Hemodiafiltration online, high efficiency hemodiafiltration (high convective volume) what, who, when

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July 1981
Start of HDF
STRASBOURG

1) HDF with bags

2) water treatment: individual bedside reverse osmosis

3) Conventional heparin

4) heating of the substitution fluid

5) membranes...

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Hemodiafiltration in children, a history

1) <u>HDF with bags, July 1981</u>: reverse osmosis at bedside, *tolerance, « blood uremic detoxification »*

2) <u>HDF on line, November 1989</u>: *purity of the dialysis fluids (germ free; « no » endotoxins)*

3) <u>daily OL-HDF, September 2002</u>: *less cachexia*

4) <u>high efficiency (autosub + technology) and daily hemodiafiltration</u> (BCM; on-line diffusive plasmatic sodium): *volume control, cardiovascular preservation, normal growth*

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Until the 1980’s, HD was only prescribed as twice weekly dialysis sessions lasting 4 to 6 hours at one time: often poorly tolerated, only offering “survival”, without quality of life

This led to changes in the dialysis regime over the 1990’s: twice weekly sessions were replaced by procedures performed three times a week.

Nevertheless, despite decades of experience and technical improvements in performing three times a week in-center HD (3x4.5 hours), patients/children treated by this conventional hemodialysis regime still have:

- ✓an increased risk of cardiovascular morbidity/mortality,
- ✓malnutrition due to protein wasting, impaired growth and
- ✓bad volume control (overhydration; high BP; LVH)

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As a result, there is a growing interest in the delivery of more intensive hemodialysis, that is:

- ✓ From HD to HDF (the addition of HF to HD, that is HDF, a complete dialysis dose) to OL-HDF (purity of the dialysis fluids),
- ✓ high efficiency HDF (hydraulic permeability of the membranes “Cordiax”; autosub+: viscosity control) : impact of the achieved convective volume, “high efficiency HDF”
- ✓ titrating treatment length (4.5 hours ?; reduction in UF demands per dialysis session; UF rate< 1.25%/h BW; IDWG<4%; Cooling T_D=36° ; Euvolemia ?)
- ✓ *daily “optimyzed” dialysis* (floating dry weight; BCM®; diffusible Napl on-line; Kt/V on-line; BVM®; BTM®)

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From adequate to intensified dialysis

- « adequacy » assessment :

outcomes (morbidity/mortality/cachexia/growth) and *surrogates* like urea kinetics (diffusion process) and more (β2 microglobuline or convective volume for convection mass transport ?),

- How to improve conventional HD:

✓ high flux membrane for « all »

✓ biocompatibility/purity of the dialysis fluids (endotoxin's level),

✓ volume control (dry weight/BP/LVH): interest of an objective assessment (bioimpedancemetry, BCM), reduction in UF demands per dialysis session

✓ should HDF become the standard for in center dialysis ?

- More dialysis, more frequent/longer sessions: « daily » dialysis, daily in center high efficiency hemodiafiltration

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Uremic toxins: which to dose?

Urea Kt/V as surrogate for the diffusion process and β2 microglobulin for the convective volume as surrogate for the convective mass transport?

Focusing on middle molecules…Convective dialysis dose

Small water soluble solutes

- Asymmetric dimethylarginine
- Benzylalcohol
- ß-Guanidinopropionic acid
- ß-Lipotropin
- Creatinine
- Cytidine
- Guanidine
- Guanidinoacetic acid
- Guanidinosuccinic acid
- Hypoxanthine
- Malondialdehyde
- Methylguanidine
- Myoinositol
- Orotic acid
- Orotidine
- Oxalate
- Pseudouridine
- Symmetric dimethylarginine
- Urea
- Uric acid
- Xanthine

*CMPF is carboxy-methyl-propyl-furanpropionic acid

Protein-bound solutes

- 3-Deoxyglucosone
- CMPF*
- Fructoselysine
- Glyoxal
- Hippuric acid
- Homocysteine
- Hydroquinone
- Indole-3-acetic acid
- Indoxyl sulfate
- Kinurenine
- Kynurenic acid
- Methylglyoxal
- N-carboxymethyllysine
- P-cresol
- Pentosidine
- Phenol
- P-OHhippuric acid
- Quinolinic acid
- Spermidine
- Spermine

Middle molecules

- Adrenomedullin
- Atrial natriuretic peptide
- $ß_2$-Microglobulin
- ß-Endorphin
- Cholecystokinin
- Clara cell protein
- Complement factor D
- Interleukin 1ß
- Interleukin 6
- Kappa-Ig light chain
- Lambda-Ig light chain
- Leptin
- Methionine-enkepahlin
- Neuropeptide Y
- Parathyroid hormone
- Retinol binding protein
- Tumor necrosis factor alpha

Middle molecules

β2 - Microglobulin

EUTox European Uremic Toxin Work Group of the ESAO

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

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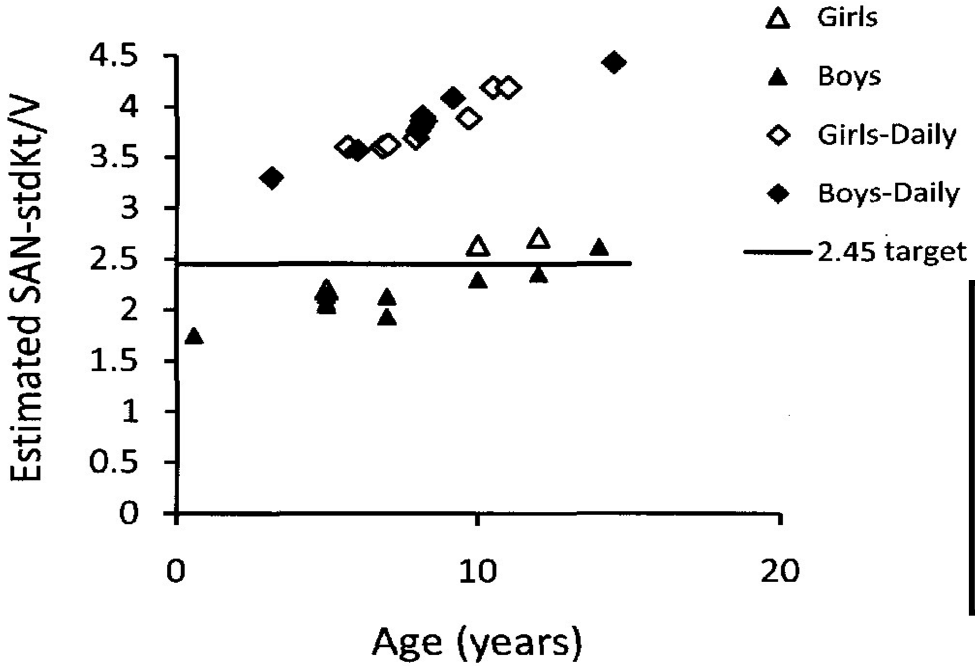
Dialysis dose and growth

(**Surface area normalized standard Kt/V: SAN**)

Daugirdas JT et al. Clin J Am So Nephro 2010, 5:821-827

Over 2.45



Fischbach et al.
NDT 2010

Could be Kt/Vurea a marker of dialysis adequacy? A surrogate+++

Figure 6. Estimated SAN-stdKt/V *versus* age in two studies in which increased growth rates were linked to intensified dialysis regimens, one with hemodialysis treatments given 3 times/wk by Tom *et al.* (10) and one using 6-times/wk hemodiafiltration by Fischbach *et al.* (11).

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Adequacy of dialysis in children:
does small solute clearance really matter ?

Goldstein SL. Pediatr Nephrol 19: 1-5, 2004

Dialysis and outcome: dialysis dose, dialysis time, specific impact of convection

- A minimum Kt/V urea (equilibrated) level of 1.2-1.4 (URR 65 to 75 %) is thought to be desirable
- Only « small solute urea clearance » prescription ? ***Dialysis prescription should be not only a « urea dialysis dose »*** : phosphate and β2 microglobuline clearances +++ (convective flow)
- Dialysis and residual renal small-solute clearance are not equivalent

Optimal Hemodialysis Prescription: Do children need more than a urea dialysis dose?
Fischbach Michel, Zaloszyc Ariane, Schaefer Betti, and Schmitt Claus Peter.International Journal of Nephrology.Volume 2011, Article ID 951391, 5 pages doi:10.4061/2011/951391

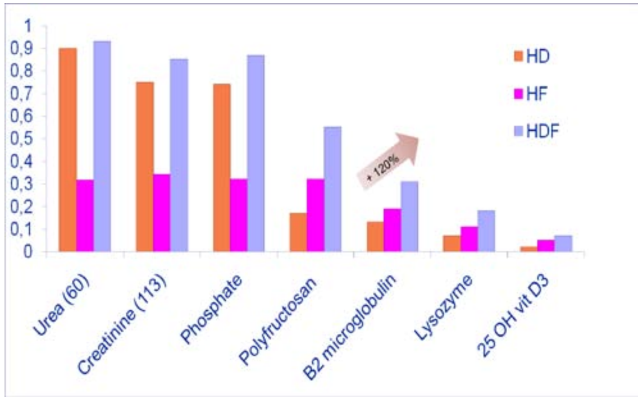
Hemodiafiltration: The addition of convective flow to hemodialysis: ***"a complete dialysis dose"***. *M. Fischbach, H. Fothergill, A. Zaloszyc, L. Seuge Pediatr Nephrol 2012, 27: 351-6*

➡ ***Kt/Vurea (diffusion) and a "high" effective convective volume (HDF)***

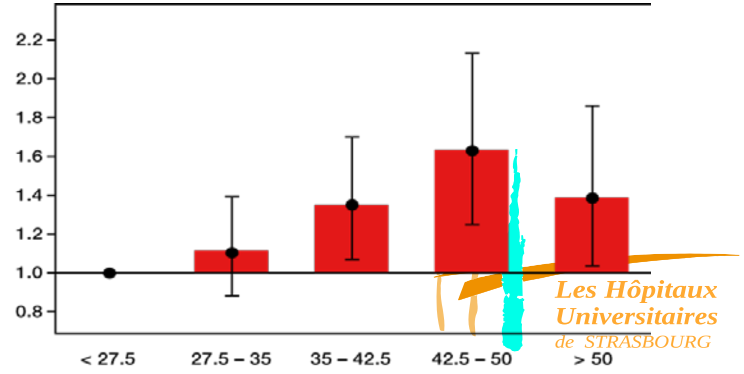
Do we need indicators of dialysis adequacy based on middle molecule removal ?

R. Vanholder, S. Elot, W. Van Biesen. Nature Clinical Practice. Nephrology 2008; 4:174-5

- From urea to MMW toxins purification : major importance of the convective flow/volume (HDF)
- At present, the most valid candidate is **β_2 microglobulin**, a threshold of **< 27.5 mg /l** (predialysis) might be proposed
- **Phosphate** should be considered as a MMW uremic toxin in terms of dialysis purification : water molecular environment
- **The need for high flux membranes and the importance of a high convective volume (HDF)**



Predialysis ß$_2$m level significantly correlated with all-cause mortality (p= 0.001) Cheung et al, JASN 2000



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From adequate to optimal dialysis

- « adequacy » assessment : outcomes (morbidity/mortality/cachexia/growth) or surrogates like urea kinetics (diffusion process) and more (β2 microglobuline or convective volume?),

- How to improve conventional HD:

✓ high flux membrane for « all » (a low, « not determined » convective volume)
✓ biocompatibility/purity of the dialysis fluids (endotoxin's level),
✓ volume control (dry weight/BP/LVH): interest of an objective assessment (bioimpedancemetry, BCM), reduction in UF demands per dialysis session
✓ should HDF become the standard for in center dialysis ?

