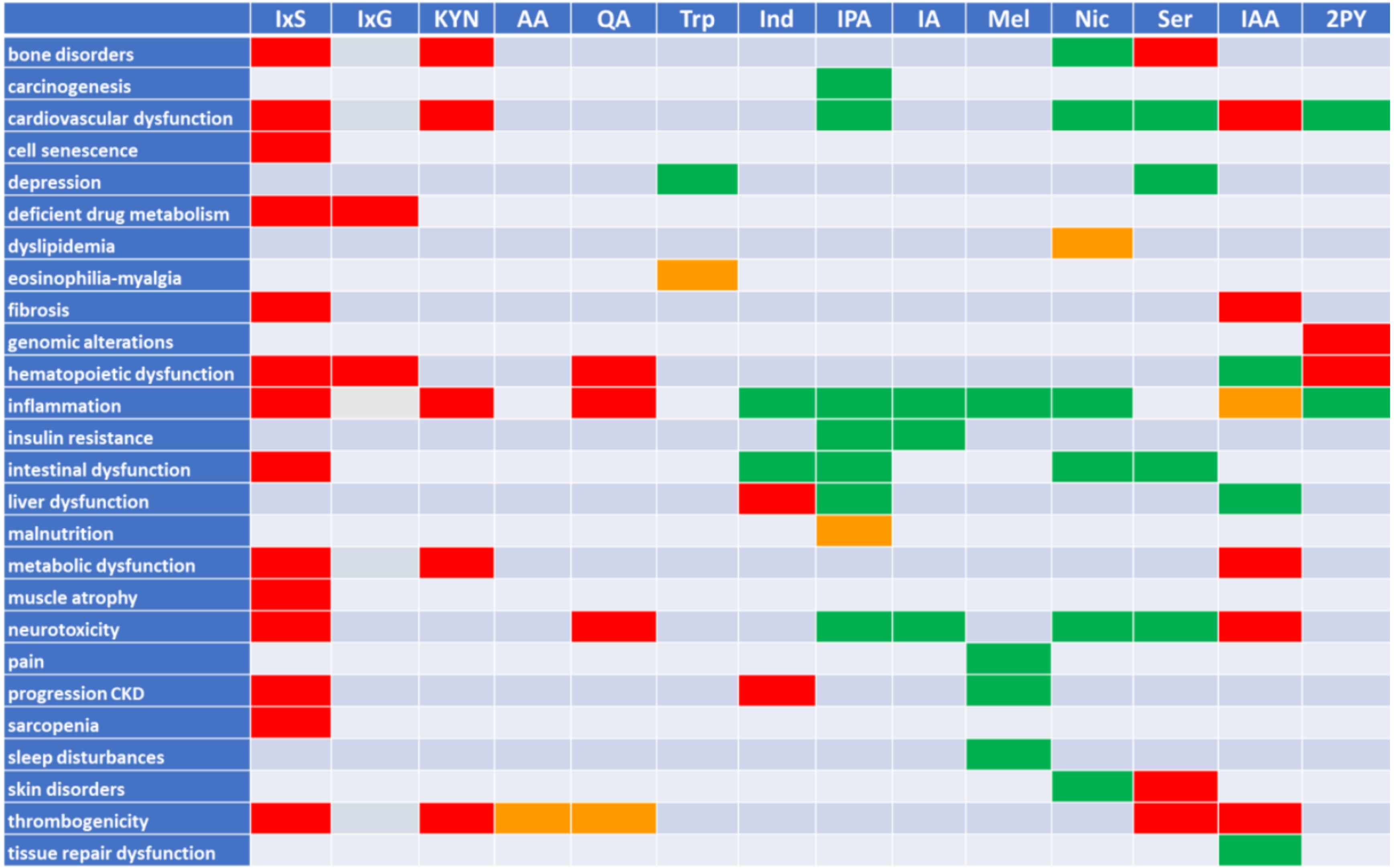
Blood Purif 2019;48:299–314

Что, если не все метаболиты при уремии токсичны? Гипотеза.



Raymond Vanholder et al Toxins 2022, 14, 221. https://doi.org/10.3390/toxins14030221

Биологические эффекты метаболитов триптофана



CKD: chronic kidney disease. IxS: indoxyl sulfate; IxG: indoxyl glucuronide; KYN: kynurenine/kynurenic acid; AA: anthranilic acid; QA: quinolinic acid; Trp: tryptophan; Ind: indole; IPA: indole-3-propionic acid; IA: indole-3-(carbox)aldehyde; Mel: melatonin; Nic: nicotinic acid/nicotinamide; Ser: serotonin; IAA: indole-3-acetic acid; 2PY: 1-methyl-2-pyridone-5-carboxamide.

Toxins 2022, 14, 221. https://doi.org/10.3390/toxins14030221

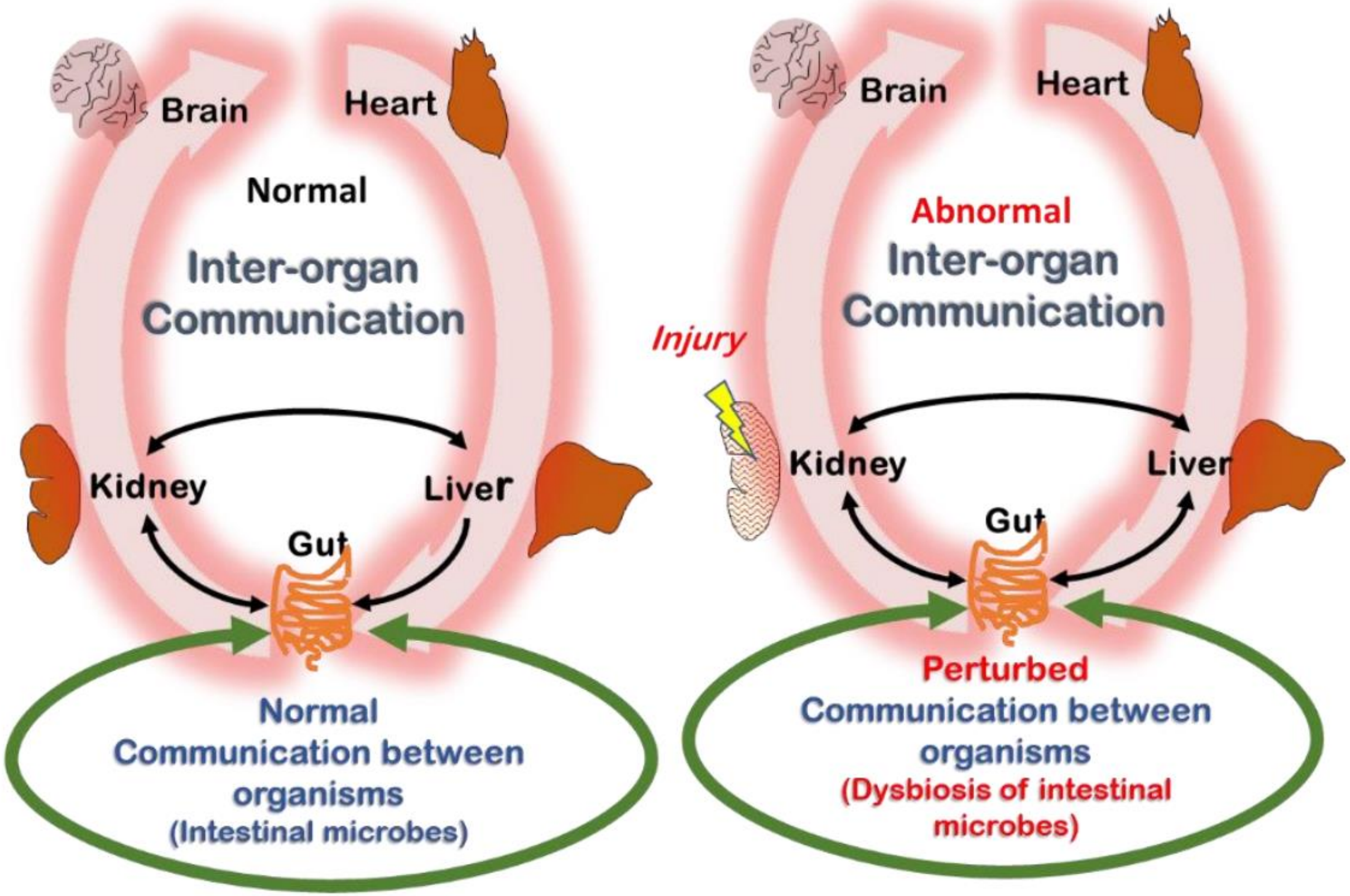
Противоположное действие пептидов, накапливающихся при уремии

Table 3. Opposite mechanisms in families of peptidic uremic retention compounds.

Toxic	Neutral or Non-Toxic
Complement factor D	Complement factor Ba
Interleukin-1β	Interleukin-1 receptor antagonist
Tumor necrosis factor-α	Soluble tumor necrosis factor receptor
Interleukin-6	Interleukin-10
Cholecystokinin	Ghrelin
Desacyl Ghrelin	Ghrelin
Leptin	Orexin A
Peptide YY	Neuropeptide Y

Toxins 2022, 14, 221

Теория RSST - дистанционного зондирования и сигнализации



Toxins 2022, 14, 221. https://doi.org/10.3390/toxins14030221

В 1991 году преобладали мембраны из целлюлозы

1991: KIDNEY PATIENTS WORLDWIDE

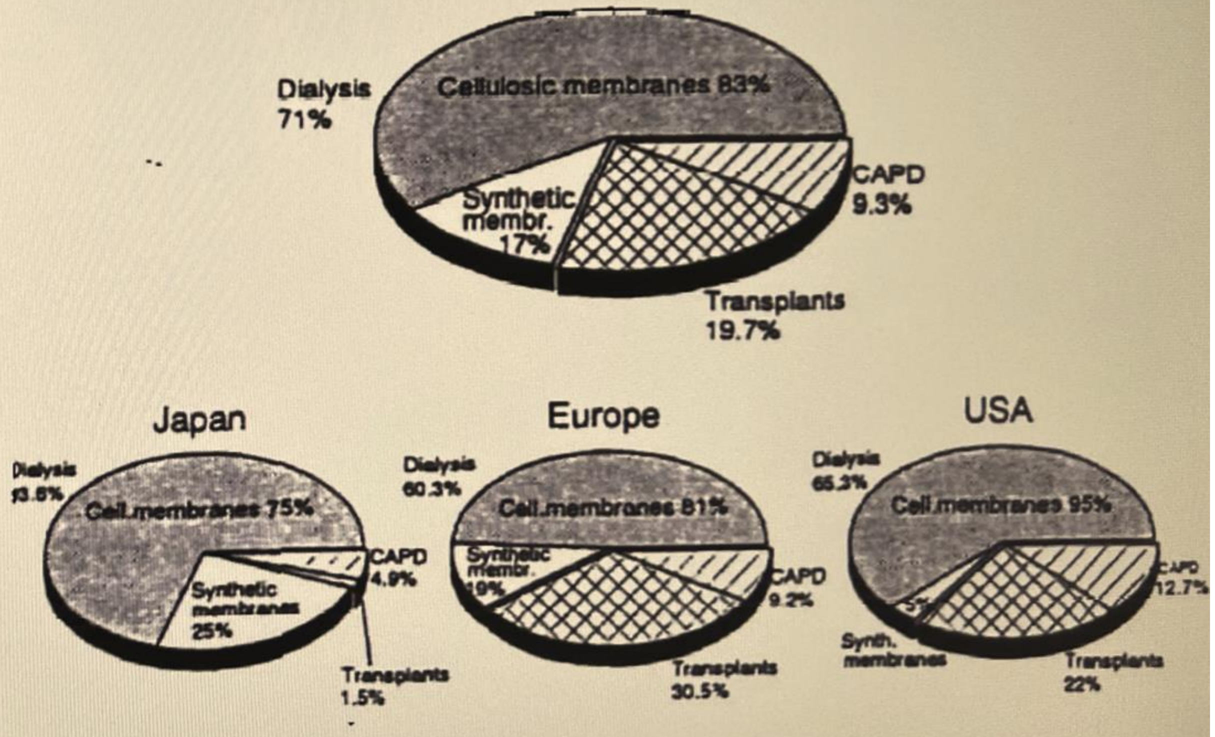
In **1991**, 450,000 uraemic patients would owe their lives to dialysis therapy.

End Stage Kidney Disease patients worldwide treated with hemodialysis therapies: 71%

- **Cellulosic membranes: 83%**
- **Synthetic membranes: 17%**

About 10% of uraemic patients used the natural peritoneal membrane in continuous ambulatory peritoneal dialysis (CAPD).

About one-fifth of patients worldwide obtained a transplanted organ.



Klinkmann H and J. Vienken J. Membranes for dialysis. NDT (1995) 10 [Suppl. 3]: 39-45

Этапы создания синтетических мембран

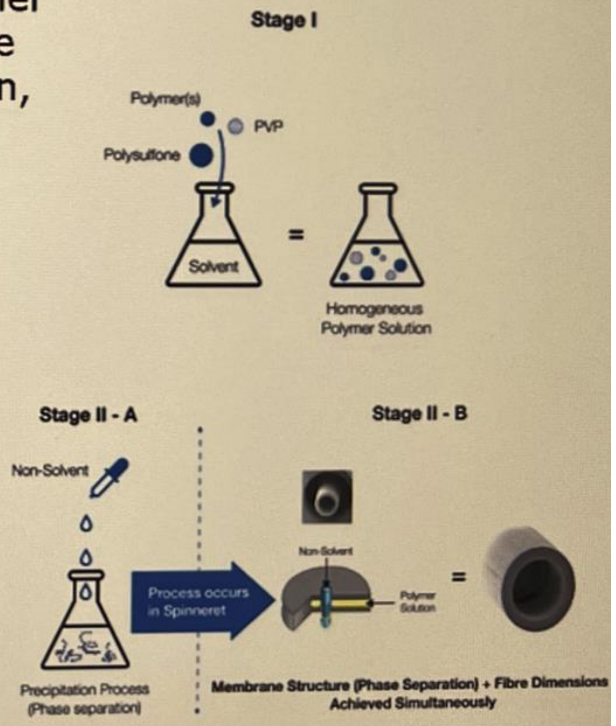
TECHNOLOGY: STAGES INVOLVED IN THE MAKING OF MEMBRANES

Stage I: A Homogenous Polymer Solution is prepared dissolving in a solvent polymer granules and copolymer solution (e.g. polysulfone and polyvinyl-pyrrolidone, PVP). Copolymers, content and molecular weight, influence the rheology of the polymer solution and the structure of the stroma. Copolymers are necessary to fine-tune solute permeability, increase hydrophilicity, prevent excessive protein deposition, coagulation, platelet adhesion, and ensure good membrane biocompatibility.

Stage II – A: The addition of non-solvent to induce precipitation culminates in phase separation.

