

HIGH VOLUME HDF – CARDIOPROTECTIVE- HOW TO ACHIEVE ?

PGS TS Phạm Văn Bùi
 BV Nguyễn Tri Phương
 ĐHYK Phạm Ngọc Thạch
 GS Thịnh giảng ĐH Liège, Belgium
 Chủ tịch liên chi hội lọc máu TPHCM
 Chủ tịch hội lọc máu Thế Giới

Content



- 1 WHY HDF OL?**
- 2 CURRENT THERAPY STANDARD**
- 3 HIGH VOLUME - HDF**
- 4 HOW TO ACHIEVE HV- HDF**
- 5 CONCLUSIONS**

Page 2

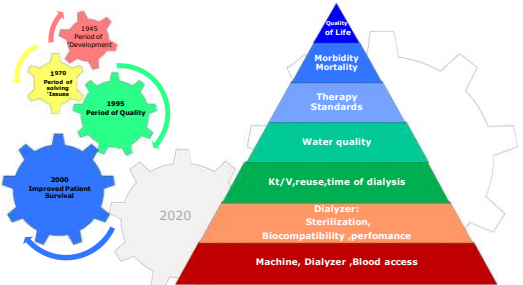
Content



- 1 WHY HDF OL?**
- 2 CURRENT THERAPY STANDARD**
- 3 HIGH VOLUME - HDF**
- 4 HOW TO ACHIEVE HV- HDF**
- 5 CONCLUSIONS**

Page 3

Focus & improvement in Dialysis till...



The diagram illustrates the focus and improvement in dialysis over time. It features a pyramid with five levels, representing different aspects of dialysis care. To the left of the pyramid, there are four gears representing different periods of development and improvement:

- 1945 Period of Development** (Red gear)
- 1979 Period of Access Types** (Yellow gear)
- 1995 Period of Quality** (Green gear)
- 2000 Improved Patient Survival** (Blue gear)

A large grey gear labeled **2020** is positioned at the base of the pyramid, indicating the current focus. The pyramid levels from top to bottom are:

- Quality of Life**
- Morbidity Mortality**
- Therapy Standards**
- Water quality**
- KT/V, reuse, time of dialysis**

Below the pyramid, the following factors are listed:

- Dialyzer: Sterilization, Biocompatibility, performance**
- Machine, Dialyzer, Blood access**

Today's Haemo Dialysis

- The best Dialysis practices
- Computerized machines
- Synthetic dialyzer membranes

Fluids & Electrolytes

UF Target
Na+ Healthy
Urea Adequacy in V solute clearance

Patient Survival Rates by Dialysis and Transplant

MISSED OUT!

Transplants in the U.S. by State. <http://optn.transplant.hrsa.gov/facetData/rpt/Data.asp>. Accessed August 10, 2013

Amyloidosis
Hyperparathyroidism
Hyperphosphataemia

Carpal Tunnel Syndrome

1,200
100
0

Normal Kidney Function

- Cardiovascular Disease
- Carpal Tunnel Syndrome
- Anemia
- Renal Osteodystrophy
- Mainnutrition
- Dialysis Encephalopathy
- Uremic Neuropathy

Molecular weight in 10³

Table 1: Uremic toxins (n = 7)

Toxin	Mr	Ca	Co	Mr	Mr	Ca	Co
Indoxyl sulfate	350	100	100	100	100	100	100
Indoxyl glucuronide	460	100	100	100	100	100	100
Indoxyl acrylate	320	100	100	100	100	100	100
Indoxyl succinate	320	100	100	100	100	100	100
Indoxyl pyruvate	320	100	100	100	100	100	100
Indoxyl propionate	320	100	100	100	100	100	100
Indoxyl benzoate	320	100	100	100	100	100	100

Table 2: Dialyzable toxins (n = 7)

Toxin	Mr	Ca	Co	Mr	Mr	Ca	Co
Urea	60	100	100	100	100	100	100
Creatinine	113	100	100	100	100	100	100
Uric acid	168	100	100	100	100	100	100
Phosphate	136	100	100	100	100	100	100
Calcium	40	100	100	100	100	100	100
Sodium	23	100	100	100	100	100	100
Potassium	39	100	100	100	100	100	100

