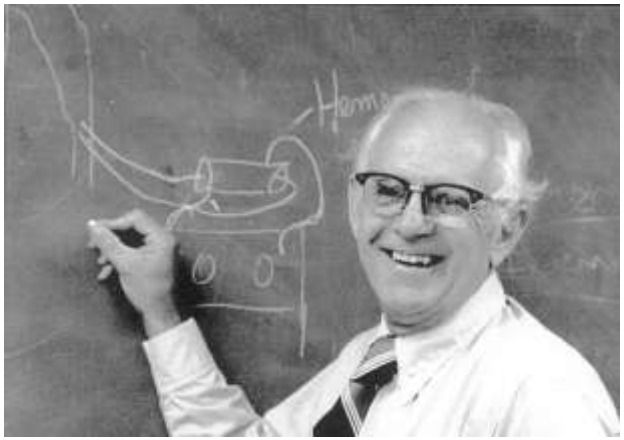
Prescribing the dose of dialysis

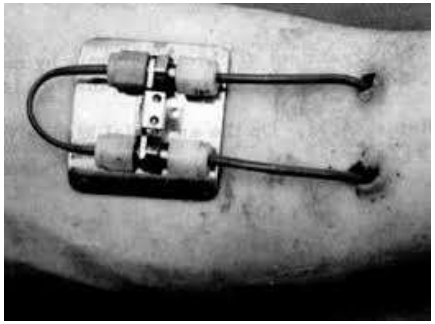


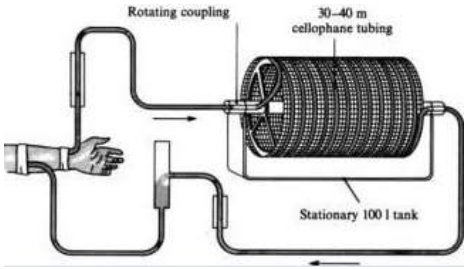
Dr Mélanie HANOY, CHU Rouen

Actualités Necker

Le 21 mai 2019

Clyde Shields (1921–1971)





60 years ago…

FIRST CHRONIC HEMODIALYSIS PATIENT

- **March 1960** :
  - First session of 76 h
  - Next sessions depending on arterial pressure and dyspnea (every 7 to 14 days for 24 to 48h)

Adequate Dialysis: What's that ??

- **By the End of 1960s - 2 goals:**
  - Eradication of **signs and symptoms of uremia** (blood pressure, albumin, pericarditis, neuropathy, concept of dry weight (1969))
  - Rehabilitation

- **1965 - Square meter / hour hypothesis:**
  - Importance of removing **middle molecule ++** (neuropathy) : **Minimum number of hours of dialysis per week** > maintenance of specific levels of blood urea and creatinine

→ **Dialysis Index = $(3.5 \times 10^{-3})\ [(T_D K_B + 168\ K_K) / S]$**

TD = Weekly Dialysis Time
KB = MM clearance (Mb characteristics and UF)
KK = Residual renal creatinine clearance
S = body surface area

Adequate Dialysis: What's that ??

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  - Rehabilitation

- **1965 - Square meter / hour hypothesis:**
  - Importance of removing **middle molecule ++** (neuropathy) : **Minimum number of hours of dialysis per week** > maintenance of specific levels of blood urea and creatinine

- **1969**: Clinical improvement with **increased frequency** of sessions for a same weekly duration (De Palma, 1969) (4h x 3 $\neq$ 6h x 2)

- **In the 1970s**: Shortening sessions

Babb et al. Trans Am Soc Artif Intern Organs 1971; 17: 81 – 91

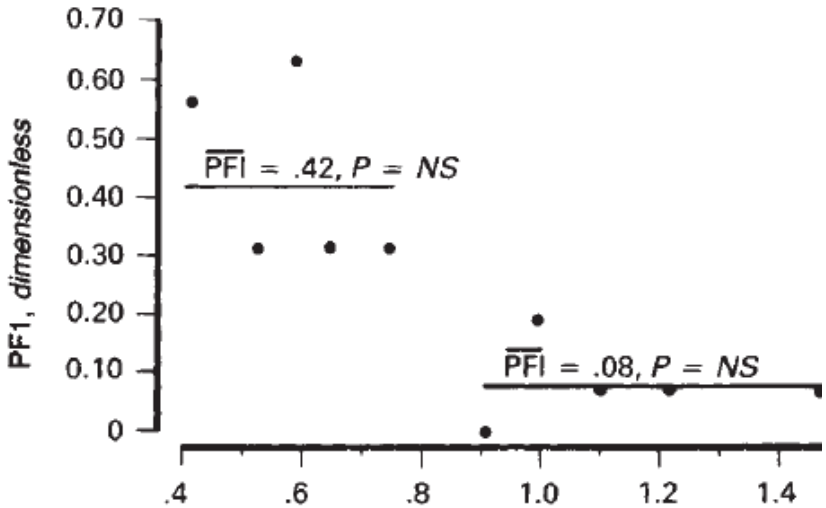
Kt/V_{UREA} = Yardstick of HD adequacy

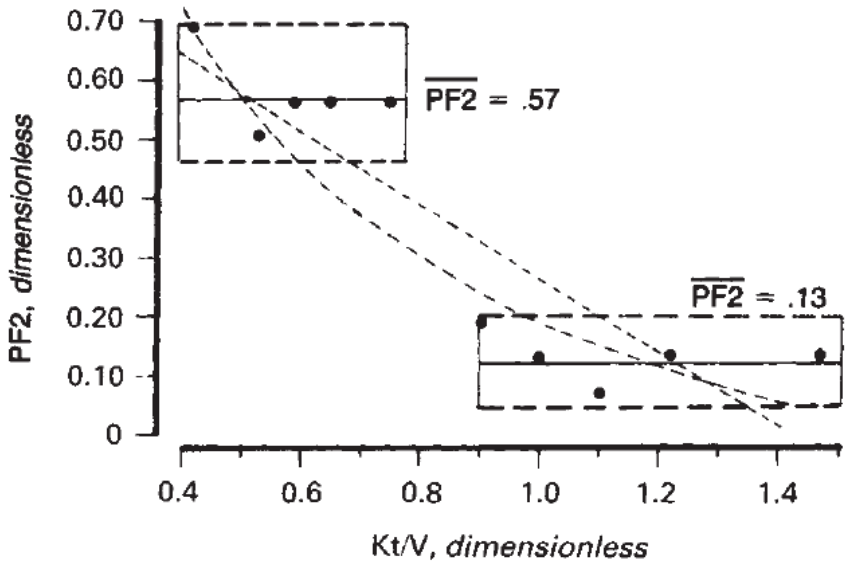
- **In the late 1970s and early 1980s….**
  - **Shorter dialysis** = measure of dialysis adequacy based on **urea kinetics**
  - **1975: National Cooperative Dialysis Study (NCDS)**
    - Randomized controled trial to define quantitative criteria for the adequate dose of dialysis
    - Criterion of dialysis dose: Urea kinetics coupled with monitoring of nutrition (Kt/V)
    - Is there a relationship between residual morbidity and magnitude of dialysis prescibed ??

      ⇨ **Comparison of outcomes btw high (16 mmol/L) or low (8 mmol/L) urea levels and short (2,5 – 3,5 h) or long dialysis (4,5 – 5,5 h)**

Lowrie EG. Et al. Kidney Int Suppl 13; 1983: S1 –S7
Sargent JA. et al. Kidney Int Suppl 13; 1983: S19- S25
Parker TF. et al. Kidney Int Suppl 13; 1983: S42 – S49

Adequate Dialysis - NCDS



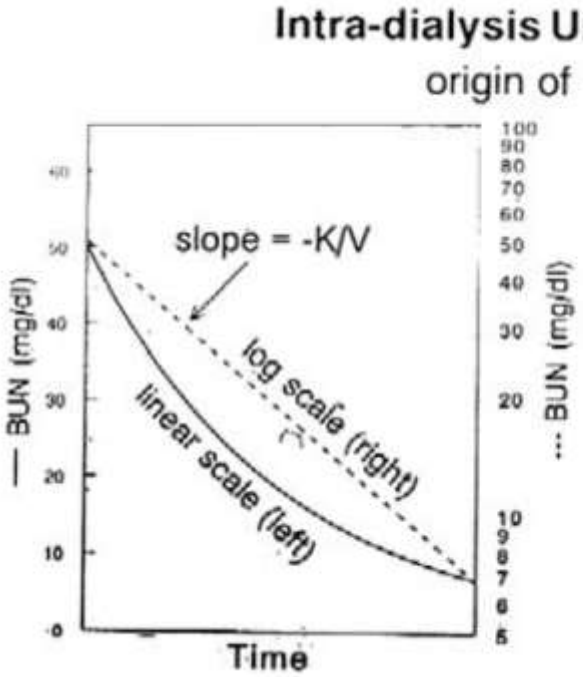


⇨ **Correlation between MORBIDITY and Kt/V**

Patients with high urea and short dialysis are more hospitalized than patients with high urea and long dialysis … but … *p = 0.056*

Gotch FA, Sargent JA.A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526-34

