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HEMODIAFILTRATION

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Disclosures

- Nothing to disclose

Learning Objectives

At the end of this presentation, learners will be able to:

- Explain the physiologic rationale for HDF
- Summarize the current evidence supporting HDF
- Identify practical considerations for implementing high-volume HDF

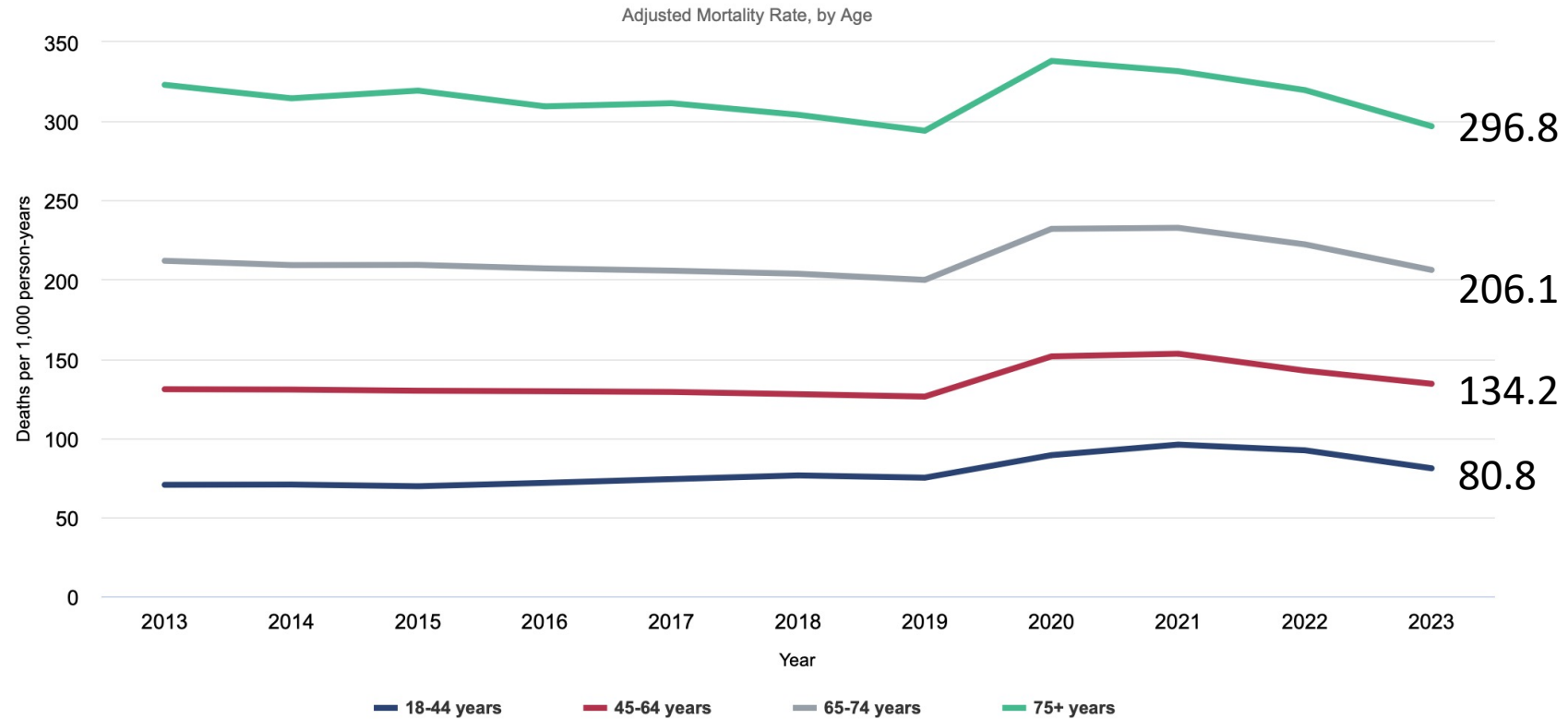
Audience Response

My experience with hemodiafiltration and other convective dialytic therapies is best characterized as:

- Extensive
- Minimal
- None

All-cause mortality in adults on hemodialysis

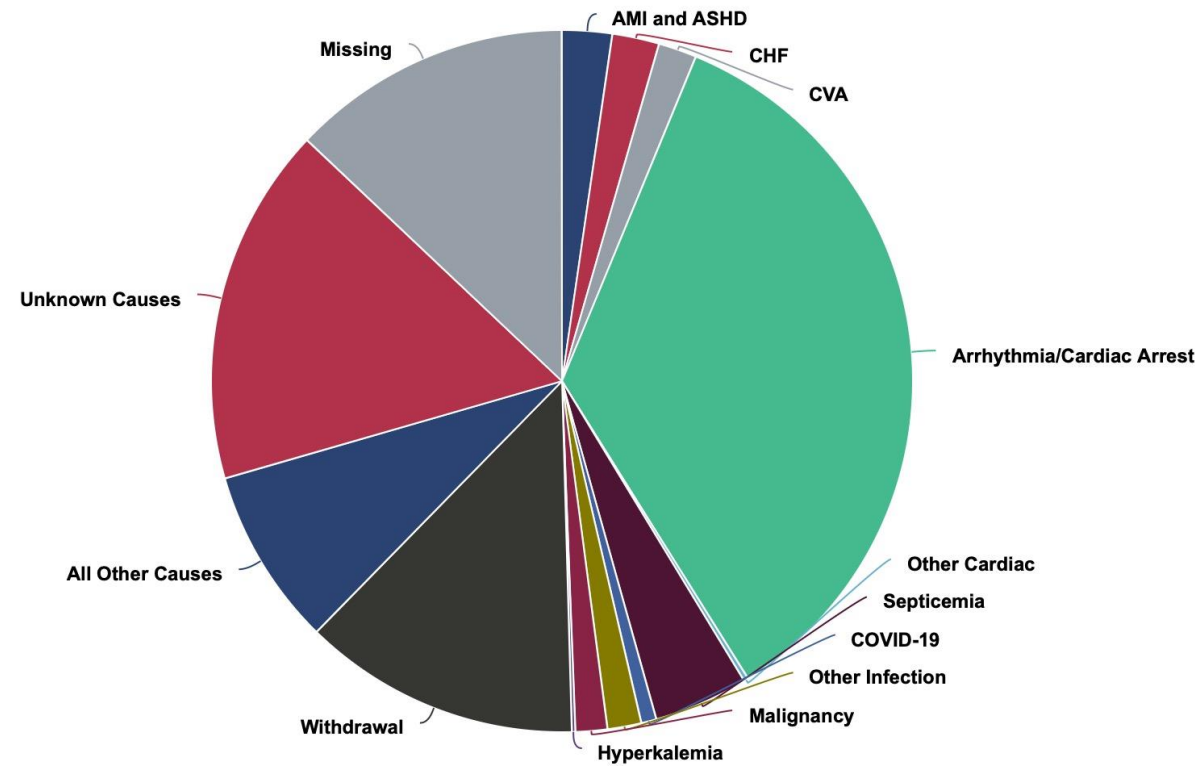
Figure 6.1b All-cause mortality in adults on hemodialysis, by patient characteristics, 2013-2023



Data Source: 2025 United States Renal Data System Annual Data Report

60% of ESKD deaths are due to cardiovascular causes

Figure 6.6a Percentages of cause-specific mortality in people with ESKD on hemodialysis who died in 2023