- More dialysis, more frequent/longer sessions: « daily » dialysis, daily in center high efficiency hemodiafiltration

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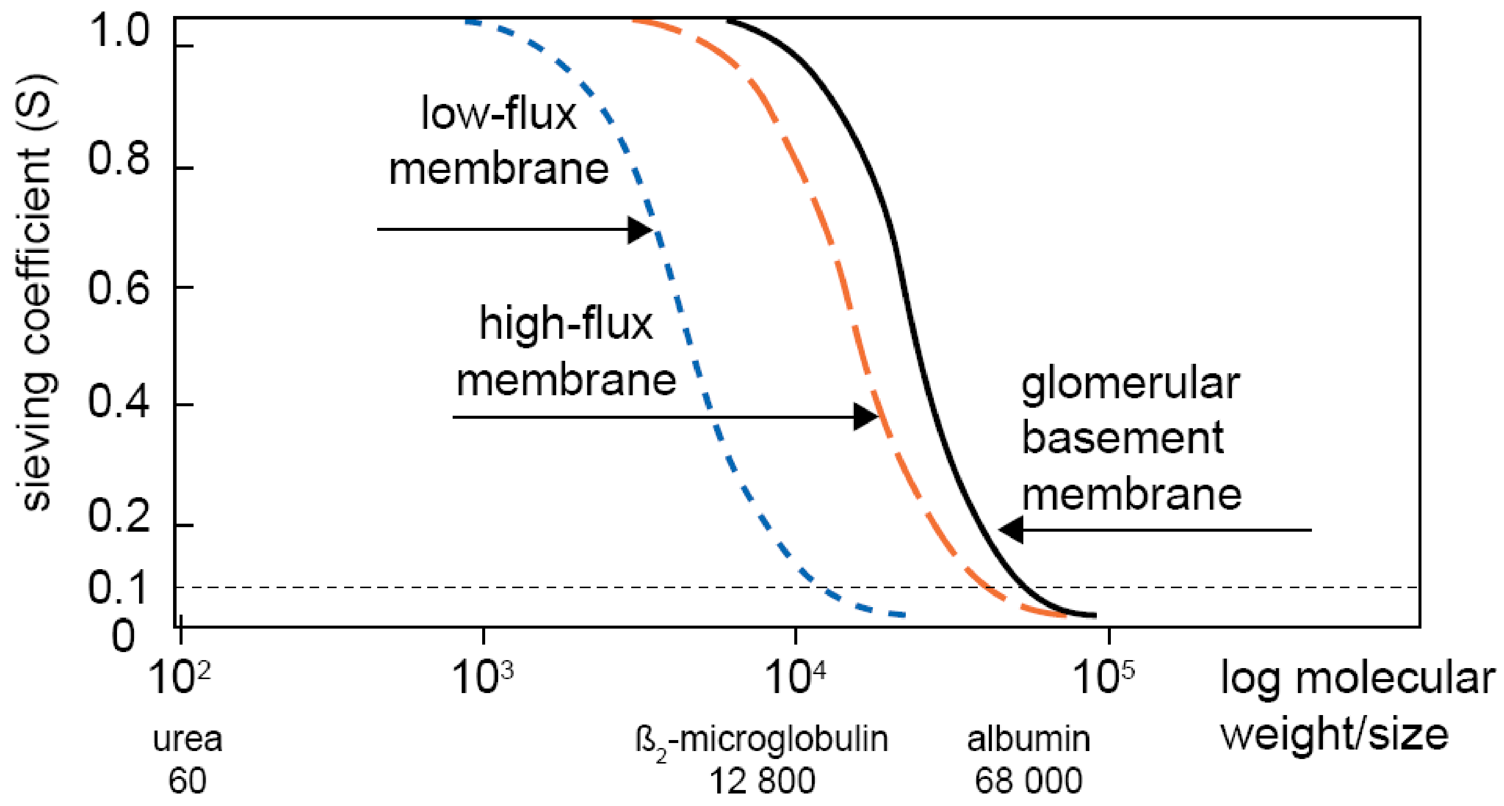
Membrane permeability :

diffusion process (urea) - convective flow (β_2 microglobulin)

low flux/high flux membranes, molecular permeability, from urea to other uremic toxins



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High-flux or low-flux dialysis? High-flux membranes recommended for all patients

Tattersall J, Canaud B, Heimburger O et al (2010) High-flux or low-flux dialysis: a position statement following publication of the Membrane Permeability Outcome study. Nephrol Dial Transplant 25:1230-1232

Guideline 2.1 (EBPG, 2002) : *synthetic, high-flux membranes should be considered to delay long-term complications of HD therapy*.

Specific indications include: to reduce dialysis-related amyloidosis (III); to improve control of hyperphosphataemia (II); to reduce the increased cardiovascular risk (II); to improve control of anaemia (III).

Guideline 2.1(ERBP Advisory Board, 2010): *synthetic,high-flux membranes should be used to delay long-term complications of HD therapy* in patients at high risk (alb<40 g/L) (level 1A: strong recommendation based on high-quality evidence).

In view of underlying practical considerations, and the observation of a reduction of an intermediate marker (ß$_2$-microglobulin), synthetic, high-flux membranes *should be recommended even in low-risk patients* (level 2B: weak recommendation, low quality evidence)

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Required water quality for the use of high-perfomance membranes

Ikuo Aoike. Saito A, Kawanishita H, Yamashita AC, Mineshima M (eds):High-Performance Membrane Dialyzers. In Contrib Nephrol. Basel, Karger; 2011, vol 173, pp 53-57.

- The clinical benefits of high-performance (HPM) dialyzers have often been reported since the advent of the synthetic polyacrylonitrile dialysis membrane.
- HPMs, which have high permeability, eliminate a wide spectrum of uremic toxins and offer excellent biocompatibility, are now essential for hemodialysis, hemofiltration, and hemodiafiltration.
- For HPMs whose mean pore size is enlarged to allow better dialysis membrane performance, however, the dialyzing fluid must be **highly purified** to prevent endotoxins contamination .

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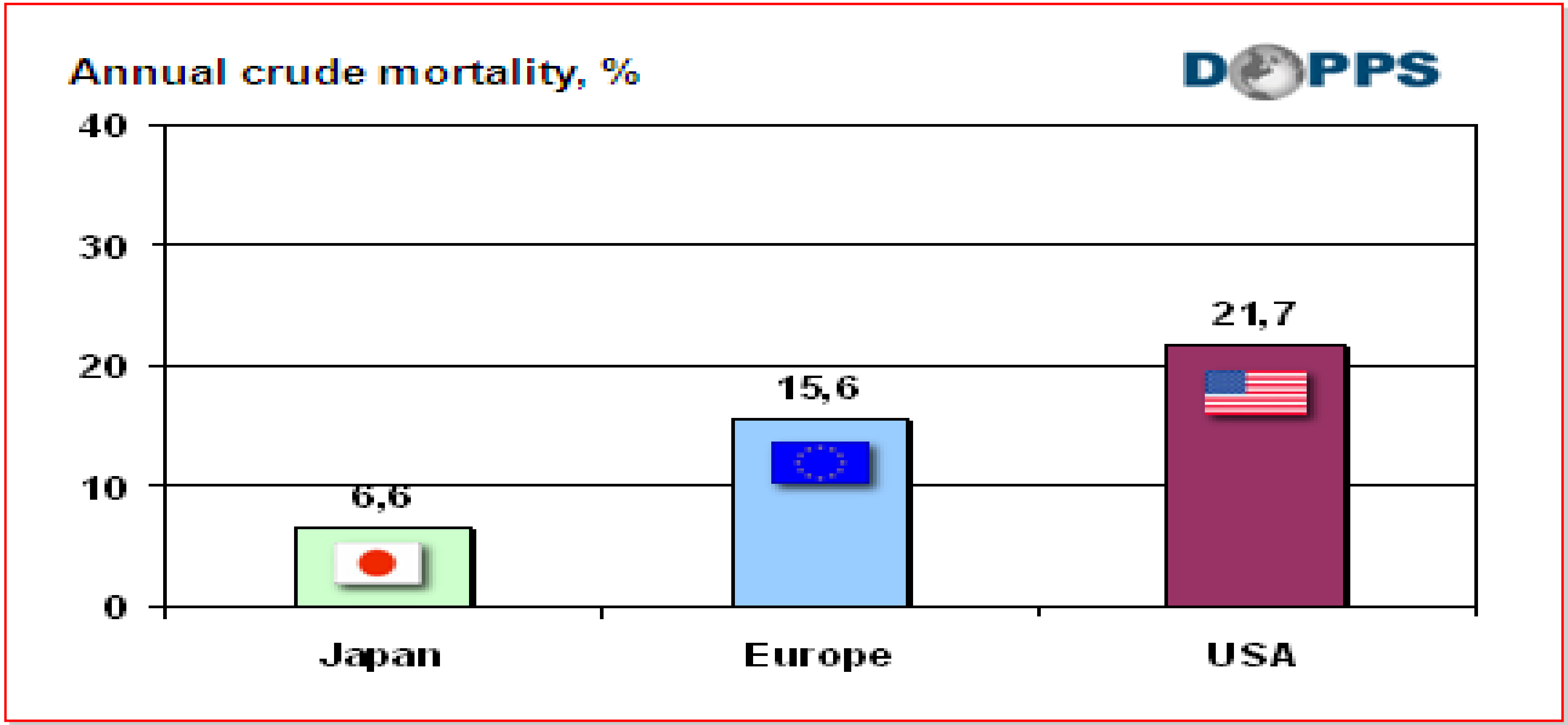

Masakane Ikuto ASN 2008:
mortality risk and dialysis fluids purity

1)Endotoxines in the dialysat < 0,05 UI/ml
in 93,6 %dialysis center from Japan

2) Mortality risk correlate to the endotoxin level in the dialysate:
RR 1 if < 0.001 ET/ml versus RR 1.48 if 0.1 à 0.25 ET/ml

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Recommandations for a « standard » dialysate

	Endotoxines
FRANCE	< 0,25 UI / ml
ISO 23500	< 0,5 UI / ml
JAPON	< 0,05 UI / ml

Recommandations for an « ultrapur » dialysate

	Endotoxines
FRANCE	< 0,25 UI / ml
ISO 23500	< 0,03 UI / ml
JAPON	< 0,001 UI / ml

Recommandations for the substitution fluid (convective volume)

	Endotoxines
FRANCE	< 0,05 UI / ml
ISO 23500	< 0,03 UI / ml
JAPON	< 0,001 UI / ml

A.Ragon, P.Brunet, D.Jaubert, G.Lebrun, A.Duval-Sabatier
Pôle Urologie – NéphrologieAssistance Publique – Hôpitaux de Marseille. Décembre 2012

Optimal Hemodialysis Prescription: Do children need more than a urea dialysis dose?

Fischbach Michel, Zaloszyc Ariane, Schaefer Betti, and Schmitt Claus Peter

International Journal of Nephrology
Volume 2011, Article ID 951391, 5 pages doi:10.4061/2011/951391

1) **If economically feasible**, high-flux membranes should be used in combination with ultrapure disposable dialysate, but small convective volume that is backfiltration risks, and low efficiency HDF…for the same price !

