Newly classification of middle molecular and the target of dialysis therapy

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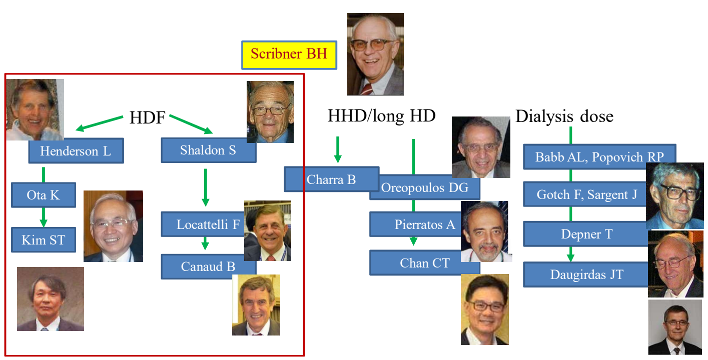
Disclosure of Financial Relationships

The author declares no conflicting interest

Hideki Kawanishi

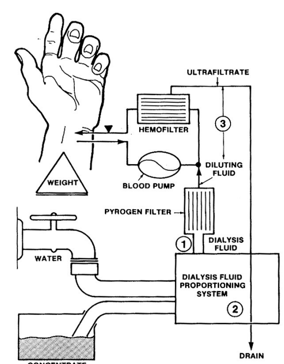
Historical development of HD/HDF



Start of On-line HDF

On-line prepared substitution fluid: on-line HDF

Henderson L, Trans, Am Soc Artif Intern Organs 1978



2004, Chicago

Fundamental of dialysis therapy = Solutes removal

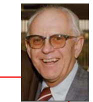
$Gi - KtN = 0$

Gotch F, Kidney Intern 58 (Suppl 76),2000

$$Gi - KtN - Kr = 0$$

- High Q_B — HD/HDF
- Long time — Nocturnal — Continuous
- Quotidian (daily)
- CAPD

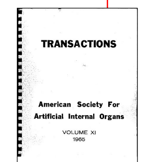
Why we need a High flux dialyzer: middle molecules theory



Started the middle molecules: 500 to 2,000 daltons

Scriber BH "Discussion", Trans Am Soc Artif Int Organs 1965; 11:29

- PD, patients feel better on less dialysis
  - Peritoneal membrane is leaky,
  - Higher MW substances more efficiently than HD
- We need a leaky membrane for hemodialyzer ⇒ high flux dialyzer



Furthermore, as we've mentioned in the past, if it is true that the patients feel better on less dialysis, there is a chance that because the peritoneal membrane is leaky, we are removing with peritoneal dialysis certain higher molecular weight substances more efficiently than with hemodialysis, and this may account for the better results, and suggest that we need a leaky membrane for a hemodialyzer.

Middle molecules theory by Babb

500 to 2000 daltons

- American Society for Artificial Internal Organs: April 1971 - Volume 17 - Issue 1 - p 81-91

THE GENESIS OF THE SQUARE METER-HOUR HYPOTHESIS

Albert L. Babb, Robert P. Popovich, T. Graham Christopher, and Belding H. Scribner

- American Journal of Kidney Diseases, Vol. I, No.1 (July), 1981

The Middle Molecule Hypothesis in Perspective

Albert L. Babb, Ph.D., Suhail Ahmad, M.D., Jonas Bergström, M.D., and Belding H. Scribner, M.D.

Kidney International, Vol. 63 (2003), pp. 1934–1943

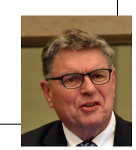
Review on uremic toxins: Classification, concentration, and interindividual variability

RAYMOND VANHOLDER, RITA DE SMET, GRIET GLORIEUX, ANGEL ARGILÉS, ULRICH BAURMEISTER, PHILIPPE BRUNET, WILLIAM CLARK, GERALD COHEN, PETER PAUL DE DEYN, REINHOLD DEPPISCH, BEATRICE DESCAMPS-LATSCHA, THOMAS HENLE, ACHIM JÖRRES, HORST DIETER LEMKE, ZIAD A. MASSY, JUTTA PASSLICK-DEETJEN, MARIANO RODRIGUEZ, BERND STEGMAYR, PETER STENVINKEL, CIRO TETTA, CHRISTOPH WANNER, and WALTER ZIDEK, For the EUROPEAN UREMIC TOXIN WORK GROUP (EUTox)

Uremic toxin

Vanholder R et al. EUROPEAN UREMIC TOXIN WORK GROUP (EUTOX), Kidney Inter 2003; 63: 1934-1943

- Free water-soluble low-molecular-weight solutes
- Middle molecules
- Protein-bound solutes



Free water-soluble low-molecular-weight solutes (N = 45)

Vanholder R et al., KI 2003; 63: 1934

1-methyladenosine	Erythritol	Orotidine
1-methylguanosine	γ-guanidinobutyric acid	Oxalate
1-methylinosine	Guanidine	Phenylacetylglutamine
ADMA	Guanidinoacetic acid	Pseudouridine
αketo--guanidinovaleric acid	Guanidonosuccinic acid	SDMA
α-N-acetylarginine	Hypoxanthine	Taurocyamine
Arab(in)itol	Malondialdehyde	Threitol
Argininic acid	Mannitol	Thymine
Benzylalcohol	Methylguanidine	Uracil
β-guanidinopropionic acid	Myoinositol	Urea
β-lipotropin	N2,N2-dimethylguanosine	Uric acid
Creatinine	N4-acetylcytidine	Uridine
Creatine Guanidines	N6-methyladenosine	Xanthine
Cytidine	N6-threonylcarbamoyladenosine	Xanthosine
Dimethylglycine	Orotic acid	

Middle molecules (N = 21)

Vanholder R et al., KI 2003; 63: 1934

Adrenomedullin	k-Ig light chain
Atrial natriuretic peptide	λ-Ig light chain
β2-microglobulin	Leptin
Cholecystokinin	Methionine-enkephalin
Clara cell protein (CC16)	Neuropeptide Y
Complement factor D	Parathyroid hormone
Cystatin C	Retinol-binding protein
Degranulation inhibiting protein Ic	Tumor necrosis factor-a
Delta-sleep inducing peptide	
Endothelin	
Hyaluronic	
Interleukin-1	
Interleukin-6	

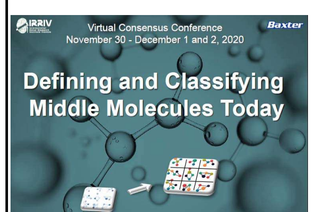
Protein-bound solutes (N = 26)