Data Source: 2025 United States Renal Data System Annual Data Report

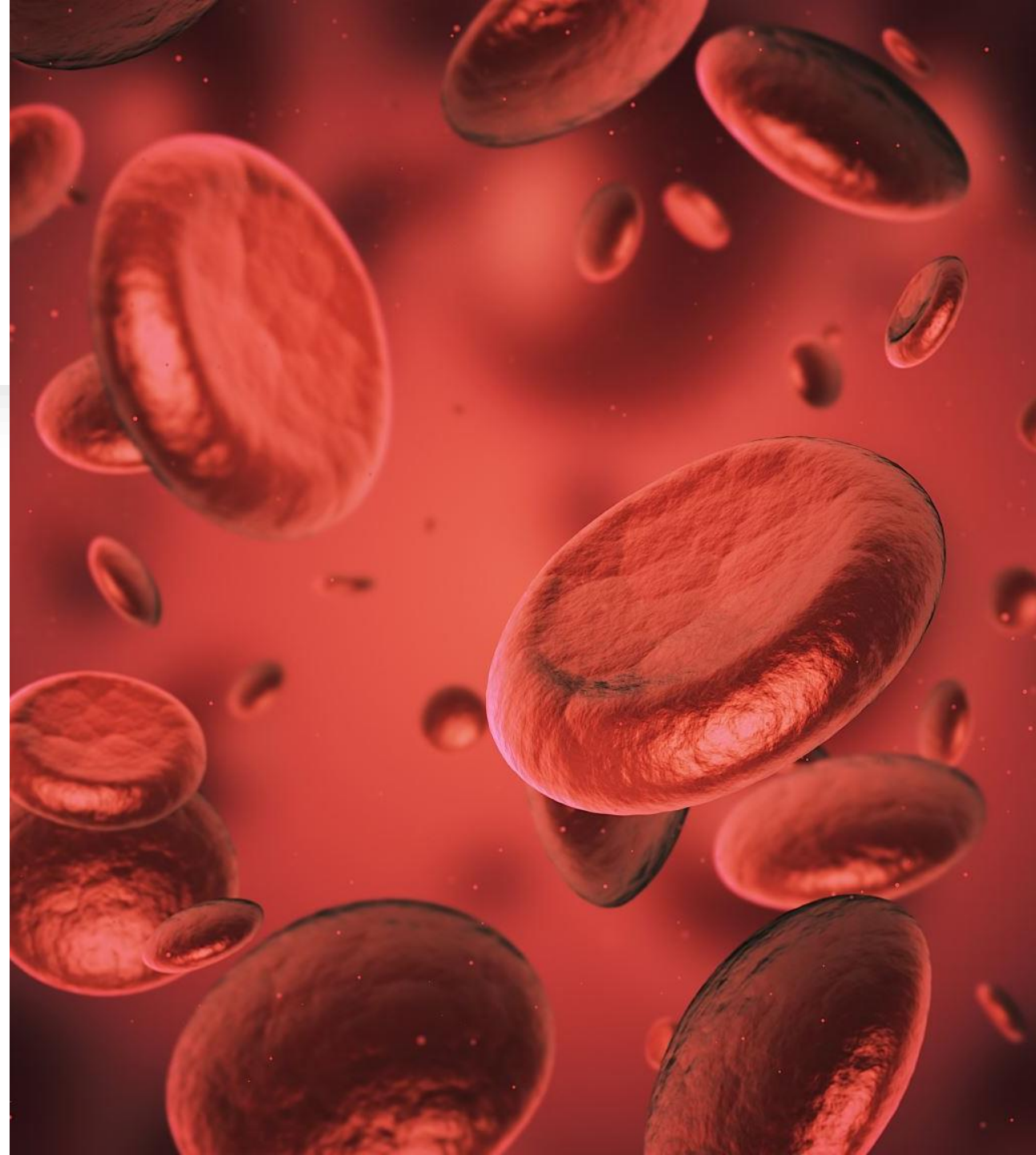
Understanding solute clearance

Urea is the prototype small solute

- The EUTox classification has designated solutes with mass less than 500 Da as “low molecular mass.”
- Urea has served as the prototype for free, low-molecular-mass uremic solutes, i.e., the small solutes

Urea clearance

- Urea clearance can approach the extracorporeal blood flow because urea moves rapidly out of red blood cells as well as the plasma during the passage of blood through the dialyzer
- Urea has a low mass
 - Diffusivity of small solutes declines with increased mass
 - Diffusive clearance can be represented by a mass transfer area coefficient (KoA) for that solute



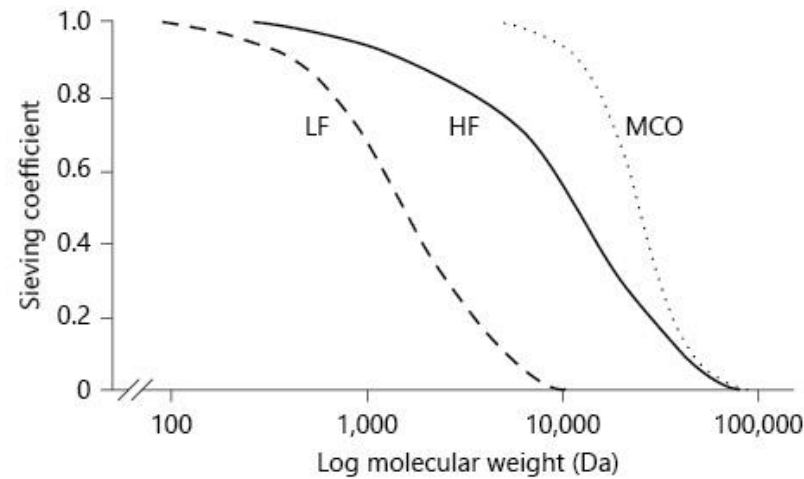
Middle molecule clearance

- Solutes with mass between 500 and 45,000 Da are designated as “middle molecules” in the EUTox classification
- Middle molecules have reduced clearance relative to urea
 - Increasing mass slows the rate at which solutes diffuse
 - Increasing mass eventually keeps solutes from entering the fluid channels in the membrane through which they must pass to get from the blood to the dialysate side of the membrane

β -2 microglobulin is the prototype middle molecule

- In the 1980s evidence accumulated that β -2 microglobulin caused dialysis-related amyloidosis
- This finding promoted effort to use membranes more permeable to larger solutes
- β -2 microglobulin has been adopted as the prototype larger solute (middle molecule)

Sieving curves for low-flux, high-flux, and MCO membranes



HEMO Study

High Flux High Dose	High Flux Standard Dose
Low Flux High Dose	Low Flux Standard Dose

Kt/V Goals in HEMO

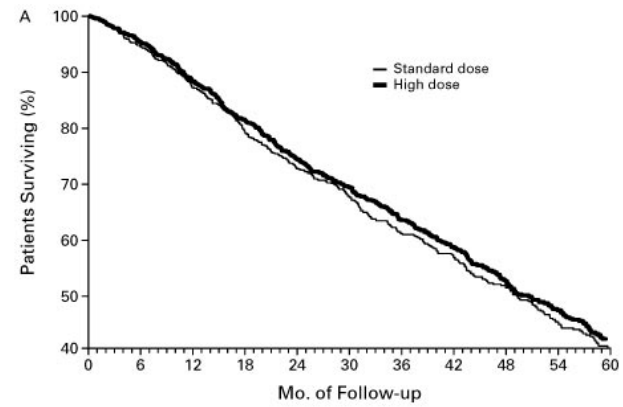
Standard Dose

- eKt/V 1.05

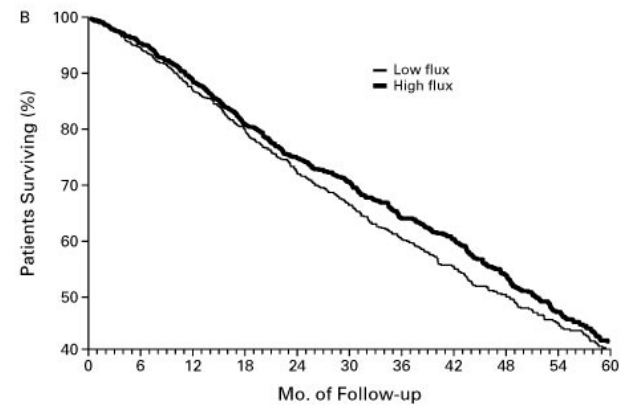
High Dose

- eKt/V 1.45

Survival Curves for the Treatment Groups



No. AT Risk										
Standard dose	854	759	630	524	451	392	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

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

HEMO Study Conclusions

- No evidence that higher dialysis doses improved mortality
- No evidence that high flux dialysis improved mortality relative to low flux dialysis

Should we
consider more
than urea (small
solute)
clearance?