β_2m , amyloidosis and ESRD

β_2 microglobulin

- Continuously produced by most cells of the body as part of our immune system
- Accumulates in ESRD
- Protein of MW 11,800D

Dialysis related amyloidosis

- Deposition in body tissue of the protein β_2m as amyloid fibrils

Results in

- Carpal tunnel syndrome
- Destruction in bone tissue
- Chronic pain and mobility

Carpal Tunnel Syndrome

Phosphate in ESRD

- Persistent \uparrow phosphate levels will cause:
 - Deposition of 'calcium phosphate' in the soft tissue
 - Reciprocal hypocalcaemia

Keep in mind...

CALCIUM-PHOSPHORUS RELATIONSHIP
- The Up and Down -

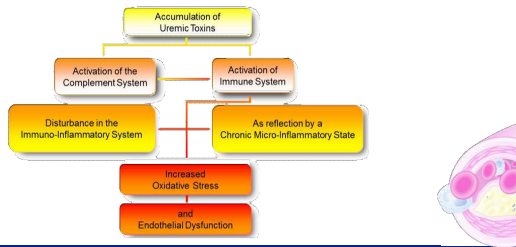
Uremic calcemion: \downarrow (Too high)
Phosphorion: \downarrow (Too high)

Uremic calcemion: \uparrow (Too low)
Phosphorion: \uparrow (Too low)

Kinsley Smith, 1990

Other Contributing Factors

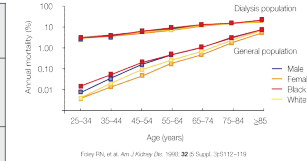
The high incidence of CVD in patients with ESRD is related to the accumulation of uremic toxins in the middle and large-molecular weight range



CVD – The unresolved issue in Dialysis

Despite significant therapeutic improvements in recent years, cardiovascular disease (CVD) remains the leading cause of death for dialysis patients

	Coronary Artery Disease	Left Ventricular Hypertrophy	Heart Failure
General Population	5 % to 12 % at age 45 - 64 at age > 65	20 %	5 % at age 60
Haemodialysis Population	40 %	75 %	40 %



Dialysis patients, at all ages, have much greater risk of cardiovascular death than general population

Cardiovascular risk factors in dialysis patients

- In addition to the traditional risk factors for CVD, patients with stage 5 CKD are additionally exposed to a broad range of potential risk:

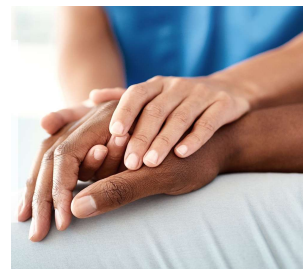
New approaches are required to deliver **Cardioprotective Dialysis** and achieve better outcomes



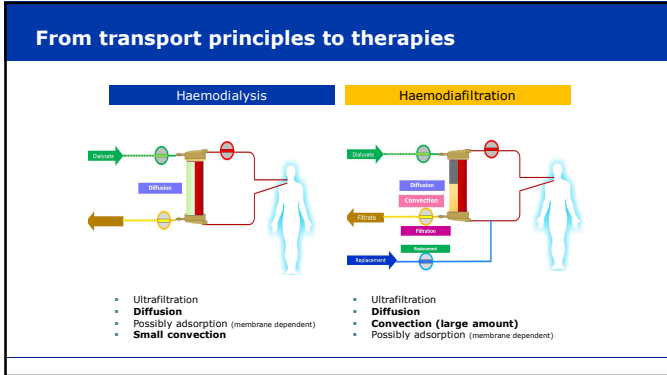
¹ Ferraz et al. Am J Kidney Dis 2009; 53: 77-87
² Ferraz et al. JASN 2002; 13: 1988-1995
³ Paruch et al. JASN 2006; 23: 2331-43

