Hemodiafiltration: practical points

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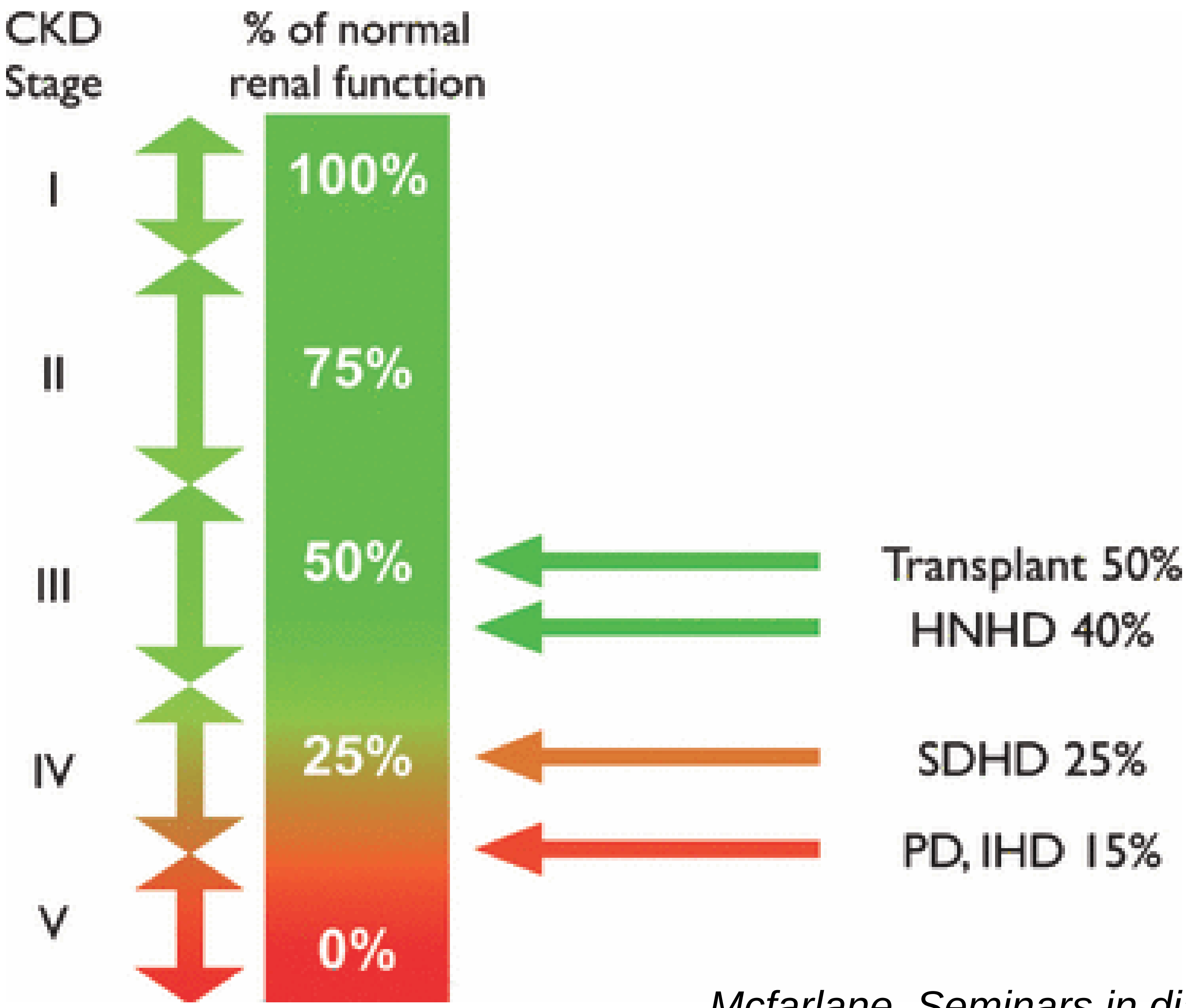
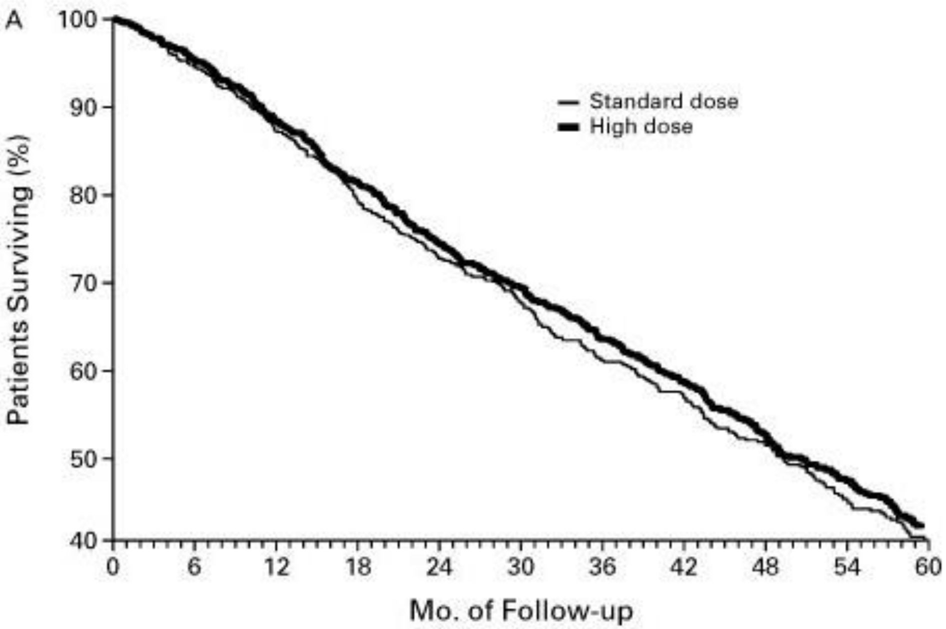
Effectiveness of RRT modalities

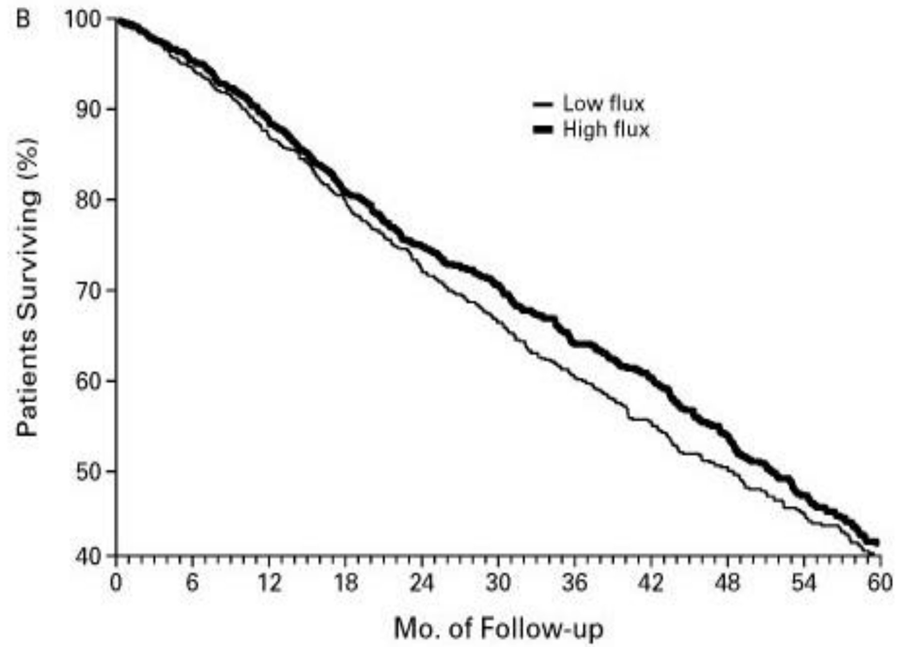


Mcfarlane, Seminars in dialysis, 2009

No benefit from increased urea clearance



No. at Risk										
Standard dose	854	759	630	524	451	382	315	253	197	149
High dose	857	753	637	538	470	399	327	266	219	166



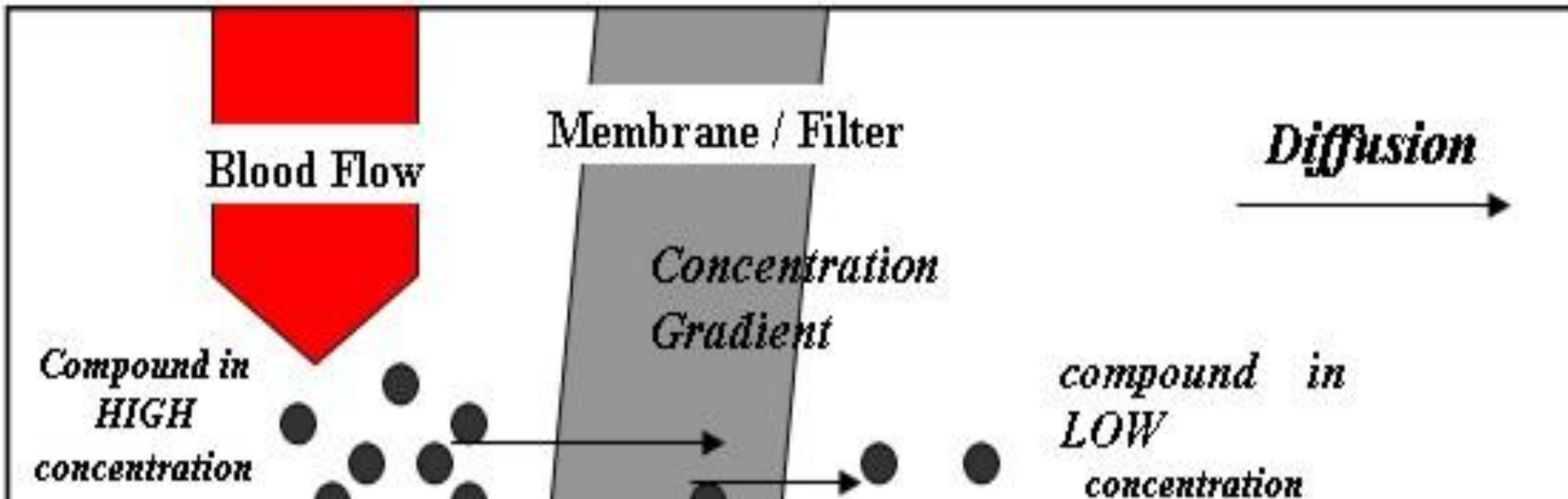
No. at Risk										
Low flux	851	750	632	525	446	383	307	250	203	149
High flux	860	761	635	537	473	399	335	269	212	160

HEMO study, NEJM, 2002

Outline

- Mechanisms of hemodiafiltration (HDF)
- Theoretical advantages of HDF vs HD
- Clinical benefits of HDF vs conventional HD
  - lessons from adult studies
  - focus on growth and nutrition
- Practical aspects of setting up HDF in your unit

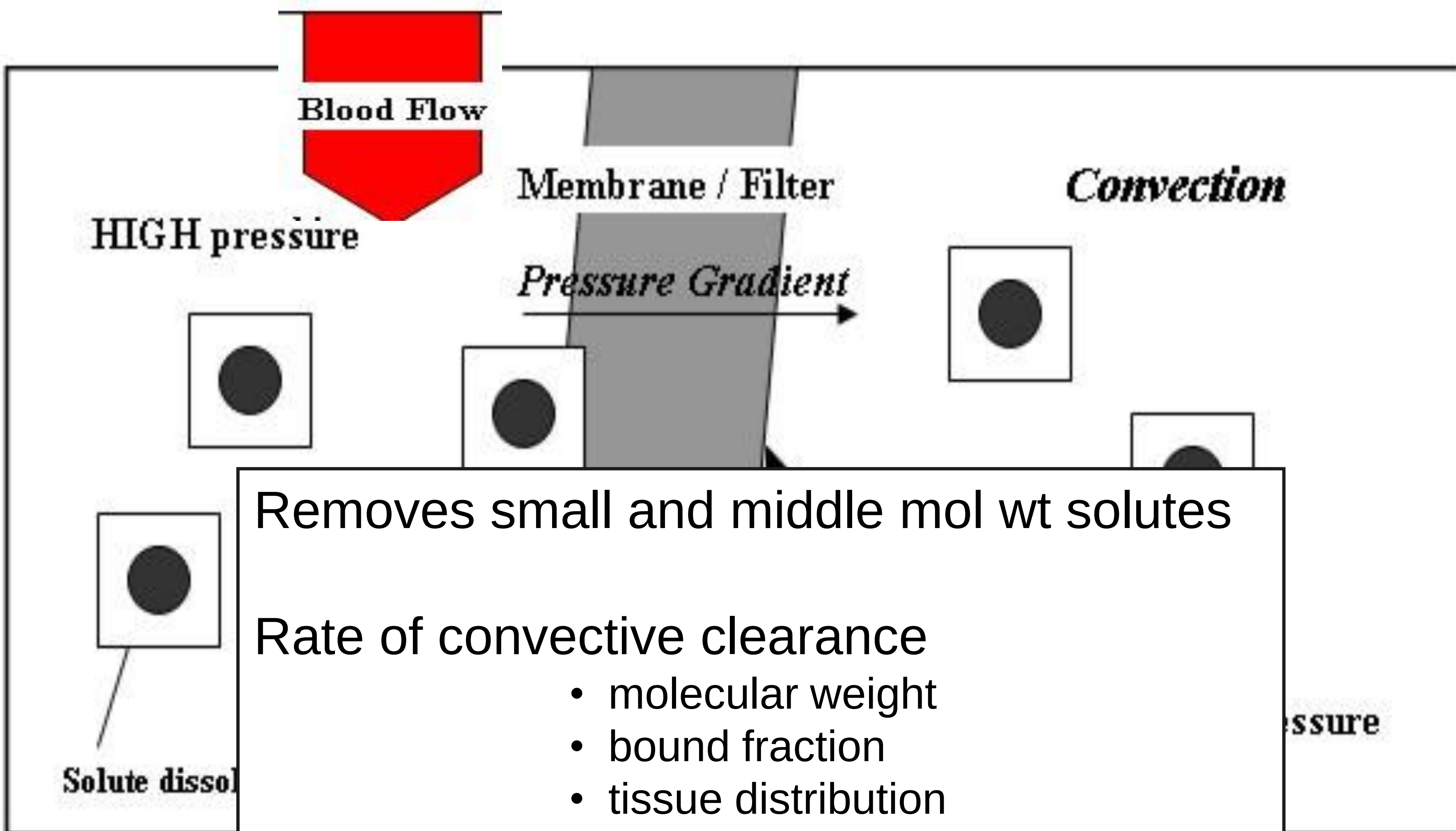
Diffusion



Rate of diffusion $\propto$ concentration gradient
$\propto 1/\sqrt{\text{mol weight}}$