2) **High efficiency Hemodiafiltration** (high convective volume), is a safe routine replacement therapy : *a "complete" use of a high flux membrane, with a large determined convective volume (no more cost, but more efficiency)*

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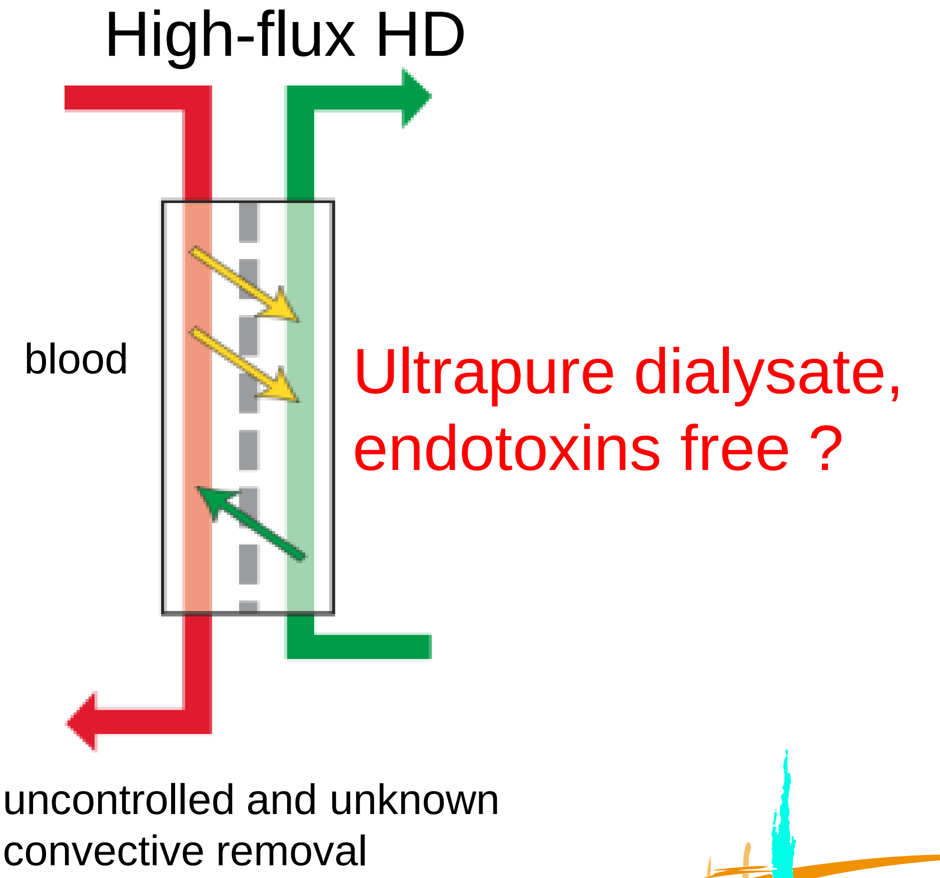
High-flux membrane dialysis : limitations

1) not determined, low-dose convective volume (UF and backfiltration

2) purity of the dialysate ?

Not determined and internal convective flow (« push/pull »), that is « internal » hemodiafiltration compenstate by backfiltration, from dialysate (purity, endotoxines free ?)

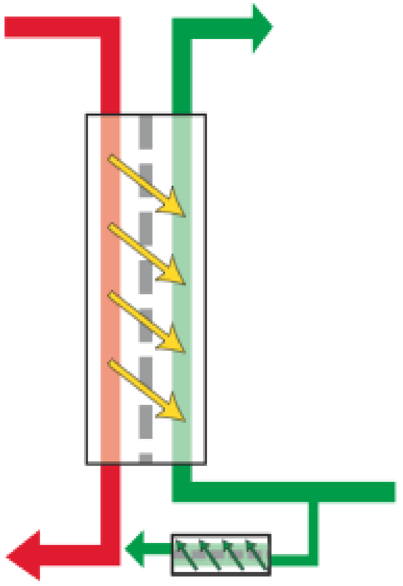


Lebedo I, Blankestijn PJ (2010) Haemodiafiltration – optimal efficiency and safety. Nephrol Dial Transplant Plus 3:8-16

From HDF to OL-HDF :

double filtered dialysate allows for ultrapure substitution fluid production

HDF is the addition of a determined, high convective volume to HD. The convective flow (HF) requires ultrafiltration (UF) of the plasma. *If the convective flow exceeds the desired weight loss, the fluid balance is maintained by an infusion of replacement fluid, as applied in HF or HDF*.



On line substitution fluid production is obtained *by cold sterilization that is ultrafiltrated ultrapure dialysate*

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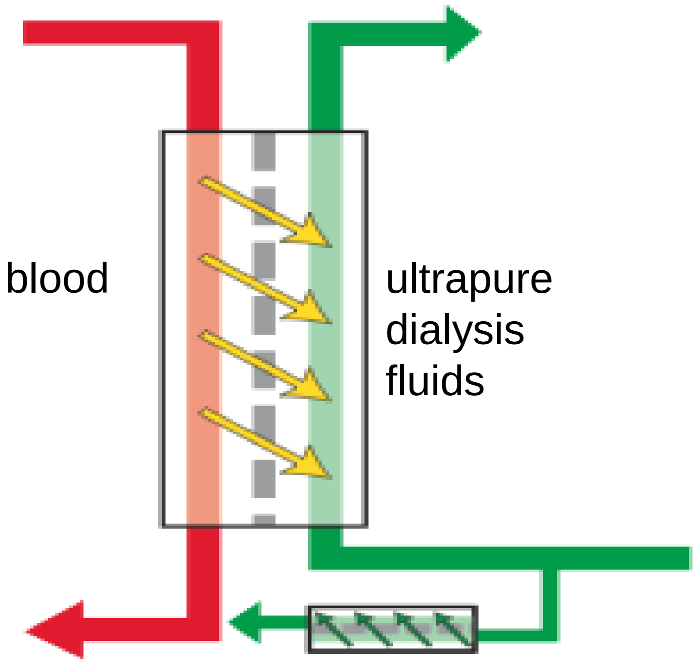
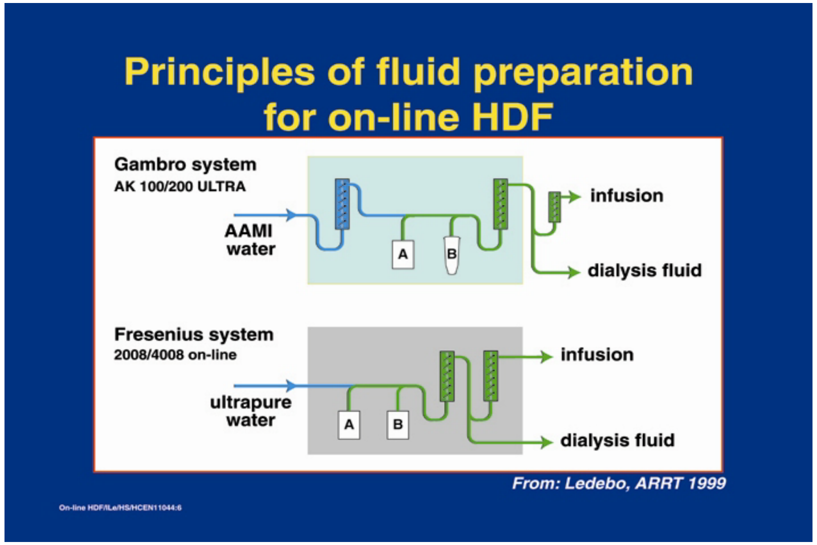
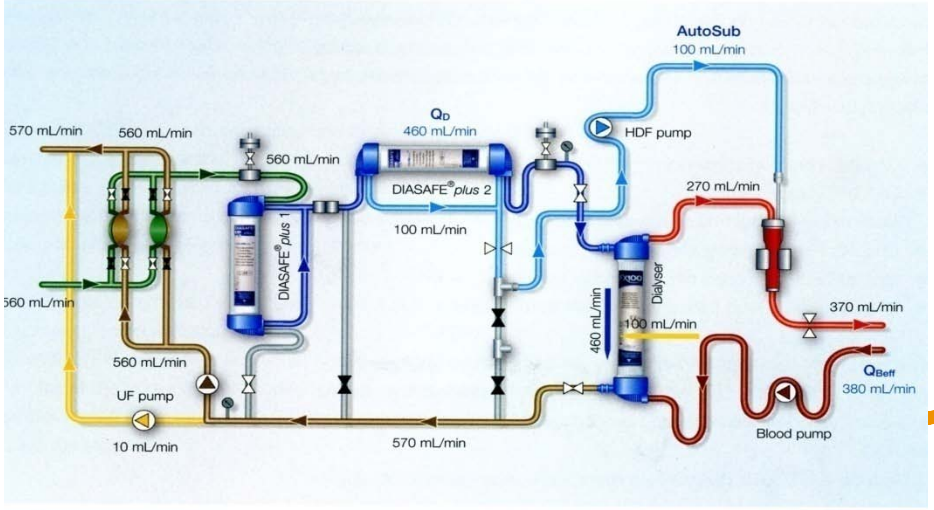
On line HDF : substitution fluid is produced on line from the fitered dialysate

On-line HDF



controllable and measurable convective removal





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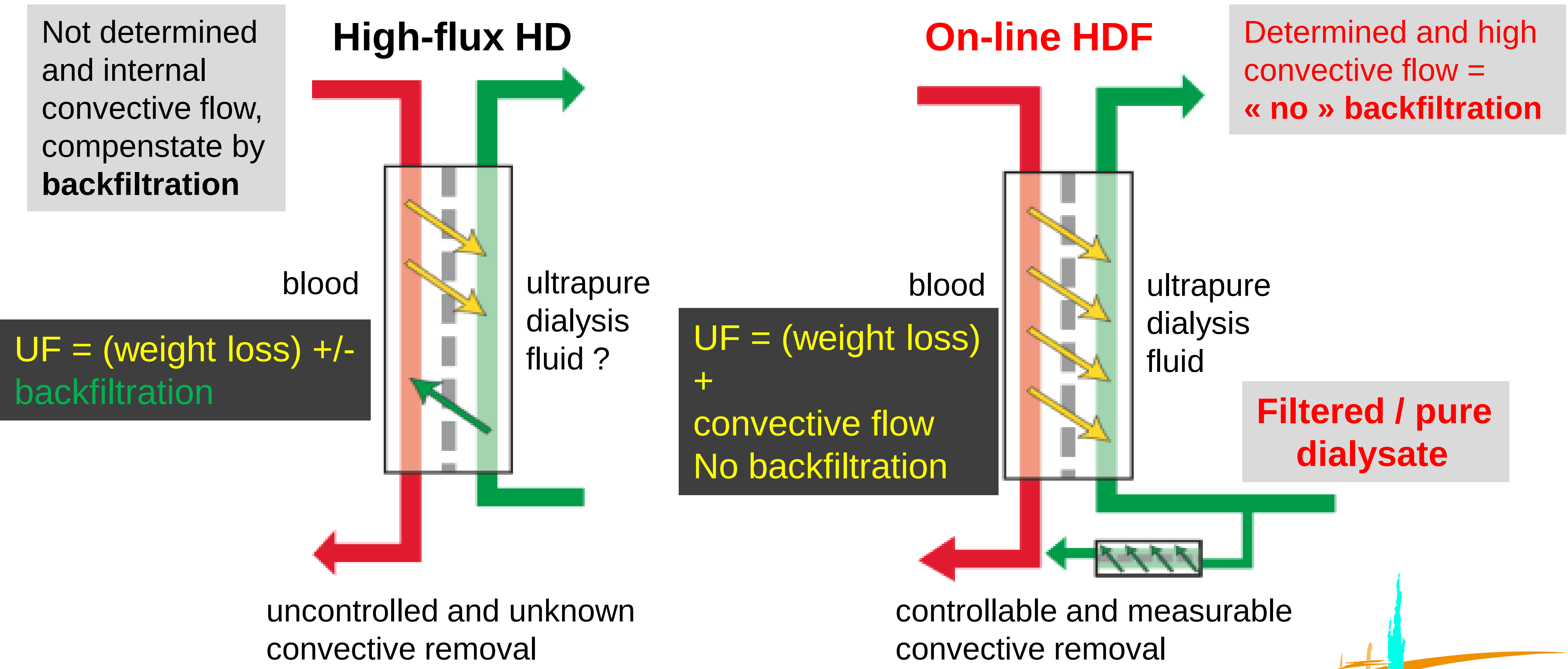
High-flux membrane dialysis or secured OL-HDF (a complete dialysis dose)



Lebedo I, Blankestijn PJ (2010) Haemodiafiltration – optimal efficiency and safety. Nephrol Dial Transplant Plus 3:8-16

The effect of on-line hemodiafiltration on improving the cardiovascular function parameters in children on regular dialysis

FI Fadel et al., Saudi J Kidney Dis Transplant 2015; 26(1):39-46

Converting from HD to OL-HDF predilution, there was:

✓***a significant decrease in hs-CRP (from 7.9±8.9 to 3.4±3 µg/mL) (P=0.01)***

✓a significant decrease in frequency of diastolic dysfunction (*P*=0.04), while ***systolic function (FS and EF) improved significantly (P=0.007 and 0.05, respectively),***

✓but LVMI and MBPI pre or post dialysis did not change

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- More dialysis, more frequent/longer sessions: « daily » dialysis, daily in center high efficiency hemodiafiltration

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Dialysis adequacy today, a European perspective : morbidity,mortalty,cardiovascular outcome, nutrition,

Locatelli F, Canaud B. Nephrol Dial Transplant 2012; 27:3043-8

1) Highly permeable membranes for « all »
2) One should consider, as a new standard in HD, *that the minimal treatment time of **270 min = 4.5 h***, depending on the patient's weight or V, be delivered and an UF rate of no >10 ml/h/kg applied for patients treated as a thrice weekly schedule (Movelli E et al. NDT 2007)
3) Assessing and correcting underlying chronic inflammation: purity of the dialysis fluids, the Japanese experience (Endotoxin <0.001 U/ml)
4) The volume of substitution, a surrogate of the convective dialysis dose, should be considered as a critical factor for patient survival.
5) Technological improvement will never replace neither the expertise of caregivers or individualized care.

