

A simple registry trial of expanded hemodialysis

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Disclosures – Pavel Rochanov

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Unrestricted research grant (Baxter Healthcare)

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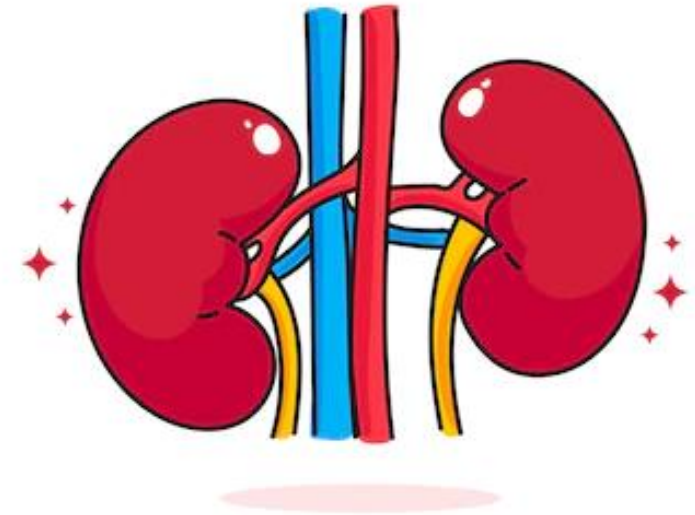
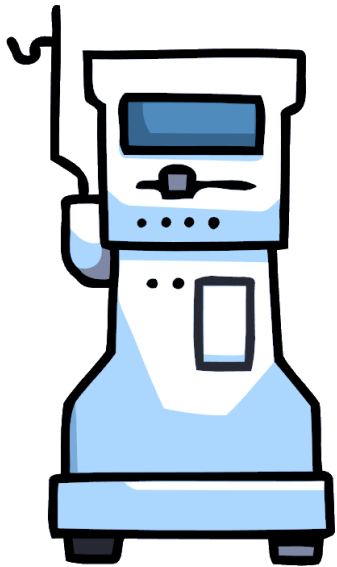
Advisory boards (Amgen, Bayer, Astra-Zeneca, GSK)

Clinical trial funding (Bayer, Astra-Zeneca)

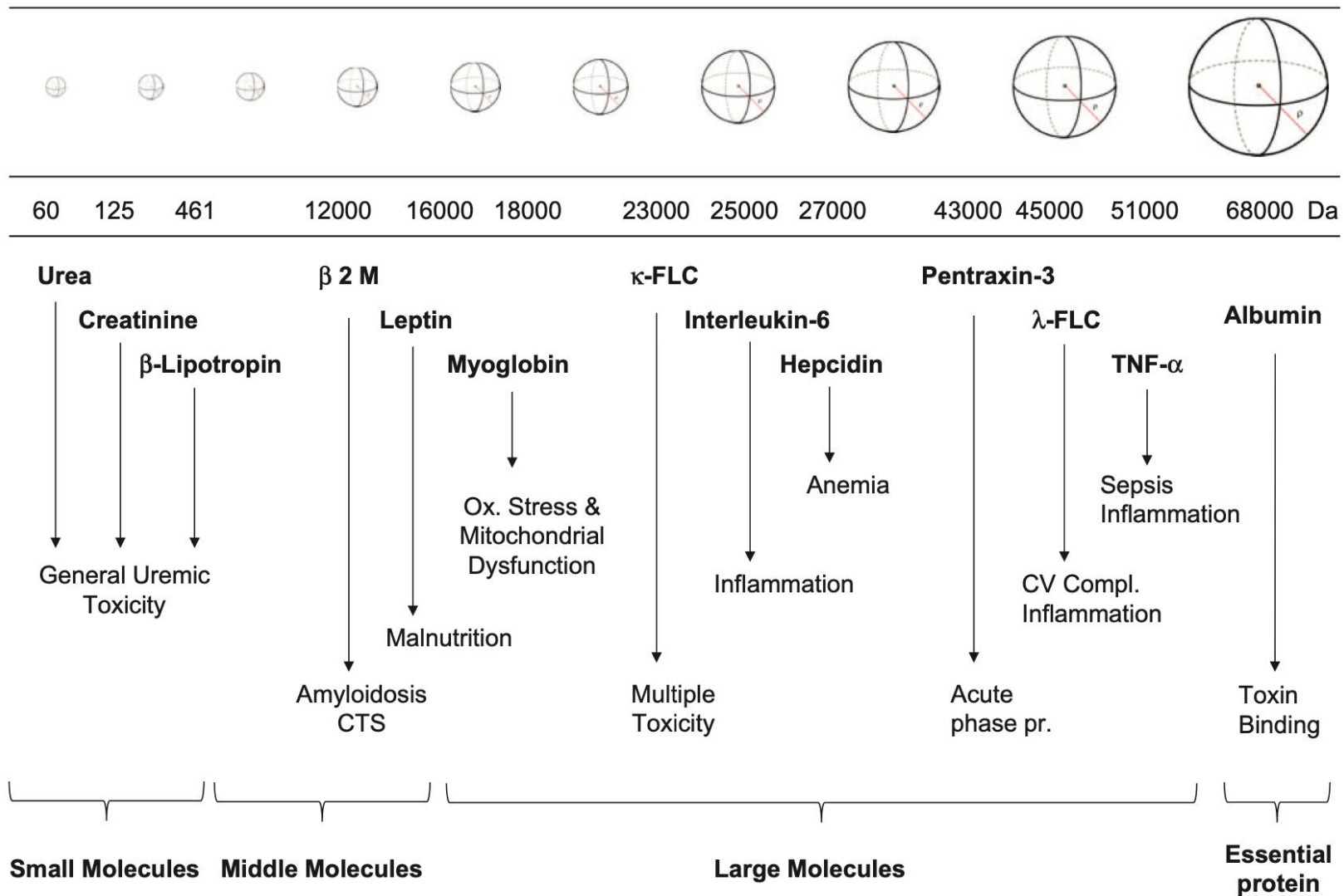
Session outline

1. The what and why of expanded hemodialysis (HDx)
2. Why we need a robust trial of HDx on clinical outcomes
3. Online-hemodiafiltration as a model
4. Designs of two large trials in online-hemodiafiltration
5. Design of a simple, registry-based trial of HDx
6. QoL substudy
7. Vulnerabilities
8. Questions for us
9. Questions for you