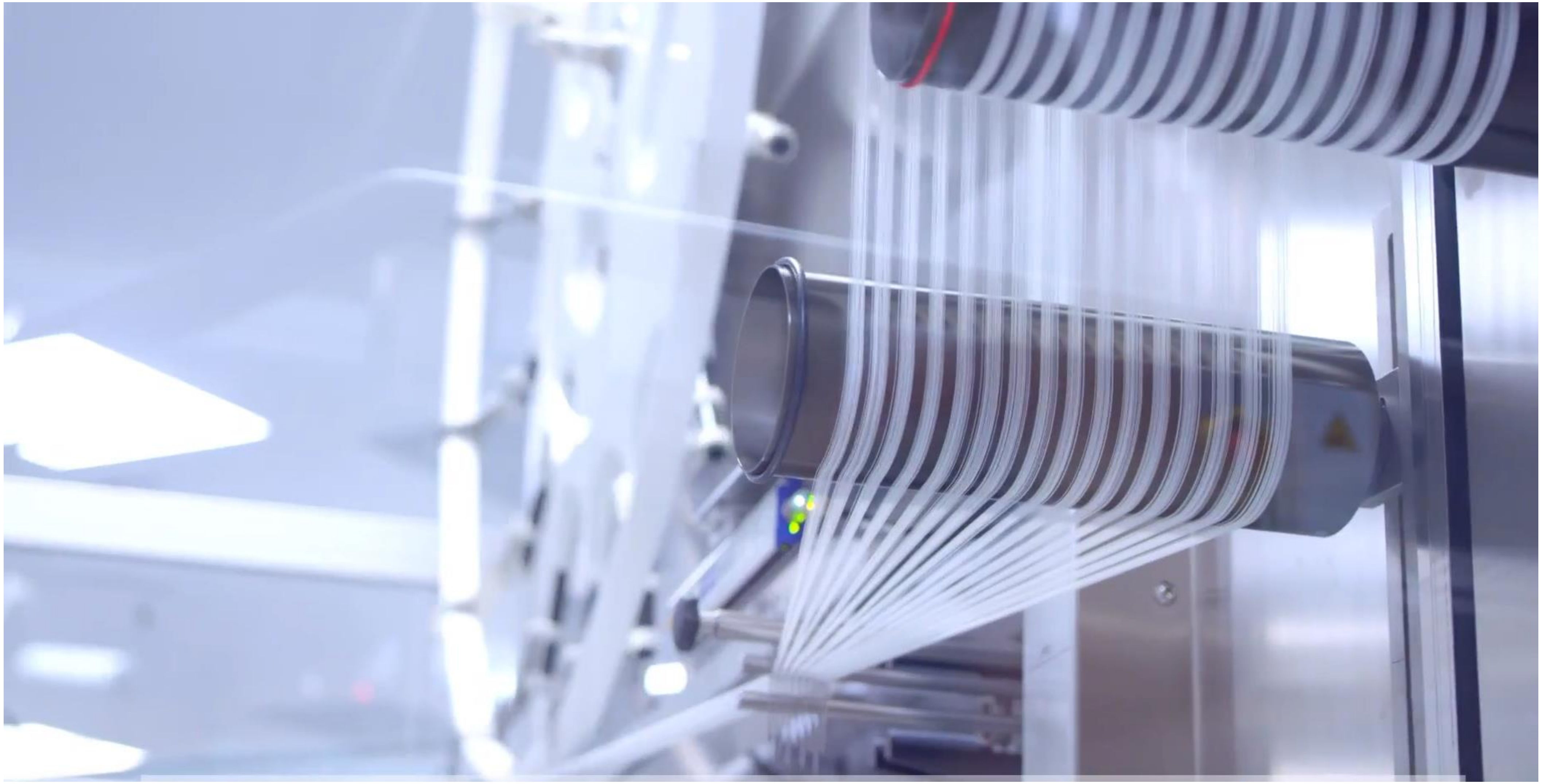
Stage II – B: The nano-controlled thermodynamic 'spinning' process (extrusion) occurs in the spinneret and defines surface roughness, fiber dimensions (wall thickness and lumen diameter), porosity of the membrane wall, and consequently the membrane performances:

- Small solute diffusive permeability KoA, (pore density)
- Hydraulic permeability, Kuf (pore density, mean pore size, pore size distribution)
- Sieving properties, sieving coefficient (mean pore size, pore size distribution)



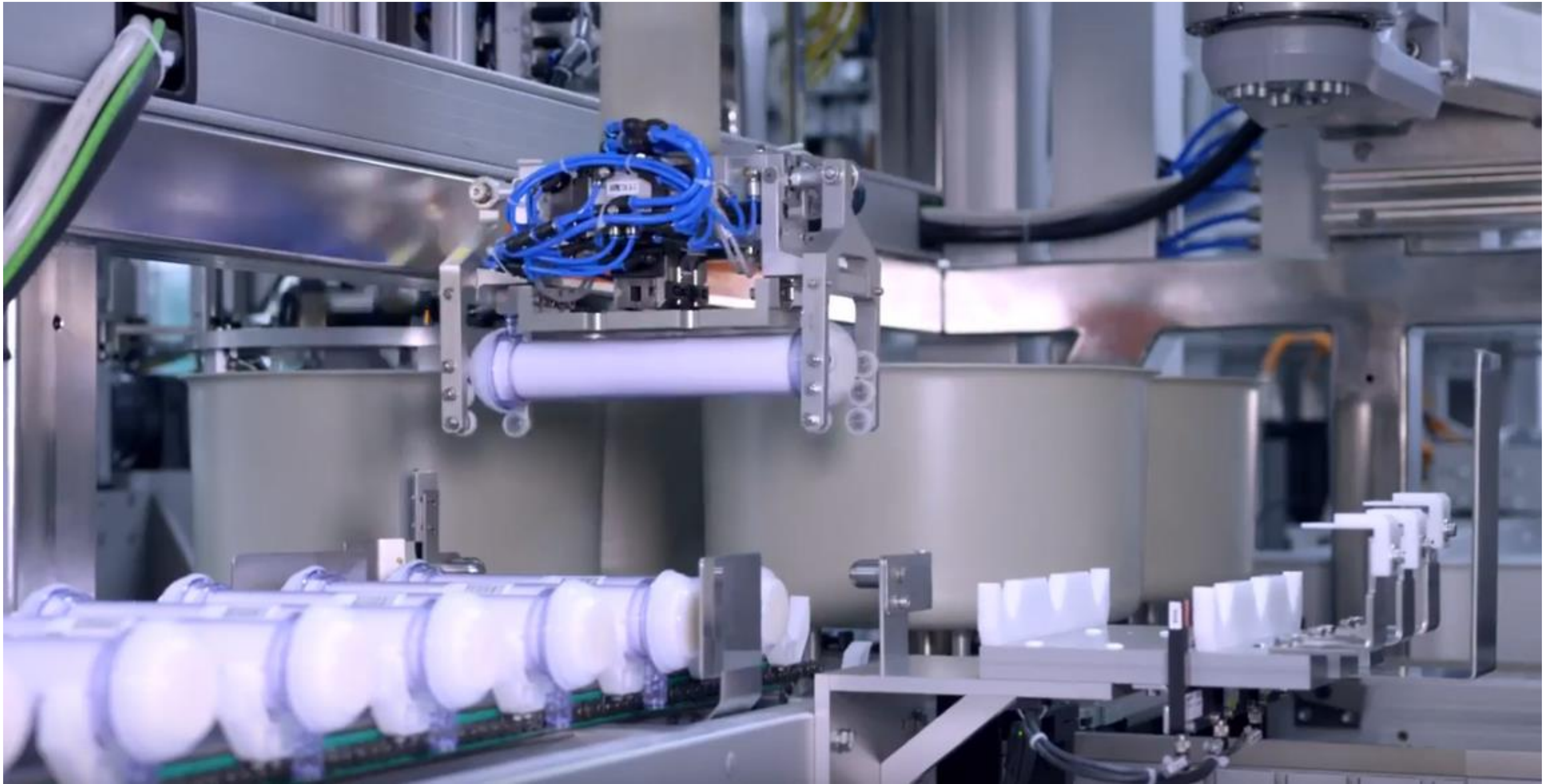
Bowry SK, and Chazot C. The scientific principles and technological determinants of haemodialysis membranes. Clin Kidney J. 2021 Dec; 14(Suppl 4): i5–i16.

СОВРЕМЕННОЕ РОБОТИЗИРОВАННОЕ ПРОИЗВОДСТВО ДИАЛИЗАТОРОВ, ГЕРМАНИЯ

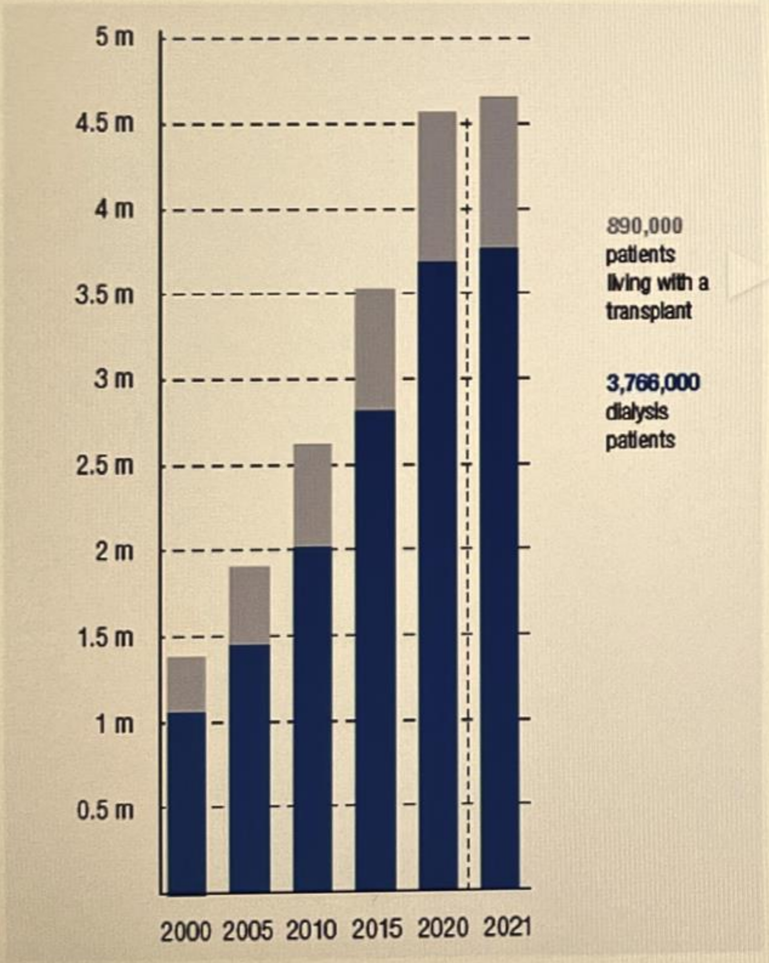


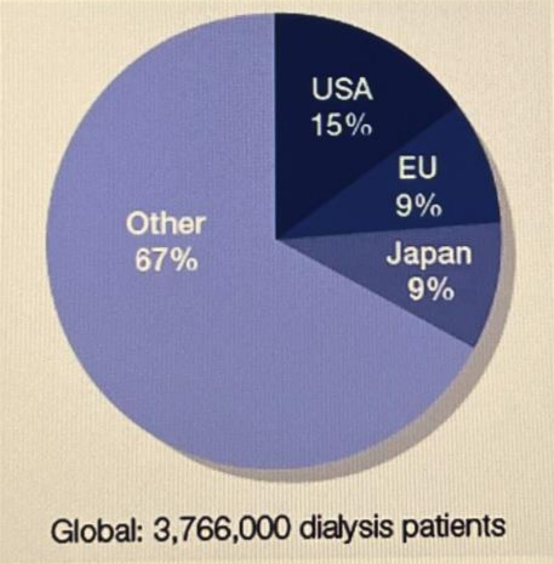
СОВРЕМЕННОЕ РОБОТИЗИРОВАННОЕ ПРОИЗВОДСТВО ДИАЛИЗАТОРОВ, ГЕРМАНИЯ

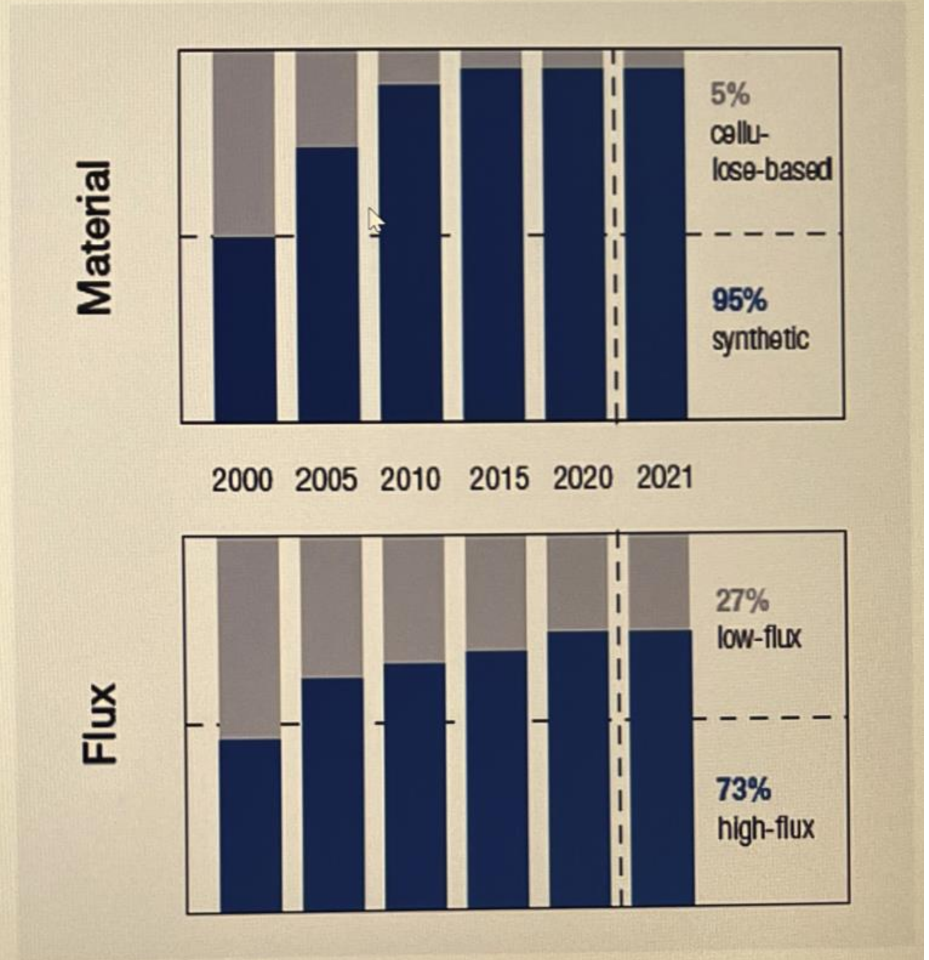
B|BRAUN
SHARING EXPERTISE



1991 – 2021: KIDNEY PATIENTS WORLDWIDE







Moeller S et al. Fresenius Medical Care: ESKD Patients in 2021 A Global Perspective

Мир современных гемодиализных мембран

- Низкопроницаемые (низкопоточные) мембраны LFHD
- **Низкопроницаемые (низкопоточные) мембраны с высоким КоА LFHEHD**
- Высокопроницаемые мембраны HFHD
  - Покрытые мембраны (вит Е, гепарин), **технология Endexo**
  - Адсорбирующие белок мембраны
  - Сверхпроницаемые мебраны, или альбумин-проницаемые мембраны (НСО), допускающие потери белка (до 4 г)
- **Высокопроницаемые универсальные селективные мембраны HFHD, HDF**
- Высокопроницаемые мембраны с отсечкой больших средних молекул (МСО) HFHD (Увеличен размер пор = неизбежна потеря альбумина- - какая потеря допустима?)