Acceptation of Kt/V_{UREA} as a single mesure of dialysis adequacy



if G, dV = 0

$$\frac{dC}{dt} = -k \cdot C$$

$$k = \frac{K}{V}$$

$$C = C_0 \cdot e^{\frac{-K \cdot t}{V}}$$

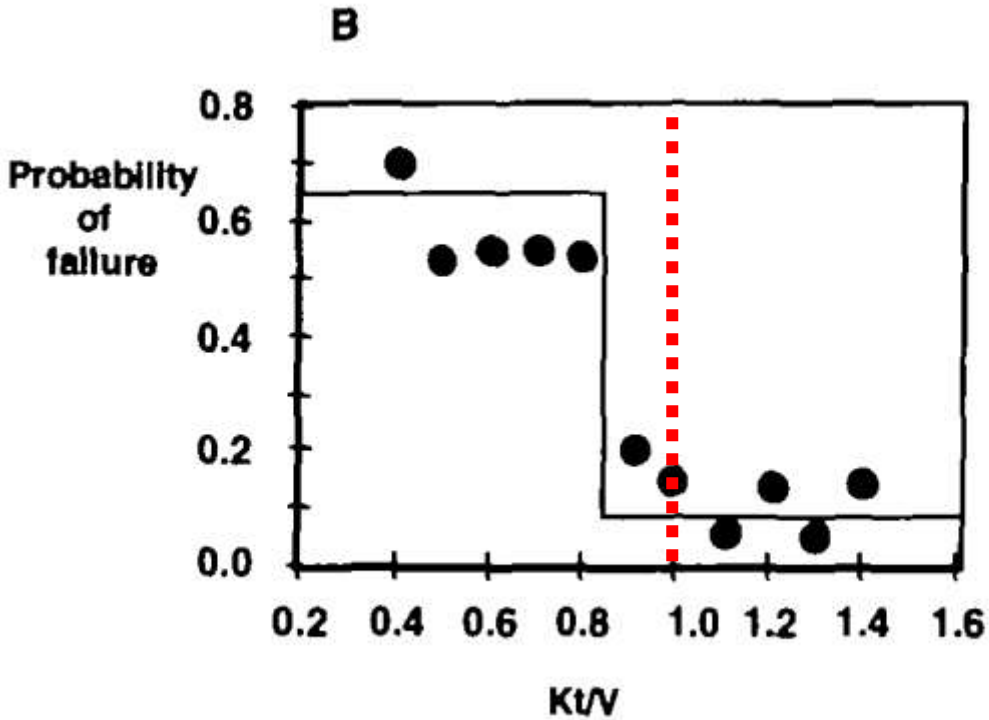
$$\boxed{\frac{K \cdot t}{V} = \ln\left(\frac{C_0}{C}\right)}$$

⇨ **Justified short Dialysis !!!**
Just need blood sampling to measure pre and post concentration of urea

Lowrie EG. et al. Kidney Int Suppl 13; 1983: S1 –S7

Kt/V_{UREA}:  ???

1985 - Kt/V_{UREA} = dependent variable of PCR

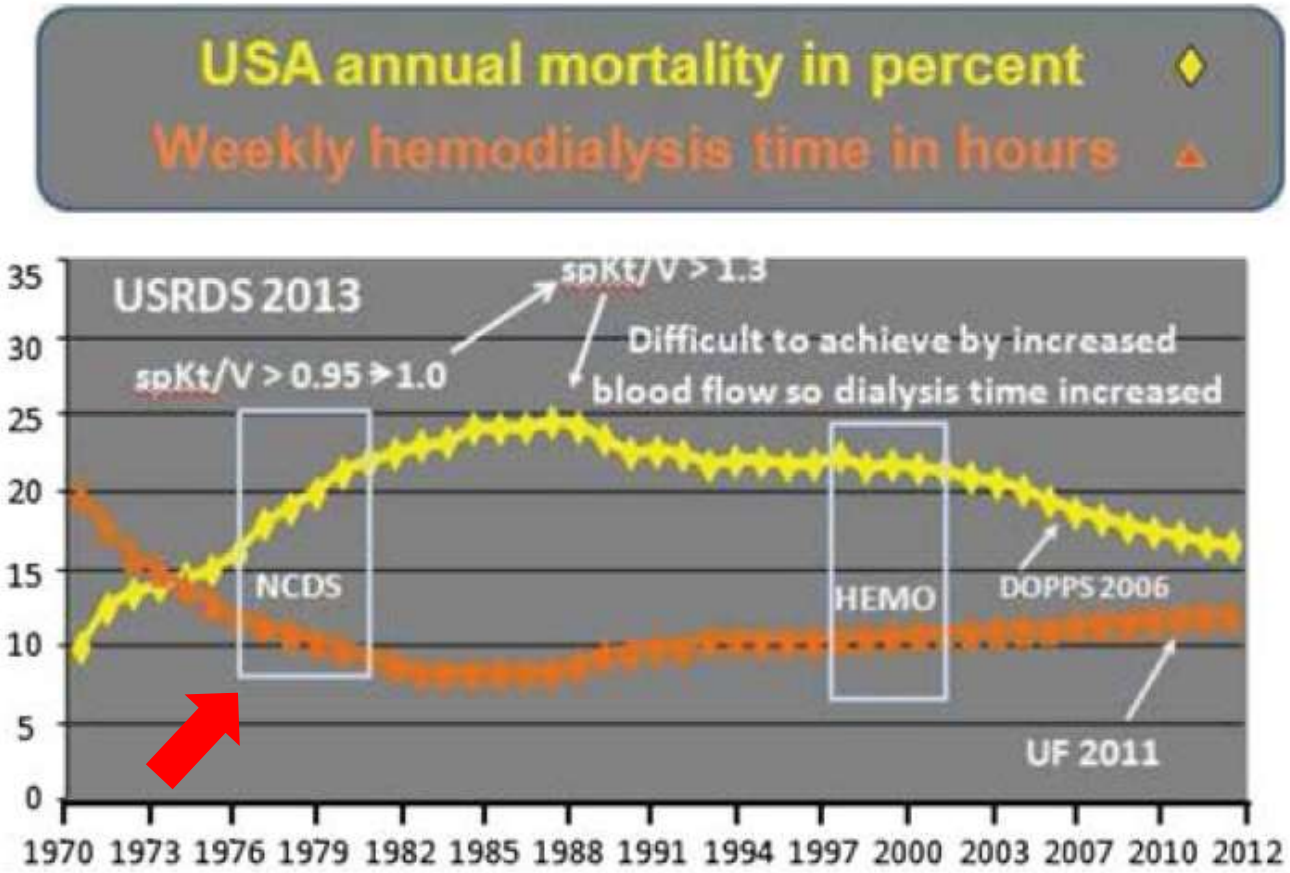


Kt/V_{UREA} = 1 : Indicator of dialysis adequacy with a thrice weekly dialysis scheme with cellulosic dialysers and adequate nutrition

Gotch FA, Sargent JA.A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int. 1985;28:526-34

Evolution of the Kt/V_{UREA} target

Time of dialysis by week (h)



1970 to 1988
Mortality / year
10 to 25%!!

From Observational Studies

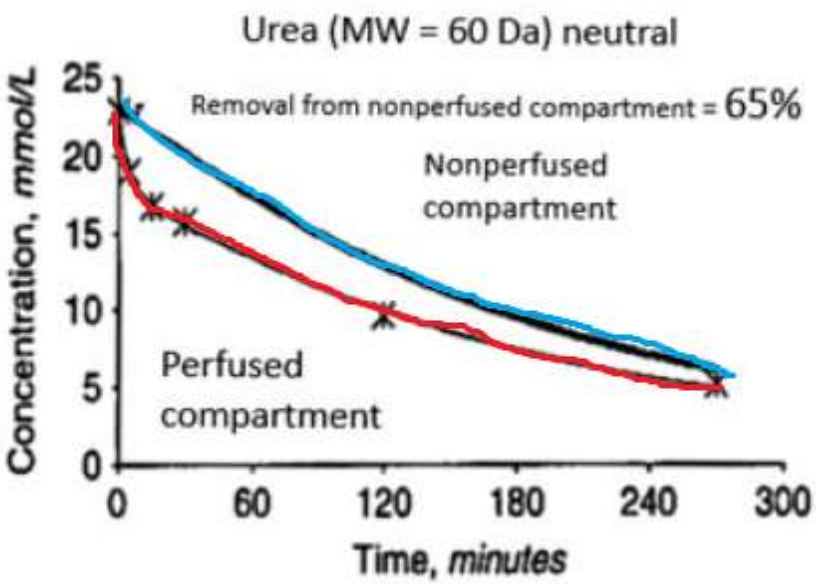
445 patients - 10 year actuarial survival of 75%
Mean Kt/V_{UREA} 1.66 ± 0,44

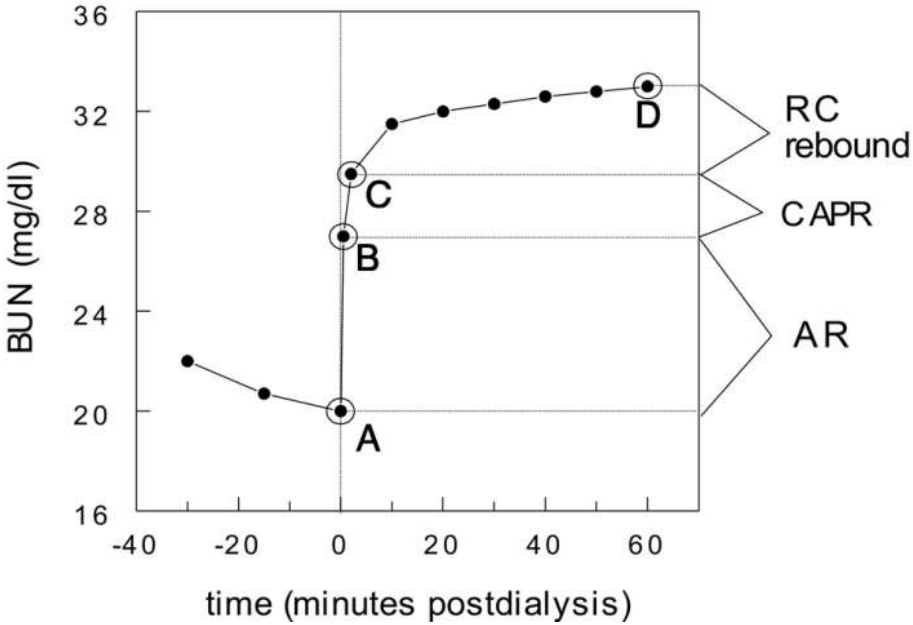
	# pts	% Patient survival, *years* 5	10	15	20	*P*
KT/V[a]						
<1.60	222	85	71	50	33	
≥1.60	223	91	82	63	57	<0.005
Total	455	87	75	55	43	
MAP[b]						
<99 mm Hg	222	93	85	67	53	
≥99 mm Hg	223	81	65	43	—	<0.001
Total	445	87	75	55	43	