Vanholder R et al., KI 2003; 63: 1934

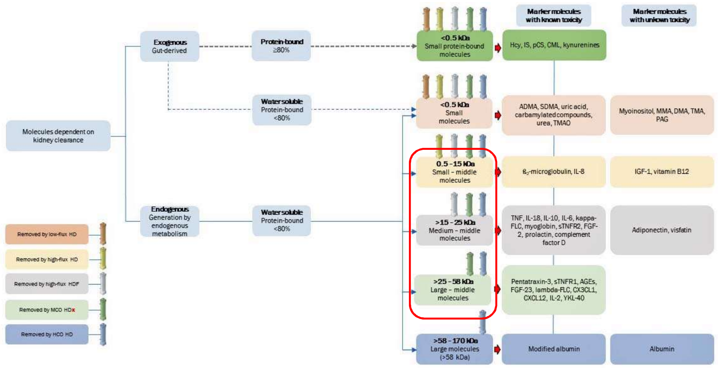
2-methoxyresorcinol	Phenols	Methylglyoxal	AGE
3-deoxyglucosone	AGE	N–(carboxymethyl)lysine	AGE
CMPF		p-cresol	Phenols
Fructoselysine	AGE	Pentosidine	AGE
Glyoxal	AGE	Phenol Phenols	
Hippuric	Hippurates	P-OHhippuric axid	Hippurates
Homocysteine		Putrescine	Polyamines
Hydroquinone	Phenols	Quinolinic acid	Indoles
Indole-3-acetic	Indoles	Retinol-binding protein	Peptides
Indoxyl sulfate	Indoles	Spermidine	Polyamines
Kinurenine	Indoles	Spermine	Polyamines
Kynurenic	Indoles	Orotic acid	
Leptin	Peptides		
Melatonin	Indoles		

New classification of Middle molecules : 500D - 58kD

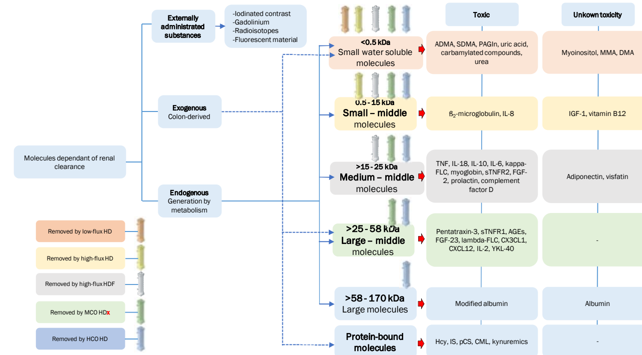
Classification of Uremic Toxins and their Role in Kidney Failure,
CJASN 2021;16 :1918-1928
Rosner M, Reis T, Husain-Syed F, Vanholder R, Hutchison C, Stenvinkel P, Blankestijn P, Cozzolino M, Juillard L, Kashani K, Kaushik M, Kawanishi H, Massy Z, Sirich T, Zuo L



Classification of Uremic Toxins and their Role in Kidney Failure, CJASN 2021

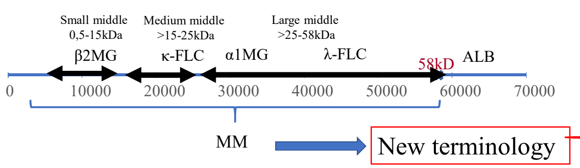


Classification of Uremic Toxins and their Role in Kidney Failure, CJASN 2021



Middle molecules

- Definition of MM: MW 500 to < 58kD (glomerular filtration)



0.5 - 15 kDa Small – middle

>15 - 25 kDa Medium – middle

>25 - 58 kDa Large – middle

>58 - 170 kDa Large molecules

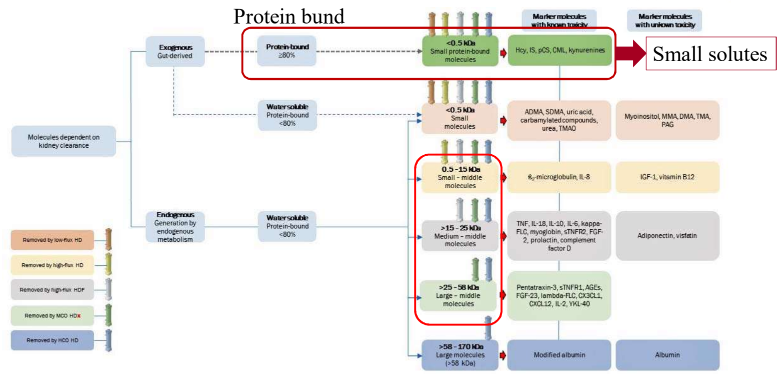
Table 1. The different classes of uremic toxins as used in this publication.

Class of Molecules	MW Range	Prototype	MW Prototype
Small water-soluble compounds	<500 Da	Urea	60
Protein bound compounds	Mostly < 500 Da	Indoxyl sulfate	213.2
Middle molecules	≥500 Da	β_2-microglobulin	11.818

MW: molecular weight; Da: Dalton.

Vanholder R et al., Toxins 2018

Classification of Uremic Toxins and their Role in Kidney Failure, CJASN 2021



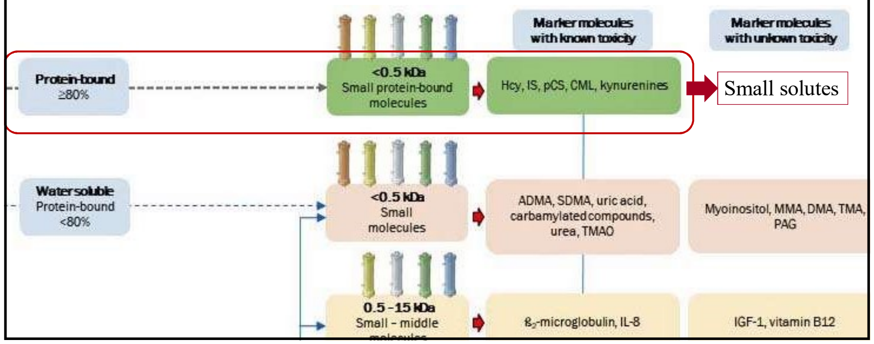

REVIEW

Classification of Uremic Toxins and Their Role in Kidney Failure

Mitchell H. Rosner, Thiago Reis, Faeq Husain-Syed, Raymond Vanholder, Colin Hutchison, Peter Stenvinkel, Peter J. Blankestijn, Mario Cozzolino, Laurent Juillard, Kianoush Kashani, Manish Kaushik, Hideki Kawanishi, Ziad Massy, Tammy Lisa Sirich, Li Zuo, and Claudio Ronco