Современные диализные мембраны разных производителей

Table 1. Commercial dialyzers in the current market.

Country	Dialyzer Series Name	Brand	[a] Polymeric Material(s)	Sterilization
Germany	FX-class	Fresenius	PSf (Helixone)	Inline steam
	F-series		PSf	Inline steam
	Hemoflow™		PSf	Ethylene oxide, steam or electron beam
	Purema	Membrana	PES	Gamma ray
The United States of America	Polyflux L	Baxter	PAES, PVP and PA	Steam
	Theranova		PAES and PVP blend BPA-free	Steam
	Revaclear		PAES and PVP blend BPA-free	Steam
	Xevonta	B Braun	PSf	Gamma
	Diacap Pro		α PSf pro	Oxygen free gamma
Japan	ELISIO S	Nipro	PES (polynephron)	Gamma ray
	Sureflux		CTA	Gamma ray
	Solacea™		CTA	Oxygen free gamma
	APS-U	Asahi	Asahi PSf	Gamma sterilized wet type
	ViE Series		Vitamin E-coated PSf	Gamma sterilized wet type
	Rexeed Series		PSf	Gamma ray and
	KF-201 Series		EVAL	Gamma ray
	Toraysulfone TS	Toray	PSf	Gamma ray
	Filtryzer		PMMA	Gamma ray
	Renak	Kawasumi	PSf	Gamma ray
China	F15	WEGO	PSf	Gamma ray
	HF15		PSf	Gamma ray

[a] BPA (bisphenol A); CTA (cellulose triacetate); EVAL (ethylene vinyl alcohol copolymer); PA (polyamide); PAES (polyarylethersulfone); PES (polyethersulfone); PMMA (polymethylmethacrylate); PSf (polysulfone); PVP (polyvinylpyrrolidone).

N Said et al Membranes 2021, 11, 767

Современная классификация мембран (одна из, неполная) цит. по А.Ю. Земченкову

Категория	КУФ (мл/час)/ /ммHg/м²)	β_2-микроглобулин		Альбумин	
		клиренс (мл/мин)	коэф. просеи-вания	потери за сеанс (г)	коэф. просеивания
низкопоточные	<12	<10	-	0	0
высокопоточные	14-40	20-80	<0,7-0,8	<0,5	<0,01
со **средней** точкой отсечения	40-60	>80	0,99	2-4	<0,01
белок-теряющие	>40	>80	0,9- 1,0	2-6	0,01-0,03
с **высокой** точкой отсечения	40-60		1,0	9-23	<0,2

Сверхвысокопоточные

Storr M et al (2018)

Что такое высокопоточный диализатор?
Нет единства в определении понятий

B|BRAUN SHARING EXPERTISE

KUF BASED CLASSIFICATION OF MEMBRANES IN DIFFERENT STUDIES

	Kuf (ml/h/mmHg) LOW	MID	HIGH	
1995 Akizawa et al.	> 3		> 5	
2001 Clark and Ronco	< 12	12–30	> 30	
2002 HEMO Study	< 14		> 14	
2005 Ward	< 6	6–20 (?)	20–40	
2009 MPO Study	< 10		> 30	In the study, groups were separated: low-flux = 9.8 mL/h/mmg; high-flux = 44.7 mL/h/mmHg
2013 EGE Study	≤ 18		≥ 46	
2013 Tatterasall and Ward EUDIAL			> 20	
2017 Golper	< 15		> 15	
2018 Ronco and Clark	8	8–30 (?)	> 30	
2018 Haroon and Davenport	< 10	10–20	> 20	

Unlike the HEMO Study, the difference between the Kuf values for the low-flux versus high-flux patient groups was statistically significant

KDOQI HD ADEQUACY GUIDELINE: 2015 UPDATE

Guideline 5: Hemodialysis Membranes[1]

5.1 We recommend the use of biocompatible, either high- or low-flux hemodialysis membranes for intermittent hemodialysis. (1B)

" For this guideline, we reviewed 3 large RCTs[2-4] that tested the hypotheses that high- versus low-flux dialyzers could improve either survival or CV outcomes in patients undergoing maintenance HD

The Work Group thought that high-flux dialyzers should be used preferentially. However, factors such as cost should be considered.

In locations with cost restraints, patients with diabetes, lower serum albumin, or longer dialysis vintage should be considered a priority for selection of high-flux dialyzers".

1. Daurgirdas JT et al. KDOQI clinical practice guideline for hemodialysis adequacy: 2015 update Am J Kidney Dis. 2015;66(5):884-930
2. Eknoyan G, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347: 2010–2019
3. Locatelli F, et al. Membrane Permeability Outcome (MPO) study group: effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol 2009; 20: 645–654
4. G. Asci, et al. The impact of membrane permeability and dialysate purity on cardiovascular outcomes. J Am Soc Nephrol, 24 (6) (2013), pp. 1014-1023

B|BRAUN
SHARING EXPERTISE

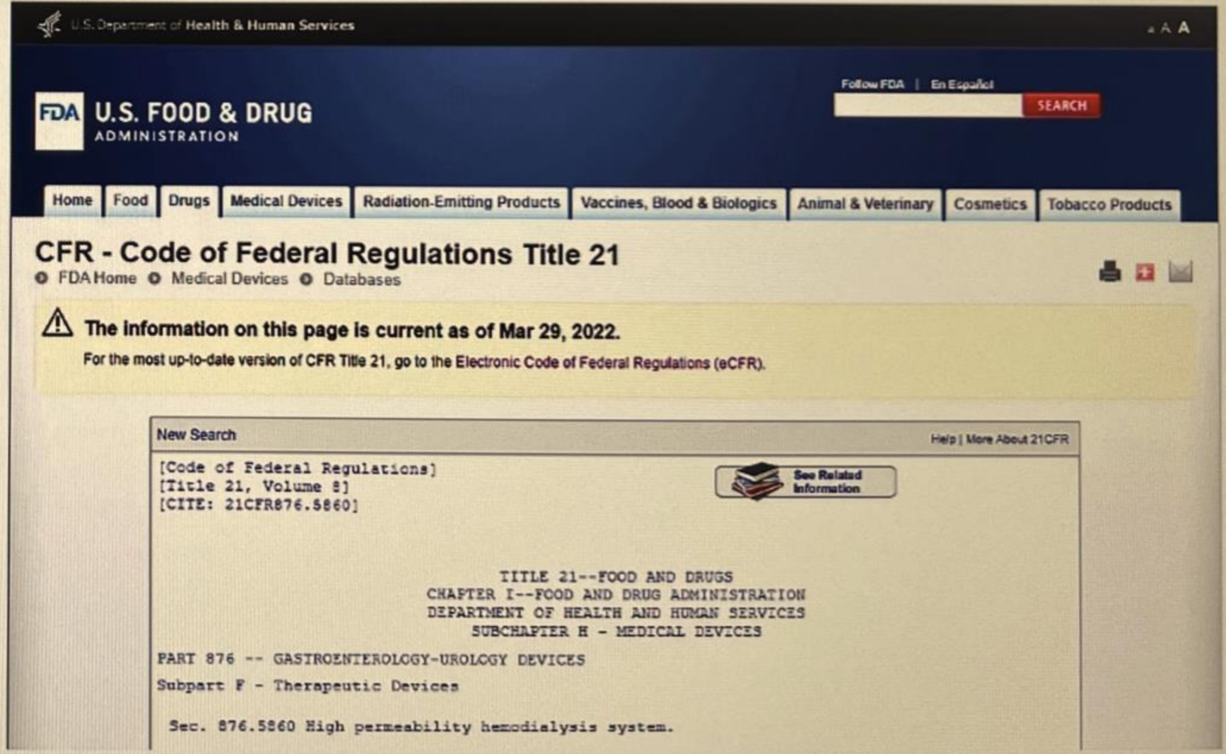
■ 2022: FDA CFR - CODE OF FEDERAL REGULATIONS TITLE 21*

High permeability hemodialysis system (Mar 29, 2022)

...

The hemodialyzer consists of a **semipermeable membrane with an in vitro > 8 mL/h/mmHg**, as measured with bovine or expired human blood, and is used with either an automated ultrafiltration controller or another method of ultrafiltration control to prevent fluid imbalance.

...



*: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=876.5860

B|BRAUN
SHARING EXPERTISE

Классификация и характеристика диализных мембран

Table 1. The classification and characteristics of dialysis membranes.

	MWRO(Da)	MWCO(Da)	Water Permeability (mL/h/mmHg/m^2)	Sieving Coefficient		Pore Radius (nm)
				β2m	Albumin	
Low-flux	2000–3000	15,000	10–20	-	<0.010	2.0–3.0
High-flux	4000–10,000	15,000–16,000	200–400	0.7–0.8	<0.010	3.5–5.5
Medium cut-off	10,000–13,000	60,000–100,000	600–850	1	0.008	5.0
High cut-off	15,000–20,000	200,000–300,000	1100	1	0.200	8.0–12.0

The membrane classification is based on the ultrafiltration coefficient (Kuf). The cut off value is defined by MWRO and MWCO. Abbreviations: MWRO, molecular weight retention onset; MWCO, molecular weight cut-off; β2m, beta-2 microglobulin.

