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Expanded Hemodialysis (HDx) for all: a Bold Step or Premature Leap?

Te-Hui Kuo, MD, MA, PhD

Director of Hemodialysis Room, Division of Nephrology,
Department of Internal Medicine, National Cheng Kung University Hospital

Dec 7, 2025

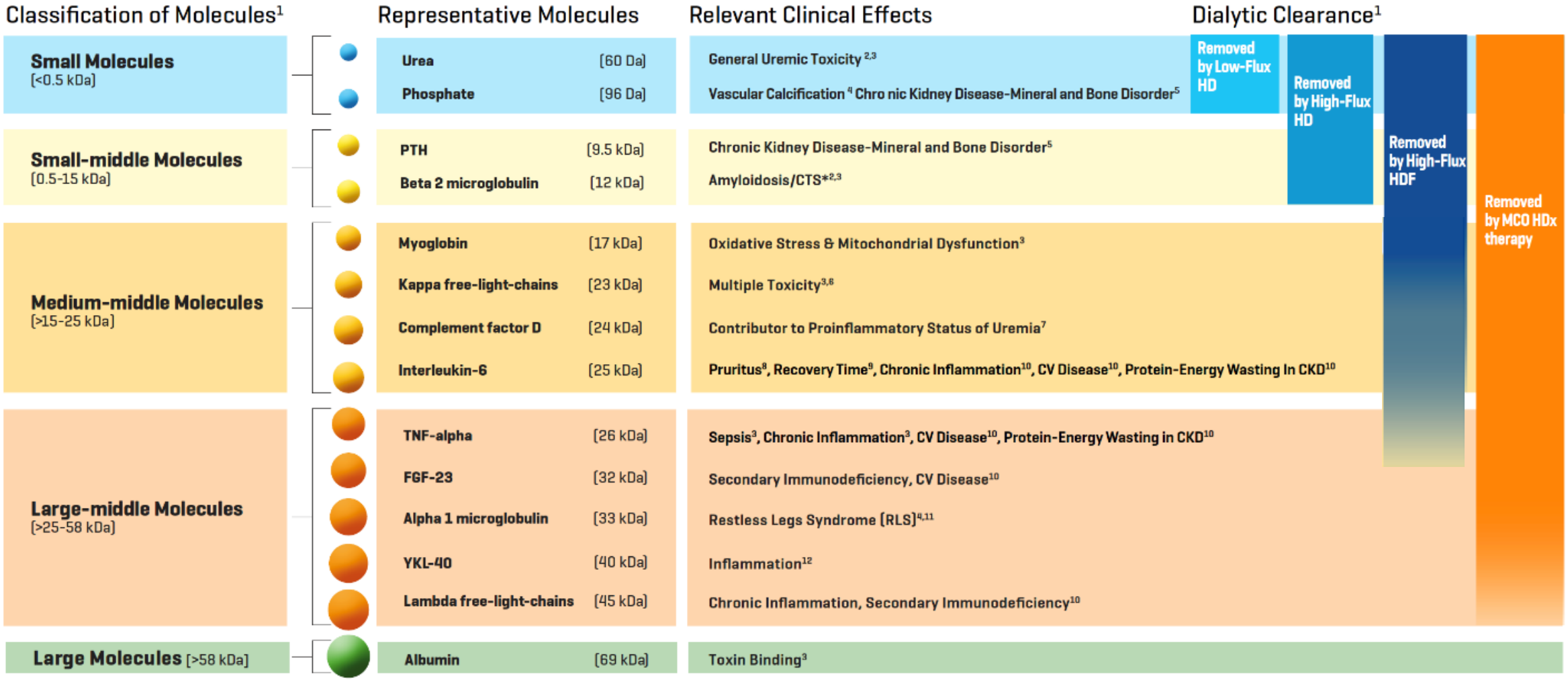
Disclosure of conflicts of interest

- Nothing to declare

What is HDx (Expanded Hemodialysis)?