⁴ Cheung et al. JASN 2008; 17: 546-555
⁵ Kalantar-Sabet et al. Clin Dialy 2009; 138: 471-479
⁶ Levin et al. Am J Kidney Dis 2001; 38 (6): 1386-1427

Content



- 1 WHY HDF OL?
- 2 CURRENT THERAPY STANDARD
- 3 HIGH VOLUME - HDF
- 4 HOW TO ACHIEVE HV- HDF
- 5 CONCLUSIONS

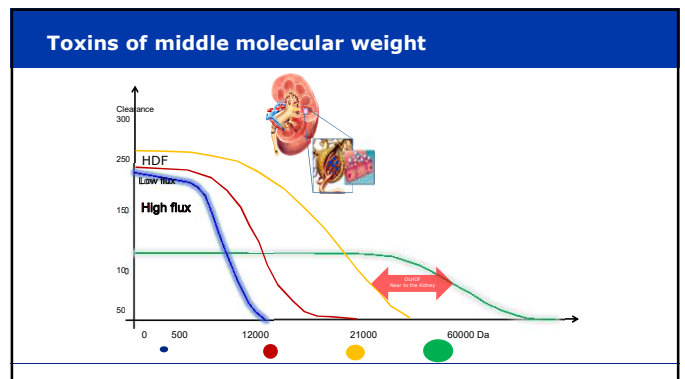
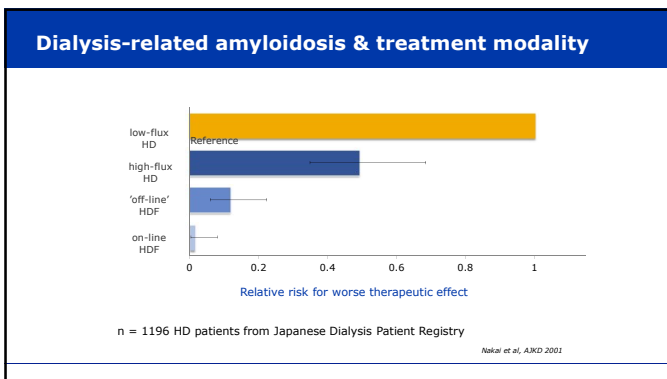


EUTox - European Uremic Toxin Work Group

At present, about 90 different uremic toxins have identified, and this number certainly represents only a minority of toxins that accumulate during chronic renal failure and contribute to the uremic syndrome

	Molecular Weight	Uremic Toxins (examples)	Low-Flux Diffusion	High-Flux Convection	HDF
Small Molecular Weight (SMW)	< 500 D	Water-soluble (non-protein bound) Urea (60D), creatinine (113)	Yes	Yes	Yes
		Protein Bound P-cresol (108D), homocysteine	No	Minimal	Yes Enhanced
Middle Molecular Weight (MMW)	500 – 12,000 D	B2m (11.8 D), AGEs (10 kDa), Parathyroid hormone (9,223D)	No	Limited	Yes, Enhanced
High Molecular Weight (LMW)	>12,000 D	Leptin (18D), Complement factor D (protein 24kD)	No	No	Yes

EUTox group identified at least 22 middle molecules, of which 12 have a MW >12,000Da – substantial number of these bioactive molecules are linked to inflammation, oxidative stress, malnutrition and cardiovascular disease



A solid concept is gaining widespread acceptance

Study	Author, Year
DOPPS	Canaud B et al, 2006
RISCAVID	Panichi V et al, 2010
ITALIAN CD STUDY	Locatelli F et al, 2010
CONTRAST	Grooteman M et al, 2012
TURKISH HDF STUDY	Ok et al, 2013
ESHOL Study	Maduell et al, 2013

17

ONLINE HDF: reduced intradialytic symptoms

- Better hemodynamic cardiovascular stability

↓ Complications

- Hypotension
- Hypertension
- Muscle cramps
- Headache
- Nausea
- Arrhythmias

ONLINE HDF: Patients survival & Cardiovascular risk

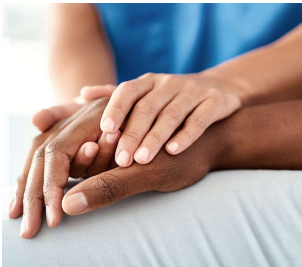
- Reducing cardiovascular risk
- Reduced risk of infection
- Improved nutritional status
- Reduced hospital admissions
- Preserved residual renal function

