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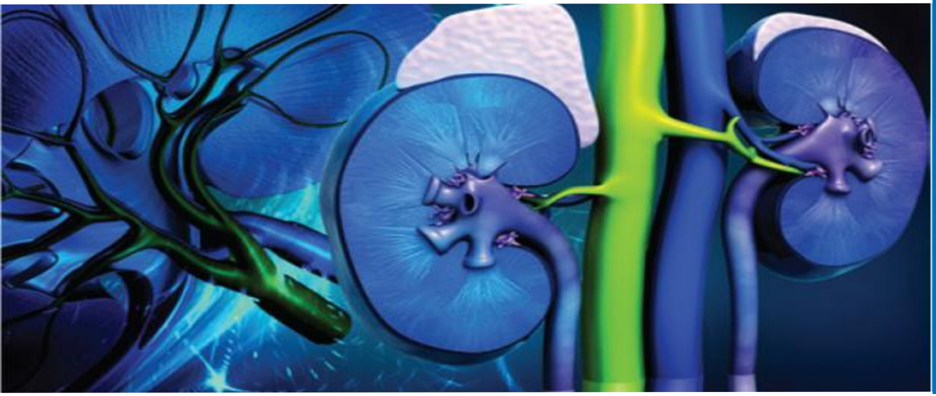
Hemo-diafiltration

A viable renal replacement therapy modality



Iranian Society of Nephrology

Tabriz, Iran

November 20, 2019

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Disclosures

- I have no conflict of interest with this activity

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Outlines

- Dialysis modalities
  - Technical aspects
- Physiological implications
- Clinical implications
- Final recommendations

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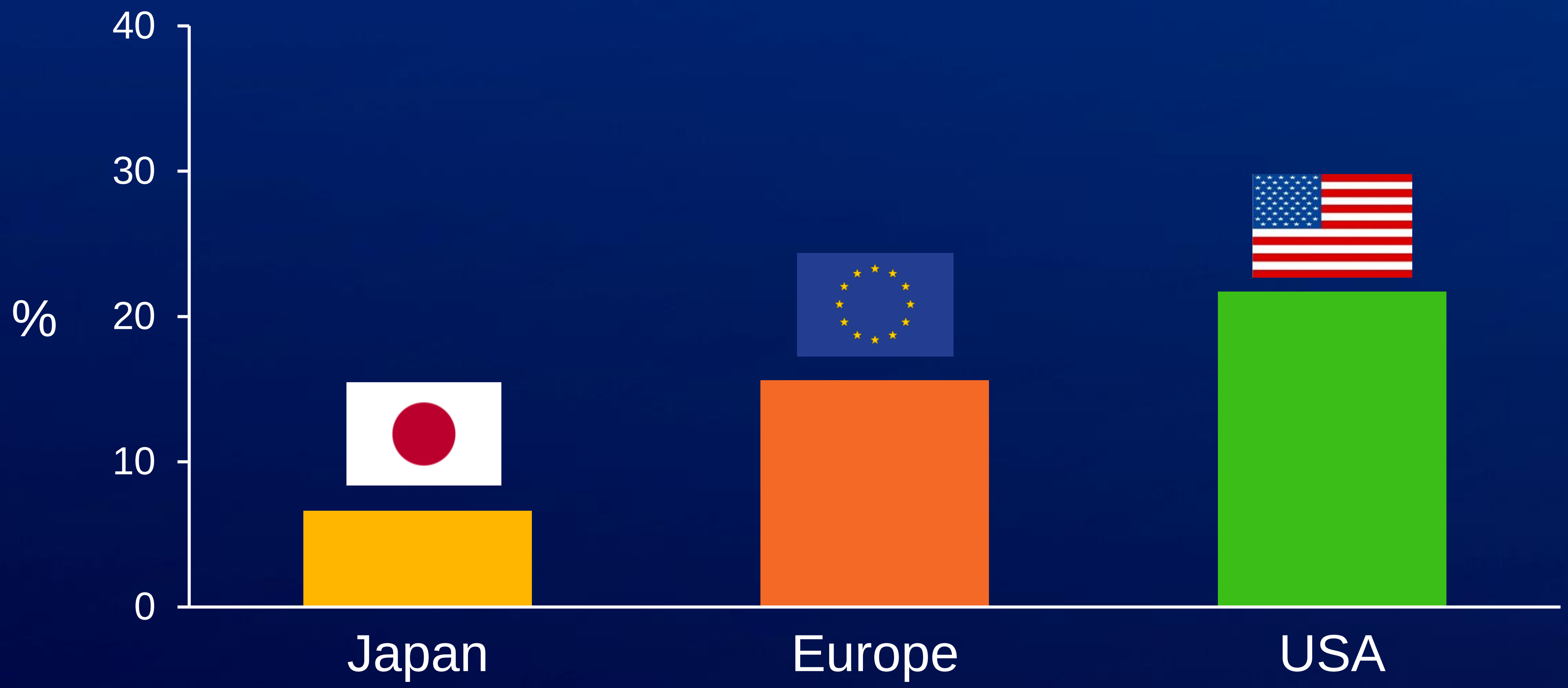
Annual Crude Mortality

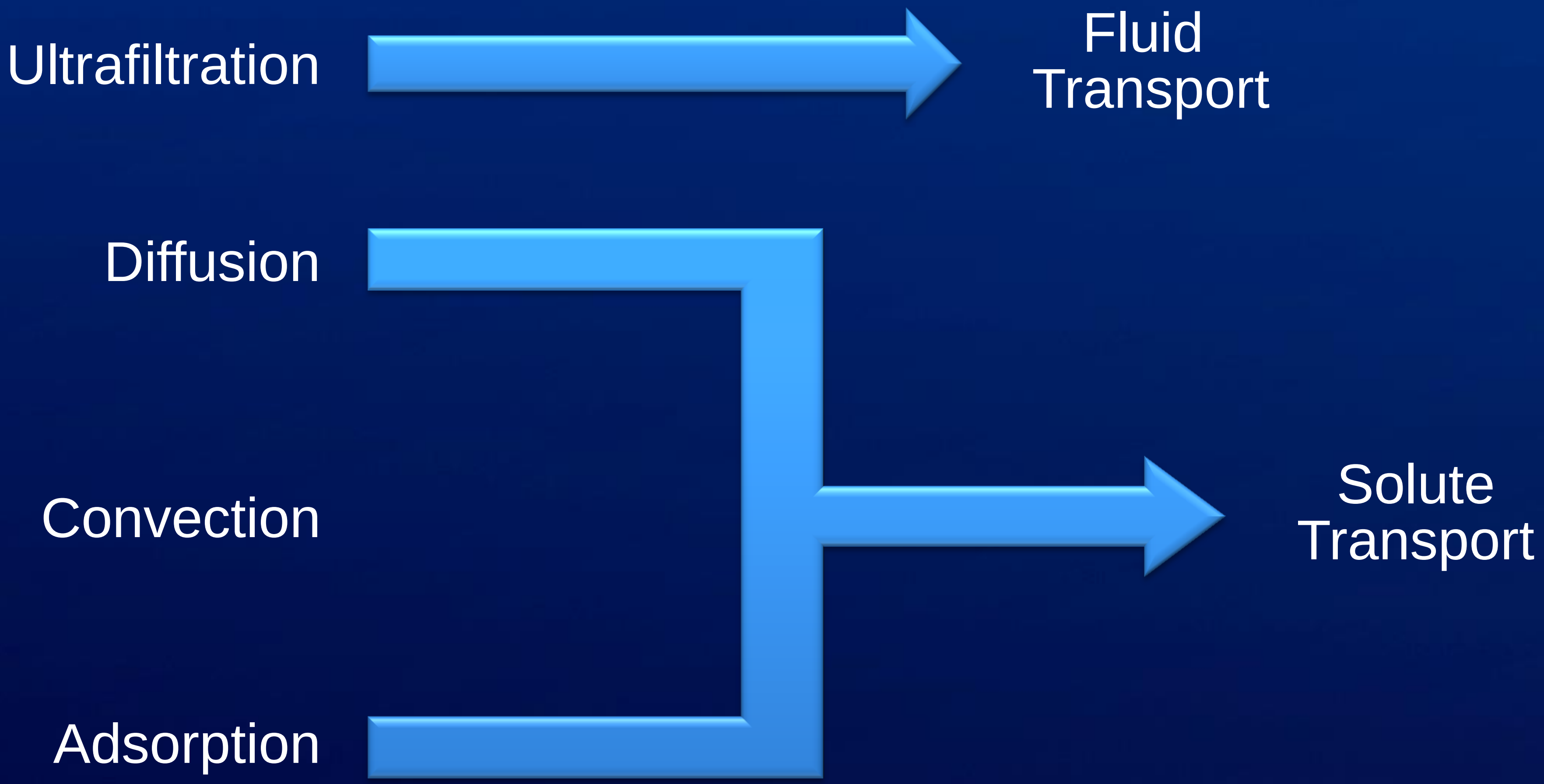
ESRD



Clearance type

Modality

Molecular Transport Mechanisms



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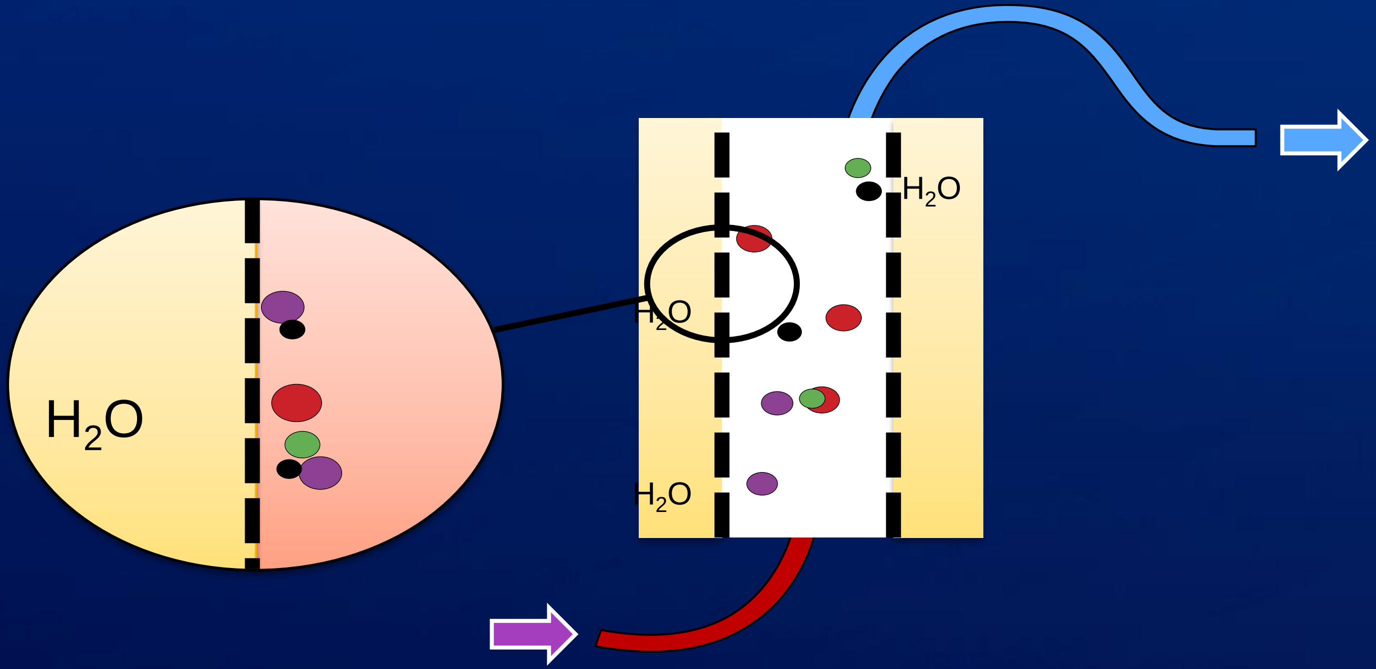
Ultrafiltration

- Fluid movement
  → Semipermeable membrane
  → Pressure gradient
- Any renal replacement modality

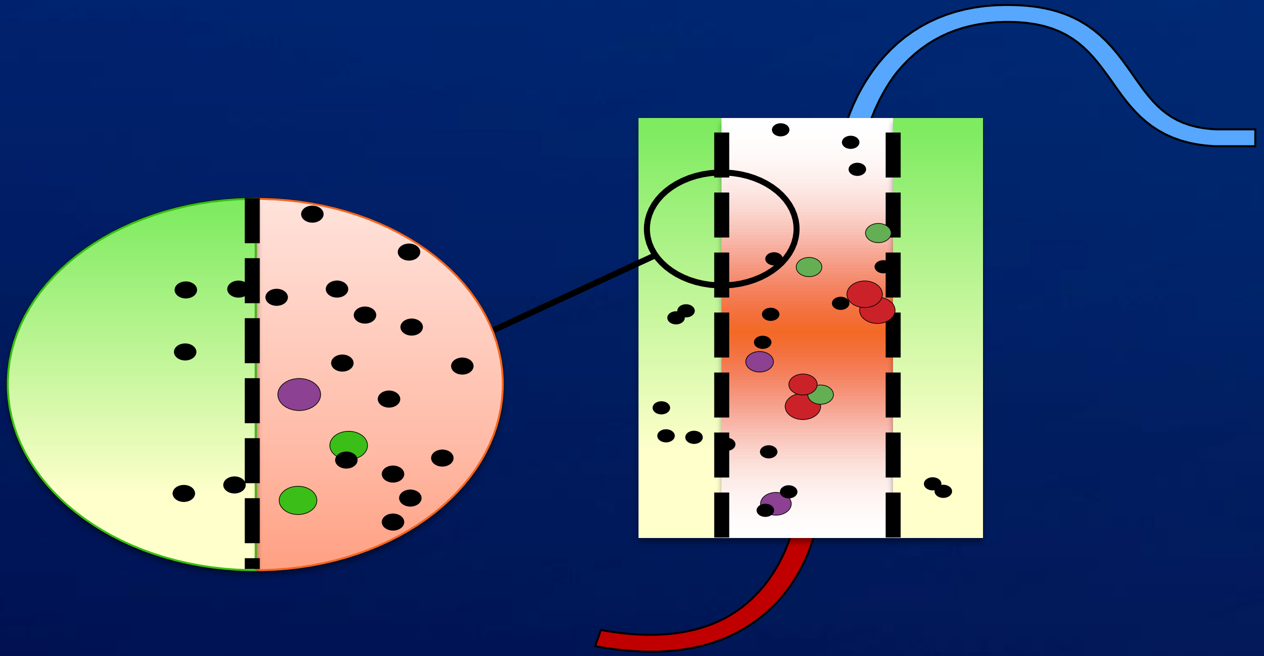


Diffusion

- Dialysate solution

→semi-permeable membrane

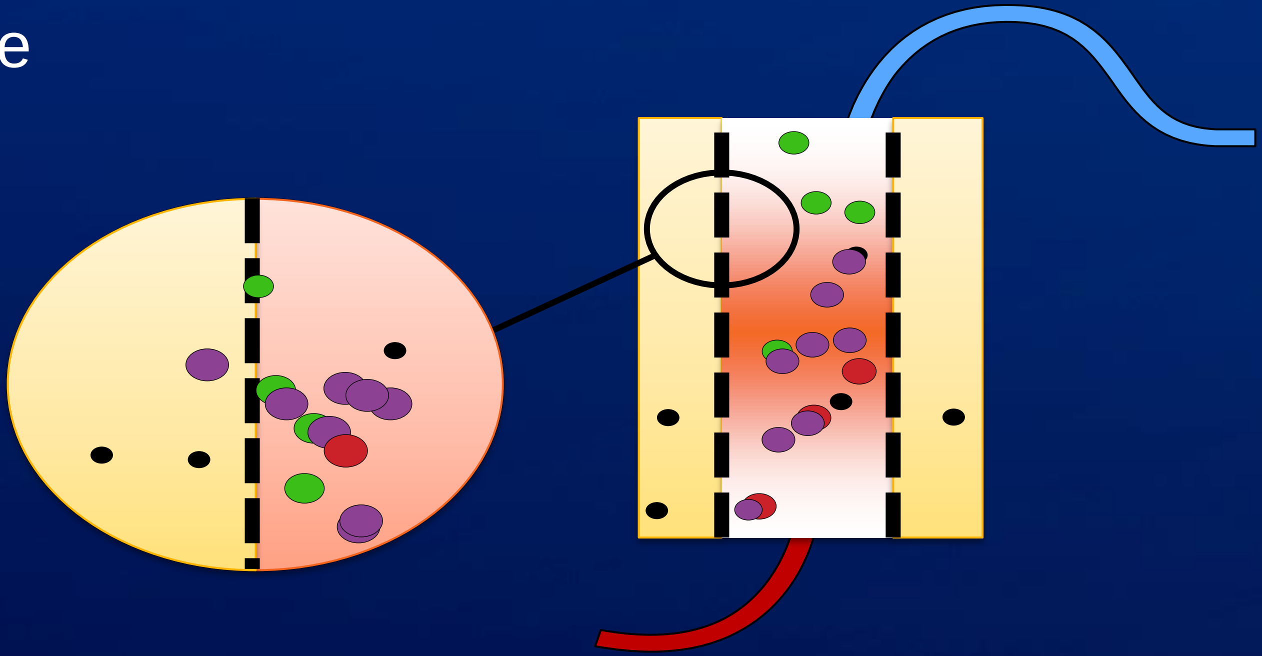
→ concentration gradient



- Counter-current
  - Dialysate-Blood flow

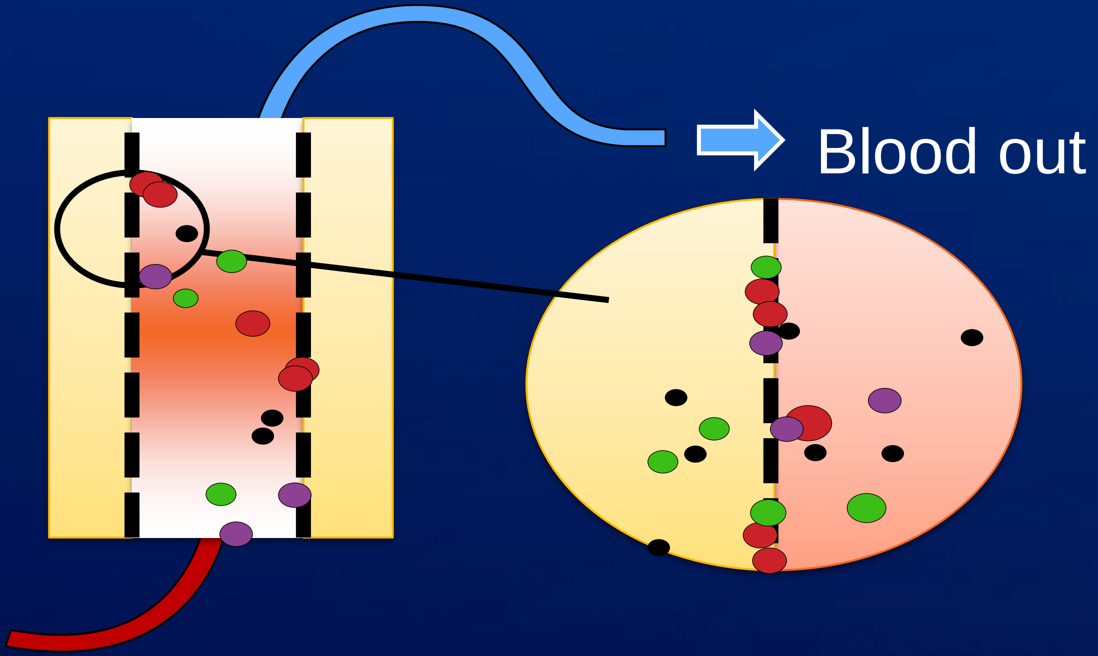
Convection

- Fluid movement
  → Semipermeable membrane
  → Pressure gradient
  → Solvent Drag
- Clearance
  - Small molecules
  - Medium molecules
  - Large molecules