Excellent removal of small molecules
Very little effect on large solute removal

Convection

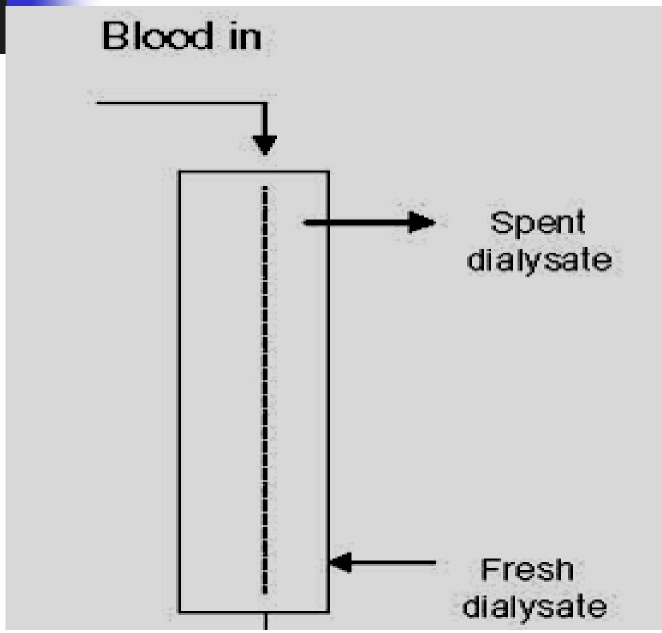


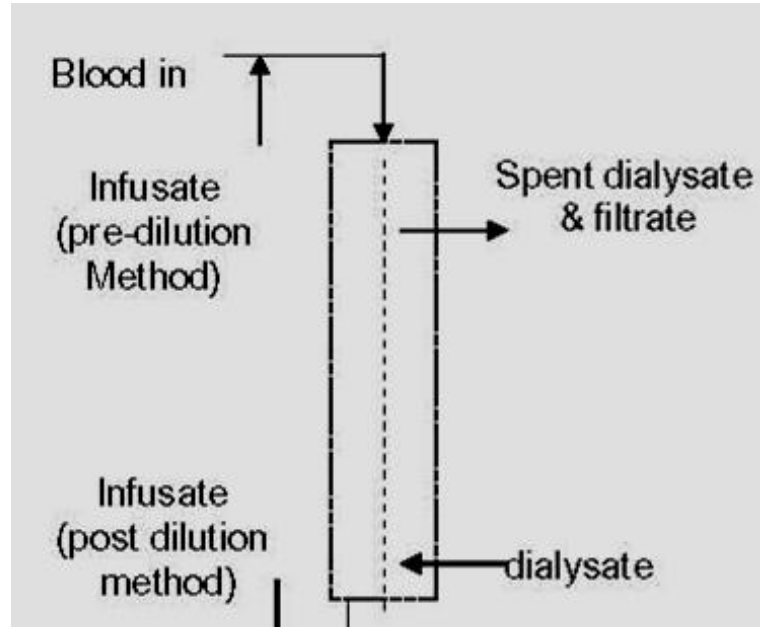
Removes small and middle mol wt solutes

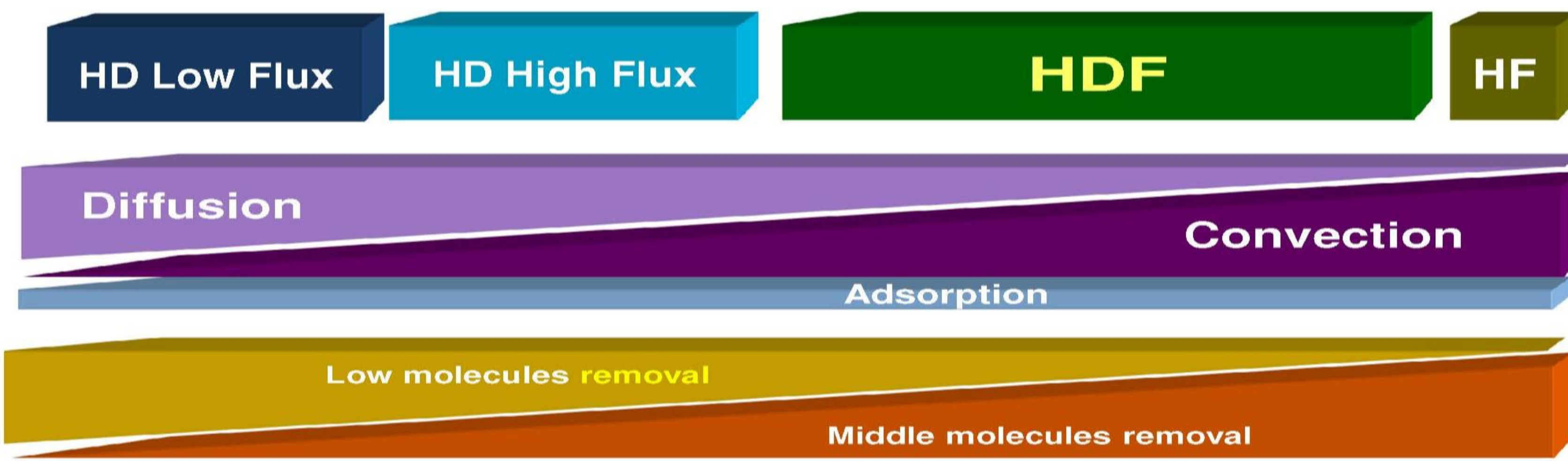
Rate of convective clearance

- molecular weight
- bound fraction
- tissue distribution
- sieving coefficient (KoA & KUF)

HDF – clearance by diffusion and convection







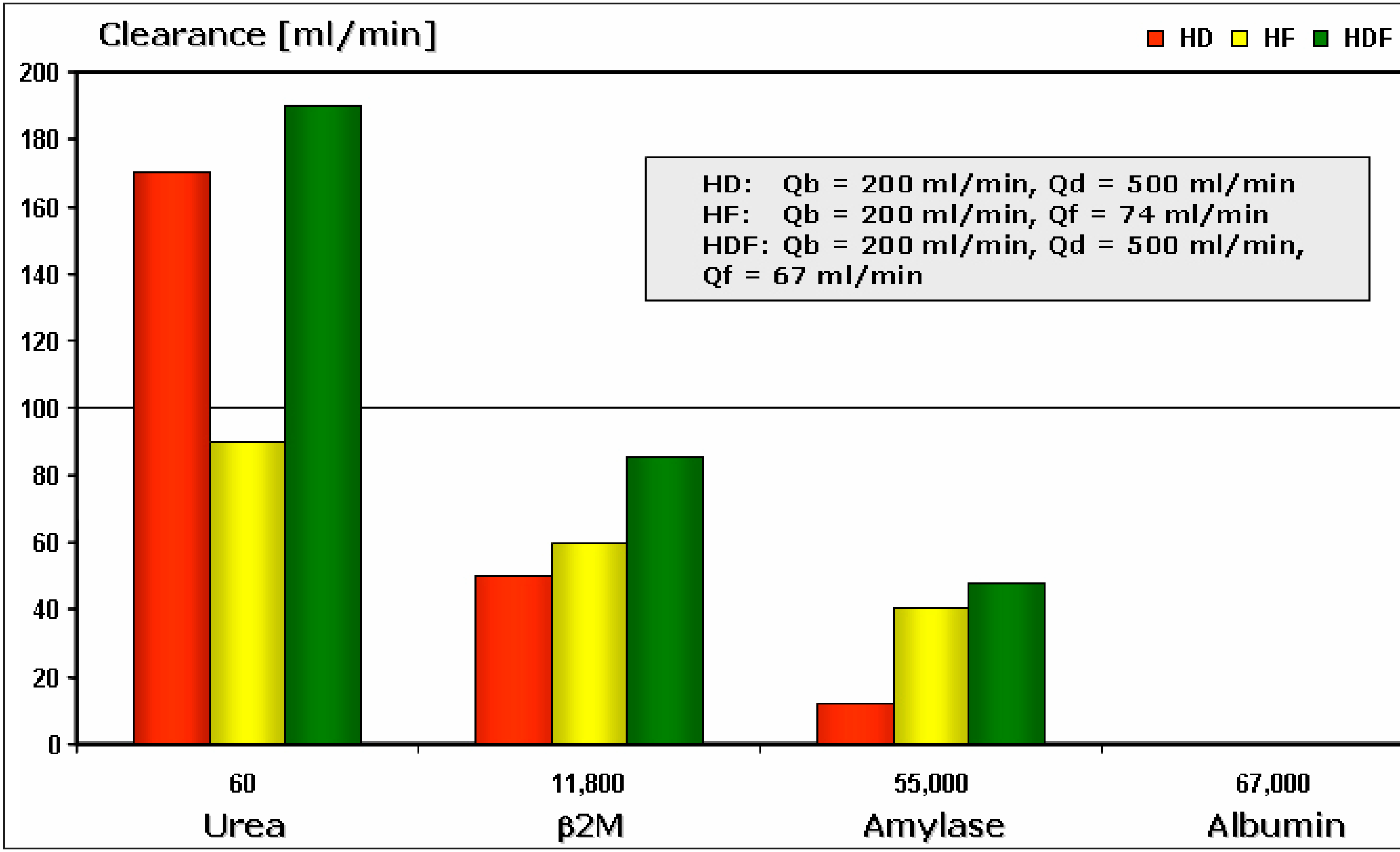
Advantages of HDF

1. Clearance of uraemic solutes across a wide molecular weight range

2. Biocompatibility

3. Hemodynamic stability

1. Clearance on HDF vs HD



$\beta_2$microglobulin clearance

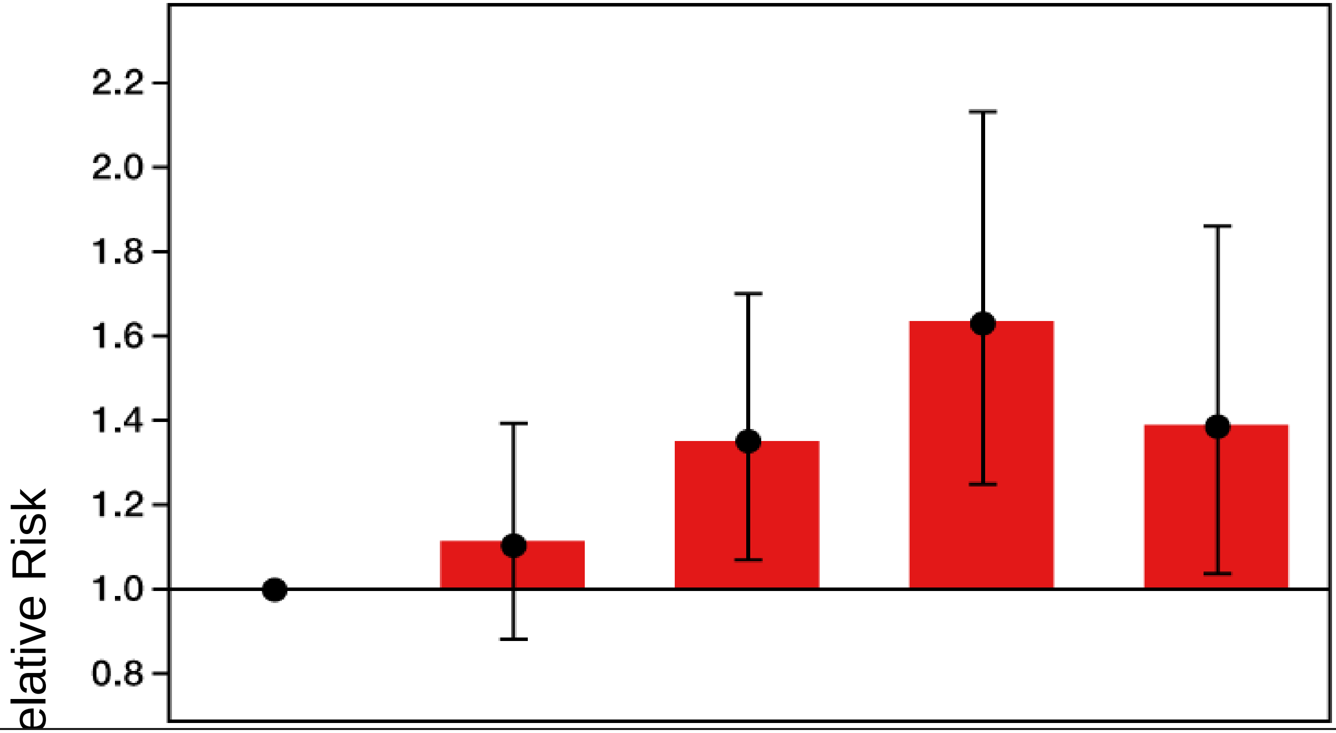
- HDF achieves 70 – 78% reduction in β_2 microglobulin (vs 40 – 50% with high-flux HD)
  Thomas et al, Semin Dialy, 2009