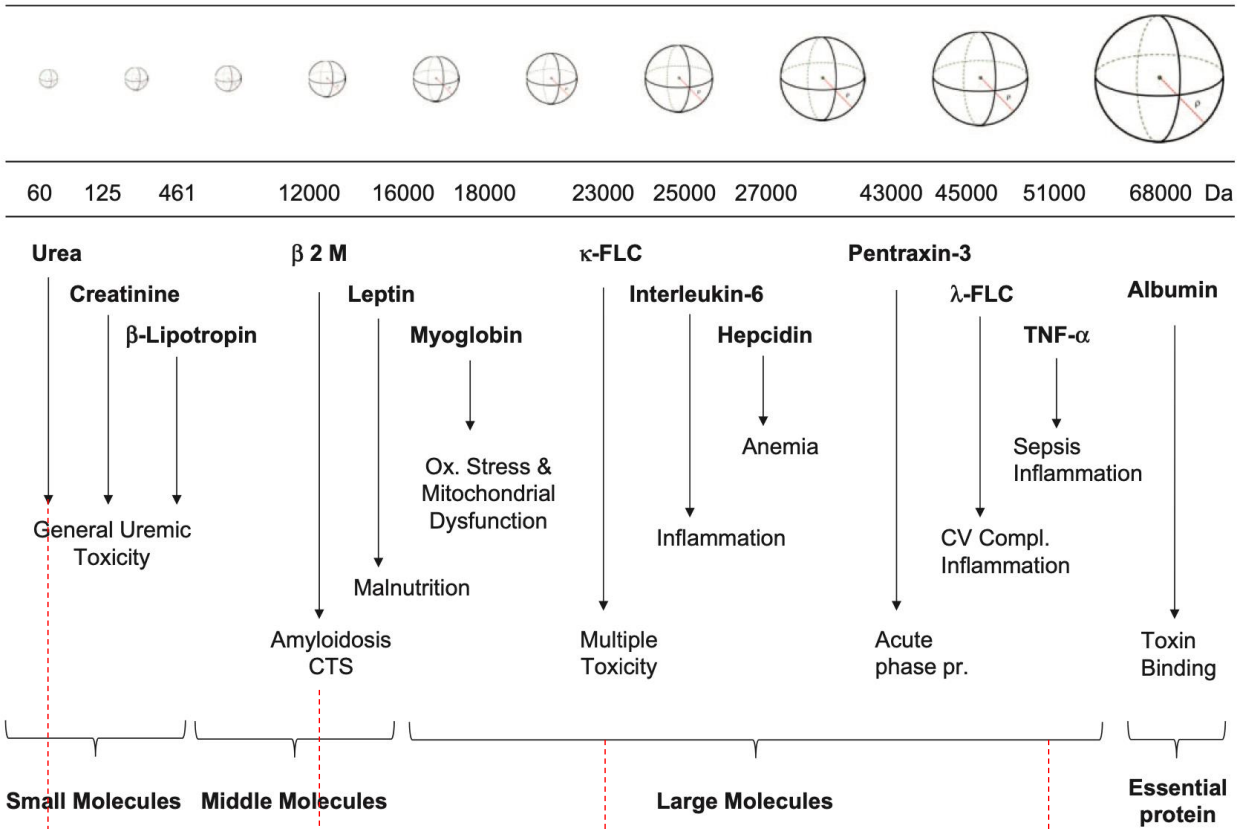
**How do we get
this thing....**



**...to do what
these guys do?**



Ronco et al. *Nephrol Dial Transplant* (2018) 33: iii41–iii47



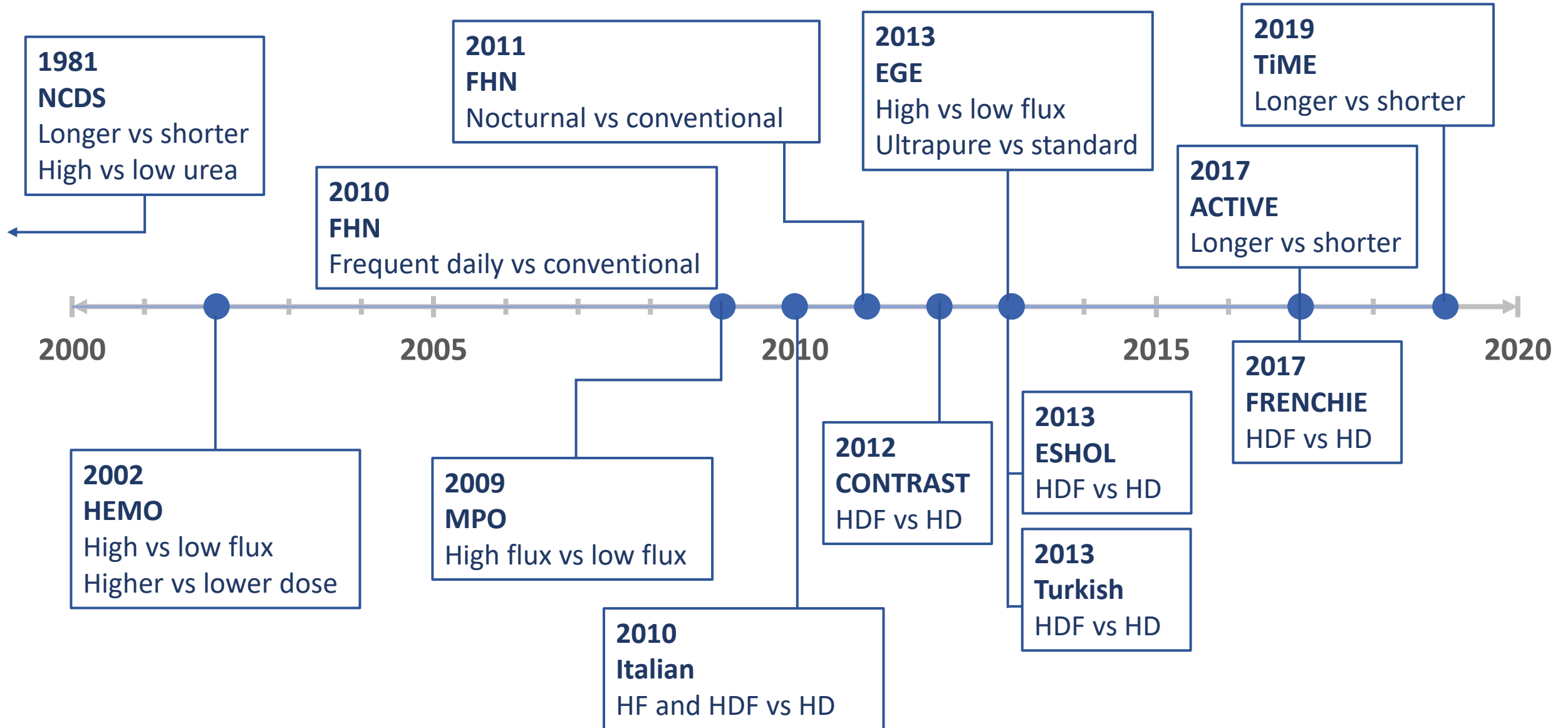
Low flux membranes

High flux membranes

Long HD and Frequent HD

Convective Therapies (HF/HDF)