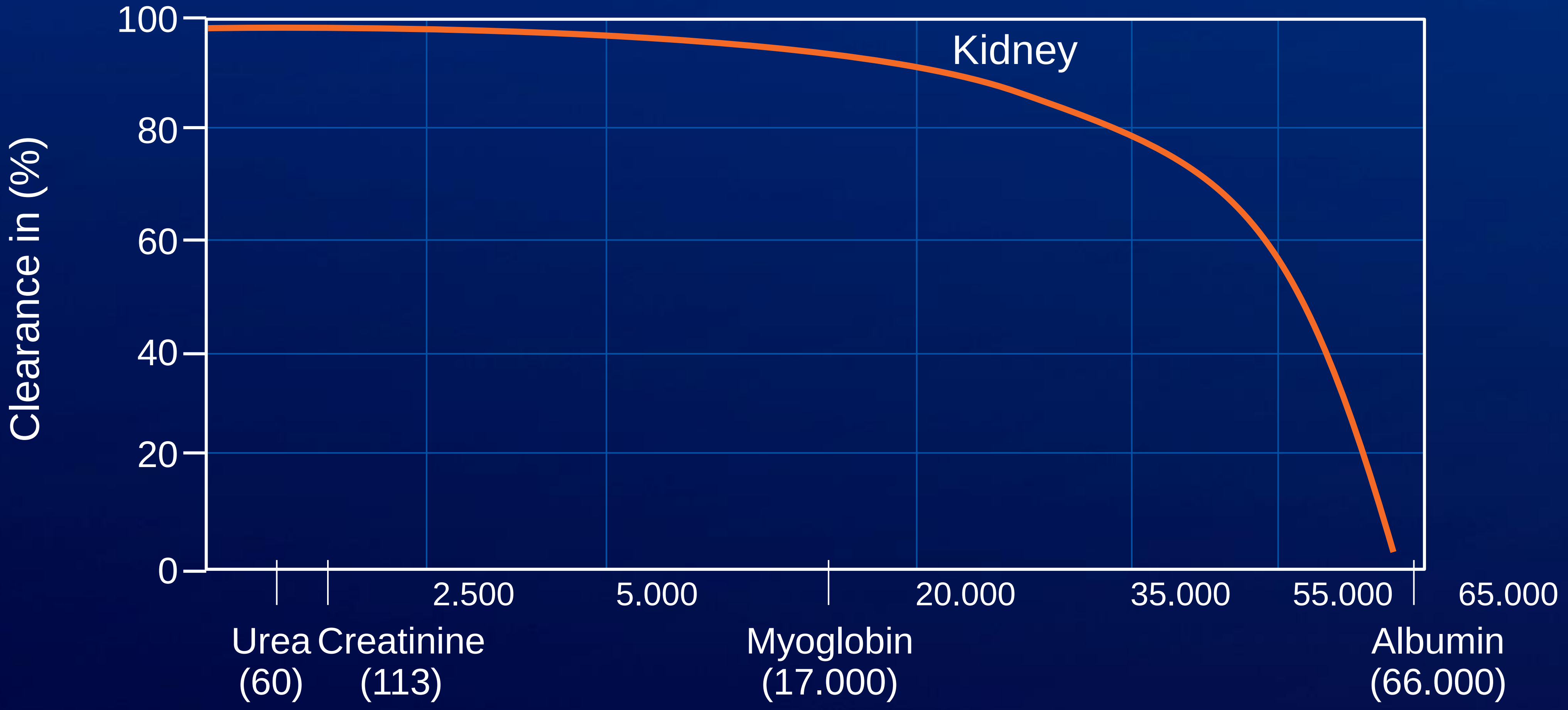


Adsorption

- Adherence to semipermeable membrane
  - Surface
  - Interior



Diffusion vs. Convection



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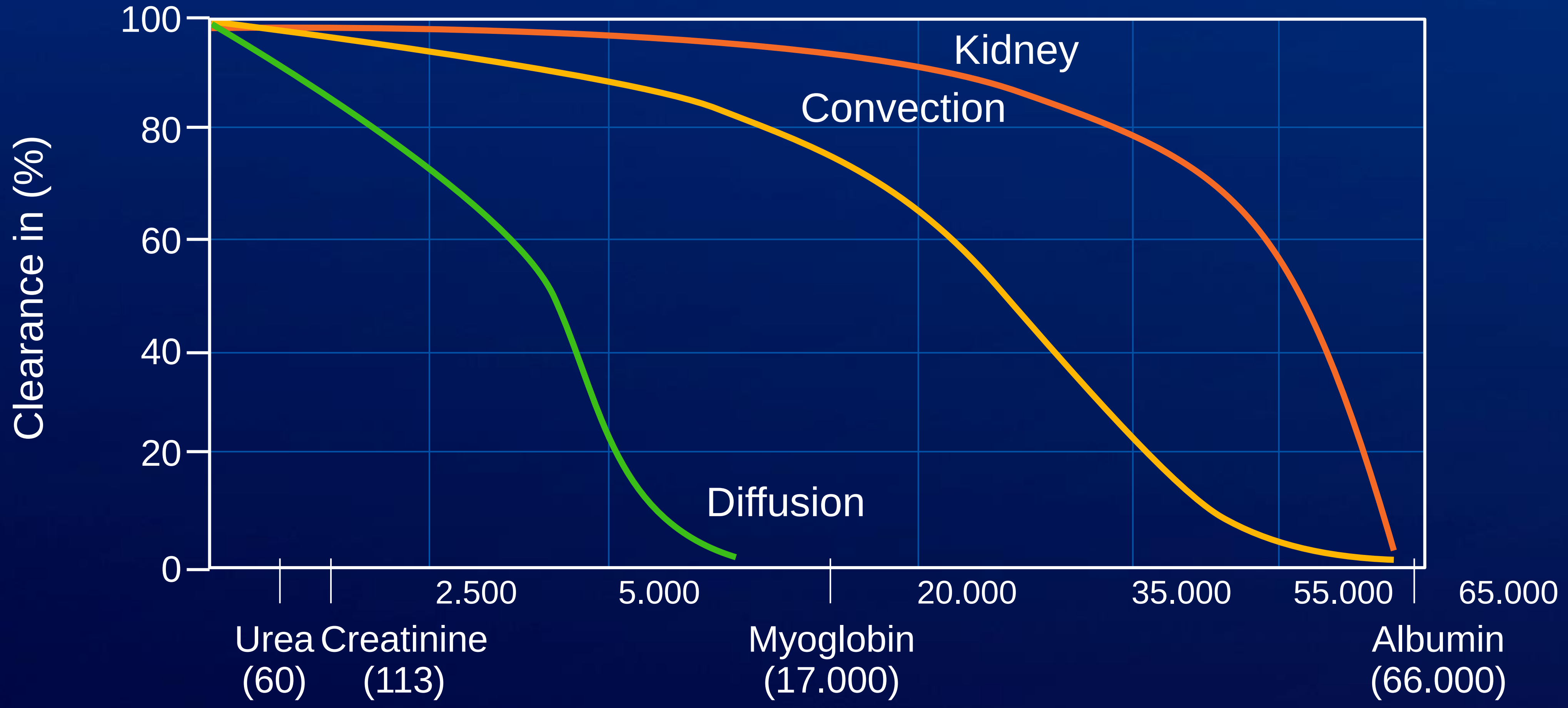
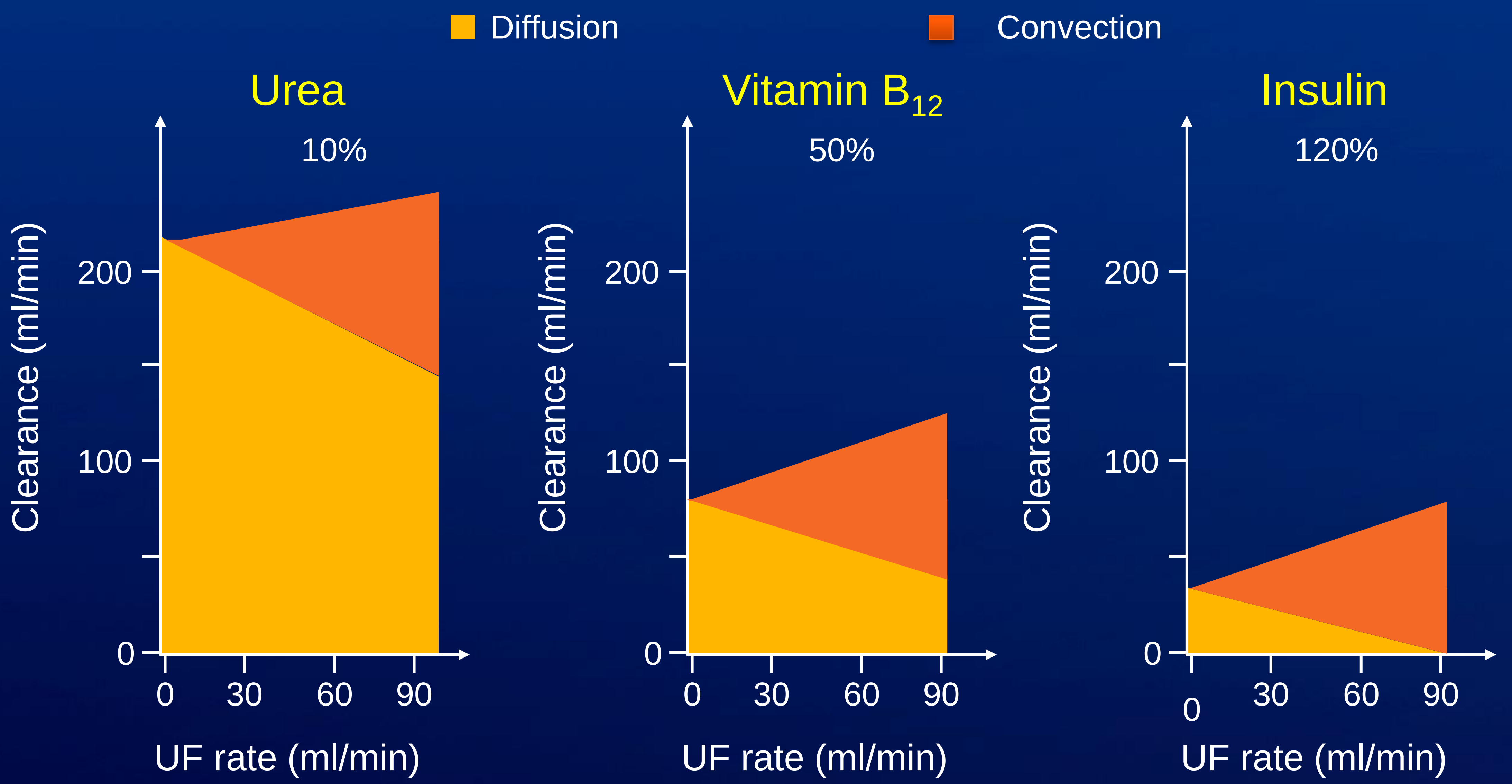
Diffusion vs. Convection





Calculated values

Ledebo I, Blankestign PJ: NDT Plus 3:8, 2010

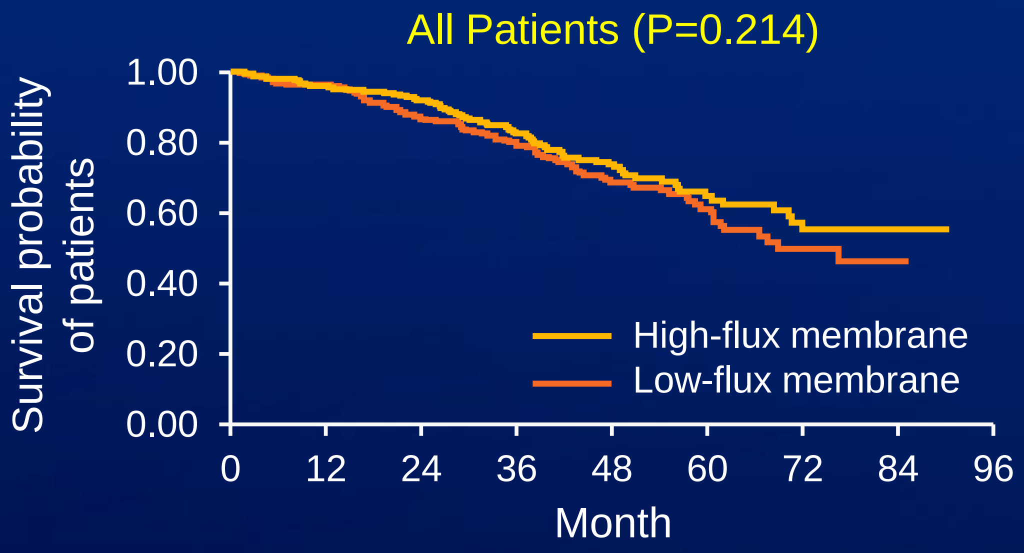
Why Middle Molecules removal?

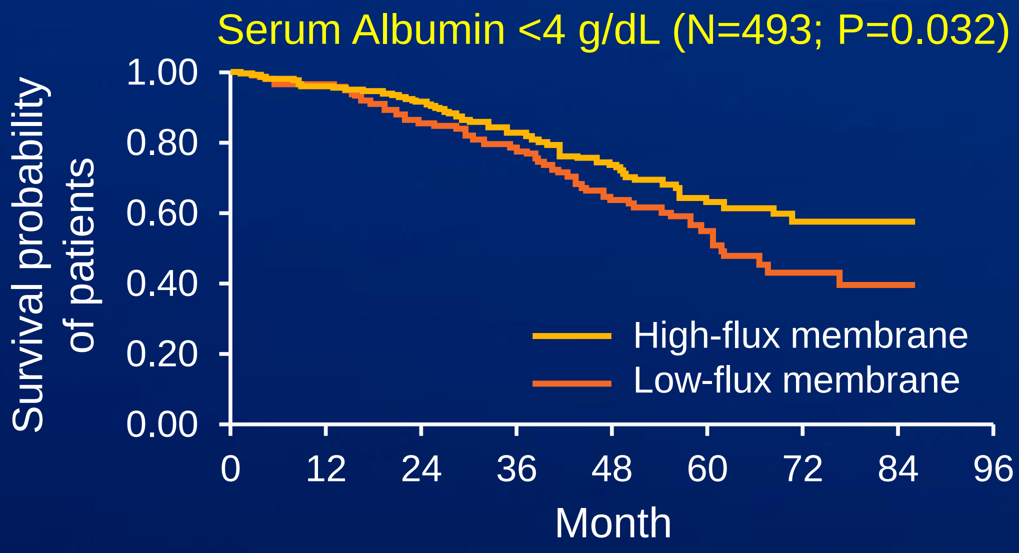
- Direct vascular toxicity
- Observational studies:
  - Association with CV / infection-related mortality
- RCTs:
  - Favorable effect of high-flux HD on the risk of death and/or hospitalization due to cardiac causes

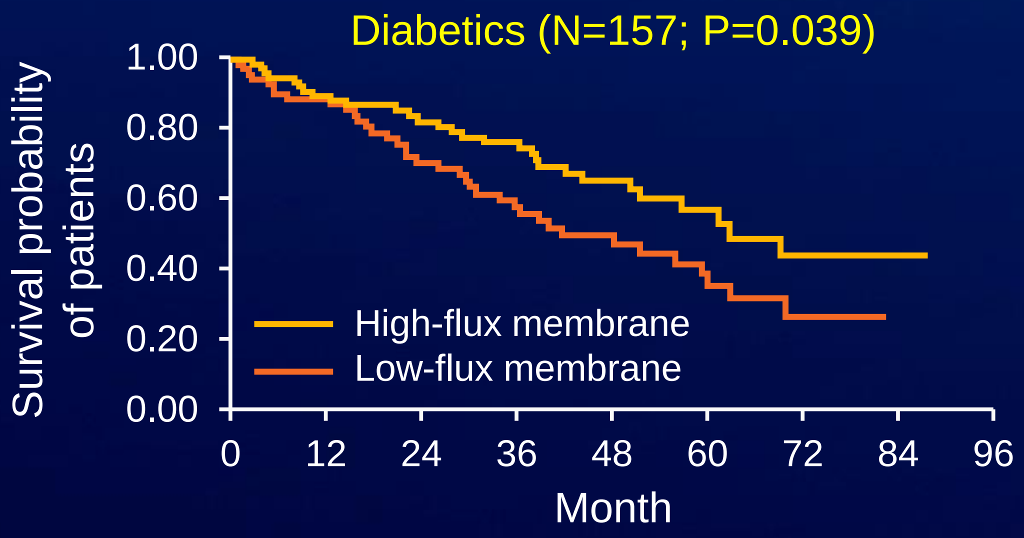
Liabeuf S et al Kidney Int 2012; 82:1297
Eknoyan et al New Eng J Med 2002; 347:2010

MPO study

RCT; low vs. high flux HD; N=738







Locatelli F et al: JASN 20:645, 2009

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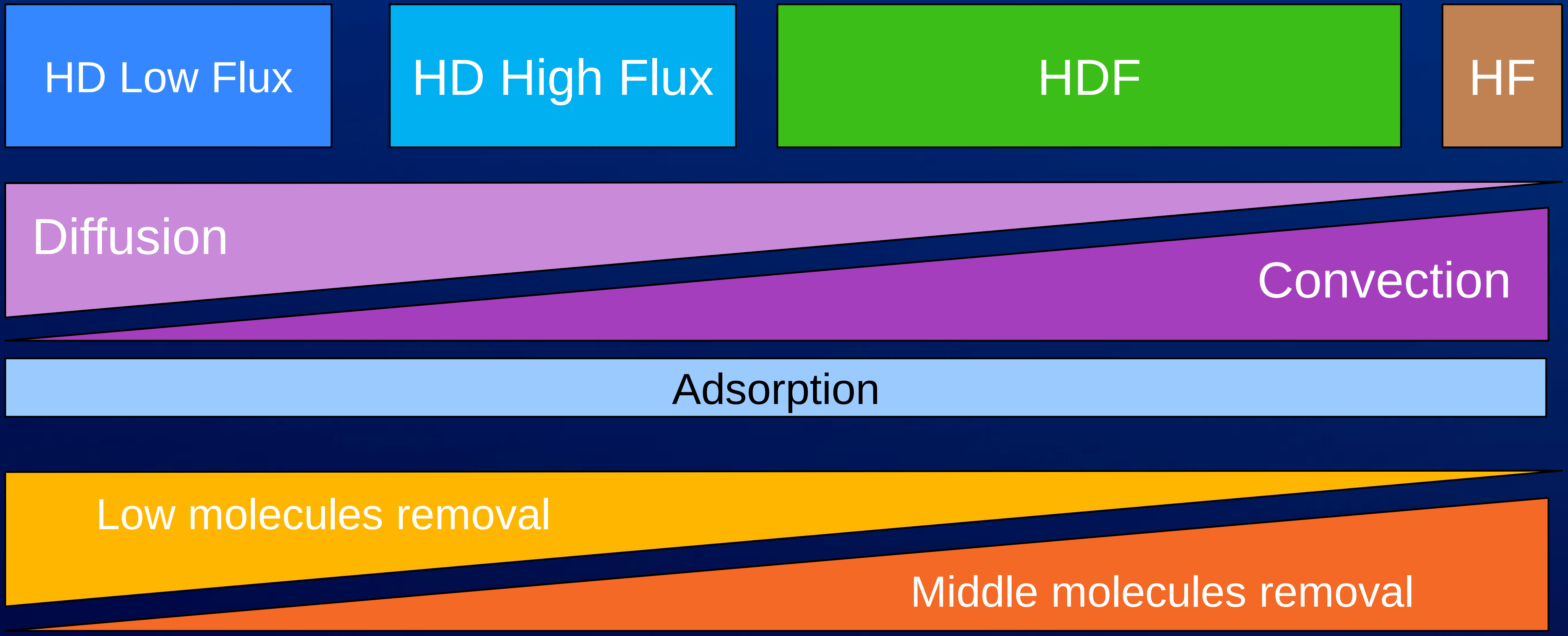
Modalities and modes of clearance



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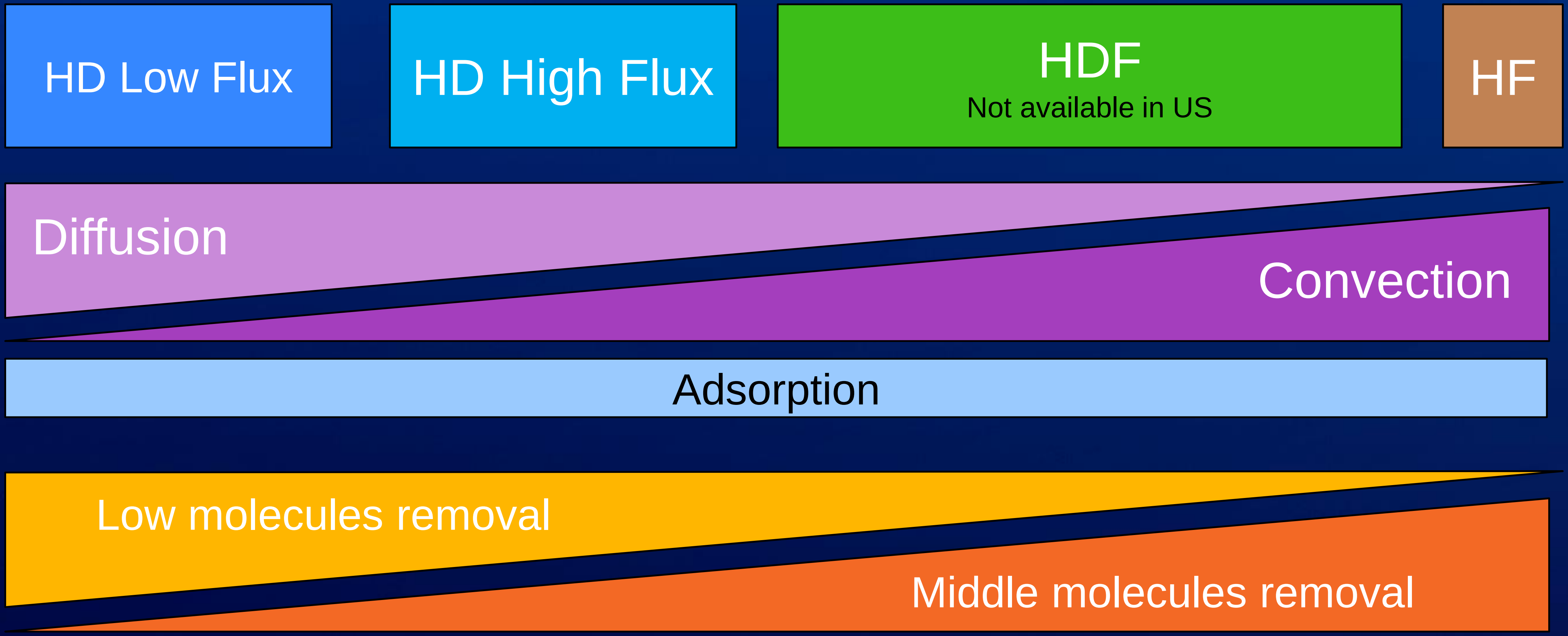
Modalities and modes of clearance



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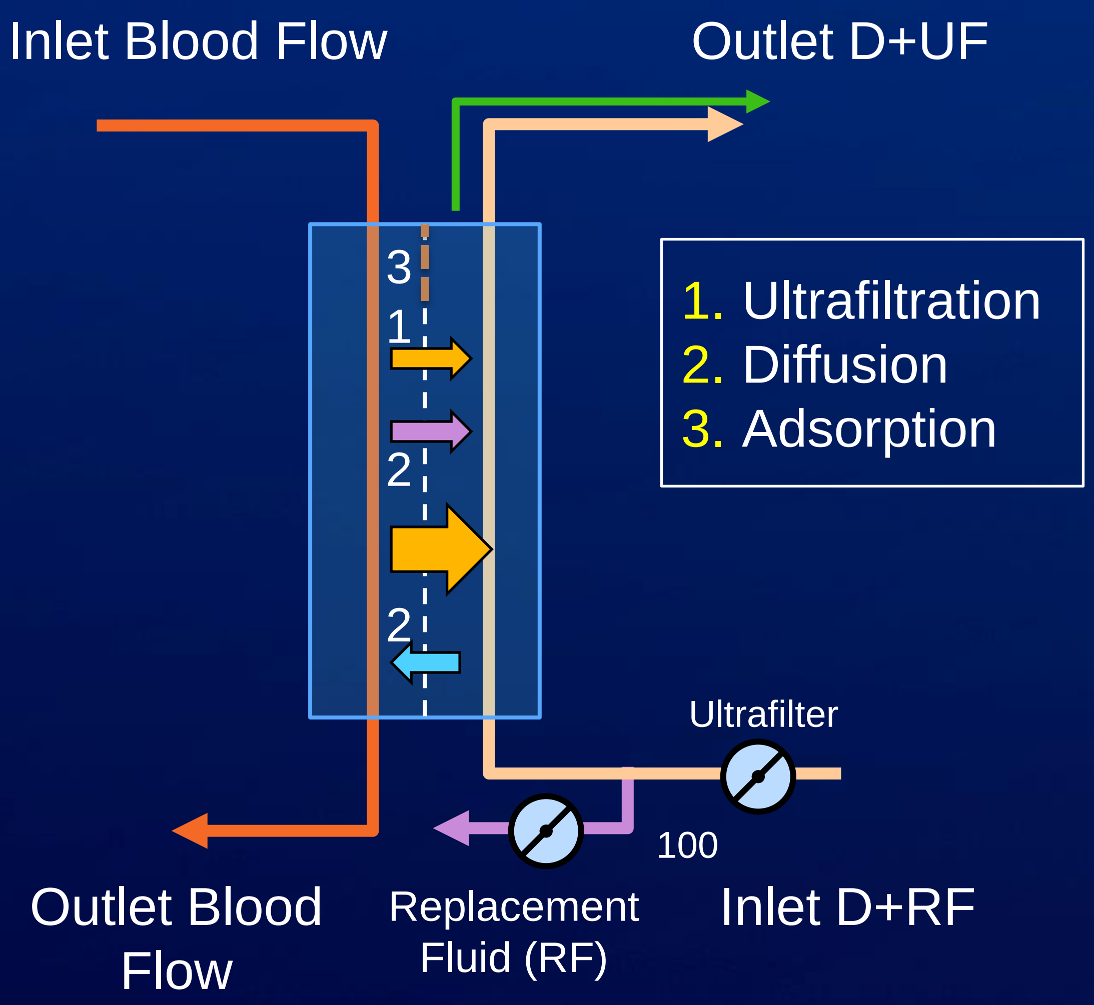
Prescription

Hemodiafiltration

HDF Clearance

Diffusive, Convective and Adsorptive



Prescription

- Treatment Schedule
  - 3 session
  - 4 hours per session (minimum)
    - Longer or more frequent (possible)
- Ultrapure bicarbonate-based dialysate
  - Composition adjusted for:
    - Pt need
    - Convection volume

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Parameter	Target range
Dialyzer	
Membrane	High flux, 1.6–2.2 m^2
Fiber internal diameter	>200 micrometer
Ultrafiltration coefficient	>20 ml/h / mm Hg / m^2
Sieving coefficient	>0.6 for β_2-Microglobulin <0.001 for albumin
Vascular access	AVF or AVG → Needles 14–15 g Tunneled CVC
Blood flow rate	350–450 ml/min
Dialysate flow rate	500–700 ml/min
Convection volume	
Post-dilution	23 L per treatment or 26 L/1.73 m^2
Pre-dilution	46 L per treatment or 52 L/1.73 m^2
Mid- or mixed dilution	35 L per treatment or 40 L/1.73 m^2
UF control	Manual: TMP <400 mm Hg; FF <25% Automated: TMP=105-300 mm Hg
Anticoagulation	UFH or LMWH