Classification of Uremic Toxins and their Role in Kidney Failure, CJASN 2021

Protein bund



Protein-Bound Uremic Toxins Relate to Residual Kidney Function, Are Not Influenced by Convective Transport, and Do Not Relate to Outcome
van Gelder MK et al., Toxins 2020, 12, 234

CONTRAST: low-flux HD vs online HDF

Removal rate

Protein-bound toxin	HD (redaction % /6M) N 38	HDF(redaction % /6M) N35	HD vs HDF, p
Kynurenine	-7.7 (-22.6 to 14.5) p<0.269	-5.9 (-20.9 to 29.3) p <0.694	0.453
Kynurenic acid	5.6 (8.6 to 69.1) p<0.111	3.2 (22.1 to 39.5) p<0.537	0.430
Indoxyl sulfate	11.9 (15.4 to 31.9) p<0.133	-8.0 (-34.6 to 15.3) p<0.092	0.045
Indole-3-acetic acid	9.2 (19.6 to 34.9) p<0.876	-10.8 (-26.0 to 14.0) p<0.615	0.356
p-Cresyl sulfate	-8.8 (-28.9 to 29.5) p<0.510	-2.7 (-27.4 to 10.2) p<0.199	0.854
p-Cresyl glucuronide	-7.0 (-38.1 to 69.8) p<0.421	7.4 (37.3 to 65.3) p<0.765	0.681
Hippuric acid	5.7 (44.6 to 54.5) p<0.531	-21.9 (-47.6 to 42.4) p<0.187	0.566

Protein-Bound Uremic Toxins Relate to Residual Kidney Function, Are Not Influenced by Convective Transport, and Do Not Relate to Outcome
van Gelder MK et al., Toxins 2020, 12, 234

CONTRAST: low-flux HD vs online HDF

Hazard ratios for all-cause mortality and new CVD events for plasma conc. at baseline

Mortality rate

				Hazard Ratio (95% CI)			
PBUT	Outcome	N	# Events	Model I	P	Model II	P
Kynurenine (μmol/L)	All-cause mortality	79	34	1.020 (0.802 to 1.298)	0.872	0.943 (0.707 to 1.256)	0.687
	CV events	78	29	1.054 (0.807 to 1.376)	0.701	0.982 (0.717 to 1.346)	0.911
Kynurenic acid (μmol/L)	All-cause mortality	80	35	0.879 (0.638 to 1.210)	0.429	1.104 (0.666 to 1.829)	0.702
	CV events	79	29	0.876 (0.622 to 1.235)	0.876	1.333 (0.798 to 2.226)	0.272
Indoxyl sulfate (μmol/L)	All-cause mortality	80	35	1.001 (0.995 to 1.006)	0.837	1.002 (0.995 to 1.009)	0.617
	CV events	79	29	1.003 (0.998 to 1.008)	0.290	1.007 (1.000 to 1.015)	0.056
Indole-3-acetic acid (μmol/L)	All-cause mortality	60	24	1.190 (0.609 to 2.323)	0.610	1.346 (0.568 to 3.192)	0.500
	CV events	59	20	1.002 (0.493 to 2.039)	0.995	1.434 (0.535 to 3.847)	0.474
p-Cresyl sulfate (μmol/L)	All-cause mortality	80	35	0.955 (0.670 to 1.362)	0.801	0.897 (0.614 to 1.310)	0.574
	CV events	79	29	0.960 (0.664 to 1.389)	0.829	1.036 (0.667 to 1.611)	0.874
p-Cresyl glucuronide	All-cause mortality	80	35	0.992 (0.767 to 1.283)	0.952	1.024 (0.782 to 1.340)	0.864
[illegible] (μmol/L)	[illegible] mortality	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	CV events	77	28	0.722 (0.457 to 1.142)	0.164	0.823 (0.445 to 1.524)	0.536

NS

Protein bound substances: is it no toxicity on bound condition?

Evidence of uremic toxin

Vanholder R et al., Toxins 2018, 10, 33; doi:10.3390/toxins10010033

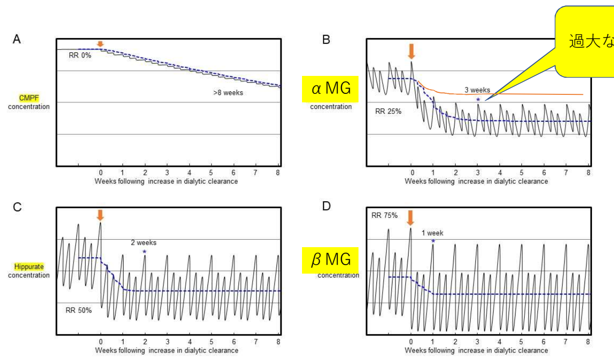
Table 8. Uremic toxins with the highest toxicity score.

Evidence Score: 4	Exp. Score	Evidence Score: 3	Exp. Score
p-Cresyl sulfate	7	AGEs	7
β_2-Microglobulin	6	Indoxyl sulfate	6
ADMA	5	Uric acid	6
Kynurenines	5	Ghrelin	5
Carbamylated compounds	3	Indole acetic acid	5
FGF-23	3	Parathyroid hormone	5
Interleukin-6	3	Phenyl acetic acid	5
TNF-α	3	TMAO	5
SDMA	2	Retinol binding protein	4
		Endothelin	3
		IgLC	3
		Interleukin-1β	3
		Interleukin-8	3
		Neuropeptide Y	3
		Lipids & lipoproteins	2

Exp.: experimental; ADMA: Asymmetric Dimethylarginine; FGF23: Fibroblast Growth Factor-23; TNF-α: Tumor Necrosis Factor; SDMA: Symmetric Dimethylarginine; AGEs: Advanced Glycation End Products; TMAO: Trimethylamine-N-Oxide; IgLC: Immunoglobulin Light Chains.