Significantly better survival in high group Kt/V 1.97 vs Kt/V 1.67

Charra B. et al. Kidney Int 1992; 41: 1286 - 1291

Concept of eKt/V_{UREA}

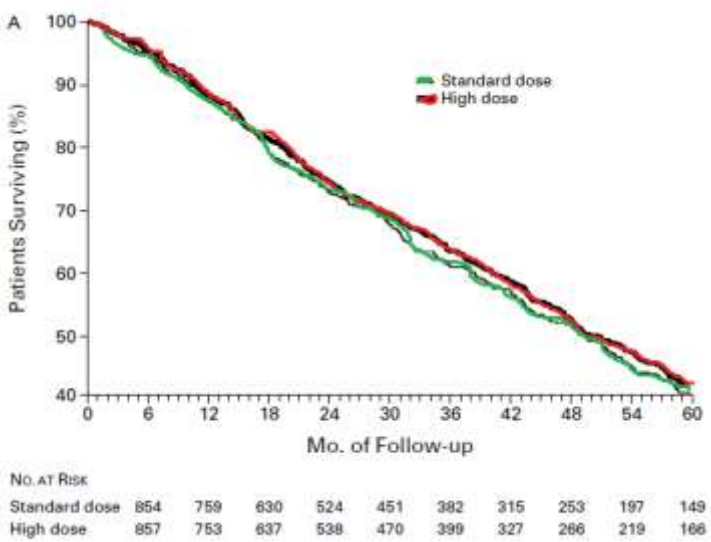


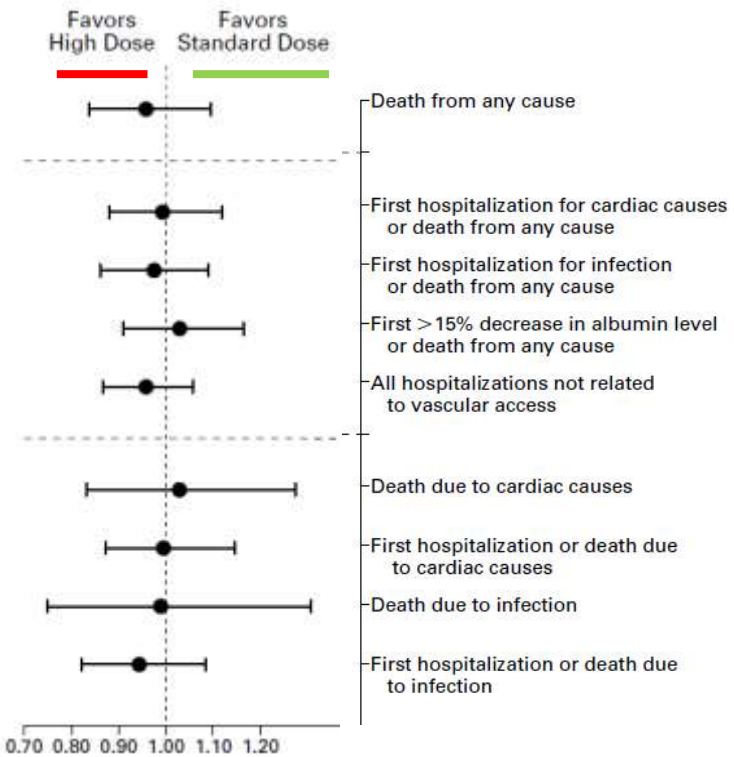


NKF. K/DOQI 2000. Am J Kidney Dis 2001; 37 (Suppl 1): S7 – S64

Hemo Study

- **NIH – Sponsored randomized controlled trial on HD outcomes – 1846 patients**
  - **High dose** dialysis : $spKt/V_{UREA}$ = 1.71 / eKt/V_{UREA} = 1.53 (t:219 min / Q_b : 375 mL/min) *vs*
    Standard dose dialysis: $spKt/V_{UREA}$ = 1.32 / eKt/V_{UREA} = 1.16 (t = 190 min / Q_b: 311 mL/min)

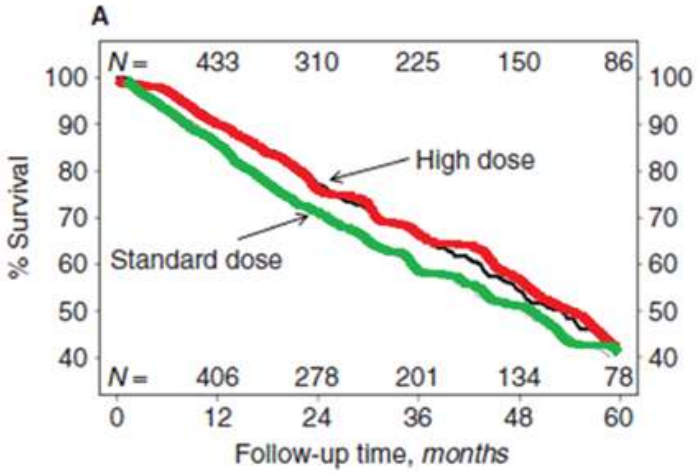




- Validation of the concept of eKt/V_{UREA}
- No major benefit from a higher dialysis dose than that recommanded by KDOQI

Eknoyan G. et al. N Engl J Med 2002; 347 (25): 2010 -2019

Problems with V
(Urea Distribution Volume)



HEMO Study

High Kt/V >
Standard Kt/V

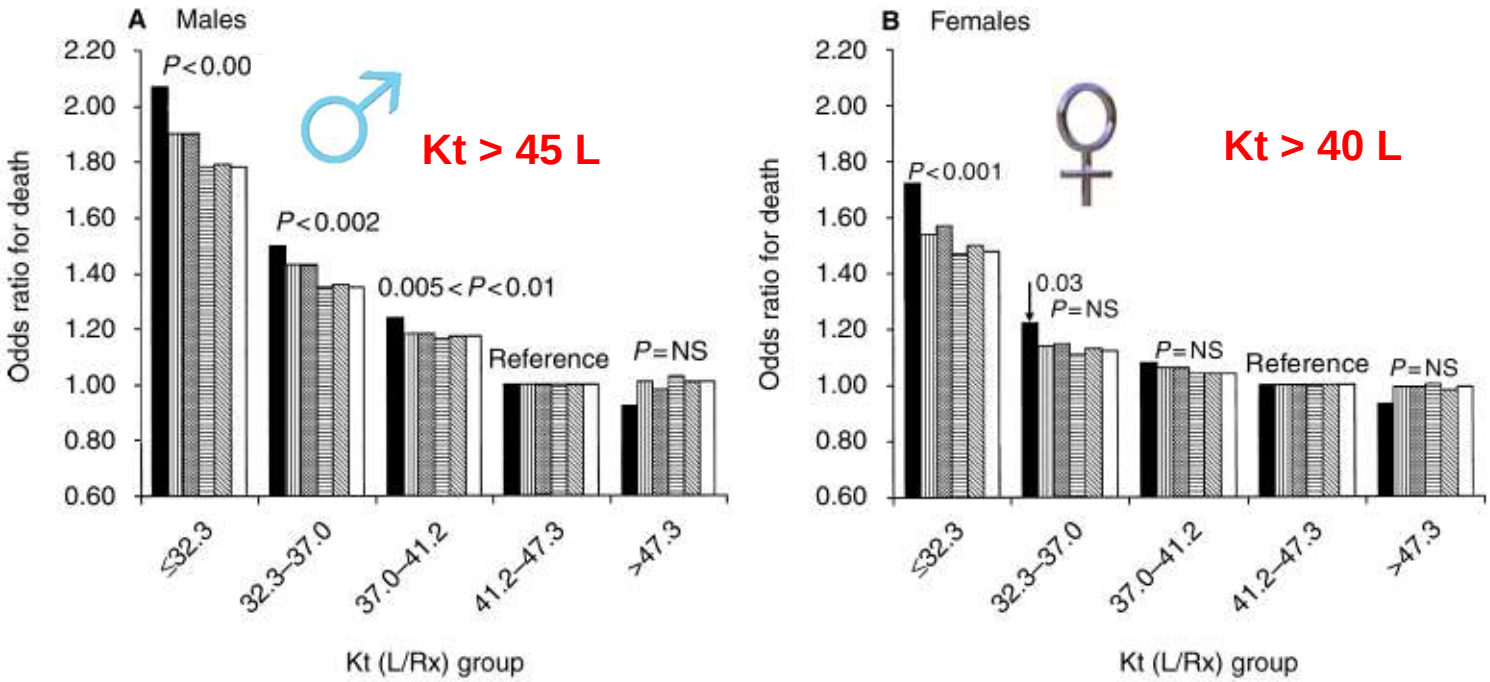
	High Dose			Standard Dose		
	t (min)	Q_b (mL/min)	Kt (L)	t (min)	Q_b (mL/min)	Kt (L)
Male	231	381	**59,6**	200	330	**45,5**
Female	210	367	**51,7**	182	295	**38,2**

Lightest and malnourished patients : Good Kt/V but worst survival

Eknoyan G. et al. N Engl J Med 2002; 347 (25): 2010 -2019
Kopple JD. Et al. Kidney Int 1999; 56: 1136 - 1148

Kt: indicator of Survival

Retrospective Study - 17 141 patients



Kt = Valid outcome-based measure of Dialysis Dose

Lowrie EG. et al. Kidney Int 1999; 56 (2): 729 - 737

Dose of Dialysis: the targets

$eqKt/V_{UREA}$ > 1.2 (= $spKt/V_{UREA}$ >1.4)