Canaud et al. cJASN 13: 1435–1443, 2018

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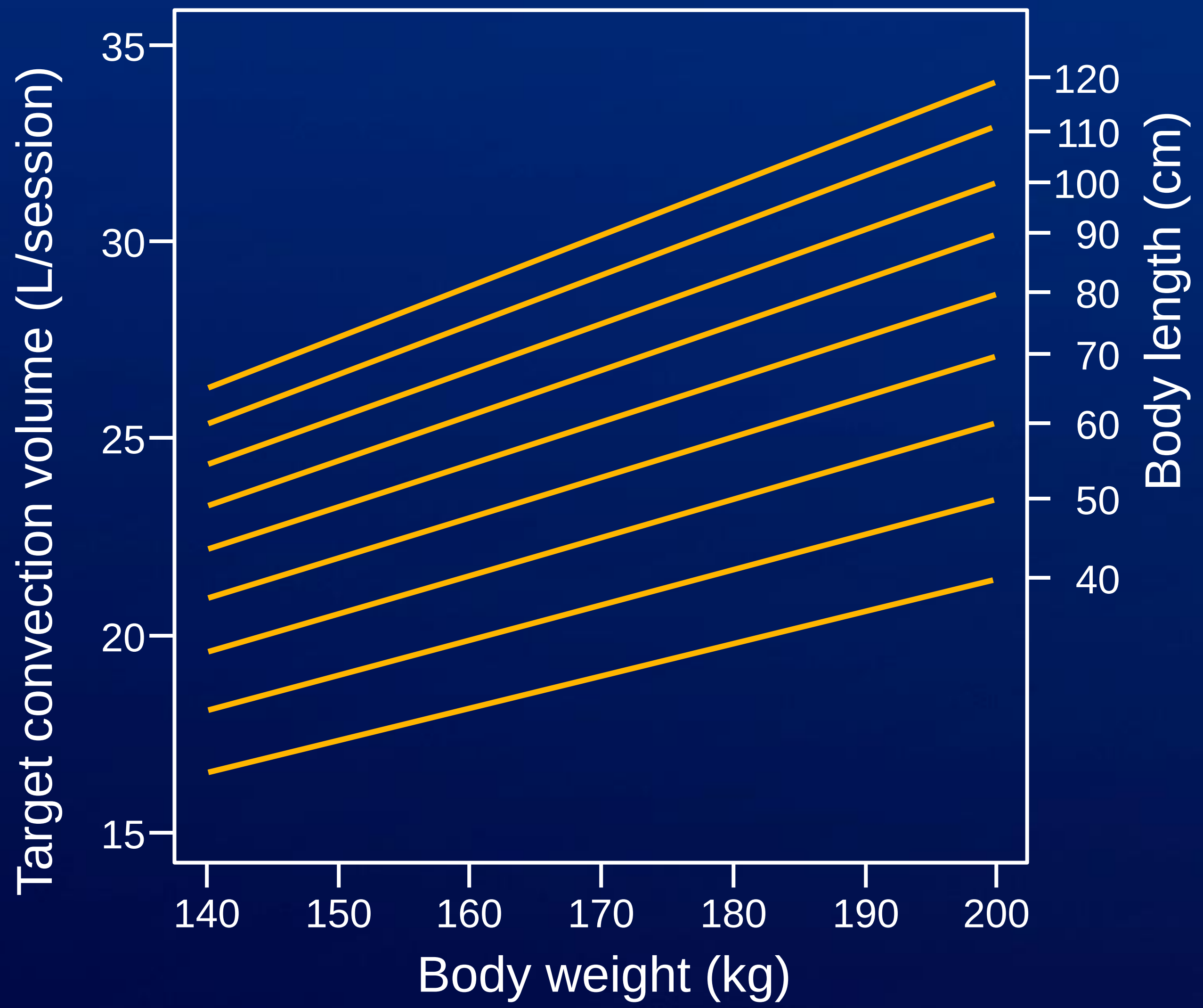
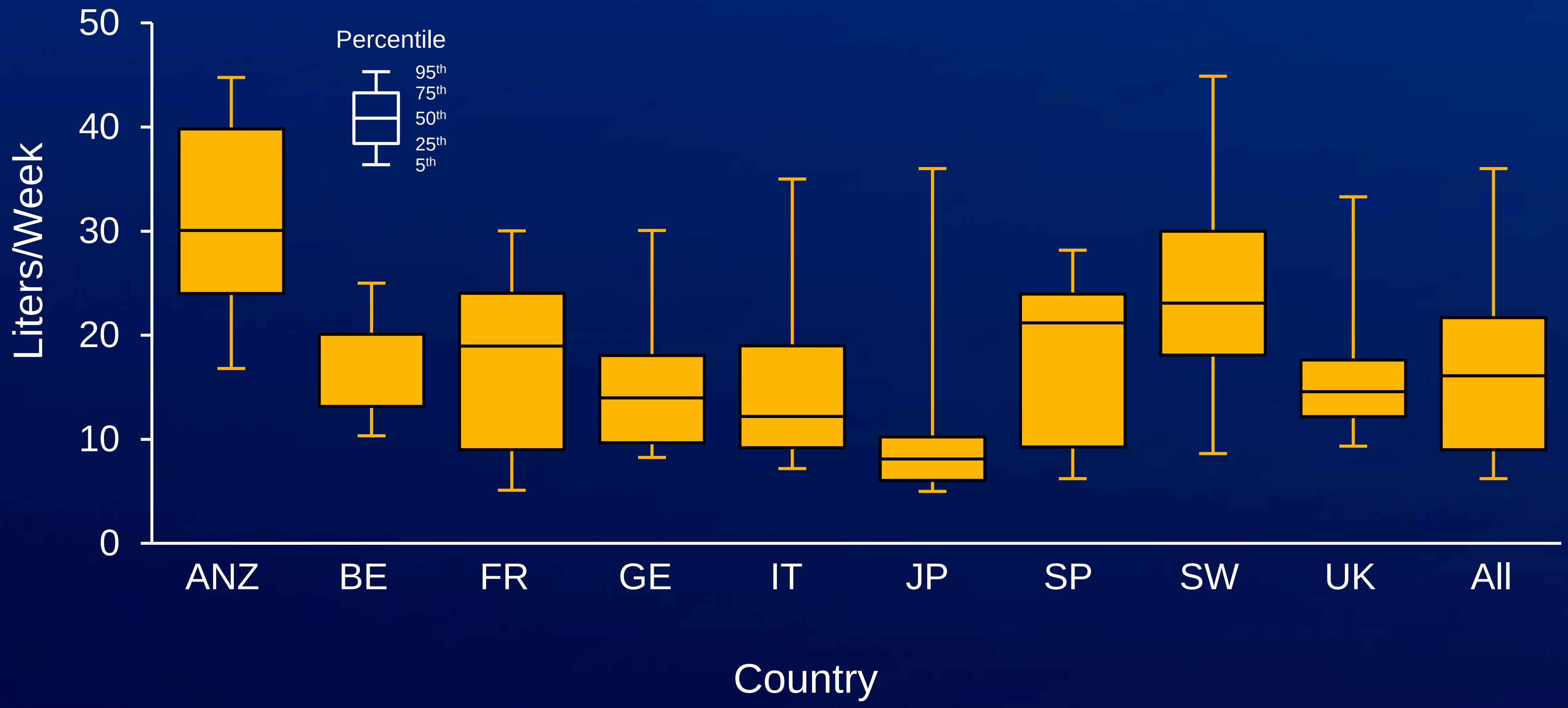
Target Convection Volume by Body Size



MAYO CLINIC

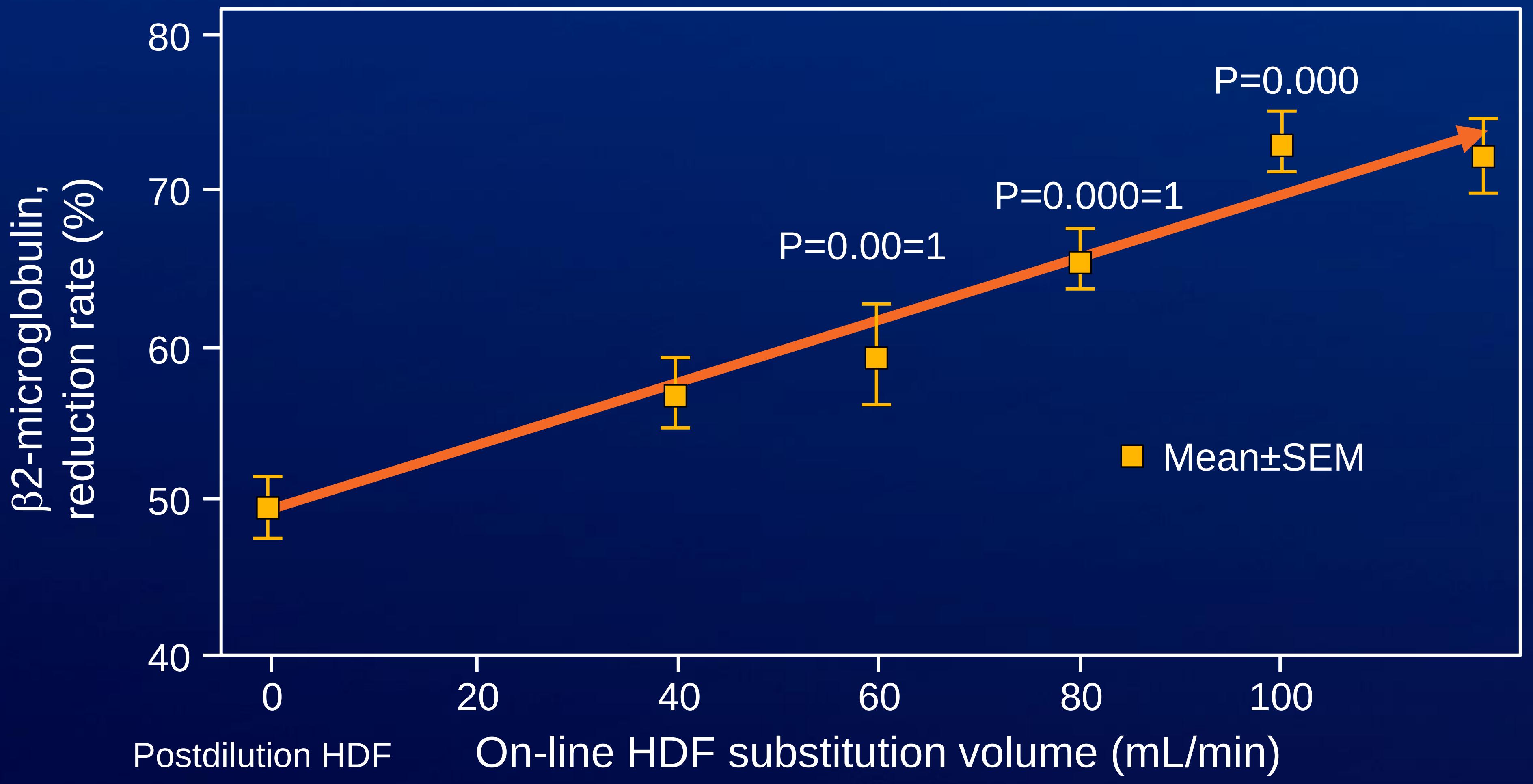
Peters et al: Nephrol Dial Transplant 31:978, 2016

Convection Volume



Convective Dose

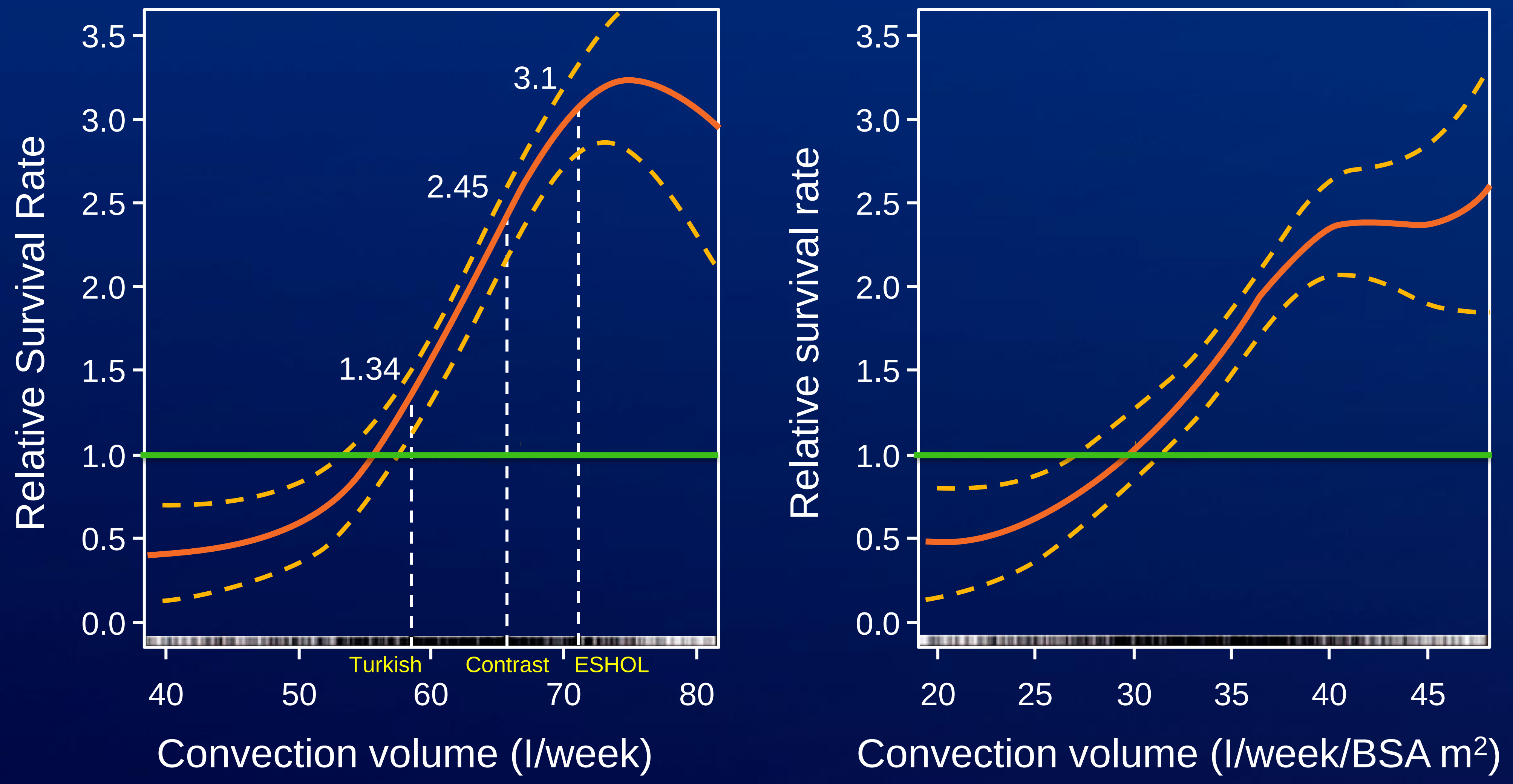
Linear Function of Substitution Volume



Lornoy W et al: Nephrol Dial Transplant 15:46, 2000

Convection dose

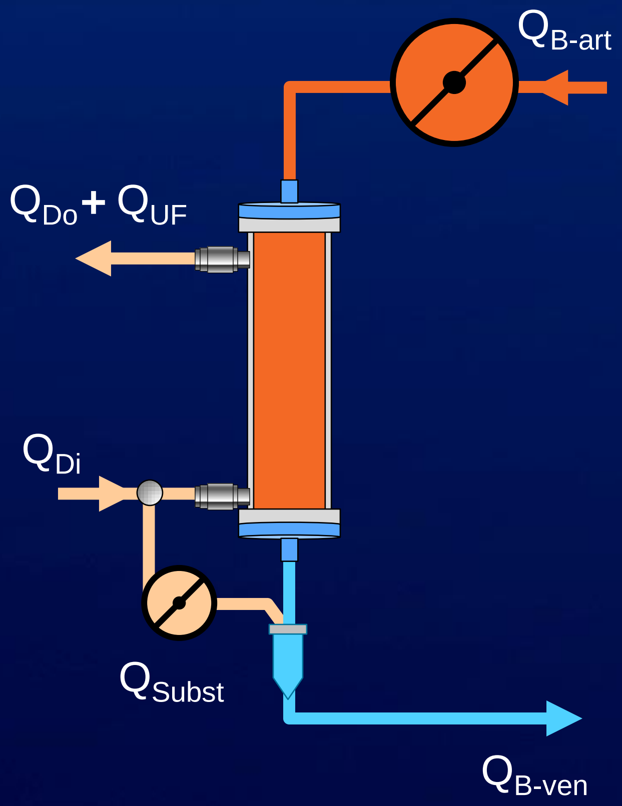
Survival



Canaud et al. Clin J Am Soc Nephrol 13: 1435–1443, 2018

Dilution methods

Post-dilution HDF



Canaud et al. Clin J Am Soc Nephrol 13: 1435–1443, 2018

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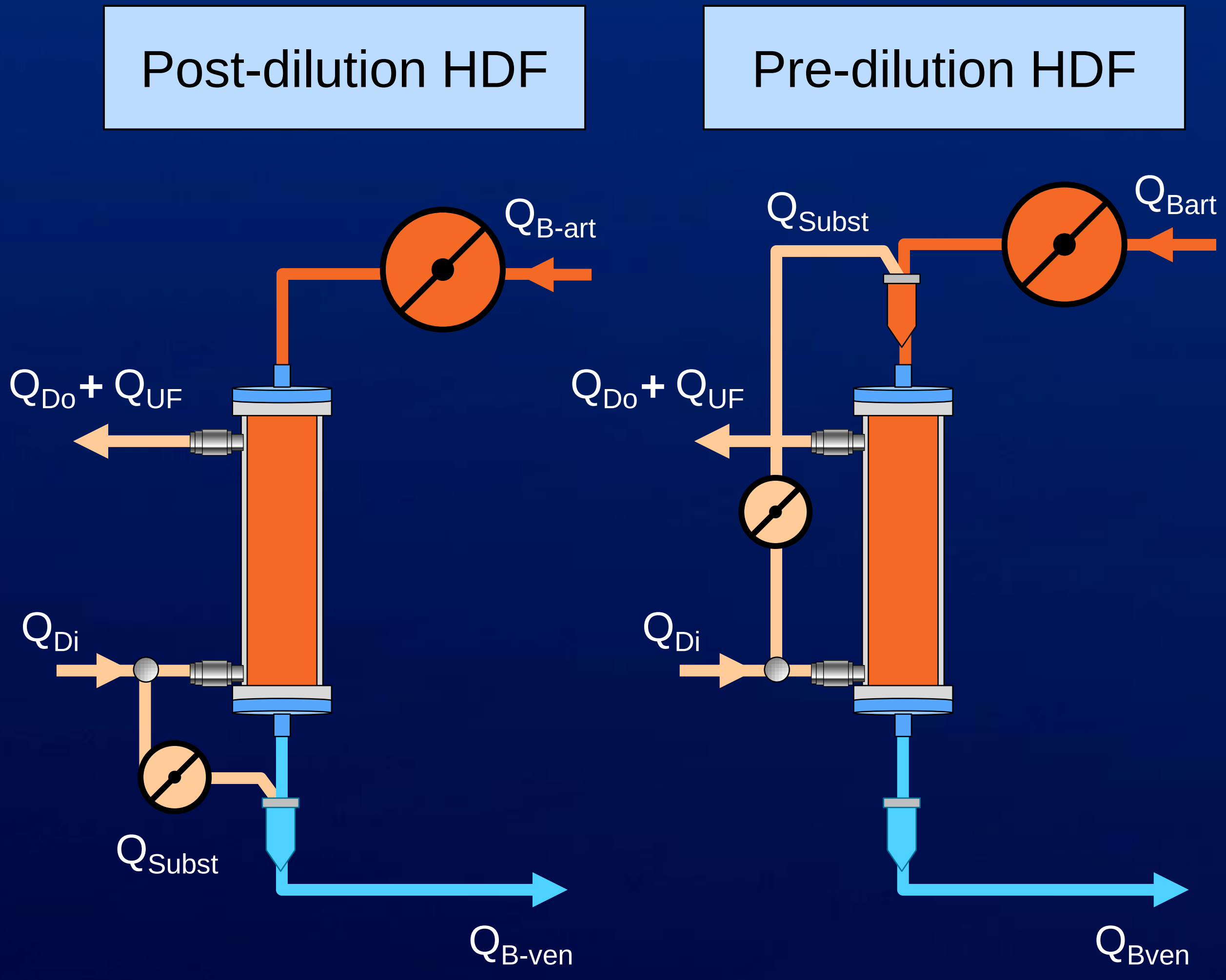
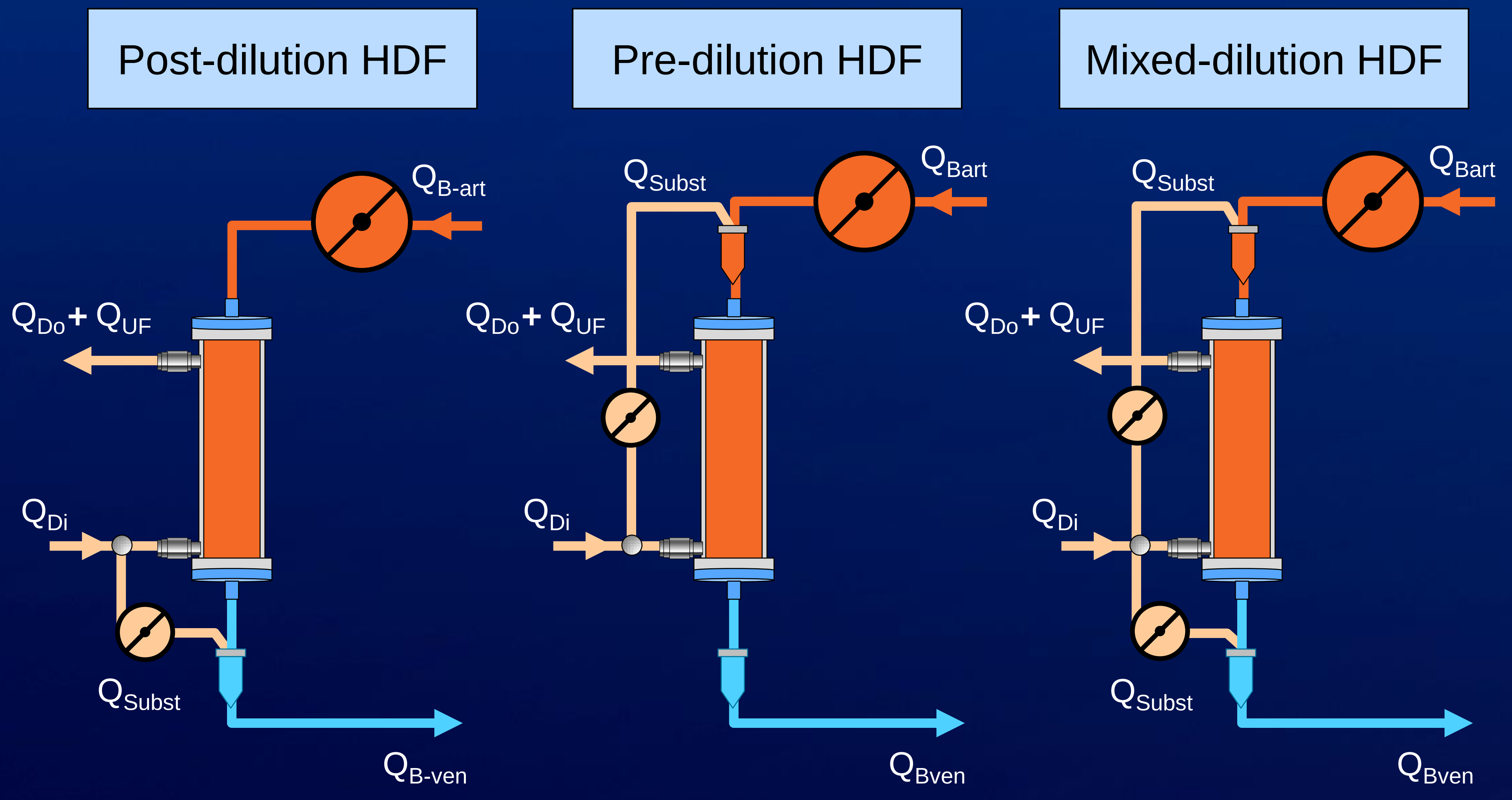
Dilution methods



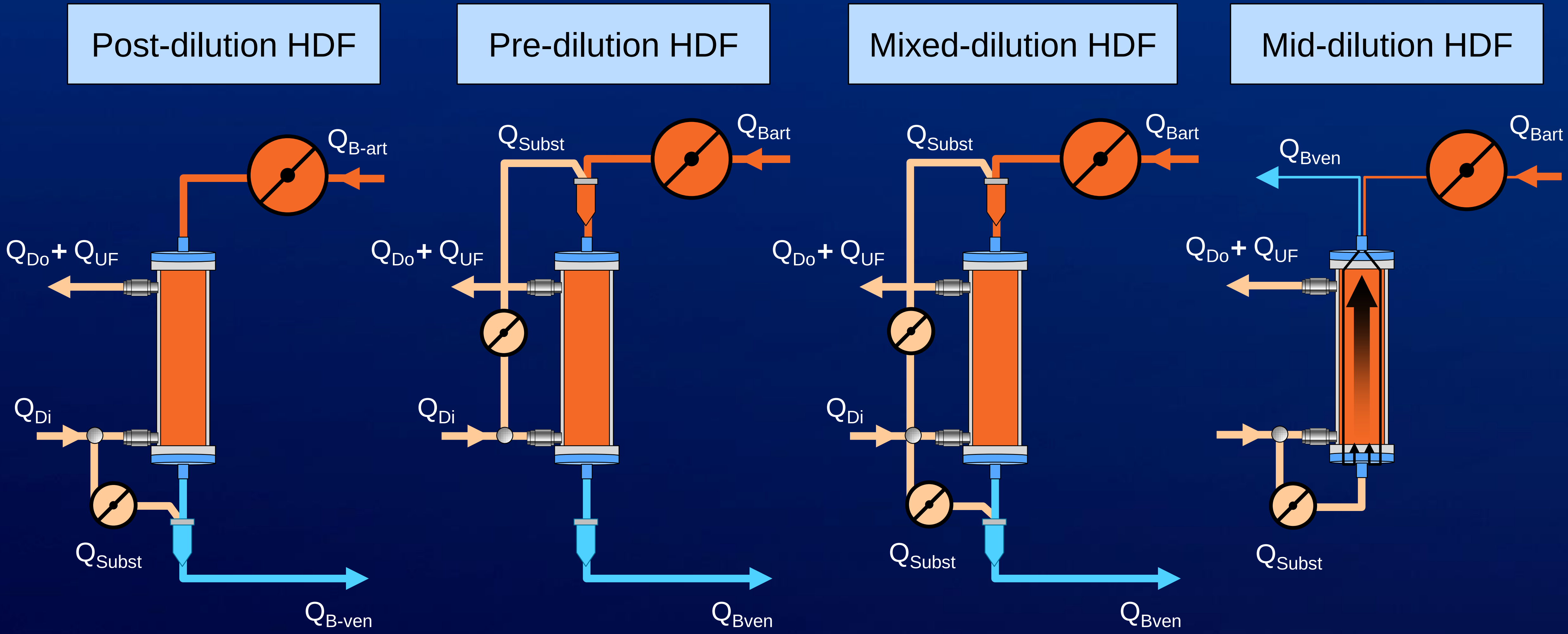
Canaud et al. Clin J Am Soc Nephrol 13: 1435–1443, 2018