Major trials of uremic solute removal



The evolution of dialysis technologies has enabled larger solute clearance...

Target (approach)	Key Trials	Main Findings
Urea (high vs low urea removal with LF-HD)	NCDS	No difference
B2M removal (LF vs HF membranes)	HEMO, MPO	No difference
Small and MM (longer or more frequent HF-HD)	FHN daily/nocturnal	Many benefits but treatment time and access are barriers
Small, middle, and large MM (convection)	Many	May improve survival and CV health but some uncertainty; challenges with implementation

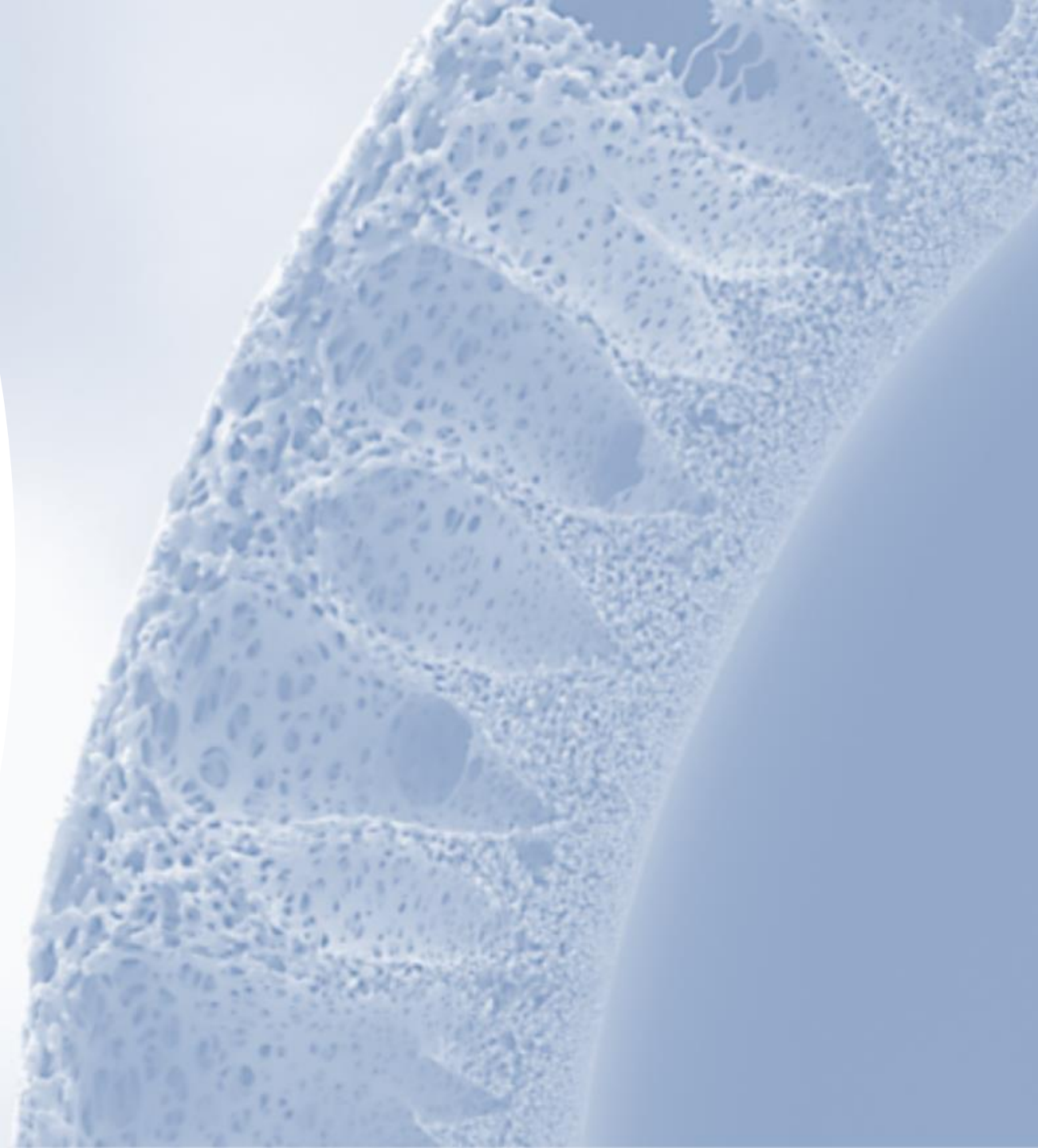
...but with newer therapies, the certainty of evidence and challenges with implementation remain

Medium cut-off (MCO) membranes are a relatively new technology designed to provide the large middle molecule clearance of convective therapies using standard hemodialysis equipment and procedures