AND

Kt > 40 L in women and **Kt > 45 L** in men

In anuric patients treated by three times per week dialysis

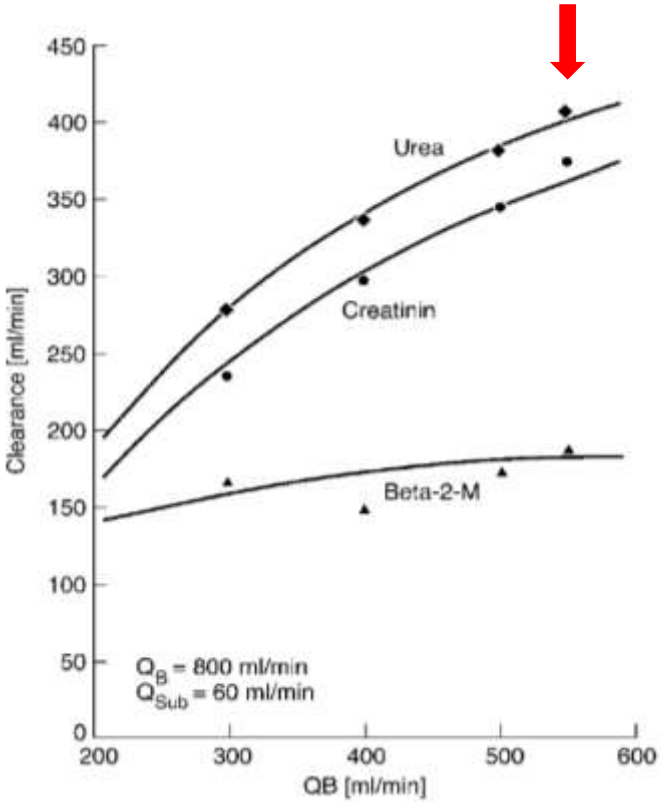
Lowrie EG. et al. Kidney Int 1999; 56 (2): 729 – 737
Tattersall J. et al. Eur Ren Assoc. Mai 2007; 22 (suppl2: ii5-21)

How to achieve these goals ?

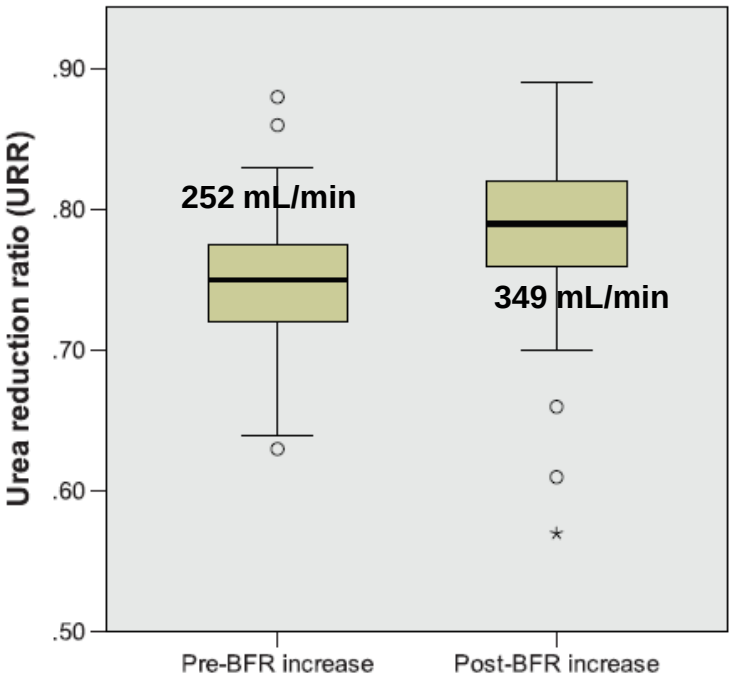
- **Effective clearance k depends on**
  - Dialyzer used
  - Blood flow rate
  - Dialysate flow rate

$$K_oA = \frac{Q_bQ_d}{Q_b - Q_d} \ln\left[\frac{1 - K_d/Q_b}{1 - K_d/Q_d}\right]$$

Impact of blood flow rate



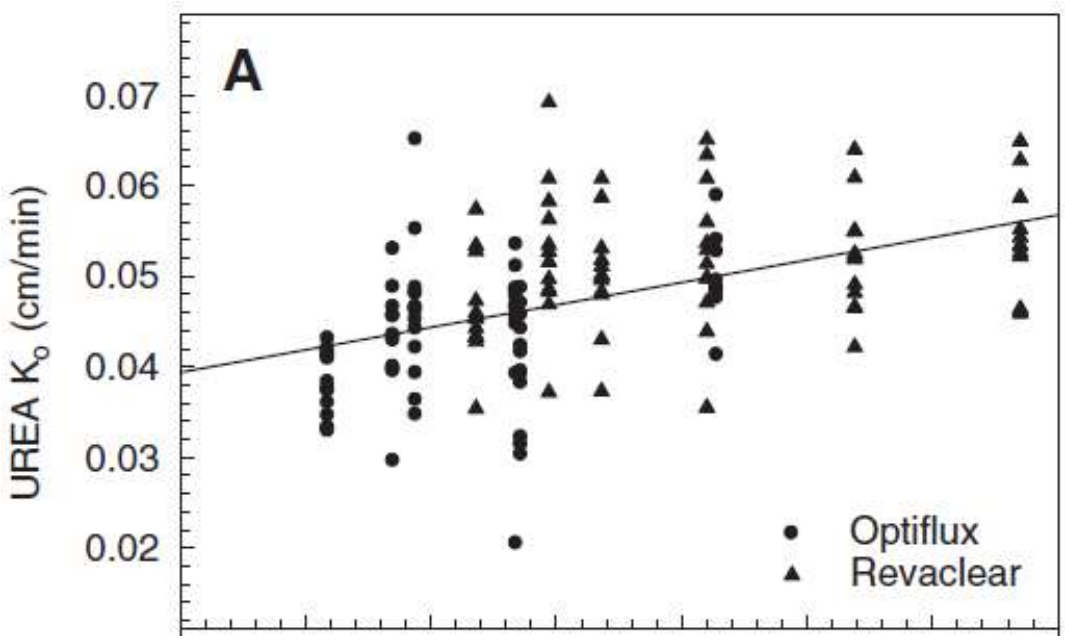
67 HD patients



Wizemann V. et al. Nephrol Dial Transplant 2001; 16 (Suppl 4): 27 – 30
Ryan P. et al. Ther Apher Dial 2018; 22: 494 - 502

Impact of Dialysate Flow rate on Clearance of Urea

20 haemodialysis patients patients - Q_b 400 mL/min – Q_d 350, 500 and 800 mL/min



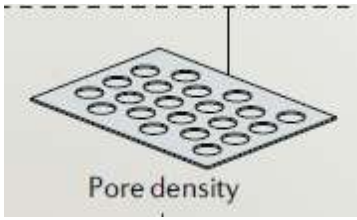
Average Dialysate Velocity

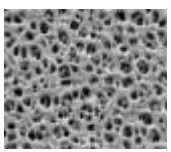
Bhimani JP. et al. Nephrol Dial Transplant 2010; 25: 3990 - 3995

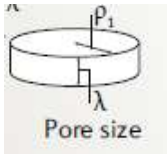
Which Dialyzer ?

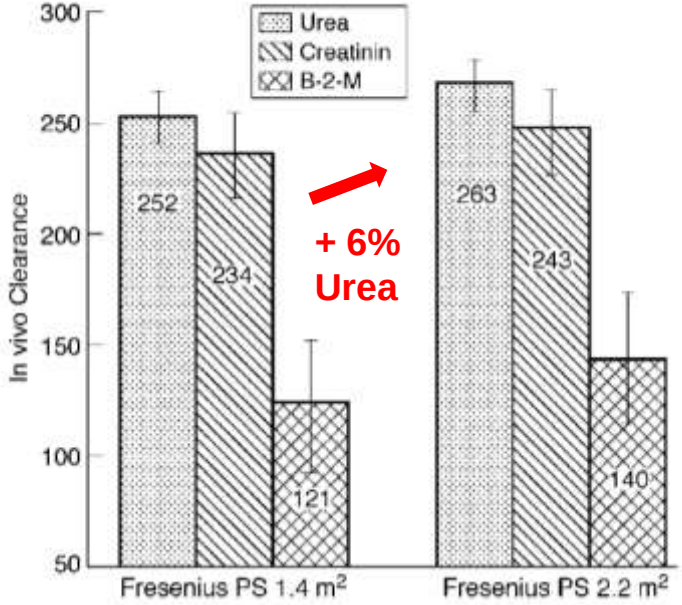
- **Dialyzer with high KoA (> 600)**
  - Depends on physical properties of dialyzer
  - Importance of a greater area

Pore density and Size





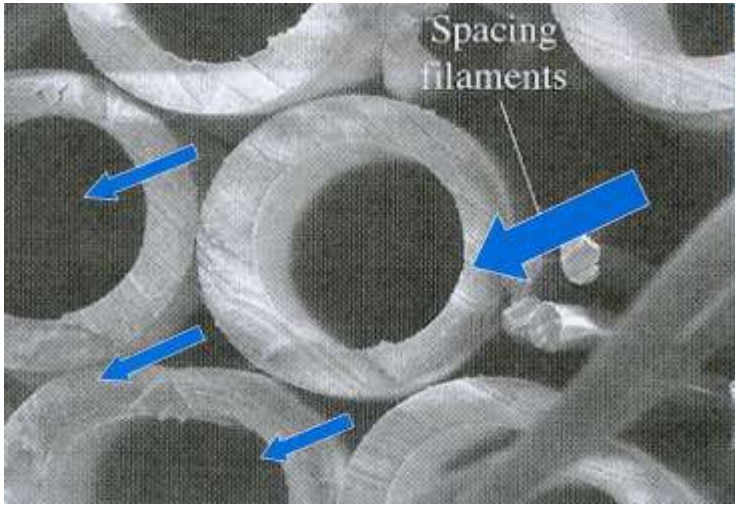




Wizemann V. et al. Nephrol Dial Transplant 2001; 16 (Suppl.4); 27 - 30

Optimization of Surface functionalization

- Improved design of blood flow distributor
- Avoid Dialysate flow channeling: spacing filaments, fiber undulation