Dilution methods



Canaud et al. Clin J Am Soc Nephrol 13: 1435–1443, 2018

Dilution methods



Canaud et al. Clin J Am Soc Nephrol 13: 1435–1443, 2018

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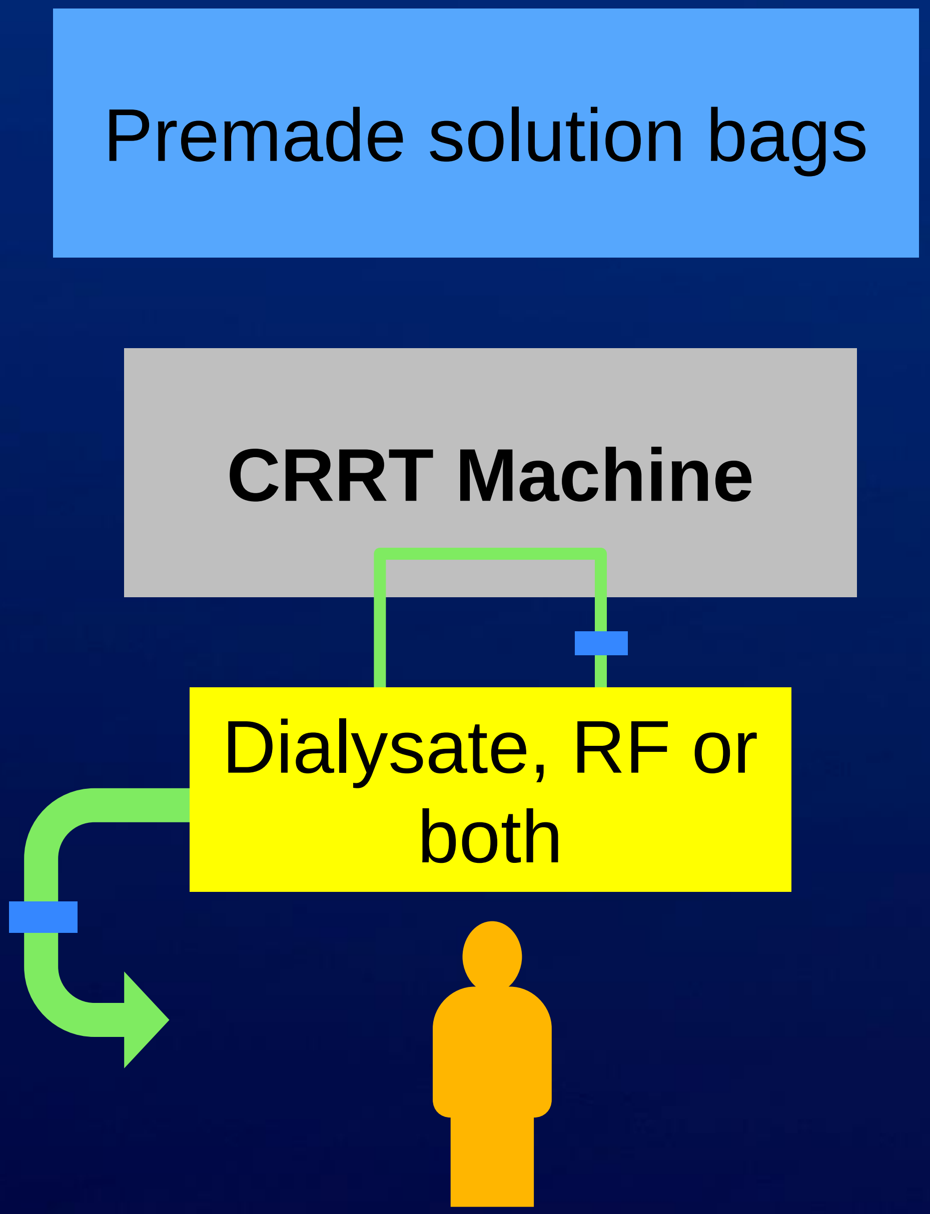
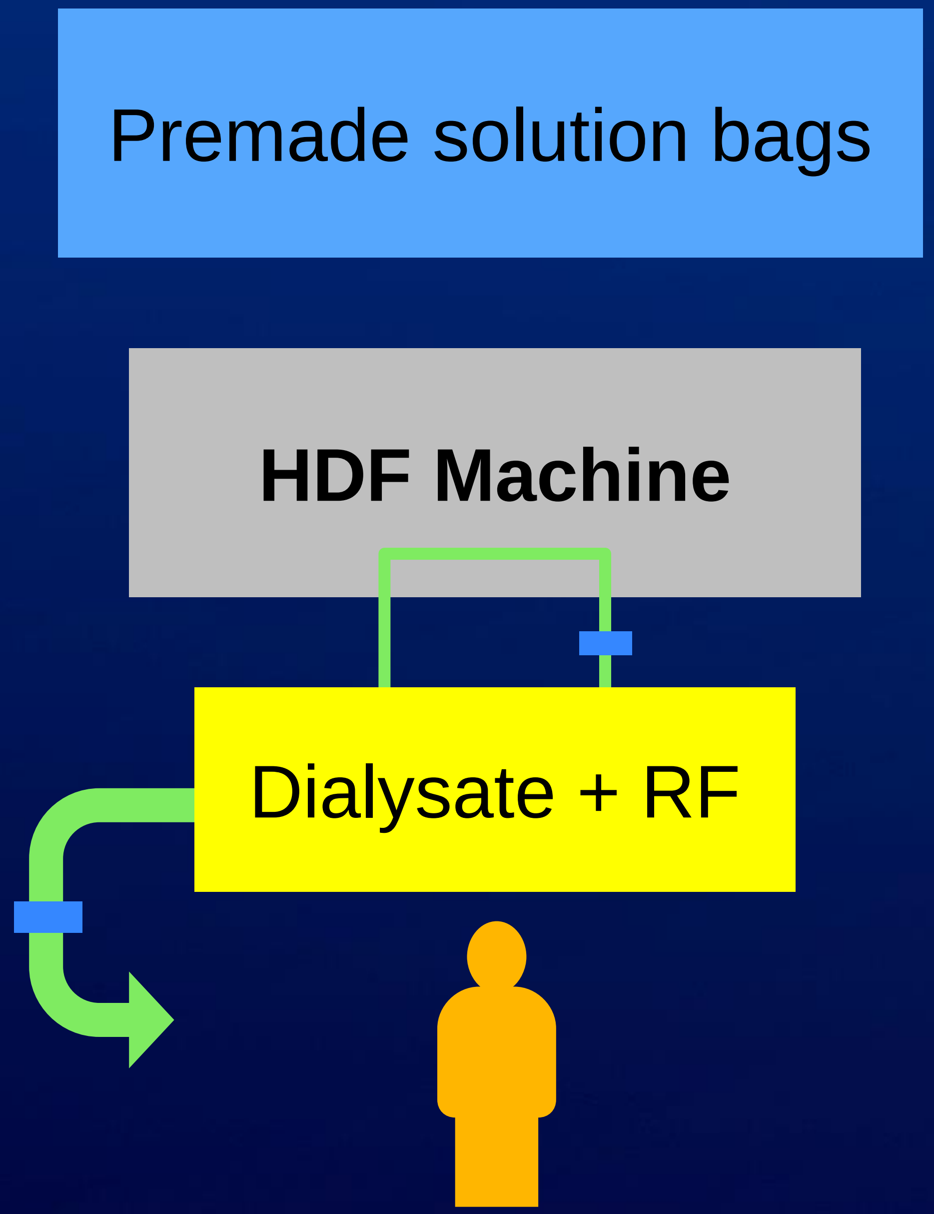
Replacement fluid preparation

CRRT

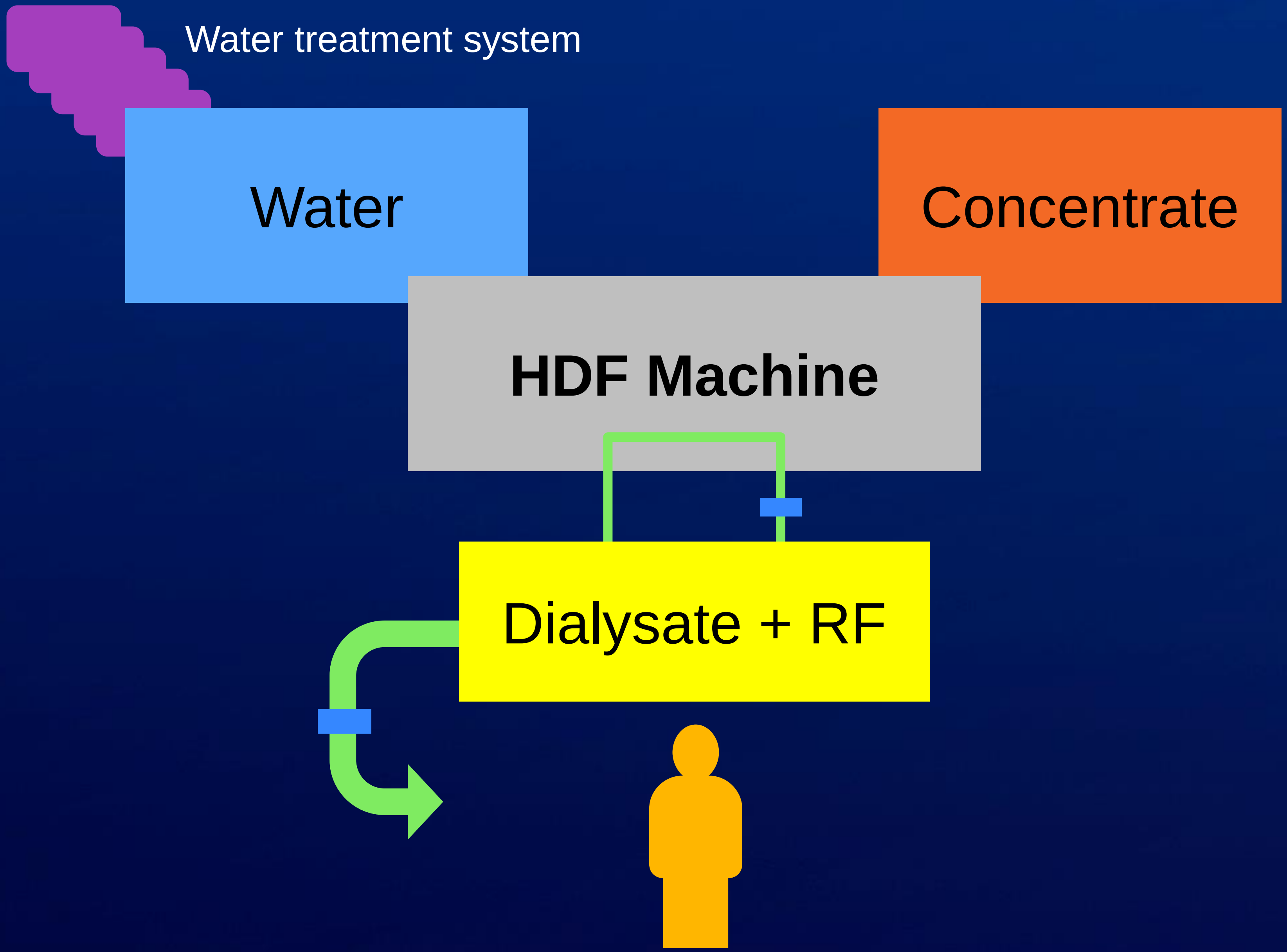


		Calcium formulas		Calcium-free formulas				Phosphorus formulas	
	Plasma4	PrismaSATE BGK 4/2.5	PrismaSATE BGK 0/3.5	PrismaSATE BGK 2/0	PrismaSATE BGK 4/0/1.2	PrismaSATE B22GK 4/0	PrismaSATE BGK 2/0	Phoxilium	
Potassium K^+ (mEq/L)	3.5-5.0	4	0	2	4	4	2	4	4
Calcium Ca^{2+} (mEq/L)	2.3-2.6+	2.5	3.5	0	0	0	0	2.5	0
Magnesium Mg^{2+} (mEq/L)	1.4-2.0	1.5	1.0	1.0	1.2	1.5	1.0	1.5	1.5
Sodium Na^+ (nEq/L)	135-145	140	140	140	140	140	140	140	140
Chloride Cl^- (mEq/L)	100-108	113	109.5	108	110.2	120.5	108	114.5	122
Bicarbonate HCO_3^- (mEq/L)	22-26	32	32	32	32	22	32	32	22
Lactate (mEq/L)	0.5-2.2	3	3	3	3	3	3	0	0
Dextrose (mg/dL)	70-110	110	0	110	110	110	0	0	0
Osmolarity (mOsm/L)	280-296	300	287	292	296	296	286	294	290
Phosphorus (mg/dL)	2.5	4.5	–	–	–	–	–	3.1	3.1

Bag-HDF

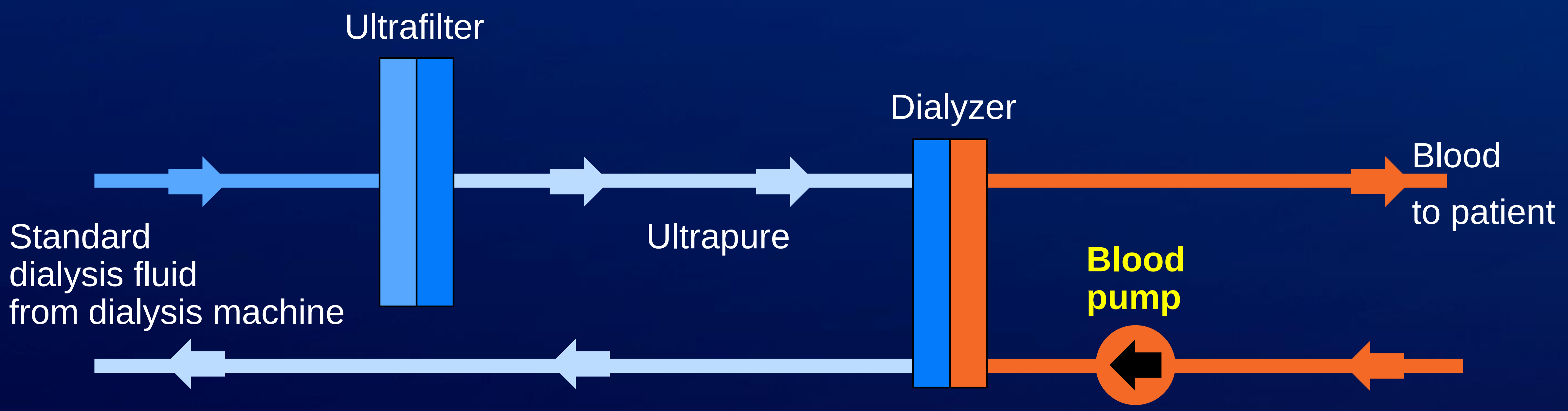


OL-HDF


Water treatment system
Water
Concentrate
HDF Machine
Dialysate + RF

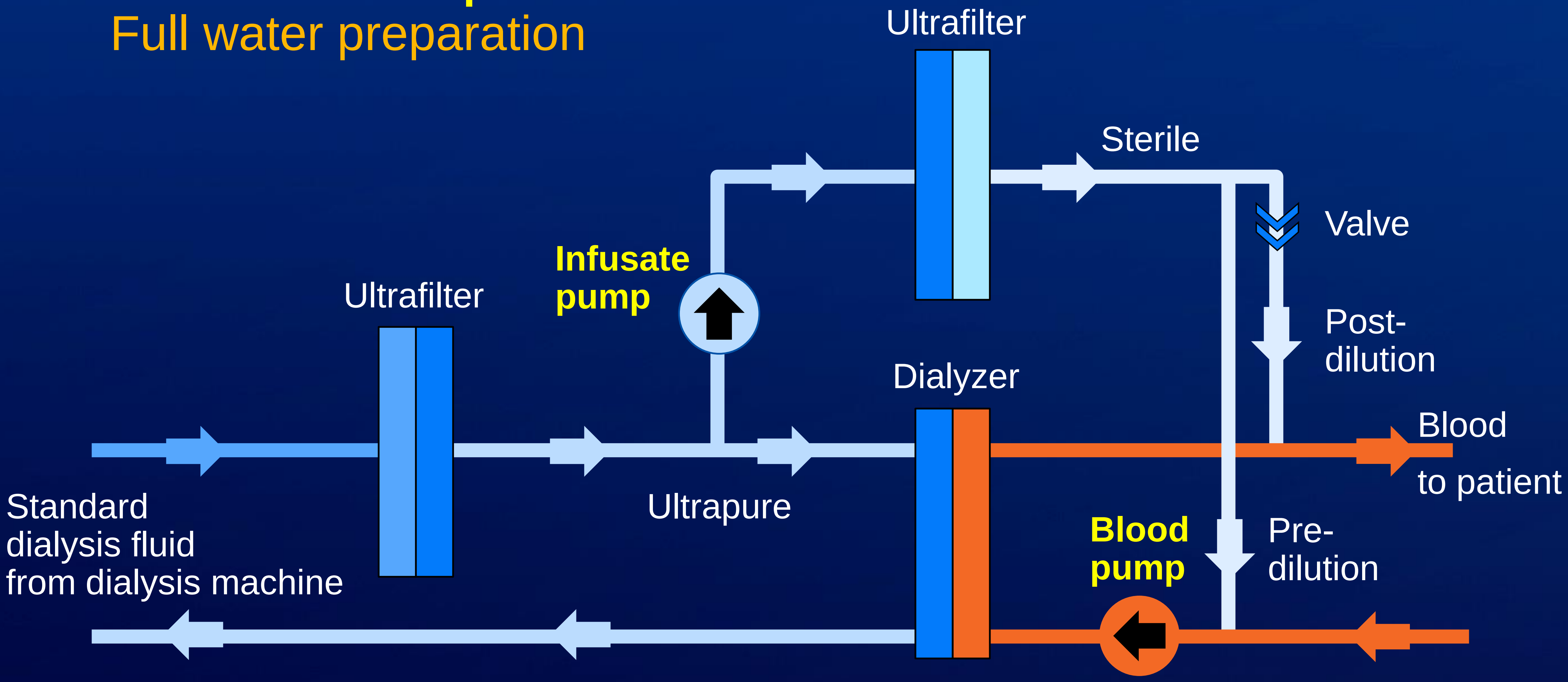
HDF concept

Dialysate component



HDF concept

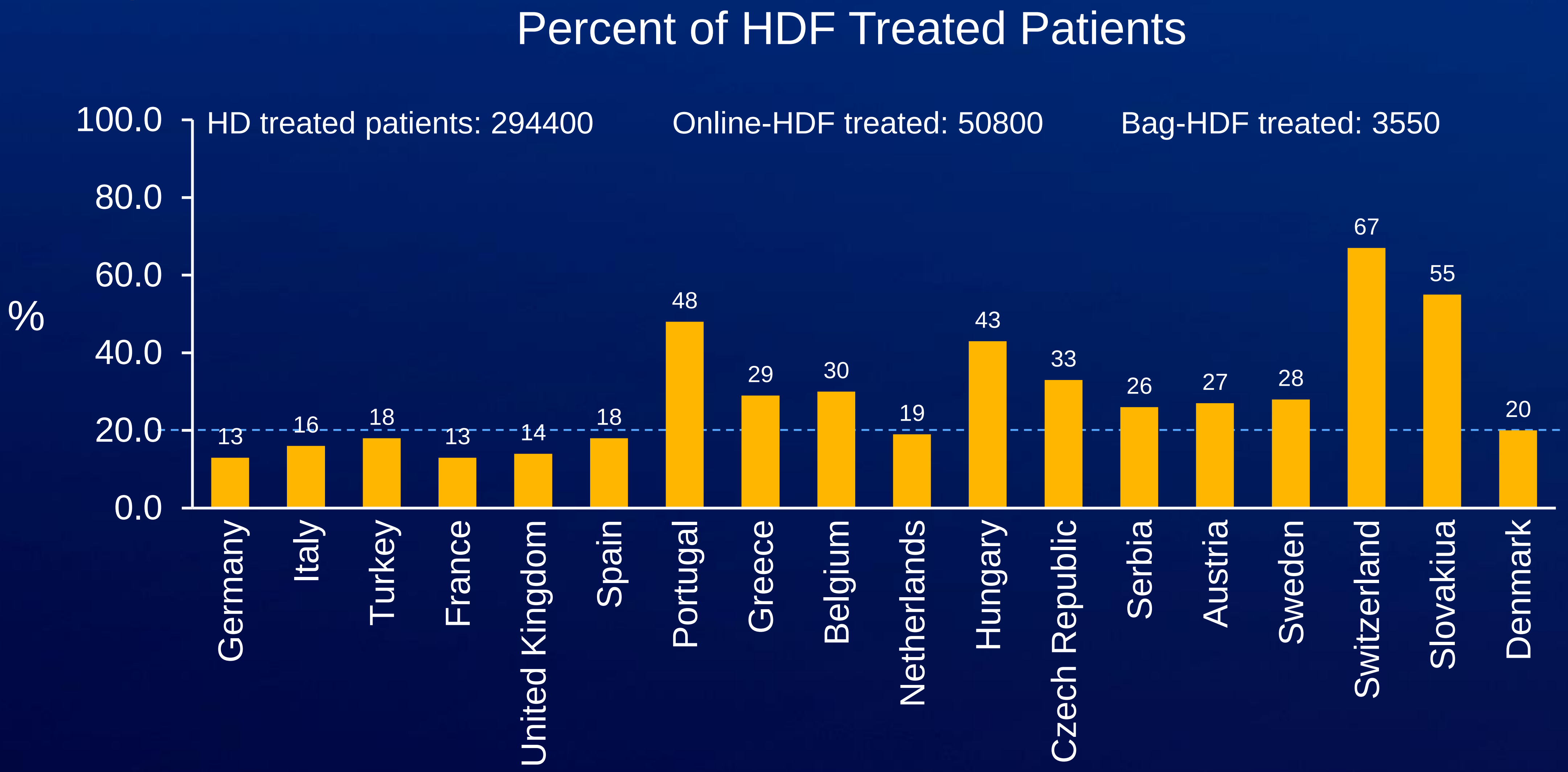
Full water preparation



Epidemiology

Prevalence of HDF

Europe 2010



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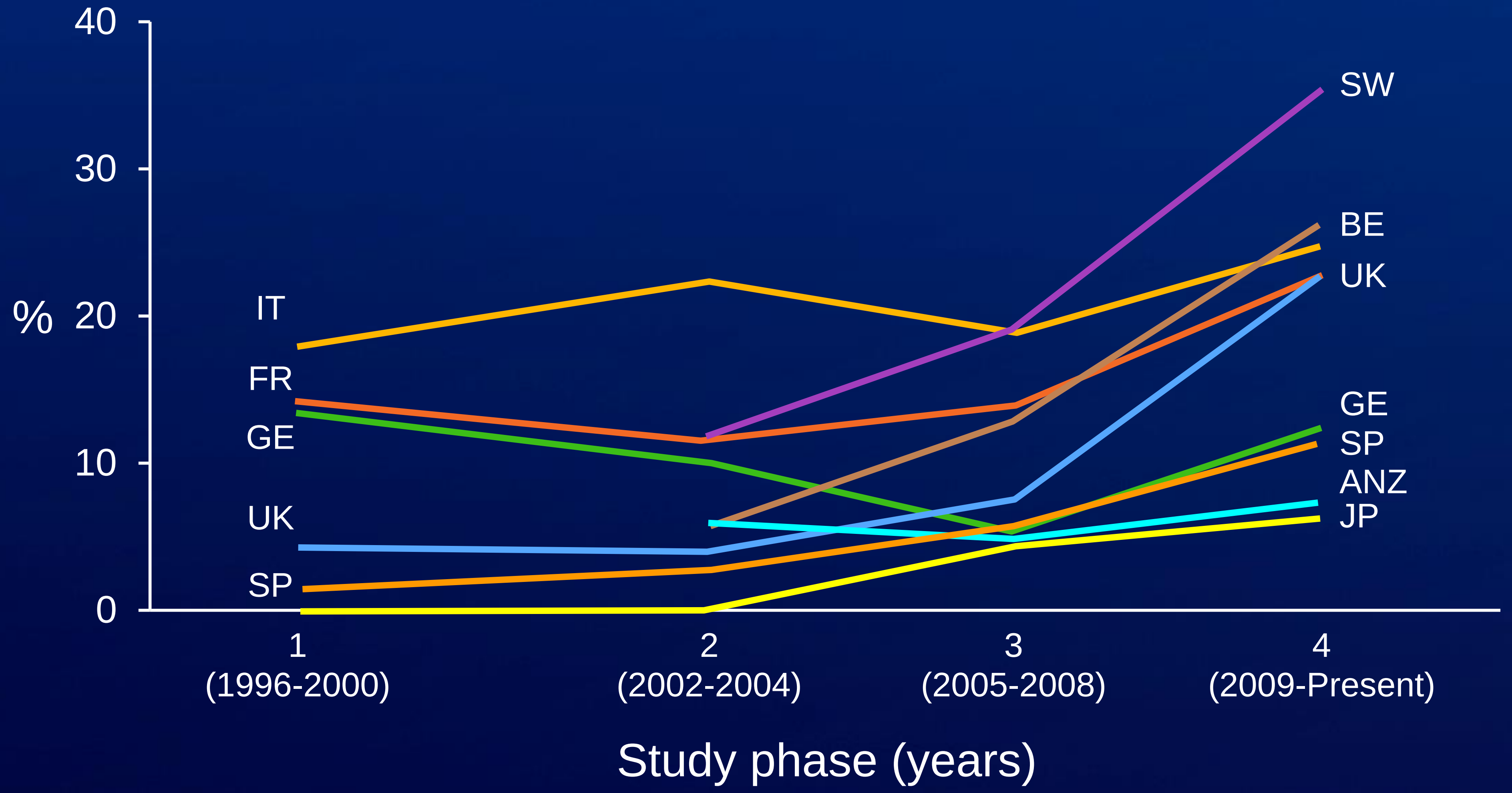
Hemodiafiltration Trends by Country