- Employing medium cut-off (MCO) membranes that remove large middle molecules (15–60 kDa).
  - Albumin: around 68 kDa
- Diffusion with internal convection to achieve HDF-like clearance (no external replacement fluid as in HDF).
- Using conventional HD machines: just replacing standard dialyzers with MCO (no extra steps)

HDx vs Standard HD vs HDF



Kawanishi. J Clin Med. 2024;13(3):647, with modification

Impact of large middle molecules

Clinical Impact	Related Large & Medium Molecules	Classification of Action	Molecular Weight
Cardiovascular Diseases, Atherosclerosis, Cardiac Hypertrophy	IL-18, IL-6, TNF-α, Pentraxin-2, FGF-23	Cytokines, Immune-Regulating Proteins, Growth Factors	21–40 kDa
Chronic Inflammation	IL-6, TNF-α, λ-FLC	Cytokines, Immune-Regulating Proteins	25–51 kDa
Secondary Immunodeficiency	Ig light chains (λ-FLC, κ-FLC), Retinol-binding protein 4, FGF-23, α1-acid glycoprotein	Immune-Regulating Proteins, Adipokine, Growth Factors	25–51 kDa
Chronic Kidney Disease – Protein-Energy Wasting	IL-6, IL-1β, TNF-α	Cytokines	25–51 kDa

Yilmaz. Clin Nephrol. 2007;68(1):1.
Stenvinkel. Semin Dial. 2013;26(1):16.
Akchurin. Blood Purif. 2015;39(1-3):84.

Pro for HDx (1): soft outcomes in toxin clearance and biomarkers

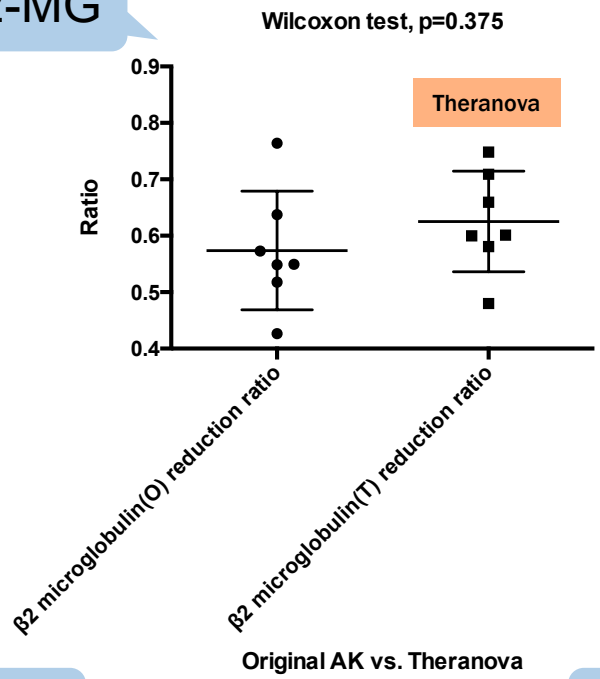
Study	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)	Key Finding
Ozarli 2024 (Turkey)	Patients on HD with heart failure (n = 51)	HDx using a medium cut-off dialyzer group (n = 25)	High-flux HD group (n = 26)	CRP, IL-18, Pentraxin-3, β2-microglobulin; pulse wave velocity; LV diastolic function	HDx significantly reduced CRP, IL-18, pentraxin-3, β2-microglobulin
Lim 2025 (Korea)	Incident hemodialysis patients starting long-term HD (n = 80)	HDx with Theranova 400 dialyzer	High-flux dialyzer of similar surface area	Change in GFR over 12 months; 24h urine volume; reduction ratios of free light chains, TNF-α, GDF-15; kidney injury markers	Higher reduction ratios of κ/λ free light chains, TNF-α, GDF-15.

Ozarli. Hemodial Int. 2024;28(3):326.
Lim. J Am Soc Nephrol. 2025;36(8):1614

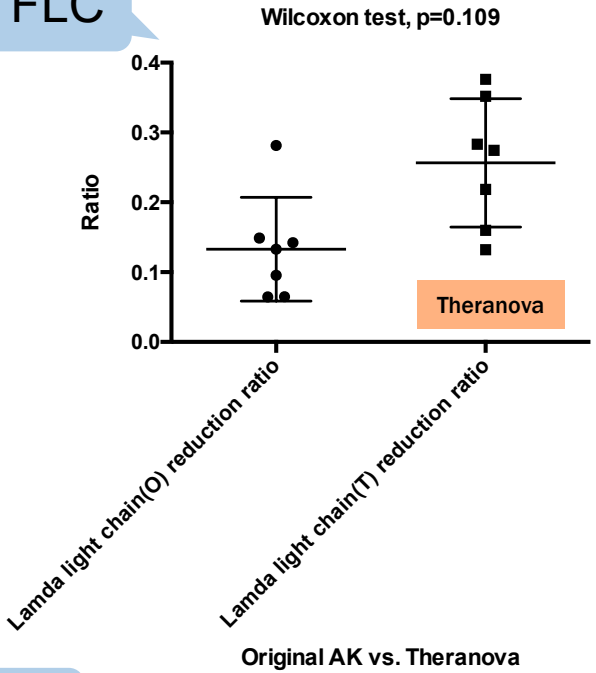
Unpublished data of 2-week testing Theranova in NCKUH in 2019/12 (n=7)