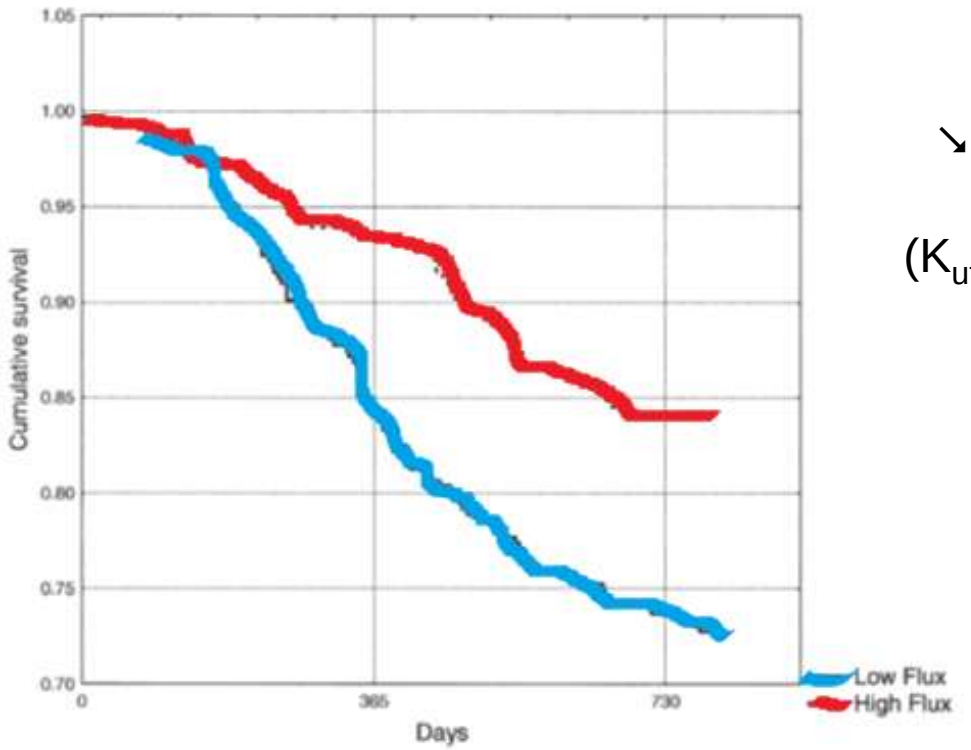


- Anticoagulation adaptation of the circuit

Ronco. C. et al. Nature Reviews Nephrology 2018

High flux Dialyzer

645 hemodialysis patients – Survival over 2 years



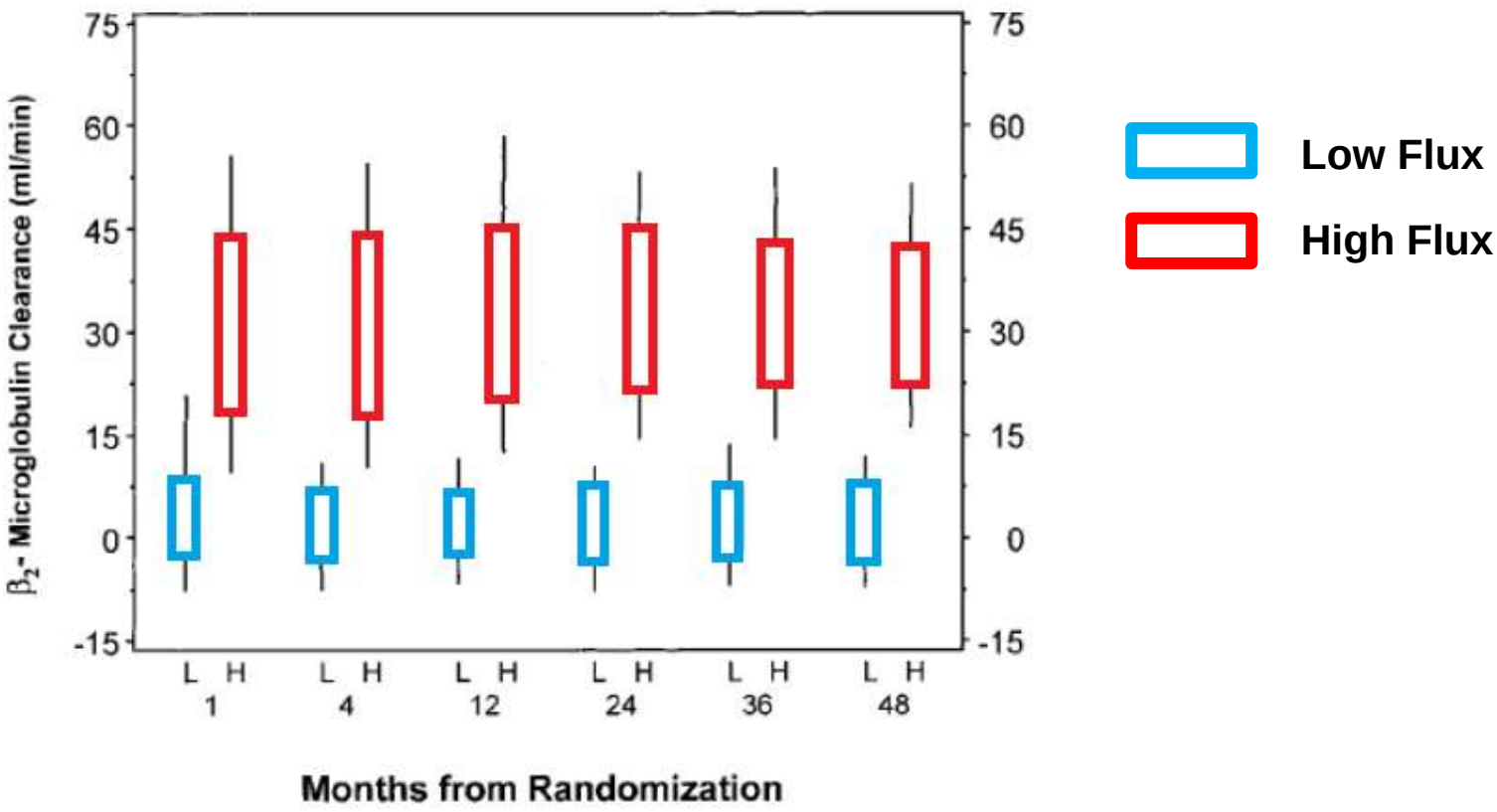
↘ **Mortality 38% with High Flux Membrane**
(K_{uf} > 20 mL/h/mmHg/m^2)

Depends on porosity = Pore Surface / Surface of the Membrane

Chauveau P. et al. Am J Kidney Dis 2005; 45 (3): 565 - 571

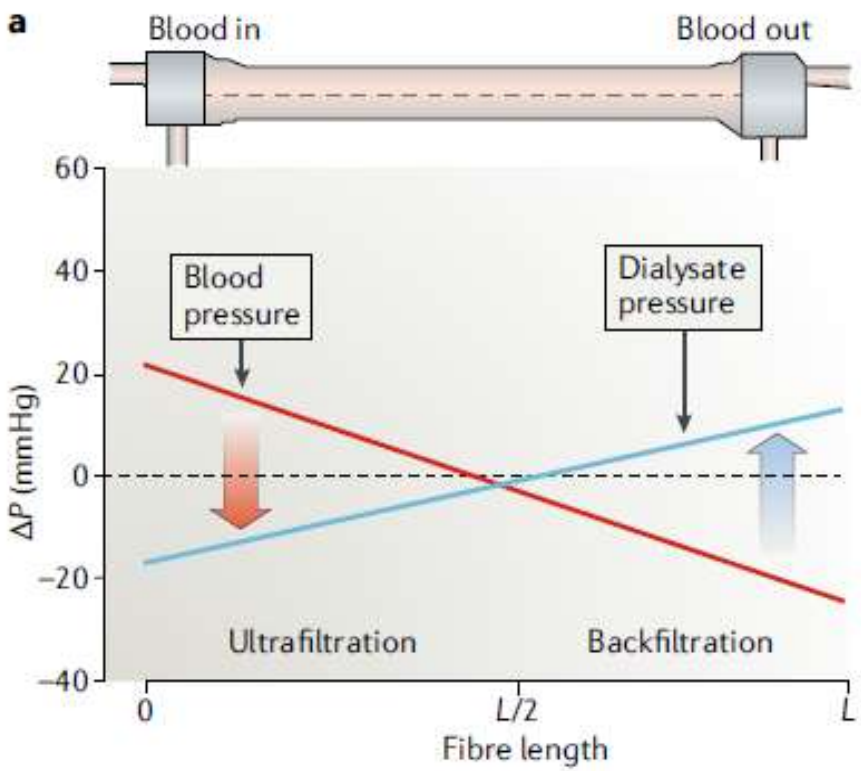
High Flux Dialyzers and clearance of β2m