Not yet Evidence of α1MG

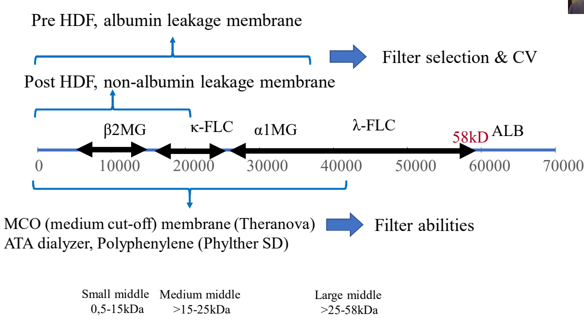
Classification of Uremic Toxins and their Role in Kidney Failure, CJASN 2021



CMPF, 3-Carboxy-4-methyl-5-propyl-2-furanpropionic acid

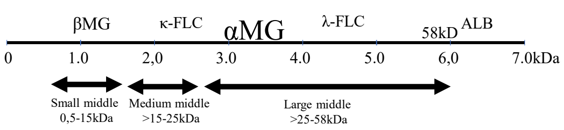
Modality selection to MM

- Definition of MM: MW 500 to < 58kD (glomerular filtration)



Modality selection to MM

- Definition of MM: MW 500 to < 58kD (glomerular filtration)
- Large middle solute: α1microglubulin (33kD)

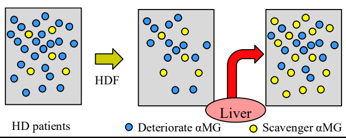


Function of α1MG hypothesis, by Kim ST

- In serum, the ratio of free and IgA bound form αMG is almost same, and the removal rate per HDF is limited to 60% (controversial by Dr Tomo)
- Physiological function：
  - Disadvantage :Cell toxicity
  - Benefit : Antioxidant action (Heme Scavenger)

Dr Tomo T
IgA bound / free %
Healthy < HD=free ↑(deteriorated)
⇒Increase cell toxicity

- Dialysis patients: the serum αMG is more than ten times higher than normal, and most of them are deteriorated (oxidized) αMG.
- Removing the deteriorated αMG → produce new αMG from the liver → recovery of antioxidant effect



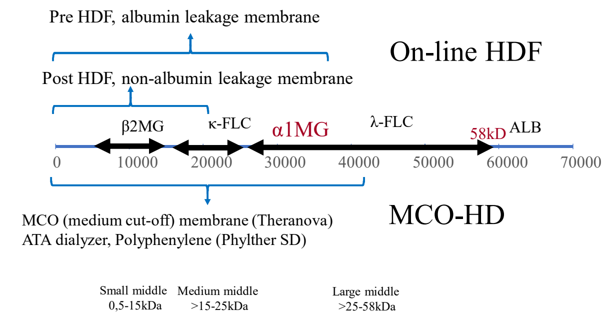
Pre HDF ≒ α1MG removal therapy

- α1MG ⇒ Anti oxidant effect (Scavenger)

⇒ Bio protective effects

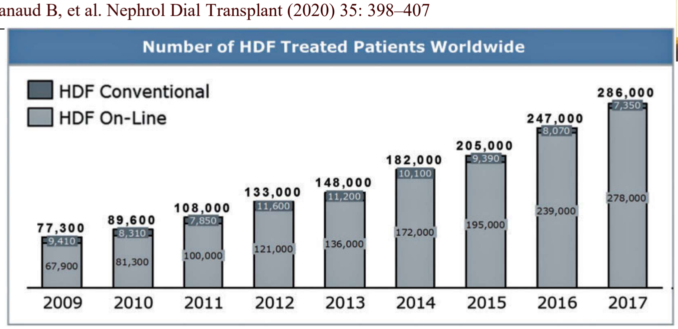
⇒ant-inflammation

Removal for α1microglubulin (33kD)



Global trends in HDF

Canaud B, et al. Nephrol Dial Transplant (2020) 35: 398–407



Global trends in HDF

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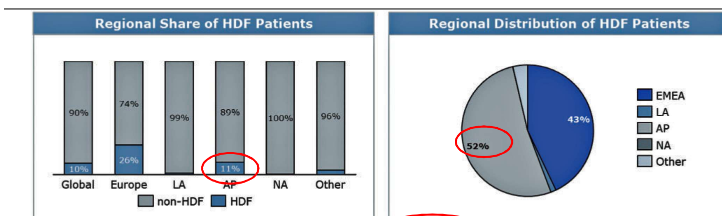
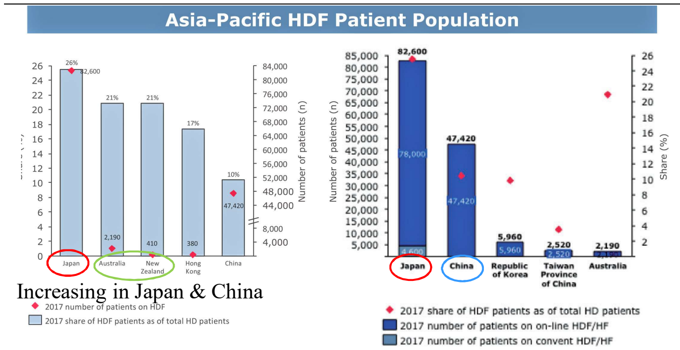


Abbreviation: LA: Latin America; AP: Asia Pacific; NA: North America.

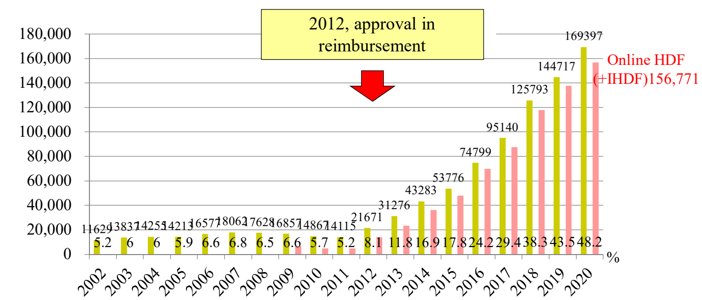
HDF increasing in Asia countries

Global trends in HDF

Canaud B, et al. Nephrol Dial Transplant (2020) 35: 398–407



HDF in Japan, JSDT



EU vs Japan

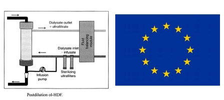
Pre dilution online HDF, albumin leakage membrane

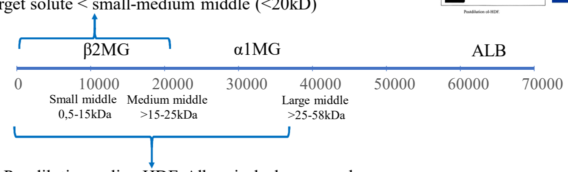
EU-Post dilution online HDF, Non-albumin leakage membrane

Higher blood flow 300-350mL/min,

Higher convection volume (CV) 20-24L

Target solute < small-medium middle (<20kD)



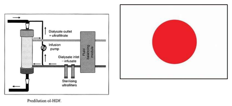


Japan-Pre dilution online HDF, Albumin leakage membrane

Low blood flow 200-300mL/min,

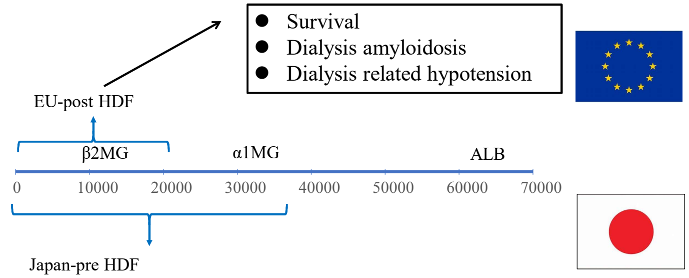
Higher convection volume (CV) 48-72L

Target solute <large middle (<35kD)



EU vs Japan, clinical evidence

- Survival
- Dialysis amyloidosis
- Dialysis related hypotension



- Survival
- Dialysis amyloidosis
- Restless legs syndrome(RLS)

Pro & Con for HDF Blood Purif. 2018;46:3-6.