DOPPS (1996-2010)



Physiologic-clinical impact

Cytokines

Cross-over, Randomized Study (N=31; HD Patients)

HF-HD → OL-HDF | HF-HD | OL-HDF | HFHD

4 months | 4 months | 4 months | 4 months | 4 months

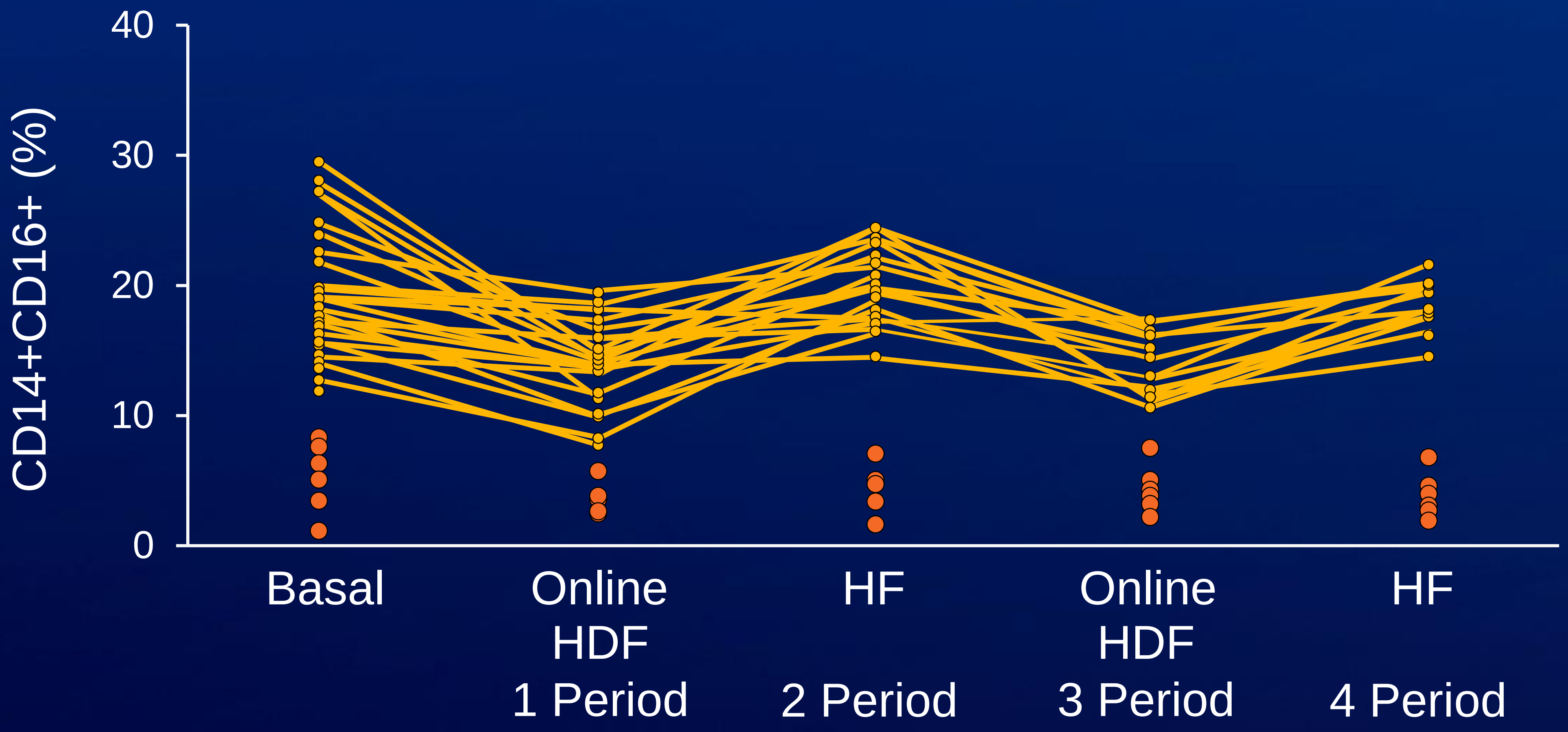
CD14+ CD16+
TNFα-IL6
Telomere length

- Polysulfone membrane
- Ultrapure dialysate
- Same dialysis conditions

Carracedo J et al: J Am Soc Nephrol 17:2315, 2006

Cytokines

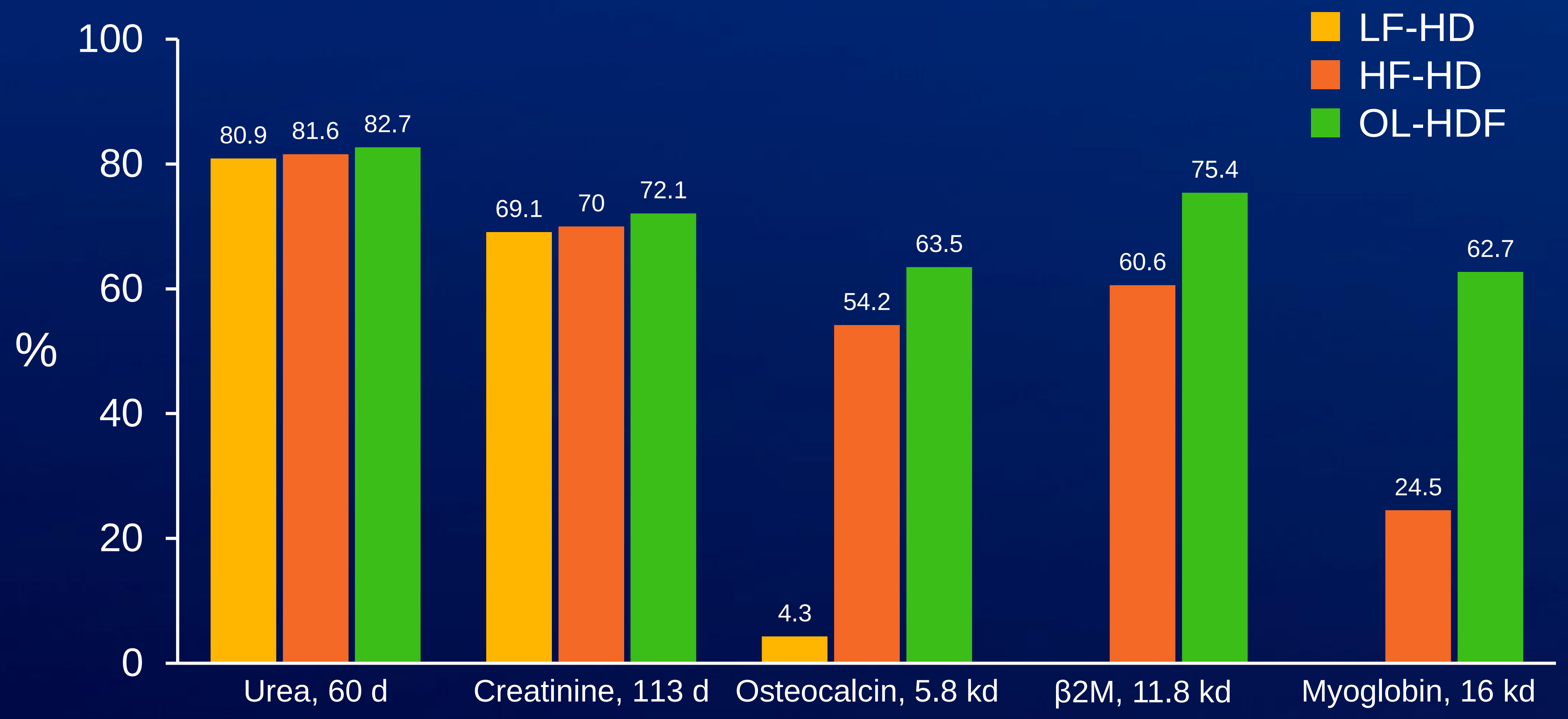
Cross-over, Randomized Study (N=31; HD Patients)



Carracedo J et al: J Am Soc Nephrol 17:2315, 2006

Reduction Proportion per Session

Prospective observational; N=23



Maduell F et al: Am J Kidney Dis 40:582, 2002

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β_2 microglobulin

Prospective observational; N=287; 2000-05

	Baseline	6 months	12 months	Period 1 P: baseline vs 6 months	Period 2 P: 6 months vs 12 months
Study group: n=30 OL-HDF					
eKt/V	1.20±0.08	1.21±0.08	1.34±0.11	NS	<0.0001
β_2 microglobulin (mg/dL)	35.0±9.6	34.9±9.2	24.5±9.0	NS	<0.0001
Controls: n=35 Low Flux HD					
eKt/V	1.22±0.06	1.23±0.07	1.22±0.06	NS	NS
β_2 microglobulin (mg/dL)	36±12	37±13	37±11	NS	NS

Movilli E et al: Nephro Dial Transplant 0:1-6, 2011

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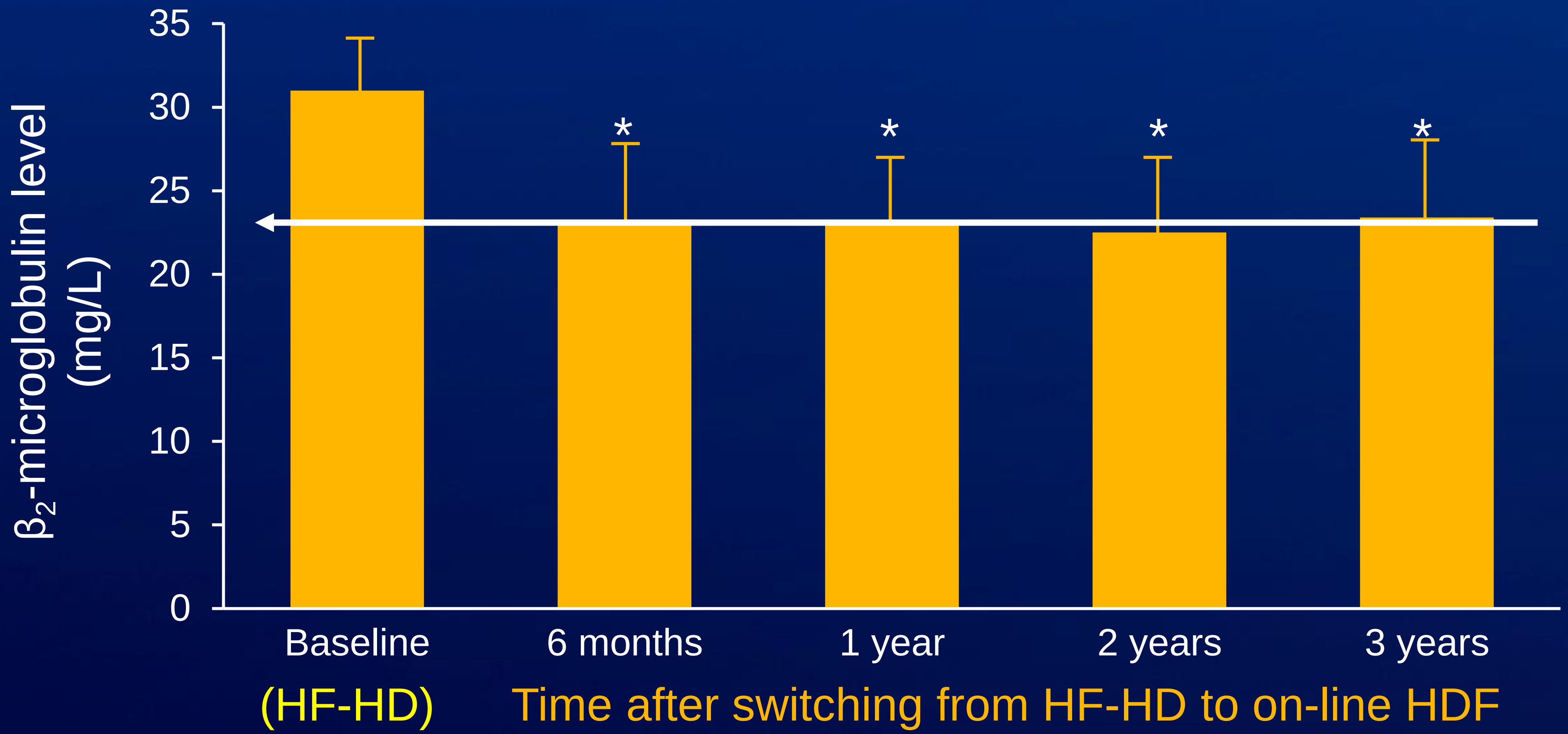
β_2-microglobulin clearance

Prospective observational study in 3 years; N=22



Tiranathanagul K et al: Ther Apher Dial 13:56, 2009

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Intradialytic complications

Prospective observational study in 3 years; N=22

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

OL-HDF in Southeast Asia: 3 years experience
22 HD patients HFHD → OL-HDF

Tiranathanagul K et al: Ther Apher Dial 13:56, 2009

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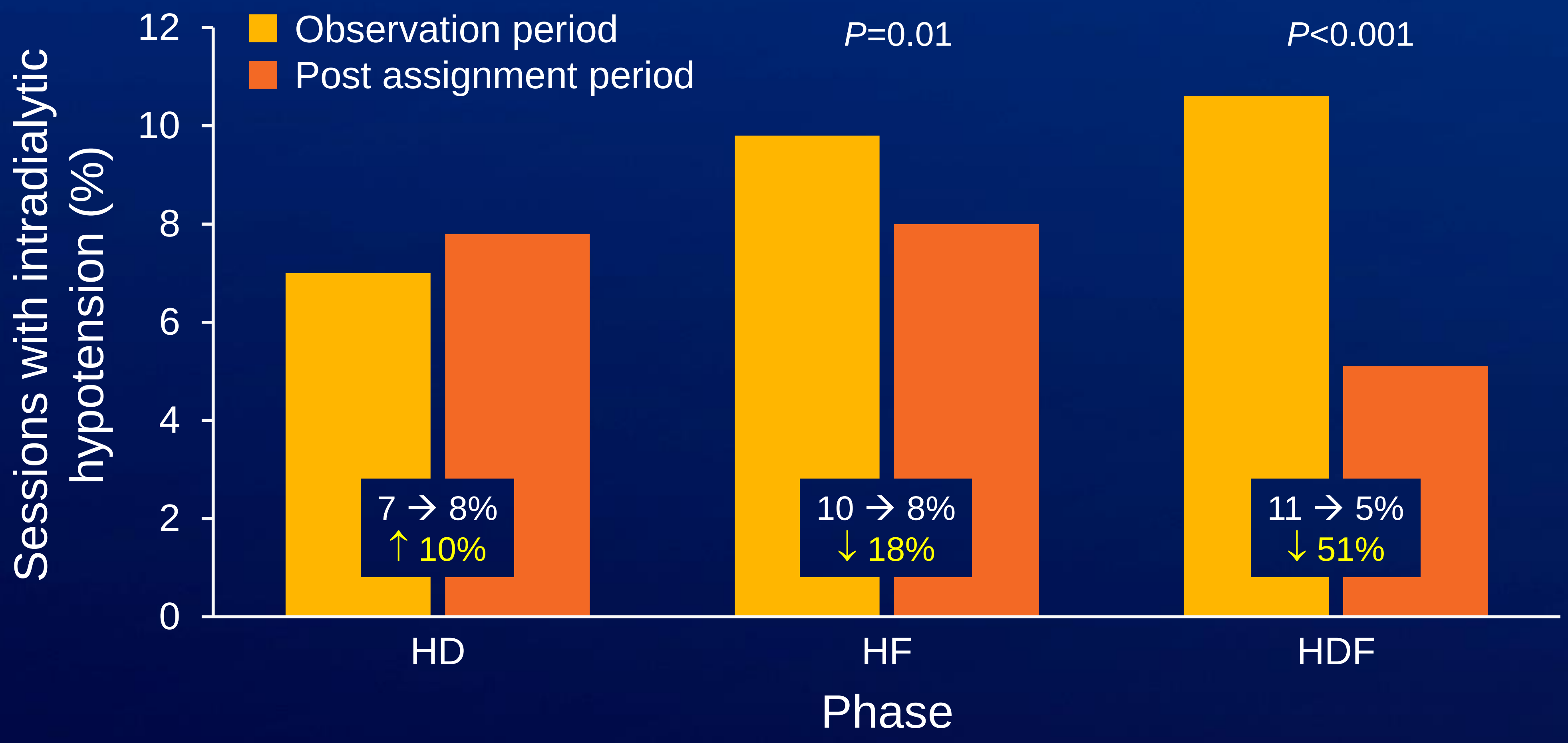
Intradialytic Symptomatic Hypotension (7.5%)

Multicenter open-label, RCT (Italy); 146 Pts; 28,950 RRT sessions
HD/OL-HF/OL-HDF → 2/1/1



Locatelli F et al: J Am Soc Nephrol 21:1798, 2010

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Pediatrics → Growth

Role of daily vs. standard HDF

Patient (n=15)	Mean±SD	
Height (SD Score)		
Start of Daily OL-HDF	- 1.5±0.3	
End of Daily OL-HDF (1)	+0.2±1.1	
Mid-parental target height (2)	- 0.3±0.7	
(1) – (2) (SD Score)	+0.3±0.4	
Growth velocity (centimeters per year)		
The year before daily	3.8±1.1	
First year of daily	14.3±3.8	
Mean over daily	5.9±2.2	
BMI	kg/cm^2	%
At start of daily	16.5±2.0	48±24
End of daily	18.0±2.4	65±26

Fischbach M et al: Nephrol Dial Transplant, 2009

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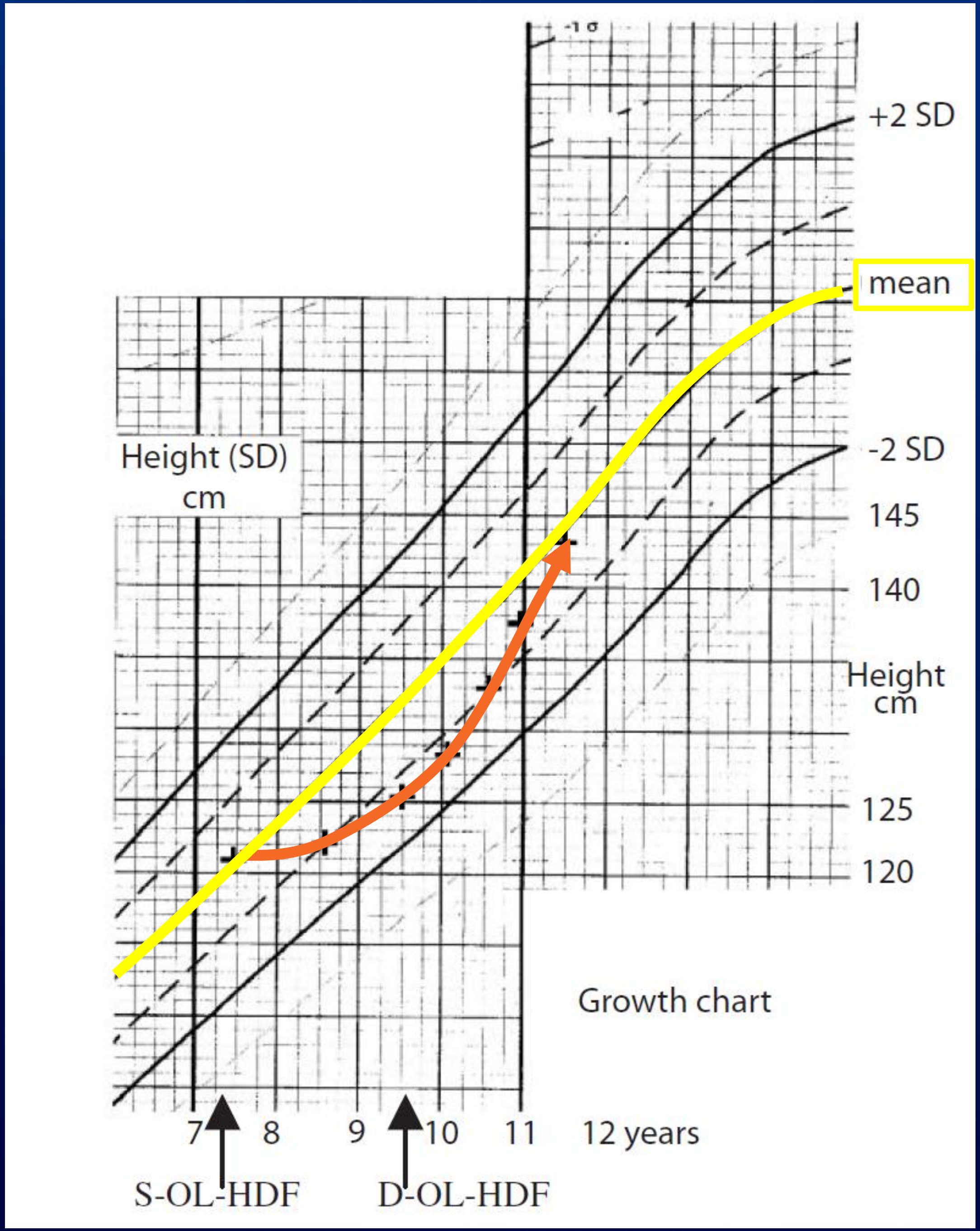
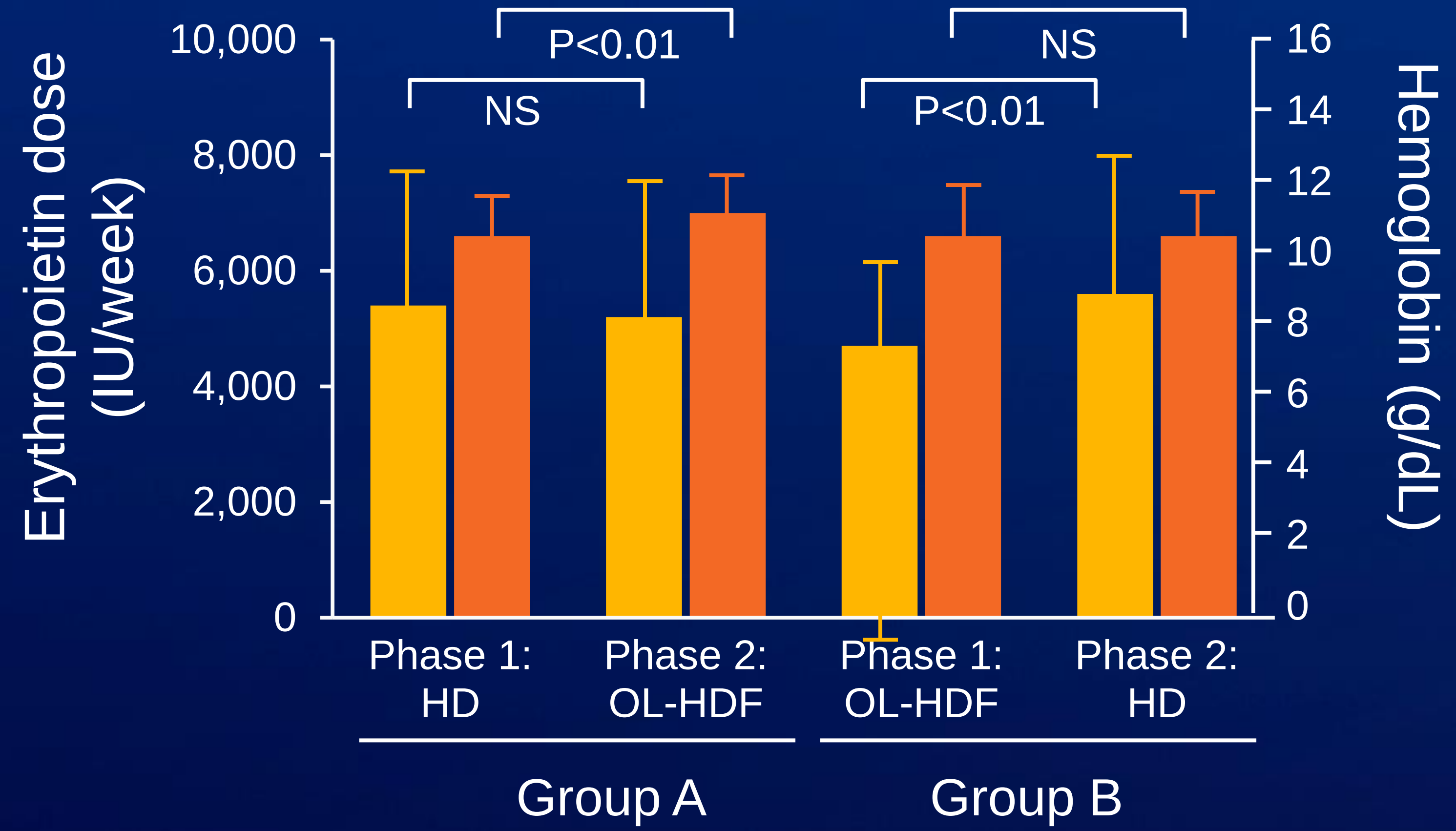