ONLINE HDF: Patients survival by Clearance

Outcome of Better Clearance :

- Reduction of amyloidosis
- Improving control of hyperphosphataemia
- Improving the control of anaemia.
- Reducing risk of Hypoparathyroidism

Content

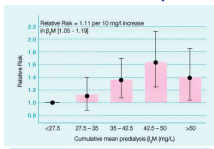


- 1 WHY HDF OL?
- 2 CURRENT THERAPY STANDARD
- 3 HIGH VOLUME - HDF
- 4 HOW TO ACHIEVE HV- HDF
- 5 CONCLUSIONS

Page 24

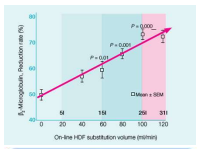
Why is it that high substitution volumes are so important in ONLINE HDF ?

All-cause Mortality



→ High β_2 -M blood levels are associated with increased mortality risk

β_2 -M Removal



→ The higher the volume of substitution – the better the removal of middle molecules!

Cheung AK et al, J Am Soc Nephrol 2006; 17: 546-555 Lornoy W et al, Nephrol Dial Transplant. 2000; 15: 49-54

High Volume HDF- studies

- The outcome all-cause mortality was significantly reduced for the patients being treated with High Volume HDF.

DOPPS (2005):
High-efficiency* HDF reduces mortality risk (35 %) compared to Low-Flux HD (p<0.01).
(*High efficiency = Sub. Vol. >17.4 L/session)

Turkish (2011):
HDF treatment with high substitution volume* provides better survival compared to low-flux HD (p=0.03).
(*HighVolumeHDF = Sub. volume > 21L)

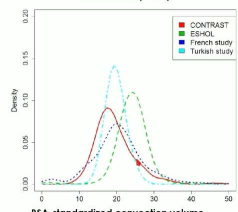
⇒ VOLUME matters!

Contrast (2012):
High-volume HDF* reduces mortality risk compared to low-flux HD (p=0.003).
(*High-volume HDF = Sub. Vol. 221.95 L/session)

30% risk reduction in all-cause mortality vs. high-flux HD (p=0.01)

The Survival Benefit of HDF is Dependent on Convective Volume and Commences at 23.0 Liters

BSA-standardized convection volume distribution by study



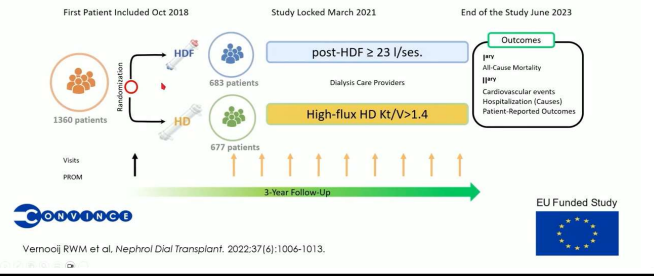
BSA-standardized convection volume

Cause of Mortality	On-line HDF: BSA-adjusted convection volume (L/session)		
	<19	19-23	>23
All-causes			
unadjusted	0.91 (0.74; 1.13)	0.88 (0.72; 1.09)	0.73 (0.59; 0.91)
adjusted	0.83 (0.66; 1.03)	0.93 (0.75; 1.16)	0.78 (0.62; 0.98)
Cardiovascular			
unadjusted	1.00 (0.71; 1.40)	0.71 (0.50; 1.01)	0.69 (0.48; 0.98)
adjusted	0.92 (0.65; 1.30)	0.71 (0.49; 1.03)	0.69 (0.47; 1.00)
Infections			
unadjusted	1.50 (0.93; 2.41)	0.96 (0.56; 1.65)	0.56 (0.30; 1.08)
adjusted	1.50 (0.92; 2.46)	0.97 (0.54; 1.74)	0.62 (0.32; 1.19)
Sudden death			
unadjusted	1.24 (0.80; 1.91)	0.91 (0.57; 1.47)	0.6 (0.35; 1.03)
adjusted	1.09 (0.69; 1.74)	1.04 (0.63; 1.70)	0.69 (0.39; 1.20)

Values are HRs and 95% CI. Adjusted for age, sex, albumin, creatinine, history of cardiovascular diseases and history of diabetes.
Table adapted from Peters et al., 2014.