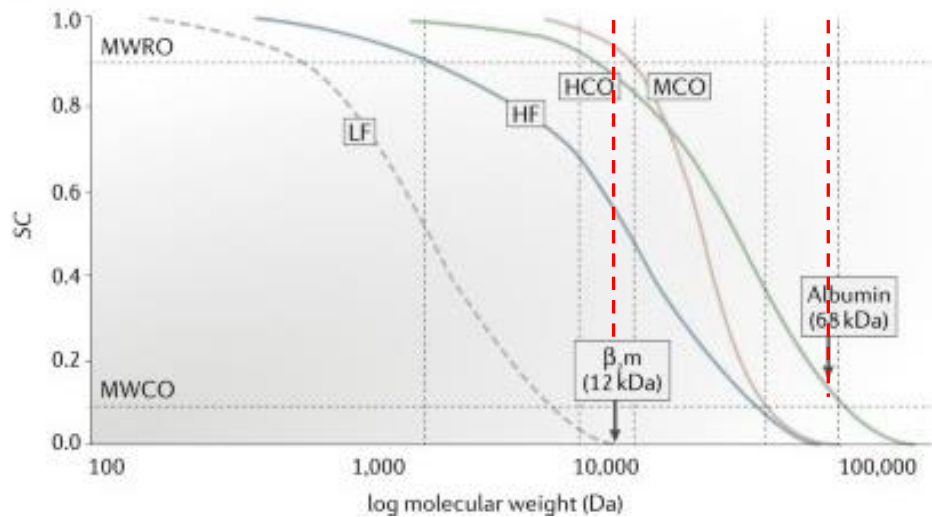
Also referred to as:

Expanded Hemodialysis (HDx)

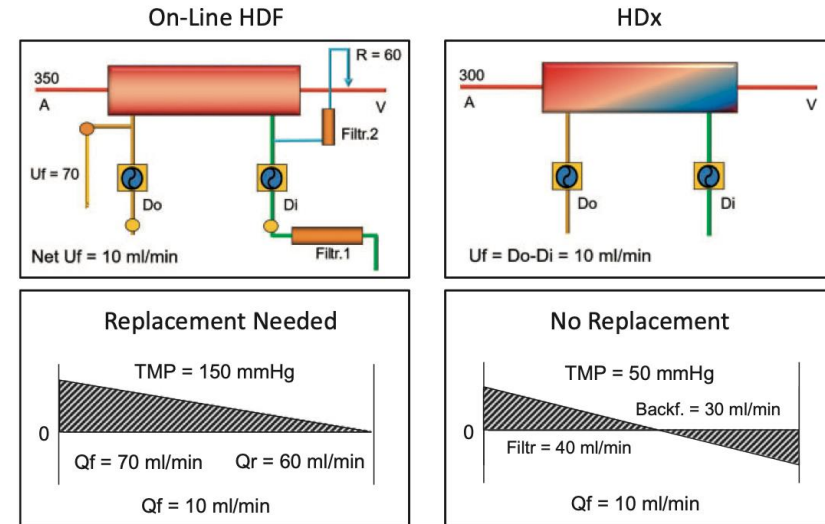
High retention-onset membranes



Properties of medium cut-off (MCO) membranes



Pore size distribution is narrow – this maximizes the removal of large middle molecules while limiting the removal of large essential proteins such as albumin



Fiber diameter is narrow – this promotes internal filtration that is then compensated by back-filtration without the need for replacement fluid or large TMP

Original Basic Research

Clinical Outcomes With Medium Cut-Off Versus High-Flux Hemodialysis Membranes: A Systematic Review and Meta-Analysis

Canadian Journal of Kidney Health
and Disease

Volume 9: 1–16

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Rachel Couban¹, Celina Wu², and Gihad Nesrallah^{2,3} 

Original Basic Research

Effects of Medium Cut-Off Versus High-Flux Hemodialysis Membranes on Biomarkers: A Systematic Review and Meta-Analysis

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Using GRADE Systematic Review Methods...

Screened and extracted in duplicate

RoB using Cochrane (RS) and ROBINS-I (NRS)

2082 citations screened

28 eligible studies

RS – crossover (N=8), parallel arm (N=2)

NRS – crossover (N=14), cohort (N=4)

1883 participants, 1366 patient-years

Crossover designs enabled paired sample statistics for pooling effects

HDx may improve survival and hospitalization, but the evidence remains uncertain

Survival (small favourable trend; moderate certainty)

Study populations were healthy – event rates 3- to 4-fold lower than USRDS (CER=2.2%) – would require >5000 patients to detect a 20% effect

Hospitalization (low certainty) and **Hospital days** improved (low certainty)

Many hospitalization events are unrelated to uremia and dialysis complications – not expected to improve with HDx – may have attenuated effect

HDx improved several additional outcomes (low to moderate certainty)

Overall QoL

KDQOL – effects, burden, symptoms, PCS

Minutes to recover

Symptom severity

Restless legs syndrome

Infection

EPO and iron utilization

Moderate to large reduction in several large MM

Limitations: ceiling effects, risk of bias (open-label)

Strengths: crossover designs provided more statistical power and carryover effects biased towards the null

Clinical effects were potentially important and concordant with effects on biomarkers...

KDQOL subscales exceeded MID threshold (2.5-5.0) – clinically important

Minutes to recover – effect size comparable to nocturnal HD

Effects on PROs were large and consistent with mechanism of effect including changes in biomarkers (reduced TNF-alpha and IL-6 expression)

Infection rates – supports possible beneficial effects on immune function

Concluding remarks...

MCO "expanded" dialysis is a simple and scalable intervention that may improve several important clinical and physiological outcomes

The certainty of evidence for survival and hospitalization is limited by primarily non-randomized study design (risk of bias) and low event rates

The certainty of evidence for PROs is limited by lack of blinding of study participants

A larger and more rigorous trial is needed to build the evidence-base for this promising technology

Trials of convective therapies provide useful insights for designing future trials of HDx