The role of daily vs. standard HDF

Fischbach M. Et al: Nephrol Dial Transplant 19: 2360, 2004

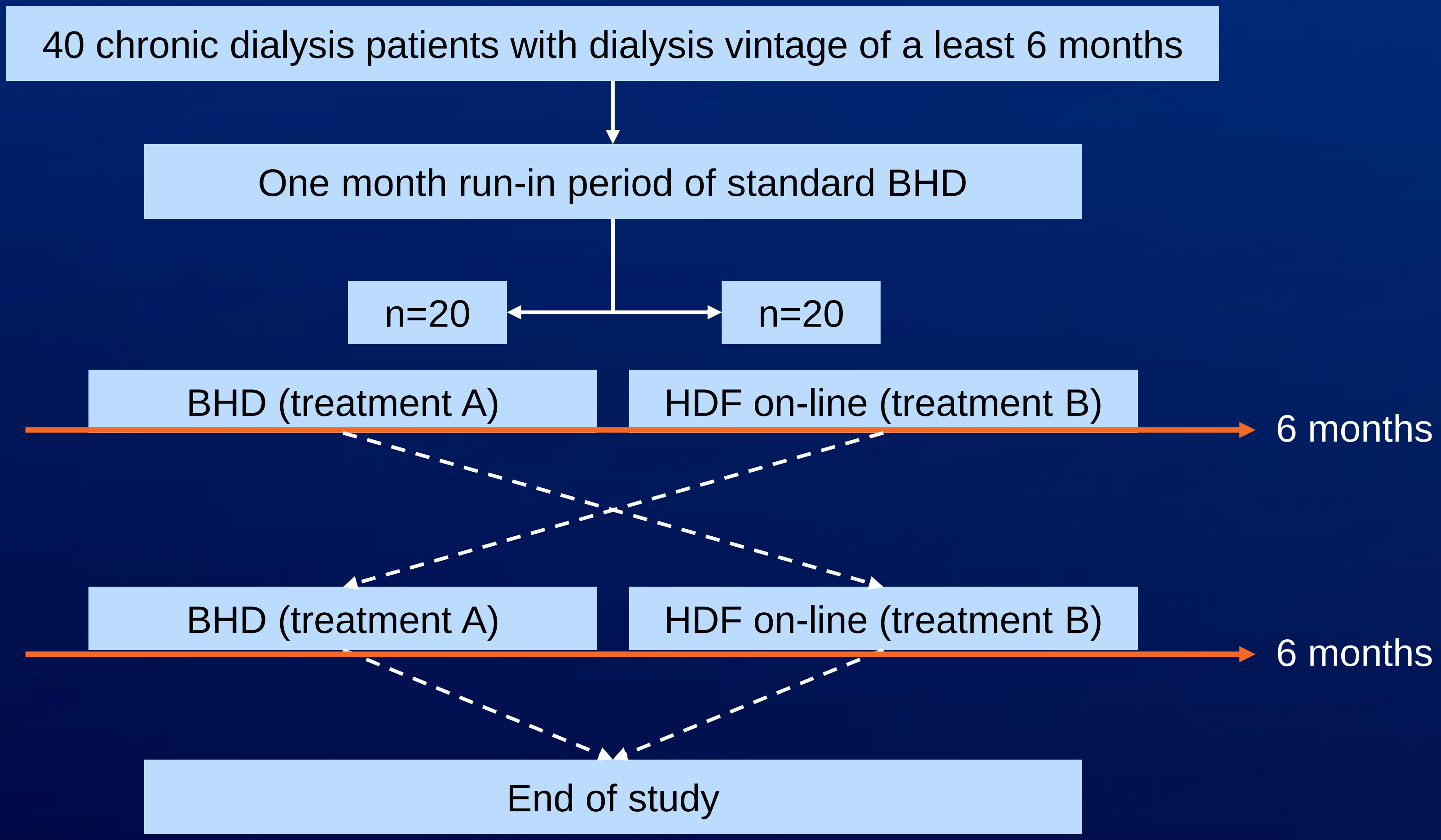
Anemia and ESA dosage

Cross over trial; N=70, HD Patients



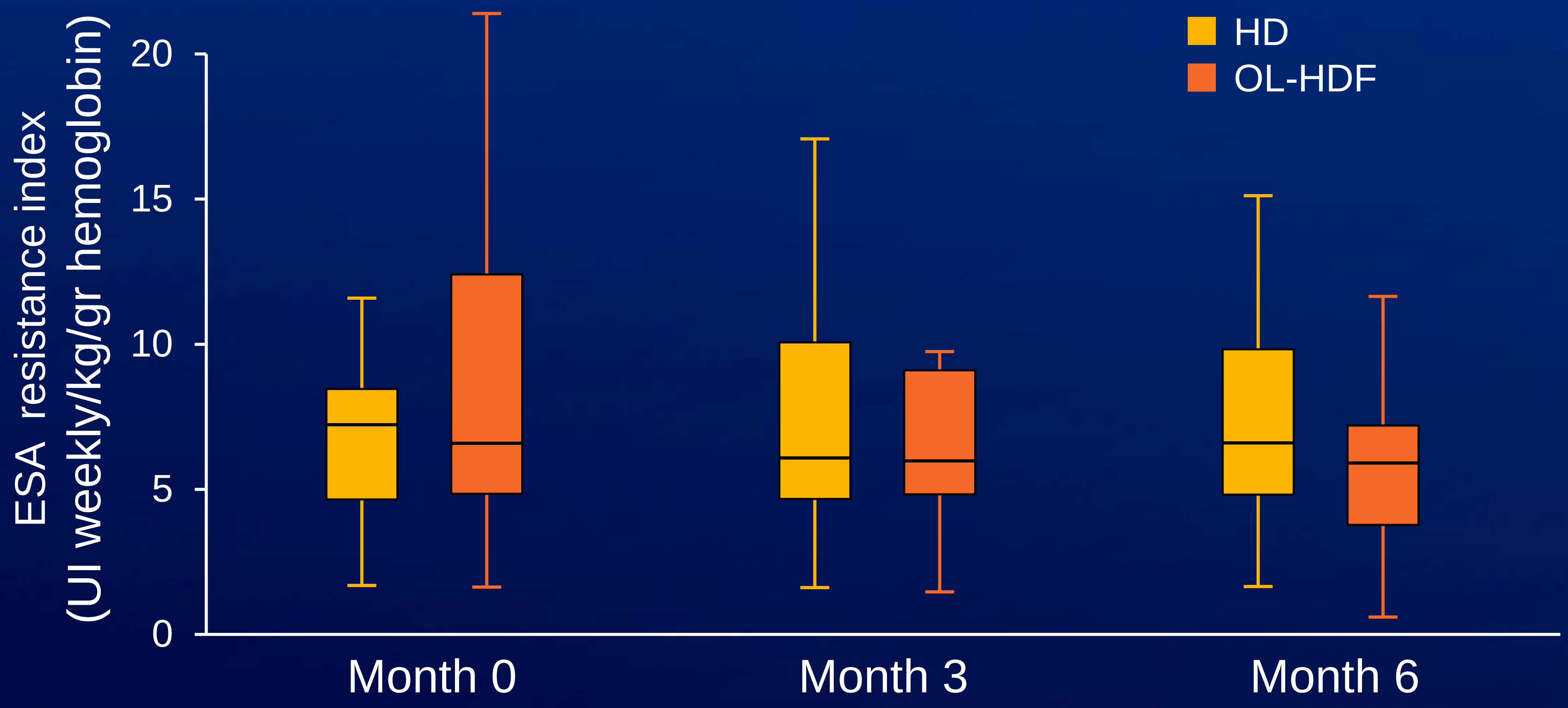
Vaslaki L et al: Blood Purif 24:163, 2006

REDERT study

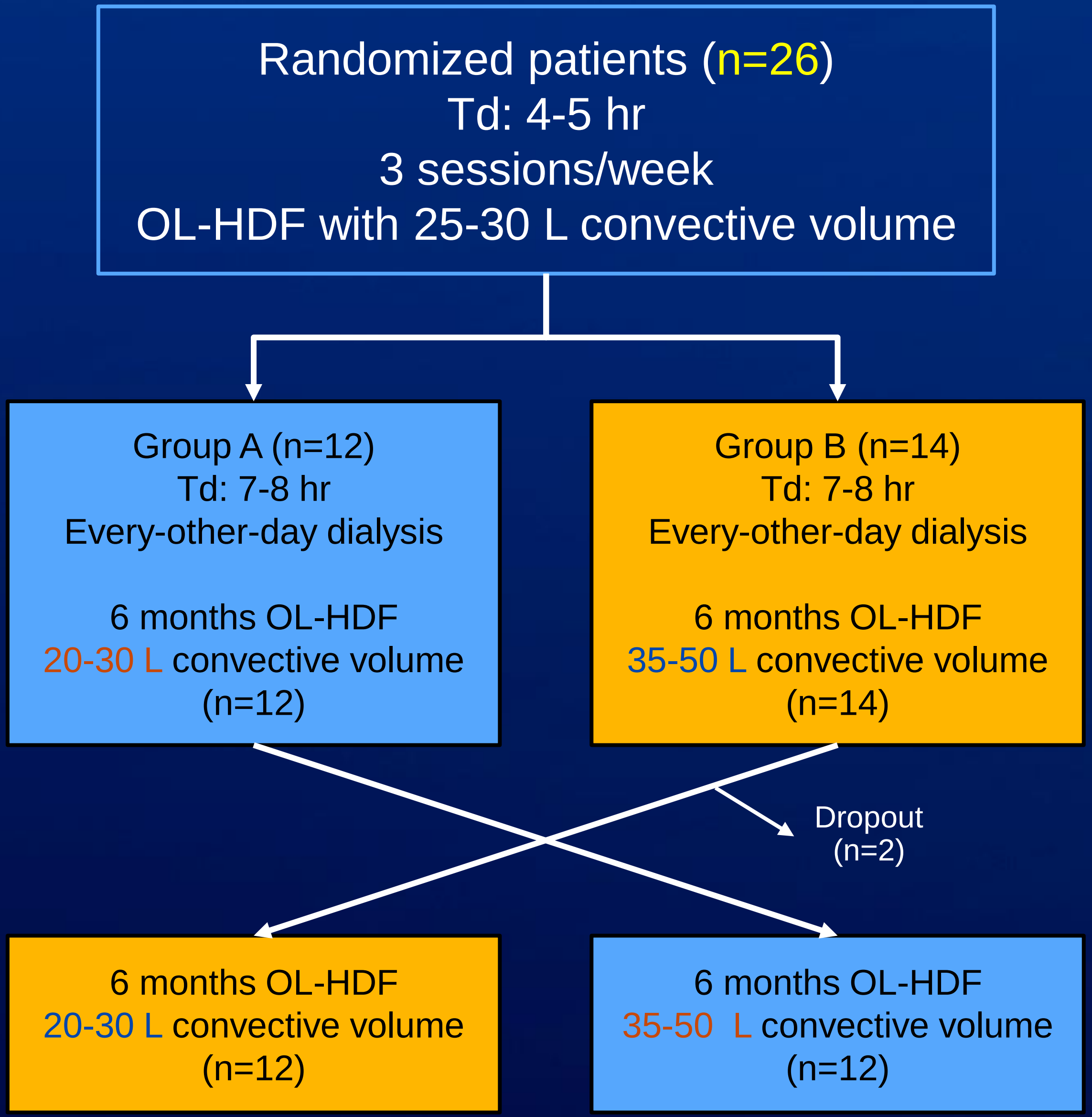


Panichi et al: Nephrol Dial Transplant 30: 682,

REDERT study



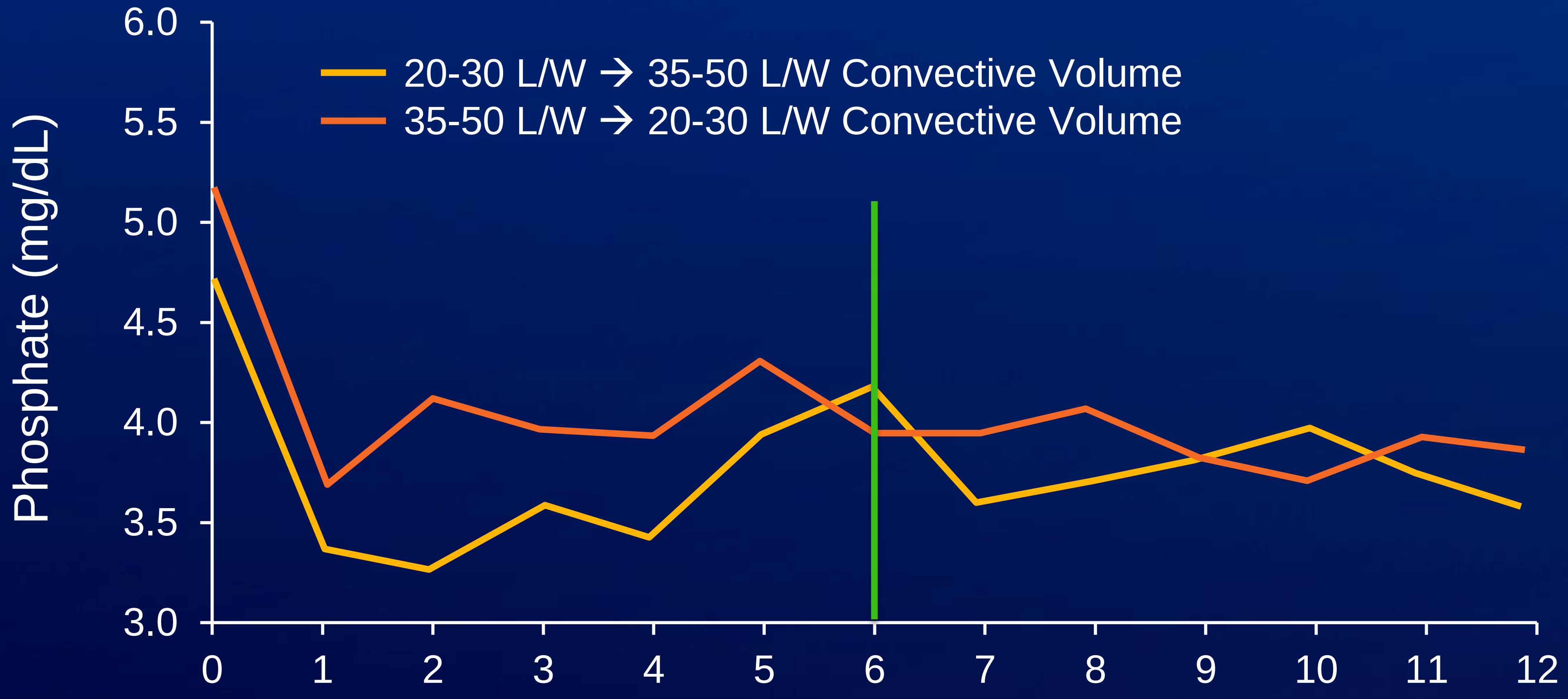
Panichi et al: Nephrol Dial Transplant 30: 682,



Maduell F et al: 2011; Nephro Dial Transplant 27(4): 1619-1631.

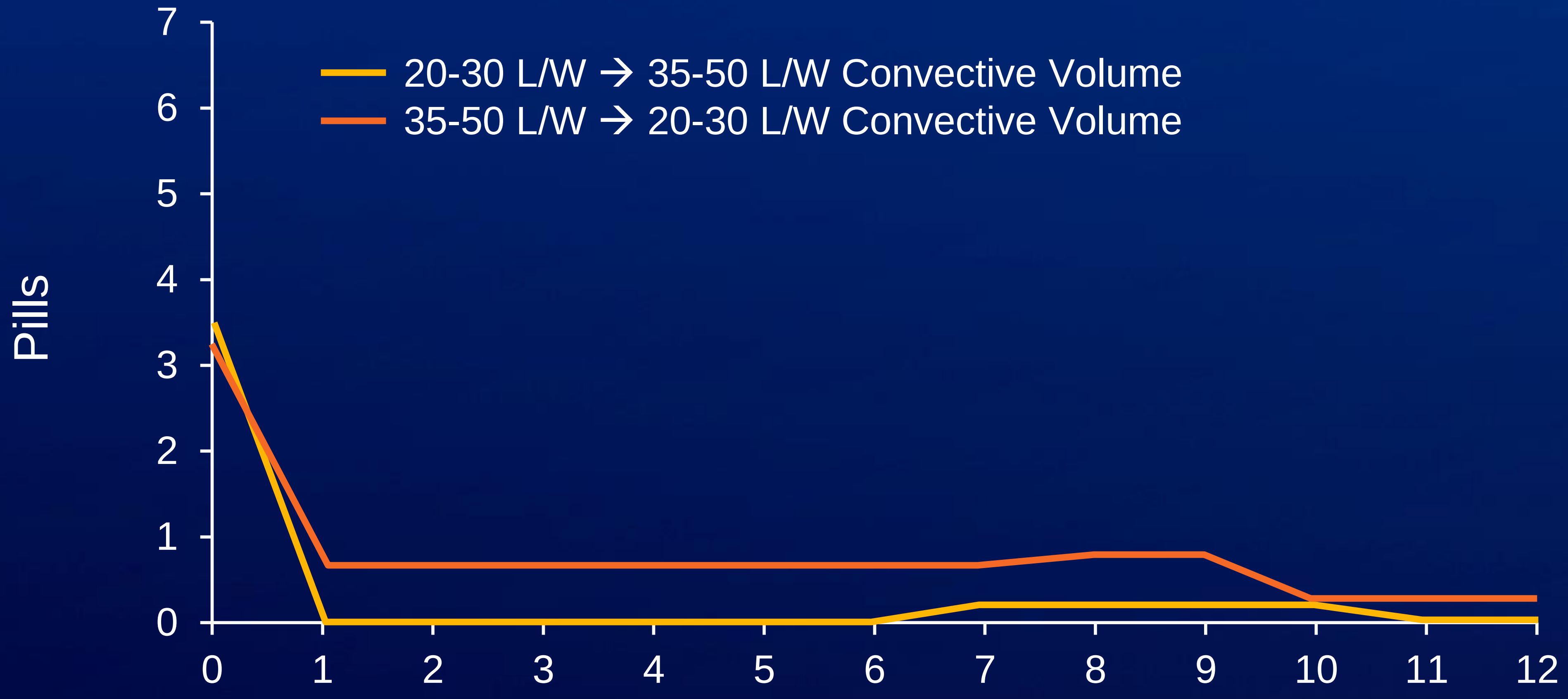
Phosphate

All stable pts
4–5 h thrice-weekly post-dilution OL-HDF → nocturnal every-other-day OL-HDF



Maduell F et al: 2011; Nephro Dial Transplant 27(4): 1619-1631.

Phosphorus Binders



Maduell F et al: 2011; Nephro Dial Transplant 27(4): 1619-1631.

European Results from DOPPS

Country	No.	Patients (%)			
		Low-efficiency HDF	High-efficiency HDF	Low-flux HD	High-flux HD
France	460	5.4	8.9	45.9	39.8
Germany	440	11.1	4.8	50.5	33.6
Italy	443	14.7	5.4	74.9	5.0
Spain	383	1.8	0.0	61.4	36.8
UK	439	2.3	2.5	83.4	11.8
All	2165	7.2	4.5	63.1	25.2

Low-efficiency HDF includes replacements of 5-15 L/session
High-efficiency HDF includes replacement of 15-25 L/session

Canaud B et al: Kidney Int 69:2087, 2006

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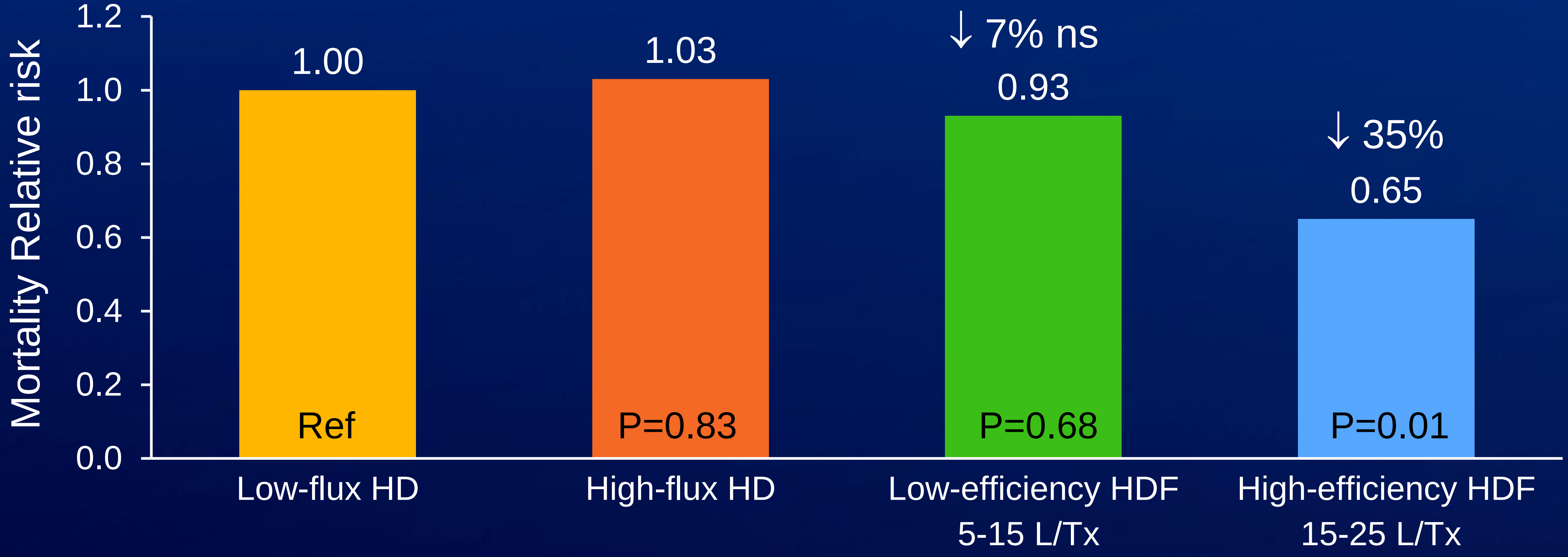
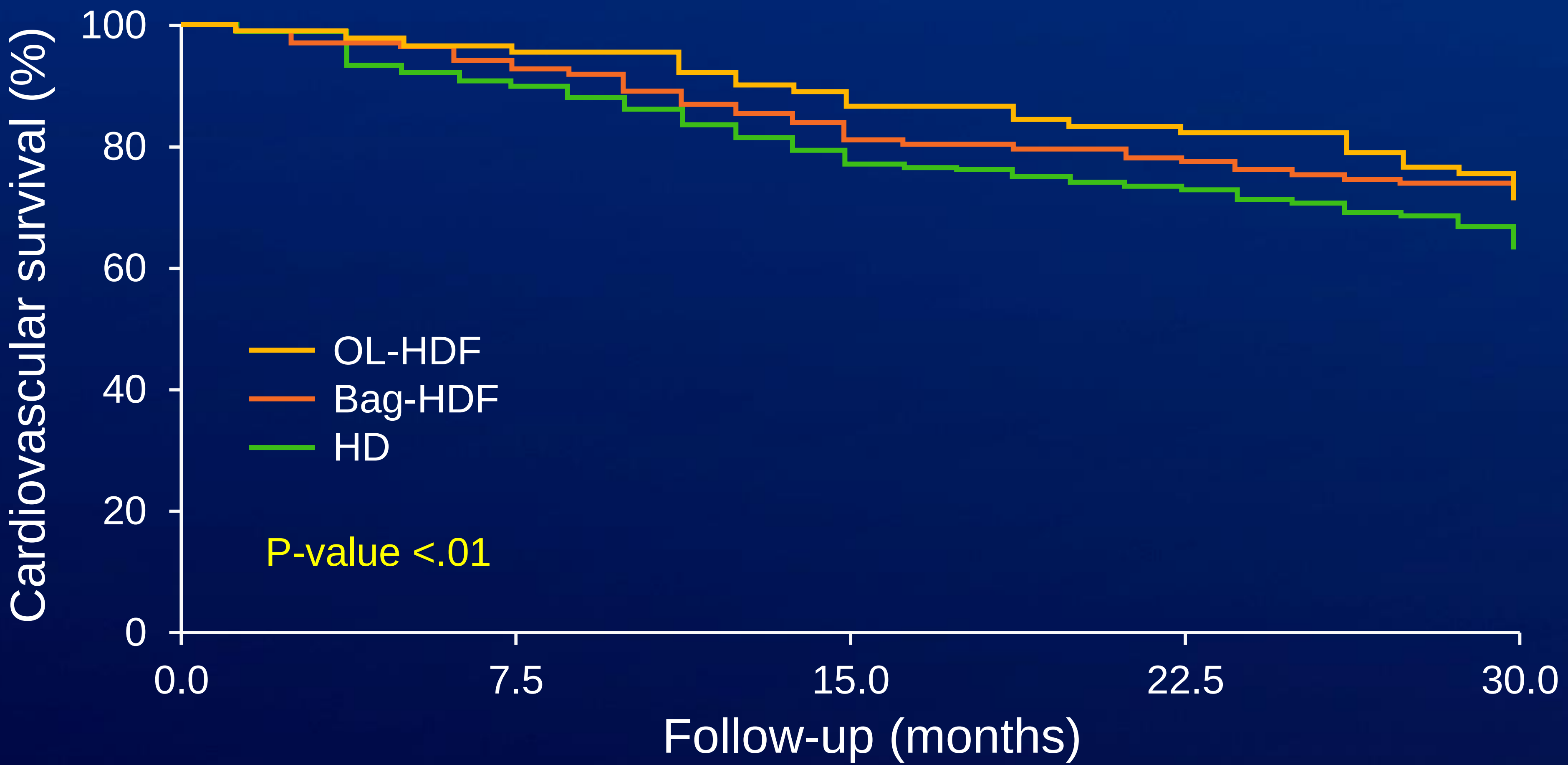
European Results from DOPPS