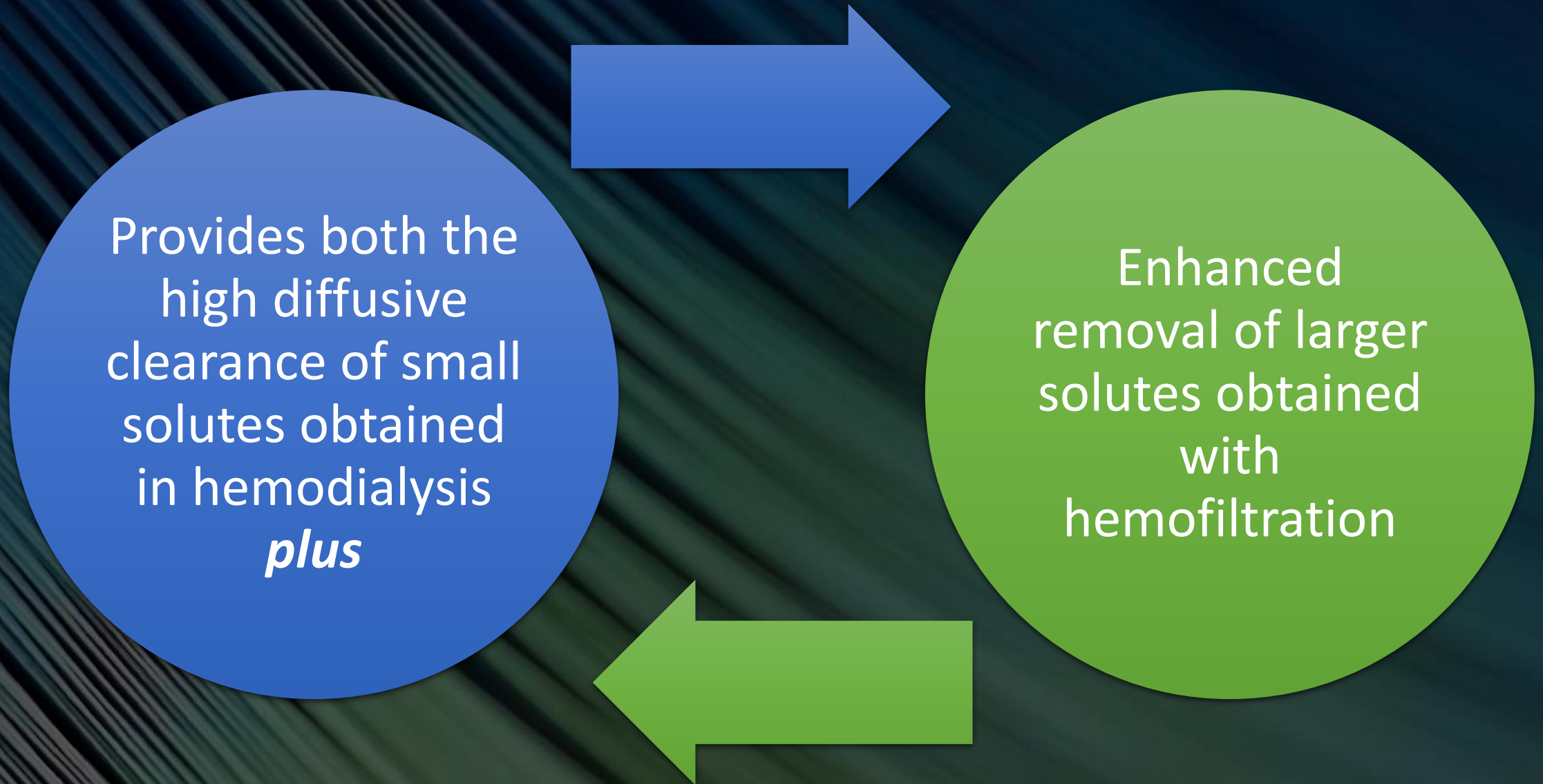
Solute removal in hemodialysis

- Solute removal in hemodialysis occurs by diffusion
- Because diffusion coefficients decrease rapidly with increasing molecular size, removal of larger uremic toxins is modest in hemodialysis

Solute removal in hemofiltration

- Solute removal in hemofiltration occurs by convection
- Small solute removal is modest because it cannot exceed the ultrafiltration rate
- Hemofiltration provides greater clearance of larger solutes than hemodialysis
 - Sieving coefficients, which together with ultrafiltration rate, determine convective clearance, decrease only gradually with increasing molecular size

Hemodiafiltration



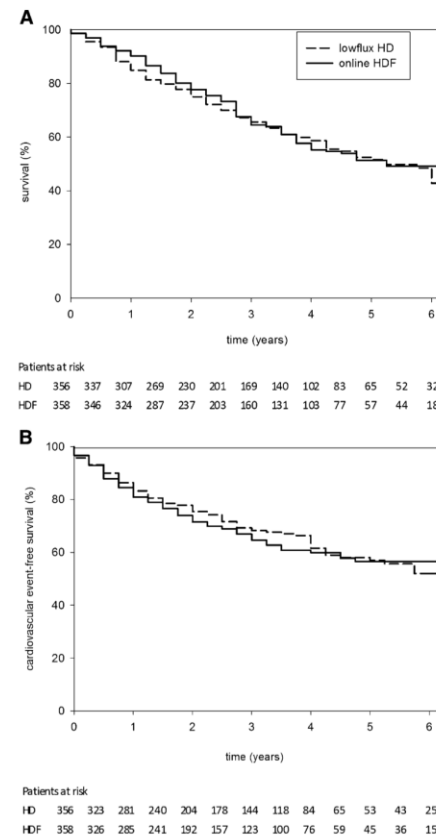
Outcomes potentially related to clearance of larger solutes

- Mortality
- Cardiovascular morbidity and mortality
 - Vascular calcification
- Inflammation
- Quality of life measures
 - Sleep
 - Fatigue
 - Pruritus

Is there a benefit of more convective clearance?