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Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study

E. Movilli et al. NDT 2007; 22:3547-3552

Ultrafilteration rate and mortality

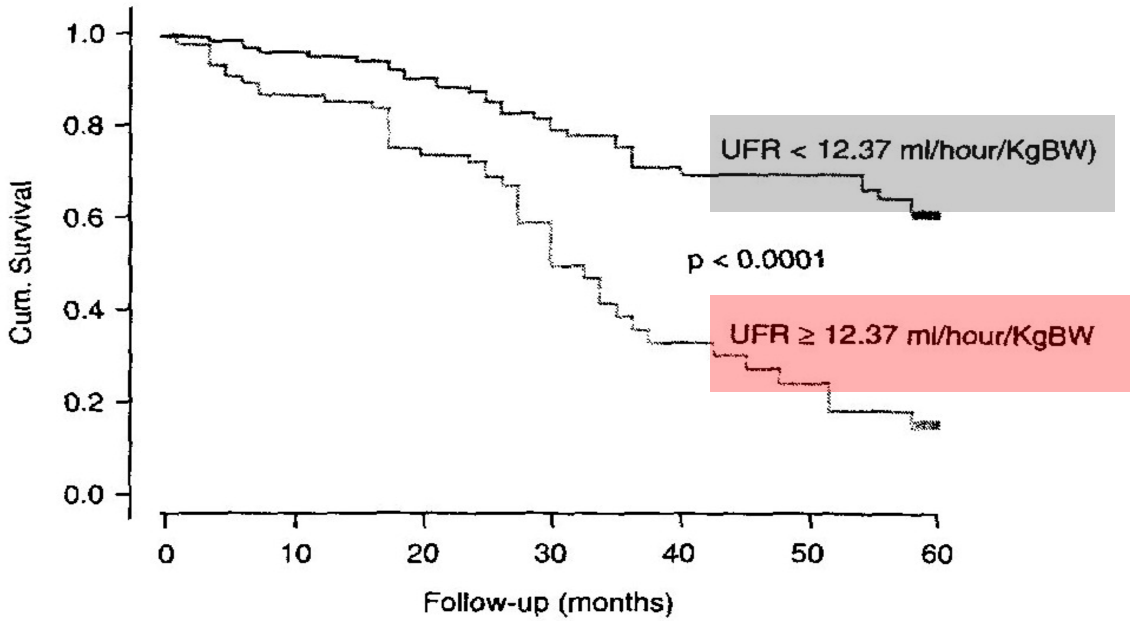

Fig. 3. Survival curves adjusted for significant predictors at Cox regression analysis by using UFR as categorical variable defined according to the receiver operating characteristic (ROC) derived UFR threshold of 12.37 ml/h/kg BW.

- From 65% to less than 20% survival at 5 years if BW loss per hour (UF rate) was over 12mL/H/kgBW
- Importance of dialysis time
- Reduction in UF demands per hour/session

UF rate< 1.25%/h BW (floating dry weight) IDWG<4% ? Euvolemia ? Cooling T_D=36°

M Fischbach et al Pediatr Nephrol 2015

- Huang SH, Filler G, Lindsay R, McIntyre CW (2014) Euvolemia in hemodialysis patients: a potentially dangerous goal? Semin Dial doi: 10.1111/sdi 12317
- Flyth JF, Brunelli SM (2011) The risk of high ultrafiltration rate in chronic hemodialysis : implications for patient care. Semin Dial; 24:259-265
- Paglialonga F, Consola S, Galli, MA, Testa S, Edefonti A (2015). Interdialytic weight gain in oligo anuric children and adolescents on chronic haemodialysis. Pediatr Nephrol 2015
- Movilli E, Gaggia P. Zubani R, Camerini C, Vizzardi V, Parrinello G, Savoldi S, Fischer MS, Londrino F, Cancarini G (2007) Association between high ultrafiltration rates and mortality in uraemic patients on regular haemodialysis. A 5-year prospective observational multicentre study. Nephrol Dial Transplant; 22:3547-3552

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Longer dialysis session lenght is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis : results from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

F. Tentori, J. Zhang, Yun Li et al. NDT 2012; 4180-88

Combined effects of longer treatment time and improved dialysate purity: the « Japanese » experience

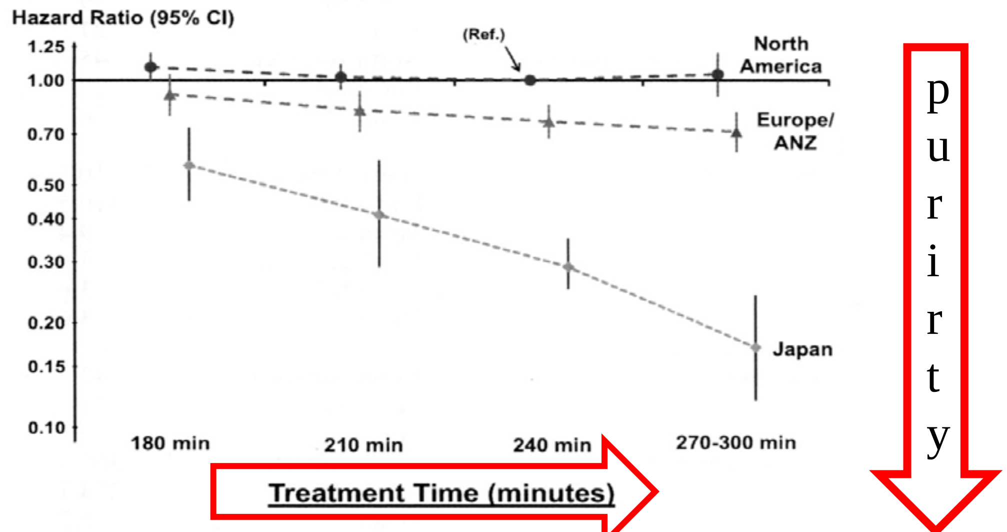
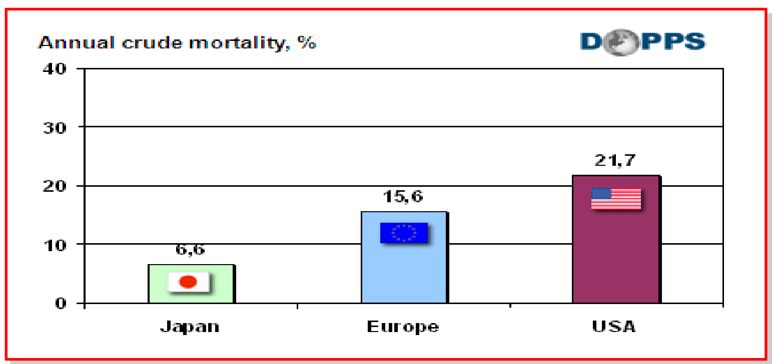


Fig. 4. Association between prescribed TT and mortality by region. Interaction between TT and region ($P < 0.0001$). Longer TT was associated with lower mortality in Eur/ANZ [HR = 0.94 (95% CI: 0.91–0.97) per 30 min TT, $P = 0.0002$] and Japan [HR = 0.75 (95% CI: 0.69–0.81), $P < 0.0001$] but not in North America [HR = 0.98 (95% CI: 0.95–1.02), $P = 0.28$]. Model was adjusted for age, sex, race, time on dialysis, BMI, 13 summary comorbid conditions, residual kidney function, prescribed blood flow rate and catheter use, stratified by study phase and accounted for facility clustering. The chosen reference category was for North American patients with prescribed TT at 240 min.



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Hémodiafiltration modalities

If the convective flow exceeds the desired weight loss, the fluid balance is maintained by an infusion of replacement fluid (bags, dialysate, on-line substitution), as applied in HF or HDF

- Conventional , classical , historical HDF : substitution fluid (bags/costs+++) with « balanced » compensation (1978)
- High flux hemodialysis i.e. internal HDF: highly permeable membranes with retrofiltration due to the high hydraulic permeability coefficient (dialysate backfiltration risks)
- On line HDF :substitution fluid produced from the « ultrafiltered ultrapur dialysate » (1987)

