Haemodiafiltration (HDF)- Controversies Prevail?

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20/5/2012

Changing paradigms of renal replacement therapy in chronic kidney disease patients: ultrapure dialysis fluid and high-efficiency hemodiafiltration for all?

A challenging European perspective

Canaud B, ***Kidney Int***. 2009; 76: 591-593

Outline of Lecture

- Introduction
- Limitation/complication of conventional dialysis
- Convective Therapy
- Practice pattern of HDF in the world
- Evidence of benefits of HDF- ??
- Who/when to start
- Prescription of HDF
- Conclusion

Introduction

Patients undergoing chronic intermittent hemodialysis have a high risk of cardiovascular morbidity and mortality

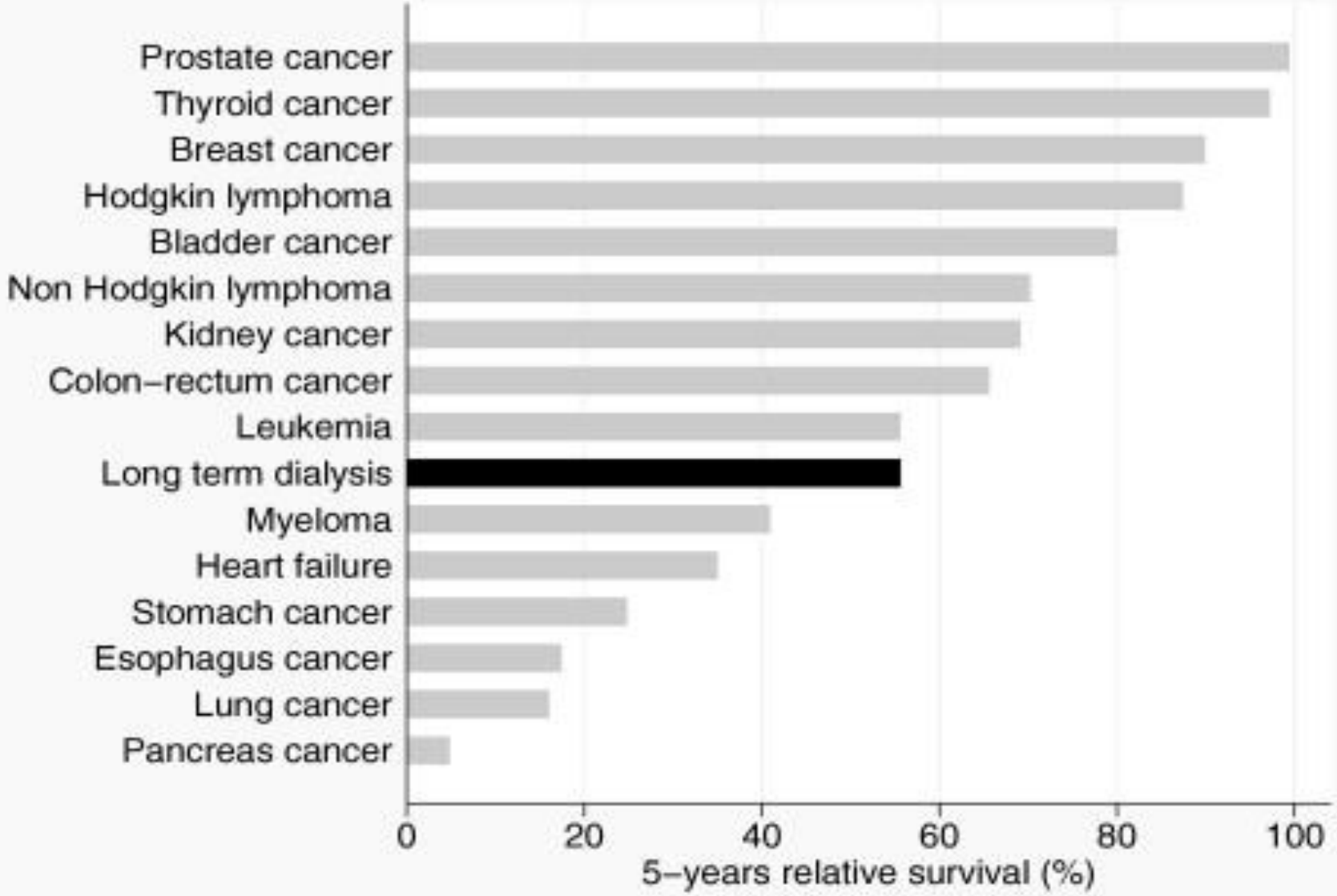
Of the potential risk factors involved, retention of uremic toxins in the middle molecular mass range (0.5–40 kD) might play an important role

Hemodiafiltration (HDF) and probably originated from work done in the late 70's by Leber et al. in Giessen, Germany

Leber HW, Wizemann V, Goubeaud G, Rawer P, Schutterle G. Simultaneous hemofiltration / hemodialysis: an effective alternative to hemofiltration and conventional hemodialysis in the treatment of uremic patients. *Clin Nephrol* 9:115-121, 1978

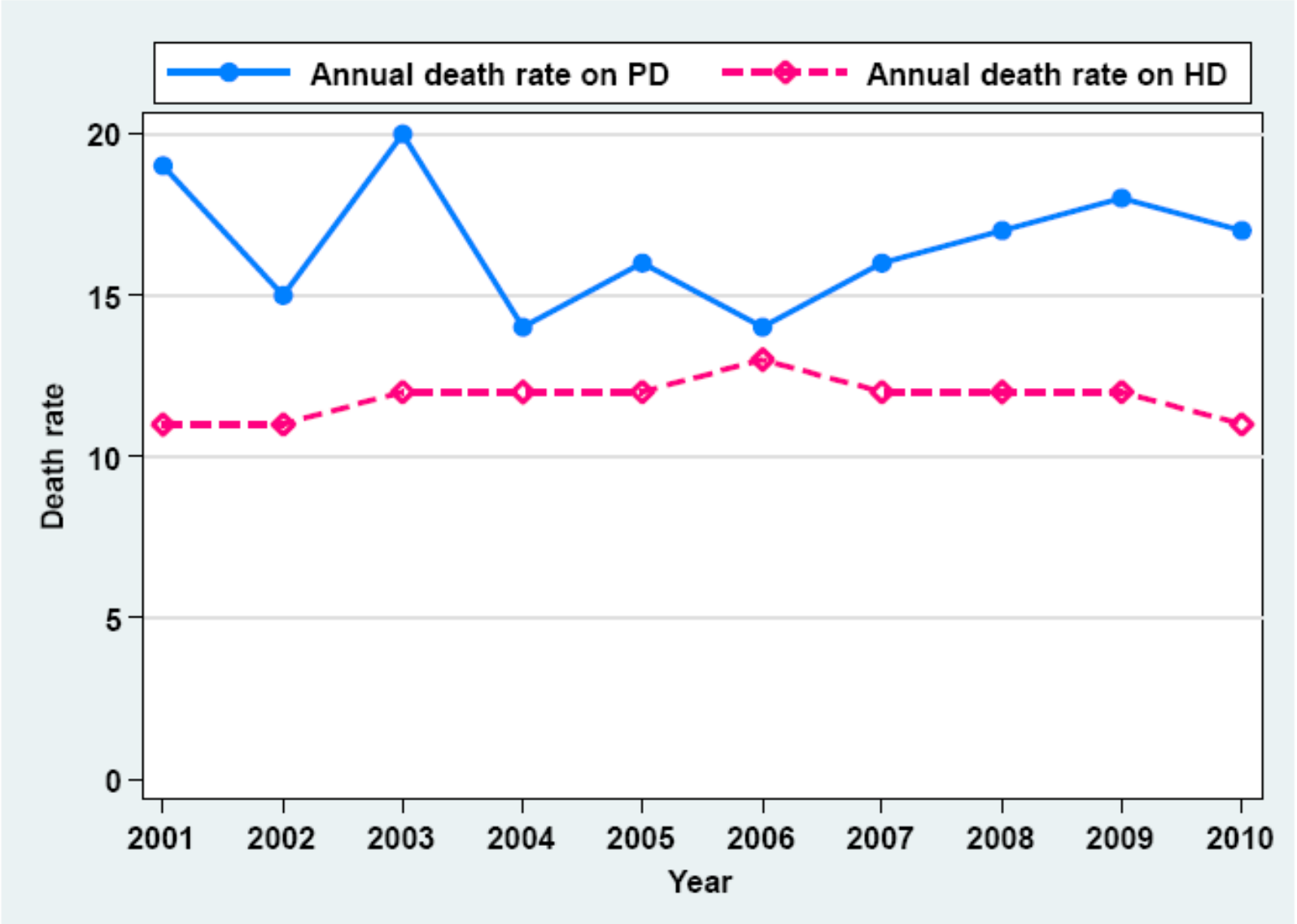
Facts : Dialysis is associated with high mortality and significant morbidity

- **High mortality**
  - Accelerated cardiovascular disease
  - Infection
  - Cachexia
- **Frequent dialysis-related morbidity**
  - Accelerated atherosclerosis
  - Vascular calcification
  - Left ventricular hypertrophy
  - Bone mineral disorders
  - Protein Energy Wasting
  - Ageing
  - ß2M-amyloidosis
  - …



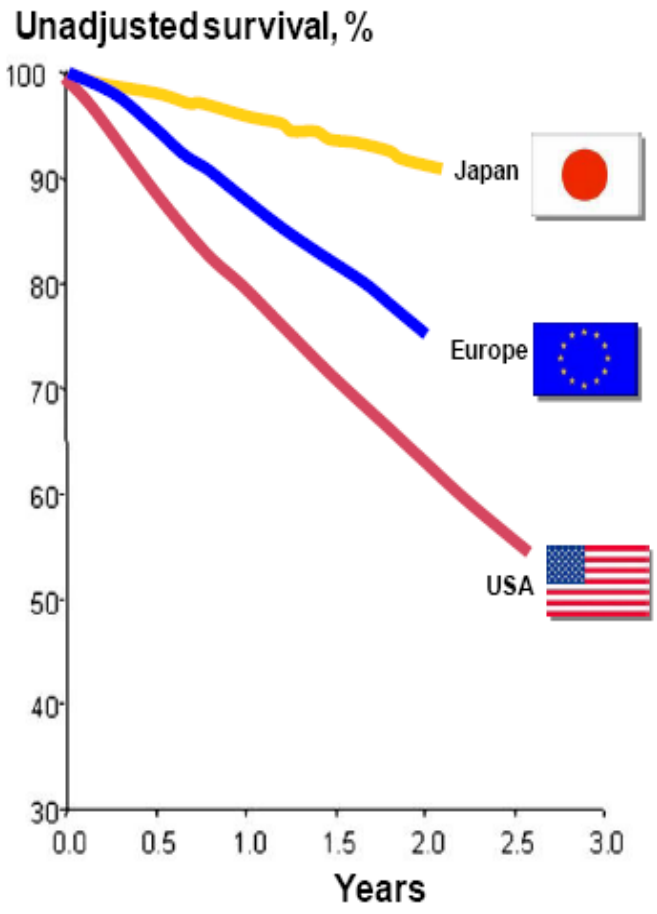
Maurizio Nordio et al 2012,AJKD

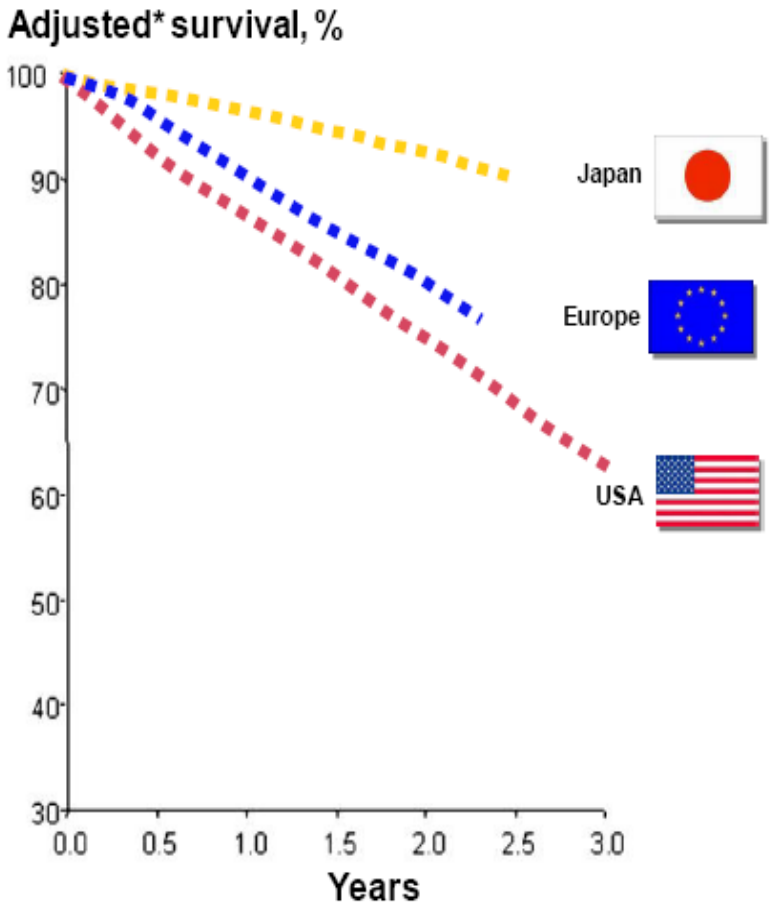
Figure 3.1.1: Death Rates on Dialysis 2001-2010



18th MDTR report 2010, Malaysia

Mortality in dialysis patients remains desperately high despite technological progresses in HD