Pro

Extended Editorial

Blood Purification
Blood Purif 2018;46:7–11
DOI: 10.1159/000487918

Is There Not Sufficient Evidence to Show That Haemodiafiltration Is Superior to Conventional Haemodialysis in Treating End-Stage Kidney Disease Patients?

Bernard Canaud[a, b] Ellen Busink[c] Christian Apel[c] Sudhir K. Bowry[d]
[a]Centre of Excellence Medical, Fresenius Medical Care Deutschland, Bad Homburg, Germany; [b]Montpellier University, School of Medicine, Montpellier, France; [c]Centre of Excellence Health Economics, Market Access and Policy Affairs EMEA, Fresenius Medical Care Deutschland, Bad Homburg, Germany; [d]Scientific Value Creation, Fresenius Medical Care Deutschland, Bad Homburg, Germany

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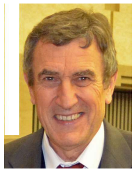


Con

Extended Editorial

Blood Purification
Blood Purif 2018;46:3–6
DOI: 10.1159/000487917

Is There Enough Evidence to Prove That Hemodiafiltration Is Superior?

Hideki Kawanishi
Tsuchiya General Hospital, Hiroshima, Japan

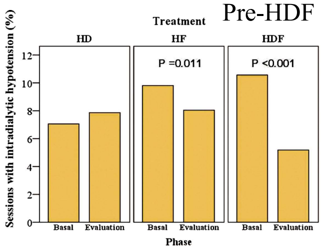
Doubts about effectiveness of On-line HDF

- Removal capacity: prevention of dialysis amyloidosis
- Prevention of dialysis hypotension ?
- Improvement of patient's survival ?
- Decrease of dialysis related Uncertain complaint?

Dialysis hypotension

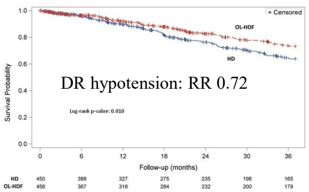
- Evidence

Pre-HDF



Italian prospective multicenter study
Locatelli F et al., JASN 2010;21:1798

Post-HDF



ESHOL study
Maduell et al., JASN 2013; 24:487-97

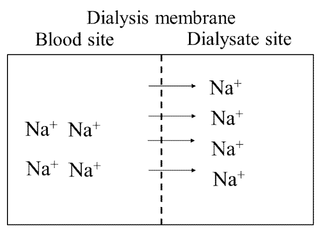
Prevention of dialysis hypotension??

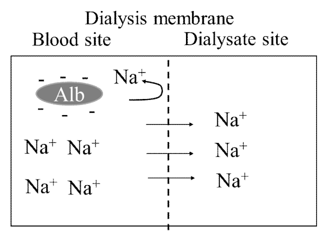
Mechanism

- Gibbs-Donnan effect
- Cool dialysis effect on post-HDF

Prevention of dialysis hypotension
Gibbs-Donnan effect

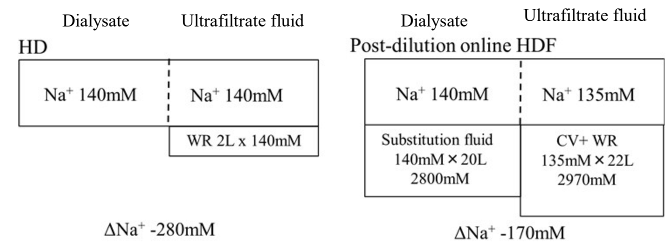
- Gibbs-Donnan effect: The electrolyte reaches equilibrium by diffusion through the dialysis membrane; however with at non-diffusible anion (such as albumin), there are increases on the blood side of the membrane, the ion equilibrium collapses, and the diffusibility of Na+ as a cation decreases





Gibbs-Donnan effect

- HD, Na+ is the same in the plasma and dialysate; the balance is −280 mM with 2 L of water removal. Post-HDF the albumin concentration on the blood side increases due to hemoconcentration. Na+ in the ultrafiltrate decreases to 135 mM due to the Gibbs-Donnan effect, and the Na+ equilibrium was −170 mM.



Prevention of dialysis hypotension
Cool dialysis effect, Donauer et al., NDT 2003;18:1616-1622

- HD vs post ol-HDF, cool HD vs ol-HDF,
  - Donauer J et al., NDT 2003:18: 1616-1622
- Study A: HD vs post ol-HDF (CV 50mL/min): 25 session, crossover
- Study B: Cool HD (35,6°C) vs post ol-HDF : 25 session

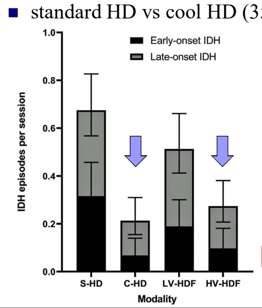
		Hypotension	Cystic BP change mmHg	Minimum Blood volume%	A-V temperature ℃	Energy transfer ratio (W)
A	ol-HDF	1/25	-3.8	91.8	-1.2	-16.6
	HD	10/25	-17.2	94.0	-0.4	-5.4
B	ol-HDF	1/25	-12.2	92.9	-1.2	-15.9
	cool HD	1/25	-7.4	93.5	-1.1	-16.3

Post ol-HDF = cool dialysis?