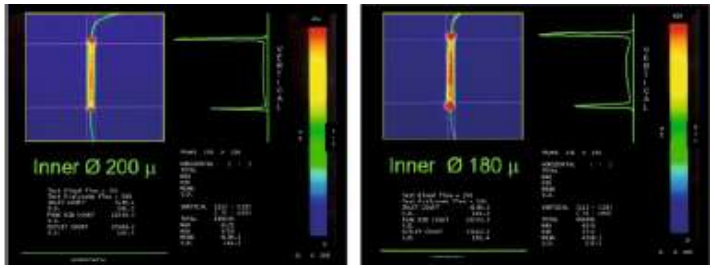
1846 patients from Hemo Study

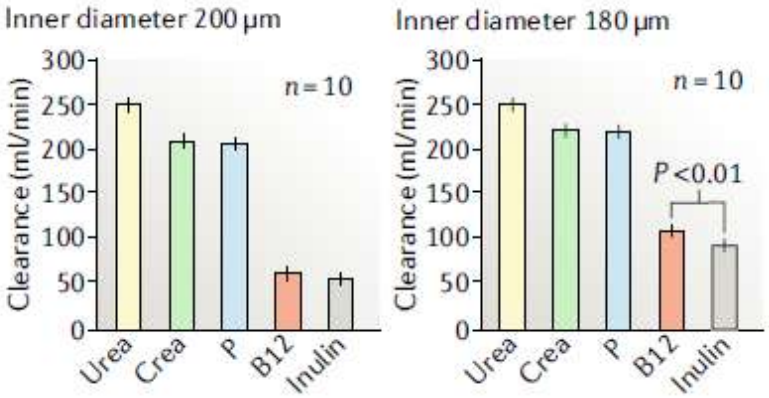


Cheung AK. et al. J Am Soc Nephrol 2003; 14: 3251 - 3263

Impact of Backfiltration on large molecule clearance





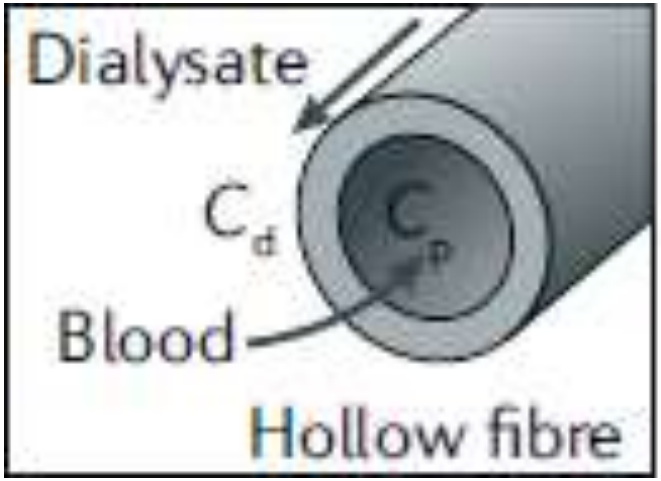


↘ Inner diameter
↗ Fiber Length

Ronco. C. et al. Nature Reviews Nephrology 2018

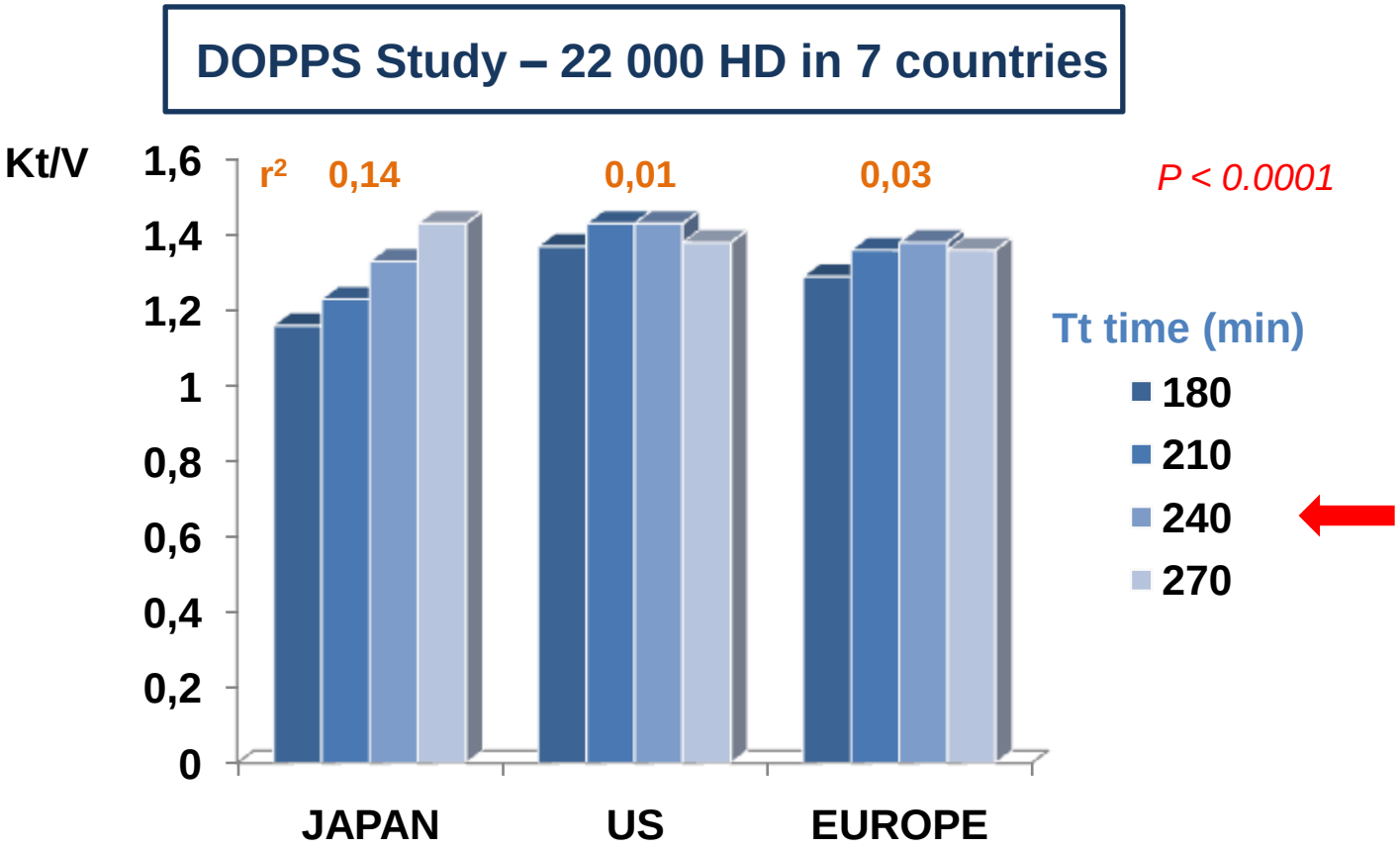
The best is to test dialyzers commercialized by the industry !!!

Optimization of Concentration Gradient of solutes



How to achieve these goals ?

- **Which length of session?**



Saran R. et al. Kidney Int 2006; 69 (7): 1222 - 1228

Longer Treatment Time is associated with lower Mortality

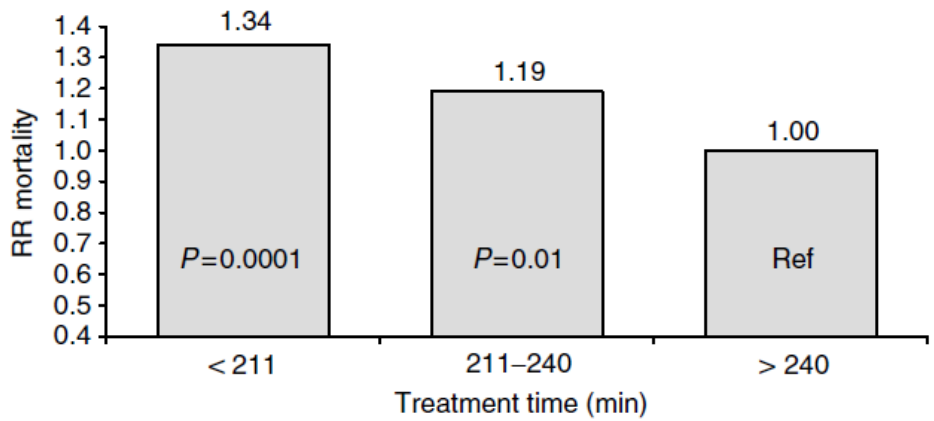
DOPPS

From DOPPS Study (Japan, Europe, Australia and New Zealand, Canada and US)

MORTALITY IN US: 22% Higher than Europe and 40% Higher than Japan

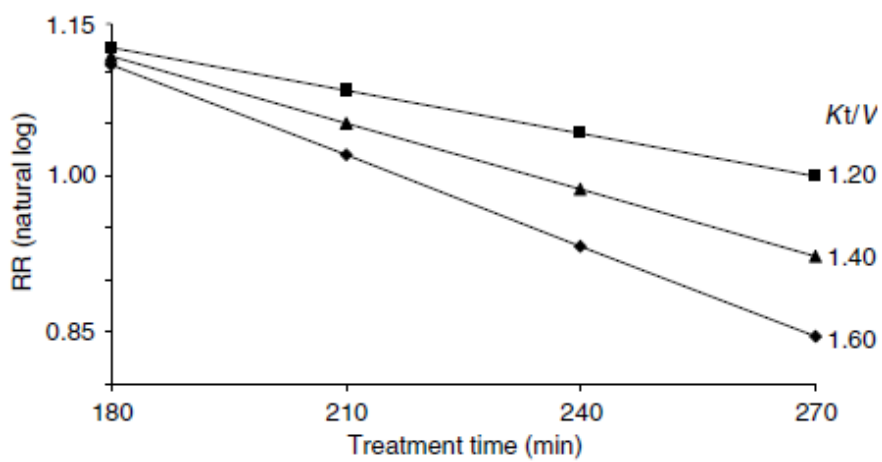
NCDS (p = 0,056)	GE	UK	SP	FR	IT	US	JP
Delivered Dose (Kt/V_{sp})	1,26	1,36	1,31	1,49	1,37	**1,43**	1,37
% $Kt/V_{sp} < 1,2$	45	30	36	17	28	**20**	28
Session Duration (mn)	243	226	214	247	218	**213**	246
KoA (mL/min)	748	740	876	770	740	**860**	866
PrescribedQ_b (mL/min)	247	314	324	294	308	**401**	195

Longer Treatment Time is associated with lower Mortality



↘ 7% mortality for every extra 30 min *(p < 0.0001)*

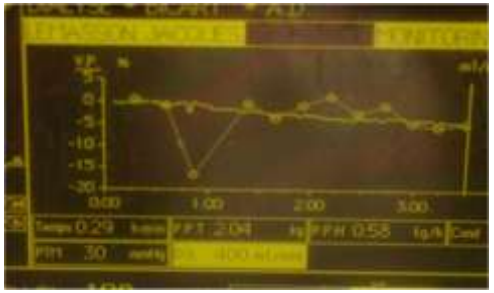
⚠ **18% of dialysis patients 3 times a week have dialysis durations of less than 4 hours (REIN Register 2016)!!**

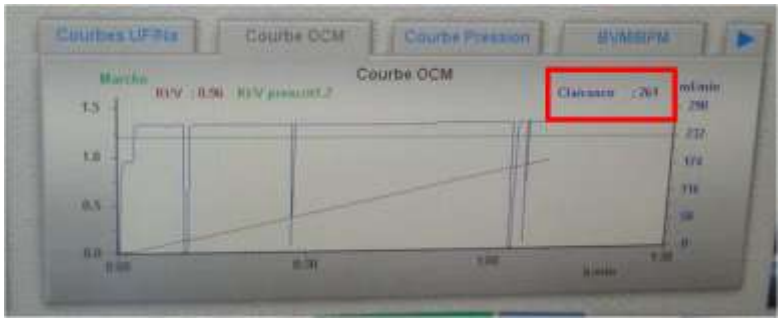


Saran R. et al. Kidney Int 2006; 69 (7): 1222 - 1228

The « V » : What ?