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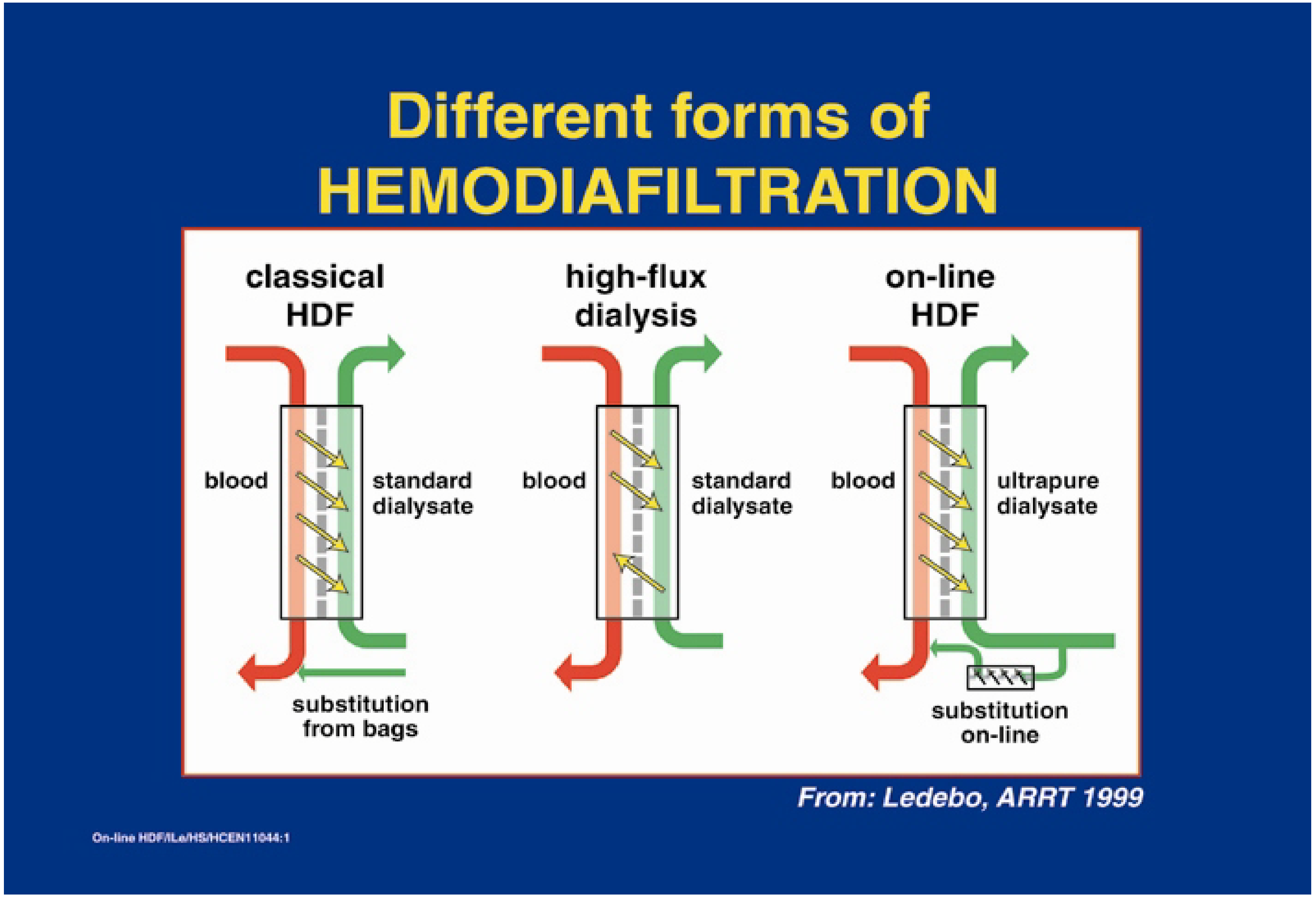
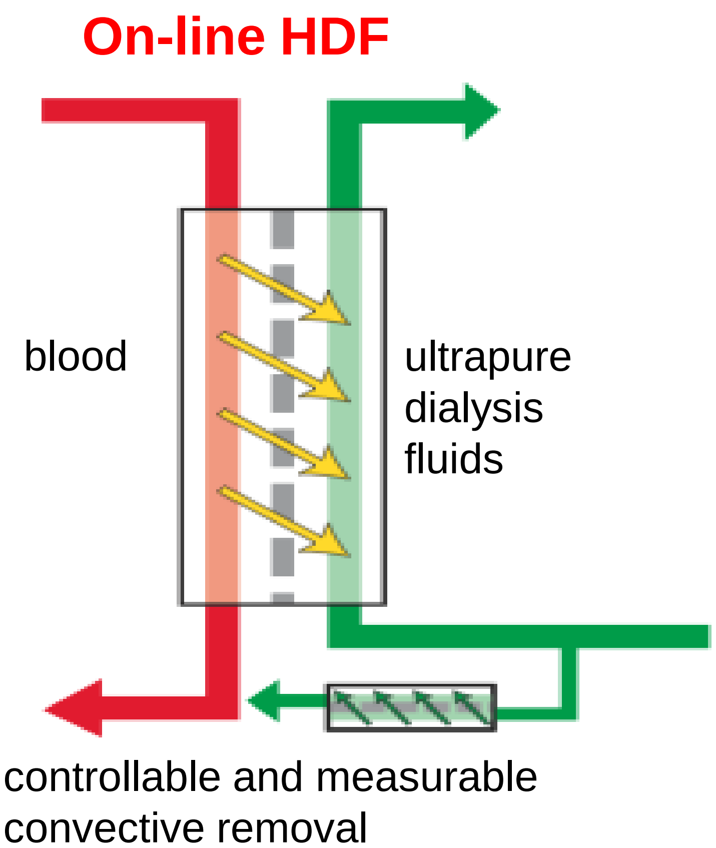
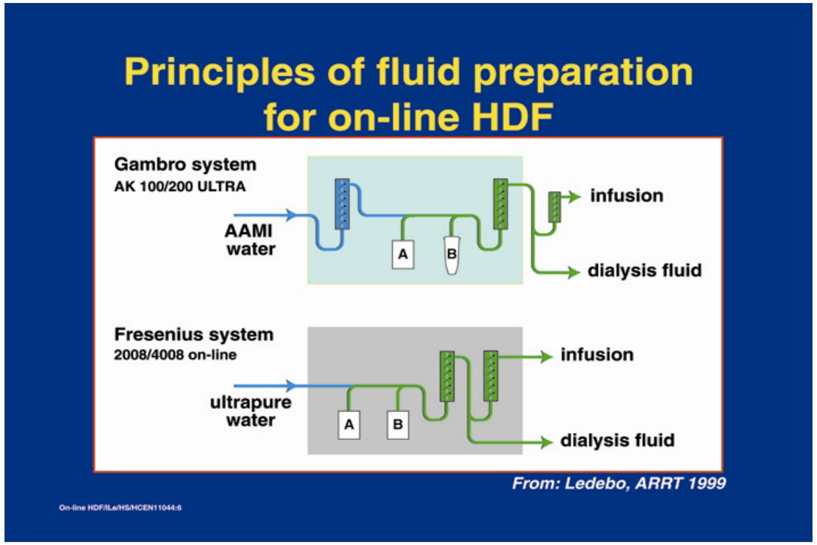
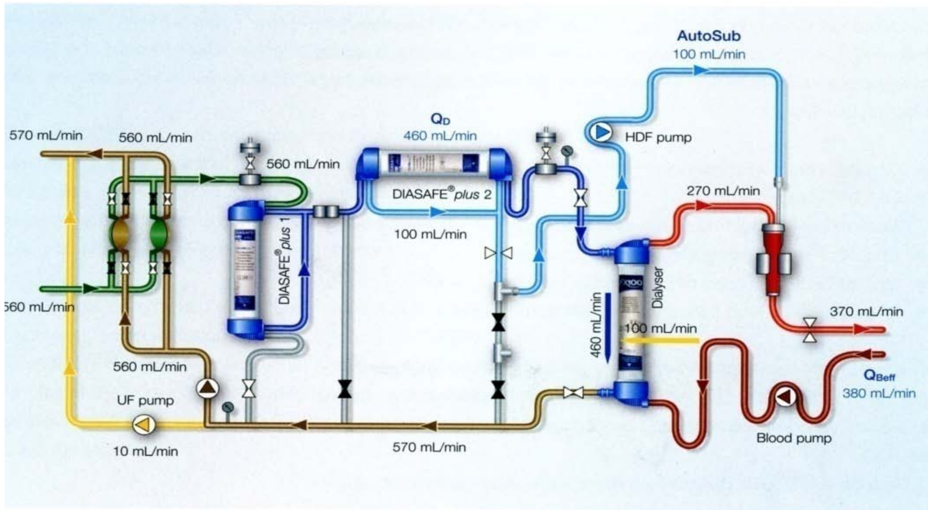
Different forms of HDF: internal HDF, classical HDF (with bags), on-line HDF



On line HDF: substitution fluid is produced on line from the double filtration of the dialysate







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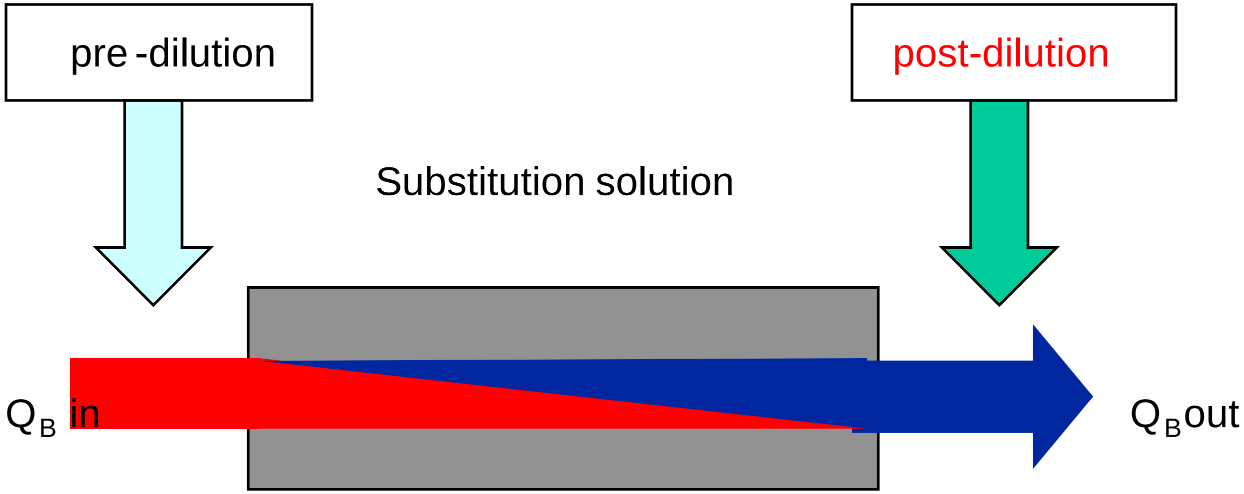
Hemodiafiltration, HD and HF

The convective transport (HF) requires ultrafiltration (UF) of the plasma, i.e. the convective flow. *If the convective flow exceeds the desired weight loss, the fluid balance is maintained by an infusion of replacement fluid, as applied in HF or HDF*.



In HDF addition of substitution solution can be made before the filter called *predilution* mode, after the filter, *postdilution* mode, or mixed

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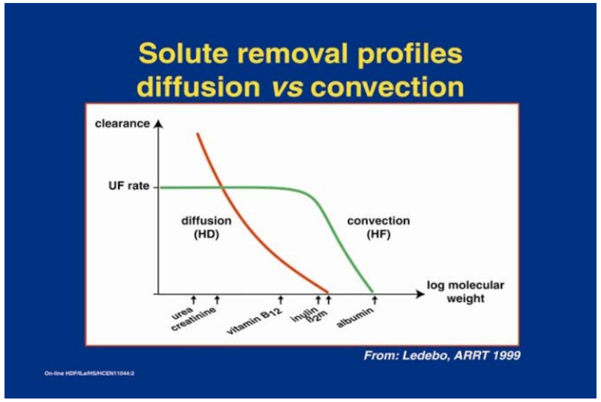
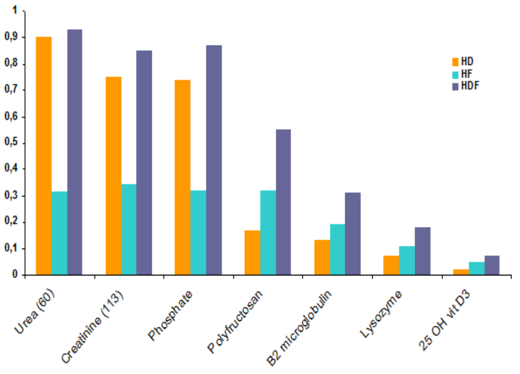
Principles of blood purification

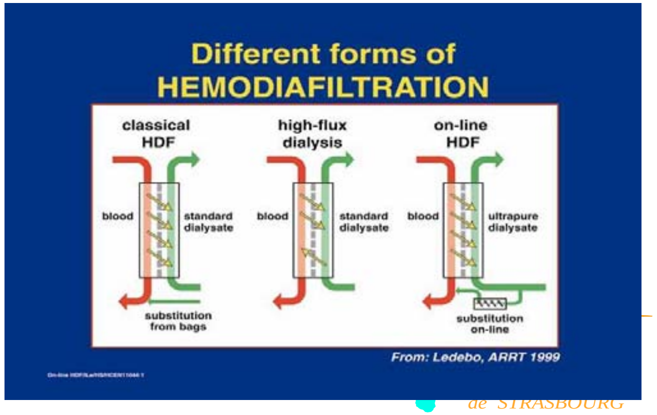
- Diffusive Process (HD) : low MW uremic toxins removal i.e.urea

- Convective mass transport (HF) :   middle Mw uremic toxins removal i.e.phosphate

- Membrane adsorption (+++/PMMA/Torray ?)