Peters SAE et al. Nephrol Dial Transplant 2016;31(6):978-84.

Confirming Clinical Benefits of Hemodiafiltration (HDF) in Real-World Settings Was the Challenge: Adequately Dosed HDF vs. High-Flux Hemodialysis (HD)



Participating 61 Clinics In 8 Countries

- Diaverum: 17 clinics
- B-Braun: 14 clinics
- Fresenius Medical Care: 23 clinics
- Academic: 7 clinics



Patient Characteristics at Baseline – 1 -

European Multinational Pragmatic Randomized Clinical Trial

Study Design
1360 prevalent HD pts
>3mo. Ht-HF
683 post-HDF > 23l/ses.
677 Ht-HD EBPG

Primary Outcomes
• All-cause deaths

Secondary Outcomes
• Non-fatal CV events
• All-cause hospitalization
• PROMs

Characteristic	High-Dose Hemodiafiltration (N=683)	High-Flux Hemodialysis (N=677)
Age — yr	62.5±13.5	62.3±13.5
Female sex — no. (%)	247 (36.2)	257 (38.0)
Region — no. (%)		
Western Europe	223 (32.7)	218 (32.2)
Eastern Europe	224 (32.8)	233 (34.4)
Southern Europe	226 (33.1)	226 (33.4)
Cardiovascular disease — no. (%)†		
Any	296 (43.3)	316 (46.7)
Coronary heart disease‡	130 (19.0)	147 (21.7)
Diabetes mellitus — no. (%)	230 (33.7)	251 (37.1)
Smoking — no./total no. (%)		
Never	360/683 (52.7)	318/673 (47.3)
Current	98/683 (14.3)	109/673 (16.2)
Past	225/683 (32.9)	246/673 (36.6)
Alcohol consumption — no./total no. (%)		
Never	357/679 (52.6)	343/674 (50.9)
Current	175/679 (25.8)	199/674 (29.5)
Past	147/679 (21.6)	132/674 (19.6)
Body mass index — no. (%)§	27.4±5.6	27.5±5.7
Body surface area — m²¶	1.86±0.22	1.86±0.22

Blankestijn PJ et al. *N Engl J Med* 2023;389(8):700-709.

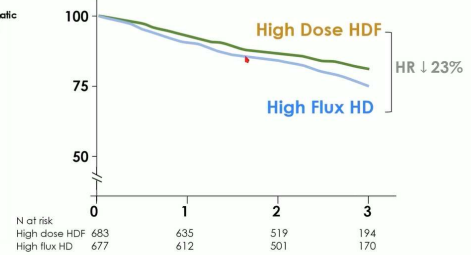
High-dose HDF Treatment Improves Overall Survival In CONVINCE Study Patients

European Multinational Pragmatic Randomized Clinical Trial

Study Design
1360 prevalent HD pts
>3mo. Ht-HF
683 post-HDF > 23l/ses.
677 Ht-HD EBPG