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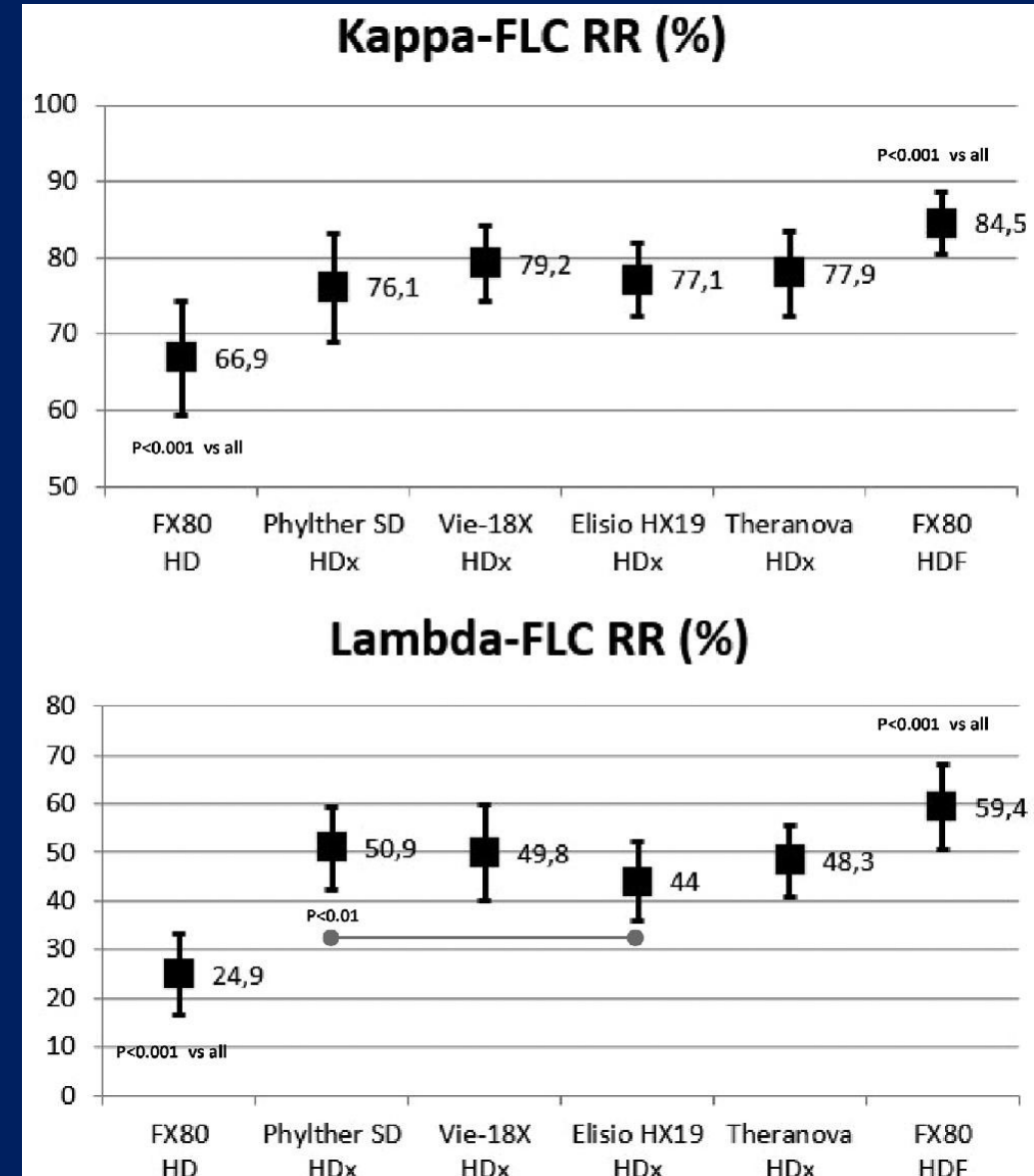
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Dialyzers with MCO properties

- Theranova 400™, polyarylethersulfone, Baxter
- Phylther 17-SD™, polyphenylene, Medtronic
- Elisio HX19™, polyethersulfone, Nipro, coming to Canada soon
- Vie-18X™, polysulfone, Asahi, not Health Canada approved yet