- Hemodiafiltration is not widely practiced in the United States
- More commonly utilized in Europe and Japan
- Utilizes a substitution fluid to provide the convective clearance

CONTRAST Study: LF-HD versus HDF



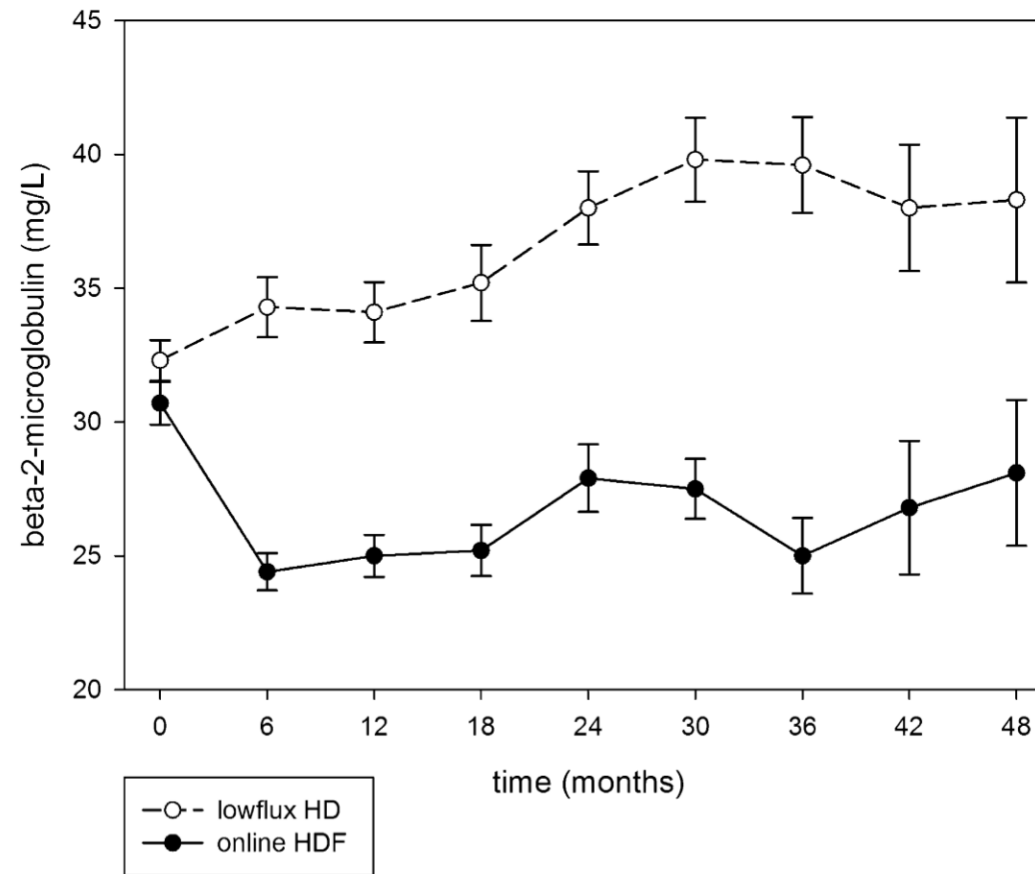
Grooteman MPC et al, J Am Soc Nephrol 23: 1087–1096, 2012

Risk of all-cause mortality and fatal and nonfatal CV events stratified by convection volume

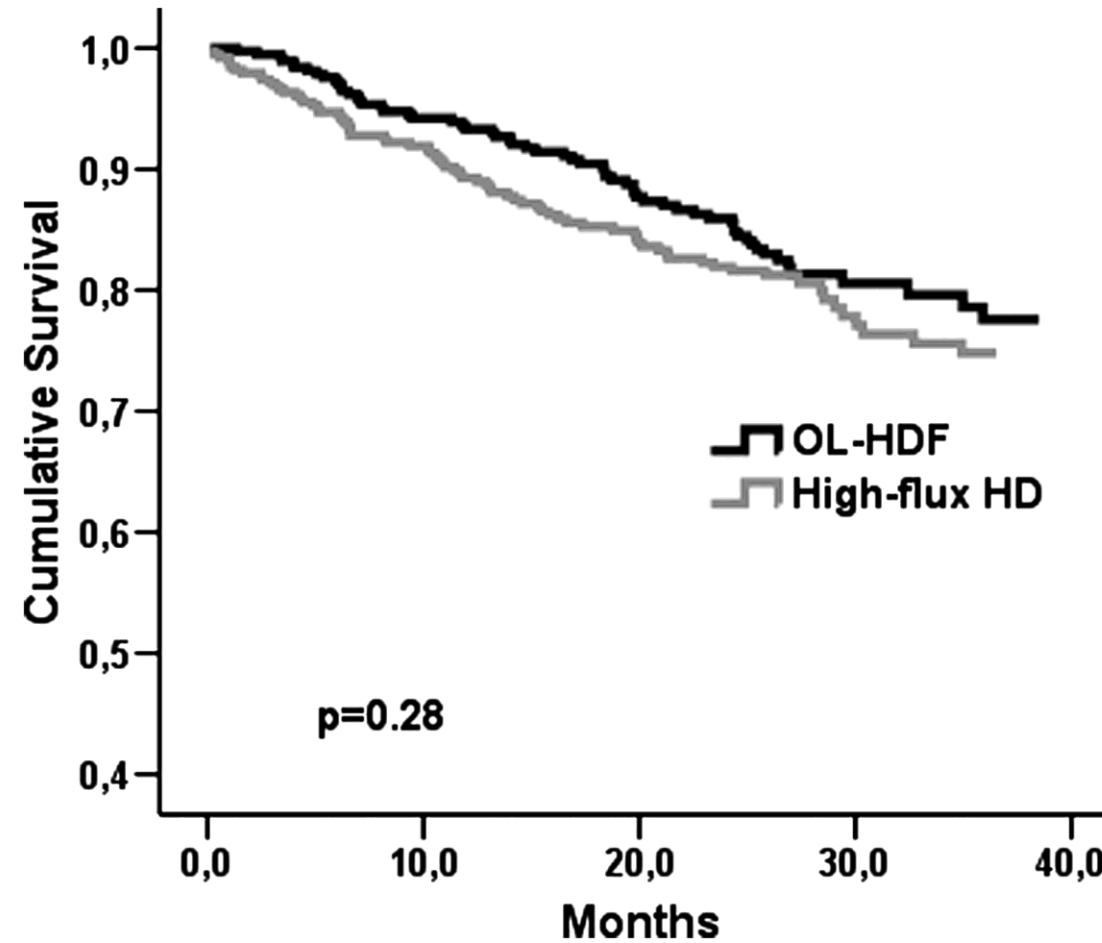
	Hemodialysis	Online Hemodiafiltration Convection Volume Tertiles			P for Trend
		<18.17 L	18.18–21.95 L	>21.95 L	
Total mortality					
crude	1.0	0.95 (0.66–1.38)	0.83 (0.57–1.22)	0.62 (0.41–0.93)	0.010
adjusted ^a	1.0	0.79 (0.53–1.14)	0.77 (0.51–1.14)	0.65 (0.42–0.99)	0.012
adjusted ^b	1.0	0.80 (0.52–1.24)	0.84 (0.54–1.29)	0.61 (0.38–0.98)	0.015
Fatal and nonfatal cardiovascular events					
crude	1.0	1.37 (0.94–1.98)	1.06 (0.72–1.56)	0.76 (0.50–1.16)	0.473
adjusted ^a	1.0	1.41 (0.92–2.11)	0.93 (0.62–1.40)	0.77 (0.48–1.21)	0.369
adjusted ^b	1.0	1.35 (0.86–2.11)	1.04 (0.66–1.62)	0.72 (0.44–1.19)	0.475