High-Volume HDF and Cool HD on Intradialytic Hemodynamics: A Randomized Cross-Over Trial

Rootjes PA et al., Kidney Int Rep 2022;7, 1980–90

- 40 pts, every 2 week, cross-over, The Netherlands
- standard HD vs cool HD (35.5°C), vs Low HDF(15L) vs High HDF(22.6L)



Modality	Total IDH episodes per session	*P*-value[a]	Early IDH episodes per session	*P*-value[a]
S-HD	0.68	Ref	0.32	Ref
C-HD	0.21	<0.0005[b]	0.07	<0.0005[b]
LV-HDF	0.51	0.21	0.19	0.09
HV-HDF	0.27	<0.0005[b]	0.10	0.001[b]

High-Volume HDF and Cool HD on Intradialytic Hemodynamics: A Randomized Cross-Over Trial

Rootjes PA et al., Kidney Int Rep 2022;7, 1980–90

- 40 pts, every 2 week, cross-over, The Netherlands
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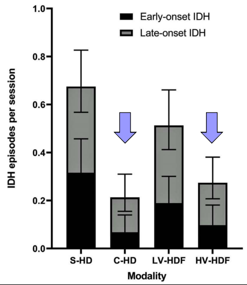


Supplementary Table S1. Body temperature before and after dialysis

	S-HD	C-HD	LV-HDF	HV-HDF
Body temperature (°C)				
Pre-dialysis	36.2 ± 0.4	36.3 ± 0.4	36.2 ± 0.5	36.1 ± 0.5
Post-dialysis	36.6 ± 0.4	36.3 ± 0.4	36.6 ± 0.4	36.5 ± 0.3
Delta	0.30	0.04	0.35	0.38
P-value*	<0.0005	0.43	<0.0005	<0.0005

Post ol-HDF ≠ cool dialysis?

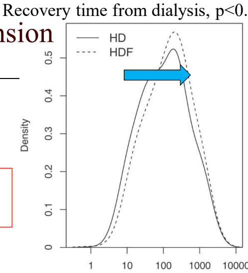
Denial for prevention of dialysis hypotension

Smith JR et al., Am J Kidney Dis. 2017;69:762-770

- HFHD vs post-online HDF(20L)
- Blind・random crossover
- HD 50 vs HDF 50pts, 8 week

Hypotension : RR 1.52
Blood pressure/body fluid side effect :RR 1.81

Recovery time from dialysis, p<0.001



Adverse Events for HD and HDF, Per Session

Variable	HD Sessions	HDF Sessions	RR (95% CI)	P
Symptomatic hypotension[a]	112 (5.2)	168 (8)	1.52 (1.21-1.92)	<0.001
AEs potentially related to BP/fluid shifts[b]	61 (3.0)	109 (5.3)	1.81 (1.33-2.46)	<0.001
AEs not classically related to BP/fluid shifts[c]	88 (4.3)	87 (4.3)	1.00 (0.75-1.34)	0.9
Extra tinzaparin dose(s) or clotting of circuit[d]	14 (0.7)	37 (1.8)	2.68 (1.46-5.00)	0.002

Survival : EU-RCT

CLINICAL RESEARCH www.jasn.org

CONTRAST *JSN 2012;23:1087-1096*

Effect of Online Hemodiafiltration on All-Caus[e] Mortality and Cardiovascular Outcomes

Muriel P.C. Grooteman,[*,†] Marinus A. van den Dorpel,[‡] Michiel L. Bots,[§] E. L... Neelke C. van der Weerd,[*] Albert H.A. Mazairac,[‖] Claire H. den Hoedt,[‡‖] Ing... Tweel,[§] Renée Lévesque,[¶] Menso J. Nubé,[*,†] Piet M. ter Wee,[*,†] and Peter J... for the CONTRAST Investigators

CLINICAL RESEARCH www.jasn.org *JSN 2013 ; 24:487-497*

ESHOL

High-Efficiency Postdilution Online Hemodiafiltration Reduces All-Cause Mortality in Hemodialysis Patients

Francisco Maduell,[*] Francesc Moreso,[†] Mercedes Pons,[‡] Rosa Ramos,[§] Josep Mora-Macià,[‖] Jordi Carreras,[¶] Jordi Soler,[**] Ferran Torres,[††‡‡] Josep M. Campistol,[*] and Alberto Martinez-Castelao,[§§] for the ESHOL Study Group

Nephrol Dial Transplant (2013) 28: 192–202
doi: 10.1093/ndt/gfs407
Advance Access publication 9 December 2012

Turkish

Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with hig[h-flux] dialysis: results from the Turkish OL-HDF Study

Ercan Ok[1], Gulay Asci[1], Huseyin Toz[1], Ebru Sevinc Ok[1], Fatih Kircelli[1], ... Ender Hur[1], Meltem Sezis Demirci[1], Cenk Demirci[1], Soner Duman[1], Ali ... Siddig Momin Adam[2], Ismet Onder Isik[2], Murat Zengin[2], Gultekin Suley... Mehmet Emin Yilmaz[4] and Mehmet Ozkahya[1] and On behalf of the 'Tur[kish] Haemodiafiltration Study'

www.kidney-international.org clinical trial

French

Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly

see commentary on page 1279

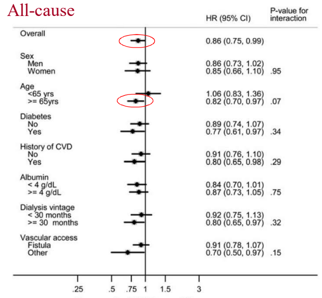
Marion Morena[1,2,3], Audrey Jaussent[4], Lotfi Chalabi[5], Hélène Leray-Moragues[6], Leila Chenine[6], Alain Debure[7], Damien Thibaudin[8], Lynda Azzouz[9], Laure Patrier[10], Francois Maurice[11], Philippe Nicoud[12], Claude Durand[13], Bruno Seigneuric[14], Anne-Marie Dupuy[1], Marie-Christine Picot[4], Jean-Paul Cristol[1,2,3] and Bernard Canaud[2,15]; for the FRENCHIE Study Investigators[16]

Survival : RCT

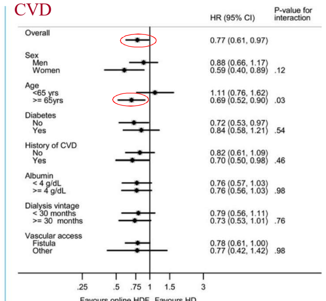
Peters SAE et al., NDT 2016; 31: 978-984

- Pooled individual participant data analysis: 2793pts, HDF50%

All-cause

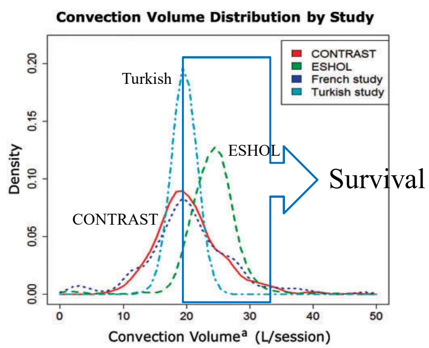


CVD



Global trends in HDF

Canaud B, et al. Nephrol Dial Transplant (2020) 35: 398–407



Questions about RCTs

Vernooij RDM et al., Nephrol Dial Transplant (2022) 37: 1006–1013

- The RCTs were not designed to study the effects of convection volumes, with no randomized treatment targets
- The possibility of confounding by indication cannot be excluded (patients with the least comorbidities and conferring a lower mortality risk).
- This study population might not reflect the dialysis population given the low mean age (i.e. 53 years) and little information reported on the selection procedure and participating centers
- The theoretical relationship between improved survival and solute removal is unclear.
- No upper limit for CV is provided.