- No signs of amyloidosis after 8 yrs on HDF (vs 100% pts on HD have amyloid by 13 yrs)

  Canaud et al, NDT, 1998

- 82% reduced incidence of carpal tunnel syndrome and 67% reduced incidence of erosive arthritis
  Dember et al, Semin Dialy, 2006

Predialysis $ß_2m$ levels correlate with mortality (HEMO Study)



For every 10 mg /l increase in predialysis B_2M there is a 11% increase in the relative risk of death

Cheung et al, JASN 2000

Other middle molecules cleared by HDF

- Parathyroid hormone
- Inflammatory cytokines (IL-6, IL-8, IL-12)
- Homocysteine
- Guanidine
- Polyamines

Influence endothelial function:
- Reduce nitric oxide production
- Promote AGE formation
- Affect cell cycle and cause senescence

- Appetite suppressants (leptin, cholecystokinin, tryptophan)
- Complement factor D

2. Reduced inflammation and oxidative stress

1. reduces inflammation (↓ TNFα, IL-6, IL-8, IL-12)
2. suppresses oxidative stress (↓ reactive oxygen species and superoxide)
3. improves antioxidant capacity
4. reduces generation of AGEs

Mechanisms

1. Biocompatible membranes
2. ‘Ultrapure’ dialysate
3. Removal of cytokines

Chronic low-grade exposure to endotoxins

- Chronic inflammation
- Anorexia, poor nutrition and growth, catabolism, loss of lean body mass – cachexia
- Anaemia – poor ESA response
- Risk of atherosclerosis

Malnutrition – inflammation – atherosclerosis complex

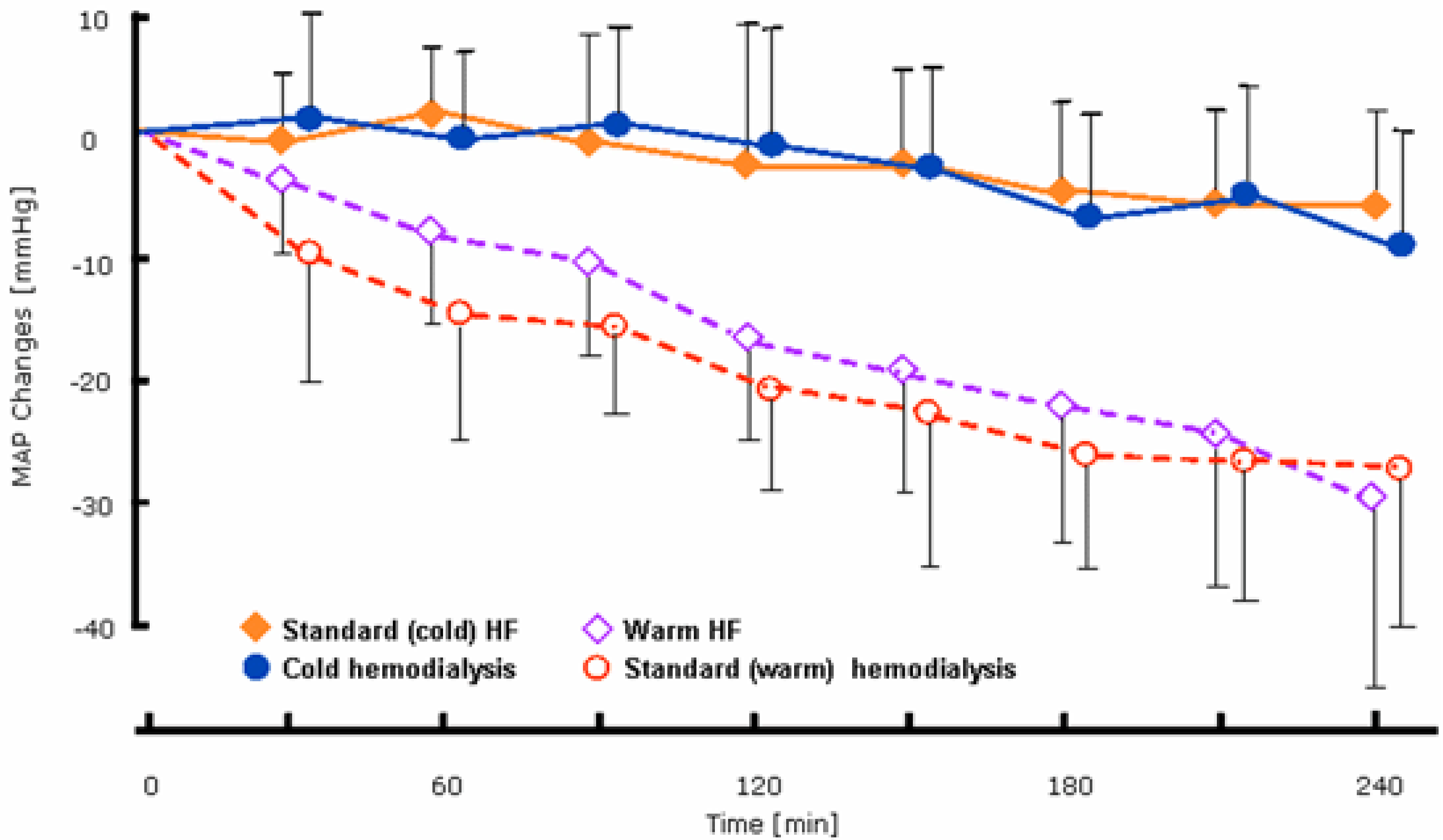
3. Hemodynamic stability

1. Fewer intra-dialytic hypotensive episodes
2. Higher UF better tolerated by patient
3. Reduced post-dialysis fatigue
4. Overall better BP control

Mechanisms:

1. Cooling of dialysate
2. Removal of vasodilating mediators
3. High Na content of infusion fluid

Cooling is a part of on-line HDF

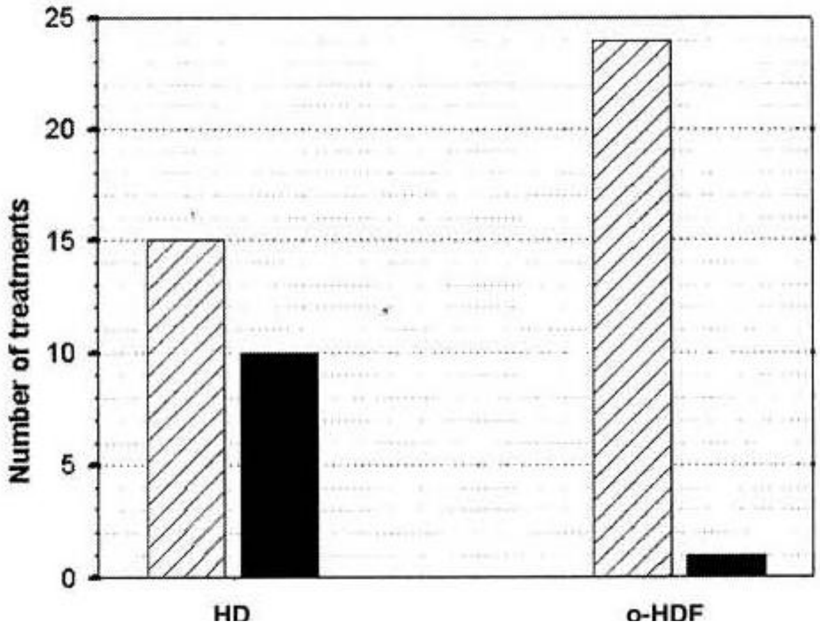


Based on Maggiore Q, et al. *Trans Am Soc Artif Intern Organs* 28: 523-527, 1982

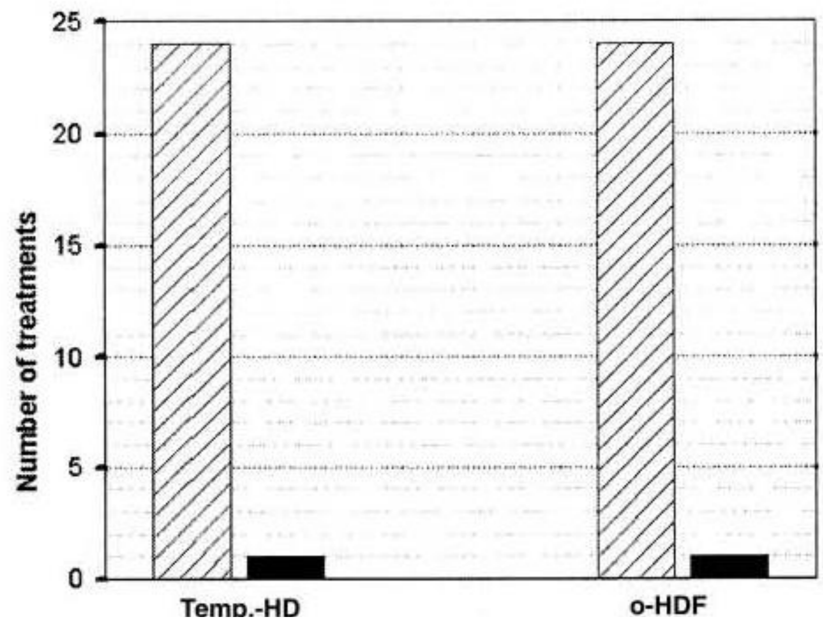
Reduced risk of intra-dialytic hypotension on HDF

- Blood returning to the patient is cooler during o-HDF than HD - enhanced energy loss within the extracorporeal system

- In the patients' circulation the mean blood temperature is lower during o-HDF than HD