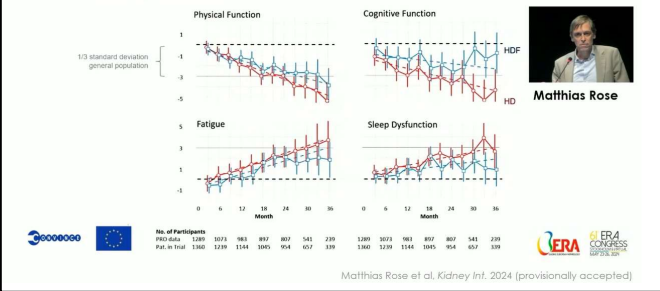
Primary Outcomes
• All-cause death

Secondary Outcomes
• Non-fatal CV events
• All-cause hospitalization
• PROMs

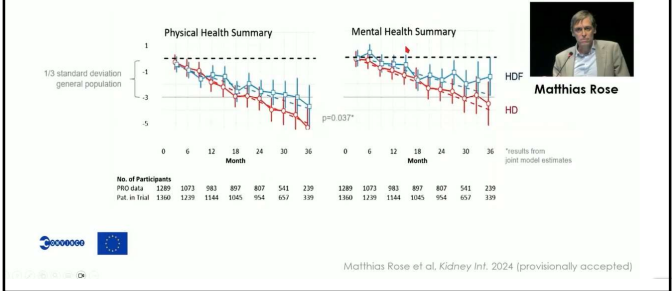


Blankestijn PJ et al. *N Engl J Med* 2023;389(8):700-709.

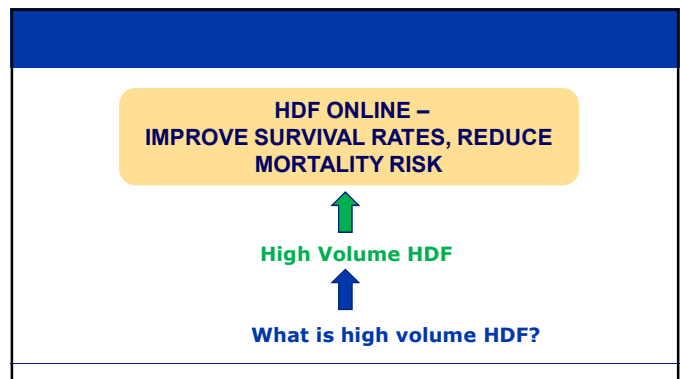
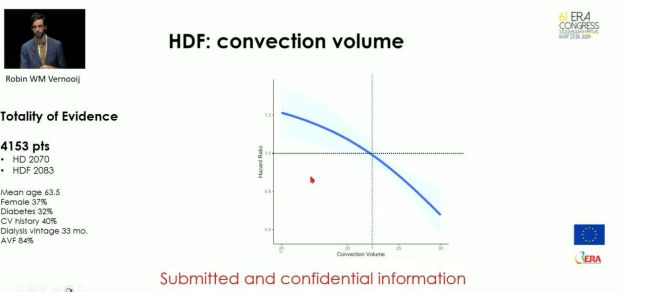
The CONVINC Trial Found Positive Effects of HDF on HR-QOL in Patients With Kidney Disease on Dialysis



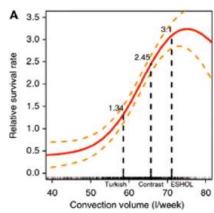
The CONVINC Trial Found Positive Effects of HDF on HR-QOL in Patients With Kidney Disease on Dialysis



Totally of Evidence: Risk Reduction in All-Cause Mortality is Confirmed to be Convective Dose-Dependent



HV HDF OL – Post dilution- Convection Volume



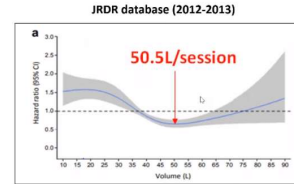
Convection Volume, L/1.73m ² per session	Hazard Ratio	
	HD N=1469	HDF N=1467
All-cause mortality		
All	1.0	0.86 (0.75-0.99)
<19	1.0	0.83 (0.66-1.03)
19-23	1.0	0.93 (0.75-1.16)
>23	1.0	0.78 (0.62-0.98)
Cardiovascular mortality		
All	1.0	0.77 (0.61-0.97)
<19	1.0	0.92 (0.65-1.30)
19-23	1.0	0.71 (0.49-1.03)
>23	1.0	0.69 (0.47-1.00)

Convection volume >23L/session (high Volume HDF)