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Blood purification dialysis modalities : diffusion versus convection

Diffusive Process (hemodialysis)

Membrane area

Mass transport coefficient

Concentration gradient

Blood flow x extraction coefficient

$$K_{HD} = Q_B \times \frac{c_i - c_o}{c_i}$$

i, o : in outlet solute concentrations

Convective mass transport (hemofiltration)

Ultrafiltrate flow (Q_{UF})

Hydraulic permeability

Transmembrane pressure (TMP ; mmHg)

Sieving coefficient (S)* Molecular permeability

$$*S = \frac{2\ C_{UF}}{c_i + c_o}$$

C_{UF} : ultrafiltrate solute concentration

$K_{HF} = Q_{UF} \times S$ (postdilution)

$Q_{UF} < 1/3\ Q_B$ (in practice)

Simultaneous purification: diffusion process and convection mass transport i.e. hemodiafiltration

one minute of dialysis « is equal» to two minutes of purification, one of HD and another one of HF

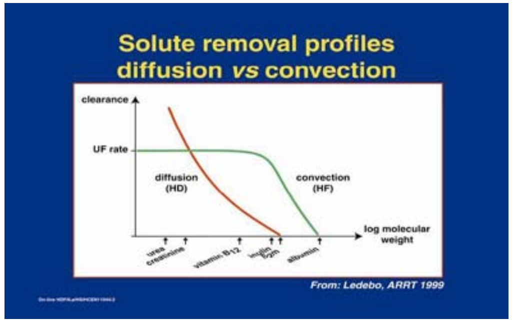
$$K_{HDF} = K_{HD} + x\ Q_{UF}\ x\ 0.46$$

$$K_{HDF} = K_{HD}\ (1 - Q_{UF}\ x\ S/Q_B) + K_{HF}\ \text{(Granger)}$$

with $Q_{UF}\ x\ S = K_{HF}$ and $Q_B = K_{max}$

$$K_{HDF} = K_{HD} + K_{HF} - \frac{K_{HD}\ x\ K_{HF}}{K_{max}}$$

If K_{HD} is equal to K_{max} then $Q_{HDF} = K_{HD}$



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Uremic toxins

Vanholder R et al. KI 2003; 1934-43

The small water soluble compounds (prototype urea): < 500D

The protein-bound compounds (prototype p-cresol)

The larger "middle molecules" (prototype $ß_2$-microglobulin): > 500D

Low MW < 500 D^2	Middle large MW >500 <60 000	Protein bound compounds
Urea	β2 m	Paracresol
Guamidine	Leptine	Indoxyl sulfate
Phosphate	AGE	
Acide urique	Interleukines, TNFα	
Oxalate	Ig light chain	Homocysteine
	PTH	

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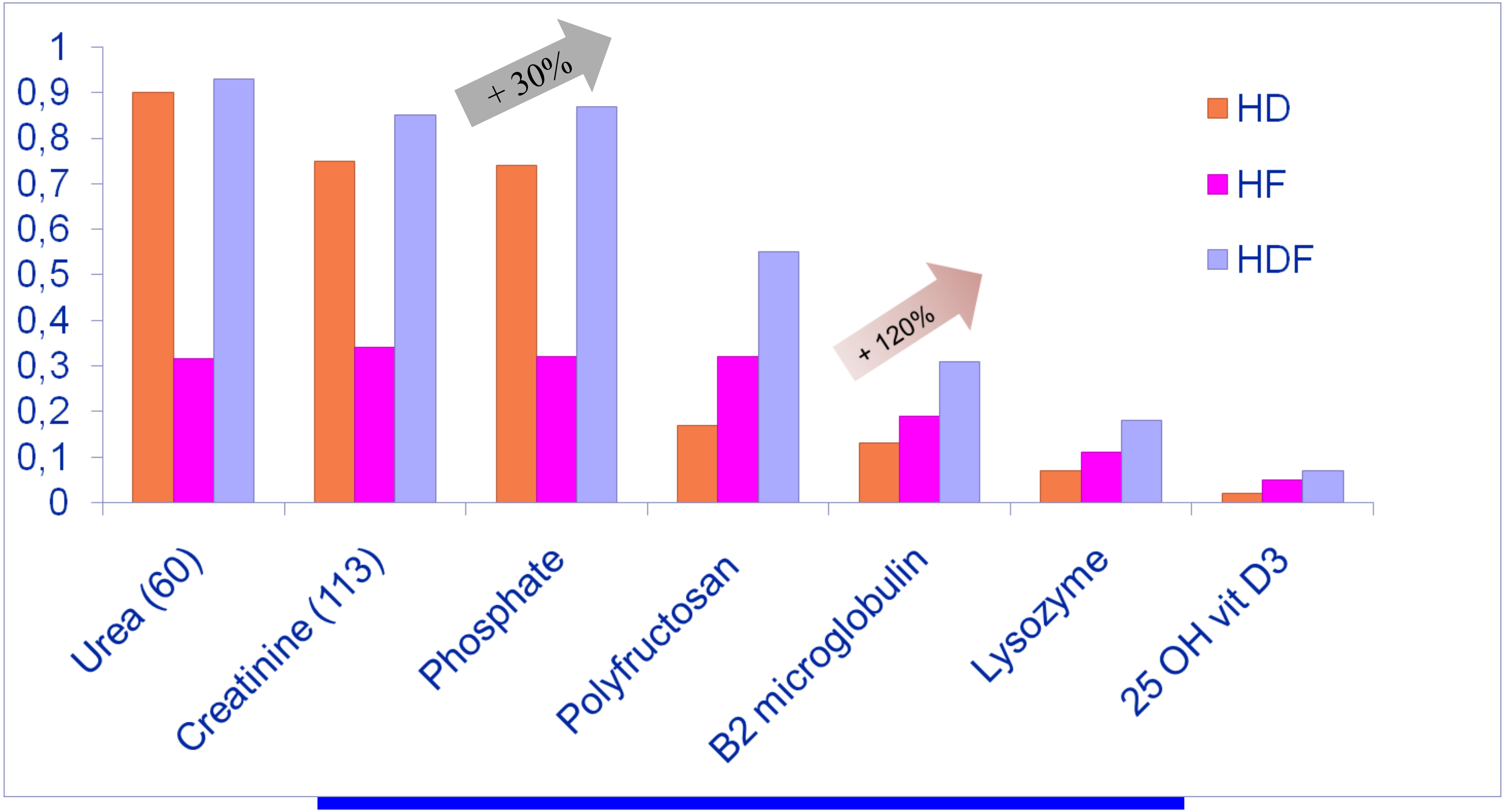


HDF allows an optimal blood purification not only for urea, but also for the middlemolecular weight compounds (Babb theory)

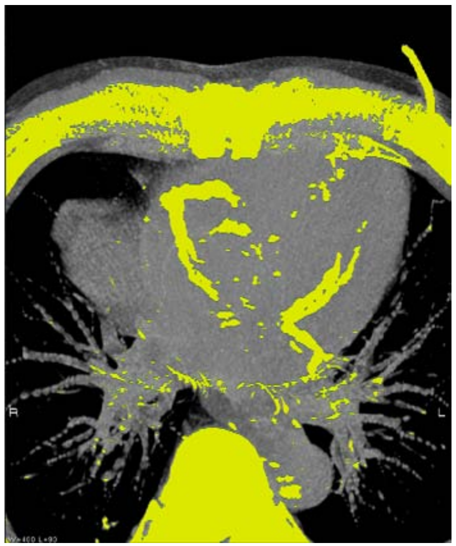
From M Fischbach et all .Contr Nephrol1985

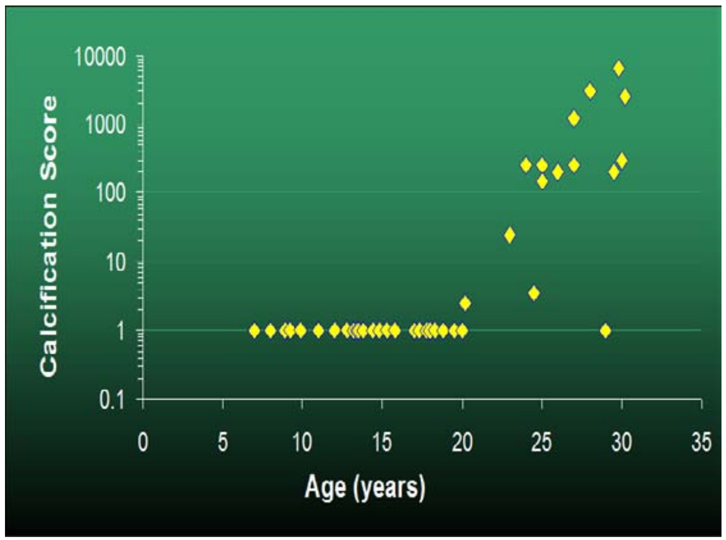
Hyperphosphatemia, a « silent killer »

(FGF23;Klotho) of patients with renal failure

K. Amann, M.C. Gross, G.M. Landon, E. Ritz Nephrol Dial Transplant 1999;14:2085-87

coronary calcification : Ca x P





17 young adult patients with childhood onset of CRF (median 26 years at screening time): *coronary calcifications* were found in 7 out of 17 patients

Premature atherosclerosis in young adults and childhood onset chronic renal failure

OH J. et al. J Am Soc Nephrol 2000; 11:A857 and Circulation 2002; 106:100-105

The effect of dialysis modality on phosphate control : HD compared to HDF.

The Pan Thames Renal Audit

A. Davenport et al. Nephrol Dial Transplant 2010; 25:897-901

- HDF offers improved phosphate control compared to standard intermittent HD

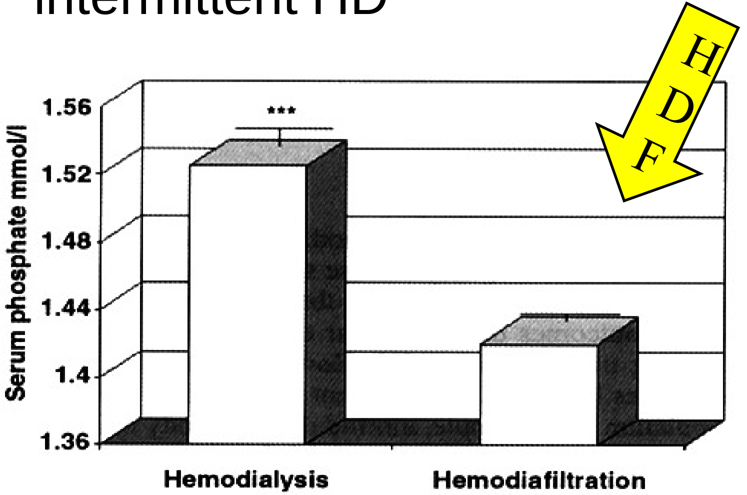


Fig. 1. Serum phosphate in hemodialysis and hemodiafiltration cohorts. Data expressed as mean (SEM). ***$P < 0.001$.

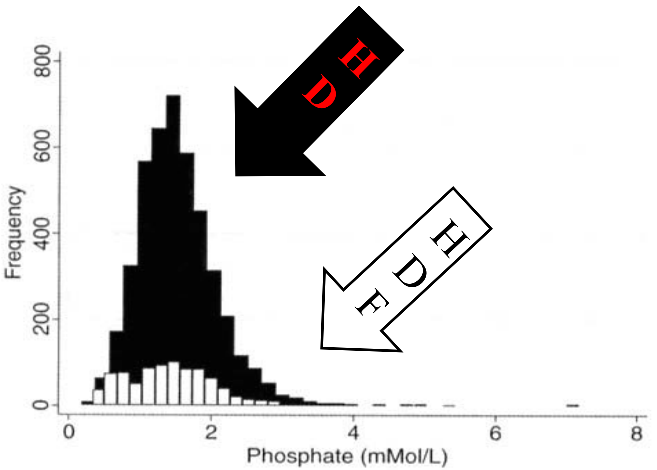


Fig. 2. Frequency distribution curves of the pre-dialysis midweek serum phosphate concentrations in the haemodialysis patients (black bars) and haemodiafiltration patients (white bars).