Without cooling of HD dialysate

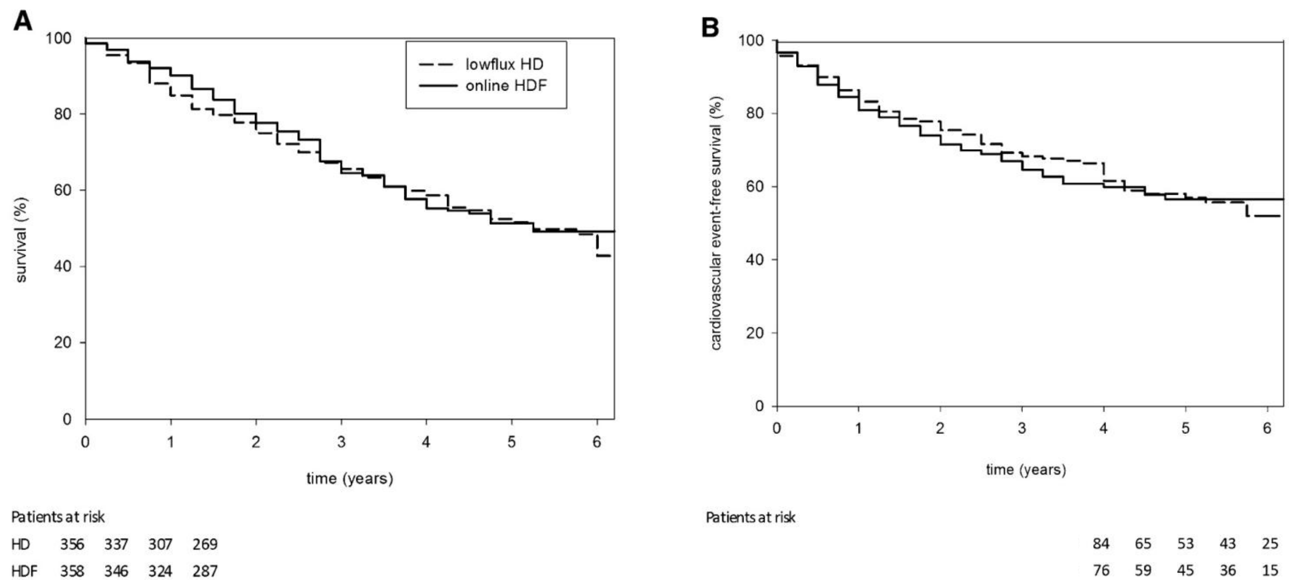


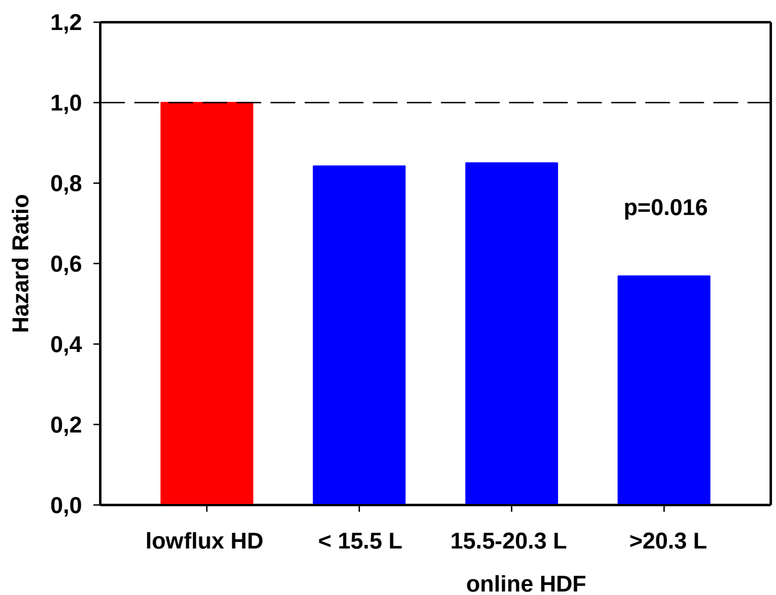
Cooling of HD dialysate

Blankestijn et al, KI, 2010

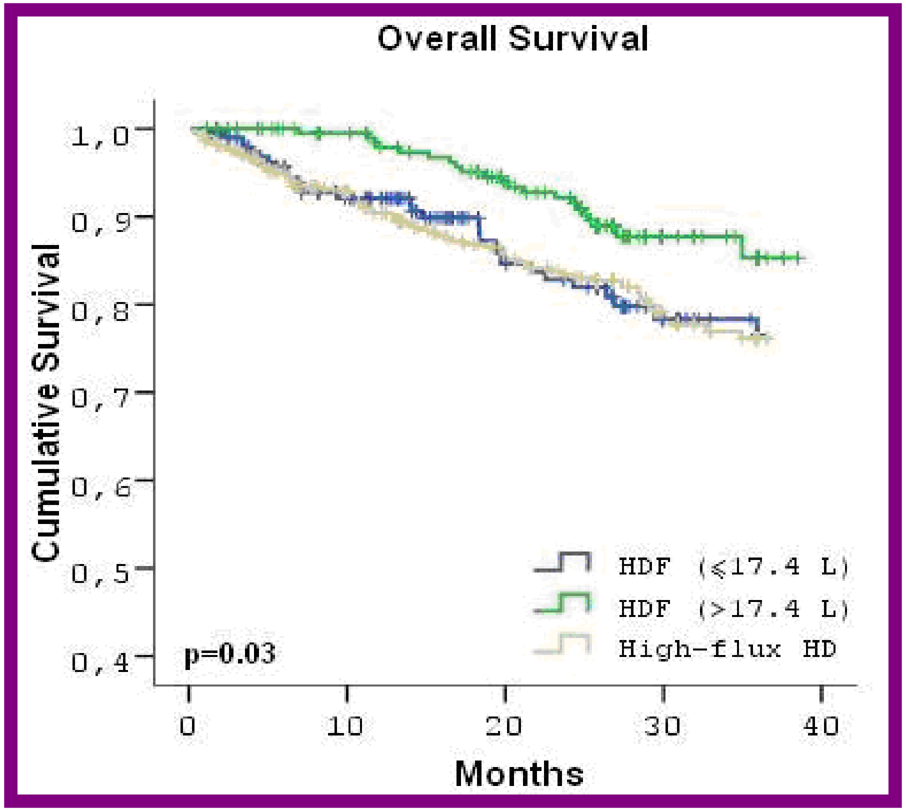
Cardiovascular and survival advantage of HDF vs HD

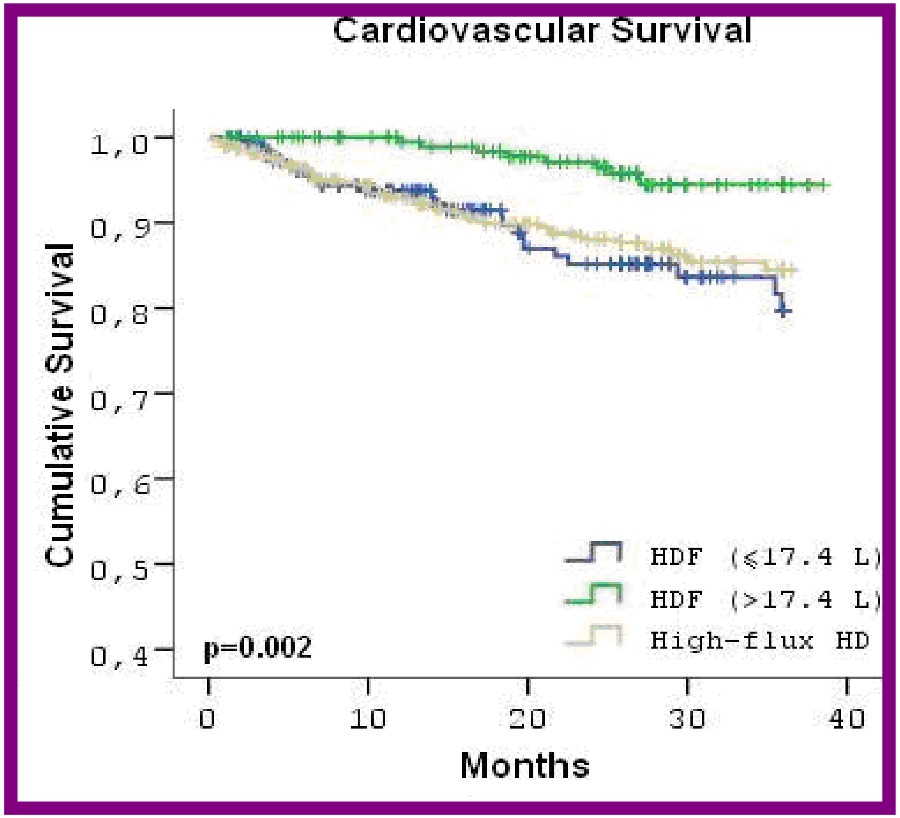
1. Dutch HDF Study: CONTRAST





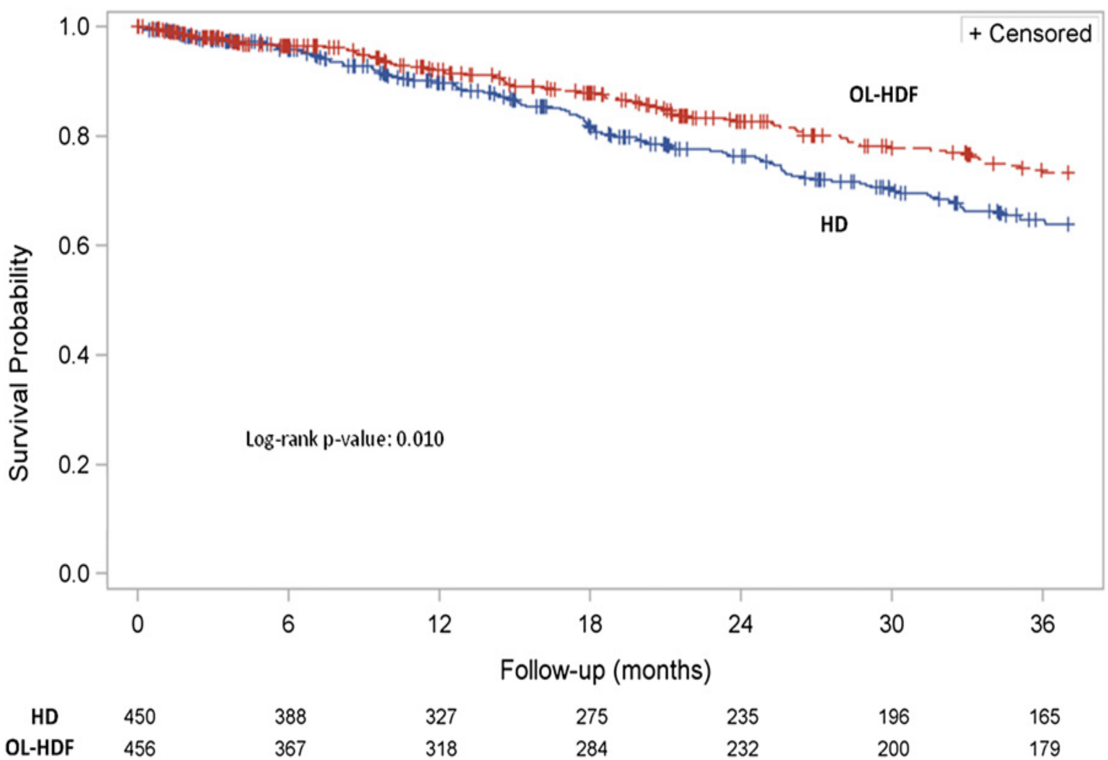
2. Turkish HDF Study: High vs Low Efficiency HDF

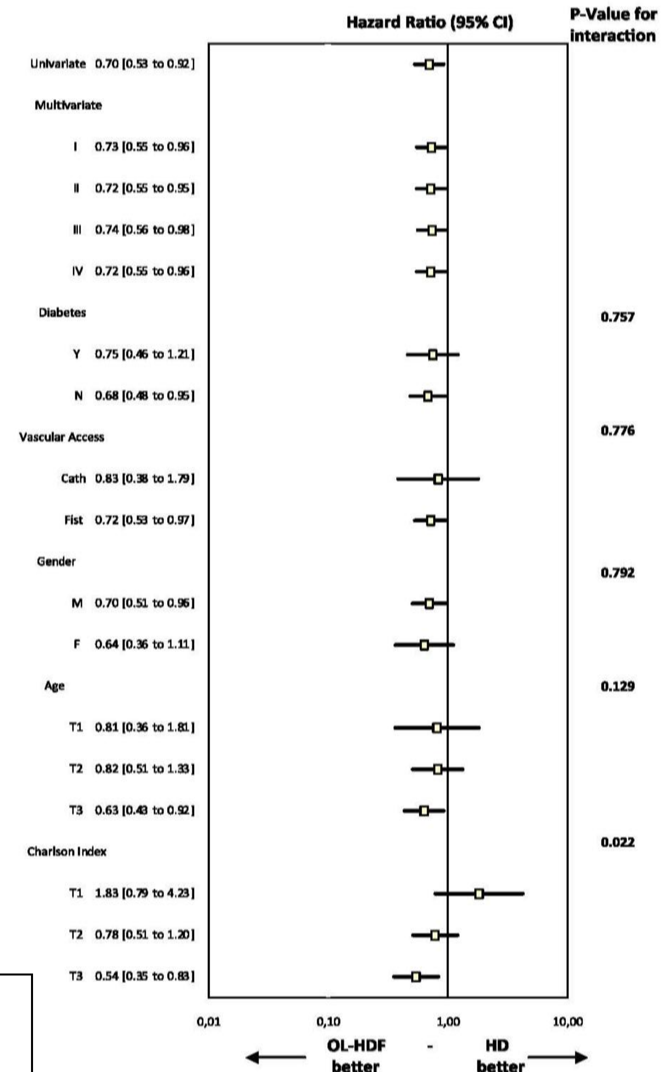




OK E; Kircelli F; Turkish Online Haemodiafiltration Study; NDT 2013

3. Spanish HDF Study: High vs Low Efficiency HDF





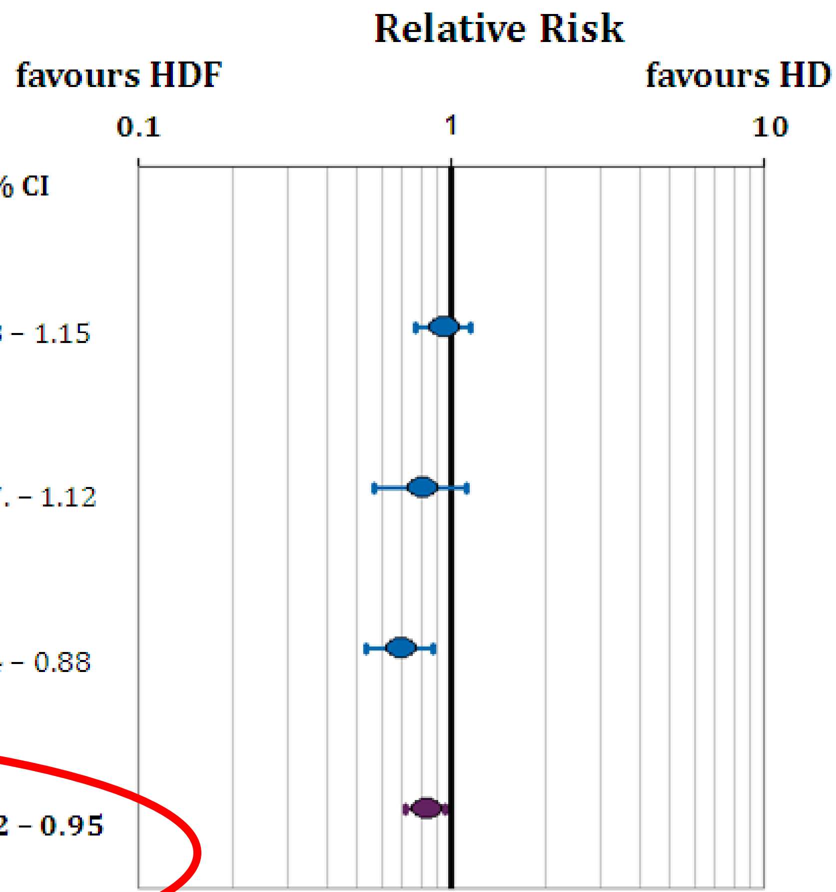
switching 8 patients from HD to HDF prevents one death / year

Caution!

On-line HDF provides better overall and CV survival only when high convective volumes are achieved.