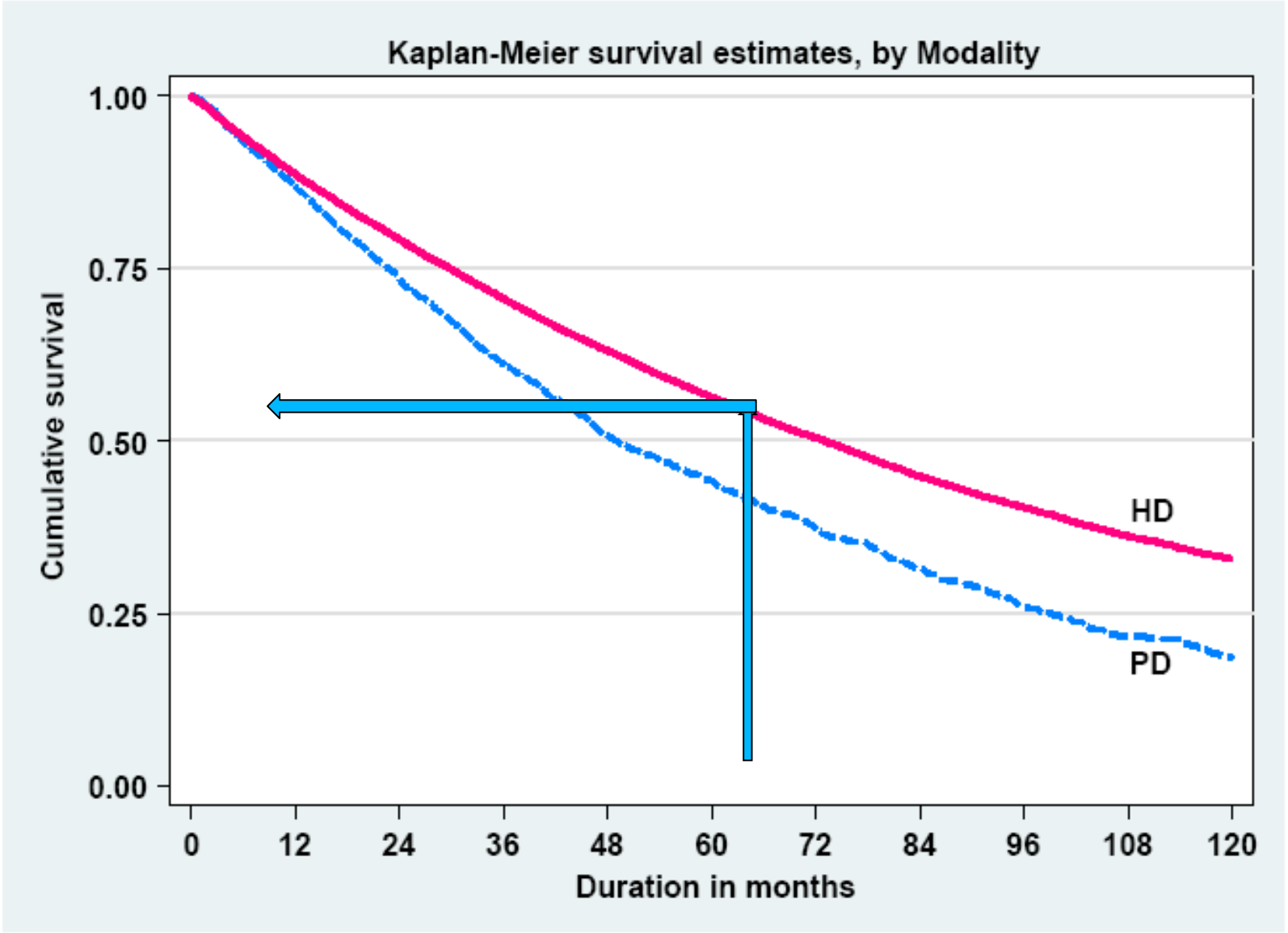


DOPPS

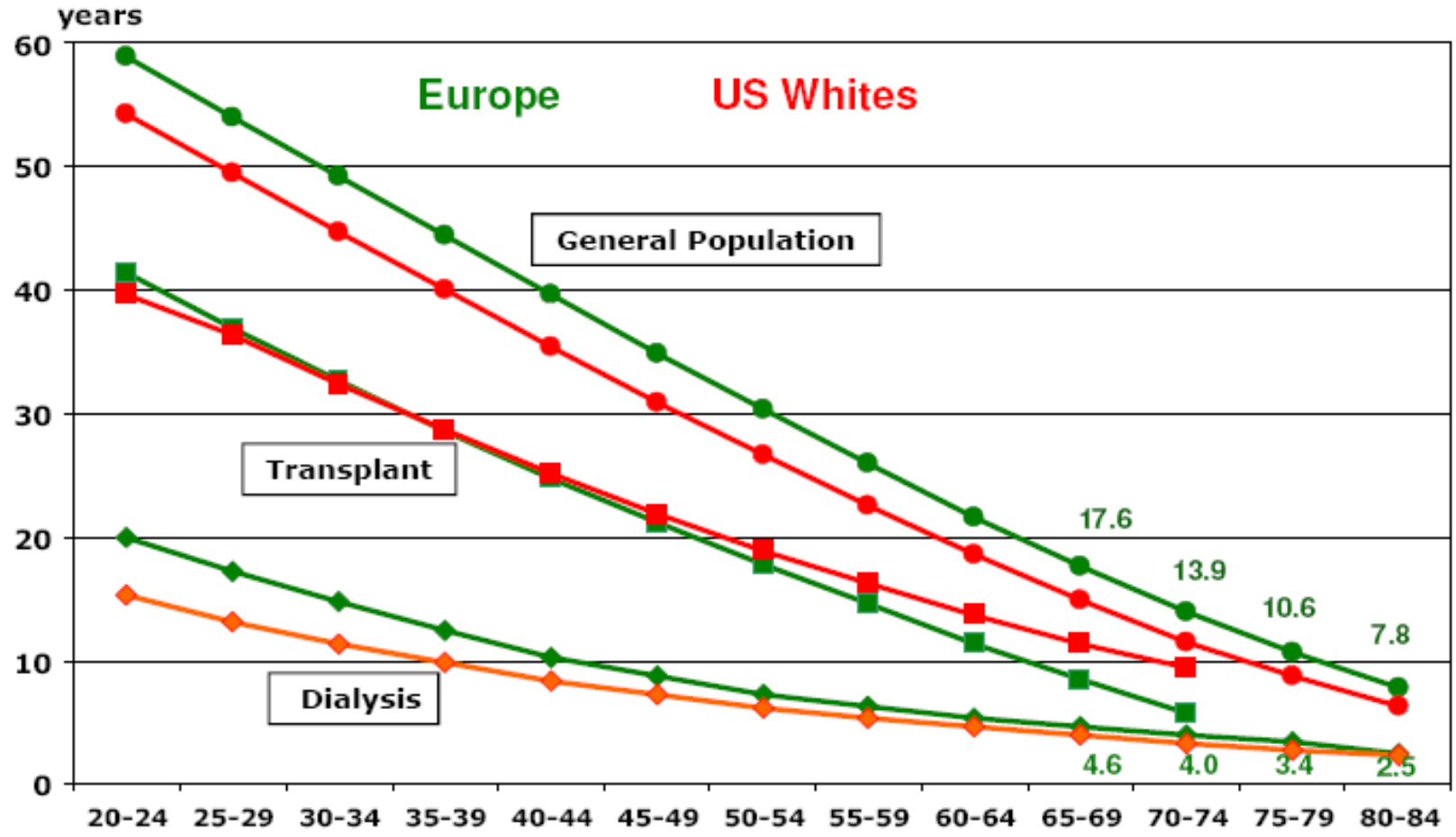
* Age, Sex, Race, 14 Comorbidities

Goodkin DA et al. *J Am Soc Nephrol*. 2003; 14:3270-3277

Figure 3.2.1(a): Patient survival by dialysis modality analysis (censored for change of modality)



Expected remaining lifetimes in adult CKD Stage 5 as compared to the General Population



ERA-EDTA Registry data and USRDS data

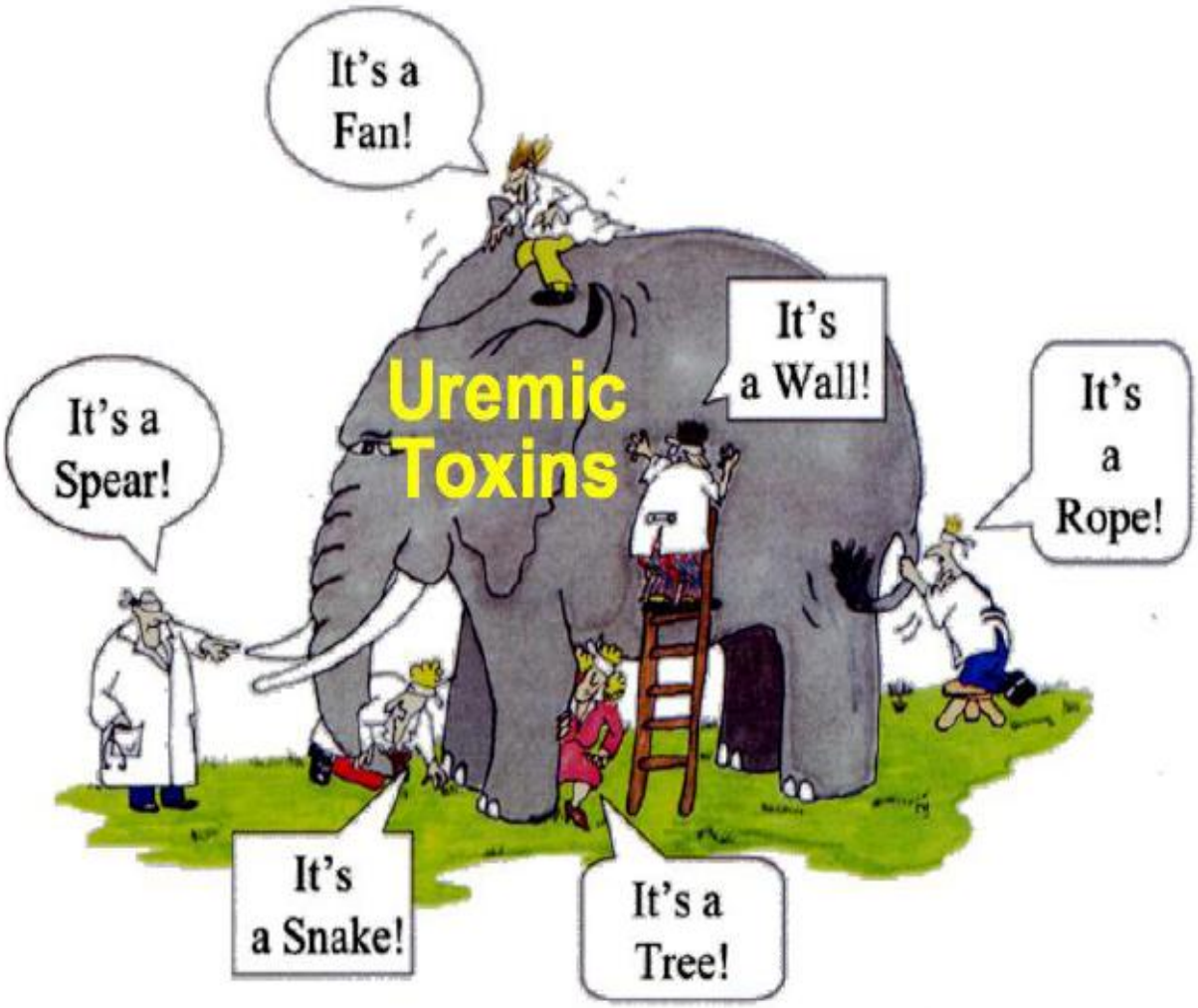
Table 3.1.2: Causes of Death on Dialysis 2001-2010

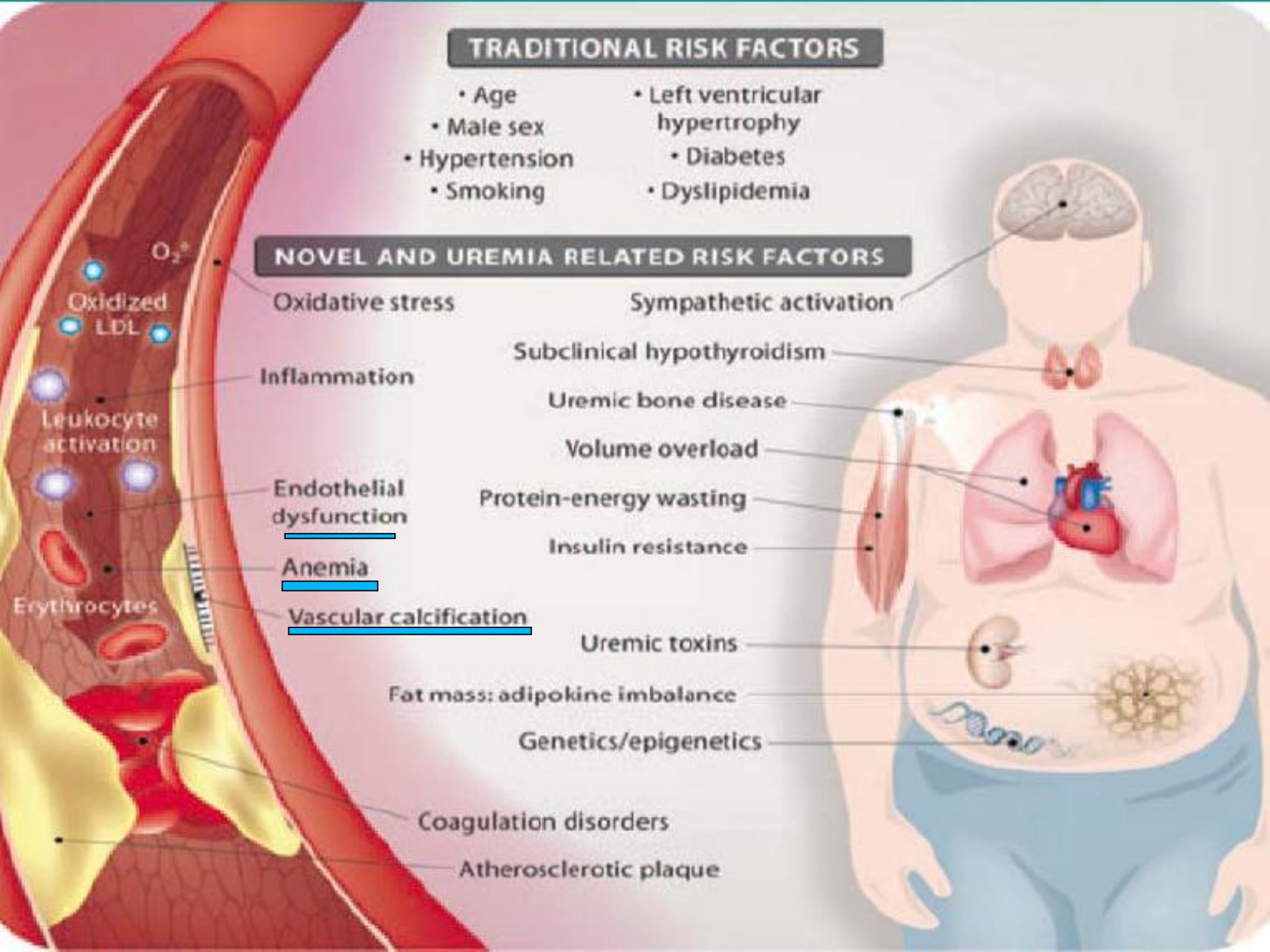
Year / Causes of Death	2001		2002		2003		2004		2005	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	221	26	313	33	341	28	341	26	376	25
Died at home	228	27	212	22	290	24	307	23	320	21
Sepsis	134	16	148	15	197	16	166	13	179	12
PD peritonitis	30	4	16	2	14	1	13	1	22	1
GIT bleed	18	2	24	3	29	2	24	2	29	2
Cancer	18	2	18	2	28	2	20	2	28	2
Liver disease	11	1	16	2	25	2	29	2	26	2
Withdrawal	20	2	18	2	26	2	9	1	11	1
Others	89	10	104	11	161	13	325	25	406	27
Unknown	81	10	90	9	100	8	84	6	116	8
TOTAL	850	100	959	100	1211	100	1318	100	1513	100