New HDF study, RCT

Vernooij RDM et al., Nephrol Dial Transplant (2022) 37: 1006–1013

CONVINCE (EU)

- HDF(CV ≥ 23L) vs HFHD
- All-cause mortality
- Cardiovascular events
- Cause and infection-related hospitalizations
- Patient-reported outcomes
- Cost-effectiveness

- 3 years follow-up

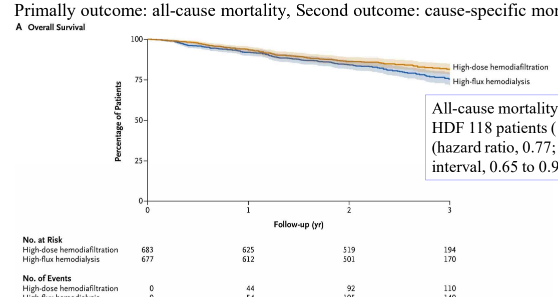
H4RT (UK)

- HDF(CV 21L) vs HFHD
- Mortality or hospitalization with a CVD or infection
- All-cause mortality
- Cardiovascular and infection related morbidity and mortality
- Health-related quality of life (HRQoL)
- Cost-effectiveness
- Environmental impact
- 32 -50 months follow-up

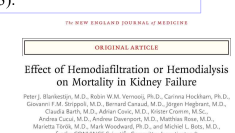
Results of CONVINCE

Blankestijn PJ et al., N Engl J Med. 2023 Jun 16. doi: 10.1056/NEJMoa2304820

- 2018 to 2021, Total 1360, High-dose HDF (CV>23L) 683, High-flux HD 677,
- Medial follow up 30m, mean CV 25.3L
- Primally outcome: all-cause mortality, Second outcome: cause-specific mortality, CVD, infection



All-cause mortality
HDF 118 patients (17.3%) vs HD 148 (21.9%)
(hazard ratio, 0.77; 95% confidence interval, 0.65 to 0.93).



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure

Peter J. Blankestijn, M.D., Robin W.M. Vernooij, Ph.D., Carinna Hockham, Ph.D., Giovanni F.M. Strippoli, M.D., Bernard Canaud, M.D., Jörgen Hegbrant, M.D., Claudia Barth, M.D., Adrian Covic, M.D., Krister Cromm, M.Sc., Andrea Cucui, M.D., Andrew Davenport, M.D., Matthias Rose, M.D., Marietta Török, M.D., Mark Woodward, Ph.D., and Michiel L. Bots, M.D., for the CONVINCE Scientific Committee Investigators*

Results of CONVINCE

Blankestijn PJ et al., N Engl J Med. 2023 Jun 16. doi: 10.1056/NEJMoa2304820

- Second outcome: cause-specific mortality, CVD, infection

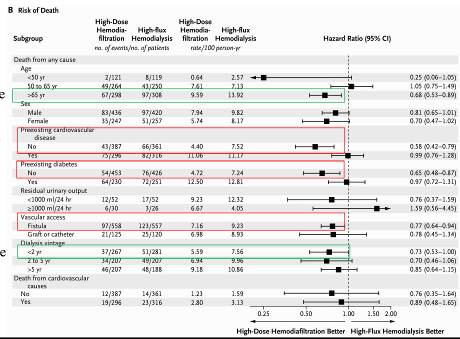
Elderly age

Non CVD

Non DM

AVF

Early vintage



CVD death: HR 0.81 (0.49-1.33)
CVD outcome: 1.07 (0.86 -1.33
recurrent hospitalization: 1.11; (0.98-1.25)

Influence by COVID19

Haemodiafiltration for all: are we CONVINCE?

Shroff R et al., , the EuDial Working Group
Nephrology Dialysis Transplantation 2023, https://doi.org/10.1093/ndt/gfad136

- Several questions remain unanswered, in the post hoc analyses of CONVINCE

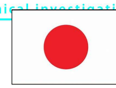
1. A lower mortality was only seen in patients on AVF. It would be interesting to know the comparative blood flow rates and convection volumes through different access types.
2. Clearance of middle molecules are more likely to influence outcomes, but have not been reported.
3. When outcomes are stratified by convection volume it may become apparent that somewhat lower convection volumes may also achieve beneficial effects
4. HDF advantage was seen in elderly and early introduction, but stratified analysis is needed
5. The study was conducted during the COVID-19 pandemic and its impact cannot be ignored

Pre-HDF in Japan

www.kidney-international.org

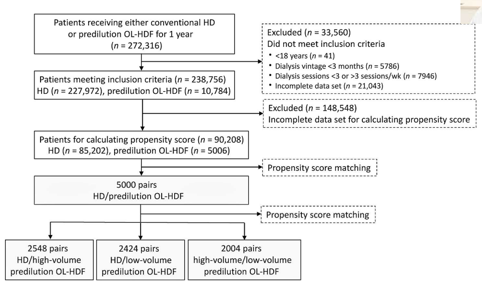
clinical investigation

Kidney International (2019) 95, 929–938



Predilution online hemodiafiltration is associated with improved survival compared with hemodialysis

Kan Kikuchi , Takayuki Hamano , Atsushi Wada , Shigeru Nakai and Ikuto Masakane

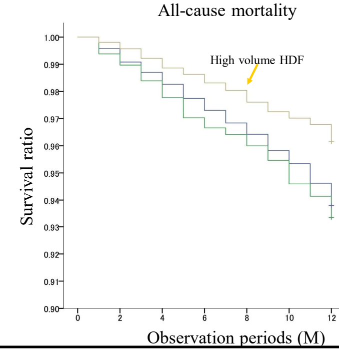


JRDR
2012-2013

Improvement of patient's survival : pre-online HDF

JRDR: propensity score matching, Kidney International (2019) 95, 929–938

All-cause mortality



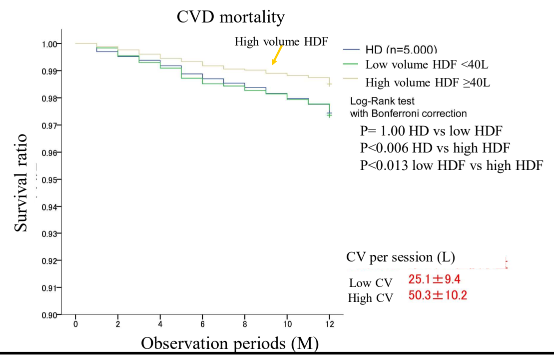
Log-Rank test
with Bonferroni correction
P= 1.00 HD vs low HDF
P<0.001 HD vs high HDF
P<0.001 low HDF vs high HDF