Grooteman MPC et al, J Am Soc Nephrol 23: 1087–1096, 2012

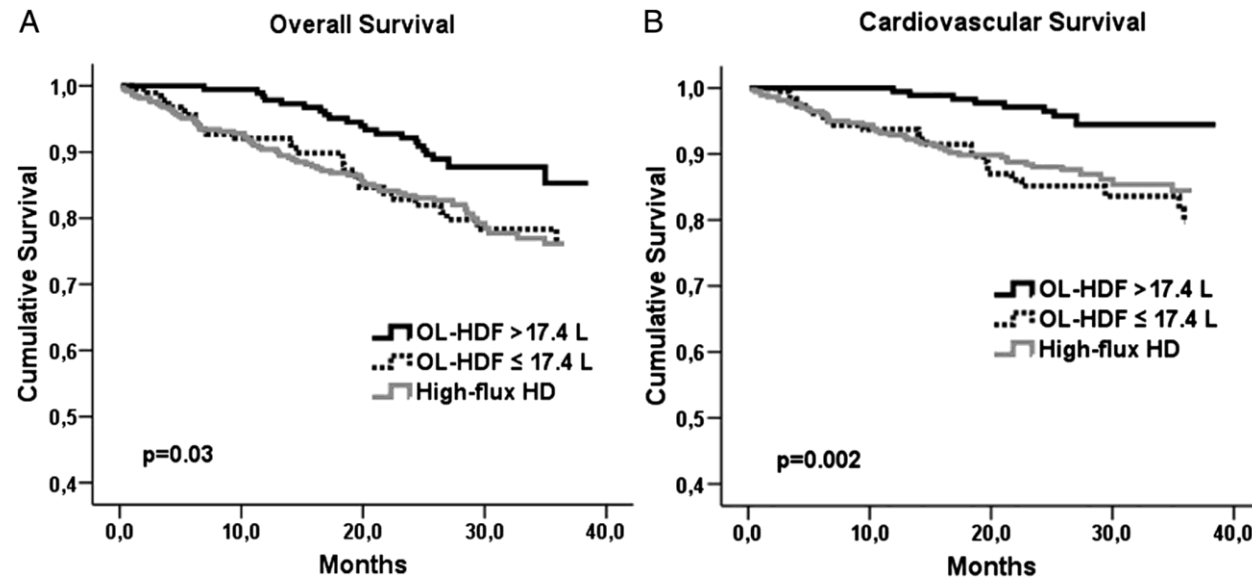
β -2 microglobulin levels in the two study arms



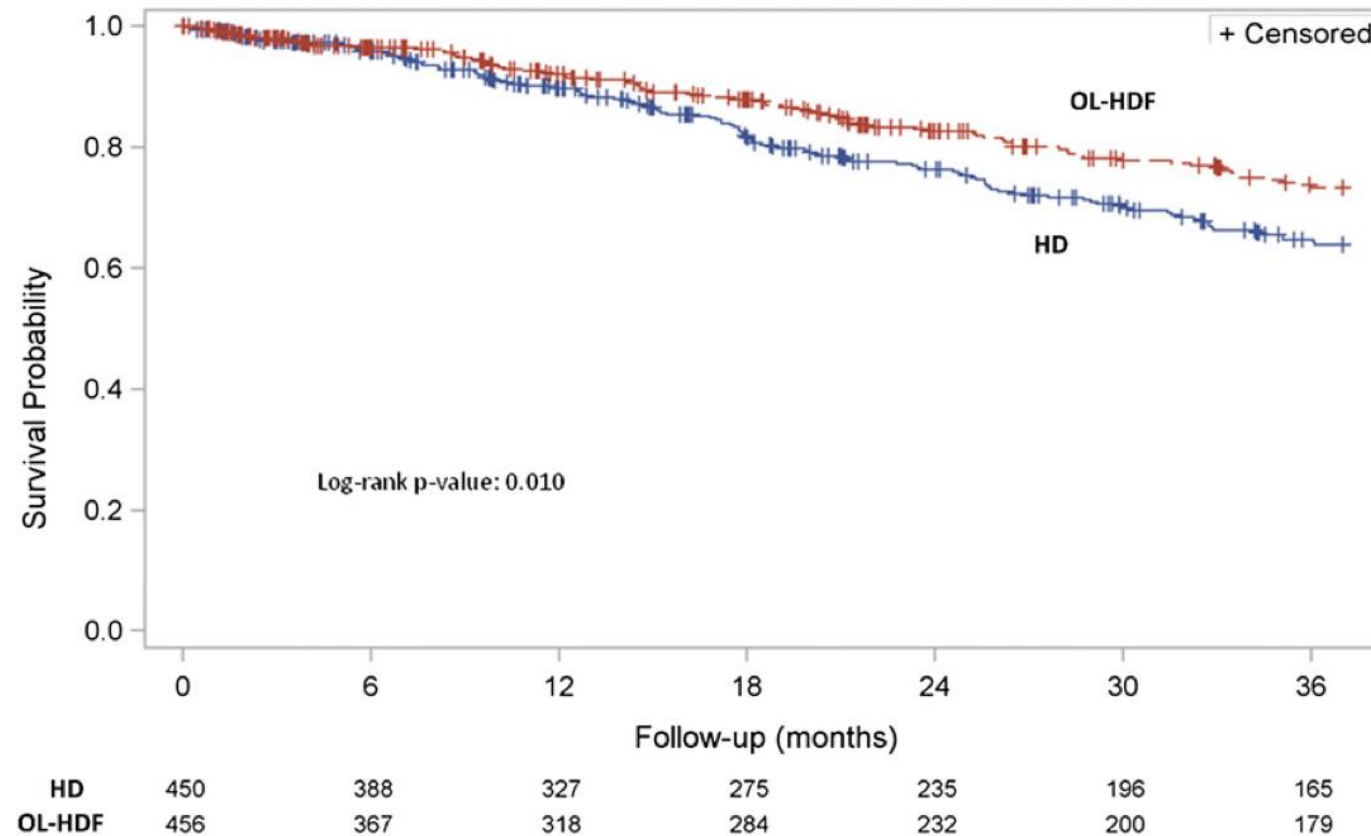
Turkish Study: Composite event-free survival in patients treated with OL-HDF and high-flux HD



Turkish Study: Overall (A) and cardiovascular survival (B) among the treatment group stratified by convection volume



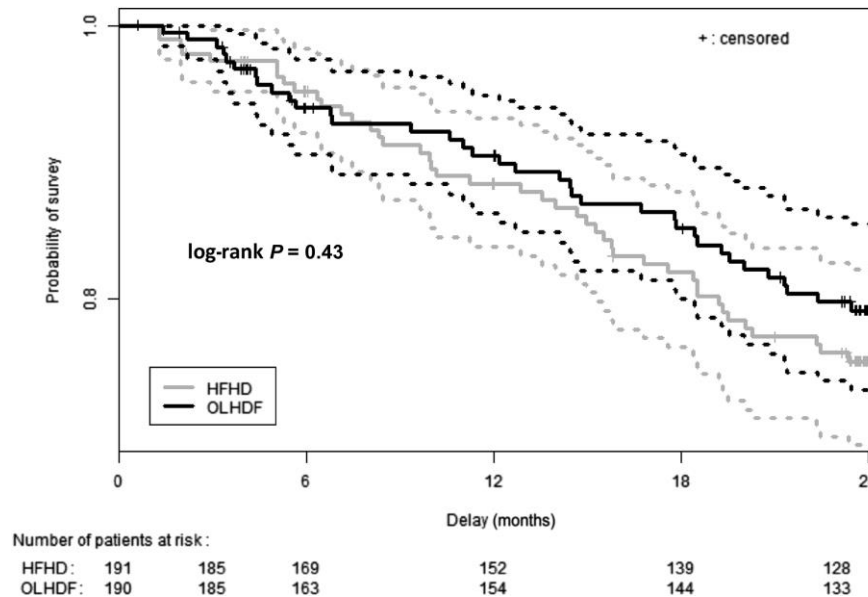
ESHOL: Median convection volume of 22.9-23L