Year / Causes of Death	2006		2007		2008		2009		2010	
	n	%	n	%	n	%	n	%	n	%
Cardiovascular	517	28	516	26	682	31	871	34	871	34
Died at home	354	20	343	17	423	19	492	19	507	20
Sepsis	235	13	222	11	336	15	570	22	605	24
PD peritonitis	22	1	16	1	25	1	30	1	34	1
GIT bleed	26	1	31	2	43	2	44	2	51	2
Cancer	41	2	34	2	53	2	54	2	69	3
Liver disease	35	2	37	2	44	2	26	1	31	1
Withdrawal	23	1	27	1	24	1	34	1	29	1
Others	392	22	552	28	366	17	195	8	108	4
Unknown	170	9	206	10	194	9	262	10	269	10
TOTAL	1815	100	1984	100	2190	100	2578	100	2574	100

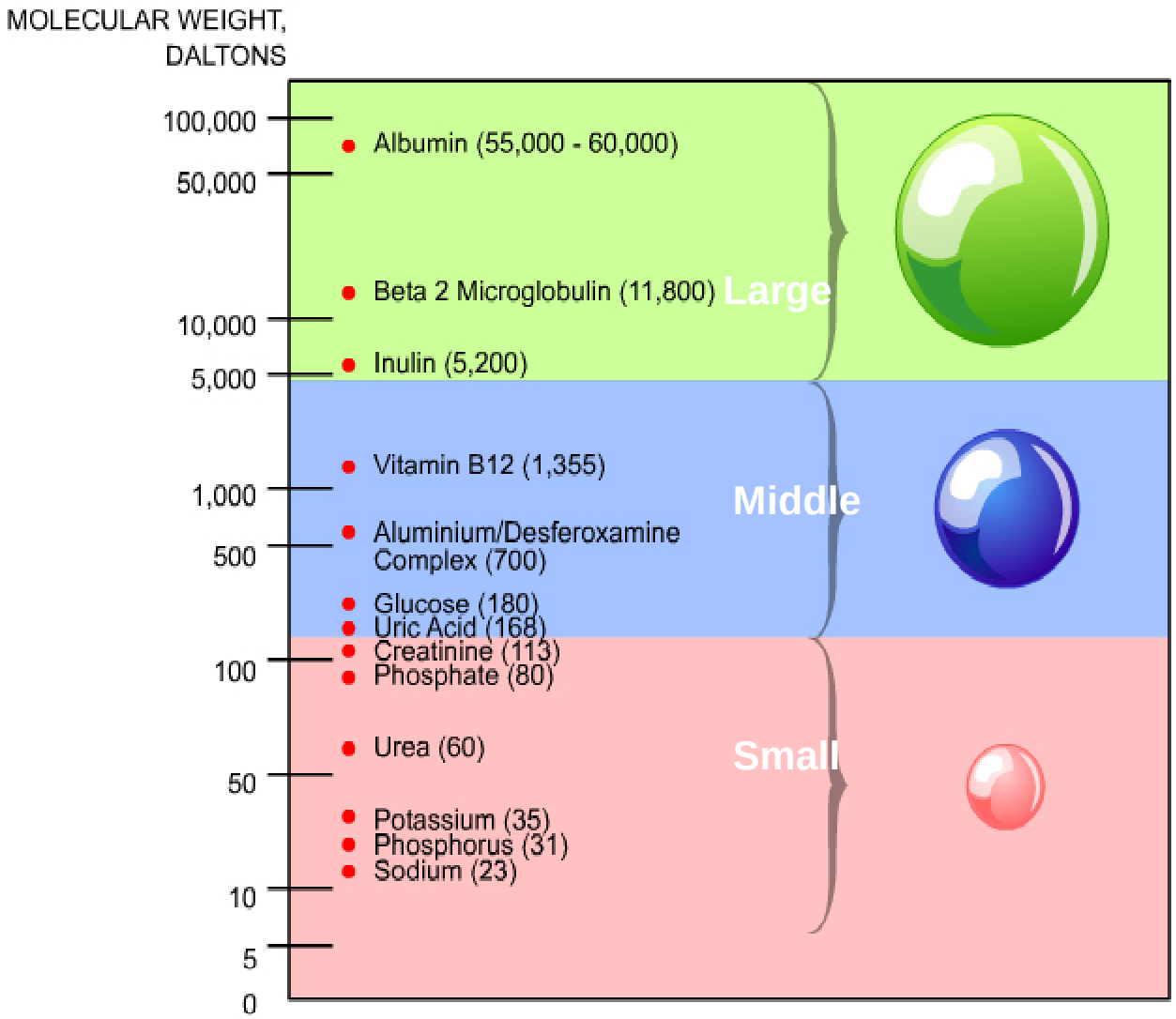
18th MDTR report 2010, Malaysia

Uremic toxins remain an obscure world for Nephrologist




TRADITIONAL RISK FACTORS
• Age
• Male sex
• Hypertension
• Smoking
• Left ventricular hypertrophy
• Diabetes
• Dyslipidemia
NOVEL AND UREMIA RELATED RISK FACTORS
O_2^-
Oxidized LDL
Oxidative stress
Sympathetic activation
Subclinical hypothyroidism
Inflammation
Uremic bone disease
Leukocyte activation
Volume overload
Endothelial dysfunction
Protein-energy wasting
Insulin resistance
Anemia
Erythrocytes
Vascular calcification
Uremic toxins
Fat mass: adipokine imbalance
Genetics/epigenetics
Coagulation disorders
Atherosclerotic plaque

Molecular Weights



Uremic toxins is a complex mixture

European Uremic Toxin Work Group of the ESAO

Small water soluble solutes	Protein-bound solutes	Middle molecules
Asymmetric dimethylarginine	3-Deoxyglucosone	Adrenomedullin
Benzylalcohol	CMPF*	Atrial natriuretic peptide
ß-Guanidinopropionic acid	Fructoselysine	$ß_2$-Microglobulin
ß-Lipotropin	Glyoxal	ß-Endorphin
Creatinine	Hippuric acid	Cholecystokinin
Cytidine	Homocysteine	Clara cell protein
Guanidine	Hydroquinone	Complement factor D
Guanidinoacetic acid	Indole-3-acetic acid	Cystatin C
Guanidinosuccinic acid	Indoxyl sulfate	Degranulation inhibiting protein I
Hypoxanthine	Kinurenine	Delta-sleep-inducing peptide
Malondialdehyde	Kynurenic acid	Endothelin
Methylguanidine	Methylglyoxal	Hyaluronic acid
Myoinositol	N-carboxymethyllysine	Interleukin 1ß
Orotic acid	P-cresol	Interleukin 6
Orotidine	Pentosidine	Kappa-Ig light chain
Oxalate	Phenol	ambda-Ig light chain
Pseudouridine	P-OHhippuri	eptin
Symmetric dimethylargini	Quinolinic ac	ethionine-enkepahli
Urea	Spermidine	europeptide Y
Uric acid	Spermine	arathyroid hormone
Xanthine		etinol binding prote
		umor necrosis factor al

*CMPF is carboxy-methyl-propyl-furanpropionic acid

Forgotten toxins
Na
H_20
K
Phosphate...

Endothelium toxins
Indoxyl sulfate
Para Cresyl Sulfate

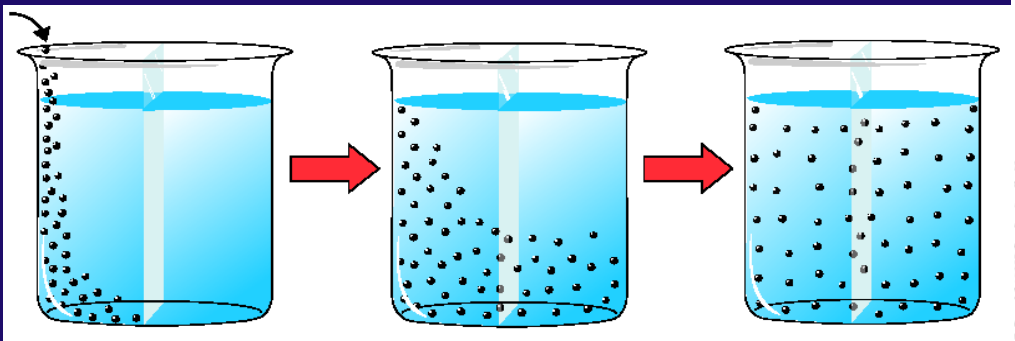
Inflammatory mediators or biomarkers
IL1, IL6, TNF
B2M..

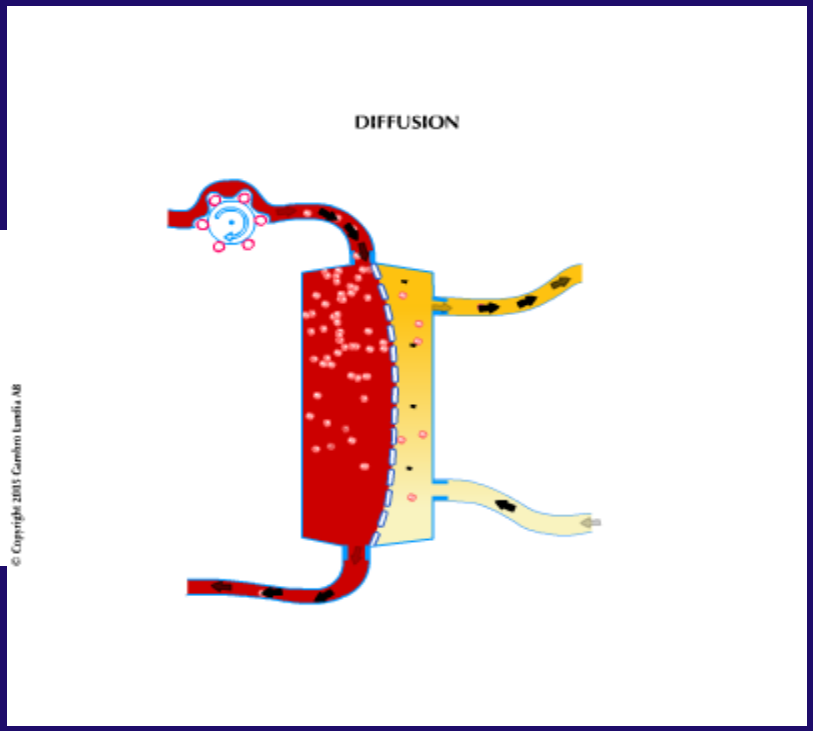
Vanholder R. et al New insights in uremic toxins. *Kidney Int*, 2003, 63; 84: S6–S10

Why haemofiltration might be an answer to a better renal replacement modality??