On-line urea clearance estimation on sleceted monitors (K and Kt)





3 methods suitable for routine estimation of V

Anthropometric Watson formula

V_{Wat}

Body composition Monitor (BCM) (FMC) based on bio-impedance

V_{BCM}

Indirect Estimation from measured of Kt / $(Kt/V)_{sp}$ ratio

V_{Daug}

Koubaa A. et al. Nephrol Ther 2010; 6 (6): 532 - 536

The « V » : What ?

15 patients, 25 dialysis sessions
Comparison V_{Wat}, V_{BCM} et V_{Daug} to V_{DDQ} (Gold Standard)

	V_{DDQ}	V_{BCM}	V_{Wat}	V_{Daug}
		- 3%	+ 20%	- 1,3%
Médiane [extrêmes] (L)	29,2 [20,6–40,6]	28,5 [20,3–41,8]	34,5 [24,5–50,1]	28,9 [20,6–37,3]
Moyenne ± S.D. (L)	29,9 ± 5,2	29,1 ± 5,6	36,2 ± 7,1	29,5 ± 4,6
%	42,9 ± 8,2	41,8 ± 8,1	51,1 ± 5,6	42,2 ± 6,8
p		0,02	< 0,001	0,24
r		0,94	0,75	0,85

Koubaa A. et al. Nephrol Ther 2010; 6 (6): 532 - 536

Anemia

Blood pressure

Nutritional Status

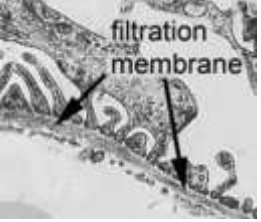
Kt / V_{UREA}

Not alone !!!!

Phospho-Calcium balance

Hemodynamic Stability

Hydro-sodic status

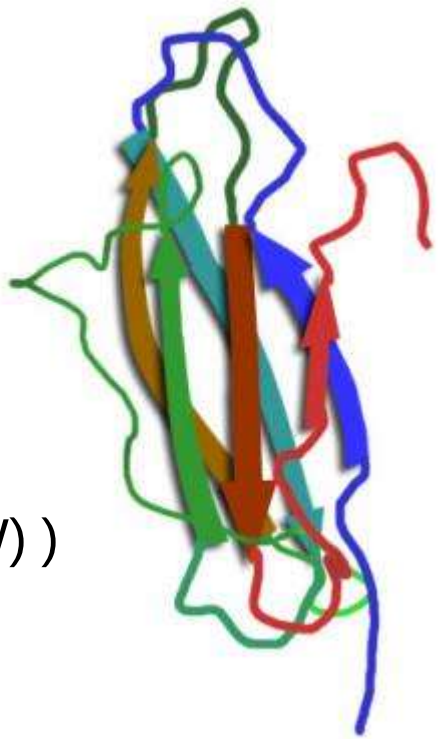


The convective Dose of Dialysis

- **1965 (Seattle Group):** Responsible molecules bigger than urea and creatinine but smaller than molecules in peripheral neuropathy :
  « Middle Molecules »

⇨ **How to remove ?**

- ↗ membrane porosity and membrane surface area
- ↗ duration of dialysis
- Interest of residual renal function
- Convective therapy (HDF1977 (Leber HW))



HDF_{ol} Purification targets

Diffusive dose

$_{eq}Kt/V_{UREA} > 1,2$

AND

Kt > 40 to 45 L

Convective dose

Convective Volume (CV) ???

=

SV

(Substitution Volume)

+

Ultrafiltration

What Convective Dose in HDF post dilution ?

STUDY	Design	n patients	Primary Outcome	Mean CV (Liters)	Results	Results All cause Mortality
CONTRAST 2012	HDF ol post vs HD LF	714	All-cause Mortality	20,7	NS	↘ 39% mortality if CV > 21,95 L
TURKISH 2013	HDF ol post vs HD HF	782	Composite Death from any cause and non fatals CV evts	20,7	NS	↘ 46% mortalité if SV > 17,4 L
ESHOL 2013	HDF ol post vs HD HF	906	All-cause Mortality	23,7	↗ 30% Survey with HDF	↘ 40% and 45% mortality if CV > 23 L and 25 L

Grooteman M. et al. J Am Soc Nephrol 2012; 23: 1087–1096
OK E. et al. Nephrol Dial Transplant 2013;28: 192 - 202
Maduell et al. J Am Soc Nephrol 2013; 24: 487-497

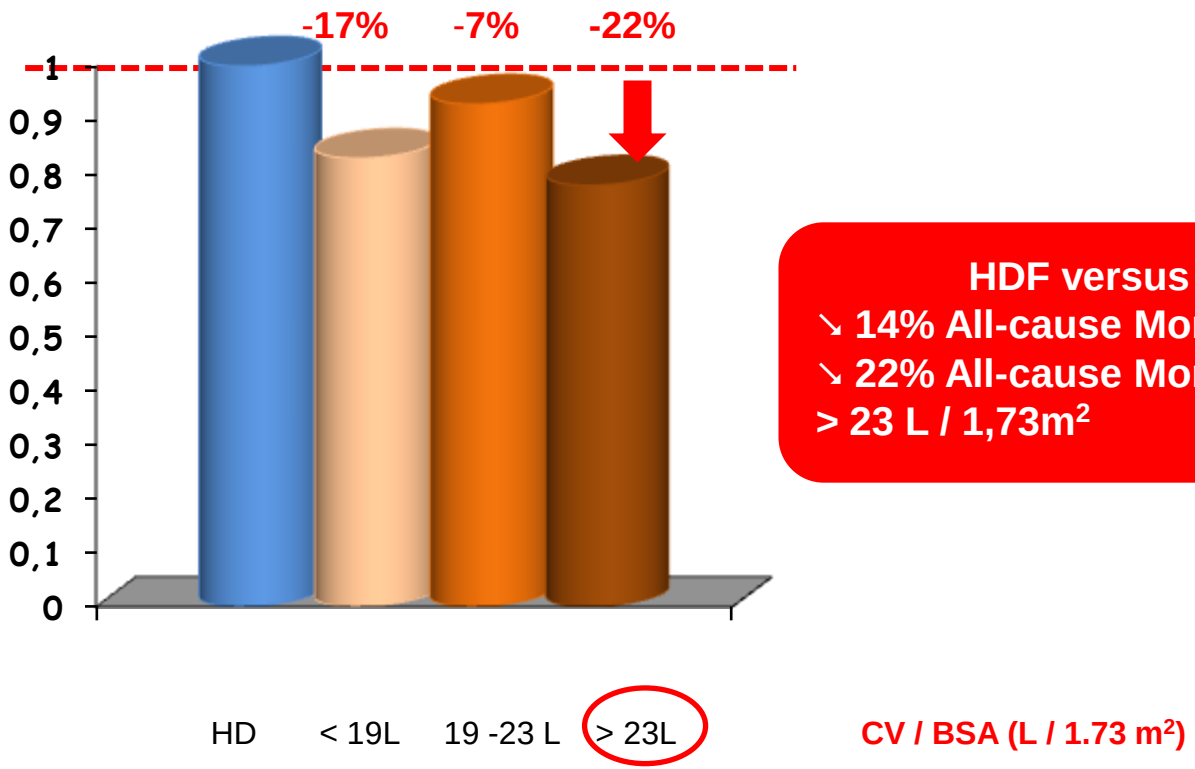
What Convective Dose in HDF post dilution ?