Meta-analysis: all cause mortality

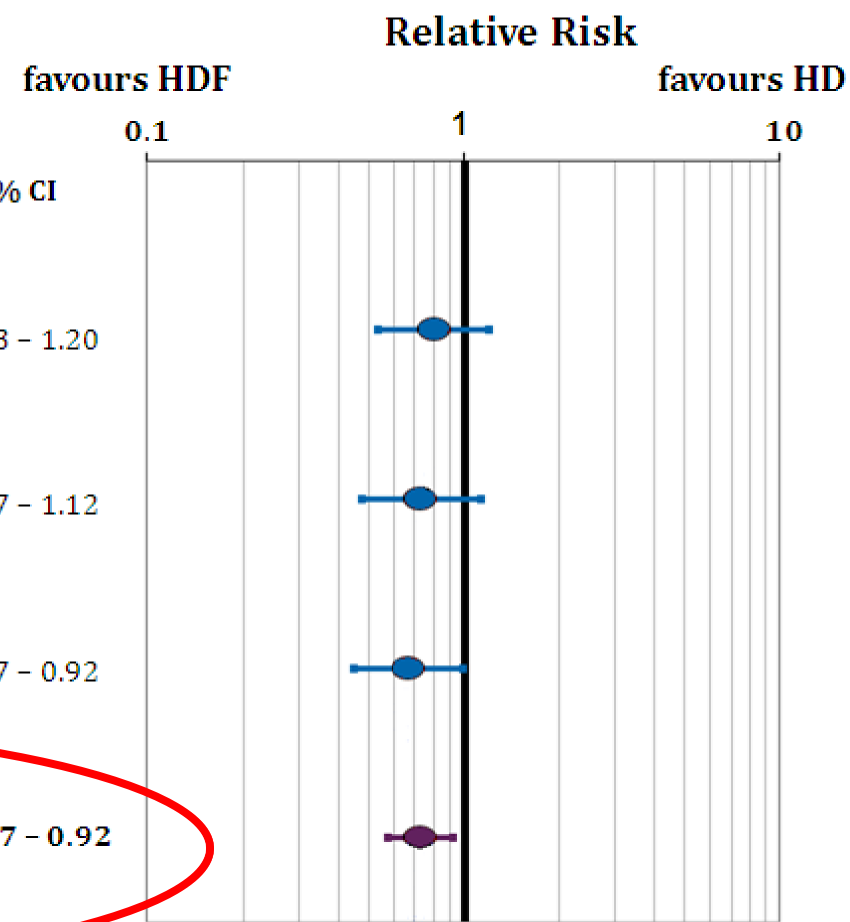
Study name	HDF (Events/Pat)	HD (Events/Pat)	RR	95% CI
Grooteman et al.	131/358	138/356	0.94	0.78 – 1.15
Ok et al.	52/391	65/391	0.80	0.57. – 1.12
Maduell et al.	85/456	122/450	0.69	0.54 – 0.88
Pooled	**268/1205**	**326/1197**	**0.83**	**0.72 – 0.95**



Sem Dial 2014; 27:119-27

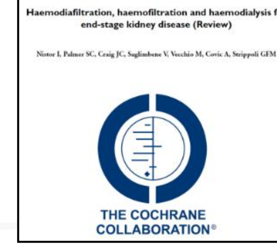
Meta-analysis: cardiovascular deaths

Study name	HDF (Events/Pat)	HD (Events/Pat)	RR	95% CI
Grooteman et al. (3)	37/358	46/356	0.80	0.53 – 1.20
Ok et al. (4)	32/391	44/391	0.73	0.47 – 1.12
Maduell et al. (5)	37/456	55/450	0.66	0.57 – 0.92
Pooled	**106/1205**	**145/1197**	**0.73**	**0.57 – 0.92**



Sem Dial 2014; 27:119-27

Cochrane review - 2015


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

Nistor I, Palmer SC, Craig JC, Saglimbene V, Vecchio M, Covic A, Strippoli GFM

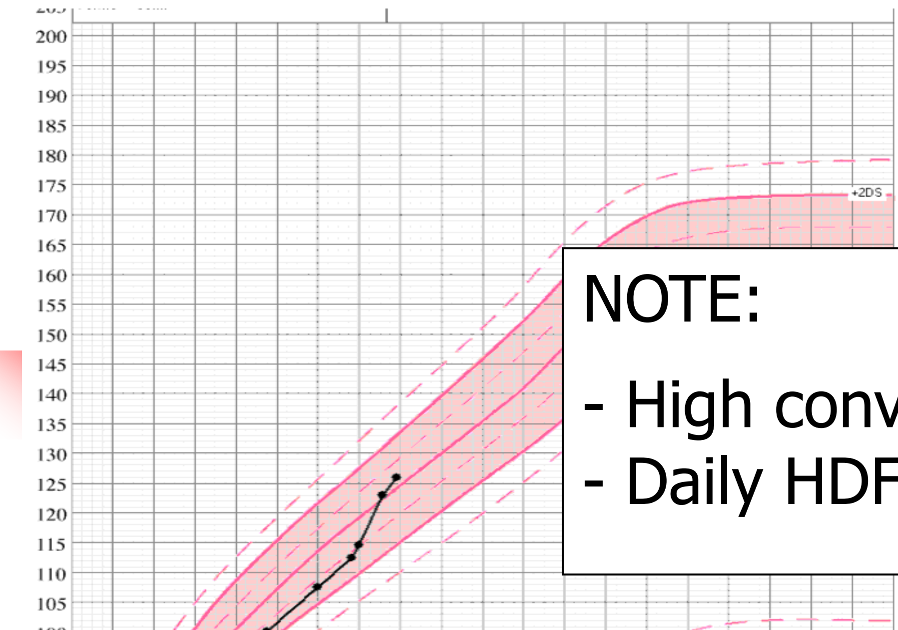
THE COCHRANE COLLABORATION®

- Convective dialysis had no significant effect on all-cause mortality (11 studies, 3396 participants: RR 0.87, 95% CI 0.72 to 1.05).
- Convective dialysis significantly reduced cardiovascular mortality (6 studies, 2889 participants: RR 0.75, 95% CI 0.61 to 0.92).
- Effects on nonfatal cardiovascular events & hospitalisation inconclusive.

Criticism

- Studies on HF were also included under ‘convective therapies’
- Studies with different end-points were combined
- Some studies were underpowered to examine CV or all-cause mortality.

Growth on daily HDF



NOTE:

- High convective volume
- Daily HDF

Height SDS

- start: -1.5 ± 0.3
- end: +0.2 ± 1.1
- target height relative to mid-parental height: +0.3

Height velocity

- before daily HDF: 3.8 ±1.1 cm/y
- first year of daily HDF: 14.3 ± 3.8 cm/
- mean : 10.4 cm/y

Growth study in children

- 15 children on daily HDF; mean age: 7.3 (2.8 – 16.7 yrs)
- 7 converted from PD & 5 from 3/week HD
- Vascular access: fistula (n=13) & catheter (n=4)
- Pre-dilution HDF; Qb & Qd adjusted to achieve a Kt/Vurea ≥1.4 per session x 18 hours per week

Fischbach et al; NDT, 2010

Dialysis efficiency & tolerance

- Mean weekly Kt/V_{urea} =10
  - dialysis dose ~ 35% GFR

- Phosphate: 1.39 (1.65 - 0.63) mmol/l
  - despite high protein intake (>2 g/kg/day)
  - 2/15 child on chelators

- CRP – normal in 13/15 (2 children had chronic infections)

- β2 microglobulin 13.5 ± 3.5 mg/L

Dialysis dose and growth

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).

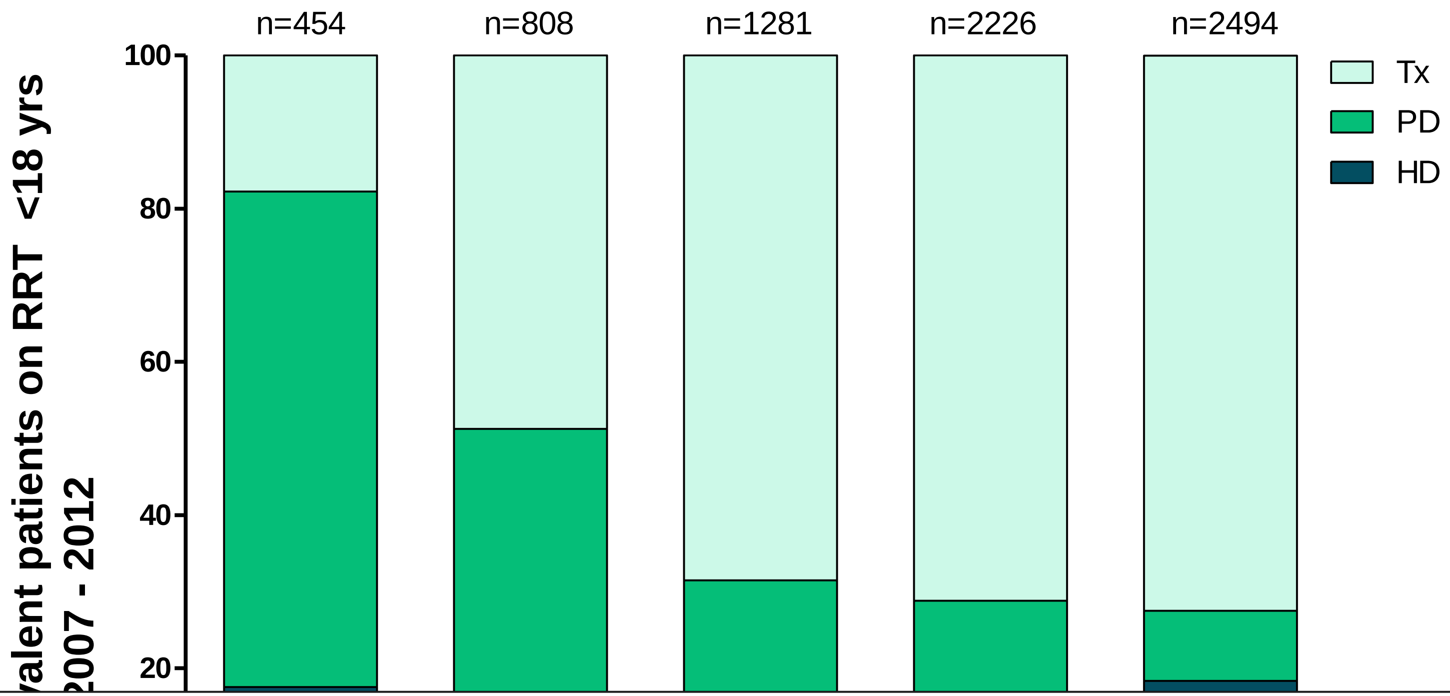
Daugirdas et al; Clin JASN 2010

Anabolic effect of daily HDF

- Stimulates appetite - removal of circulating satiety factors (leptin, cholecystokinin, tryptophan)
- Correction of metabolic acidosis. Acidosis can:
  - activate the ubiquitin-proteosome pathway & increase protein degradation
  - suppresses endogenous GH secretion
- Minimises inflammatory cytokine release
- ? Removal of somatomedin and gonadotropin inhibitors by HDF
- ? reverses rhGH resistance

Schaefer et al, NDT 2010

Paediatric HDF in Europe



144 cases of HDF in children in 2013

(~12% of all HD cases)

ESPN/ERA-EDTA registry

The effects of HDF vs conventional HD on growth and cardiovascular markers in children

3H (HDF, Hearts and Height) study

HDF, hearts & height study

International Pediatric Hemodialysis Network

Kidney Research UK
Funding research to save lives

FRESENIUS MEDICAL CARE

Hypothesis

Children on HDF compared with HD have improved:

- Cardiovascular risk profile
- Growth and nutritional status
- Quality of life

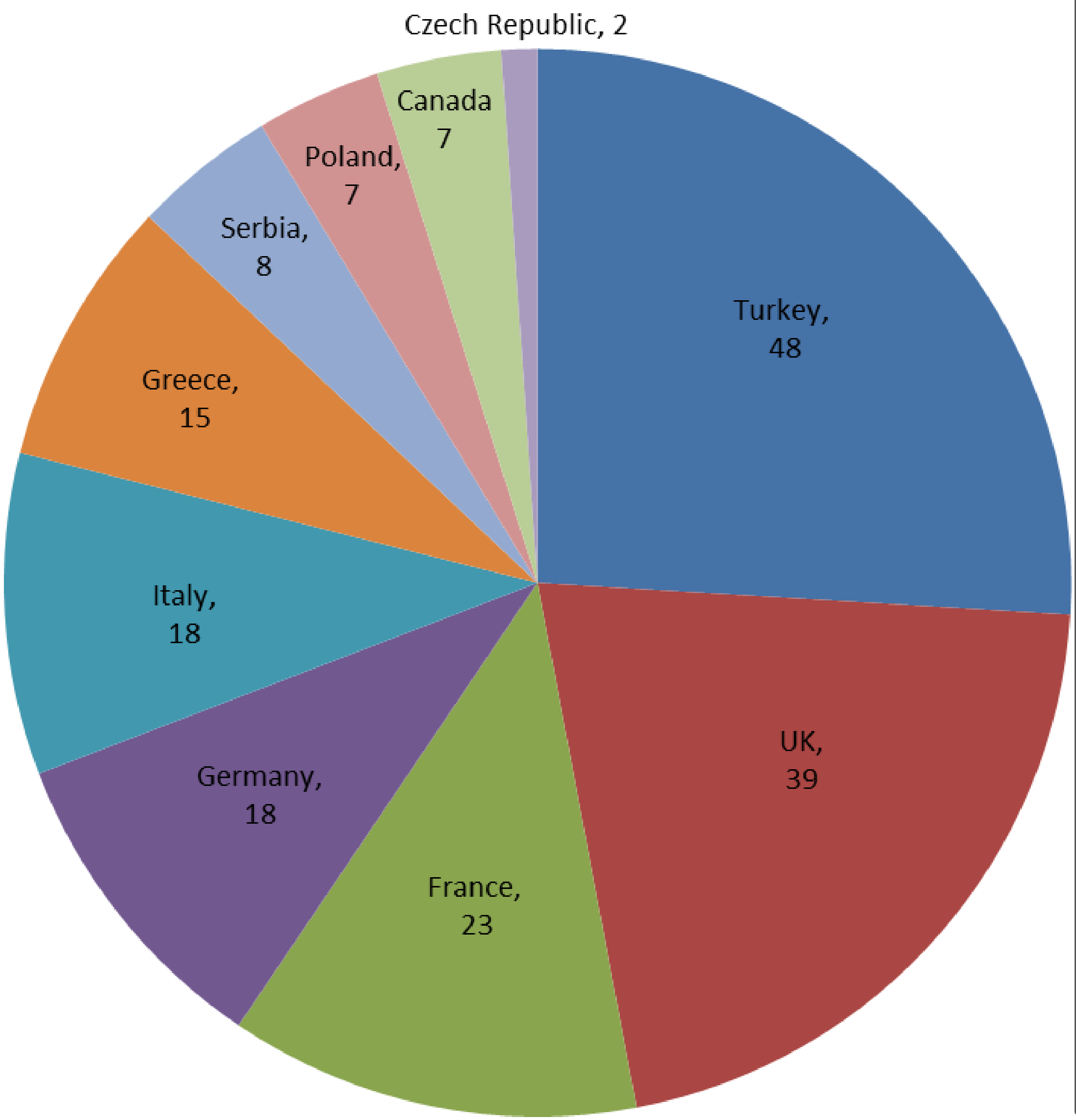
Primary outcome measures:

- Change in carotid artery intima-media thickness (cIMT) standard deviation score (SDS)
- Change in height SDS

Secondary outcome measures:

- *For nutritional status*
  - Body mass index SDS
  - Markers of appetite regulation and nutritional status
- *For cardiovascular status*
  - 24-hour mean arterial BP SDS
  - Left ventricular mass index
  - Pulse wave velocity SDS
  - Biomarkers of cardiovascular disease
- *Quality of life (QoL) questionnaires*

Recruitment



185 children screened

(from 28 centres in 10 countries)

↓

20 excluded

- No baseline scans (n = 6)
- Transplanted on day of study (n = 2)
- Did not fulfil inclusion criteria (n = 1)
- No data entry (n = 11)

↓

165 included

Conclusion

- HDF is a superior dialysis modality in adults PROVIDED high convective clearance is achieved

- Mechanisms:
  - Inproved clearance across a wide mol wt range
  - Reduced inflammation
  - Hemodynamic stability

- A study in children is under way

Practical aspects of HDF

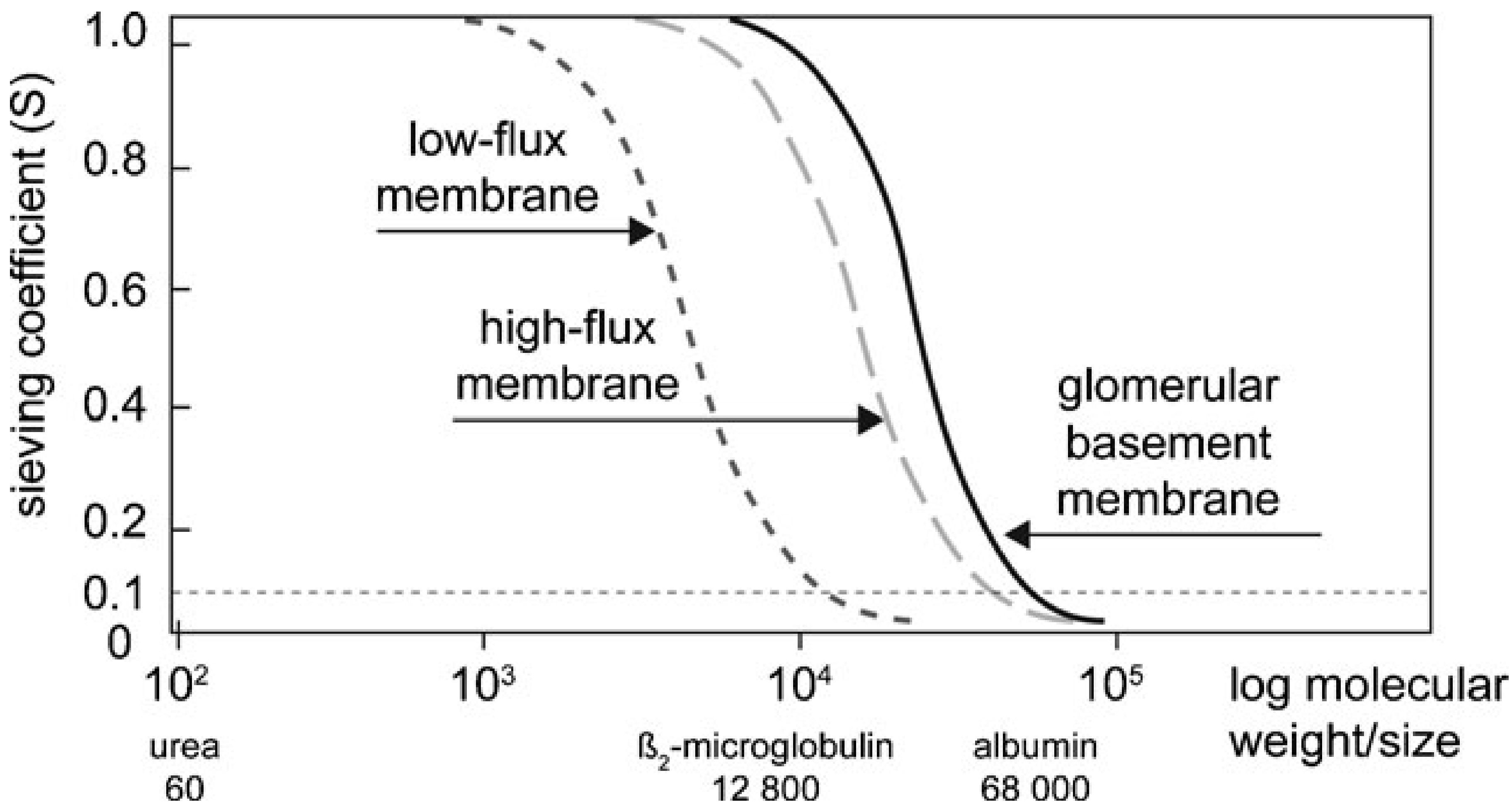
Potential limitations for setting up HDF in your centres

1. HDF machine	X newer machines can all do HDF
2. Water quality	- one time installation cost, then 1-3 monthly monitoring - must use ultrapure water with all high flux membranes
3. Staff training	X provided by company
4. Costs	£38/patient/month >HD
5. Lack of paediatric data	✓ We need a study!

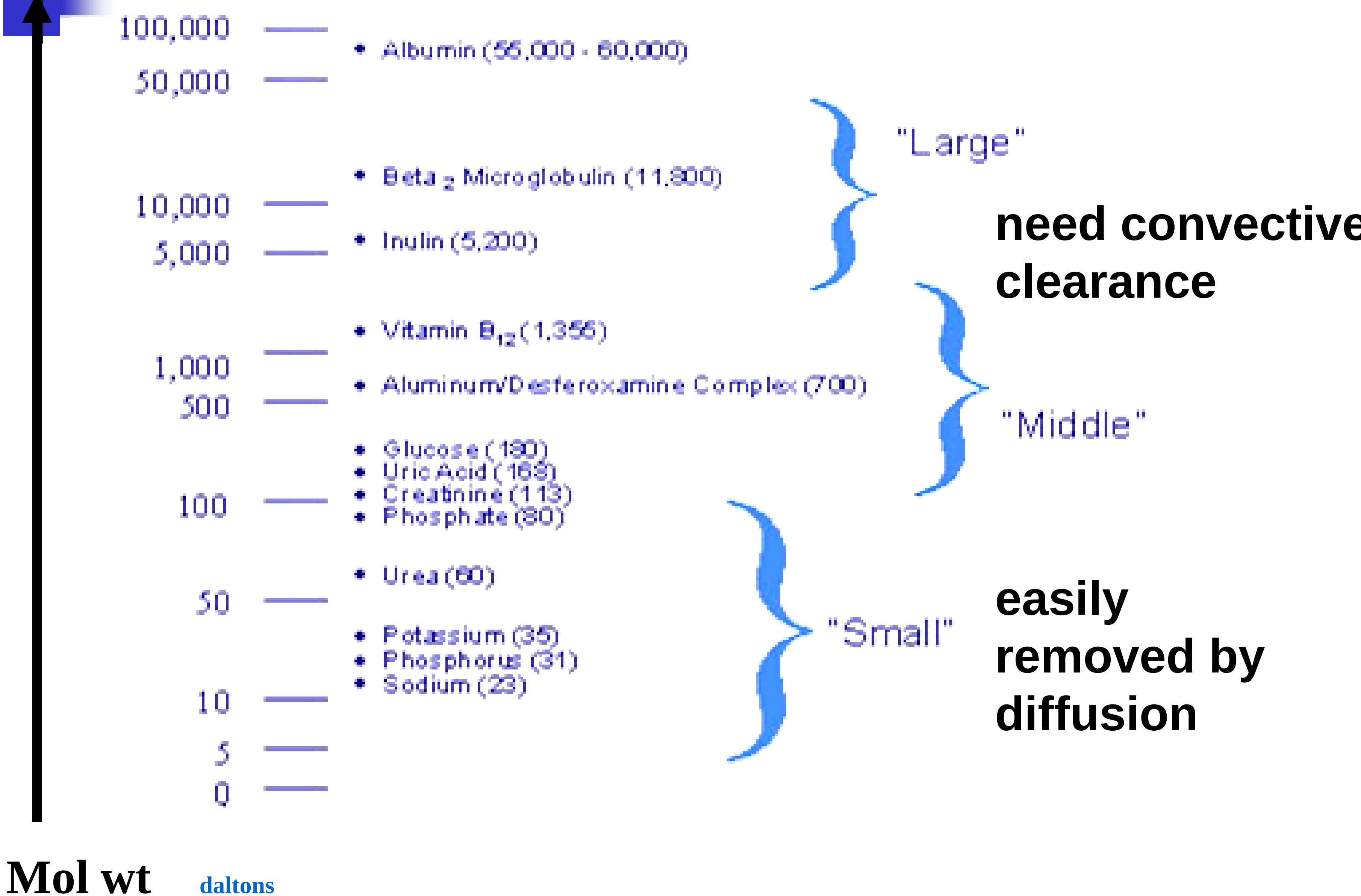
Requirements for HDF

1. High-flux membrane
2. Large quantities of IV quality fluid (‘ultrapure’ dialysate) as replacement fluid
3. Machines with accurate UF control systems