Концепция мембраны со средней точкой отсечения

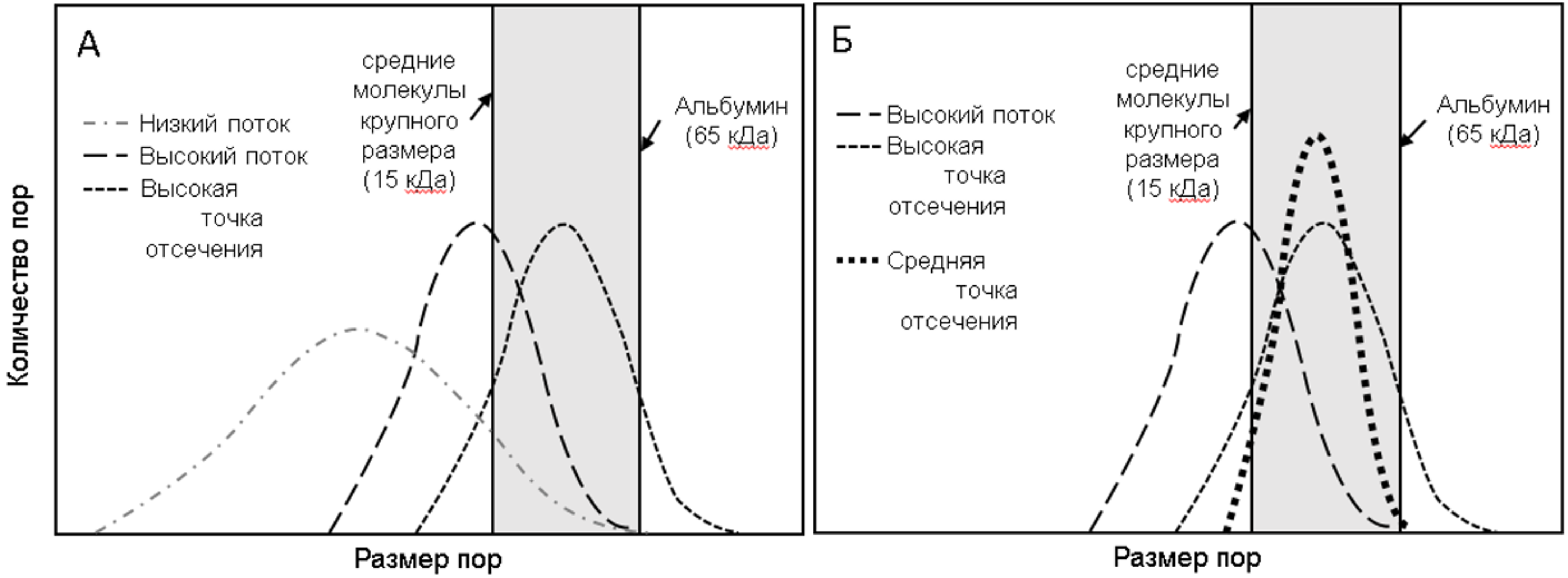


Рисунок 2. Распределение размеров пор мембран различных классов

Fig. 2. The pore size distribution in different classes' membrane

Расширенный гемодиализ - NDT 2018 Florence

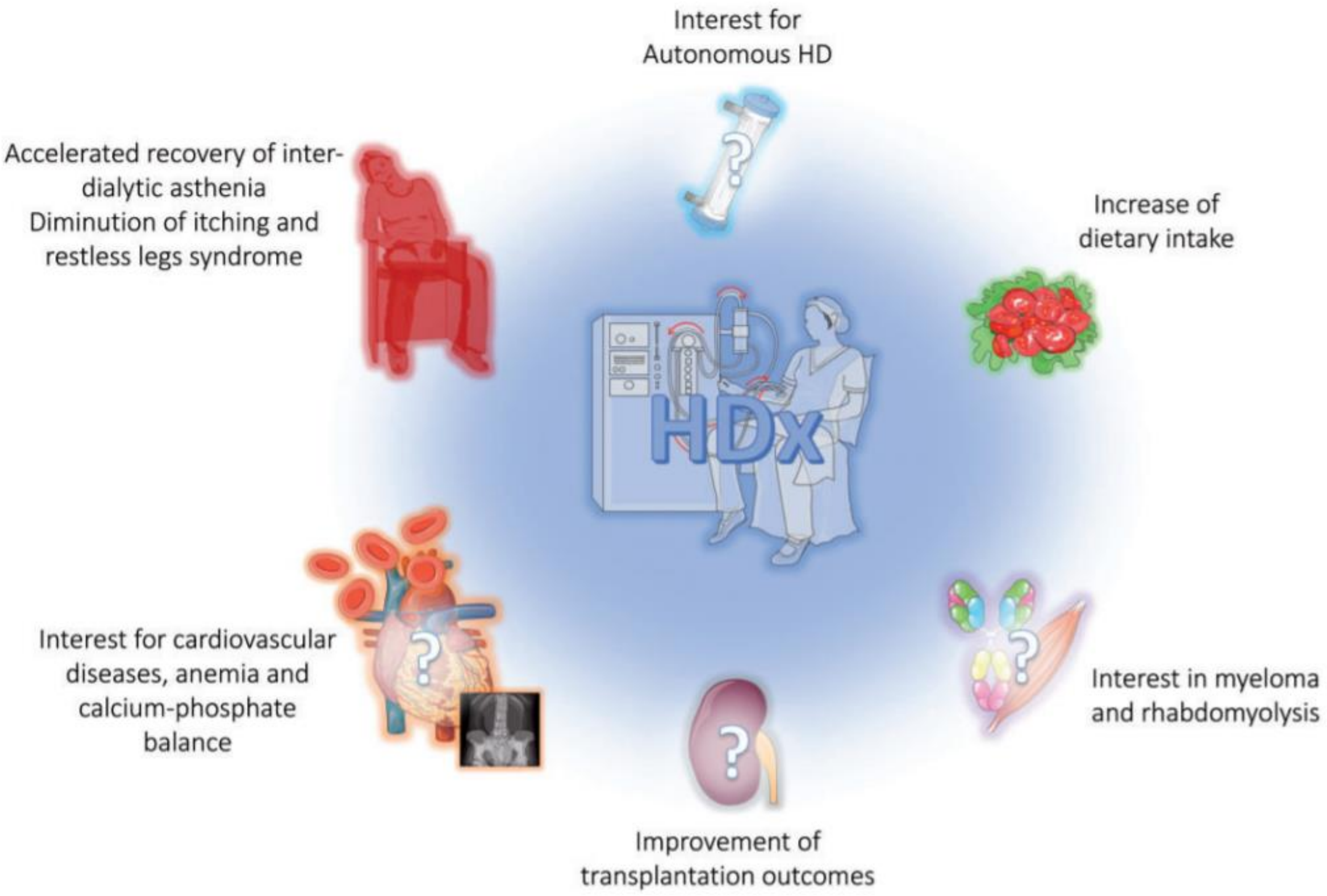
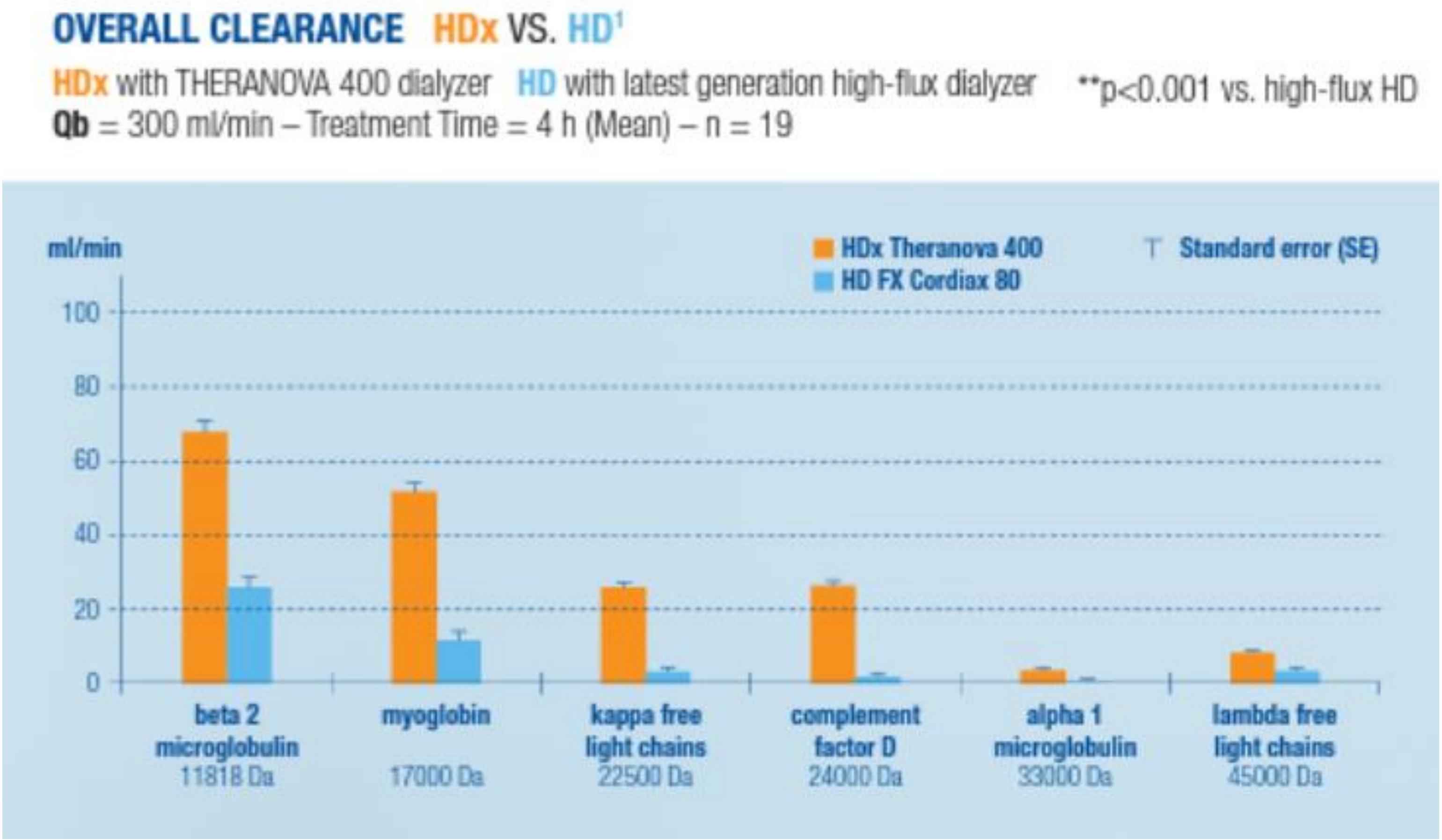


FIGURE 1: Potential development paths and clinical applications of HDx therapy.

Nevertheless, interventional studies are required to confirm or overturn these statements.

Клиренсы теранова



B|BRAUN
SHARING EXPERTISE

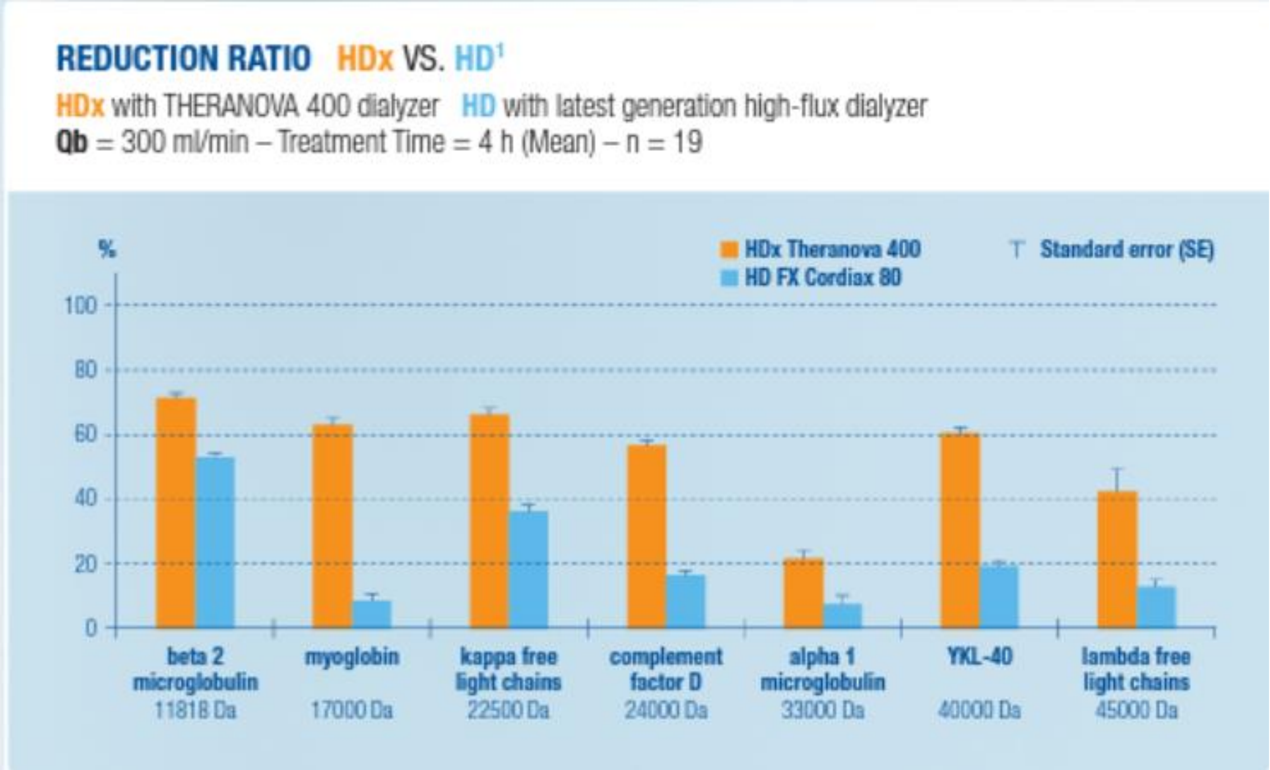
Клиренсы различных молекул, высокопоточные мембраны

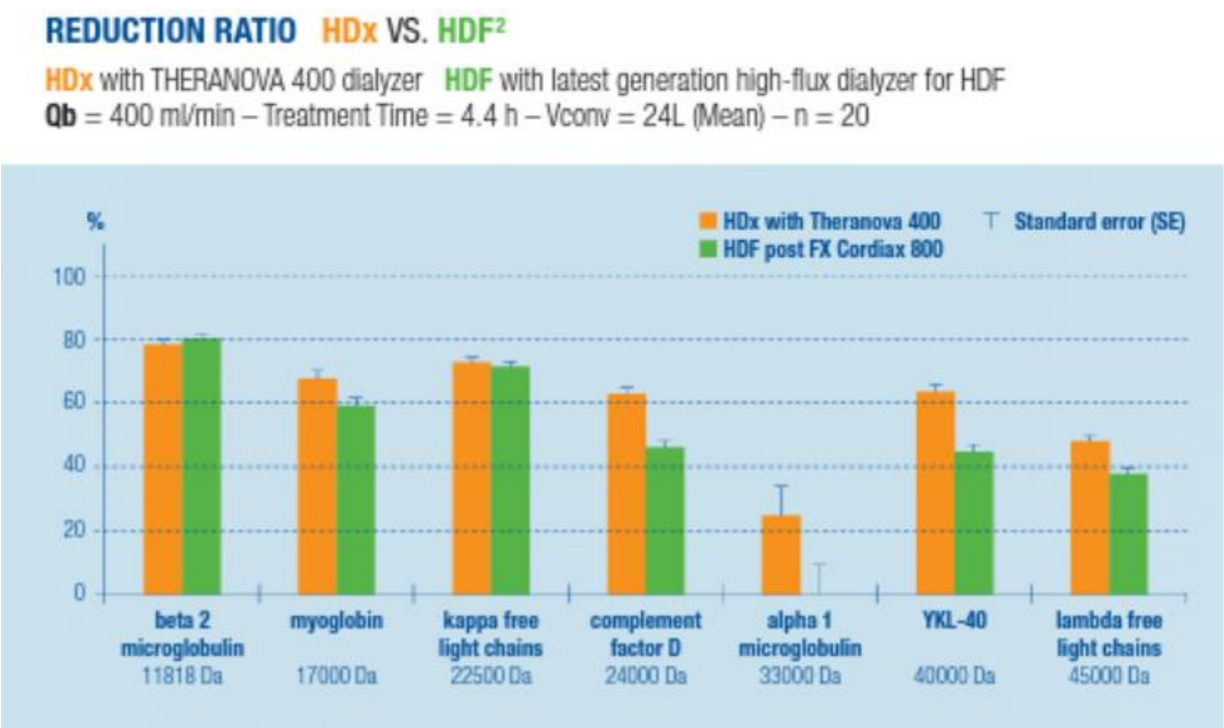
Table 4. Secondary endpoints: descriptive and superiority statistics

Laboratory test	Parameter	LS mean			P-value		
		FX CorAL 600	xevonta Hi 15	ELISIO 150H	Overall[a]	FX CorAL 600 versus xevonta Hi 15	FX CorAL 600 versus ELISIO 150H
β2-m (mL/min)	Clearance	105.74	97.23	97.73	**0.0011**	**0.0010**	**0.0019**
Myoglobin (%)	Removal rate	61.01	52.89	56.73	**<0.0001**	**<0.0001**	**0.0015**
Myoglobin (mL/min)	Clearance	50.43	39.42	50.60	**0.0003**	**0.0004**	0.9574
Creatinine (%)	Removal rate	67.24	66.68	66.27	0.6929	0.6304	0.3944
Creatinine (mL/min)	Clearance	177.70	176.75	176.73	0.8926	0.6856	0.6771
Phosphate (%)	Removal rate	61.18	60.32	59.95	0.7987	0.6561	0.5129
Phosphate (mL/min)	Clearance	184.55	184.24	184.45	0.9909	0.8951	0.9683
Urea (%)	Removal rate	73.93	73.89	73.49	0.8986	0.9658	0.6745
Urea (mL/min)	Clearance	191.91	192.85	192.90	0.8792	0.6693	0.6551

LS mean: least squares mean. P-value to conclude significant differences between groups (two-sided tests at the 5% level). P-values <0.05 are in bold.
[a]Overall test includes all three dialyzers.

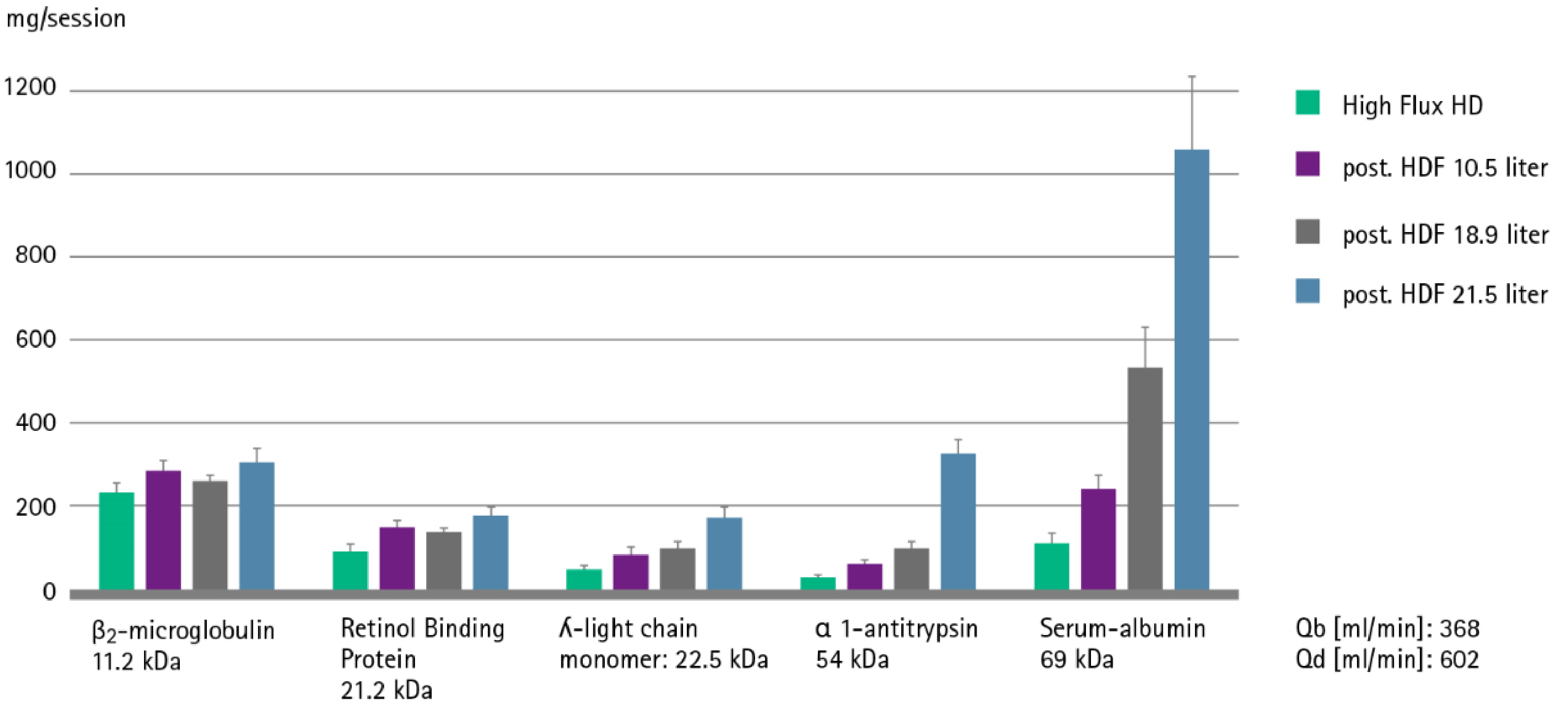
Характеристики Теранова





xevonta

МЕМБРАНА ЭКСПЕРТНОГО КЛАССА



Даже при высокообъемной ГДФ, потери альбумина ограничены 1 г/процедуру[6]

6 Gayard N et al.: Influence of high convection volumes in removal performances of on-line hemodiafiltration (HDF). Nephrol. Dial. Transplant. 2013; 28 (suppl. 1):i30-i32.