Diffusion

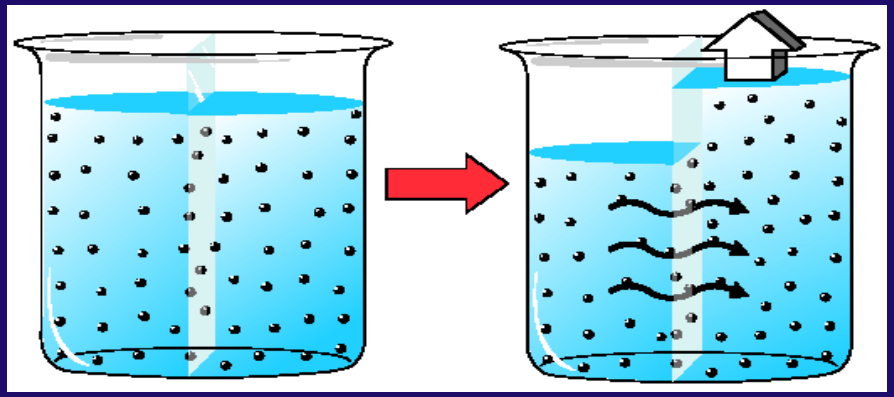
Diffusion is the movement of waste (solutes) from higher to lower concentration

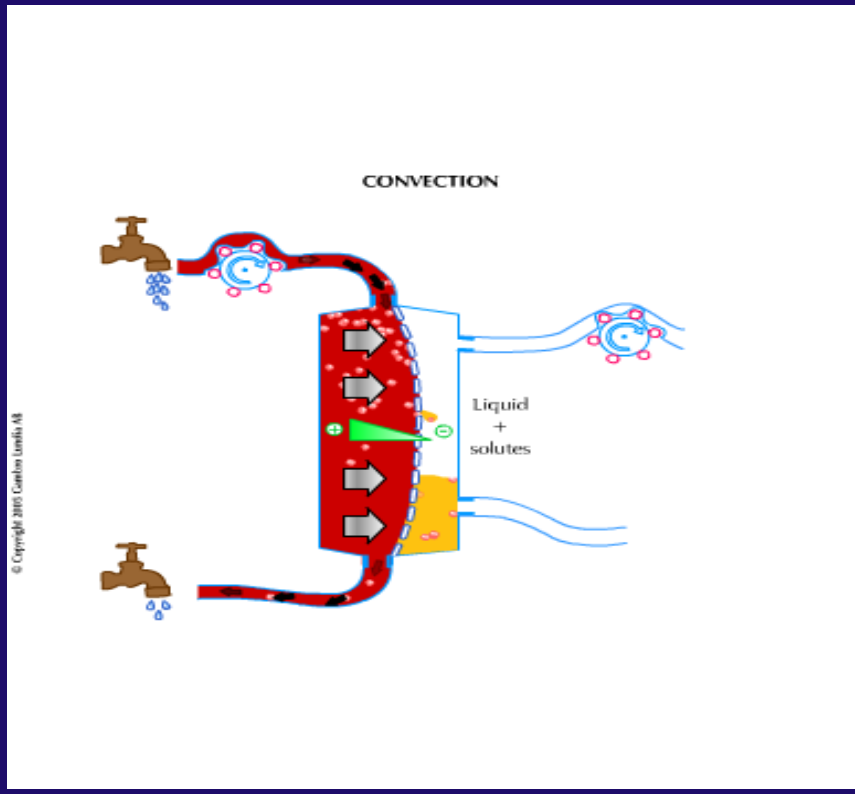




Convection

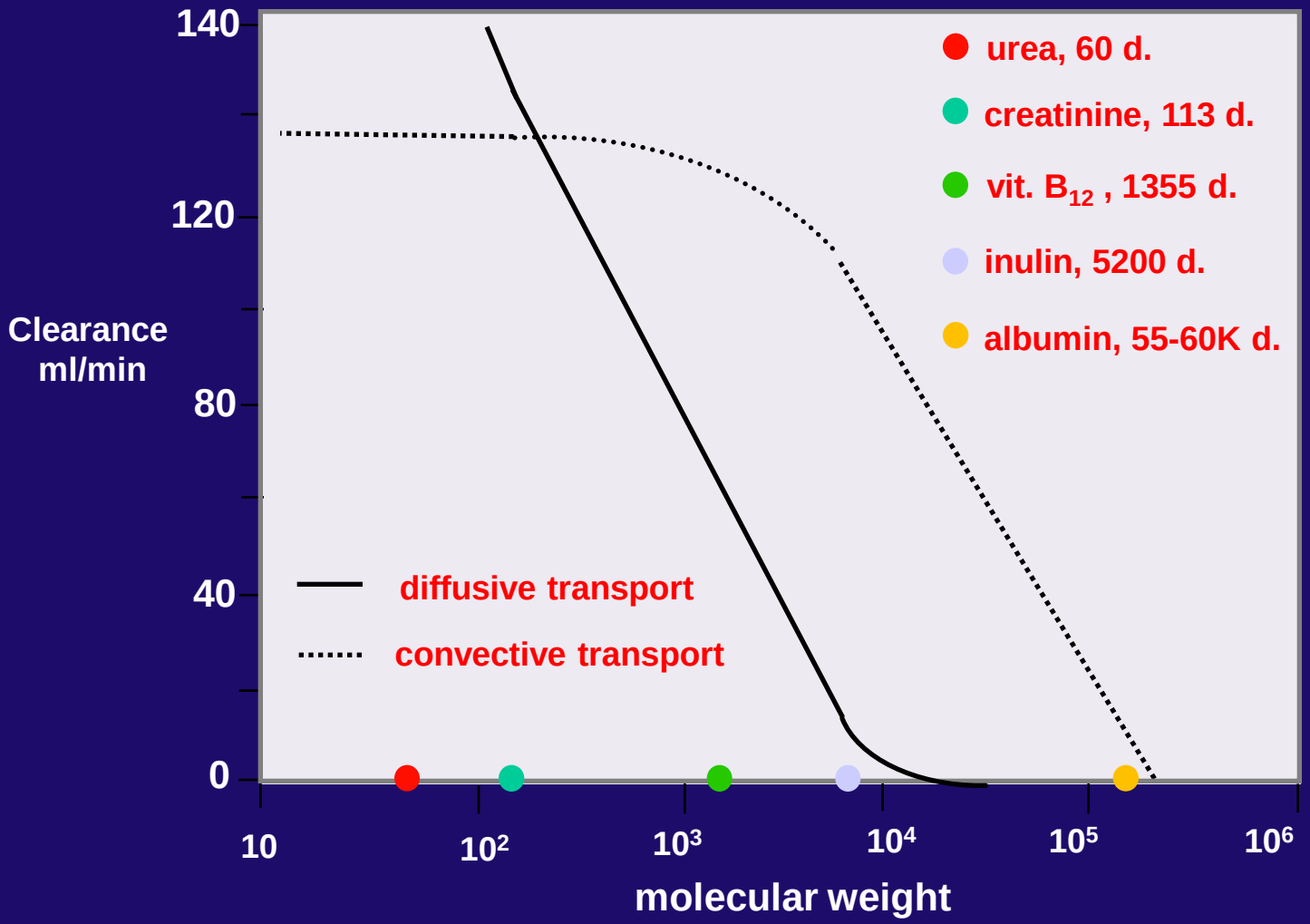
Convection is the movement of waste (solute) with fluid flow, also known as solute drag

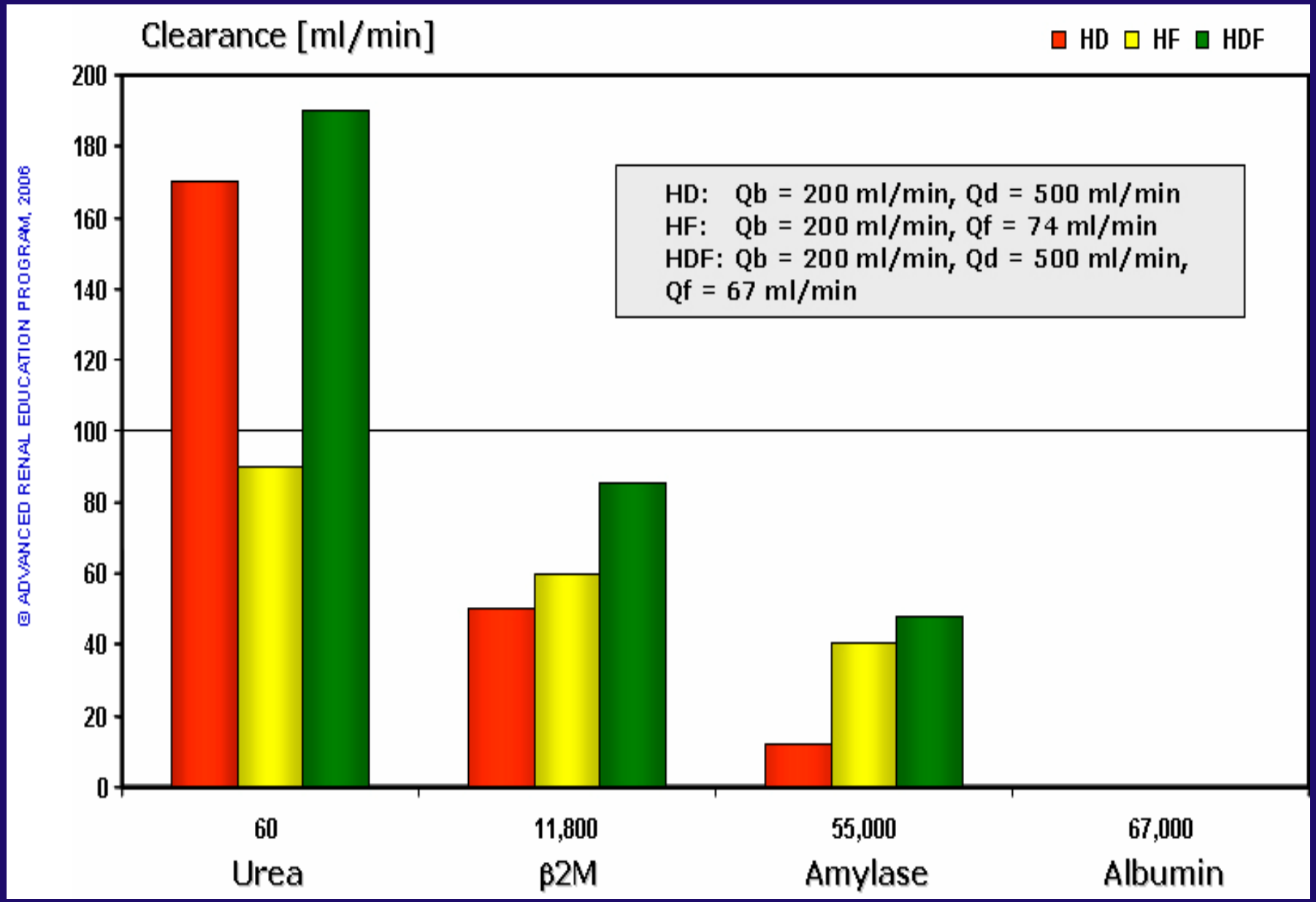




Diffusive vs. Convective Transport

Clearance for Diffusion and Convection




Clearance [ml/min]
HD
HF
HDF
200
180
160
140
120
100
80
60
40
20
0
HD: Qb = 200 ml/min, Qd = 500 ml/min
HF: Qb = 200 ml/min, Qf = 74 ml/min
HDF: Qb = 200 ml/min, Qd = 500 ml/min,
Qf = 67 ml/min
60
11,800
55,000
67,000
Urea
β2M
Amylase
Albumin
© ADVANCED RENAL EDUCATION PROGRAM, 2006

What role for hemodiafiltration ?
Rationale for using hemodiafiltration ?

- **Enhance dialysis efficacy**
  - Combine diffusive + forced convective clearances
  - Optimize solute exchange
  - Enlarge middle molecule removal
- **Improve dialysis physiology**
  - Reduce hemodynamic instability
  - Factors implicated: temperature, bicarbonate, remove vasoactive mediators…
- **Ameliorate dialysis biocompatibility**
  - Ultrapurity of dialysis fluid
  - Highly permeable synthetic biocompatible membrane
  - Protein-coating of membrane

Practice Pattern of HDF

- Not practised in the US
- Prevalence of HDF ranged from 1.8% in Spain to 20.1% in Italy

Canaud B et al KI 2006 June- DOPPS Data

Table 1 | Distribution of dialysis modality for prevalent cross-section of patients at baseline

Country	*n*	Patients (%)			
		Low-efficiency HDF[a]	High-efficiency HDF[a]	Low-flux HD	High-flux HD
France	460	5.4	8.9	45.9	39.8
Germany	440	11.1	4.8	50.5	33.6
Italy	443	14.7	5.4	74.9	5.0
Spain	383	1.8	0.0	61.4	36.8
UK	439	2.3	2.5	83.4	11.8
All	2165	7.2	4.5	63.1	25.2

[a]Low-efficiency HDF includes replacements of 5–14.9 l, while high-efficiency HDF includes replacement of 15–24.9 l.

HD, hemodialysis; HDF, hemodiafiltration.