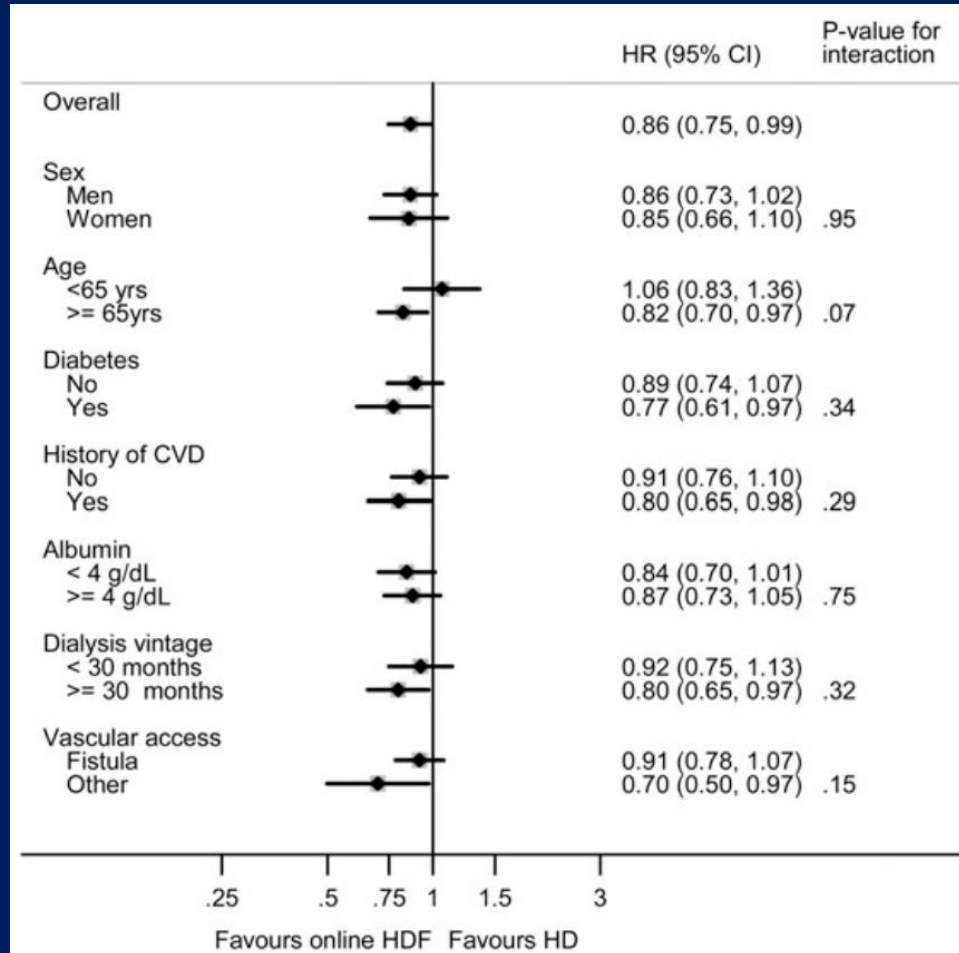


Meta-analysis of HDF vs HD on mortality

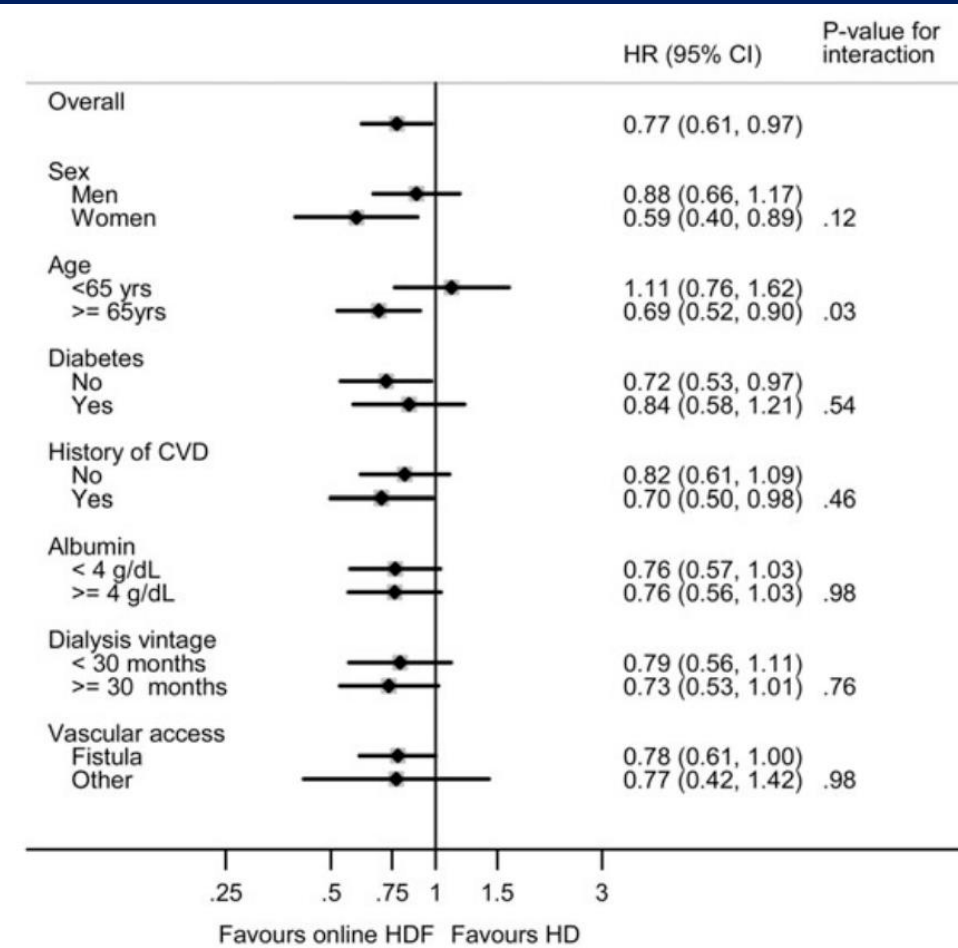
Cause	N	HD		HDF			HR (95% CI)
		Events	Events/100 PY	N	Events	Events/100 PY	
All	1369	410	12.10	1367	359	10.45	0.86 (0.75; 0.99)
CV	1302	164	4.84	1289	128	3.73	0.77 (0.61; 0.97)
Infection	1302	77	2.27	1289	73	2.13	0.94 (0.68; 1.30)
Sudden death	1302	56	1.65	1289	56	1.63	0.99 (0.68; 1.43)

Meta-analysis of HDF vs HD

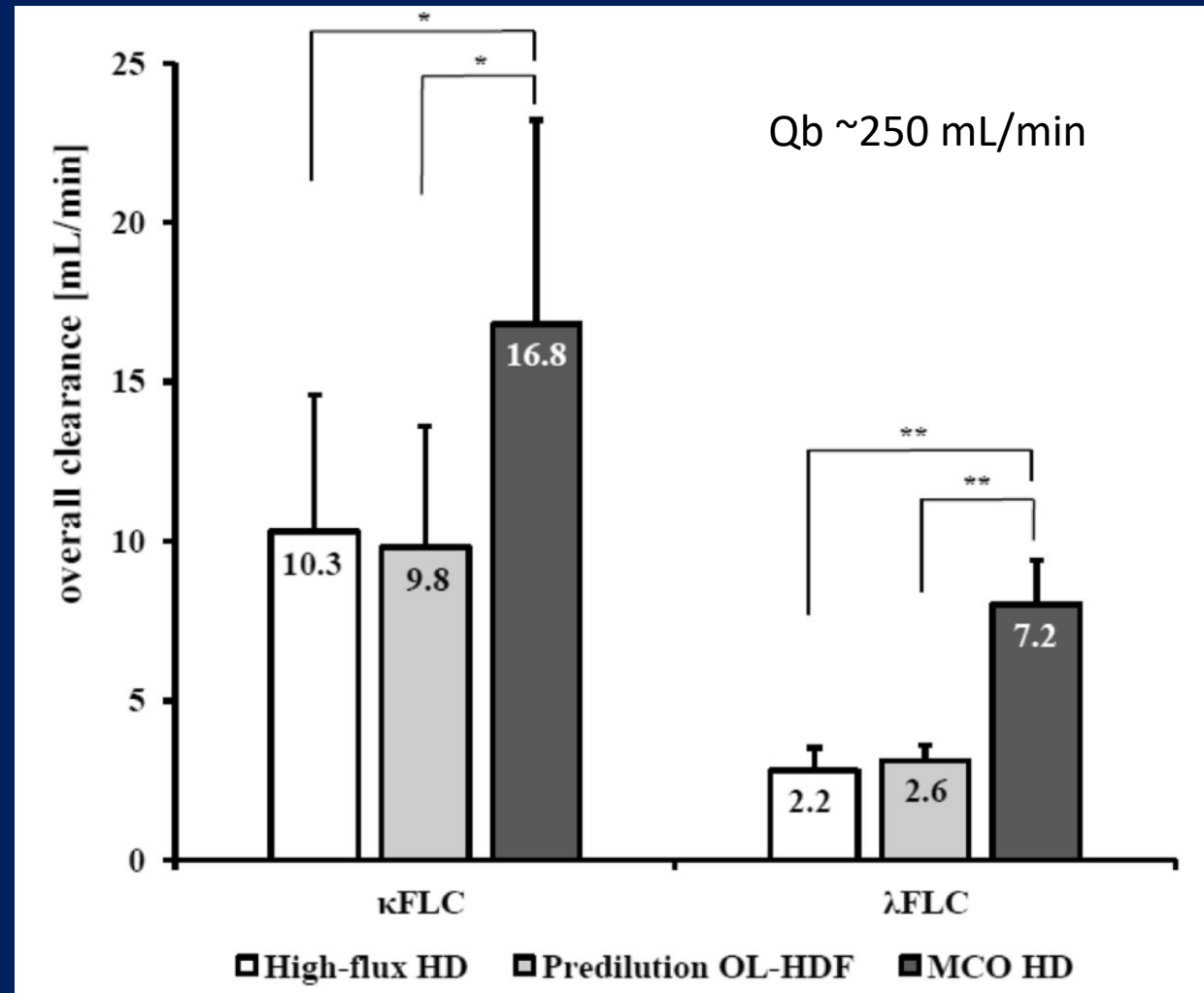
All-cause mortality



CV mortality



What about low blood flow rates?