Высокопроницаемые альтернативы нынешним диализаторам для ХФГД и ГДФ

Received: 31 January 2019 | Revised: 24 April 2019 | Accepted: 26 April 2019

DOI: 10.1111/aor.13480

MAIN TEXT ARTICLE

Artificial Organs

WILEY

High-permeability alternatives to current dialyzers performing both high-flux hemodialysis and postdilution online hemodiafiltration

Francisco Maduell[1] | Lida Rodas[1] | José Jesús Broseta[1] | Miguel Gómez[1] | Marc Xipell Font[1] | Alicia Molina[1] | Enrique Montagud-Marrahi[1] | Elena Guillén[1] | Marta Arias-Guillén[1] | Nestor Fontseré[1] | Manel Vera Rivera[1] | Nayra Rico[2]

Глобальная шкала удаления молекул: сравнение HDx и ГДФ

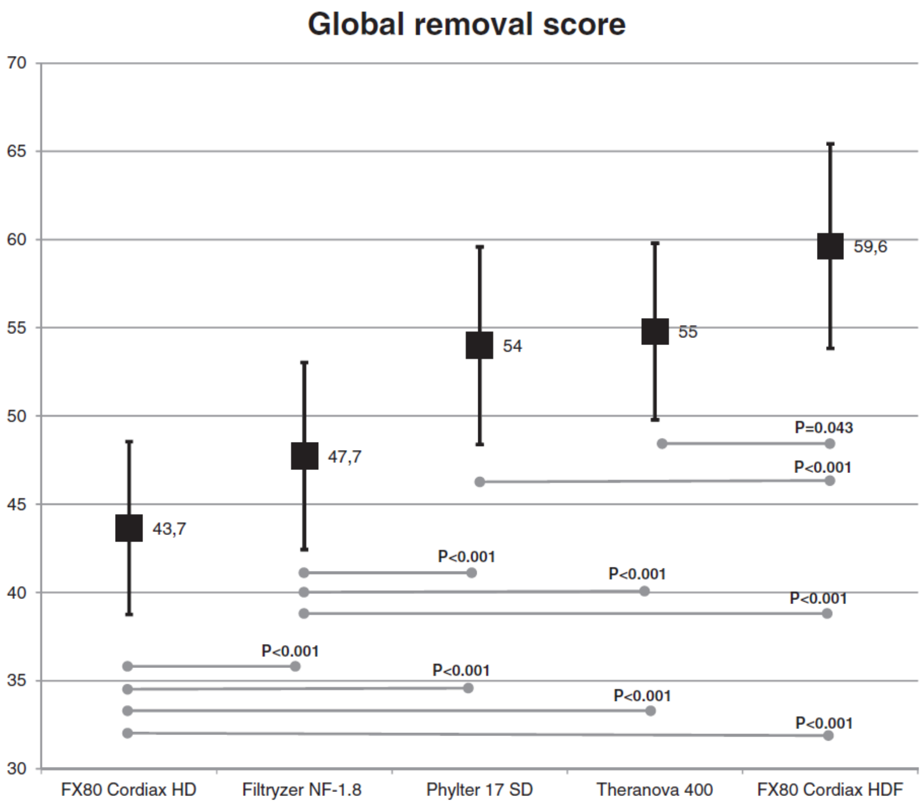
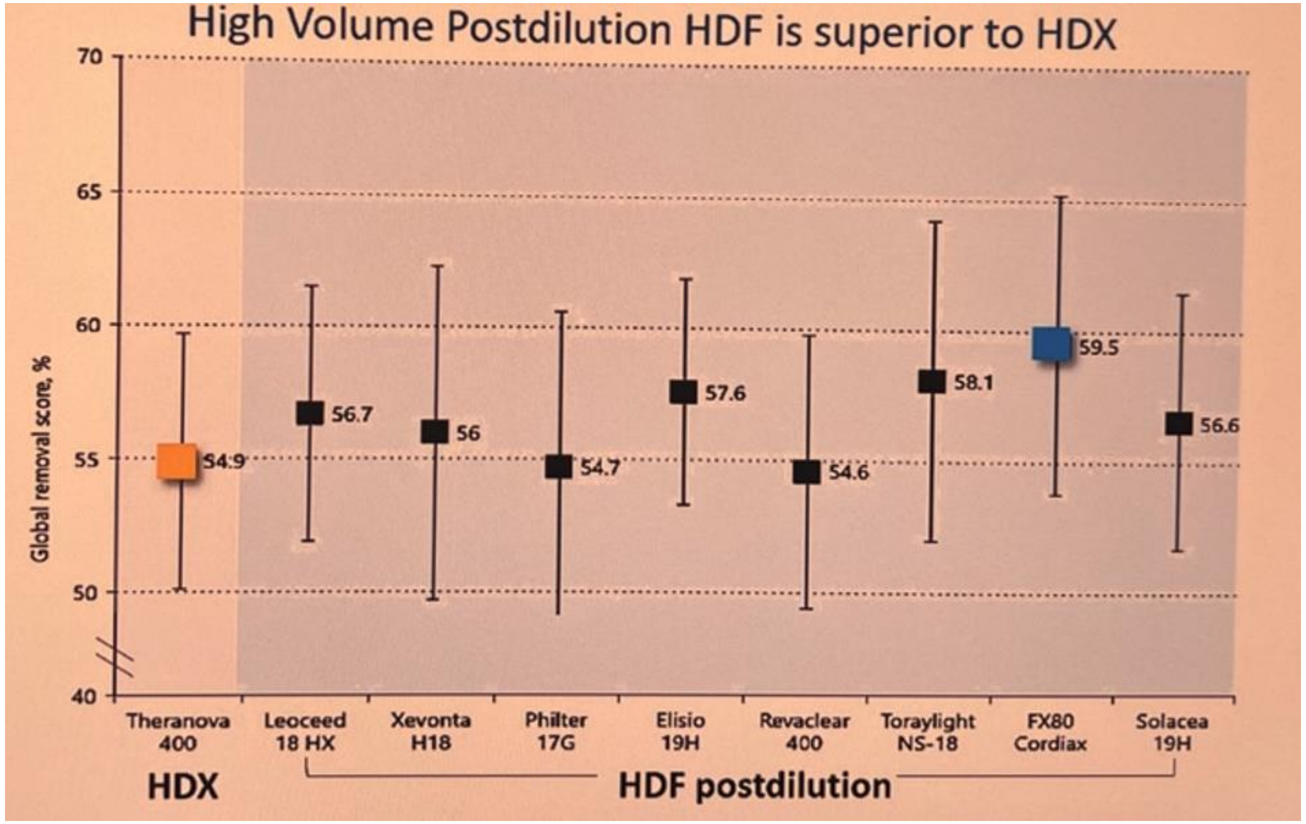


FIGURE 2 Global evaluation of removal efficacy for medium-size molecules and albumin loss in all study situations. (ANOVA for repeated data). Global removal score = (urea$_{RR}$ + β_2-microglobulin$_{RR}$ + myoglobinRR + prolactin$_{RR}$ + α_1-microglobulin$_{RR}$ + α_1-acid glycoprotein$_{RR}$ − albumin$_{RR}$)/6



Systematic Review

Effects of Medium Cut-Off Polyarylethersulfone and Polyvinylpyrrolidone Blend Membrane Dialyzers in Hemodialysis Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

B|BRAUN SHARING EXPERTISE

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Citation: Hung, Y.-H.; Lai, T.-S.; Belmouaz, M.; Tu, Y.-C.; Lai, C.-F.; Lin, S.-L.; Chen, Y.-M. Effects of Medium Cut-Off Polyarylethersulfone and Polyvinylpyrrolidone Blend Membrane Dialyzers in Hemodialysis Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Membranes* **2022**, *12*, 443. https://doi.org/10.3390/membranes12050443

Academic Editors: Makoto Fukuda, Kiyotaka Sakai and Hiroyuki Sugaya

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Abstract: The use of medium cut-off (MCO) polyarylethersulfone and polyvinylpyrrolidone blend membrane is an emerging mode in hemodialysis. Recent studies have shown that MCO membranes exhibit a middle high molecular weight uremic toxin clearance superior to standard high flux hemodialysis. We conducted a systematic literature review and meta-analysis of randomized controlled trials to investigate whether MCO membranes efficiently increase the reduction ratio of middle molecules, and to explore the potential clinical applications of MCO membranes. We selected articles that compared beta 2-microglobulin (β2M), kappa free light chain (κFLC), lambda free light chain (λFLC), interleukin-6 (IL-6), and albumin levels among patients undergoing hemodialysis. Five randomized studies with 328 patients were included. The meta-analysis demonstrated a significantly higher reduction ratio of serum β2M ($p < 0.0001$), κFLC ($p < 0.0001$), and λFLC ($p = 0.02$) in the MCO group. No significant difference was found in serum IL-6 levels after hemodialysis. Albumin loss was observed in the MCO group ($p = 0.04$). In conclusion, this meta-analysis study demonstrated the MCO membranes' superior ability to clear β2M, κFLC, and λFLC. Serum albumin loss is an issue and should be monitored. Further studies are expected to identify whether MCO membranes could significantly improve clinical outcomes and overall survival.

Мета-анализ КРИ 2022 по мембранам со средней отсечкой

В заключение, этот мета-анализ продемонстрировал способность мембран MCO лучше удалять β2M, κFLC и λFLC. Потеря сывороточного альбумина является проблемой и следует его регулярно контролировать. Ожидается, что дальнейшие исследования позволят определить, могут ли мембраны MCO улучшить клинические исходы и общую выживаемость.

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SHARING EXPERTISE

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Наша продукция

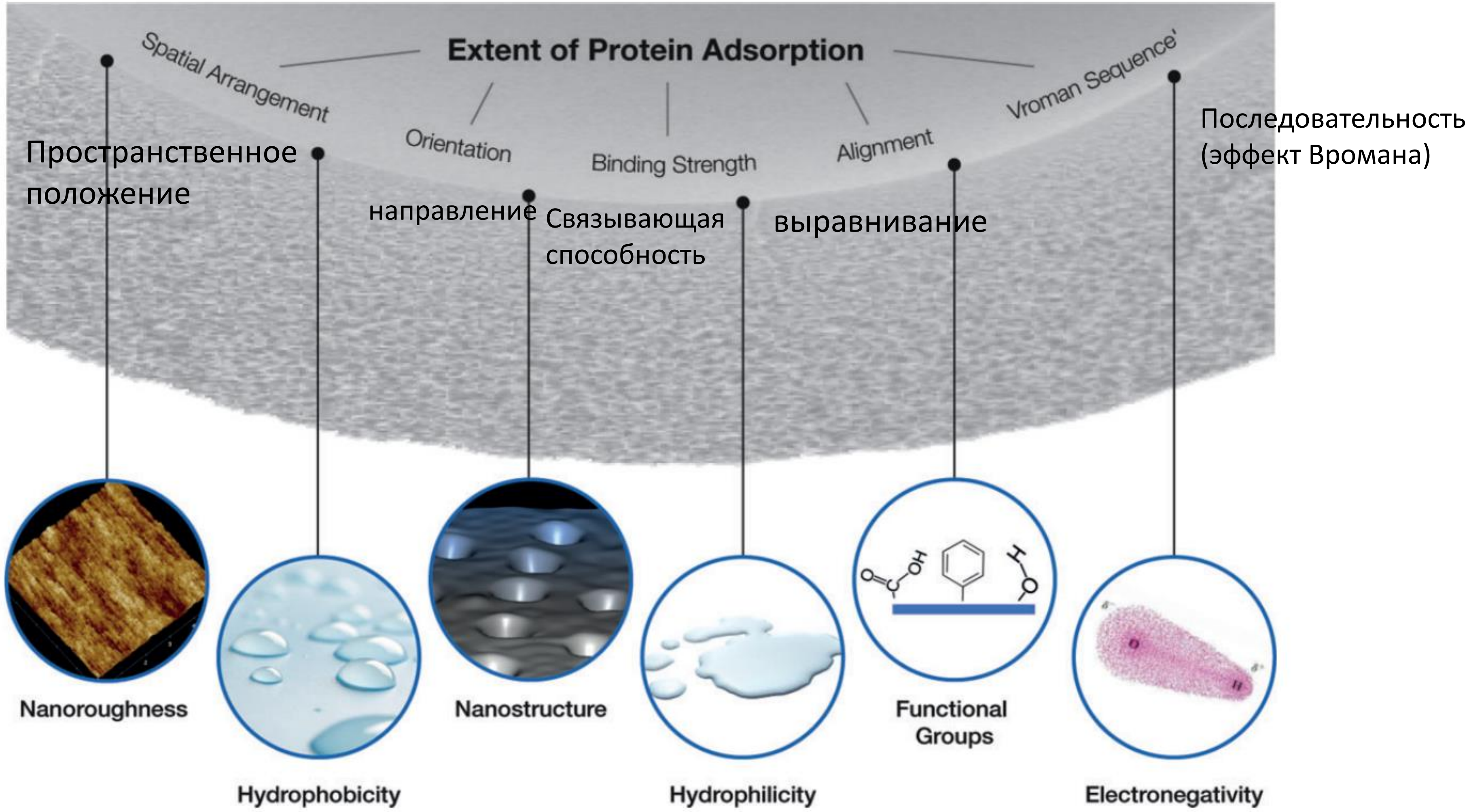
THERANOVA является безопасным и эффективным барьером для потенциальных загрязнителей диализирующего раствора. Внутренний диаметр мембраны был немного уменьшен , чтобы увеличить внутреннюю фильтрацию вдоль мембраны и усилить удаление более крупных средних молекул.