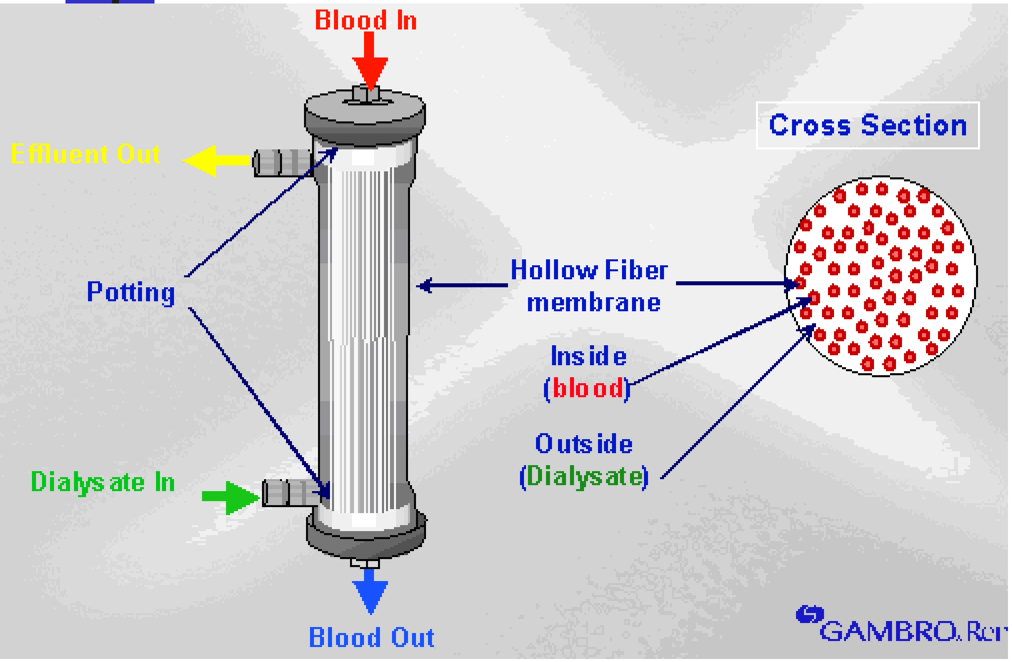
1. Dialysis Membranes

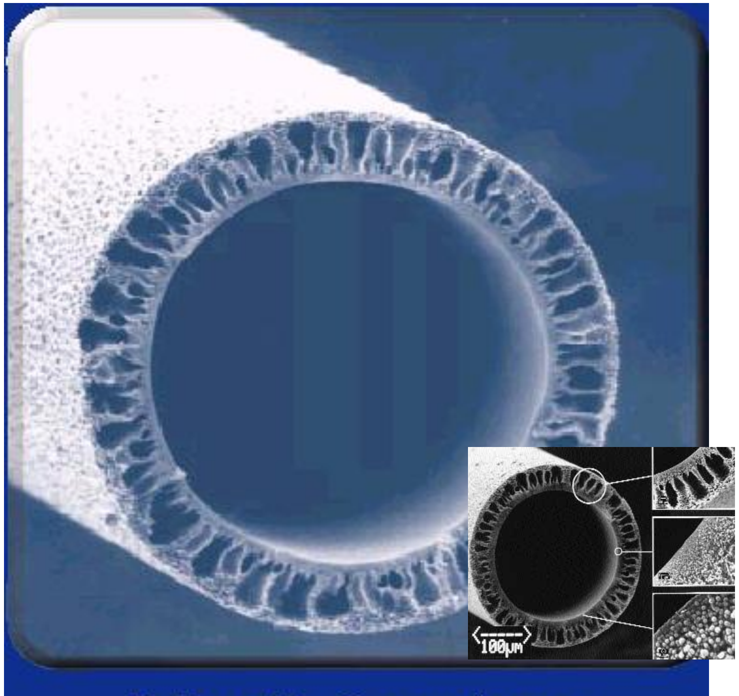


Solute clearance depends on its mol wt



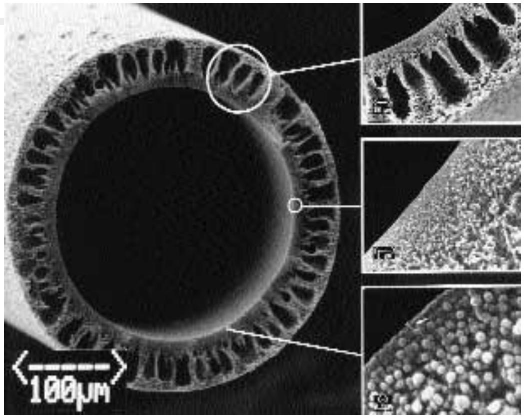
High-flux membranes





Polyamide S membrane

Characteristics of high-flux membranes



1. <u>Flux</u> - Measure of ultrafiltration capacity

Low flux: Kuf <10 mL/hr/mm Hg
High flux: Kuf >20 mL/hr/mm Hg

2. <u>Permeability</u> - Measure of the clearance of *β*2-microglobulin (= middle mol wt solutes)

Low permeability: *β* 2-microglobulin clearance <10 mL/min
High permeability: *β* 2-microglobulin clearance >20 mL/min

3. <u>Efficiency</u> - Measure of urea (= low mol wt solute) clearance

Low efficiency: KoA <500 mL/min
High efficiency: KoA >600 mL/min

Polyflux™ H

For high-flux and convective dialysis treatment

Performances in vitro

Measured according to EN 1283

Clearances in vitro [ml/min] +/-10%	Polyflux 140H				Polyflux 170H				Polyflux 210H			
Hemodialysis												
UF=0 ml/min, Q_D=500 ml/min												
Q_B [ml/min]	200	300	400	500	200	300	400	500	200	300	400	500
Urea	193	262	309	-	196	270	321	-	-	281	339	378
Creatinine	181	232	266	-	186	243	281	-	-	259	303	334
Phosphate	174	220	250	-	180	232	266	-	-	249	289	317
Vitamin B_{12}	128	149	163	-	137	162	178	-	-	183	203	218
Inulin	91	102	109	-	100	113	121	-	-	131	143	151
Hemodiafiltration												
UF=60 ml/min, Q_D=500 ml/min												
Q_B [ml/min]	200	300	400	500	200	300	400	500	200	300	400	500
Urea	198	277	332	-	199	283	343	-	-	290	359	406
Creatinine	191	252	292	-	194	262	306	-	-	274	327	363
Phosphate	187	242	277	-	191	252	292	-	-	266	314	347
Vitamin B_{12}	152	177	193	-	159	189	208	-	-	208	232	249
Inulin	120	133	141	-	128	143	153	-	-	161	174	183

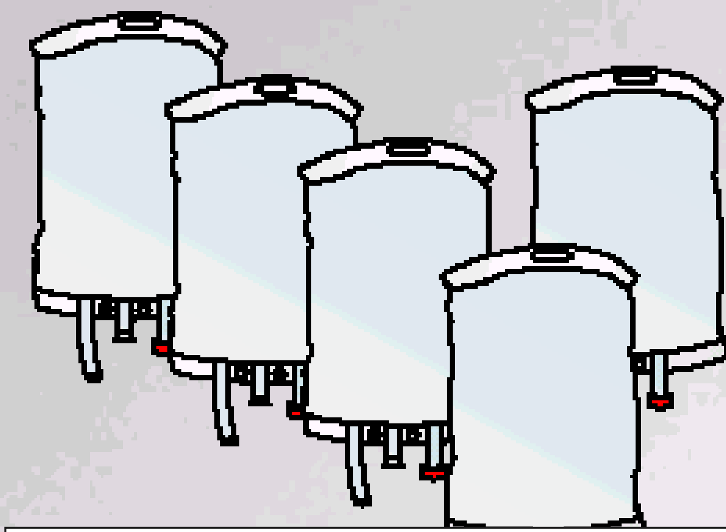
	Polyflux 140H	Polyflux 170H	Polyflux 210H
KoA for Urea	993	1145	1450
UF-coefficient*	60	70	85
UF-coefficient* [ml/h mmHg] +/-20%	60	70	85
Residual blood volume [ml]	< 1	< 1	< 1
Maximum TMP [mmHg]	600	600	600
Recommended Q_B [ml/min]	200-400	250-500	300-500
Sieving coefficients**			
Vitamin B_{12}	1.0	1.0	1.0
Inulin	1.0	1.0	1.0
β2-Microglobulin	0.70	0.70	0.70
Albumin	<0.01	<0.01	<0.01

Specifications

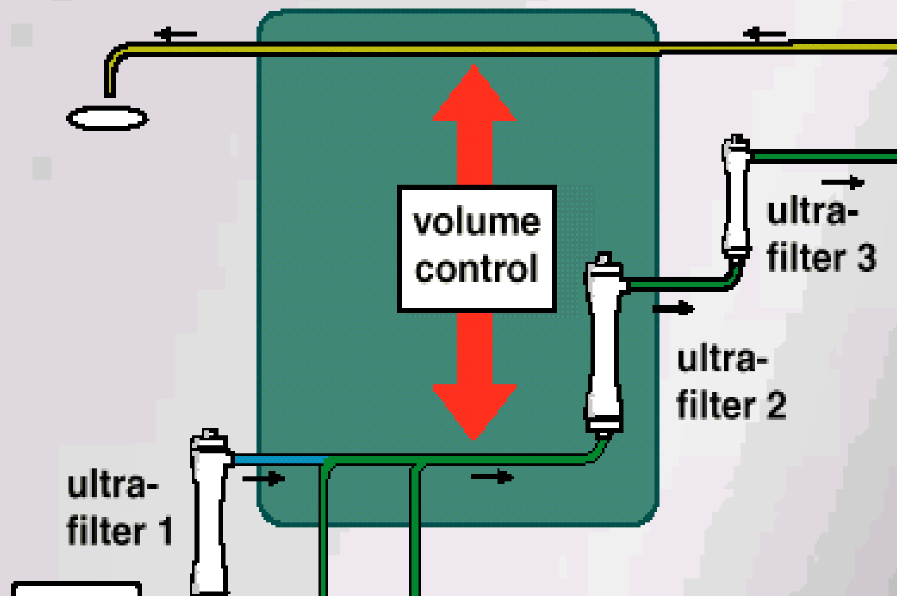
	Polyflux 140H	Polyflux 170H	Polyflux 210H
Membrane			
Effective surface area [m²]	1.4	1.7	2.1
Fiber dimensions			
Wall thickness [μm]	50	50	50
Inner diameter [μm]	215	215	215

2. Substitution fluid to drive UF

Pharmaceutical preparation **or** **on-line preparation**

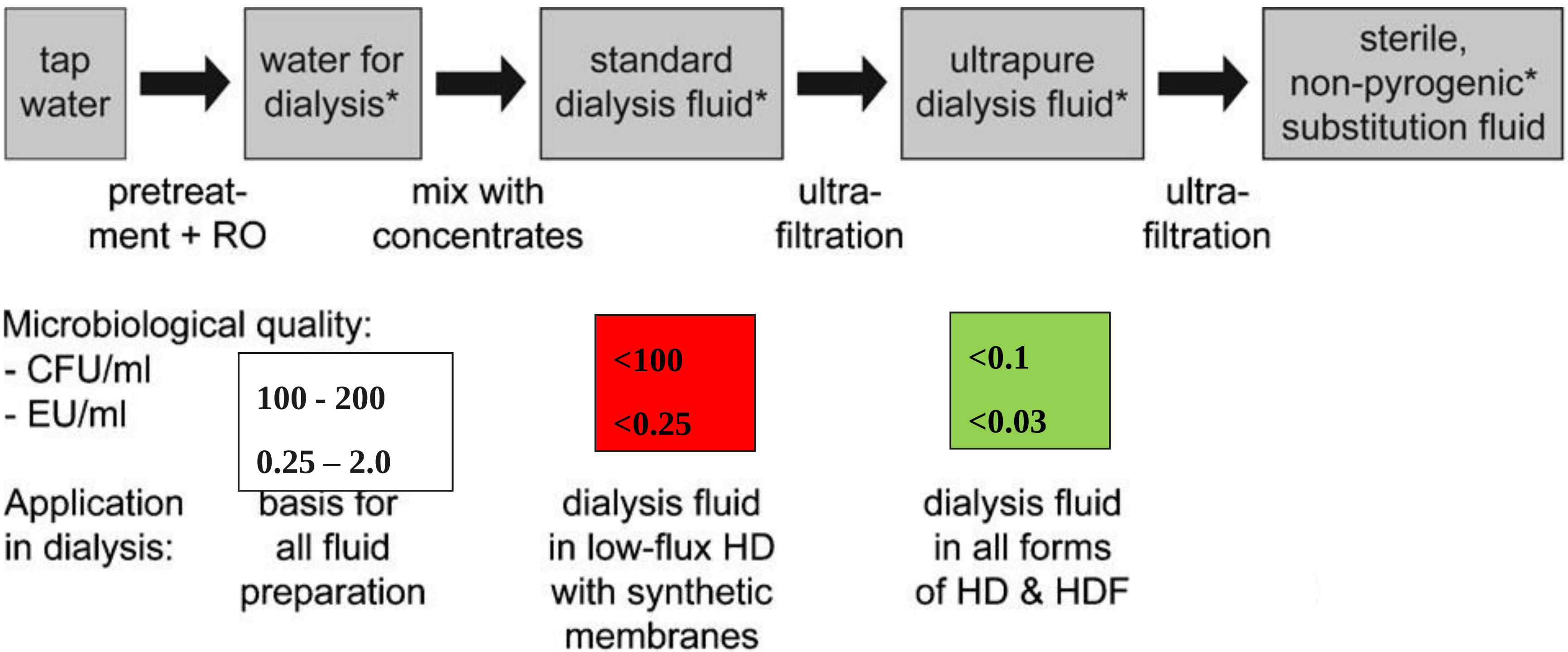


1. Large volumes of bagged fluid
2. Cannot use bicarbonate



1. Requires a high dialysate flow rate
2. Ensure fluid is of 'IV' quality

‘Ultrapure’ water for HDF



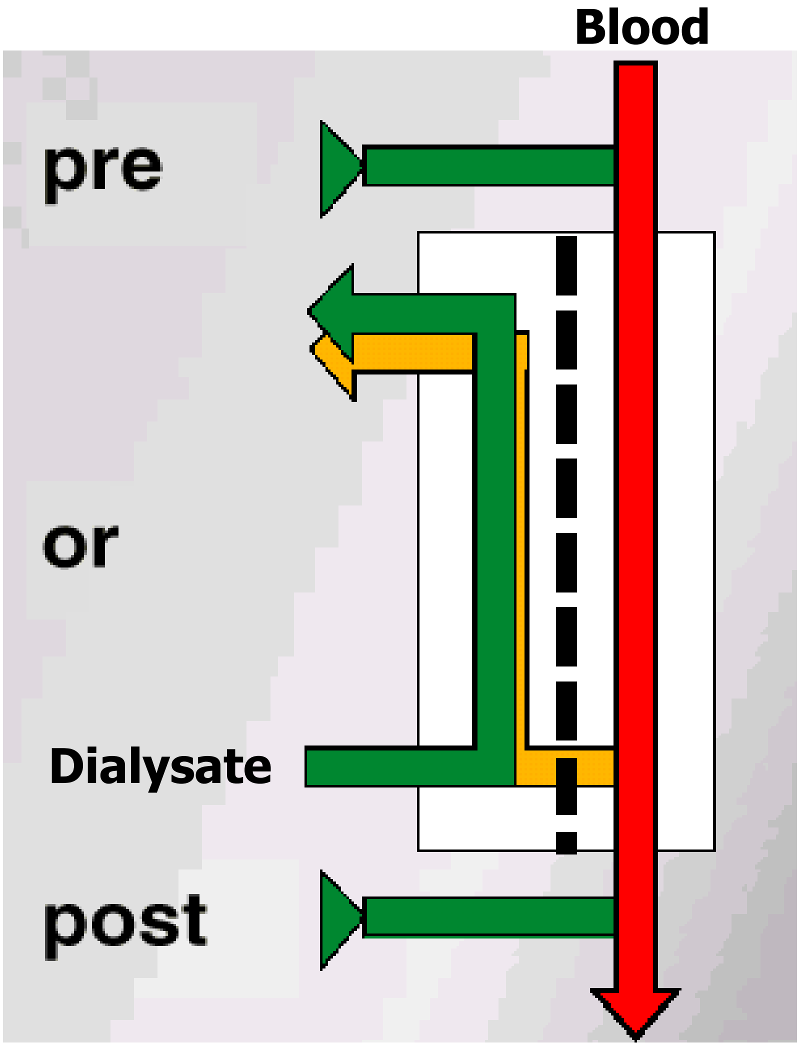
Ultrafilters:
- size selective barrier – filter particles >30-40KD
- Hydrophobic adsorption of bacteria