Impact of convective flow on phosphorus removal in maintenance haemodialysis patients

W.Lornoy et al. J. Ren Nutr 2006: 47-53

This study revealed a higher phosphorus removal and phosphorus reduction rate with postdilutional on-line HDF compared to high-flux HD. *Long-term use of on-line HDF therefore may have a positive impact on the cardiovascular status of the patients*

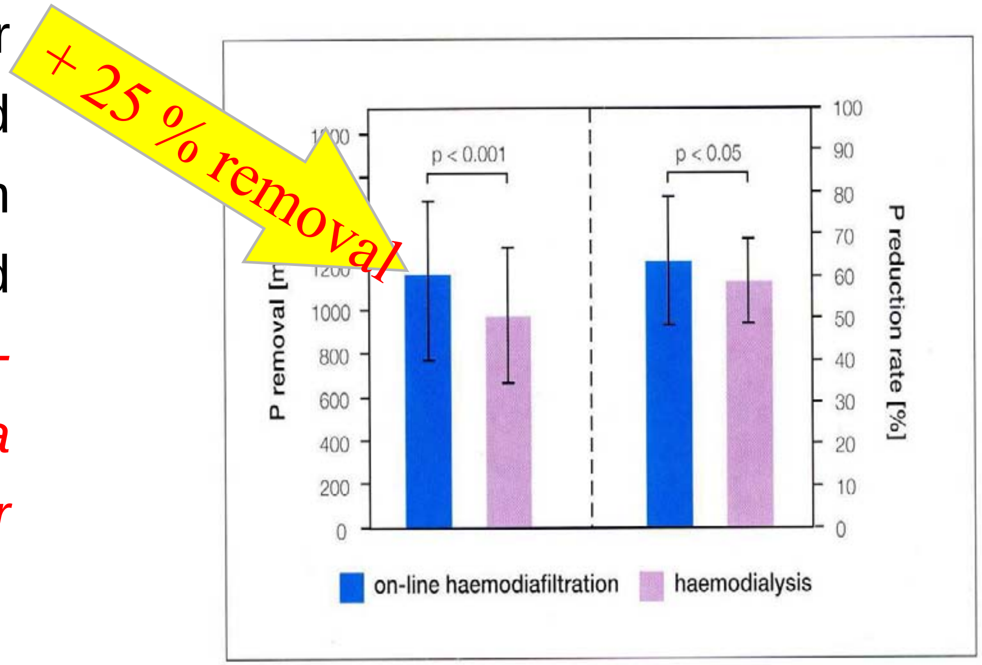


Fig. 4: *Phosphorus removal in total spent dialysate and ultrafiltrate and phosphorus reduction rate in oHDF and HD*

Phosphate should be considered as a MMW uremic toxin in terms of dialysis purification : water molecular environment; importance of the convection (HDF)

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Pre-dialysis β_2m and treatment mode, the more convective flow (HDF) the lower plasma level of β_2m

	low-flux HD	high-flux HD	high-eff HDF/HF	n
Muñoz, 2006		27	23	31
Beerenhout, 2005	43		20	19
Lin, 2001		35	22	58
Wizemann, 2000	31		18	23
Maduell, 1999		27	24	28
Koda, 1997	39	30		181
Altieri, 1997		26	23	23
Locatelli, 1996	40	29		51
Cheung, 2005	41	33		817+887
Ward, 2000		26	23	21+24
Schiffl, 2000	45	30		34+26

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Vanholder R et al. KI 2003; 1934-43

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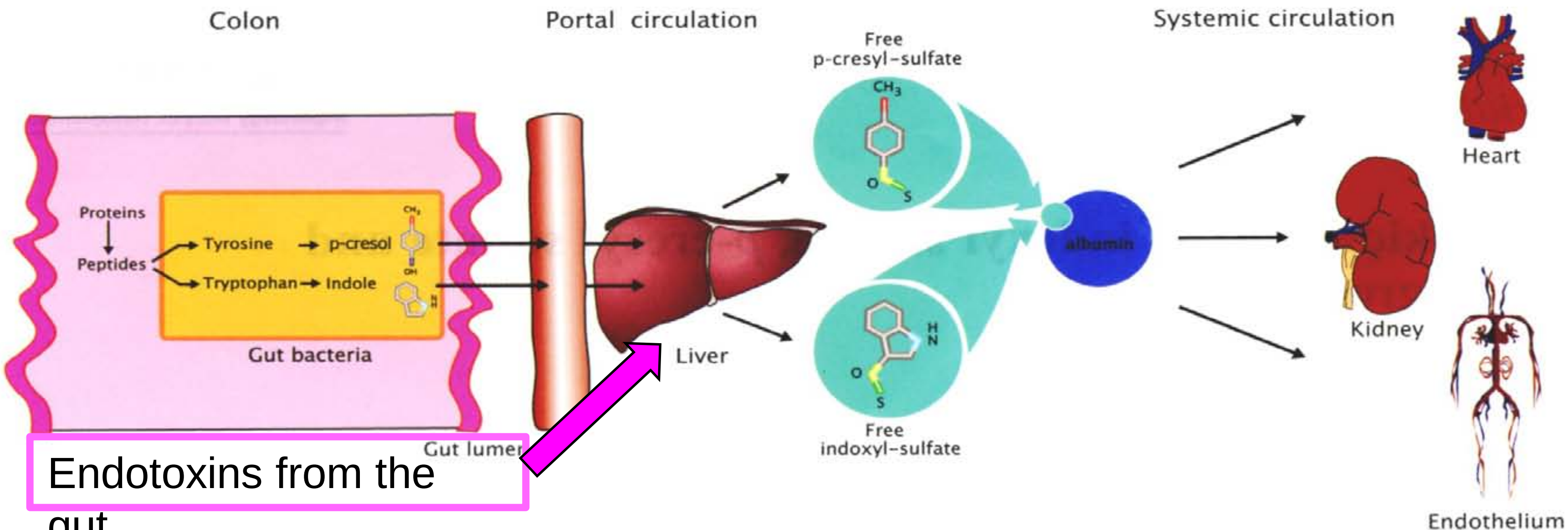
Guamidine	Leptine	Indoxyl sulfate
Phosphate	AGE	
Acide urique	Interleukines, TNFα	
Oxalate	Ig light chain	Homocysteine
	PTH	

The gut-kidney axis:

indoxyl sulfate, *p-cresyl* sulfate, endotoxins and CKD progression

Björn KI Meijers and Pieter Evenepoel.

Nephrol Dial Transplant 2011; 26:759-761



Endotoxins from the gut

CKD : a systemic disease with cross talk between the gut and the "body" (CKD-MBD-CardioVascular)

- ✓ Uremic toxins production
- ✓ "leaky" gut (endotoxins)

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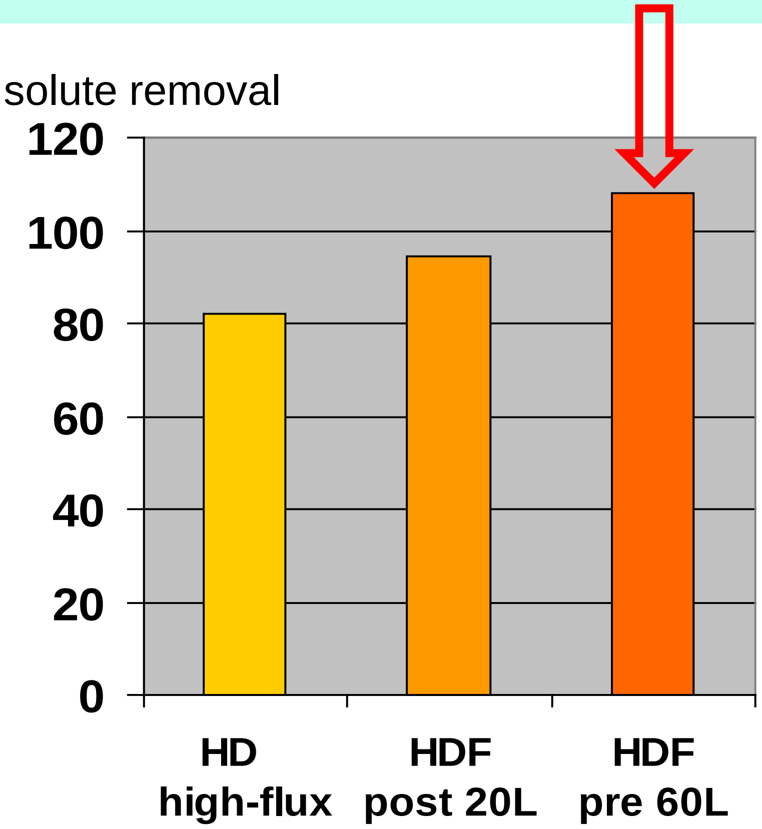
P-cresol , a protein-bound uremic toxin impact on survival

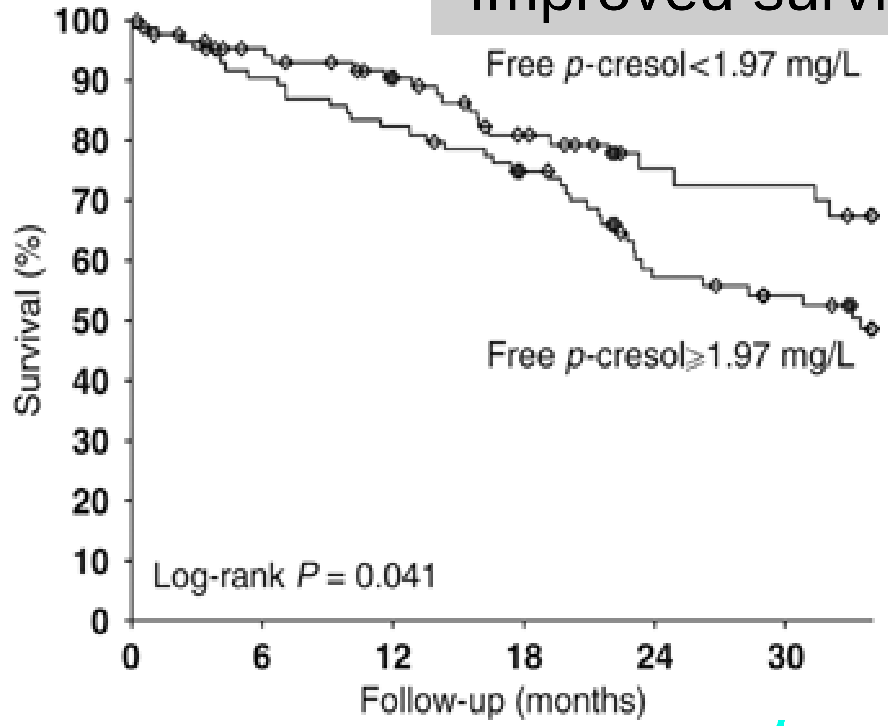
Bammens et al, AJKD 2004 and Kidney Int 2006

Total solute removal (mg)



14 patients treated w the same high-flux filter 2 wks on each modality

Improved survival



N= 175 HD patients, prosp. obs. study

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On-line HDF: *a combination of solute removal, « purification » and dialysis fluids purity*

Maduell F. Hemodialysis International 2005 ; 9:47-55

<u>HDF and blood purification impacts</u>

- Nutrition, uremic toxins and anorexia (leptin)
- Anemia, improved erythropoietin response
- Cardiovascular disease, AGE removal
- Infectious complications, complement factor D removal
- Joint pain, dialysis related amyloidosis