Two large HDF trials underway

	H4RT	CONVINCE
Design	1:1 individually randomized, open-label, concealed, stratified by site, age, residual urine volume based on 24-h collection within 6 weeks	1:1 individually randomized, open-label, concealed, stratified by site
Population	Adult maintenance HD or HDF 3x/w >4 weeks Having the potential to achieve high-volume HDF (sufficient Qb). UK (65 units invited)	Adult maintenance HD or HDF 3x/w in up to 60 sites in 10 European countries
Intervention	High-volume HDF (aiming for 21+L of substitution fluid adjusted for body surface area)	High-volume online-HDF (aiming for 23+L; “should be” post-dilution but pre and mid accepted)
Comparator	High-flux HD	High-flux HD
Primary outcome	Time to first non-cancer death or hospital admission due to a cardiovascular event or infection within 3 years	Time to death from any cause
Sample size	1550 participants (801 events) for 90% power to detect HR 0.79 allowing for 10% loss to follow-up.	1800 participants (515 events) for 90% power to detect HR 0.75
Other outcomes	All-cause mortality, CV- and infection-related morbidity and mortality, HRQoL, cost-effectiveness, and environmental impact	CV and other disease specific causes of mortality, non-fatal and fatal CV events, hospitalization for infection, all cause hospitalization, PROs, and cost-effectiveness

Two large HDF trials underway

	H4RT	CONVINCE
Outcome ascertainment	Routine healthcare database linkage Q6mo patient questionnaires	Q3mo patient questionnaires + health assessments, lab tests
Intercurrent events	Continue follow-up after transplant or modality change; censor at cancer death	Continue follow-up (on vital status) after transplant or modality change; death from any cause is primary outcome
SAE reporting	Yes	Yes
Duration	Recruitment: 18 mo Follow-up: min 32 mo; max 91 mo	Mean follow-up 2.5 years
Research staff	Baseline assessment, eligibility confirmation, consent	Baseline assessment, eligibility confirmation, consent, outcome assessments
DMC	Yes, monitors every 6-12 mo	Yes, frequency not specified
Interim analysis	Half-way with a one-sided p-value < 0.025 for treatment differences (mortality (HD) < mortality (HDF)) would be considered a meaningful difference to be explored further.	Twice (1000 pt-y and 2500 pt-y of ~4500 pt-y) with Haybittle-Peto stopping criteria (>3xSE); no alpha spent. Stopping subject to the opinion of the DSMB.
Cost	Estimated "just above" £2million	?

ADULT PREVALENT MAINTENANCE iHD PATIENTS

1:1 randomization at the individual level

Stratified by dialysis unit, age, dialysis vintage, RRF, and recent serum albumin, permuted block

Open-label

EXPANDED iHD
(medium cut-off dialyzer)

CONVENTIONAL iHD
(high-flux dialyzer)

Registry-based follow-up using linked administrative databases in

Ontario*
RATE OF CV or INFECTION-RELATED HOSPITALIZATION

Secondary outcomes

Time to death from any cause

Time to death from CV cause

Rate of CV hospitalization

Rate of infection-related hospitalization

Rate of any hospitalization

Tertiary outcomes

Days alive and out-of-hospital

Healthcare utilization costs

Time to hip fracture

Time to kidney transplantation

PROMs

Intercurrent events: Treatment Policy Estimand

Event	Handling
End of study	Censor
Emigrate from passive follow-up region	Continue with active follow-up
Loss to (active) follow up	Censor (assuming non-informative)
Death	Joint time-to-event model (informative)
Change of dialysis modality <small>(PD, home HD, nocturnal HD, short daily)</small>	Continue to follow outcomes
Transplantation	Continue to follow outcomes
Discontinuation of dialysis	Continue to follow outcomes
Reduction of dialysis	Continue to follow outcomes
Change to non-MCO dialyzer	Continue to follow outcomes

Analysis of primary outcome

- Deaths are common and causes informative drop-out on hospitalization
- Joint frailty models adjusted for baseline covariates
 - Negative binomial model to estimate hospitalization rate ratio
 - Cox (or flexible parametric) time-to-event model for all-cause mortality
 - Linked by gamma frailty term
- Inference only on the hospitalization rate ratio (2-sided alpha 0.05)

90% power to detect relative rate reduction of 15%

Control rate/p/y	Dropout % / y	Mean follow-up, y	Trial duration, y	Patients	Dialyzers
1.1	15	3.0	5	1951	455,883
1.1	15	2.4	4	2062	386,358
1.1	10	2.6	4	1980	398,373
0.6	15	2.4	4	2638	493,804
0.6	15	3.0	5	2422	565,650
0.6	10	2.6	4	2508	504,606
0.6	10	3.3	5	2280	584,316
0.4	10	3.3	5	2733	584,316
0.4	15	3.0	5	2923	682,891
0.2	15	4.0	7	3772	1,160,985

Subject to sample size re-estimation at interim analysis

Assuming dispersion parameter = 0.8

Assuming uniform recruitment rate and fully recruited by 2 years

QoL sub-study (needs work)

- ~350 patients, same randomization and eligibility as parent study
- 12-month follow-up
- Repeated measures at 0, 3, 6, 12 mo
- EQ-5D, PROMIS, LEVIL

- Joint frailty models
 - Linear mixed effects model to detect effect on score slope
 - Cox (or flexible parametric) time-to-event model for all-cause mortality
 - Linked by gamma frailty term

- Inference only on the slope (2-sided alpha 0.05)

A simple registry-based trial comparing HDx versus conventional HD in ~2500 patients

- Obtaining dialyzers >0.5 mil dialyzers
- Program-level volume discount contracts limit recruitment per site
- Reliance on healthcare providers for consent and randomization
- Monitoring safety

Thank you!