Canaud B et al: Kidney Int 69:2087, 2006

RISCAVID study

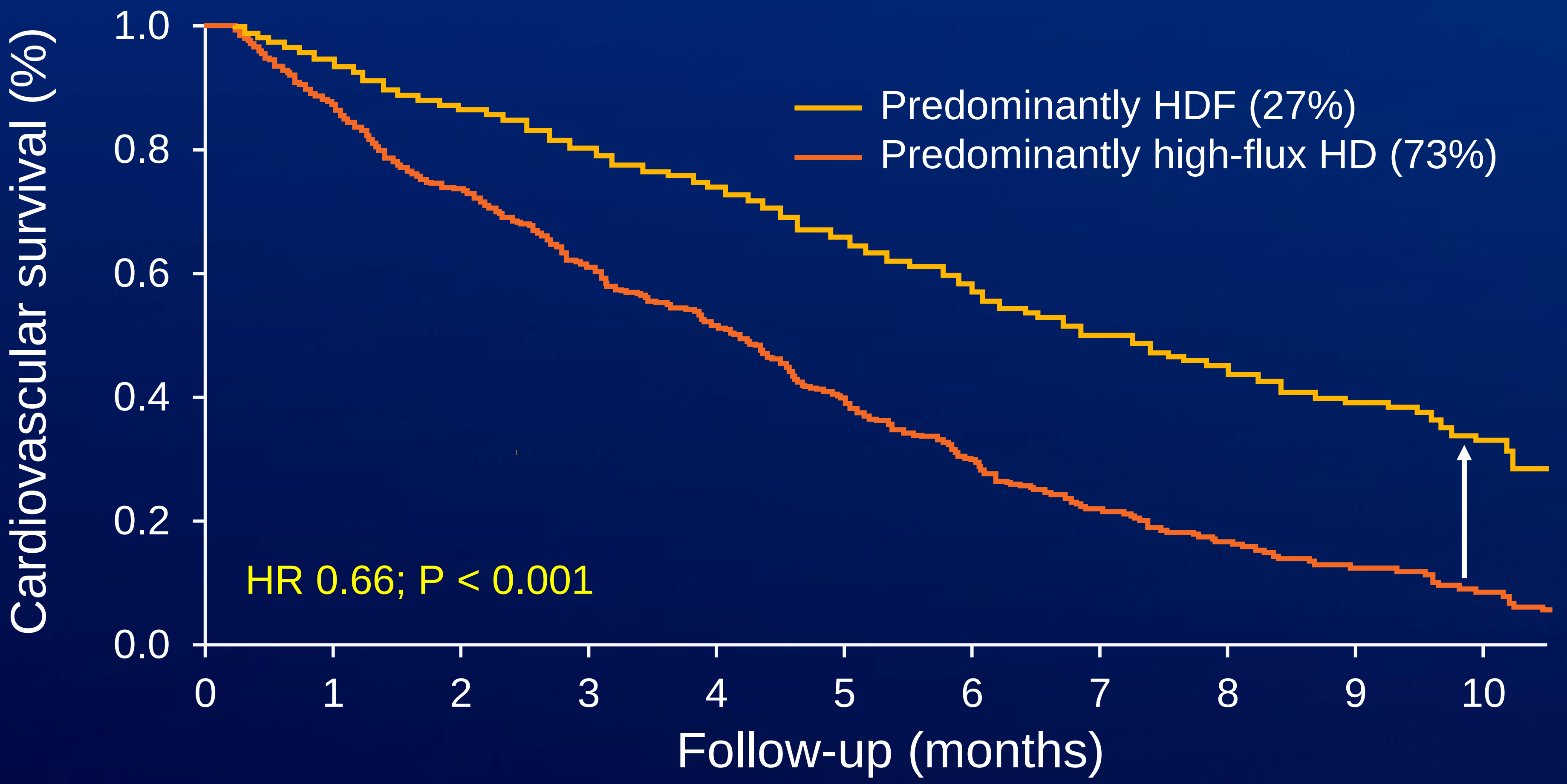
Prospective observational; N=757 HD patients



Panichi V et al: Nephrol Dial Transplant 23:2337, 2008

High flux HD vs. OL-HDF

Prospective observational study; N=858 ESRD patients



Vilar E et al: Clin J Am Soc Nephrol, 2009

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CONTRAST Study
CONvective TRAnsport STudy

714 patients underwent randomization

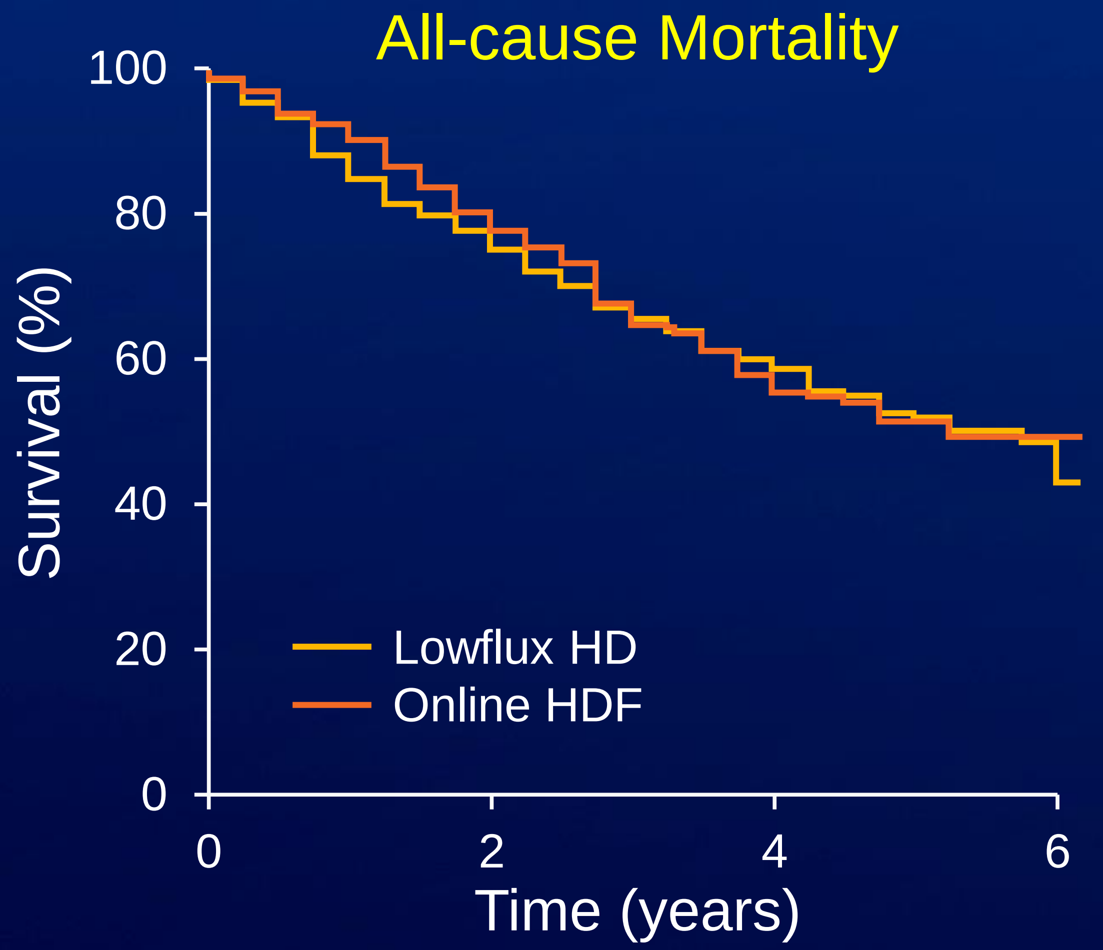
358 were randomized to online hemodiafiltration	356 were randomized to low-flux hemodialysis
131 died 78 underewent transplantation 7 switched to peritoneal dialysis 15 moved to non-participating center 21 stopped for other reasons	138 died 73 underewent transplantation 4 switched to peritoneal dialysis 9 moved to non-participating center 32 stopped for other reasons

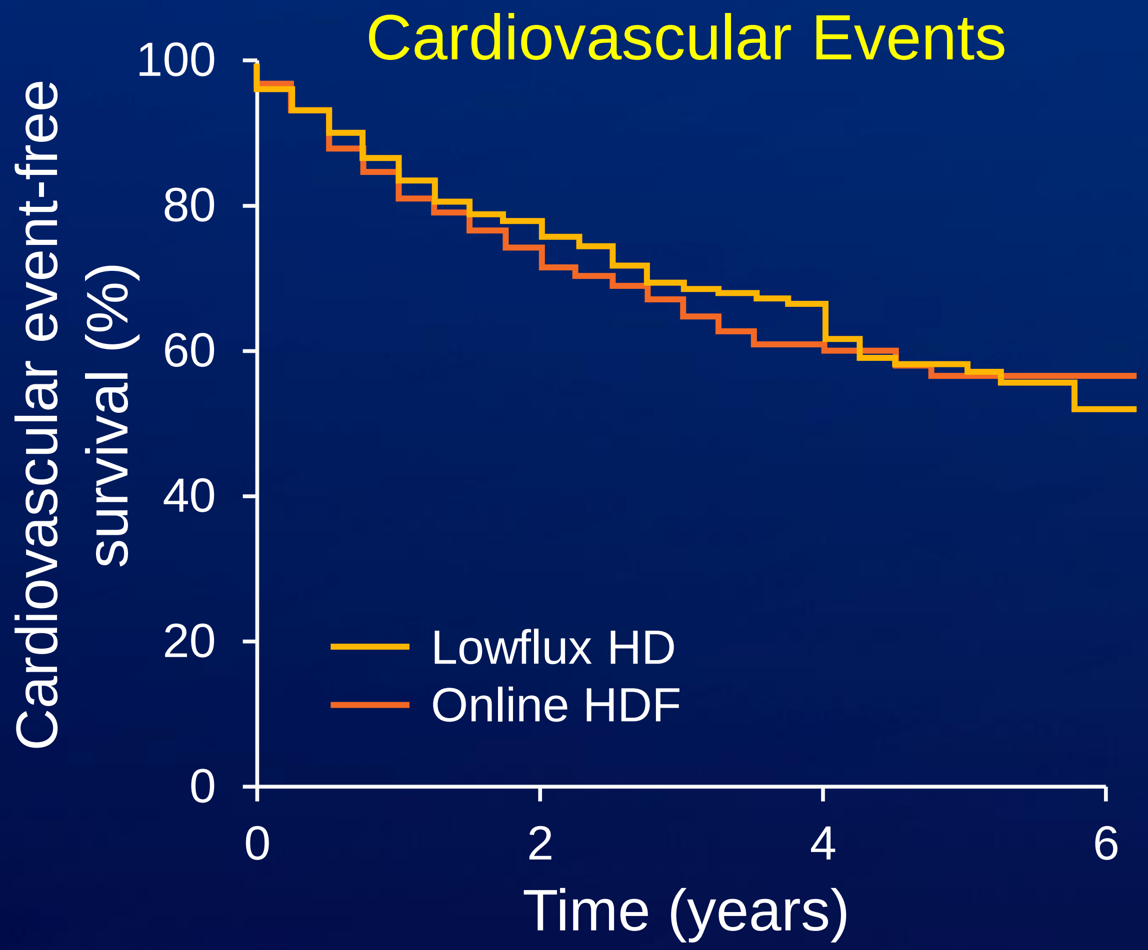
den Hoedt et al. (2015). PLoS One 10(8): e0135908.

Contrast Trial

RCT; low flux HD vs. OL-HDF; N=714

Target Convection volume = 24 L/Session; Average achieved = 19.4 L/Session





Grooteman MPC et al: JASN 23:1087, 2012

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Contrast Trial

RCT; low flux HD vs. OL-HDF; N=714

	Online hemodiafiltration convection volume tertiles			P for trend
	<18.17 L	18.18-21.95 L	>21.95 L	
Total mortality				
Crude	0.95 (0.66-1.38)	0.83 (0.57-1.22)	0.62 (0.41-0.96)	0.010
Adjusted	0.79 (0.53-1.14)	0.77 (0.51-1.14)	0.65 (0.42-0.99)	0.012
Adjusted	0.80 (0.52-1.24)	0.84 (0.54-1.29)	0.61 (0.38-0.98)	0.015
Fatal and nonfatal cardiovascular events				
Crude	1.37 (0.94-1.98)	1.06 (0.72-1.56)	0.76 (0.50-1.16)	0.473
Adjusted	1.41 (0.92-2.11)	0.93 (0.62-1.40)	0.77 (0.48-1.21)	0.369
Adjusted	1.35 (0.86-2.11)	1.04 (0.66-1.62)	0.72 (0.44-1.19)	0.475

Grooteman MPC et al: JASN 23:1087, 2012

Turkish OL-HDF study

Target convection volume >15 L/Session
Achieved volume 17.4 L/session

Screening (n=899)

Enrollment

Excluded (n=117)
- Did not meet inclusion criteria (n=82)
- Declined to give consent (n=35)

Randomization (n=782)

Allocation

OL-HDF (n=391)

High-flux HD (n=391)

Follow-up

OL-HDF:
- Transfer to other centers (n=58)
- Switch dialysis method (n=1)
- Renal transplantation (n=11)
- Early termination due to vascular access problems (n=40)
- Primary outcome (n=61)

High-flux HD:
- Transfer to other centers (n=81)
- Switch dialysis method (n=3)
- Renal transplantation (n=6)
- Primary outcome (n=73)

Completed (n=220)

Completed (n=228)

OK et al. Nephrol Dial Transplant (2013) 28: 192–202

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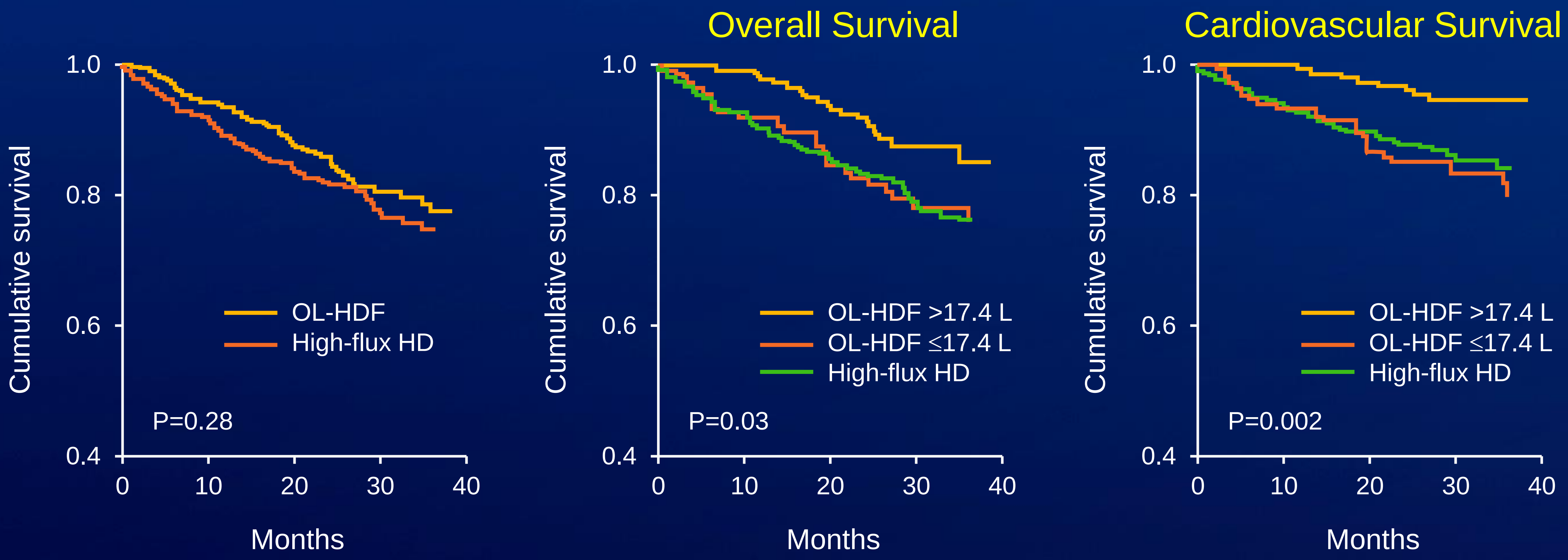
Turkish OL-HDF study



OK et al. Nephrol Dial Transplant (2013) 28: 192–202

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ESHOL Trial

Estudio de supervivencia de hemodiafiltracion on-line

939 patients were assess for eligibility

33 were excluded
- 18 did not meet the inclusion criteria
- 5 declined to participate
- 10 were excluded for other reasons

906 underwent randomization

450 were assigned to receive hemodialysis

164 discontinued the study
- 79 renal transplant
- 25 change of HD center
- 20 organizational changes
- 12 withdrawal of consent
- 8 temporary catheter
- 8 change of treatment
- 12 had other reasons

286 had primary endpoint or completed the study through month 36

456 were assigned to receive post-dilution OL-HDF

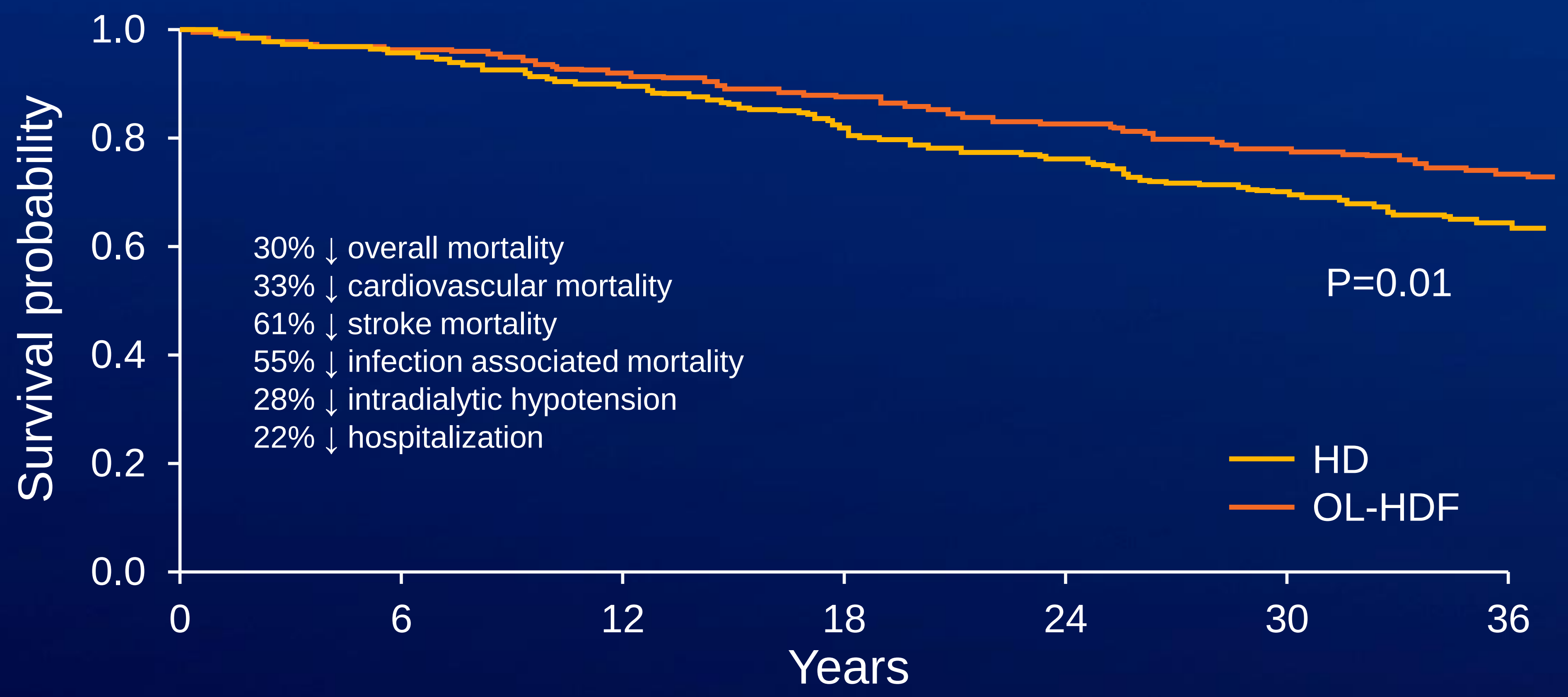
191 discontinued the study
- 101 renal transplant
- 33 change of HD center
- 13 organizational changes
- 15 withdrawal of consent
- 11 temporary catheter
- 7 change of treatment
- 11 had other reasons

265 had primary endpoint or completed the study through month 36

MAYO CLINIC

Maduell F et al: JASN 24:487, 2013

ESHOL Trial



HD	450	388	327	275	235	195	165
OL-HDF	459	367	318	284	232	200	179

Maduell F et al: JASN 24:487, 2013

ESHOL Trial

Risk of all-cause mortality results by achieved convective volume, convective volume/BMI, and convective volume/BSA

	Hemodialysis	OL-HDF			P^a	P^b
		Tertile 1	Tertile 2	Tertile 3		
Convective volume (L/session)		<23.1	23.1-25.4	>25.4		
No. (%)	124 (26.4)	33 (22.9)	27 (18.2)	23 (16.0)	0.03	0.003
HR (95% CI)	Ref	0.90 (0.61-1.31)	0.60 (0.39-0.9)	0.55 (0.34-0.84)	0.01	0.001
Convective volume/BMI (L/kg per m^2)		<0.9	0.9-1.1	>1.1		
No. (%)	124 (26.4)	25 (17.2)	32 (21.9)	26 (17.9)	0.05	0.03
HR (95% CI)	Ref	0.62 (0.4-0.94)	0.74 (0.49-1.08)	0.66 (0.42-0.99)	0.04	0.02
Convective volume/BSA (L/m^2)		<13.2	13.2-14.8	>14.8		
No. (%)	124 (26.4)	29 (20.0)	29 (19.9)	25 (17.2)	0.06	0.01
HR (95% CI)	Ref	0.75 (0.49-1.11)	0.66 (0.43-0.98)	0.62 (0.39-0.91)	0.04	0.01