HDF OI post dilution and mortality (HDF vs HD)
4 large multicenter RCTs : CONTRAST, ESHOL, French Study et Turkish Study

2793 patients – Mean age 64 years – Mean Q_b 337 mL/min – mean follow-up: 2.5 years
BSA adjusted Convection Volume

RR All-cause Mortality

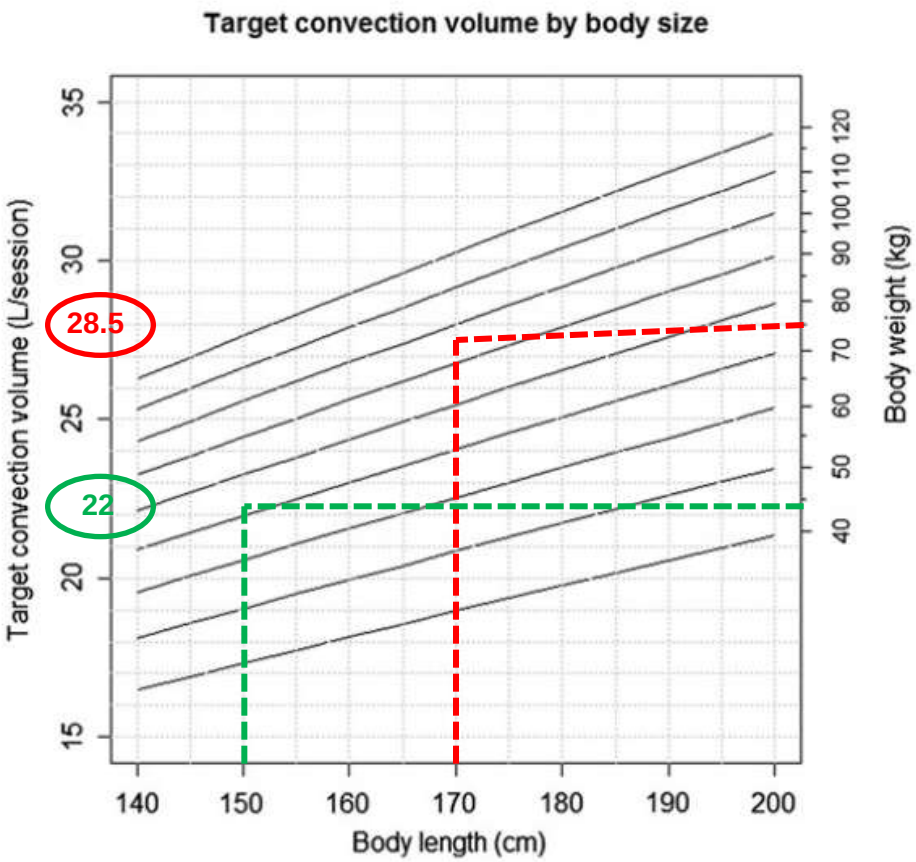
(Ajusted for age, sexe, albumin, c réatinin, diabetes, Hi story of CVD)



HDF versus HD
↘ 14% All-cause Mortality
↘ 22% All-cause Mortality if CV > 23 L / 1,73m²

Peters S. et al. Nephrol Dial Transplant 2016; 31: 978 - 984

What Convective Dose in HDF post dilution ?



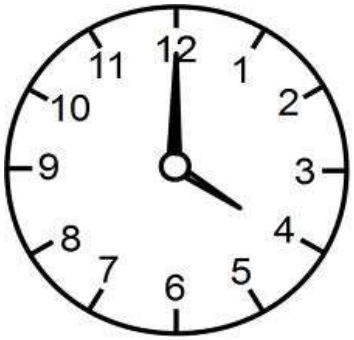
VC target per session

CV > 23,1 L
AND
CV/BSA > 23 L / 1.73 m²

Peters S. and coll. Nephrol Dial Transplant 2016; 31: 978 - 984

Determinants of convective Volume

Albumin and protide and :

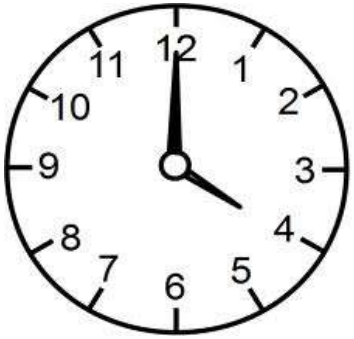


+ 10 min → CV: + 0.9 L

Lars Penne et al. Nephrol Dial Transplant 2009;24: 3493-3499

Determinants of convective Volume

Albumin and protide and :

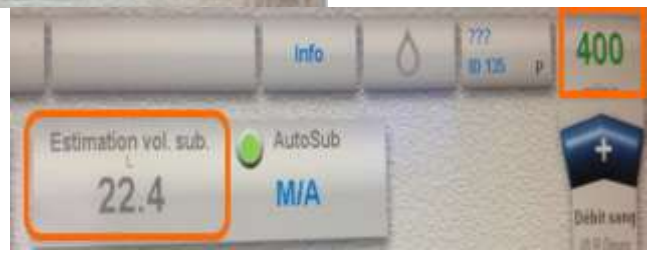


+ 10 min → CV: + 0.9 L

CV
+ 53.4 %

Lars Penne et al. Nephrol Dial Transplant 2009;24: 3493-3499

What Blood Flow (Q_b) in HDFol Post dilution ?



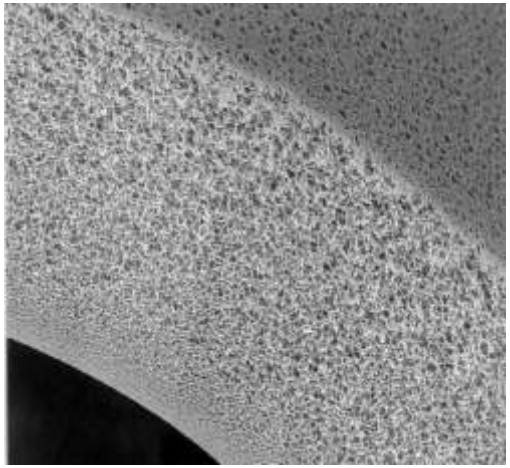
CV
+ 53.4 %

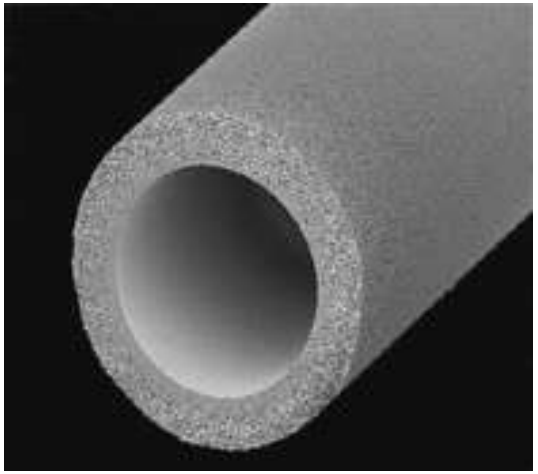
	Mean duration (min)	Mean Q_b (mL/min)	Mean CV (L)
CONTRAST	226	300	20,7
TURKISH	236	310	20,7
ESHOL	236	387	23,7

Lars Penne et al. Nephrol Dial Transplant 2009;24: 3493-3499

Which Dialyzer in HDF post dilution ?

Synthetic, biocompatible,
K_{UF} > 40 mL/h.m^2.mmHg
High KoA and SC





Which Dialyzer in HDF post dilution ?

PERFORMANCE + **SECURITY**

RR β2m > 80%
(CT β2m > 0,6)

RR Myoglobine > 65%

CV (SV + UF)
>23 L and 23L/ 1,73 m^2BSA

Loss of albumin
< 5g / session

Kim S. Contrib Nephrol. Basel, Karger 1994; 108: 23 - 37

Kawanishi H : Hemodiafiltration . Contrib Nephrol. Basel, Karger 2011; 168: 146 – 152

EUDIAL. Nephrol Dial Transplant 2013; 22: 542 - 550

Which Dialyzer in HDF post dilution ?

Q_b 400 mL/min Q_D 800 mL/min Q_S 108 mL/min (mean SV: 25,9 L)

RR ß2m

	Loss of Albumin	
	≤ 5 gram	> 5 gram
100%	FX 1000, Cordiax Pureflux, Elisio VitaPES,TS SL APS 21 U/H, Renak	APS 1050 REXEED 21 FDY 210 PHYLTER 22 S
80%	TS 2.1 UL FX 100 EVODIAL 2.2 BG 2.1	
60%		

CHU Hôpitaux de Rouen

Le Roy et al. Oral communication Société de Néphrologie Toulouse 2009

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Le Roy et al. Oral communication Société de Néphrologie Toulouse 2009

Generator with **Automated** Infusion

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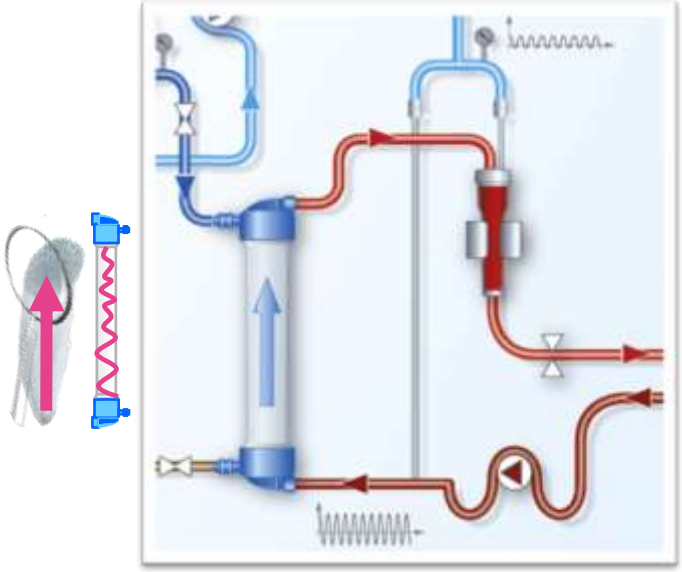
« Pressure Controlled » Mode optimized



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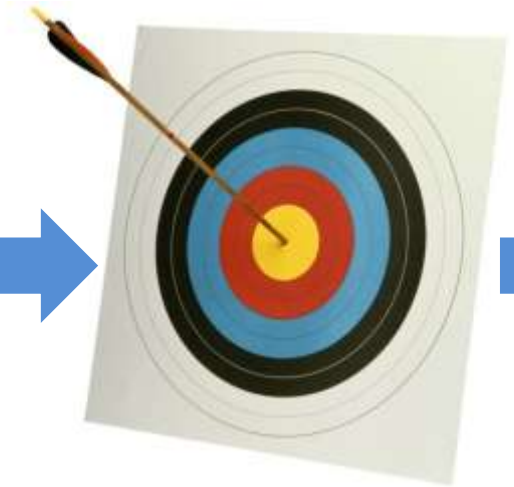
Prescribing the Dose of dialysis

$_{eq}Kt/V_{UREA} > 1,2$
AND
Kt > 40 to 45 L

Prescriptions
- Q_b
- Q_d
- Membrane
- …..



Evaluation
+++

Corrective Actions

CV > 23,1 L
AND
CV/BSA > 23 L / 1.73 m^2