Possible benefits of HDF

Previous two landmark trials

1) HEMO

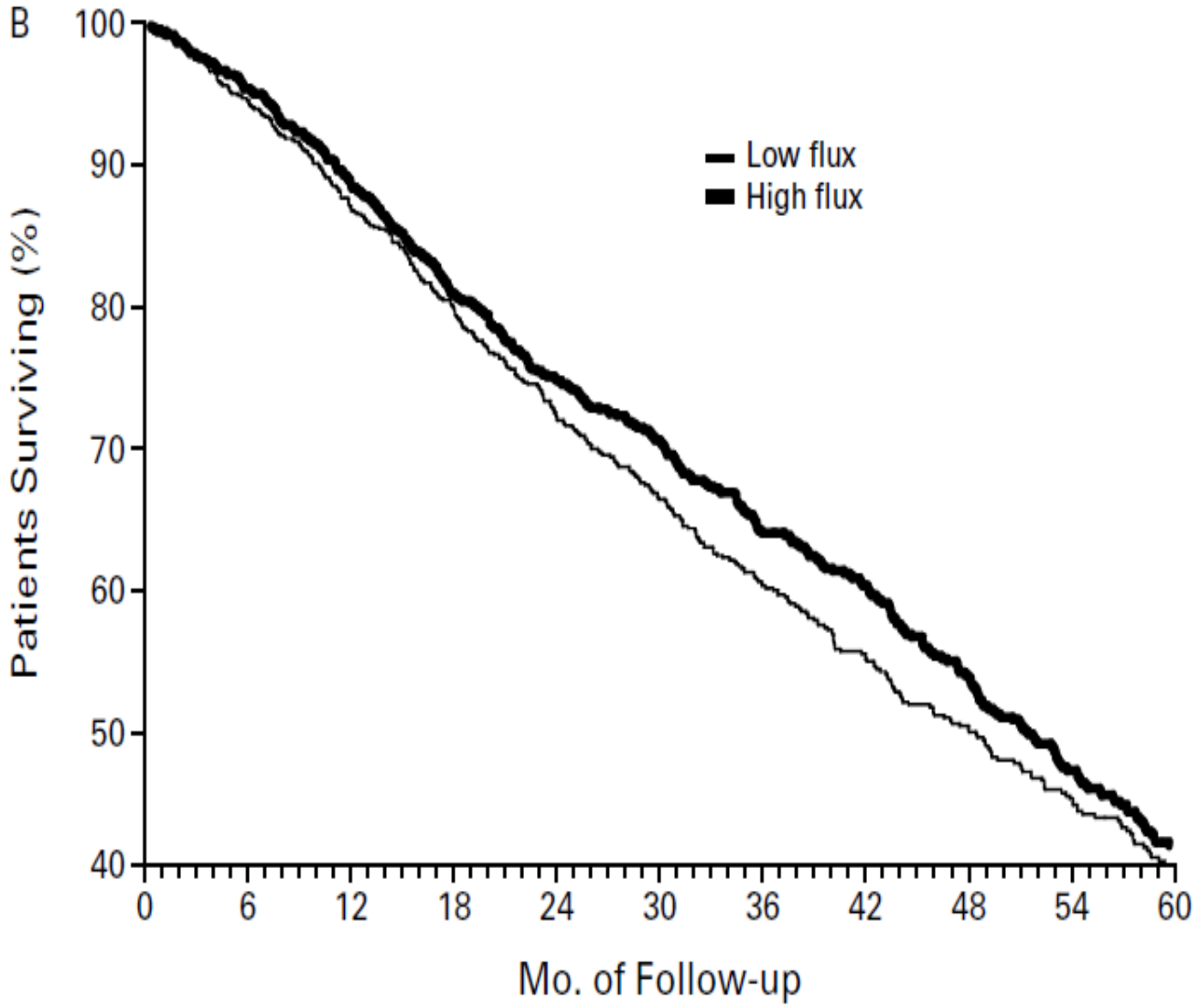
2) MPO

The New England Journal of Medicine

EFFECT OF DIALYSIS DOSE AND MEMBRANE FLUX IN MAINTENANCE HEMODIALYSIS

GARABED EKNOYAN, M.D., GERALD J. BECK, PH.D., ALFRED K. CHEUNG, M.D., JOHN T. DAUGIRDAS, M.D., TOM GREENE, PH.D., JOHN W. KUSEK, PH.D., MICHAEL ALLON, M.D., JAMES BAILEY, M.D., JAMES A. DELMEZ, M.D., THOMAS A. DEPNER, M.D., JOHANNA T. DWYER, D.SC., R.D., ANDREW S. LEVEY, M.D., NATHAN W. LEVIN, M.D., EDGAR MILFORD, M.D., DANIEL B. ORNT, M.D., MICHAEL V. ROCCO, M.D., GERALD SCHULMAN, M.D., STEVE J. SCHWAB, M.D., BRENDAN P. TEEHAN, M.D., AND ROBERT TOTO, M.D., FOR THE HEMODIALYSIS (HEMO) STUDY GROUP*

N Engl J Med 2002;347:2010-9.



No. at Risk										
Low flux	851	750	632	525	446	383	307	250	203	149
High flux	860	761	635	537	473	399	335	269	212	160

Figure 1. Survival Curves for the Treatment Groups.

The risk of death from any cause, the primary outcome, was the same in the high and standard dose groups (RR of 0.96 for high versus standard dose, CI of 0.84 to 1.10) and in the high and low flux groups (RR of 0.92).

The risk of the main secondary outcomes was also the same for both dialysis doses and both flux groups.

Subgroup analysis revealed a survival benefit for patients with more than **3.7 years** of dialysis receiving **high flux** dialysis (32 % lower risk than the low flux group).

CLINICAL RESEARCH www.jasn.org

Effect of Membrane Permeability on Survival of Hemodialysis Patients

Francesco Locatelli,* Alejandro Martin-Malo,† Thierry Hannedouche,‡ Alfredo Loureiro,§ Menelaos Papadimitriou,‖ Volker Wizemann,¶ Stefan H. Jacobson,** Stanislaw Czekalski,†† Claudio Ronco,‡‡ and Raymond Vanholder,§§
for the Membrane Permeability Outcome (MPO) Study Group

*Department of Nephrology, Dialysis and Renal Transplantation, A. Manzoni Hospital, Lecco, Italy; †Department of Nephrology, University Hospital Reina Sofia, Cordoba, Spain; ‡Department of Nephrology, University Hospital, Strasbourg, France; §Department of Nephrology, Portuguese Institute of Oncology, Porto, Portugal; ‖Department of Nephrology, Hippokration General Hospital, Thessaloniki Greece; ¶Georg-Haas-Dialysis Centre, Giessen, Germany; **Department of Nephrology, Danderyd University Hospital, Karolinska Institute, Stockholm, Sweden; ††Department of Nephrology, Transplantology and Internal Diseases, Poznań University of Medical Sciences, Poznań, Poland; ‡‡Department of Nephrology and Intensive Care, St. Bortolo Hospital, Vincenza, Italy; and §§Department of Internal Medicine, Nephrology Section, University Hospital, Ghent, Belgium

JASN 2009

Results

Patients with serum albumin ≤4 g/dl had significantly higher survival rates in the high-flux group compared with the low-flux group (*P =0.032).*

secondary analysis revealed that high-flux membranes may significantly improve survival of patients with **diabetes**.

Outcomes of HDF versus HD

Author, Year	HDF vs Comparator	Type of study	β2-M	Survival
Wizemann V et al, 2000	HDF vs LFHD	RCT	↓	=
Bosch JP et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 45%
Canaud B et al 2006	HDF+/- vs LFHD vs HFHD	Historical prospective cohort	?	↑ 35%
Jirka et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 36%
Schiffl H et al, 2007	HDF vs HFHD + UPD	RCT	↓	=
Vinhas J et al, *2007*	HDF vs HFHD	Prospective controlled study	?	↑ 50%
Panichi V et al. 2008	HDF+/- vs LFHD	Prospective controlled study	↓	↑ 15%
Santoro A et al, 2008	HF vs HFHD	RCT	↓	↑ 18%
Tiranathanagul K 2009	HDF vs HFHD	Prospective controlled study	↓	=
Vilar E et al, 2009	HDF vs HFHD	Historical prospective cohort	↓	↑ 34%

Evidence –Positive Trials

Canaud B, et al. Mortality risk for patients receiving HDF versus HD European results from DOPPS. Kidney Int 2006	**Observational trial (DOPPS)**	**35% lower mortality risk with HDF compared to low-flux hemodialysis**
Jirka T, et al Mortality risk for patients receiving hemodiafiltration versus hemodialysis. Kidney Int 2006	Observational ,prospective study .EuCliD from 56 clinics in Czech Republic, Hungary, Italy, and UK (2564 patients)	After adjustment for age, gender, co-morbidities, and time on renal replacement therapy, mortality risk reduction was 35.3%
Panichi V et al, RISCAVID trial NDT 2008	Italy (Tuscany) 757 HD patients.observational prospective study	HDF was associated with an improved cumulative survival independent of the dialysis dose.

Evidence- Negative Trials

CLINICAL RESEARCH www.jasn.org

Effect of Online Hemodiafiltration on All-Cause Mortality and Cardiovascular Outcomes

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

*Department of Nephrology, VU University Medical Center, Amsterdam, The Netherlands; †Institute for Cardiovascular Research, VU Medical Center, Amsterdam, The Netherlands; ‡Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands; §Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; ‖Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands; and ¶Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

J Am Soc Nephrol 23: ●●●–●●●, 2012

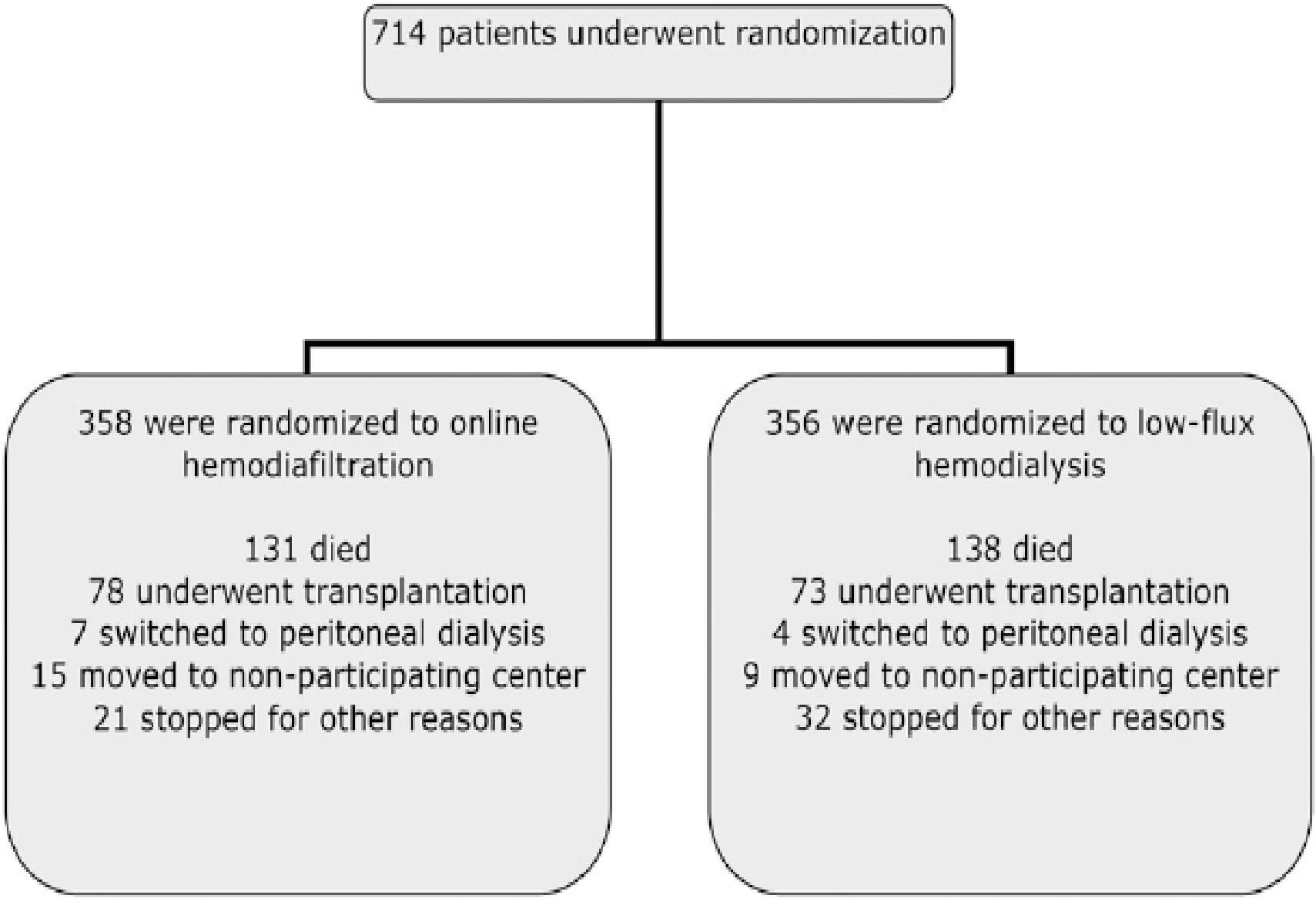


Figure 1. Enrollment, randomization, and follow-up of study participants. For mortality and cardiovascular events, all patients were followed until the end of the study.