30% lower risk of
all-cause and CV
mortality

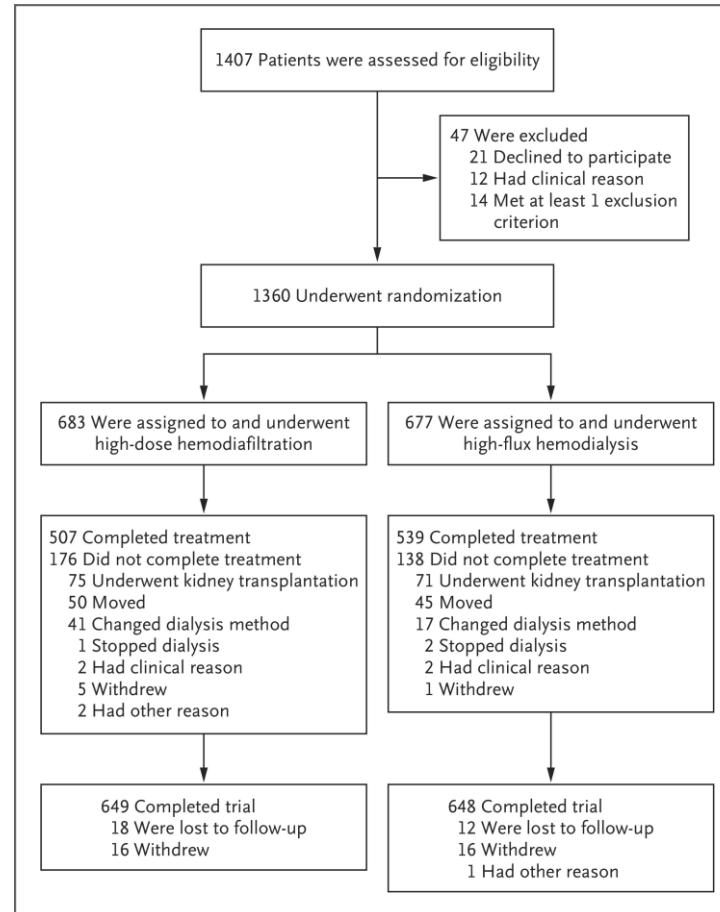
FRENCHIE Trial: Focus on treatment tolerance in individuals

No survival difference



Study Parameter	CONTRAST	Turkish	ESHOL	FRENCHIE
Comparison	LF-HD (n=358) vs. HDF (n= 356)	HF-HF (n=391) vs. HDF (n= 391)	HF-HD (n=450) vs. HDF (n=456)	HF-HD (n=191) vs. HDF (n=190)
Mean follow-up (yrs)	3.04	1.89	1.91	1.64
Target convection volume	24L per 4-hour session	> 15L per session + net UF	> 18L per session + net UF	
Delivered convection volume	20.7L per session	17.2 L per session + net UF	22.9-23.9 L per session	21L per session
Primary outcome	All-cause mortality	All-cause mortality + nonfatal CV events	All-cause mortality	Intradialytic tolerance
HR for primary outcome [95% CI], HD =1.00	0.95 [0.75 to 1.20]	0.82 [0.59-1.16]	0.70 [0.53 to 0.92]	0.94 [0.51 to 1.76]
Secondary outcomes	Fatal + nonfatal CV events (HR, 1.07; 95% CI, 0.83 to 1.39)	CV and overall mortality (HR 0.72; 95% CI, 0.45 to 1.13)	CV mortality (HR, 0.67; 95% CI, 0.44 to 1.02); infection-related mortality (HR, 0.45; 95% CI, 0.21 to 0.96)	All-cause mortality (HR, 0.83; 95% CI, 0.52 to 1.33)
Potential Limitations	Failure to deliver target convection volume	Underpowered		Underpowered

CONVINCE Trial



Baseline characteristics of study participants

Table 1. Characteristics of the Patients at Baseline.^a

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	234 (34.3)	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 — m ² ¶	1.86±0.22	1.86±0.22
Blood pressure before dialysis — mm Hg		
Systolic	141±22	141±22
Diastolic	73±14	72±15
Heart rate before dialysis — beats/min	72±11	72±12
Laboratory values		
Hemoglobin — g/dl	11.3±1.2	11.3±1.2
Serum creatinine — mg/dl	7.4±2.5	7.3±2.3
Serum urea — mg/dl	70.6±30.5	71.4±32.7
Median C-reactive protein (IQR) — mg/liter	5 (2–11)	4 (2–10)
Serum phosphate — mg/dl	4.9±1.5	4.9±1.4
Blood flow — ml/min**	369±54	367±56
Median residual urinary output (IQR) — ml/24 hr	850 (500–1300)	800 (444–1200)
Dialysis		
Median vintage (IQR) — mo	35 (16–78)	30 (14–67)
Median duration of session (IQR) — min	240 (240–248)	240 (240–245)
Median single-pool Kt/V (IQR)††	1.61 (1.45–1.83)	1.61 (1.42–1.80)
Vascular access — no. (%)		
Fistula	558 (81.7)	557 (82.3)
Catheter	90 (13.2)	94 (13.9)
Graft	35 (5.1)	26 (3.8)
Previous kidney transplantation — no. (%)	93 (13.6)	79 (11.7)

^a Plus-minus values are means ±SD. Details regarding missing data (which were omitted from calculations of means and medians) are provided in Section S4 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for serum phosphate (as inorganic phosphorus) to millimoles per liter, multiply by 0.3229. IQR denotes interquartile range.

† Cardiovascular disease (including coronary heart disease) was defined as a history of any one or more of the following conditions: angina, myocardial infarction, coronary stent or dotter procedure and coronary-artery bypass graft, congestive heart failure, atrial fibrillation, transient ischemic attack, cerebrovascular accident, abdominal aortic aneurysm or intermittent claudication; placement of pacemaker or internal defibrillator; carotid endarterectomy; stent or dotter procedure, bypass surgery, or amputation of the arteries of the lower limbs; and stent or dotter procedure of the renal arteries.

‡ Coronary heart disease was defined as a history of any one or more of the following: angina, myocardial infarction, coronary stent or dotter procedure, and coronary-artery bypass graft.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

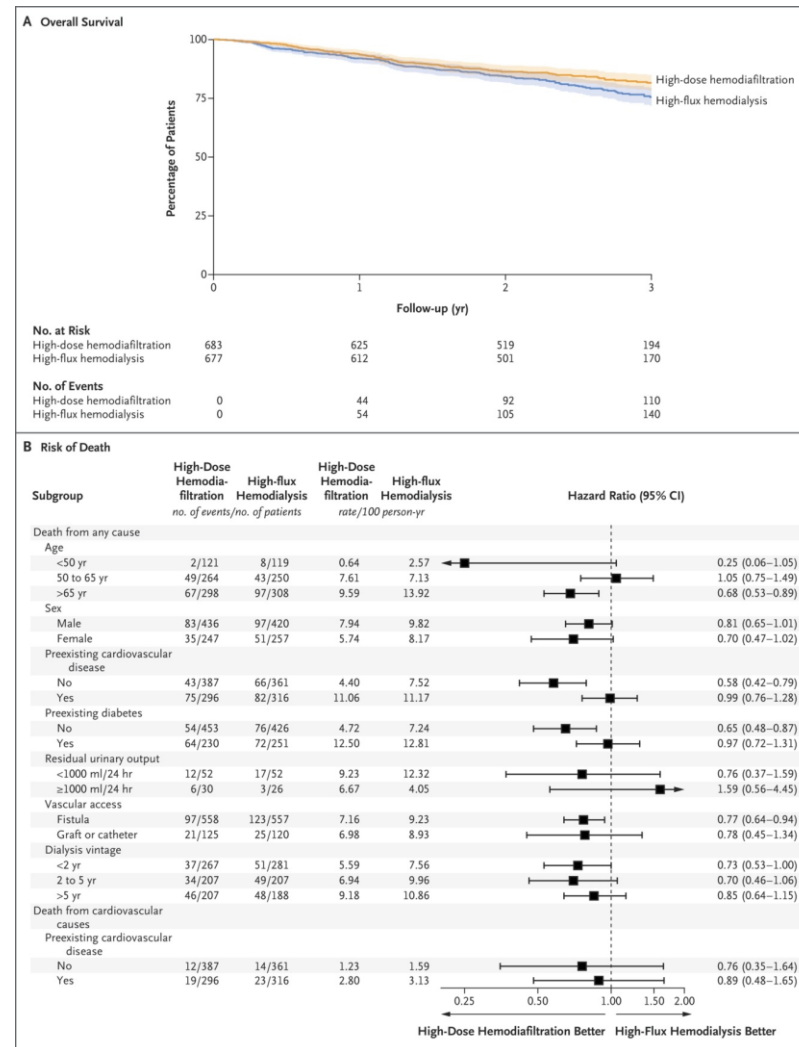
¶ The body-surface area was calculated by means of the Du Bois formula.