Questions for you



- For nephrologists, you be interested in recruiting patients at your units to such a study?
- For patients, would you be interested in participating in this study?
- For nephrologists, if the trial demonstrated reduction in hospitalization without any adverse effect, would this compel you to prescribe HDx with an MCO-type dialyzer over conventional high-flux HD?
- Do you foresee logistical challenges in making this a national study?

Questions for you (open forum)

- Which PRO instruments would you recommend?

Barriers

- Obtaining dialyzers
 - >0.5 million dialyzers
 - Asking to provide at price currently paid by centres for on-contract dialyzers
 - E.g., \$20 vs \$7-9
- Program-level volume discount contracts limit recruitment per site
 - E.g., limit 20% off-contract dialyzers (many programs already >10%)
 - Potential allowances for research
 - Contracts may be renegotiated during trial (~5 years)
 - Depending on program-level recruitment caps may need >100 dialysis units
 - Unless some contracts allow for broad participation
- No local research support
 - Healthcare providers conducting the consent and randomization procedure
 - + Central coordination
 - + Targeted regional coordination to support rapid early recruitment

Supplementary materials

No definite effects on survival or hospitalization...

Outcome № of participants (studies)	Effect (95% CI)	Absolute effect with High-Flux HD	Certainty	What Happens
Mortality (all-cause) N= 555 (4 RCTs, 4 NRS)	Rate ratio: 0.91 (0.34–2.39)	2.2%	⊕⊕⊕○ MODERATE ^{a,b}	MCO-HD may result in a slight reduction in mortality.
Hospitalization (any cause) N= 372 (1 RCT, 2 NRS)	Rate ratio: 0.86 (0.64–1.17)	17.2%	⊕⊕○○ LOW ^{a,c,d}	MCO-HD may reduce hospitalization slightly.
Hospitalization days (LOS) N= 81 (1 NRS)	MD 1.5 days lower (2.22 lower to 0.78 lower)	Mean 5.91 days	⊕⊕○○ LOW ^{e,f}	MCO-HD may reduce hospital days.
Infection (any) N= 283 (2 NRS)	Rate ratio: 0.38 (0.17–0.85)	14.4%	⊕⊕⊕○ MODERATE ^{g,h,i}	MCO-HD likely results in a reduction in infection.

...but infection rates were lower with HDx

RCTs found no effect on QoL, but had ceiling effects...

Outcome № of participants (studies)	Effect (95% CI)	Absolute effect with High-Flux HD	Certainty	What Happens
QOL (EQ-5D, KDQOL) N= 222 (2 RCTs)	MD 2.6 points higher (2.8 lower to 8 higher)	Range 59-81	⊕⊕⊕○ MODERATE ^j	MCO-HD likely results in a slight increase in quality of life.
QOL (LEVIL) N= 16 (1 NRS)	MD 16.7 points higher (6.9 higher to 26.4 higher)	Mean 52	⊕⊕⊕⊕ HIGH ^{f,k}	MCO-HD results in large increase in quality of life as measured by the LEVIL instrument.

...one NRS showed a large effect on QoL

HDx improved PCS and pruritus, but not MCS or pain...

Outcome № of participants (studies)	Effect (95% CI)	Absolute effect with High-Flux HD	Certainty	What Happens
Physical Health Composite N= 150 (2 RCTs, 2 NRS)	MD 4.62 points higher (0.27 higher to 8.96 higher)	Range 27-60	⊕⊕⊕○ MODERATE ^{i,n}	MCO-HD likely results in an increase in PHC/PCS
Mental Health Composite N= 150 (2 RCTs)	MD 3.15 points higher (5.85 lower to 12.15 higher)	Range 44-51	⊕⊕⊕○ MODERATE ⁱ	MCO-HD results in little to no difference in MHC/MCS.
KDQOL-Pain N= 49 (1 RCT)	MD 2.9 points higher (10.82 lower to 16.62 higher)	Mean 69	⊕⊕⊕○ MODERATE ⁱ	MCO-HD likely results in little to no difference in KDQOL – Pain.
Pruritus N= 49 (1 RCT)	MD 3 points lower (6.33 lower to 0.33 higher)	Mean 9.9 (out of 30)	⊕⊕⊕○ MODERATE ⁱ	MCO-HD likely reduces pruritus somewhat.

HDx improved minutes to recover and RLS...

Outcome No of participants (studies)	Effect (95% CI)	Absolute effect with High-Flux HD	Certainty	What Happens
Minutes to recover N= 89 (1 NRS)	135 minutes lower (145 lower to 125 lower)	Mean 240 minutes	⊕⊕⊕⊕ HIGH ^f	MCO-HD results in large reduction in minutes to recover after hemodialysis.
RLS N= 992 (1 NRS)	OR: 0.39 (0.29–0.53)	22.1%	⊕⊕⊕⊕ HIGH ^m	MCO-HD results in large reduction in RLS.
Symptom severity (% with ≥1 “severe” or “overwhelming”) N= 56 (1 NRS)	OR: 0.81 (0.76–0.86)	66.1%	⊕⊕⊕○ MODERATE ^f	MCO-HD likely reduces symptom severity.

...as well as symptom severity

ESA and iron utilization fell by 40%...

Outcome № of participants (studies)	Effect (95% CI)	Absolute effect with High-Flux HD (mean, range of means, or rate)	Certainty	What Happens
ERI N= 496 (1 RCT, 6 NRS)	SMD 0.73 SD lower (1.23 lower to 0.22 lower)	-	⊕⊕⊕⊕ HIGH ^{p,q}	MCO-HD reduces erythropoiesis resistance index.
Iron utilization (mg/12 wks) N= 40 (1 RCT)	MD 400 mg lower (493 lower to 307 lower)	Mean 1,000 mg	⊕⊕⊕○ MODERATE ^f	MCO-HD likely results in a reduction in iron utilization (mg per 12 weeks).
CRP N= 821 (1 RCT, 5 NRS)	SMD 0.02 SD lower (0.14 lower to 0.17 higher)	-	⊕⊕⊕⊕ HIGH ^q	MCO-HD results in little to no difference in C-reactive protein.

...CRP did not change with HDx