Type and frequency of H_2O testing

Contaminant	Frequency of testing
Total chlorine	At least weekly
Total viable counts	At least monthly
Endotoxin	At least monthly
Chemical contaminants other than chlorine	At least every 3 months

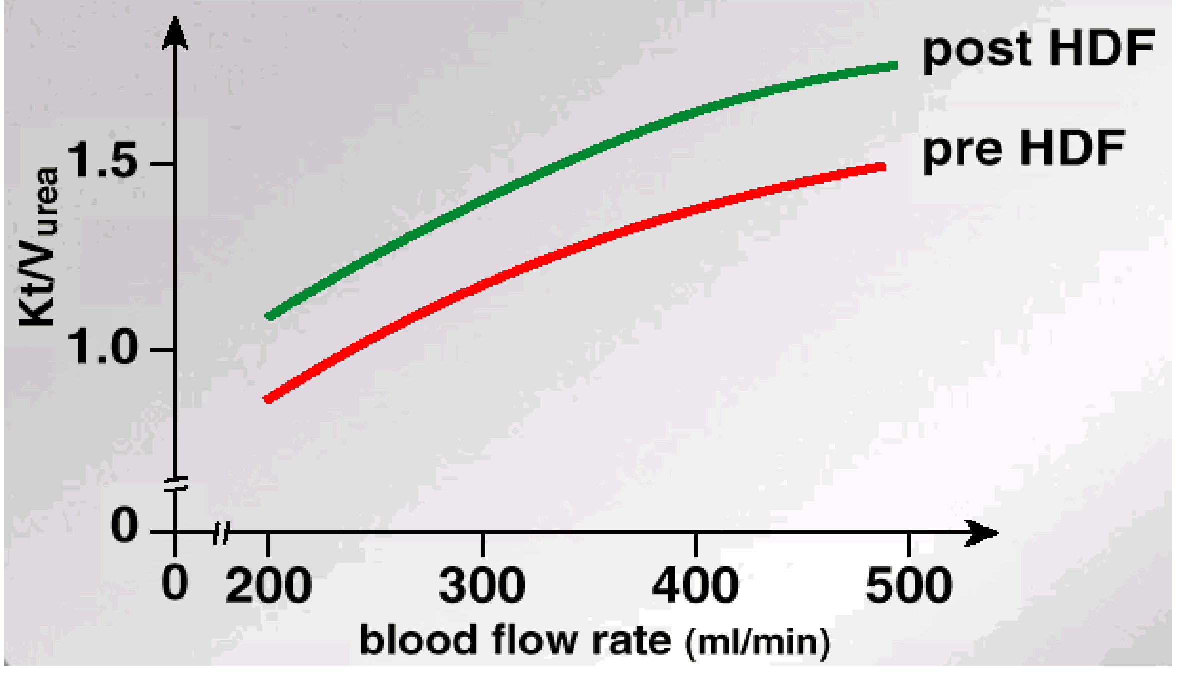
- Daily and seasonal variations in chlorine and chloramine levels
- Water supplier must know that H_2O is used for dialysis and inform of changes in additives
- If the chlorine level in the source H_2O is consistently low (<0.5mg/L) and chloramines are not used then weekly monitoring of dialysis H_2O is sufficient

Replacement of substitution fluid - pre-dilution vs post-dilution HDF



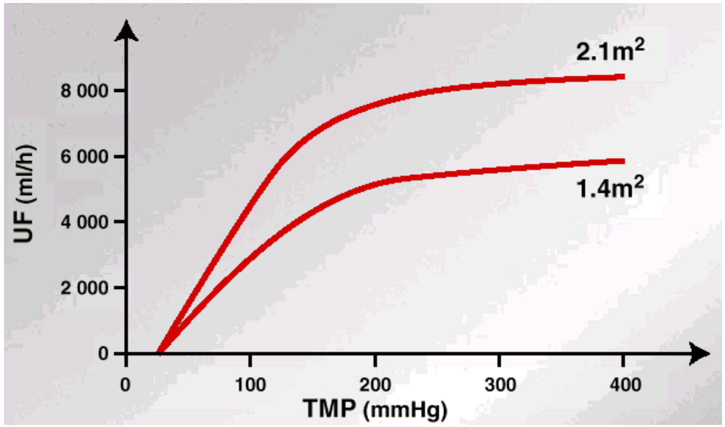
Post-dilution HDF is superior

1. Requires ½ vol of replacement fluid compared to pre-dilution
2. More efficient removal of low mol wt solutes
3. Risk of high hematocrit and filter clotting
4. Pre-dilution is only useful if low blood flows or hemodynamically unstable patient

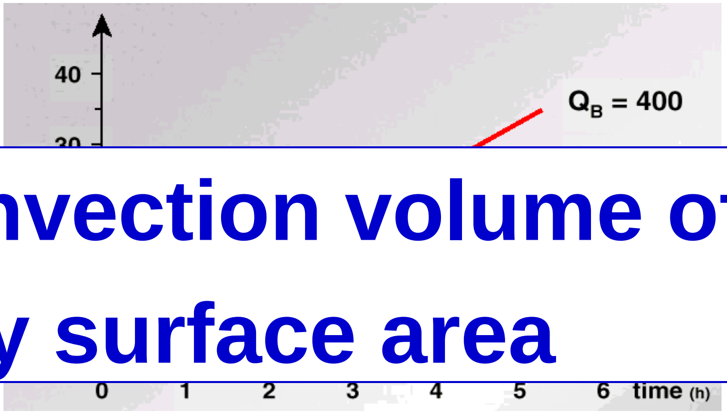


3. High UF rate for convective transport

1. membrane properties
   - flux
   - surface area

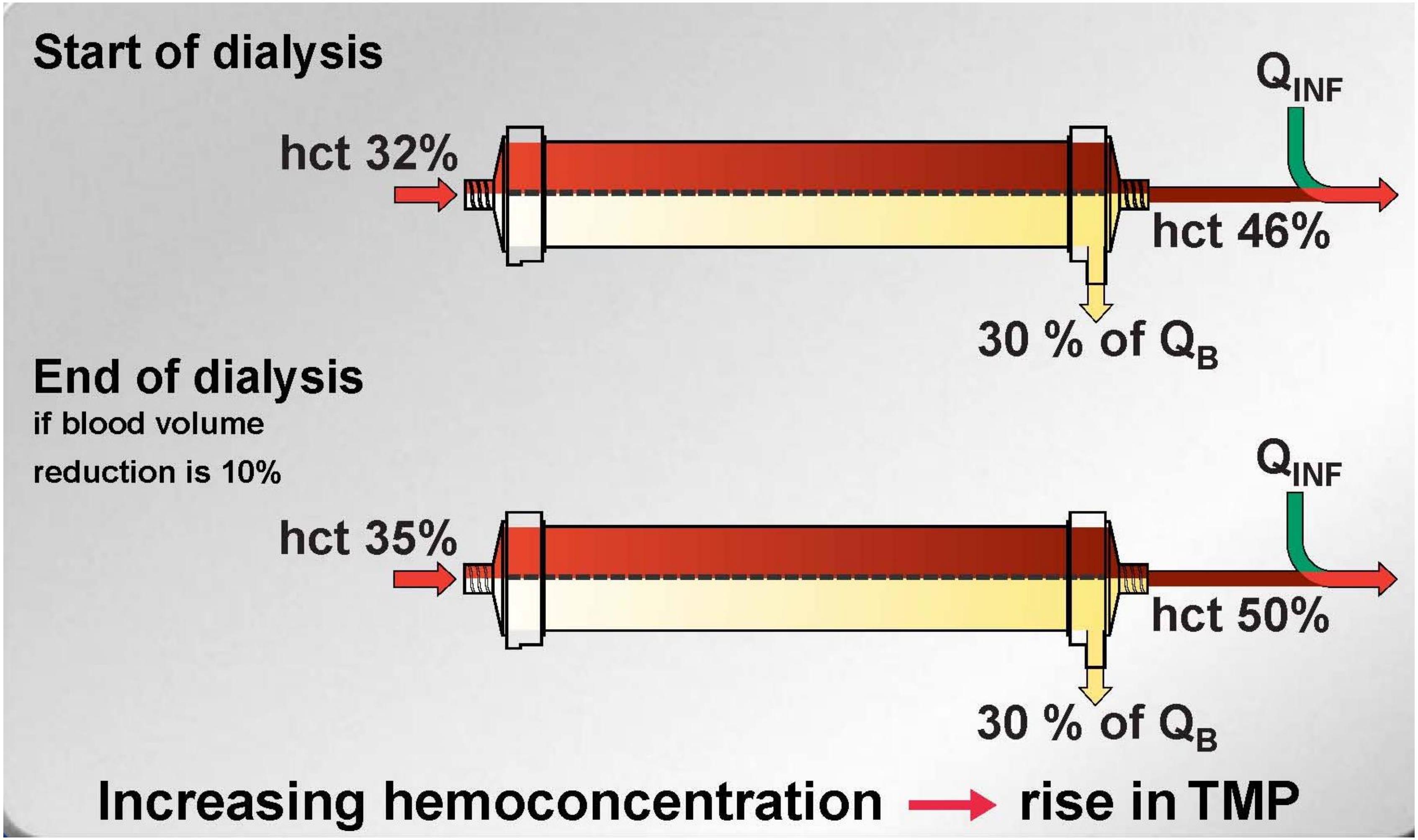


2. UF rate - depends on bl flow rate
   - optimise access
   - AVF preferred to CVL

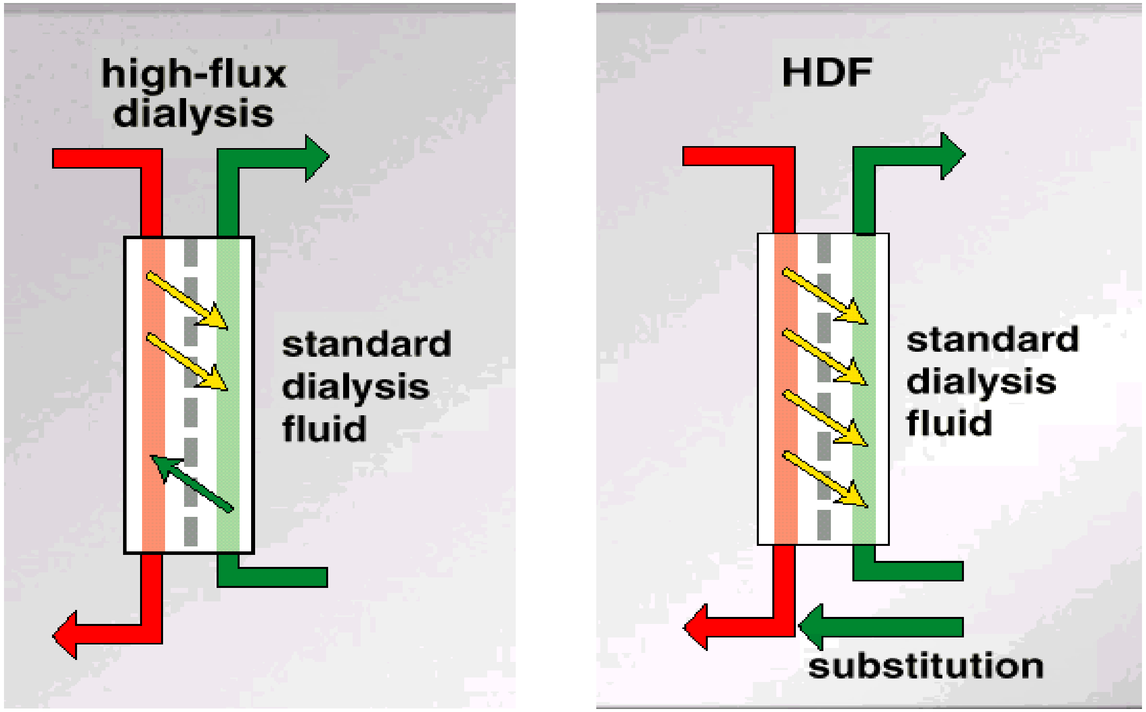


Aim for a target convection volume of $12\text{-}15 L/m^2$ body surface area

If Q_{UF} too high



Backfiltration in high-flux HD



- Small and unquantified amounts

High flux HD is the poor man's HDF!

<u>With any high flux dialyser the water must be 'ultrapure'</u>

Writing an HDF prescription

- Gambro programme:
  - Pressure control – 'ULTRA CONTROL'
  - Volume control – calculated at 25 - 30% of Qb

- Fresenius programme:
  - Auto-sub – set TMP

  Auto-sub plus – automatically calculates substitution vol based on max allowed TMP

Typical HDF prescription

15 year old boy

Wt = 42.0kg SA = 1.4m^2

Dialyser Polyflux 140

Q_b = 300ml/min

Q_d = 500 ml/min

Desired wt loss = 1.6L

Calculation if in volume control = %blood flow x number of hours x 60minutes (or consult chart)

25% x 300 x 4 x 60 = 18 litres

Subtract UF loss (1.6L) = **16.4L** substitution volume