‡ The serum creatinine value is the geometric mean of measurements taken before and after dialysis.

** Blood flow was measured through an extracorporeal circuit.

†† The single-pool urea Kt/V for hemodialysis is a dimensionless measure of the adequacy of small-molecule removal provided by a single dialysis treatment. In this measure, K represents the urea clearance by the dialyzer, t represents the treatment time, and V represents the urea distribution volume.

High-flux dialysis vs. hemodiafiltration: a randomized trial



Primary and secondary outcomes

Variable	High-Dose Hemodiafiltration (N=683)		High-Flux Hemodialysis (N=677)		Hazard Ratio (95% CI)†
	no. (%)	no. of events/ 100 patient-yr (95% CI)	no. (%)	no. of events/ 100 patient-yr (95% CI)	
Primary outcome					
Death from any cause	118 (17.3)	7.13 (5.90–8.54)	148 (21.9)	9.19 (7.77–10.79)	0.77 (0.65–0.93)
Secondary outcomes					
Death					
Cardiovascular	31 (4.5)	1.87 (1.27–2.66)	37 (5.5)	2.30 (1.62–3.17)	0.81 (0.49–1.33)
Noncardiovascular	87 (12.7)	5.26 (4.21–6.48)	111 (16.4)	6.89 (5.67–8.30)	0.76 (0.59–0.98)
Infection-related					
Including Covid-19	38 (5.6)	2.30 (1.62–3.15)	54 (8.0)	3.35 (2.52–4.37)	0.69 (0.49–0.96)
Excluding Covid-19	23 (3.4)	1.39 (0.88–2.09)	33 (4.9)	2.05 (1.41–2.88)	0.68 (0.42–1.10)
Fatal or nonfatal cardiovascular outcome‡	136 (19.9)	9.05 (7.60–10.71)	126 (18.6)	8.48 (7.07–10.10)	1.07 (0.86–1.33)
Kidney transplantation	75 (11.0)	4.80 (3.77–6.01)	71 (10.5)	4.72 (3.69–5.96)	1.01 (0.71–1.44)
Recurrent hospitalization — no.§					
For any nonfatal cause	998	61.34 (57.59–65.27)	895	56.36 (52.73–60.18)	1.11 (0.98–1.25)
Infection-related					
Including Covid-19	234	14.32 (12.54–16.28)	219	13.92 (12.14–15.88)	1.06 (0.86–1.30)
Excluding Covid-19	152	9.34 (7.92–10.95)	156	9.82 (8.34–11.49)	0.97 (0.74–1.26)

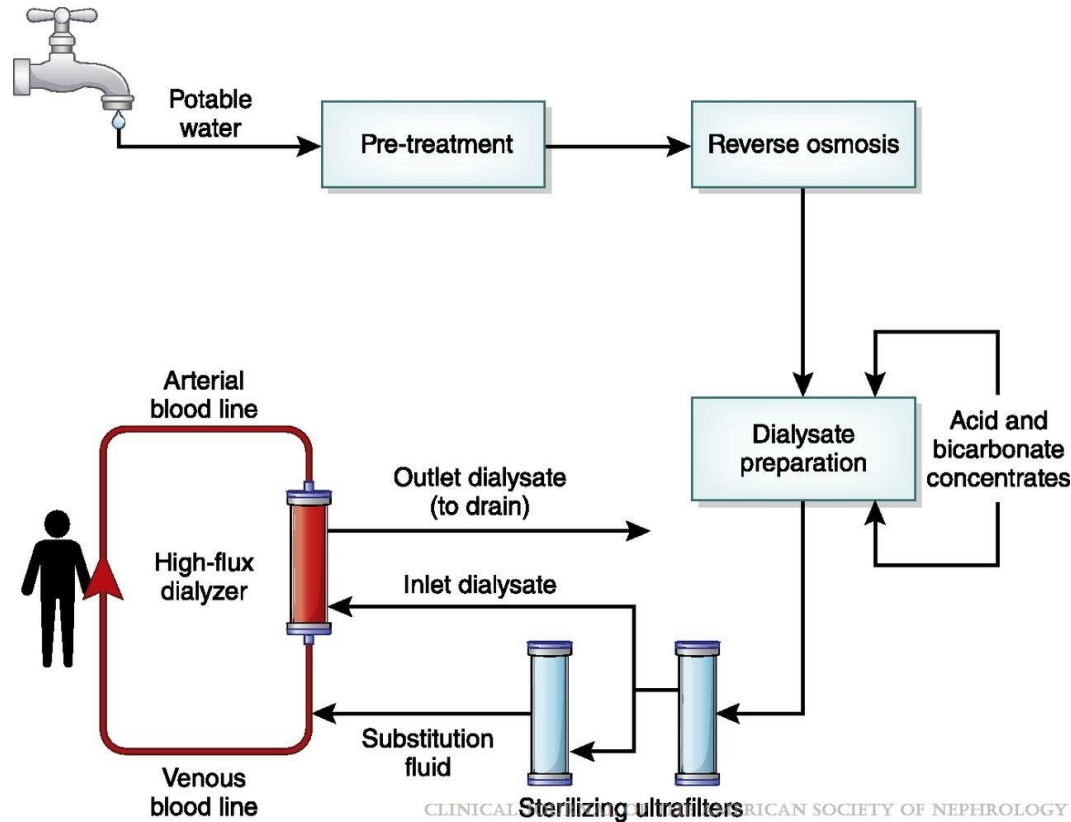
* All the listed analyses were prespecified except for the categories involving hospitalization or death from coronavirus disease 2019 (Covid-19).

† No adjustment for multiplicity was made, so the 95% confidence intervals should not be used in place of hypothesis testing.

‡ The composite outcome of fatal or nonfatal cardiovascular events includes death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, therapeutic coronary procedure (coronary-artery bypass grafting, percutaneous transluminal coronary angioplasty, or stenting), therapeutic carotid procedure (endarterectomy or stenting), vascular intervention (revascularization or percutaneous transluminal angioplasty or stenting), or peripheral limb amputation.

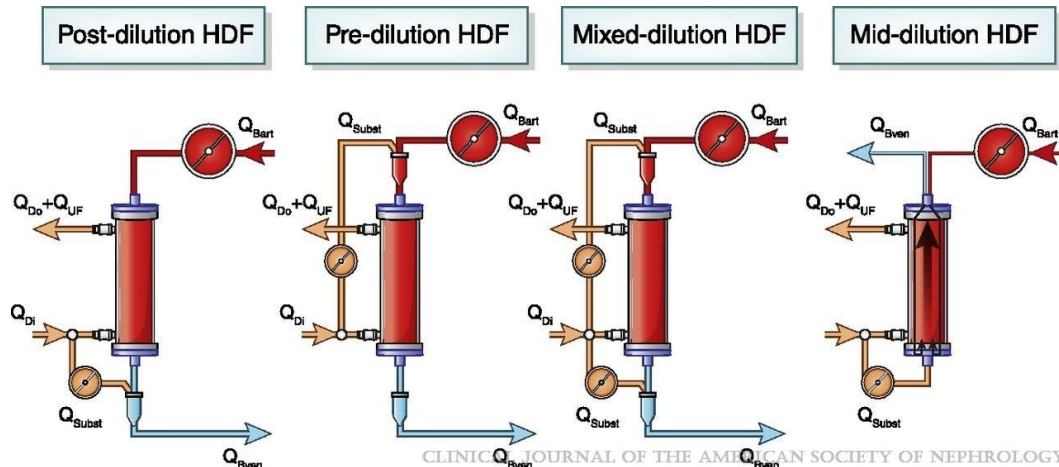
§ In this category, patients may have had more than one recurrent event, so percentages of patients are not provided.