Cinauati et al. CJASN 2018;13 (9) 1435-1443

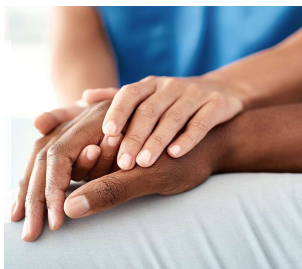
HV HDF OL – Pre-dilution- Convection Volume

Optimal convection volume: Pre-dilution HDF



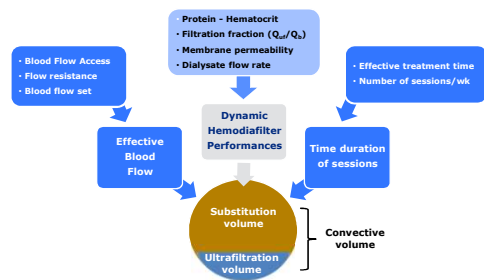
Convection volume >50.5L/ session (high Volume HDF)

Content



- 1 WHY HDF OL?
- 2 CURRENT THERAPY STANDARD
- 3 HIGH VOLUME - HDF
- 4 HOW TO ACHIEVE HV- HDF
- 5 CONCLUSIONS

HDF – Factors Affecting Convection Volume



Prescription for HV-HDF

Parameter	Target Range
Hemodialyzer	
Membrane	High flux, 1.6-2.2 m ²
Fiber internal diameter	≥200 μm
Ultrafiltration coefficient	>20 mL/h per 1 mm Hg per 1 m ²
Sinking coefficient	>0.6 for β ₂ -microglobulin; <0.001 for albumin
Vascular Access	
ART or AVG (corrected central venous catheter)	Needles, 14-15 G
Blood flow rate	350-450 mL/min
Dialysate Flow Rate	
Total (including substitution solution)	600-1000 mL/min
Dialysate	900-900 mL/min
Convection Volume	
Postdilution	23 L per treatment or 90 L/1.73 m ²
Pre-dilution	48 L per treatment or 92 L/1.73 m ²
Mix-dilution or mixed dilution	38 L per treatment or 40 L/1.73 m ²
Ultrafiltration Control	
Manual	TMP < 400 mm Hg, Filtration fraction < 0.20
Automated	TMP < 105-200 mm Hg
Anticoagulation	
Unfractionated heparin	No-dose adjustment
Low-molecular-weight heparin	Dose and injection site adjustment
Dialysate composition	Adjusted according to patient need and convection volume

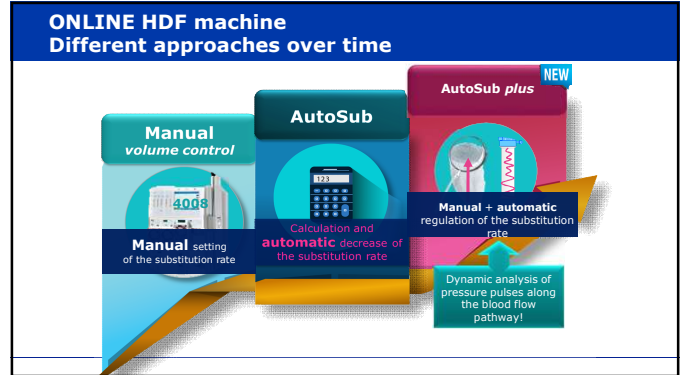
SIXTH EDITION

HANDBOOK OF DIALYSIS THERAPY

12

Hemofiltration and Hemodiafiltration

MARTIN K. KULLMANN, MD



HDF OL machine- AutoSub plus

- Task:** Maximising substitution volumes in ONLINE HDF for high convective removal of middle molecules, while avoiding haemoconcentration and filter clotting.
- Handling:**
 - AutoSub plus is automatically activated at start of treatment
 - No need of user interaction / no entering of patient specific parameter, e.g. Hct, TP value
 - AutoSub plus replaces the AutoSub function
 - Two ways to control the substitution volume in ONLINE HDF
 - AutoSub plus
 - Manual

Estimated sub goal ● AutoSub plus

35.5 I/O

Best Handling:

- No need to enter patient specific parameters (e.g. Hct, TP, prescribed dialyser)
- AutoSub plus is automatically activated at start of treatment