CV per session (L)

Low CV	25.1±9.4
High CV	50.3±10.2

Improvement of patient's survival : pre-online HDF

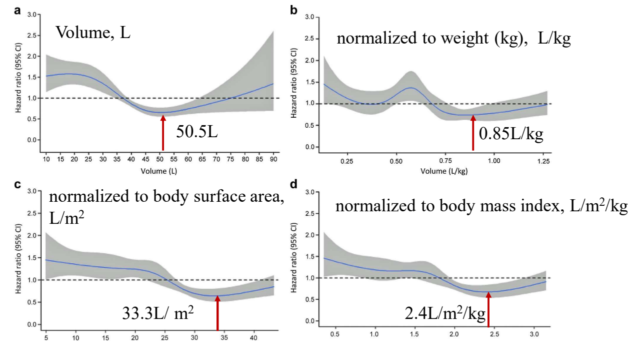
JRDR: propensity score matching, Kidney International (2019) 95, 929–938



Limitation of CV??

Kidney International (2019) 95, 929–938
Predilution online hemodiafiltration is associated with improved survival compared with hemodialysis

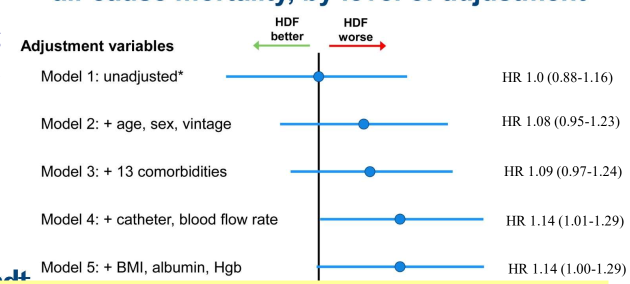
Kan Kikuchi, Takayuki Hamano, Atsushi Wada, Shigeru Nakai and Ikuto Masakane



Denial of effect of Survival, Euro-DOPPS 4-5

Locatelli F et al., Nephrol Dial Transplant 2018;33:683-689.

Association between HDF (vs. HD) and all-cause mortality, by level of adjustment



- Further trials designed to test the effect of high-volume HDF on clinical outcomes are needed to adequately inform clinical practices.

Conclusions by Locatelli F

- The results do not support the notion that HDF provides superior patient survival.
- Further trials designed to test the effect of high-volume HDF (versus lower volume HDF versus HD) on clinical outcomes are needed to adequately inform clinical practices.

ndt

Mortality risk in patients on hemodiafiltration versus hemodialysis: a 'real-world' comparison from the DOPPS

hemodialysis: a 'real-world' comparison from the DOPPS

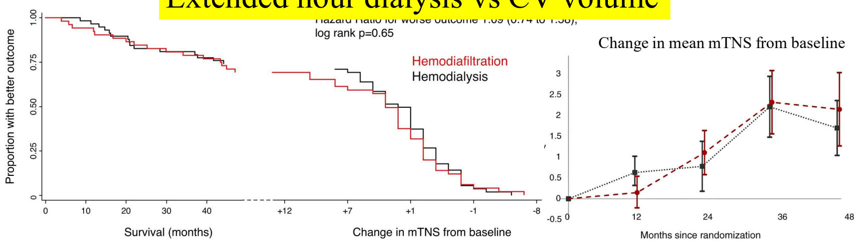
Francesco Locatelli[1], Angelo Karaboyas[2], Ronald L. Pisoni[2], Bruce M. Robinson[2,3], Joan Fort[4], Raymond Vanholder[5], Hugh C. Rayner[6], Werner Kleophas[7,8], Stefan H. Jacobson[9], Christian Combe[10], Friedrich K. Port[2] and Francesca Tentori[2,11]

Effect of Hemodiafiltration on the Progression of Neuropathy, FINESSE study

Kang A, et al., CJASN 2021; 16: 1365–1375

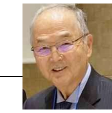
- RCT in Australia, HFHD vs Post on-line HDF (CV 24.7 (22.4–26.5))
- Age 66 (13)yo, Vintage 3.2 (1.9–5.2)yr, 5hr/session x 3times/wk
- Outcome: to

Extended hour dialysis vs CV volume

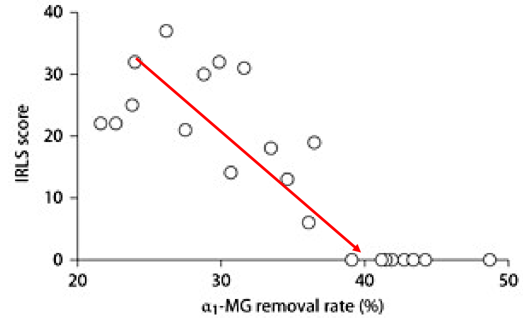


Decrease of dialysis related Uncertain complaint, RLS

Biomarkers for Evaluation of Clinical Outcomes of Hemodiafiltration,
Sakurai K. Blood Purif 2013;35(suppl 1):64-68

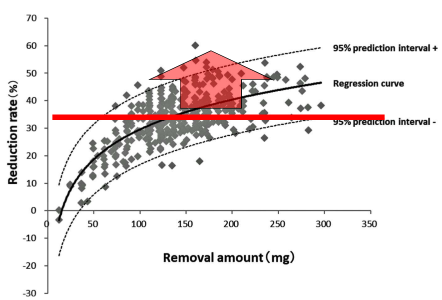


Restress leg syndrome



α1-microglobulin reduction rate as a biomarker of removal efficiency of online hemodiafiltration

Sakurai K et al., Renal Replacement Therapy 2021;7:10



Conclusion

Is there enough evidence to prove HDF is superior?

- Dialysis amyloidosis : effective
- RLS: effective
- Uncertain complaint : effective
- Dialysis hypotension: effective or not?
- Survival: unknown
- Removal α1MG: Possibility for recovery of Antioxidant effect

On-line HDF possible to effect to HD patients

Thank you for your attention

If you have any questions, e-mail to

h-kawanishi@tsuchiya-hp.jp