Schematic view of hemodiafiltration



Dialysate and substitution fluid are prepared using a purification cascade comprising reverse osmosis and two sterilizing ultrafilters. The high-flux dialyzer with polysulfone membranes acts as an additional endotoxin adsorber and provides additional microbial safety.

Modalities of hemodiafiltration

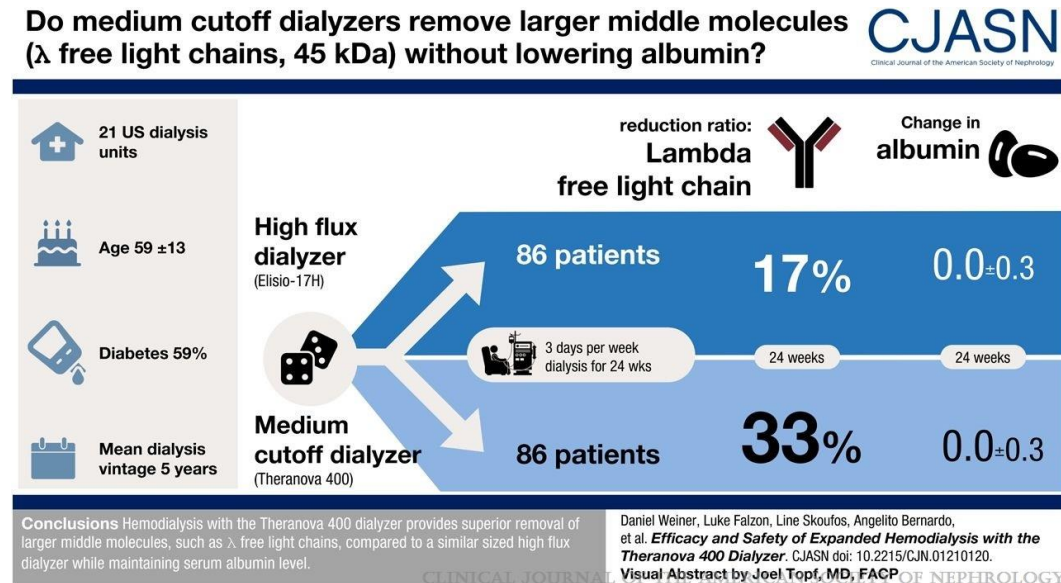


Different modalities of hemodiafiltration (HDF) are defined by the route of substitution fluid administration. Q_{Bart} , arterial blood line to dialyzer; Q_{Bven} , venous blood line to patient; Q_{Di} , inlet dialysate flow; Q_{Do} , outlet dialysate flow; Q_{UF} , ultrafiltrate flow; Q_{Subst} , substitution fluid flow.

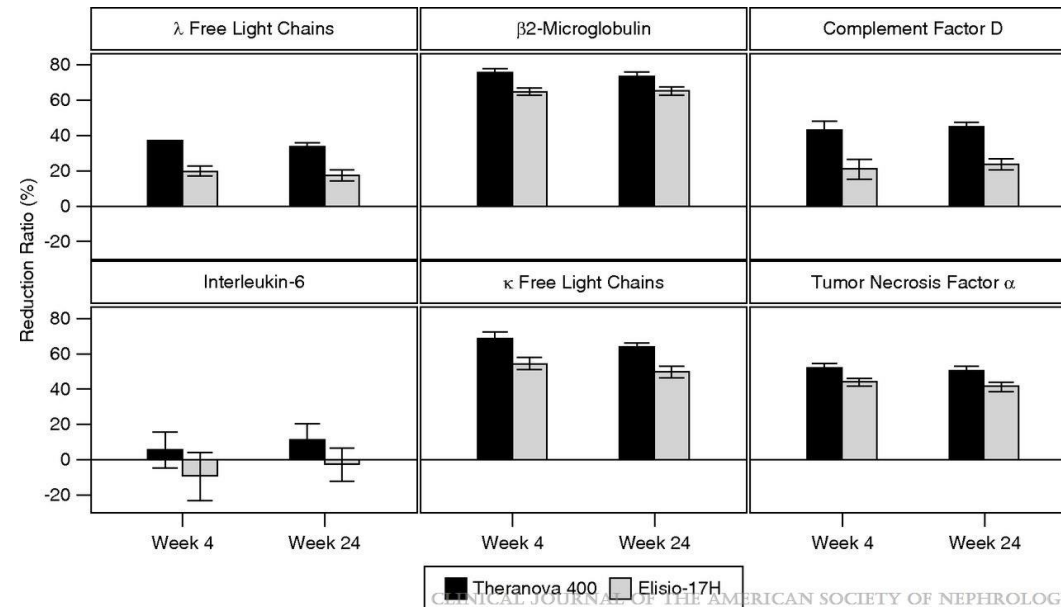
Expanded Hemodialysis (HDx)

- A technique using a “high retention onset” membrane dialyzer
- HDx allows the clearance larger molecules that typically require convection

Randomized Trial of HRO Dialyzer versus High Flux Dialyzer



Randomized Trial of HRO Dialyzer versus High Flux Dialyzer



Dialysis Glossary

Preferred term	Suggested abbreviation	Terms to avoid
Therapies		
Renal replacement therapy	RRT	Kidney replacement therapy (KRT)
Continuous renal replacement therapy	CRRT	Continuous kidney replacement therapy (CKRT), acute dialysis
Intermittent hemodialysis	IHD	Chronic dialysis, acute dialysis (the terms acute and chronic refer to duration of kidney disease rather than duration of dialysis treatment)
Prolonged intermittent hemodialysis or prolonged intermittent renal replacement therapy	Prolonged IHD or PIRRT	Sustained low-efficiency dialysis (SLED), acute dialysis
Hemodiafiltration	HDF	Online hemodiafiltration (OL-HDF) or high-volume online hemodiafiltration
Expanded hemodialysis	HDx	Middle cutoff (MCO) hemodialysis, MCO-HD, protein-leaking hemodialysis, super high-flux hemodialysis, or high-permeability hemodialysis
Isolated ultrafiltration	Isolated UF	Slow continuous ultrafiltration (SCUF)
Disposables		
Filter	-	Membrane, dialyzer, or hemodialyser
Plasmafilter	-	Membrane or plasma filter
Cartridge	-	Filter, resin, sorbent, or column

Take Home Messages

- Dialysis adequacy in the United States has focused on small solute (urea) clearance
- Large solutes (middle molecules) may be responsible for some of the excess morbidity and mortality in ESKD.
- Convective clearance is more efficient at removal of middle molecules
- Hemodiafiltration is a dialytic modality that provides both diffusive and convective clearance
- Hemodiafiltration, commonly used in Europe, may be emerging in the United States

References

- Blood Purif. 2022;51(Suppl. 1):20-31. doi:10.1159/000524512
- Eknoyan G et al. N Engl J Med 2002;347:2010-2019
- Grooteman MPC et al, J Am Soc Nephrol 23: 1087–1096, 2012
- Ok E et al, Nephrol Dial Transplant 2013; 28 (1) 192–202
- Maduell F, J Am Soc Nephrol 24: 487–497, 2013
- Morena M et al, Kidney Int 2017; 91: 1495-1509
- PJ Blankestijn et al. N Engl J Med 2023;389:700-709
- Canaud B et al. Clin J Am Soc Nephrol 2018; 13: 1435-1443
- Weiner DE et al 2020; CJASN 15: 1310-1319