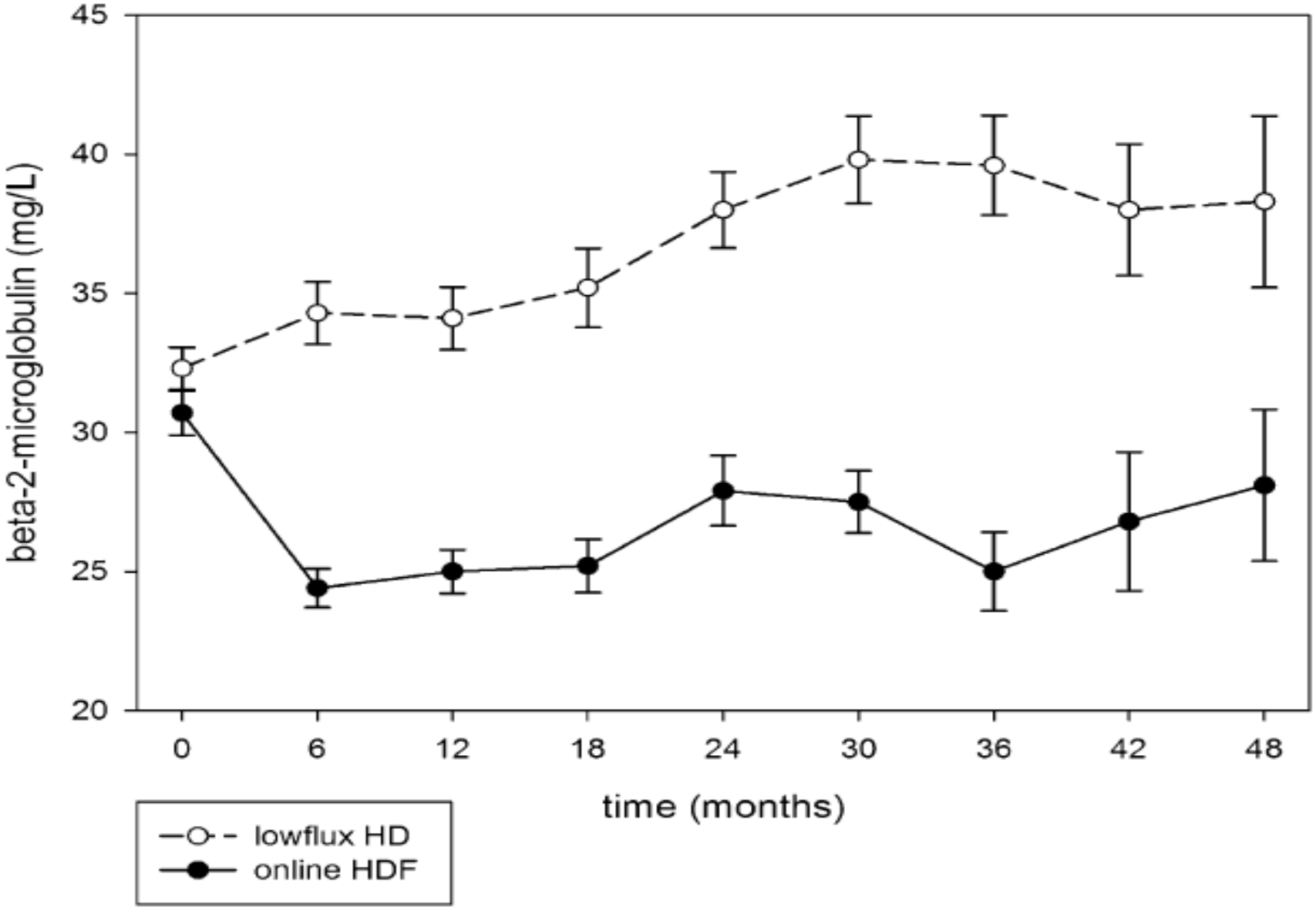
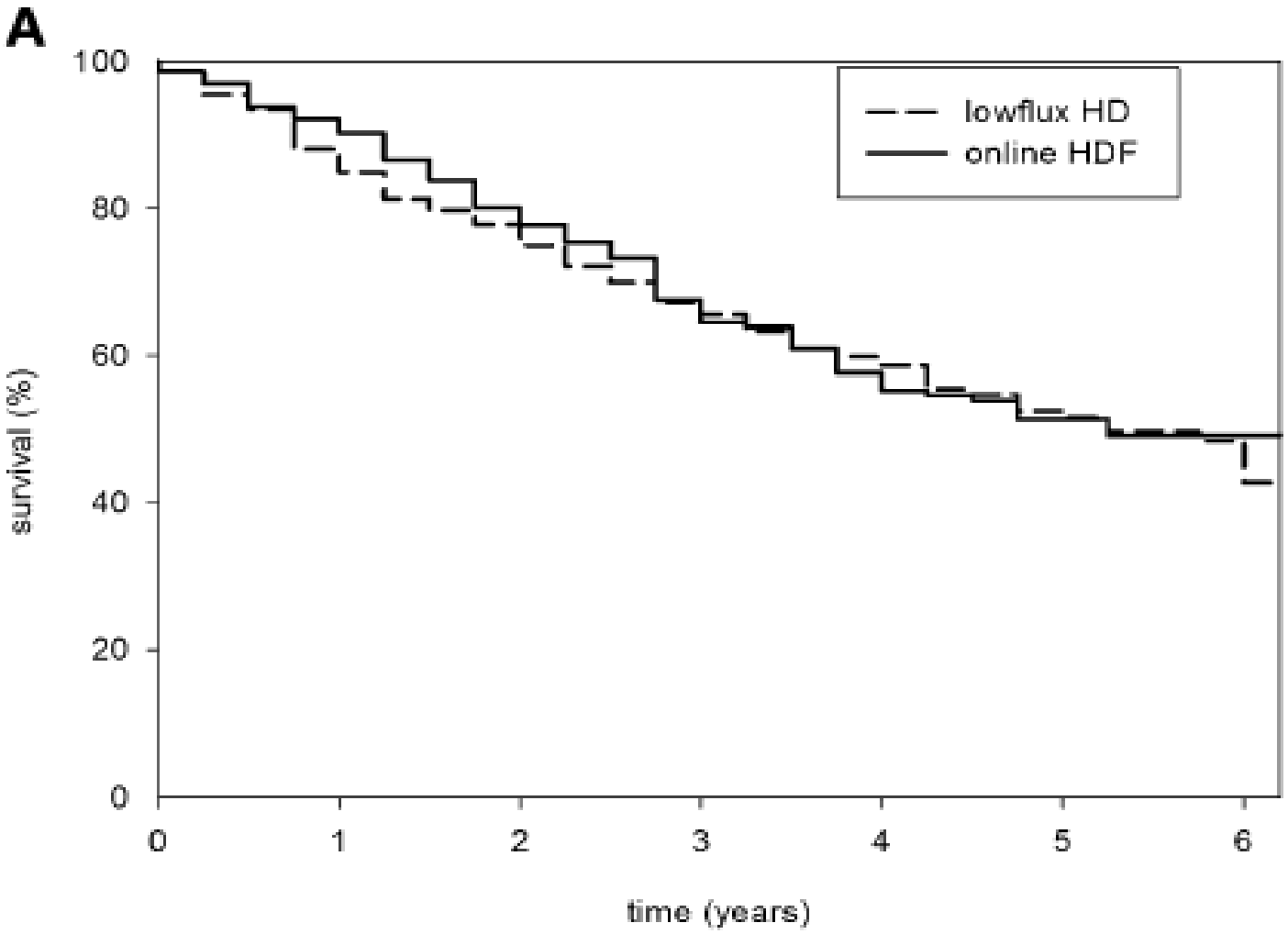
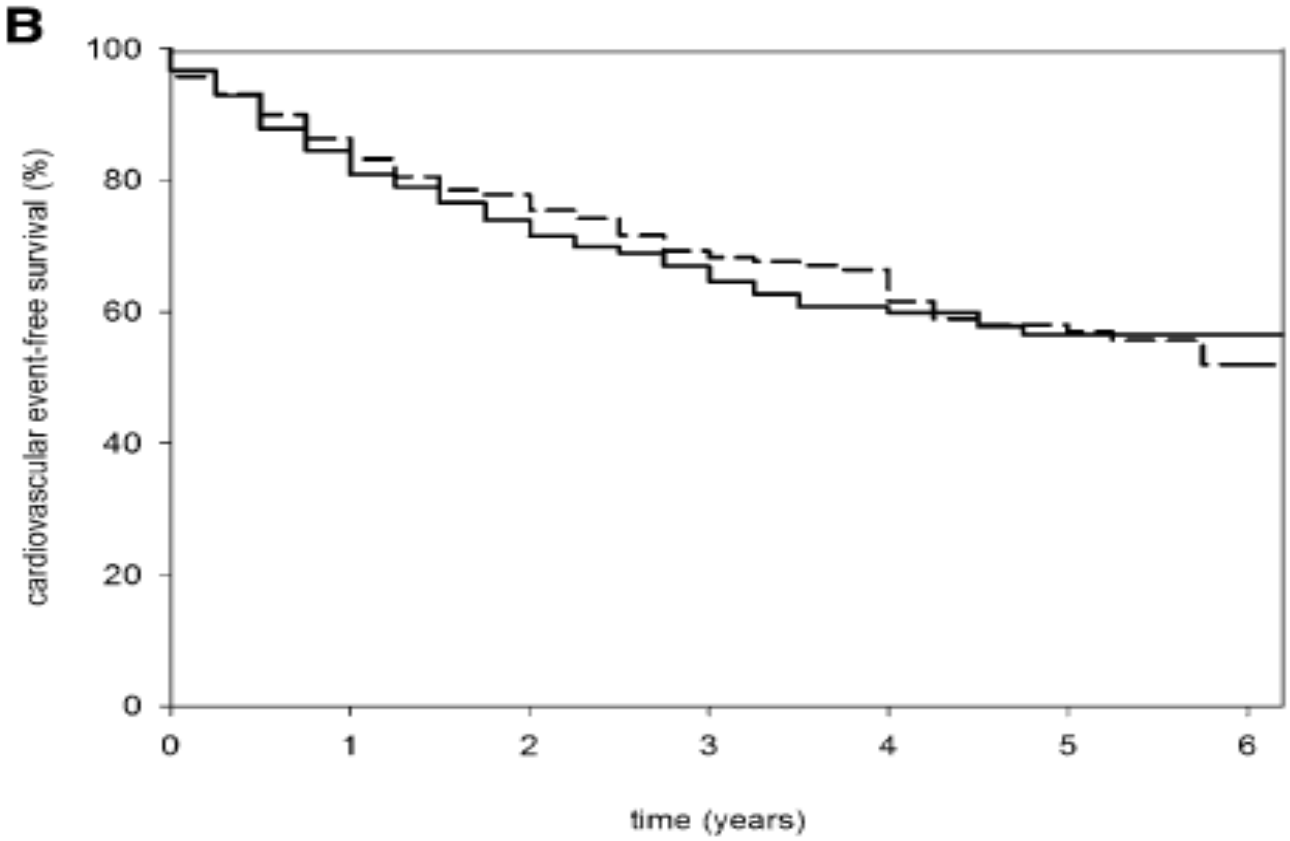


Figure 2. Predialysis β-2-microglobulin levels in patients treated with online hemodiafiltration and low-flux hemodialysis (mean $\pm$ SEM) using measurements of individuals at those time points. The difference between β-2-microglobulin levels for both treatments was significant ($P<0.001$).



Patients at risk

HD	356	337	307	269	230	201	169	140	102	83	65	52	32
HDF	358	346	324	287	237	203	160	131	103	77	57	44	18



Patients at risk

HD	356	323	281	240	204	178	144	118	84	65	53	43	25
HDF	358	326	285	241	192	157	123	100	76	59	45	36	15

Figure 3. The incidence of both all-cause mortality and cardiovascular events was not affected by treatment assignment. Survival curves for time to death from any cause (A) and for time to fatal or nonfatal cardiovascular event (B) based on life table analyses using 3-month time periods.

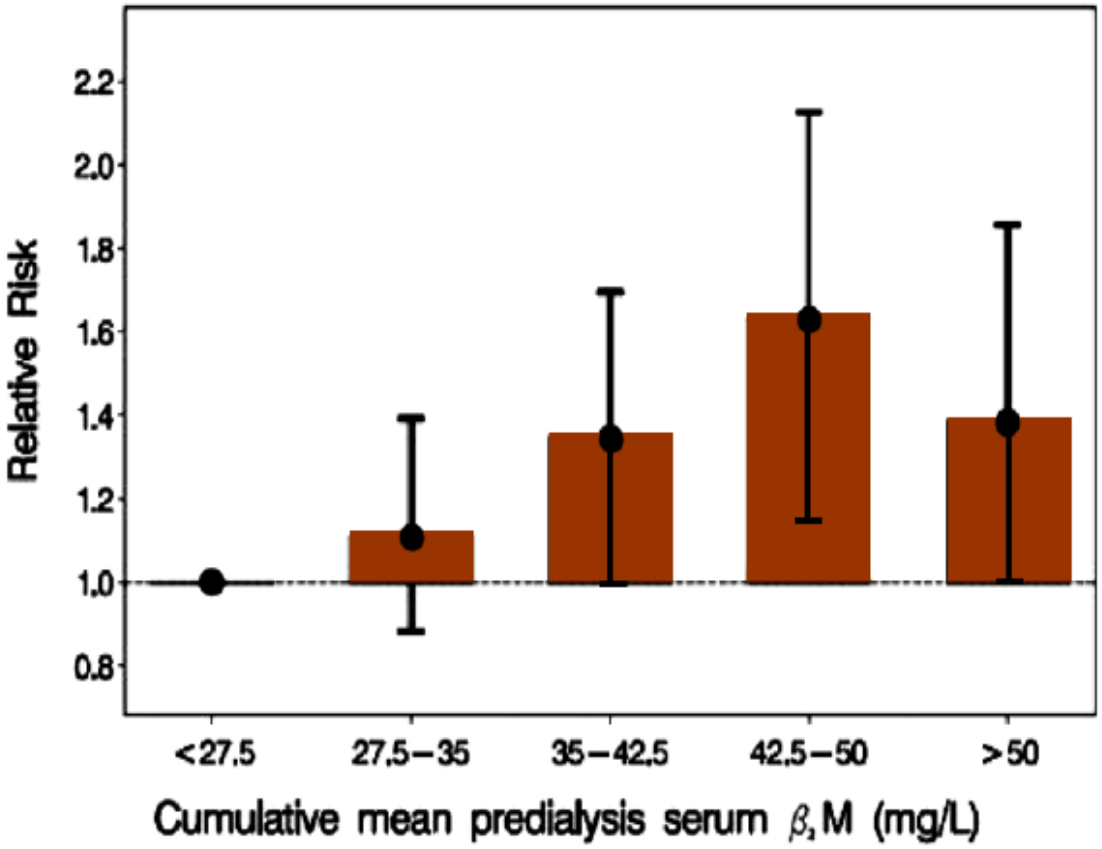
Now What??

Who and When??

Possible beneficial groups??