НЕ ИСПОЛЬЗУЙТЕ диализатор THERANOVA в режиме ГДФ или ГФ.

Для безопасного и надлежащего применения диализатора THERANOVA ознакомьтесь с соответствующими инструкциями по применению, руководством по эксплуатации или руководством пользователя.

Do not use THERANOVA dialyzers for HDF or HF due to higher permeability of larger molecular weight proteins such as albumin.

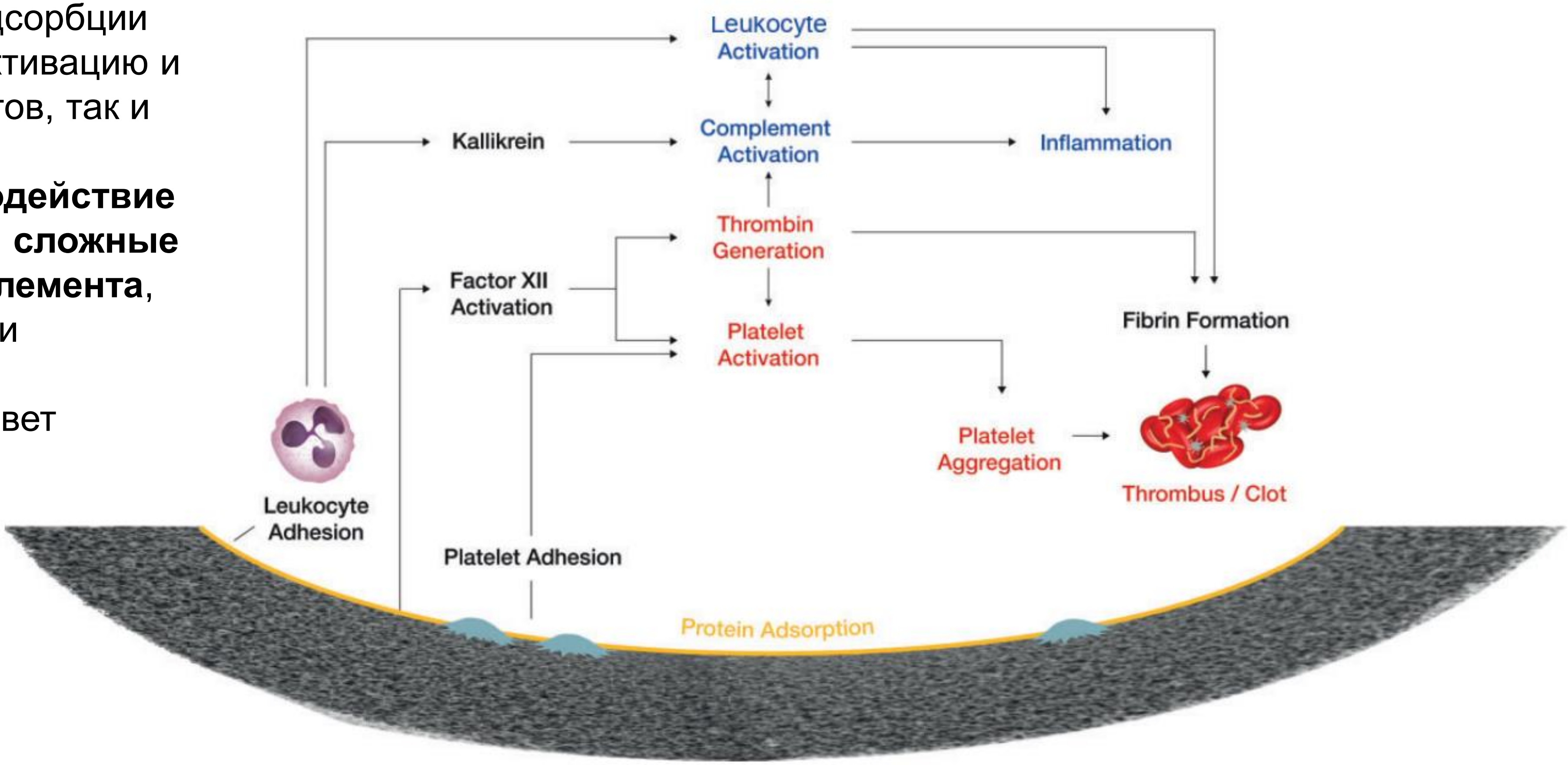
Быстрая адсорбция белков плазмы является начальным этапом взаимодействия крови с материалом мембраны



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

Различные биохимические пути, которые активируются при взаимодействии компонентов крови (плазматических и клеточных) с искусственными поверхностями.

Белок-зависимая от адсорбции активация включает активацию и адгезию как тромбоцитов, так и лейкоцитов. Рисунок **подчеркивает взаимодействие каскада коагуляции и сложные пути активации комплемента**, которые в совокупности вызывают локальный провоспалительный ответ



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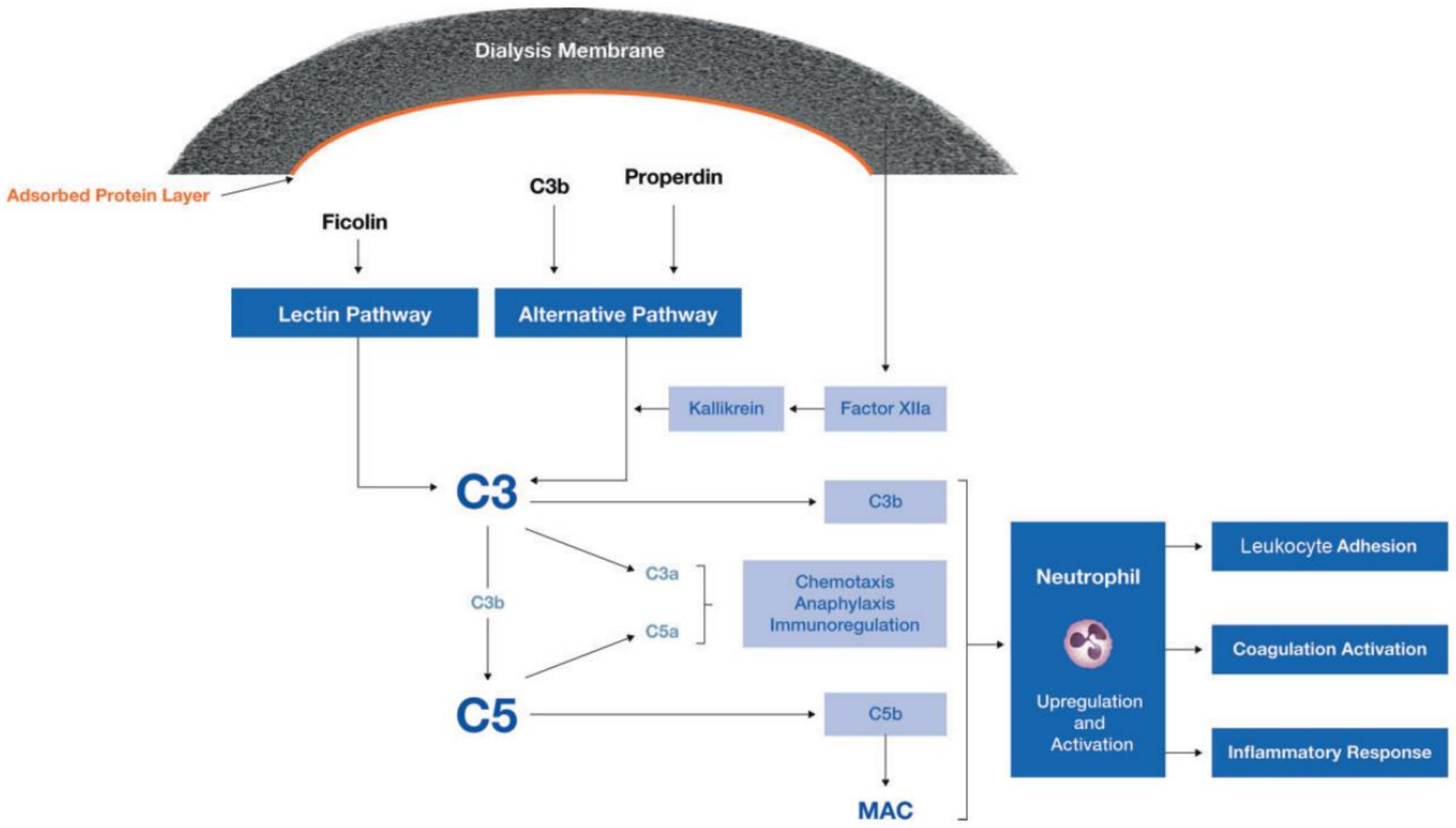
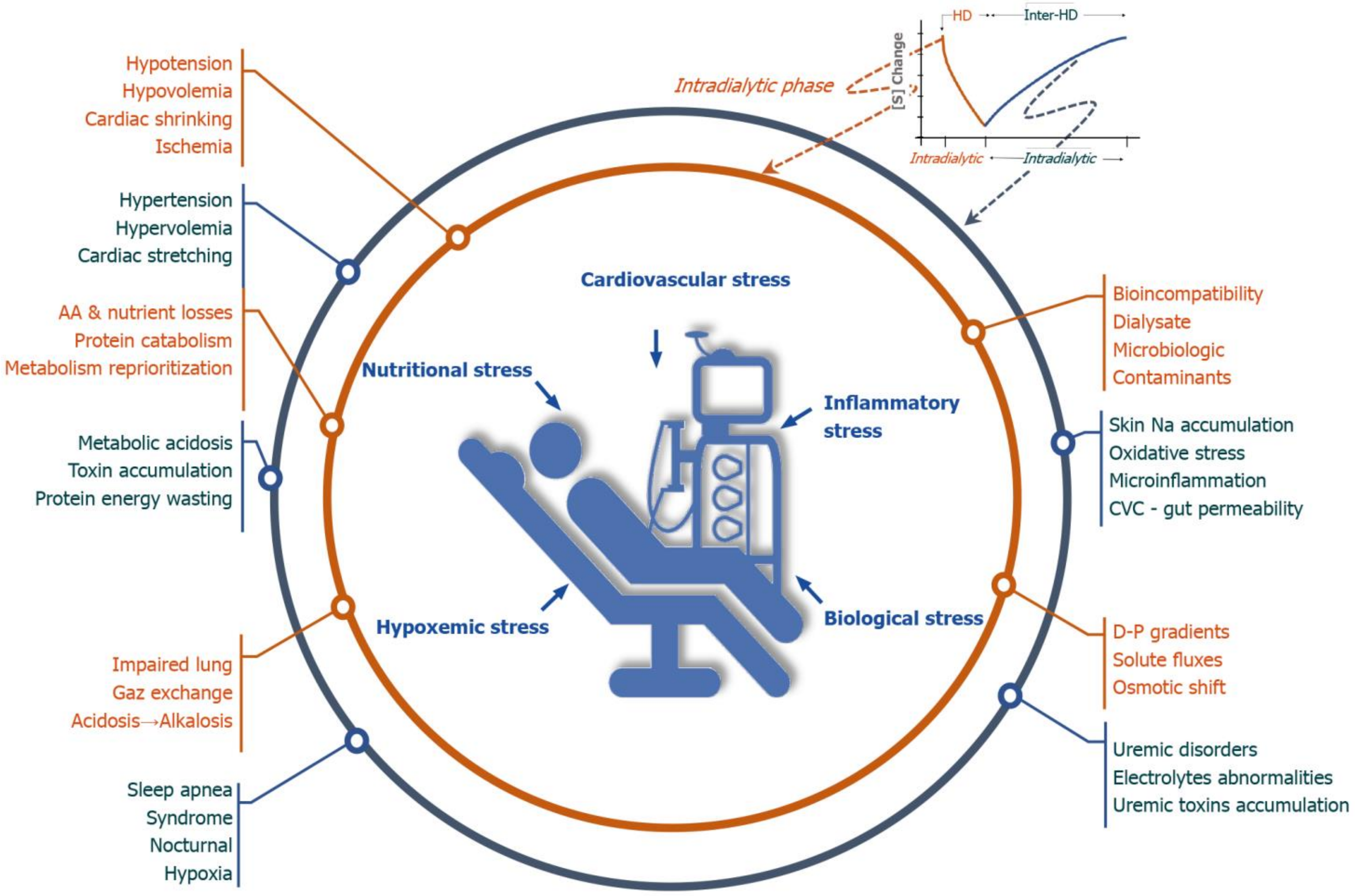
Сложная мембранозависимая активация комплемента и лейкоцитов, завершается не только запуском воспалительной реакции, но и также индуцирует прокоагулянтное состояние.



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

ЭК ЗПТ является источником регулярного стресса для пациента на ГД



DOI: 10.5527/wjn.v11.i2.39

Figure 1 Intermittent extracorporeal renal replacement therapy is the source of permanent stress in hemodialysis patients. HD: Hemodialysis; CVC: Central venous catheter.