Maduell F et al: JASN 24:487, 2013

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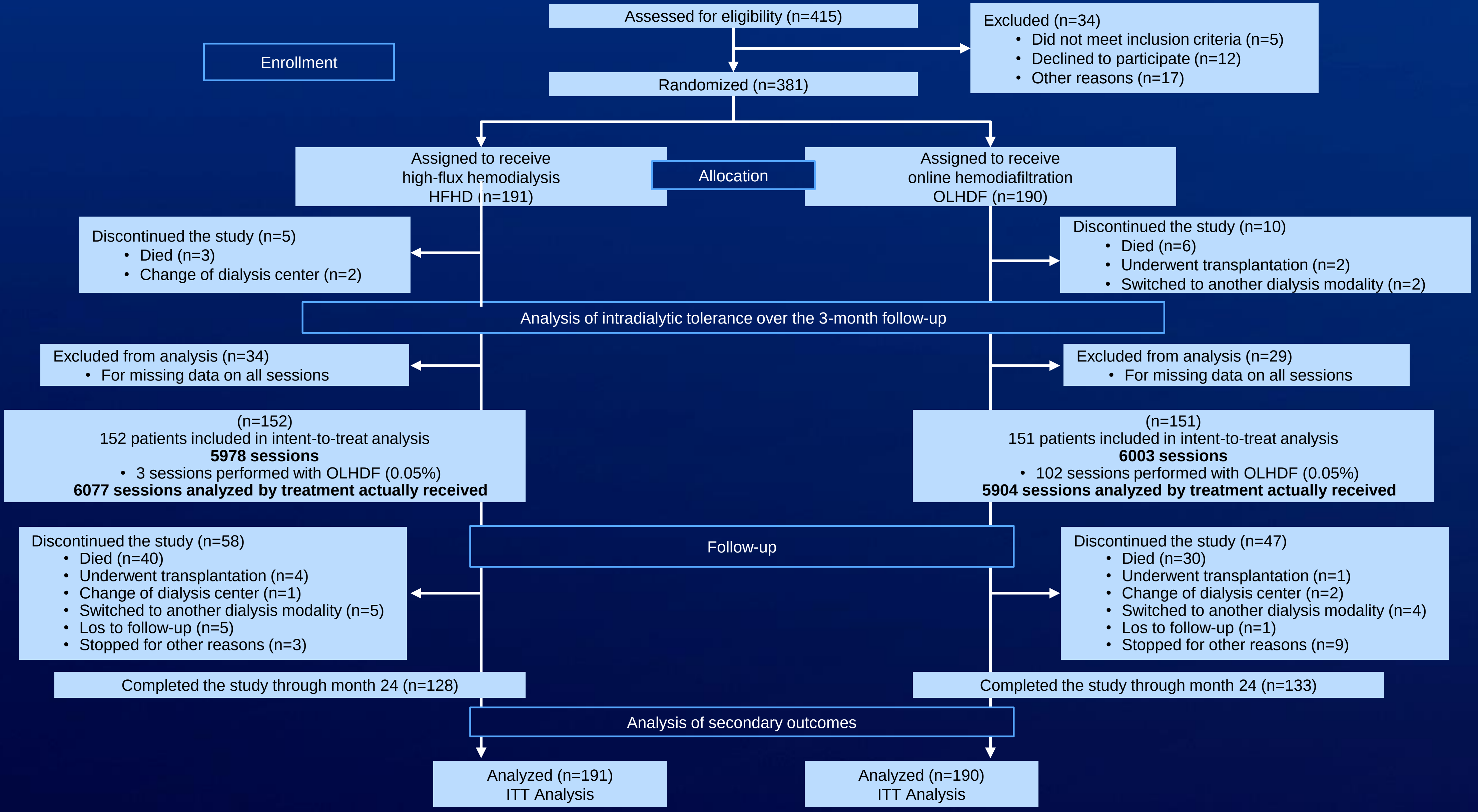
FRENCHIE Study

French Convective Vs. HD in elderly (>65 yo)



MAYO CLINIC

Morena et al: Kidney International 91, 1495, 2017

FRENCHIE Study

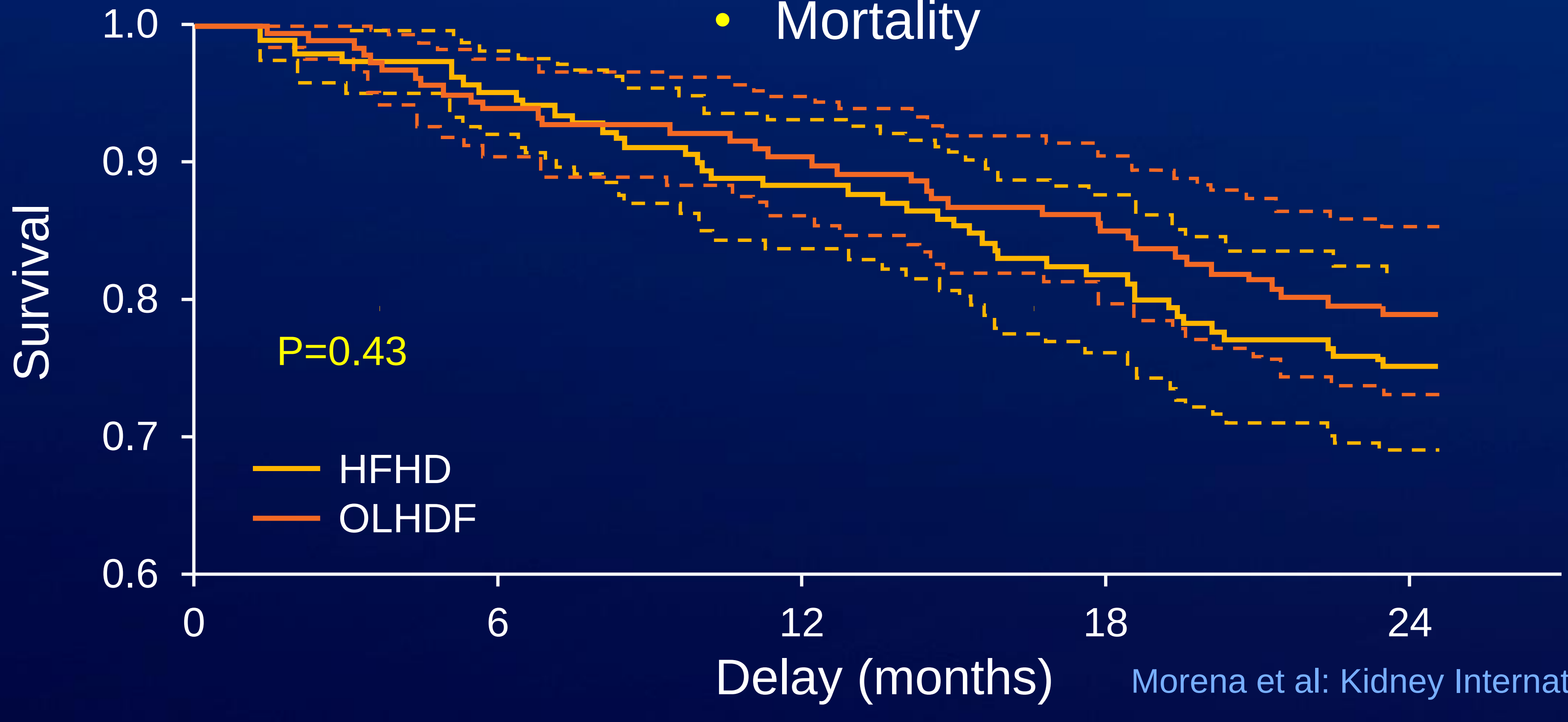
HDF vs. HD in elderly

HDF significantly better:

- Number of sessions with event
- Metabolic control (MBD and β2 MG)

No difference in:

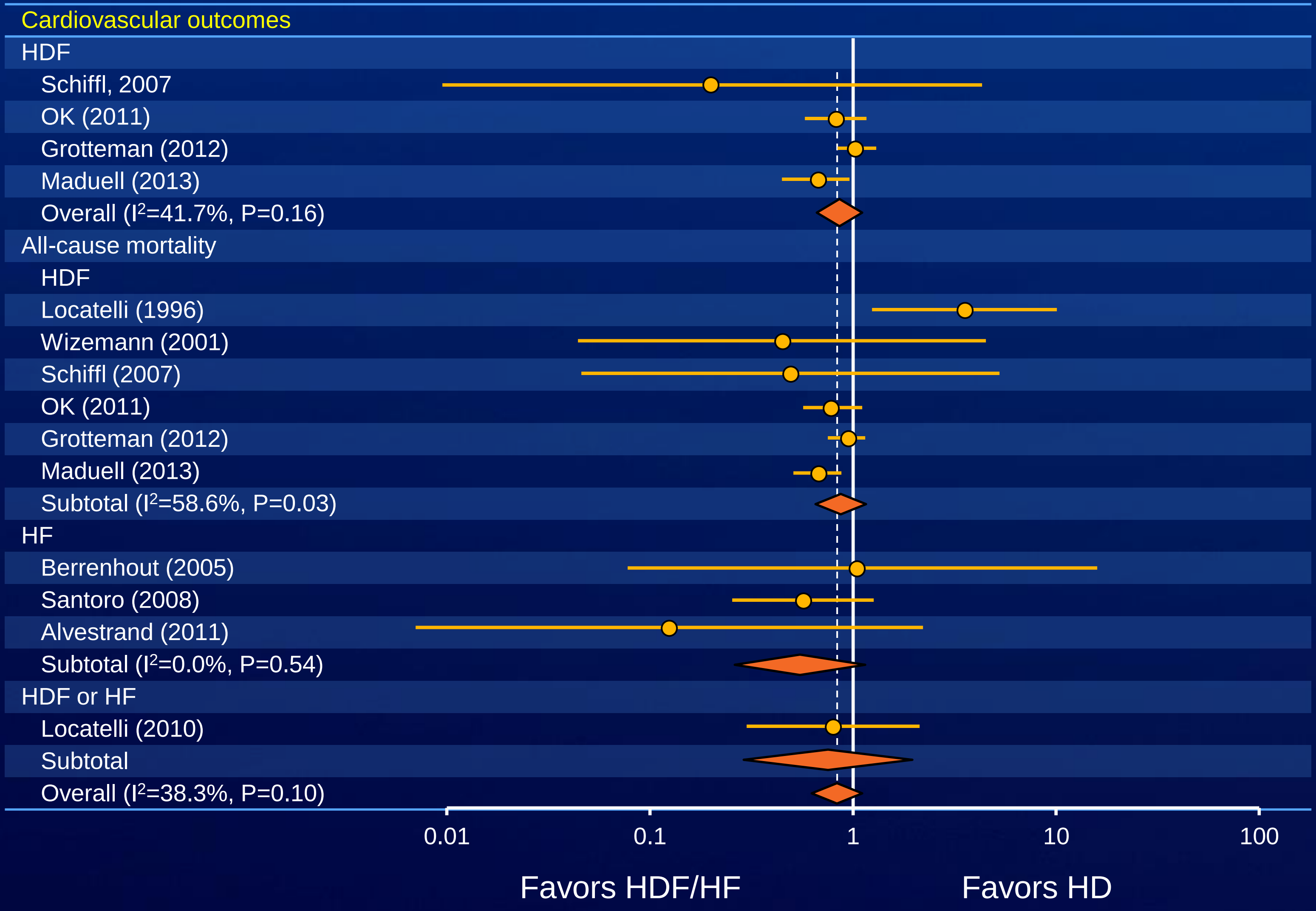
- Quality of life
- Proportion of Pts with Intradialytic event
- Mortality



Morena et al: Kidney International 91, 1495, 2017

Systematic Review

HD vs HDF

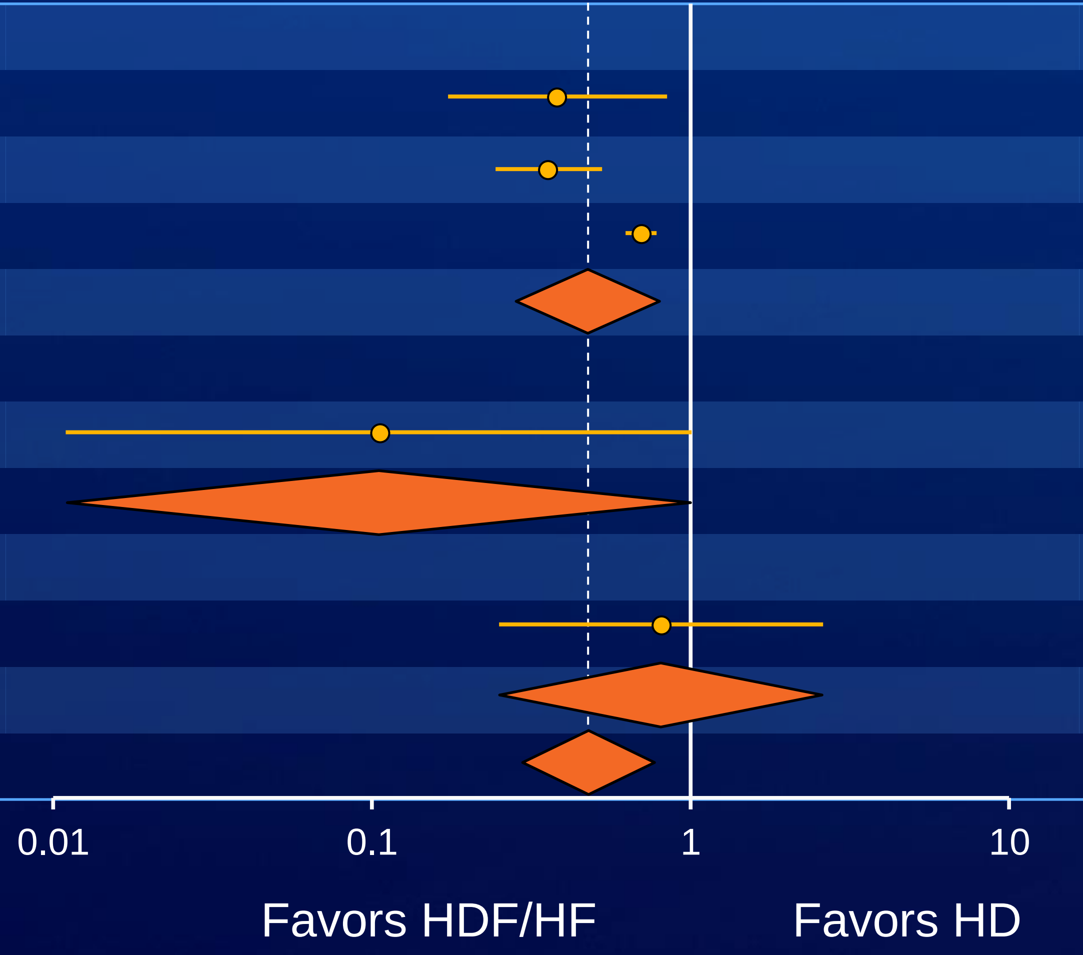


Want AY et al: AJKD 63:968, 2014

MAYO CLINIC

Systematic Review
HD vs HDF/HF

Symptomatic hypotension	RR (95% CI)
HDF	
Lin (2001)	0.39 (0.18, 0.86)
Schiffl (2007)	0.36 (0.25, 0.53)
Maduell (2013)	0.72 (0.68, 0.77)
Subtotal (I^2=86.1%, P=0.001)	0.49 (0.28, 0.86)
HF	
Santoro (2008)	0.11 (0.01, 1.04)
Subtotal	0.11 (0.01, 1.04)
HDF or HF	
Locatelli (2010)	0.84 (0.26, 2.68)
Subtotal	0.84 (0.26, 2.68)
Overall (I^2=76.7%, P=0.002)	0.49 (0.30, 0.81)



Want AY et al:
AJKD 63:968, 2014

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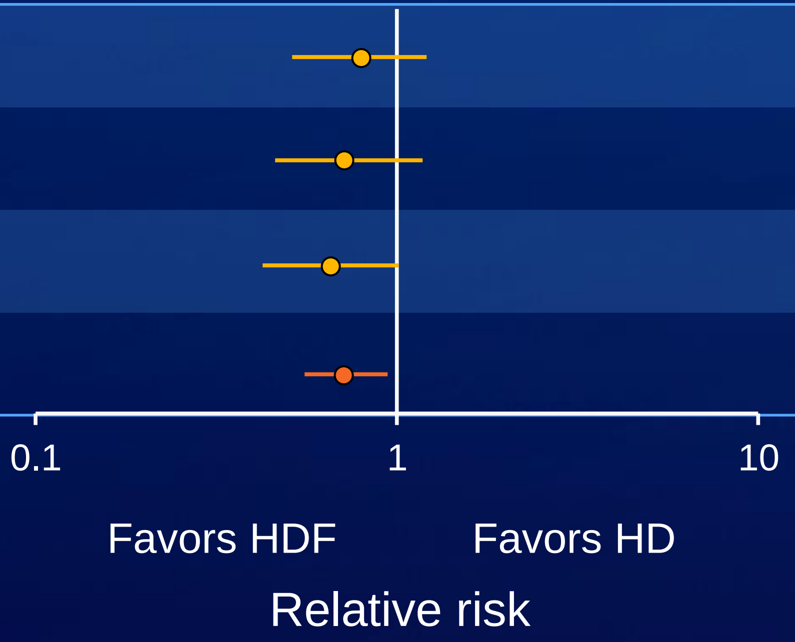
HD vs. HDF

Mortality

21 liters/session is advised

Study name	Patients (HDF/Hd)	Event nr (HDF/HD)	RR	95% CI
Grooteman et al	358/356	37/46	0.80	0.53-1.20
OK et al	391/391	32/44	0.73	0.47-1.12
Maduell et al	456/450	37/55	0.66	0.57-0.92
Pooled	1205/1197	106/145	0.73	0.57-0.92



Mostayava IM: Semin Dial, 2014

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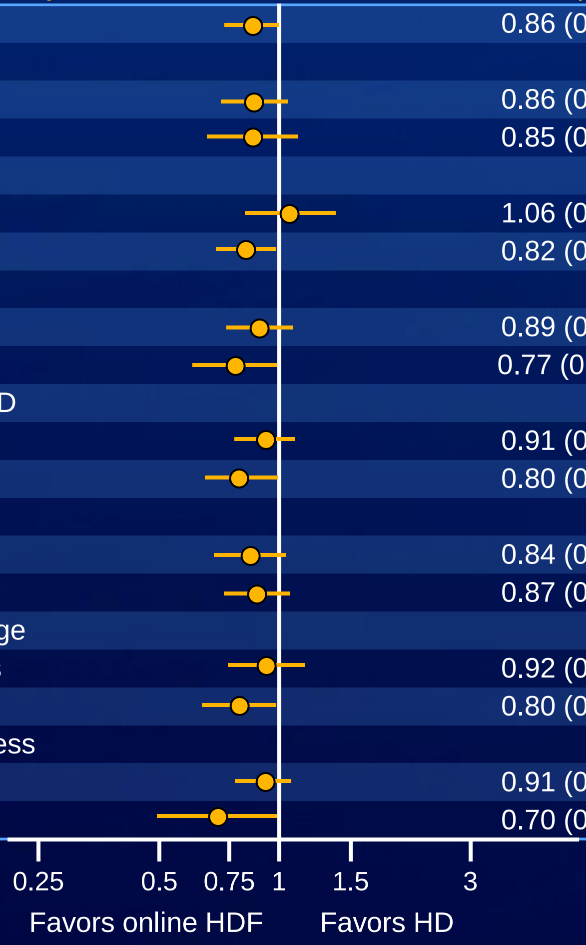
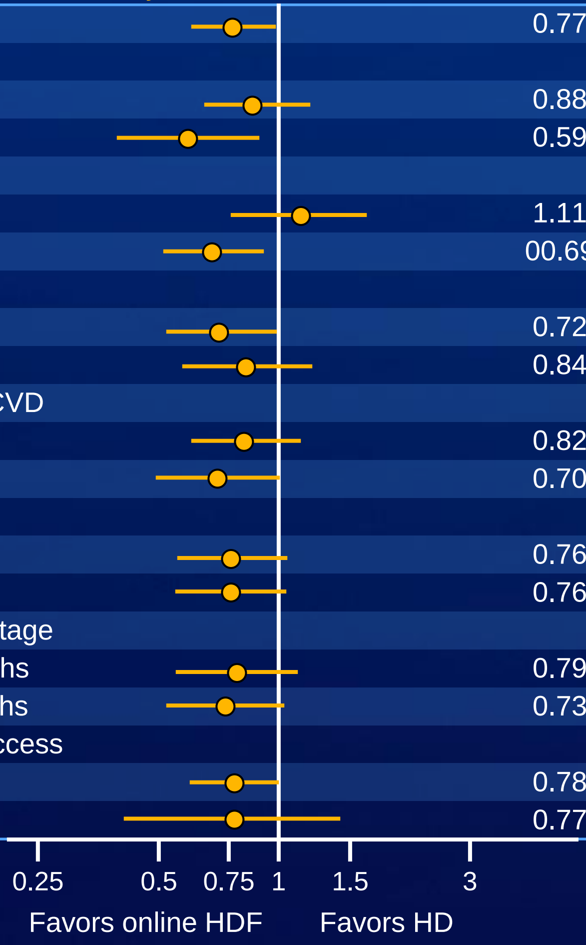
Cause	HD			HDF			HR (95% CI) for HDF vs HD
	No.	Events	Events/100 PY	No.	Events	Events/100 PY	
All-causes	1369	410	12.10	1367	359	10.45	0.86 (0.75; 0.99)
Cardiovascular disease	1302	164	4.84	1289	128	3.73	0.77 (0.61; 0.97)
Infections	1302	77	2.27	1289	73	2.13	0.94 (0.68; 1.30)
Sudden death	1302	56	1.65	1289	56	1.63	0.99 (0.68; 1.43)

All-cause mortality	HR (95% CI)	P-value for interaction
Overall	0.86 (0.75, 0.99)	
Sex		
Men	0.86 (0.73, 1.02)	
Women	0.85 (0.66, 1.10)	0.95
Age		
<65 yrs	1.06 (0.83, 1.36)	
≥65 yrs	0.82 (0.70, 0.97)	0.07
Diabetes		
No	0.89 (0.74, 1.07)	
Yes	0.77 (0.61, 0.97)	0.34
History of CVD		
No	0.91 (0.76, 1.10)	
Yes	0.80 (0.65, 0.98)	0.29
Albumin		
<4 g/dL	0.84 (0.70, 1.01)	
≥4 g/dL	0.87 (0.73, 1.05)	0.75
Dialysis vintage		
<30 months	0.92 (0.75, 1.13)	
≥30 months	0.80 (0.65, 0.97)	0.32
Vascular access		
Fistula	0.91 (0.78, 1.07)	
Other	0.70 (0.50, 0.97)	0.15



Cardiovascular mortality	HR (95% CI)	P-value for interaction
Overall	0.77 (0.61, 0.97)	
Sex		
Men	0.88 (0.66, 1.17)	
Women	0.59 (0.40, 0.89)	0.12
Age		
<65 yrs	1.11 (0.76, 1.62)	
≥65 yrs	00.69 (0.52, 0.90)	0.03
Diabetes		
No	0.72 (0.53, 0.97)	
Yes	0.84 (0.58, 1.21)	0.54
History of CVD		
No	0.82 (0.61, 1.09)	
Yes	0.70 (0.50, 0.98)	0.46
Albumin		
<4 g/dL	0.76 (0.57, 1.03)	
≥4 g/dL	0.76 (0.56, 1.03)	0.98
Dialysis vintage		
<30 months	0.79 (0.56, 1.11)	
≥30 months	0.73 (0.53, 1.01)	0.76
Vascular access		
Fistula	0.78 (0.61, 1.00)	
Other	0.77 (0.42, 1.42)	0.98



Peters et al: Nephrol Dial Transplant 31:978, 2016

Safety

- No RCTs were designed for safety assessment
- None indicated HDF is unsafe
  - CONTRAST trial → Substitution fluid with adequate quality produced online over a prolonged period of time
  - ESHOL trial → Mortality risk from infection was significantly lower in OL-HDF vs HD
  - Inflammatory markers did not differ between OL-HDF and HD

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Take Home Points

- OL-HDF
  - Likely ↑ middle molecules and phosphate removal
- CONTRAST and Turkish trials → No survival benefits
  - Survival benefits when CV > 17.5 – 22 L/session
- ESHOL trial → ↑ survival with high-volume OL-HDF with CV > 22 L/session
- Meta-analyses
  - Controversial for survival benefits

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THANK YOU FOR YOUR KIND ATTENTION

QUESTIONS & DISCUSSION

از توجه شما بسیار متشکرم