1) Patients with high beta 2 microglobulin

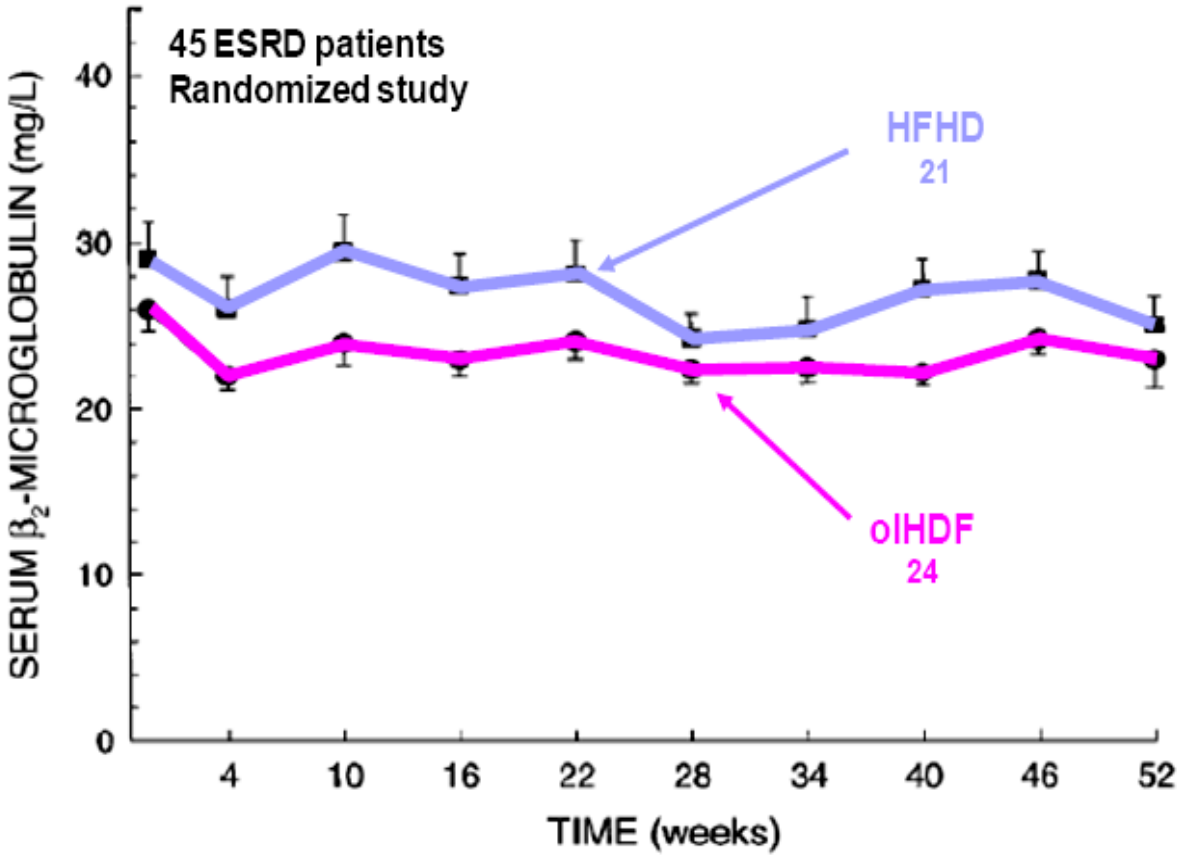
Serum ß-2 Microglobulin levels predict mortality in HD patients



HEMO Study

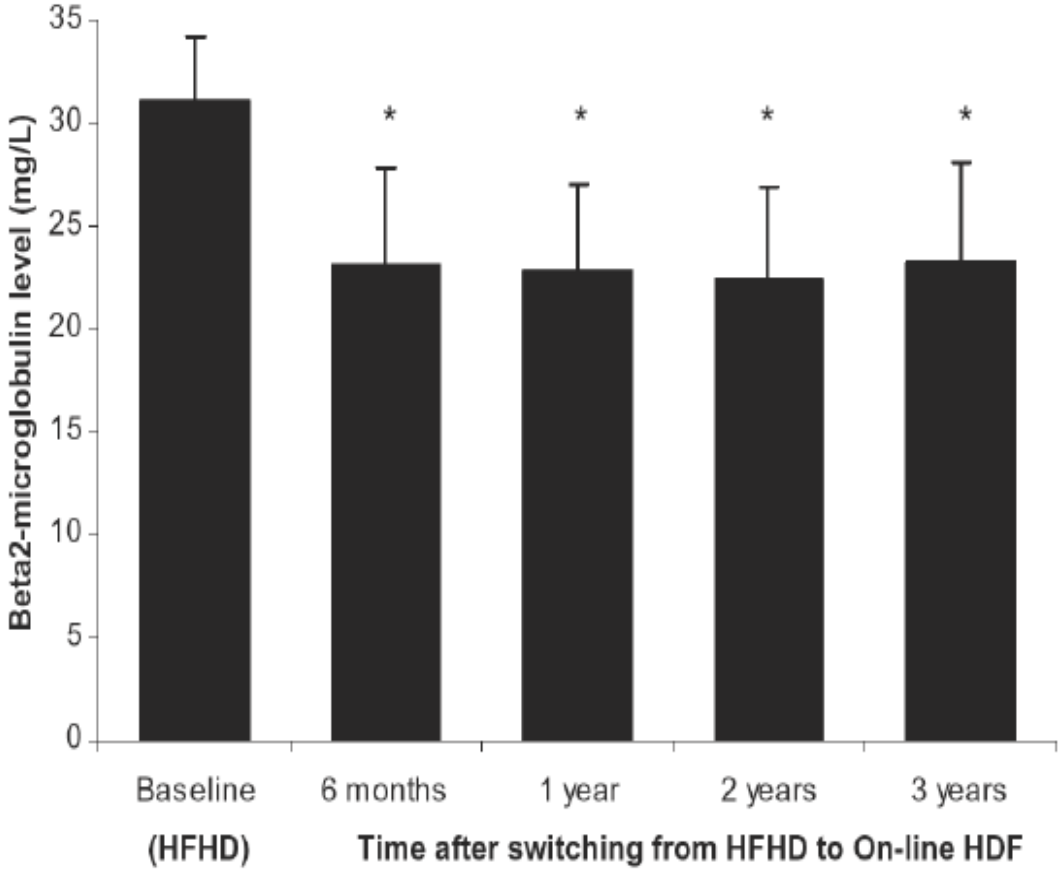
Cheung AK et al, *J Am Soc Nephrol*. 2006; 17: 546-555

ß2-M concentrations, High Flux HD versus oI-HDF



Ward R et al, *J Am Soc Nephrol* 2000; 11:2344

ß2-M concentrations is reduced after switching from HFHD to ol-HDF



Tiranathanagul K et al. *Ther Apher Dial* 2009; 13: 56-62

Analysis 5.4. Comparison 5 HF/HDF/AFB versus low-flux HD, Outcome 4 Serum beta-2 microglobulin (mg/L).

Review: Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease

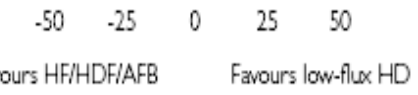
Comparison: 5 HF/HDF/AFB versus low-flux HD

Outcome: 4 Serum beta-2 microglobulin (mg/L)

Study or subgroup	HF/HDF/AFB N	Mean(SD)	Low-flux HD N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Pre-dialysis							
Beerenhout 2005	19	20.4 (10.1)	17	42.8 (17.1)		22.5 %	-22.40 [-31.71, -13.09]
Locatelli 1996	20	32.2 (14.2)	27	43.4 (9.6)		31.0 %	-11.20 [-18.40, -4.00]
Wizemann 2000	15	19.07 (2.58)	16	36.44 (8.94)		46.5 %	-17.37 [-21.94, -12.80]
Subtotal (95% CI)	**54**		**60**			**100.0 %**	**-16.59 [-21.95, -11.23]**

Heterogeneity: $Tau^2 = 10.62$; $Chi^2 = 3.76$, df = 2 (P = 0.15); $I^2 = 47\%$

Test for overall effect: Z = 6.07 (P < 0.00001)



2) Frequent Hypotensive Episodes/ Hemodynamic instability

Hemodynamic tolerance is improved in HDF

Condition	HFHD (Baseline)	On-line HDF			
		6 months	1 year	2 years	3 years
Hypotension	20.2 ± 17.1	10.4 ± 17.6	11.8 ± 16.1	10.0 ± 13.8	12.4 ± 16.1
Hypertension	2.9 ± 4.7	2.2 ± 7.7	2.4 ± 5.7	0.1 ± 0.4	0.9 ± 2.1
Muscle cramp	7.8 ± 9.5	5.3 ± 7.7	2.0 ± 2.1	3.0 ± 3.7	1.9 ± 2.3
Headache	1.7 ± 2.6	1.3 ± 3.2	0.4 ± 1.1	0.4 ± 1.1	0.3 ± 0.9

Ol-HDF in Southeast Asia: 3 years experience

22 HD patients HFHD → ol-HDF

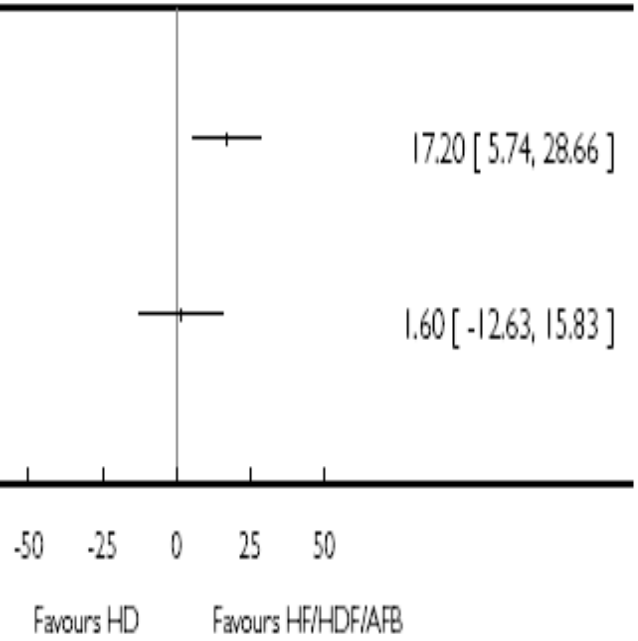
Tiranathanagul K et al. *Ther Apher Dial* 2009; 13: 56-62

Review: Haemodiafiltration, haemofiltration and haemodialysis for end-stage kidney disease

Comparison: 1 HF/HDF/AFB versus HD

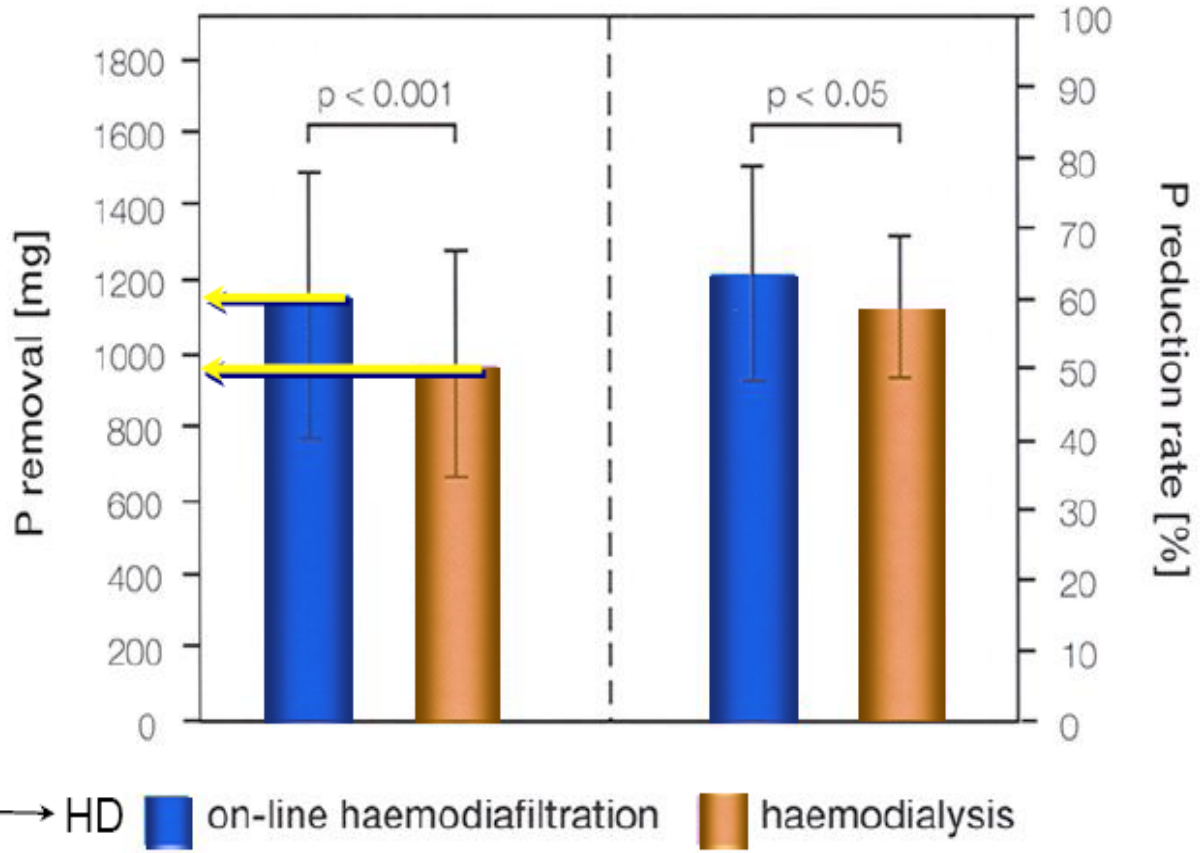
Outcome: 11 Intradialysis blood pressure (mm Hg)

Study or subgroup	HF or HDF or AFB N	Mean(SD)	HD N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Systolic blood pressure						
Lin 2001	38	109.4 (25.9)	29	92.2 (21.9)		17.20 [5.74, 28.66]
2 Mean arterial pressure						
Schrander 1999	11	106.9 (9.8)	9	105.3 (19.9)		1.60 [-12.63, 15.83]



3) Uncontrolled phosphate level?