Canaud B et al. Dialysis sickness and dialysis related morbidity 2022
DOI: https://dx.doi.org/10.5527/wjn.v11.i2.39

ZETA ПОТЕНЦИАЛ РАЗЛИЧНЫХ МЕМБРАН

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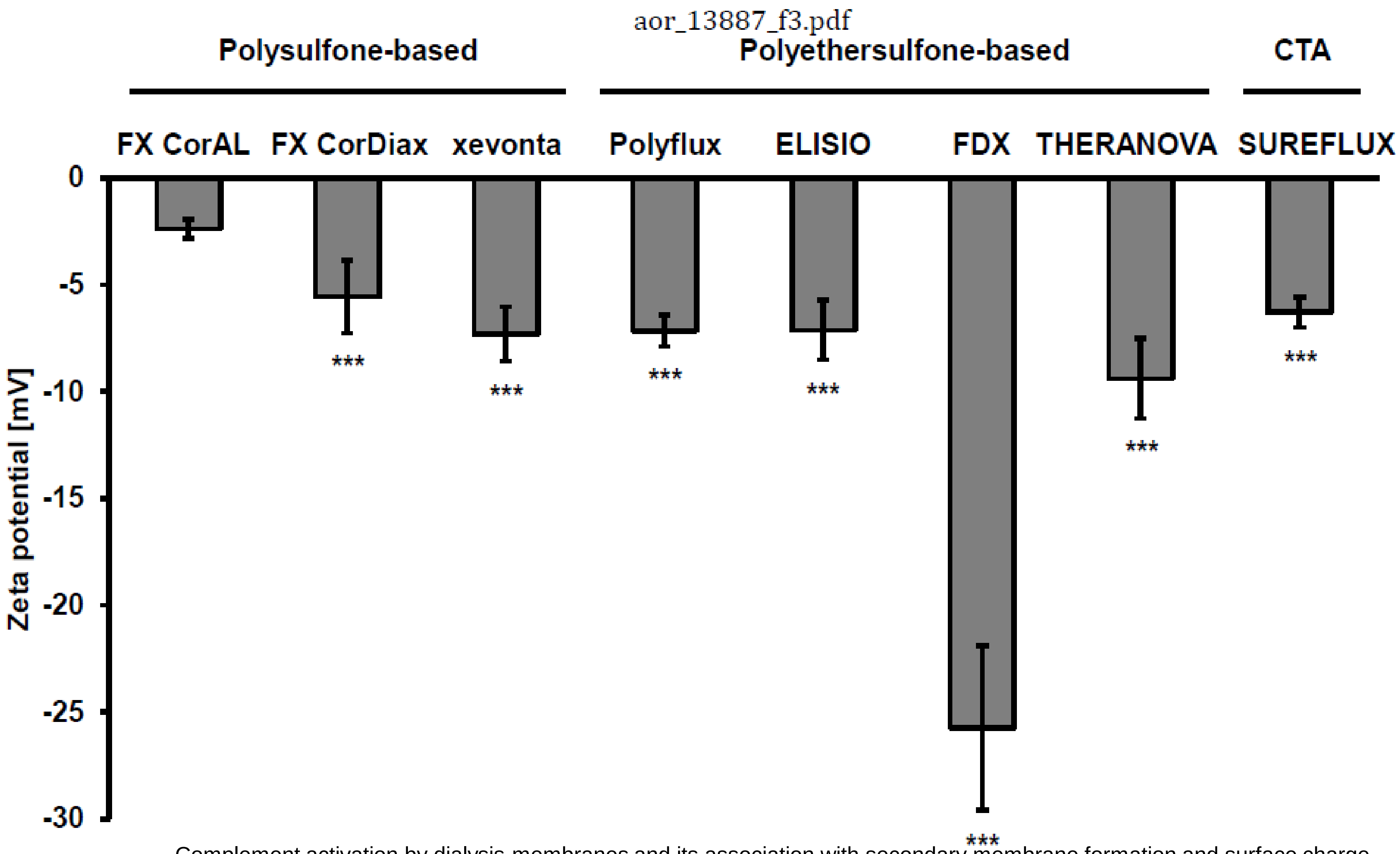

Complement activation by dialysis membranes and its association with secondary membrane formation and surface charge

Pascal Melchior, PhD1 Ansgar Erlenkötter, PhD2 Adam M Zawada, PhD1 Dirk Delinski, PhD1 Christian Schall, PhD3 Manuela Stauss-Grabo, PhD4 James P Kennedy, PhD1

Artificial Organs

https://doi.org/10.1111/aor.13887

АКТИВАЦИЯ КОМПЛЕМЕНТА

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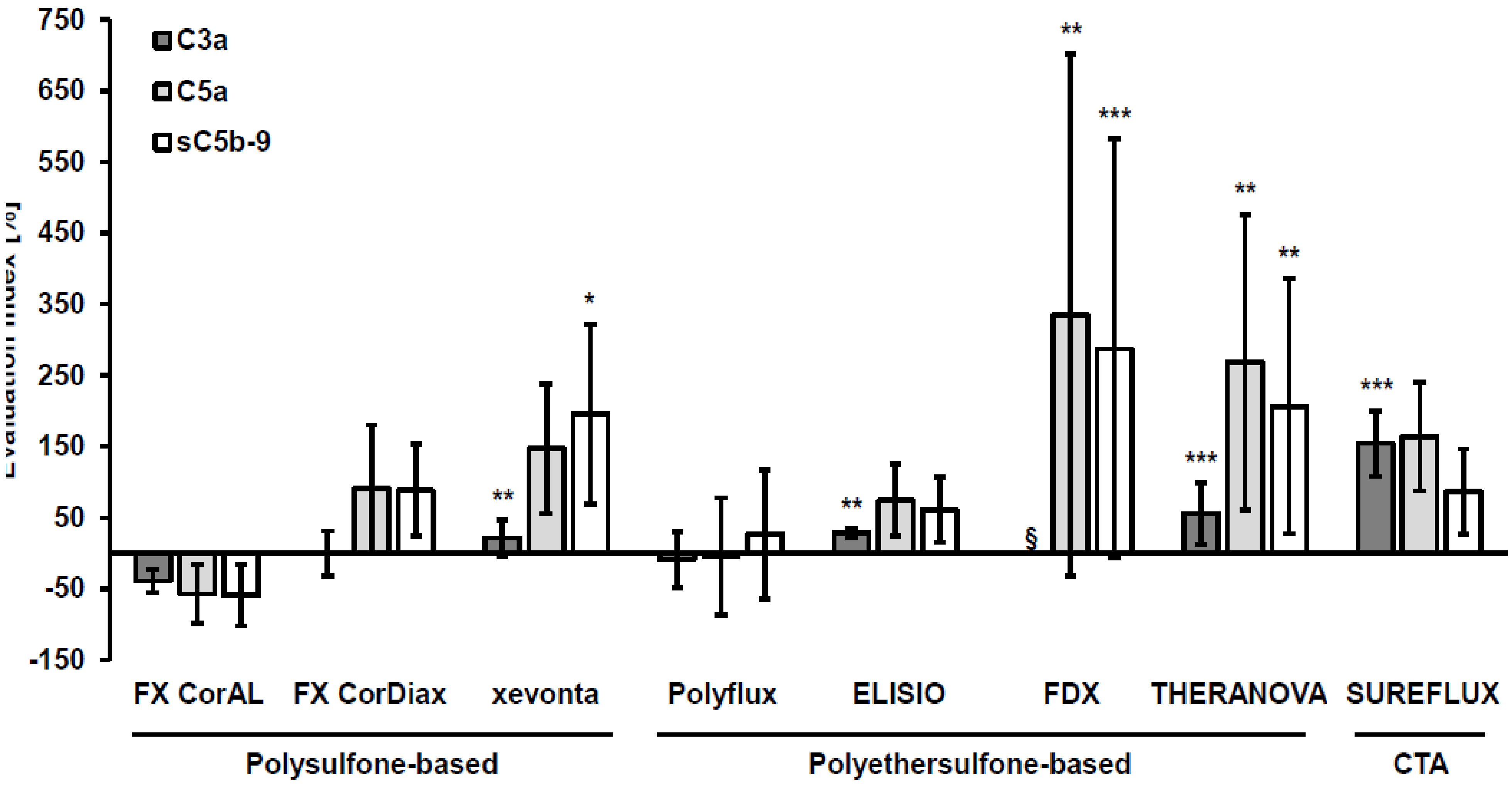

КУФ – ГИДРАВЛИЧЕСКАЯ ПРОНИЦАЕМОСТЬ

Сравнения лучших диализаторов

Синтетические диализаторы хай-флакс:

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2. ASAHI
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4. NIPRO
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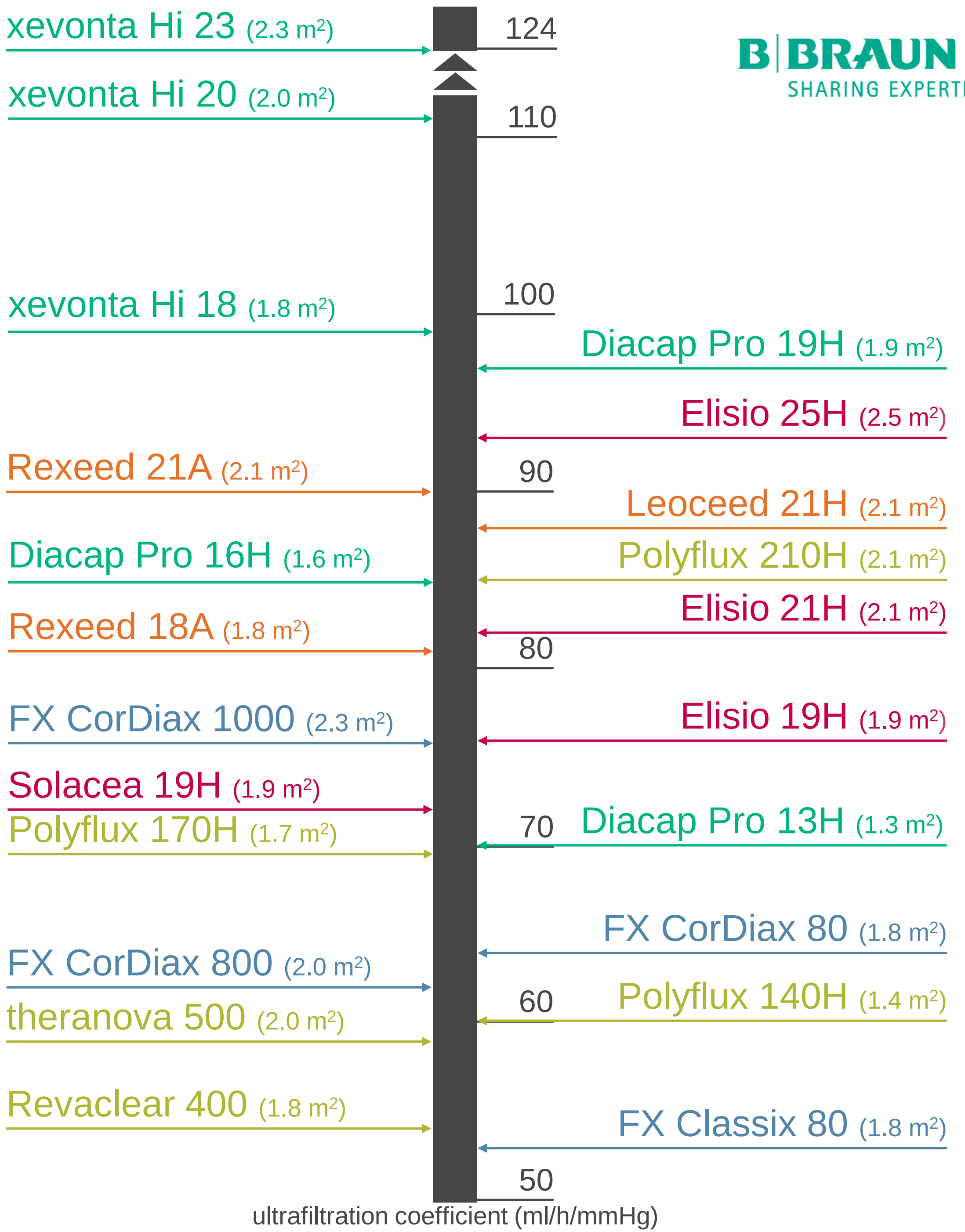


B. Braun SHARING EXPERTISE

B. Braun предлагает два самых высокопоточных диализатора :

xevonta and **Diacap Pro**

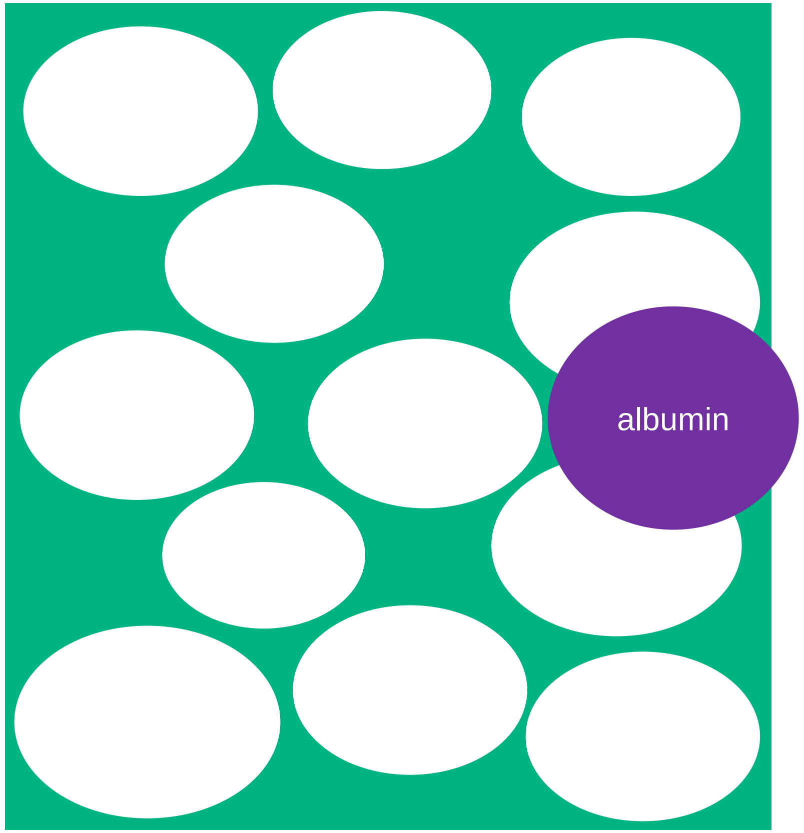
КОНЦЕПЦИЯ ПРОНИЦАЕМОСТИ/СЕЛЕКТИВНОСТИ

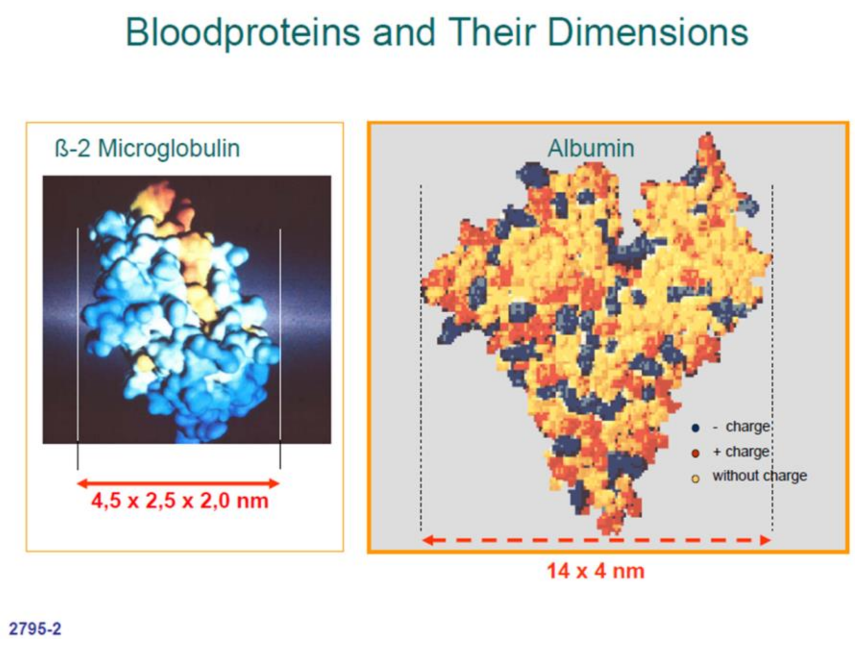
ВАЖНА ЛИ ТАКЖЕ ГИДРАВЛИЧЕСКАЯ ПРОНИЦАЕМОСТЬ?