<u>HDF and ultrapure dialysis fluid impacts</u>

- Amyloidosis
- Anemia
- Nutrition
- Joint pain, dialysis related amyloidosis

HDF versus HD : advantages

- *Optimal blood purification capacities* both for urea and middle molecular weight compounds : high level dialysis dose easely achieved . A high dialysis dose usually induce a good nutrition status, especially with an increased caloric intake (apetite)
- *Hemodynamic stability over the session* : increased tolerance to weight loss and blood pression control improvement (hemofiltration effect) : osmotic stability, compartiment preservation, peripheral vascular resistances, myocardial contractility

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HF and HDF predilution, reduce intradialytic hypotension in ESRD

F. Locatelli et al. J Am Soc Nephrol 2010; 21:1798-1807

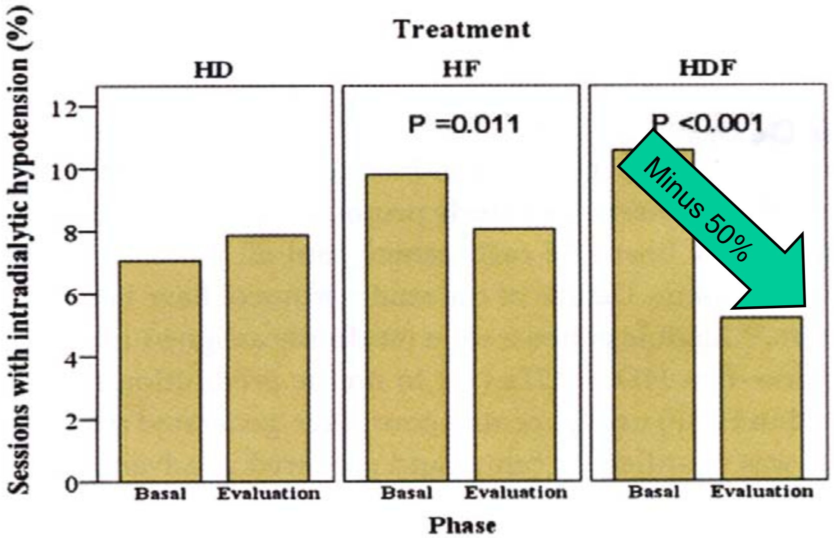

Figure 2. 7.5% of all of the 28,950 sessions were complicated by ISH. In the evaluation period compared with the basal run-in, there was a statistically significant decrease of sessions with ISH in HF (9.8 to 8.0%, decrease of 18.4%; $P = 0.011$) and in HDF (10.6 to 5.2%, decrease of 50.9%; $P < 0.001$) compared with low-flux HD group (7.1 to 7.9%, increase of 9.9%).

Intradialytic symptomatic hypotension occurrence was reduced in on line predilution HF and HDF

This lower frequency of ISH was associated in HDF, with a significant increase in predialysis SBP values (from 137.3 to 141.3 mmHg)

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Hemodiafiltration
with high permeable membranes in children

M Fischbach, G Hamel, E Tarral, J Geisert. Blood purification 1984; 2:203-206

	HD 15 h/week cuprophane 12 months	HDF 9 h/week PAN 12 months	HDF 9 h/week polysulfone 12 months
TAc urea mmoL/L	28±4	18±3	20±2
PCRn g/kg/j	0.7±0.2	1±0.1	1.8±0.3
Phosphate mmL/L	1.65±0.28	1.34±0.15	1.15±0.18
Aluminium prescription g/day	3	1.5	0.5
Hemoglobin g/dl	7.4	8.3	8.9
Need of transfusion per year	5	2	1
Date	1981	1982	1983

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High-volume online haemodiafiltration improves erythropoiesis-stimulating agent (ESA) resistance in comparison with low-flux bicarbonate dialysis: results of the REDERT study

*Panichu V, Scaletta A, Rosati A et al. Nephrol Dial Transplant **2015**; 30:682-689*

A significant reduction in hepcidine and β2microglobulin, and higher Kt/V

Is HDF more favourable than HD for treatment of renal anaemia ?

*A. Więcek and G. Piecha. Nephrol Dial Transplant **2015**; 30:523-525*

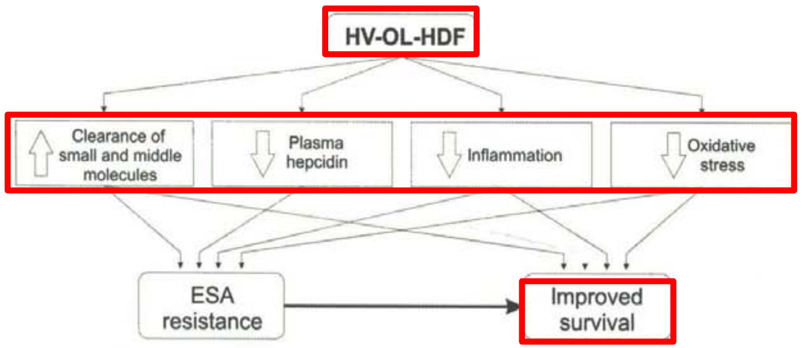

FIGURE 1: Proposed pathomechanism of improved sensitivity to ESAs in haemodialysis patients with end-stage renal disease treated with HV-OL-HDF.

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Mortality risk for patients receiving HDF versus HD: European results from the DOPPS

Canaud B et al. Kidney Int 2006

- The ***relative risk of mortality*** after adjustments for several variables (age, comorbid conditions, haemoglobin, Kt/V) was *significantly reduced by 35 % for patients receiving **high efficiency HDF*** compared to low flux HD or high flux HD

- Several explanations: HDF « package »
  - improved removal of small and larger molecules solutes (Phosphate), « surrogates » of the achieved convective volume
  - enhanced intradialytic hemodynamic stability
  - reduced inflammation due to better biocompatibility (β2 microglobulin
  - regulation of calcification inhibitors, like : fetuin-A, matrixGLA protein, osteoprotegrin

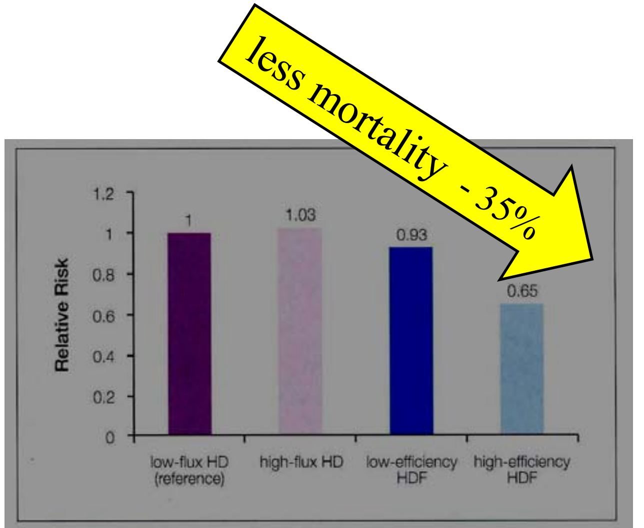

Fig. 1: Relative risk of death by dialysis modality

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High-efficiency postdilution Ol-HDF (ESHOL) reduces all-cause mortality in dialysis patients

Maduell F et al. J. Am Soc Nephrol 2013; 24:487-497

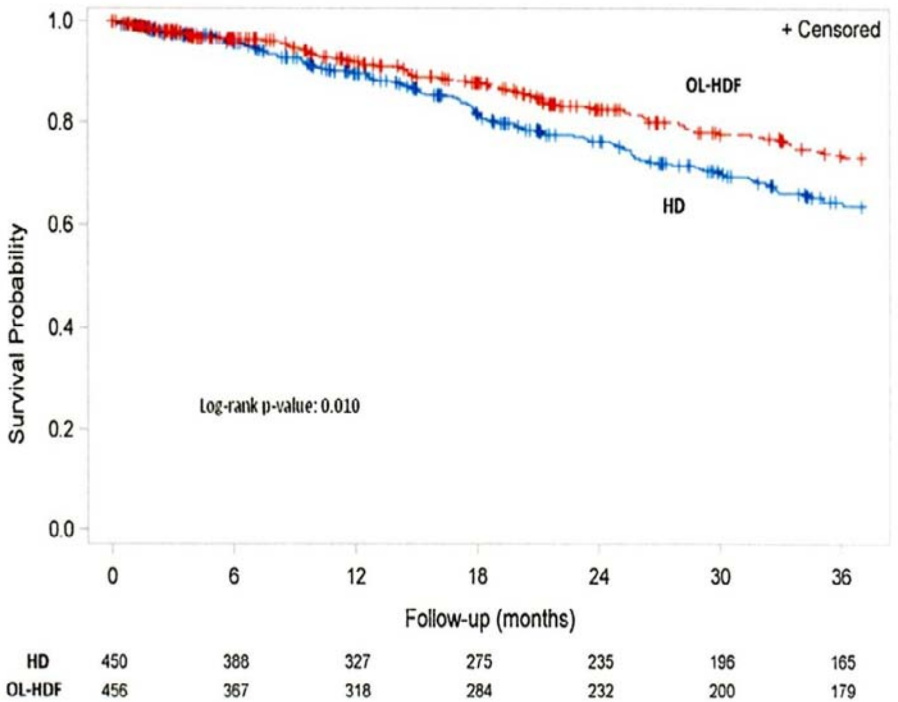

Figure 2. Kaplan–Meier curves for 36-month survival in the intention-to-treat population (P=0.01 by the log-rank test). HD, hemodialysis.

They found that high-efficiency OL-HDF (>24L/session) in patients with ESRD on hemodialysis was associated with **a 30 % reduction in all-cause mortality** compared with conventional high-flux hemodialysis

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Impact of high convective volume high efficiency hemodiafiltration

Study name	**Threshold volume for suvival benefit (observational studies)**
DOPPS (Canaud) 2006	> 15 L
Riscarid (Panichi) 2008	> 23 L
Contrast (Grooteman) 2012	> 21.95 L
Purkush (Ok) 2012	> 17.4 L
ESHOL (Madrid) 2013	> 23.1 L
Minimal convective volume, post dilution or predilution (easier to achieve?)	? 3 L/m^2/h or 12- 15L/m^2/session ?18-27 L/m^2/session

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HDF : substitution fluid optimization (convective volume), blood flow +++

- Pressure control (Gambro) : maximal efficient PTM assessed to obtain a gain of convective volume (PTM « pulses »)
- Filtration fraction (Fresenius; autosub+) : inititally based on on line hematocrite (and historically on total proteins given by the medical prescription…), improved by *viscosity on line assessment (autosub+)+++*
- Conclusion : importance of the total amount of water, not only related to the proteins (filtration fraction <50%) but also to the blood cells (hematocrite « outlet » <50%)

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Adequate HDF prescription: « quality » of a high convective volume *importance of the membrane*

- Hydraulic permeability : high convective volume

  (> 25 L in postdilution; > 60L in predilution)

- Molecular permeability : extraction coefficient

  (phosphate and β_2 m 80 %)

- Loss of albumine (< 5 gr)
- Purity of the dialysis fluids

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HDF: a complete dialysis dose

- On-line Urea Kt/V > 1.4 (V « Morgenstern or BCM)
- High convective volume (autosub+) but need for a volume of « good quality » (impact of the membrane) :
  - beta-2-microglobulin extraction coefficient >80%
  - myoglobin>65%
- Risk of « loss » in the dialysate and high convective volume (check for albumin; quality of the membrane)
- Dialysis fluids : purity, temperature control (« cooling »; BTM), NaD (on-line diffusive sodium), Ca++, HCO_3^-
- More than purification, importance of the volume control (UF and sodium balance): BCM, BP, IDWG…

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