High efficiency HDF increases the phosphate mass removal



4hrs x 3wk
HF80 - QD800
Direct dialysate quantification

22 HD pats

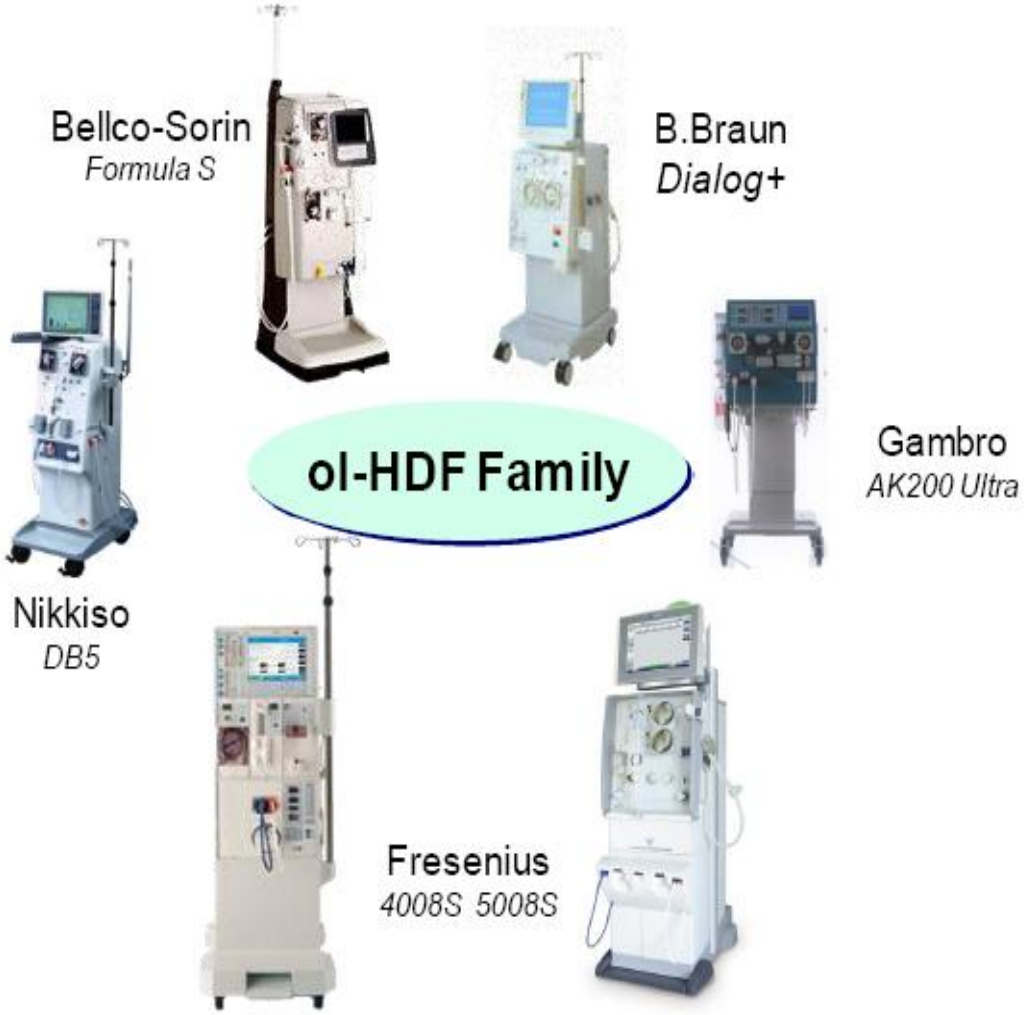
HD → HD

HDF → HDF

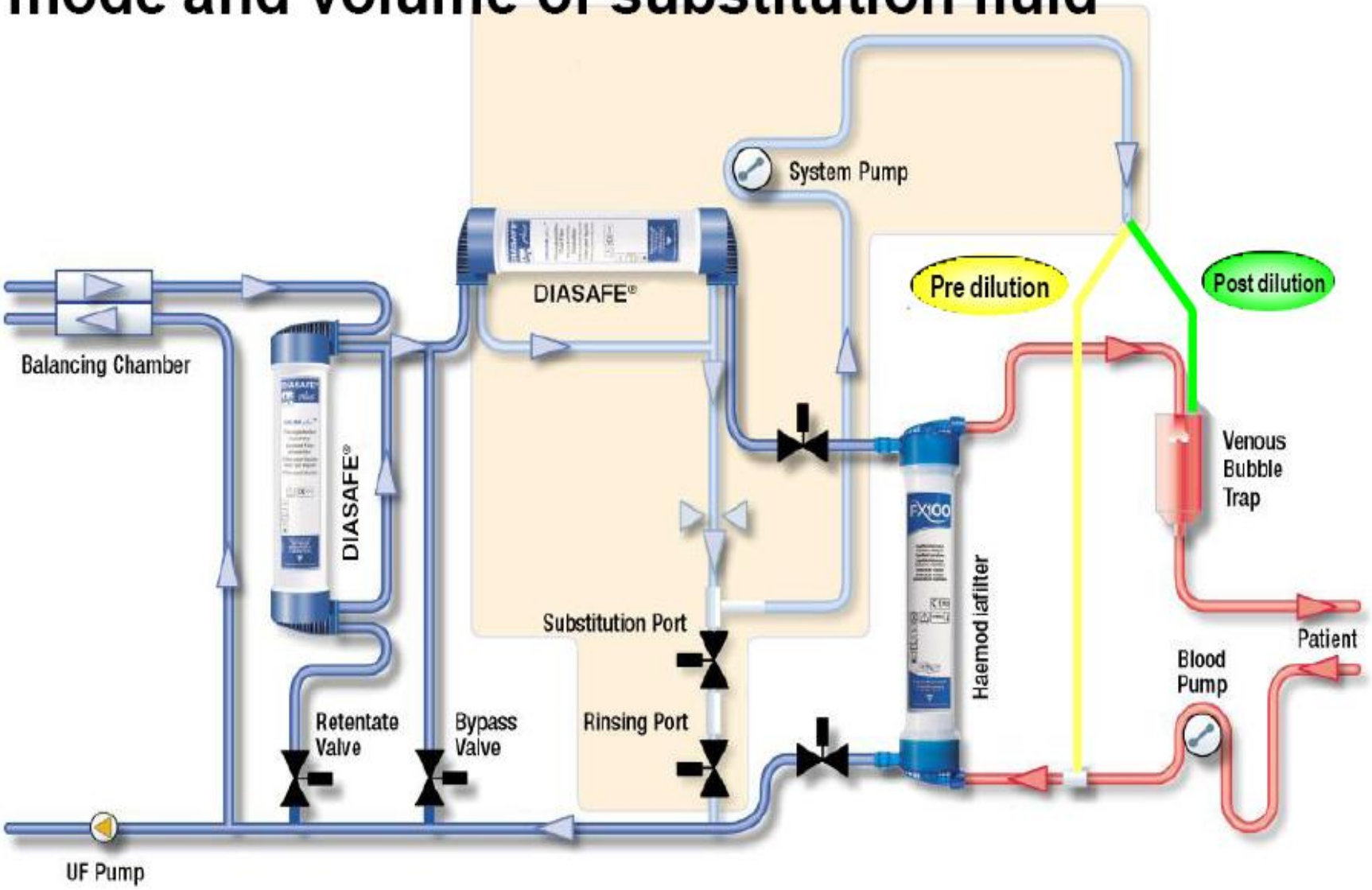
Lornoy W et al, *J Ren Nut* 2006; 16: 47-53

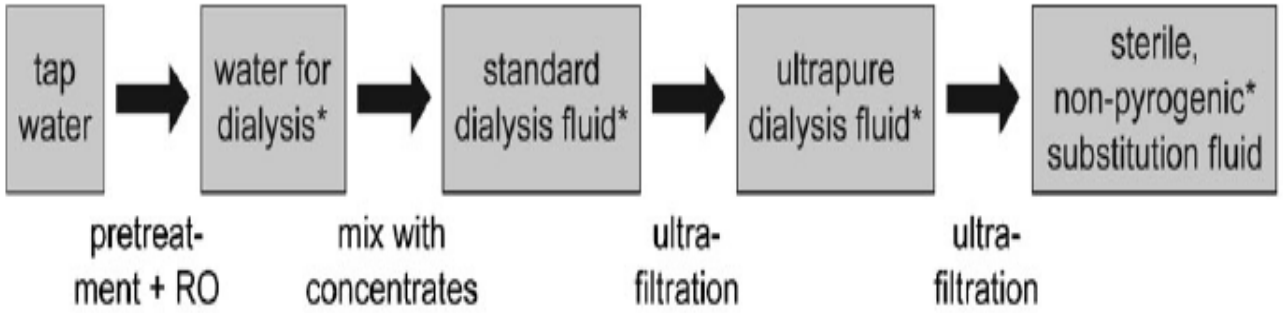
Technical Aspect

On-Line HDF requires certified machines European approved machines (EC)



On-line HDF modalities are characterized by mode and volume of substitution fluid



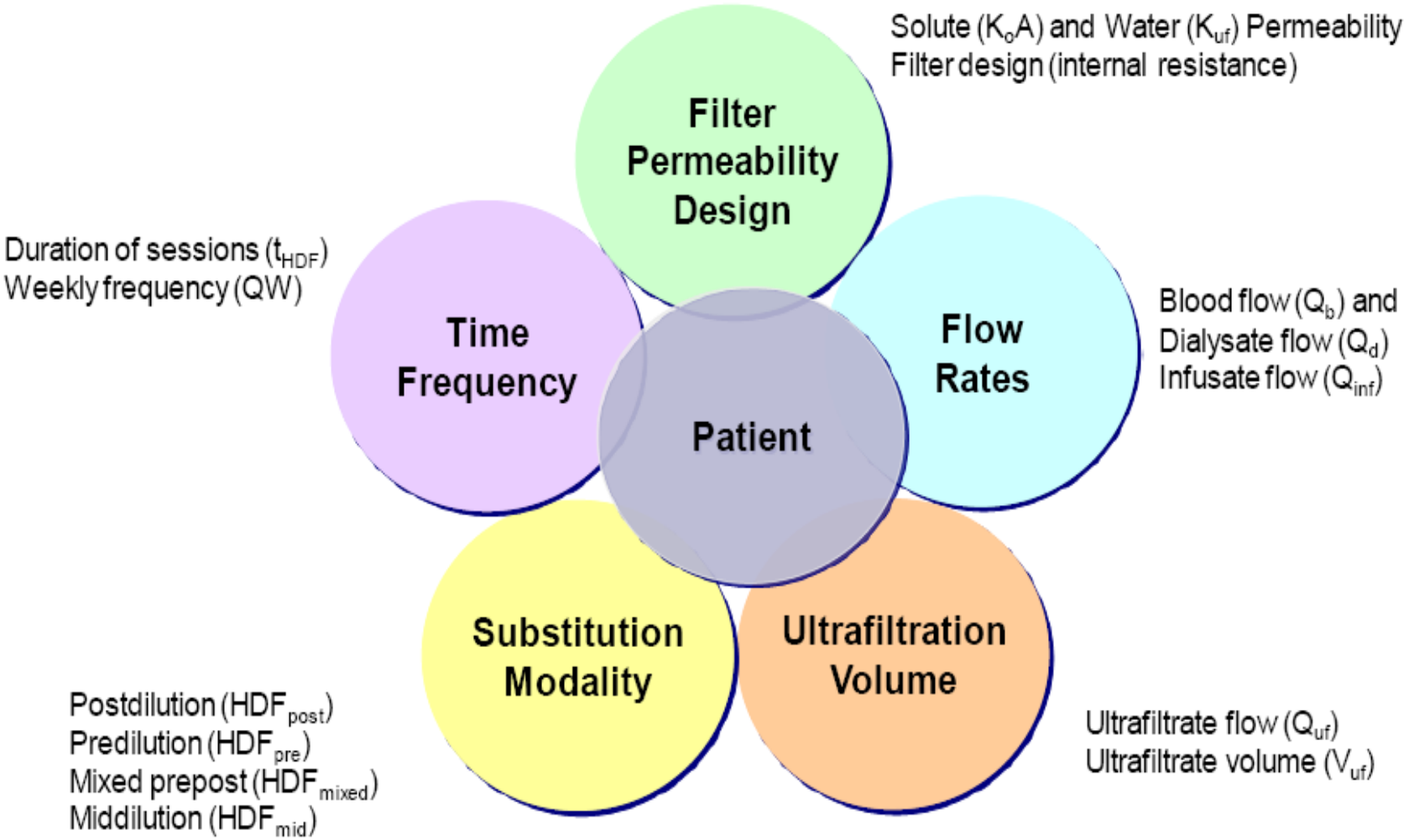


Microbiological quality:				
- CFU/ml	$<10^2$	$<10^2$	$<10^{-1}$	SAL≥6
- EU/ml	<0.25	<0.50	<0.03	<0.03
Application in dialysis:	basis for all fluid preparation	dialysis fluid in low-flux HD with synthetic membranes	dialysis fluid in all forms of HD & HDF	infusion solution in HDF & HF

* To achieve the respective quality levels the entire process must be operated with validated components and appropriate hygiene.

Fig. 4. Process steps in the preparation of fluids for dialysis starting with tap water and resulting in sterile, non-pyrogenic substitution fluid for on-line, convective therapies. (RO = reverse osmosis, CFU = colony-forming units, EU = endotoxin units, SAL = sterility assurance level).

Optimizing hemodiafiltration prescription



High-Efficiency on-line HDF is a modality that may be used to improve dialysis efficacy. What does it means?

- **Treatment schedule**
  - 3 sessions of 4 hours weekly (minimum)
- **Highly permeable synthetic membrane**
- **Large surface area > 1.8 m^2**
- **Ultrapure bicarbonate dialysis fluid**
- **High blood flow** (effective QB: 350 - 400 ml/min)
- **High dialysate flow** (500-700 ml/min) **(diffusive dose)**
- **Large volume of substitution** **(convective dose)**
  - Post-dilution (Q_{sub} : 100 ml/min, 24 l / session)
  - Pre-dilution (Q_{sub} : 200 ml/min, 48 l / session)

Discussion/Conclusion

1) Current evidence still does not support superiority of HDF compared to conventional HD
2) Special groups of chronic HD patients might get benefits from HDF compared to HD
3) Future prospective randomised trials are needed.

Randomized clinical trials in Europe

Dutch Trial
CONTRAST
LFHD vs HDF
350/350
CV events
Mortality
36 months

French Trial PHRC
HFHD vs HDF
> 65yo
300/300
Tolerance
CV events
Mortality
24 months

Catalonian Trial
HFHD vs HDF
300/300
CV events
Mortality
24 months

Turkish Trial
HFHD vs HDF
300/300
CV events
Mortality
24 months

Sometimes it's best just to jump in !

Potts M et al, *BMJ* 2006; 333:701-703

THANK YOU