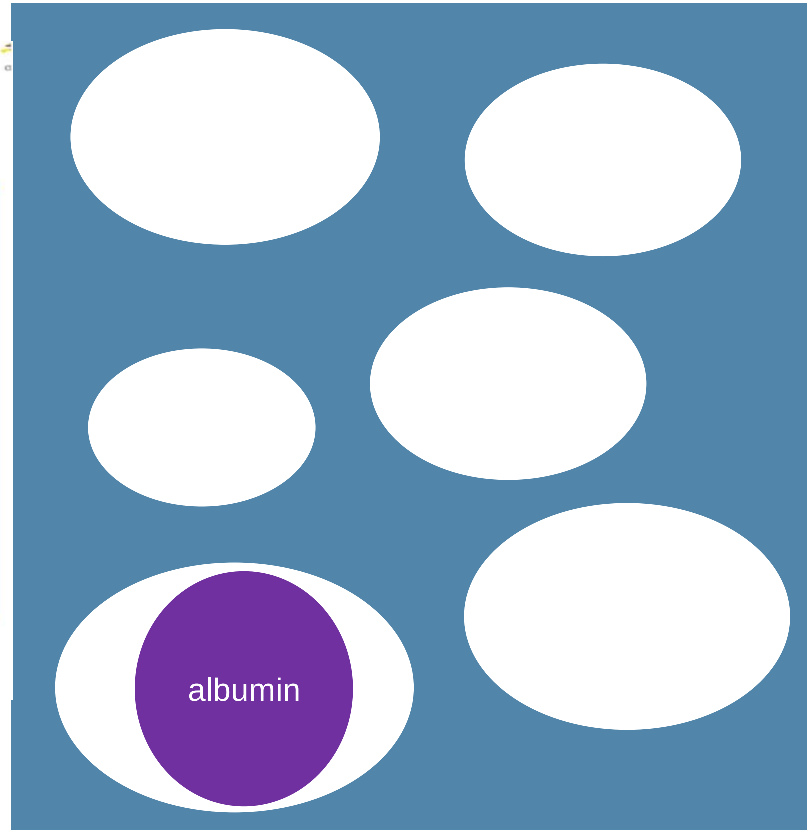
Проницаемость мембраны зависит от 3 факторов:

- Количество пор
- Размер пор
- Разница в размере пор

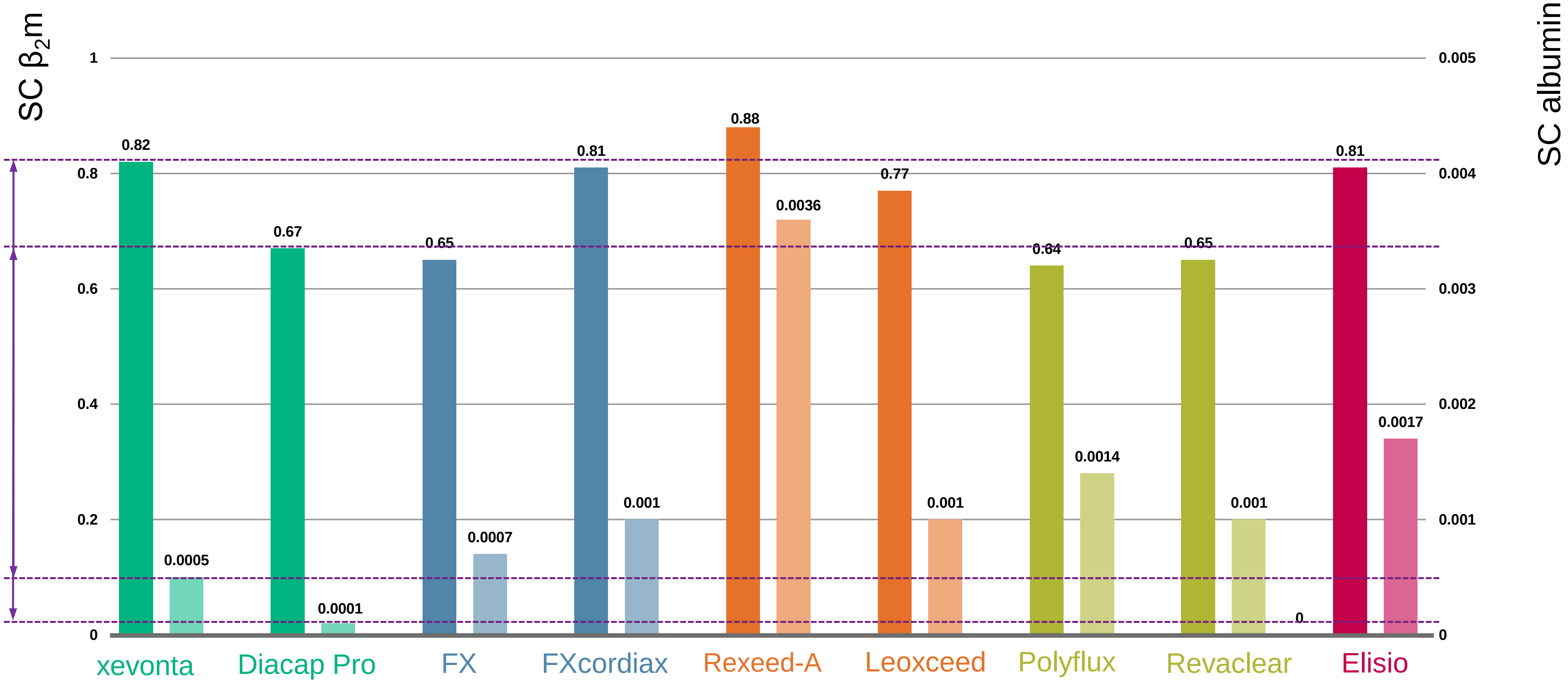
Общая проницаемость зависит от накопленной площадь всех пор (общая открытая площадь):







Коэффициент просеивания
ПОВТОРНЫЕ ИЗМЕРЕНИЯ ВЫСОКОПРОНИЦАЕМЫХ ДИАЛИЗАТОРОВ



Xevonta and Diacap Pro offer the highest ranges between elimination of $ß_2$m and retention of albumin.

Ecolab, measurement conditions according to EN 1283; 2009, 2011, 2013

Многомерная классификация диализных мембран К. Ронко

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Box 1 | **Multidimensional classification of dialysis membranes**

Use of a radar plot can provide a multidimensional classification of dialysis membranes (see the figure). The value for each parameter ranges from a minimum value at the centre to a maximum value at the circumference. The parameters are as follows.

Nature and composition

The major compositional distinction is between cellulosic (natural) and noncellulosic (synthetic) membranes. Noncellulosic synthetic membranes (polyamide, polysulfone, polyethersulfone (PES), polyacrylonitrile (PAN), polymethylmethacrylate (PMMA) and others) and modified cellulosic membranes are almost exclusively used in clinical practice. In new synthetic membranes, polymer blending enhances both biocompatibility and performance.

Structure

Most synthetic hollow fibres have a complex structure with a finely porous internal skin layer and an external support structure. The support structure may be sponge-like or finger-like, depending on the production method.

Ultrafiltration coefficient

The ultrafiltration coefficient (K_{uf}; ml/h/mmHg/m^2; also known as the hydraulic permeability coefficient) for a membrane is the ratio of the ultrafiltration rate (Q_f; ml/h/m^2) to the transmembrane pressure (TMP; mmHg). On the basis of water flux only, for low-flux membranes K_{uf} < 10 ml/h/mmHg/m^2, whereas for high-flux membranes K_{uf} = 20–40 ml/h/mmHg/m^2 and mid-flux membranes have intermediate K_{uf} values. However, modern classification schemes also incorporate solute removal parameters (see main text and below).

Molecular weight retention onset

The molecular weight retention onset (MWRO) governs the shape of the solute sieving curve for a membrane and describes the molecular weight and radius at which the sieving coefficient (*SC*) value is 0.9. Membranes with a tight pore size distribution that were designed to have a steep sieving curve have been produced with the aims of minimizing the molecular weight interval between the MWRO and the molecular weight cut-off (MWCO) and maintaining the MWCO at a value close to the molecular weight of albumin. These membranes are described as medium cut-off (MCO) membranes.

Biocompatibility

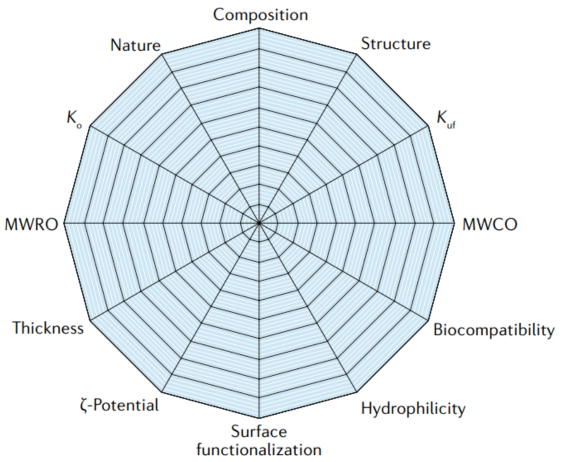
Although the biocompatibility of dialysis membranes can be judged by several criteria, complement activation has been the most widely studied parameter. Other criteria include thrombogenicity, contact activation and cytokine generation.

Hydrophilicity

The material composition of a membrane affects its interaction with water. Cellulosic membranes are hydrophilic whereas early synthetic membranes were highly hydrophobic. Modifications and new polymer blending have resulted in synthetic membranes that are less hydrophobic so that the combination of diffusive and convective mass transfer for solute removal is now possible.

Surface functionalization

The characteristics of the internal surface of the membrane are important for the interaction with the blood. New biochemical and physical



processes enable modification of the inner surface of hollow fibres by several techniques (see the main text for examples).

ζ-Potential

The ζ-potential is the electric potential at the blood–membrane interface due to the presence of electronegative charges located in the skin layer of the membrane. The process of polymerization, the chemical composition of the membrane and polymer blending potentially contribute to the ζ-potential of a membrane.

Thickness

The thickness of a membrane determines the distance that solutes must diffuse between the blood and the dialysate. The original cellulosic membranes were 15 μm thick, which was subsequently reduced to 5 μm. The original synthetic membranes were 70–100 μm thick, which has been reduced to 30 μm or less with a concomitant reduction of the thickness of the internal skin layer to approximately 1 μm or less.

Molecular weight cut-off

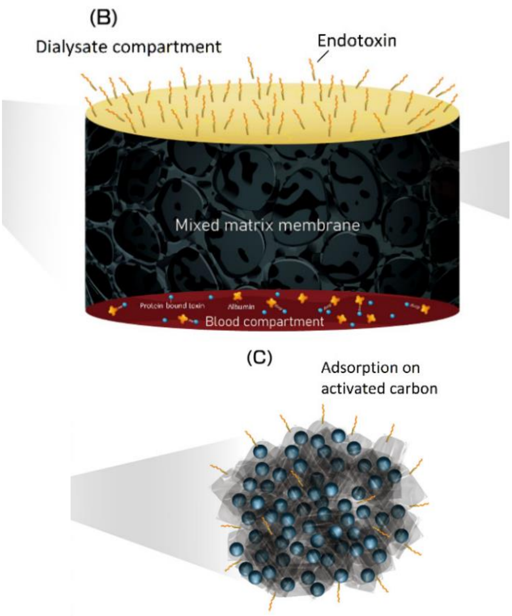
The molecular weight cut-off (MWCO) is defined as the solute molecular weight that corresponds to a *SC* value of 0.1. Pore size distribution substantially influences the MWCO value of a membrane and is of critical importance as it approaches the molecular weight of albumin owing to its effect on unwanted albumin losses during treatment.

Diffusive mass transfer coefficient

The diffusive mass transfer coefficient (K_o) is a theoretical parameter to describe membrane performance in diffusion in ideal conditions of unlimited blood flow and dialysate flow. The final characteristics of a membrane should be normalized to the membrane surface area (K_oA). K_o and K_oA are important parameters to define membrane diffusive transport capacity for a specific haemodialyser–solute combination.

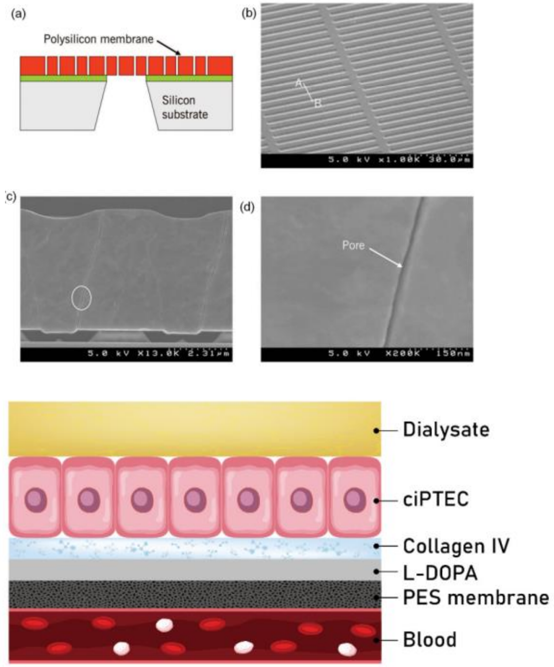
Figure adapted with permission from REF.[85], Karger.

Инновационные мембраны



Membrane Type	MWCO (kDa)	Advantage	Disadvantage	Ref.
Medium cutoff membranes	60–100	• Increases water permeability relative to both the high-flux and a virgin β2m SC of 1.0 • May have an anti-inflammatory effect • Decreases extra albumin loss compare with high-flux membranes	• Cannot reduce the serum levels of medium-sized molecules in long-term follow-up	RCTs: [35,37,39–41] Observational study: [36,38]
Graphene oxide membranes	1–3	• Improves the permeability of small molecules (MW: 0–1000 Da) with size-selective pores (≤1 nm)	• Still in in vitro studies	In vitro study: [43,44]
Mixed-matrix membranes	47	• Removes more uremic solutes by absorbing toxins • Removes about 10 times more endotoxins than conventional membranes	• Still in in vitro studies	In vitro study: [45–47]
Bioartificial kidneys	10–30	• Achieves the secretory clearance of human serum albumin-bound uremic toxins	• Concern with long term use	RCTs: [50] In vitro study: [48,49]
Vitamin E-modified membranes	10–300	• Not inferior to heparin-coated dialyzers in anti-coagulation • May decrease oxidative stress	• Have no impact on anemia parameters, lipid profiles, dialysis adequacy, blood pressure, or albumin	RCTs: [51–53,55,56] Meta-analysis: [54]
Lipoic acid-modified membranes	10	• Reduces oxidative stress in in vitro study	• Still in in vitro studies	In vitro study: [57,58]
Neutrophil elastase inhibitor modified membranes	2	• Effectively reduces the proteolytic activity of neutrophil elastase	• Lack of in vivo study of NE inhibitor-coated membranes	In vitro study: [61]

Abbreviations: MWCO, molecular weight cut-off; β2m, beta-2 microglobulin; SC, sieving coefficient; MW, molecular weight; NE, neutrophil elastase; RCT, randomized controlled trial; Ref., references.



Y A Chen et al Membranes 2022, 12, 152. https://doi.org/10.3390/membranes12020152

Производительность диализатора – важная составляющая успеха, но и другие компоненты лечения не менее важны