$$\text{Reduction ratio } \left(\frac{pre-post}{pre}\right)$$

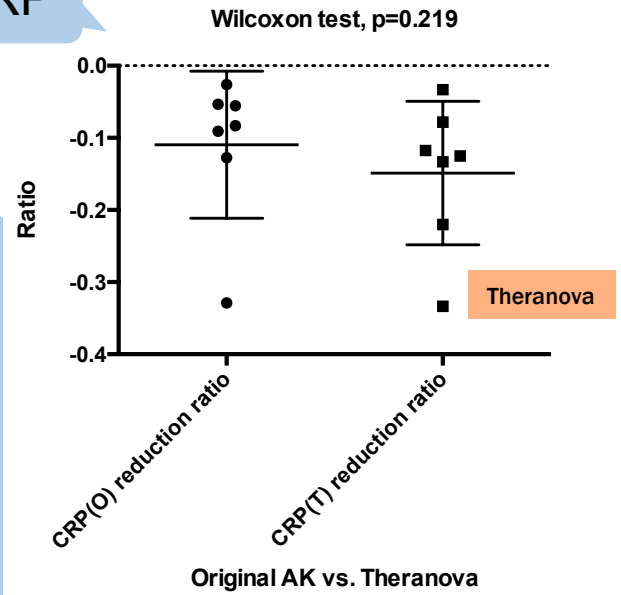
β2-MG



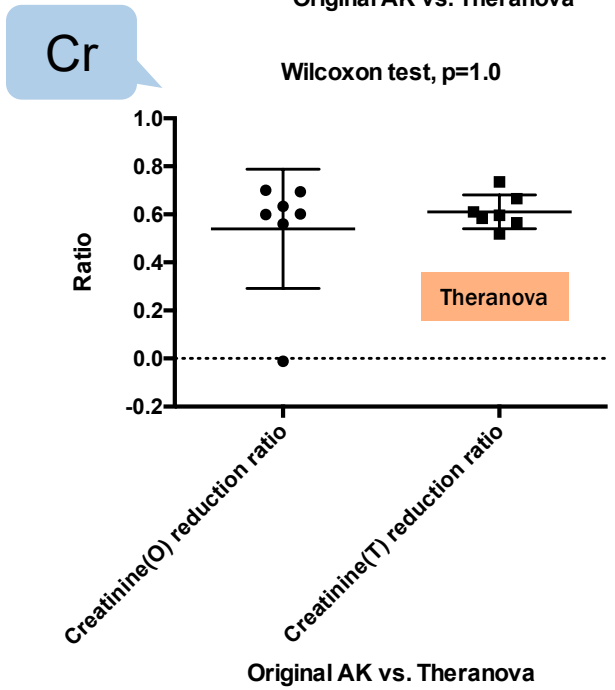
λ FLC



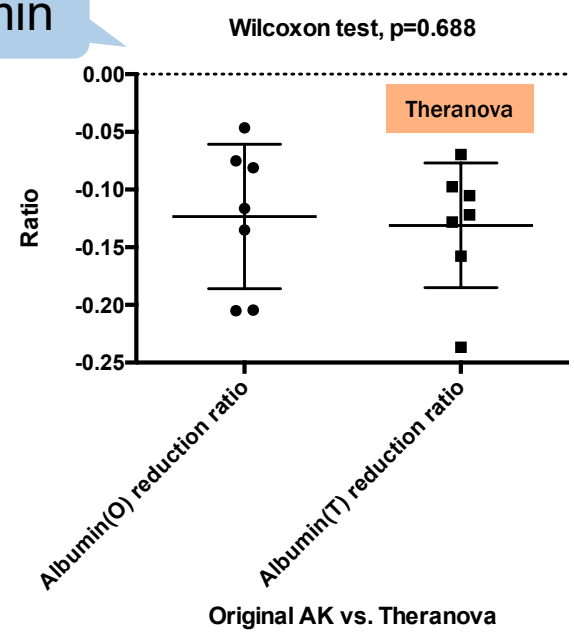
CRP



Cr



Albumin



Lim 2025: slower decline in residual renal function

OPEN

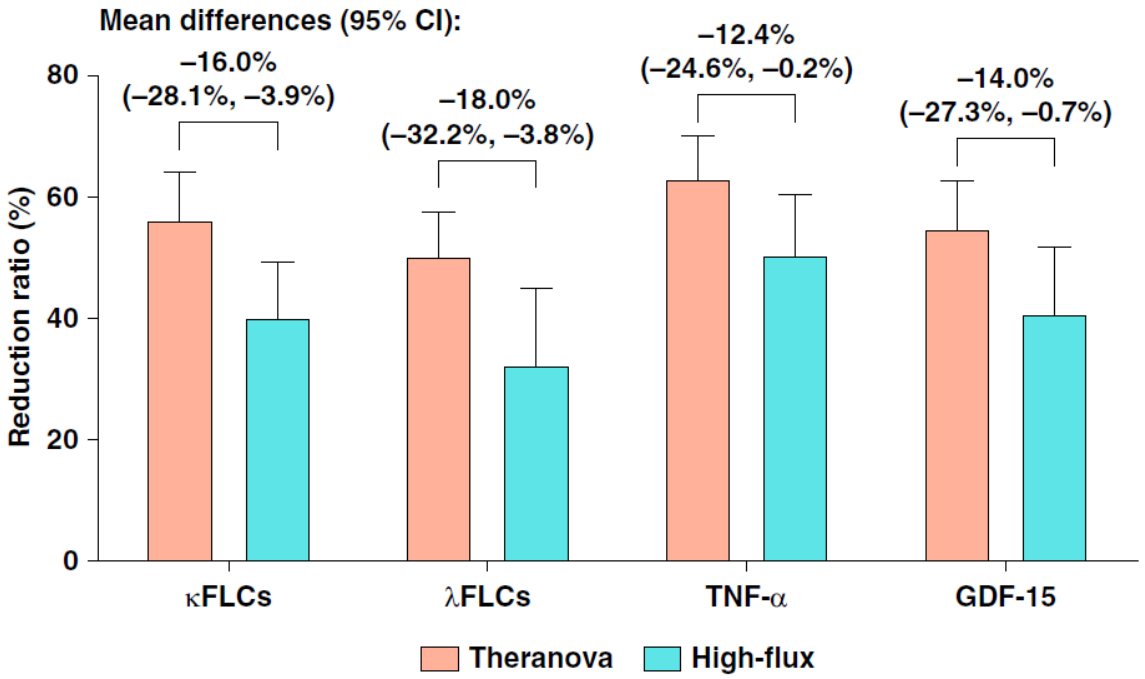
Expanded Hemodialysis with Theranova Dialyzer and Residual Kidney Function in Patients Starting Long-Term Hemodialysis

A Randomized Controlled Trial

Jeong-Hoon Lim,[1] Yu Jin Seo,[2] Yena Jeon,[3] You Hyun Jeon,[1] Hee-Yeon Jung,[1] Ji-Young Choi,[1] Sun-Hee Park,[1] Chan-Duck Kim,[1] Seok Hui Kang,[4] Jung-Hwa Ryu,[5] Duk-Hee Kang,[5] Jang-Hee Cho,[1] and Yong-Lim Kim[1]

Key Points

- This randomized controlled trial evaluated the effect of expanded hemodialysis on preserving residual kidney function in patients starting treatment with long-term hemodialysis.
- The expanded hemodialysis group with Theranova dialyzer showed smaller decrease in GFR than the high-flux group over 12 months.
- The Theranova group had a larger reduction in middle molecules and inflammatory cytokines and smaller increases in kidney injury markers.



Study design	Whether HDx slows residual kidney function (RKF) loss versus high-flux (HF) was tested in this multicenter Korean RCT
Participants	Total n=80; mean age 63; 65% male
Intervention (n=40)	Expanded hemodialysis (HDx) using Theranova 400 for 12 months
Comparator (n=40)	Conventional high-flux hemodialysis (FX CorDiax 80)
Outcomes	Change in GFR over 12 months; 24-h urine volume trajectory
Key results	HDx produced a smaller GFR decline than HF at 12 months (least-squares mean difference −1.4 mL/min/1.73 m²; 95% CI −2.4 to −0.5)

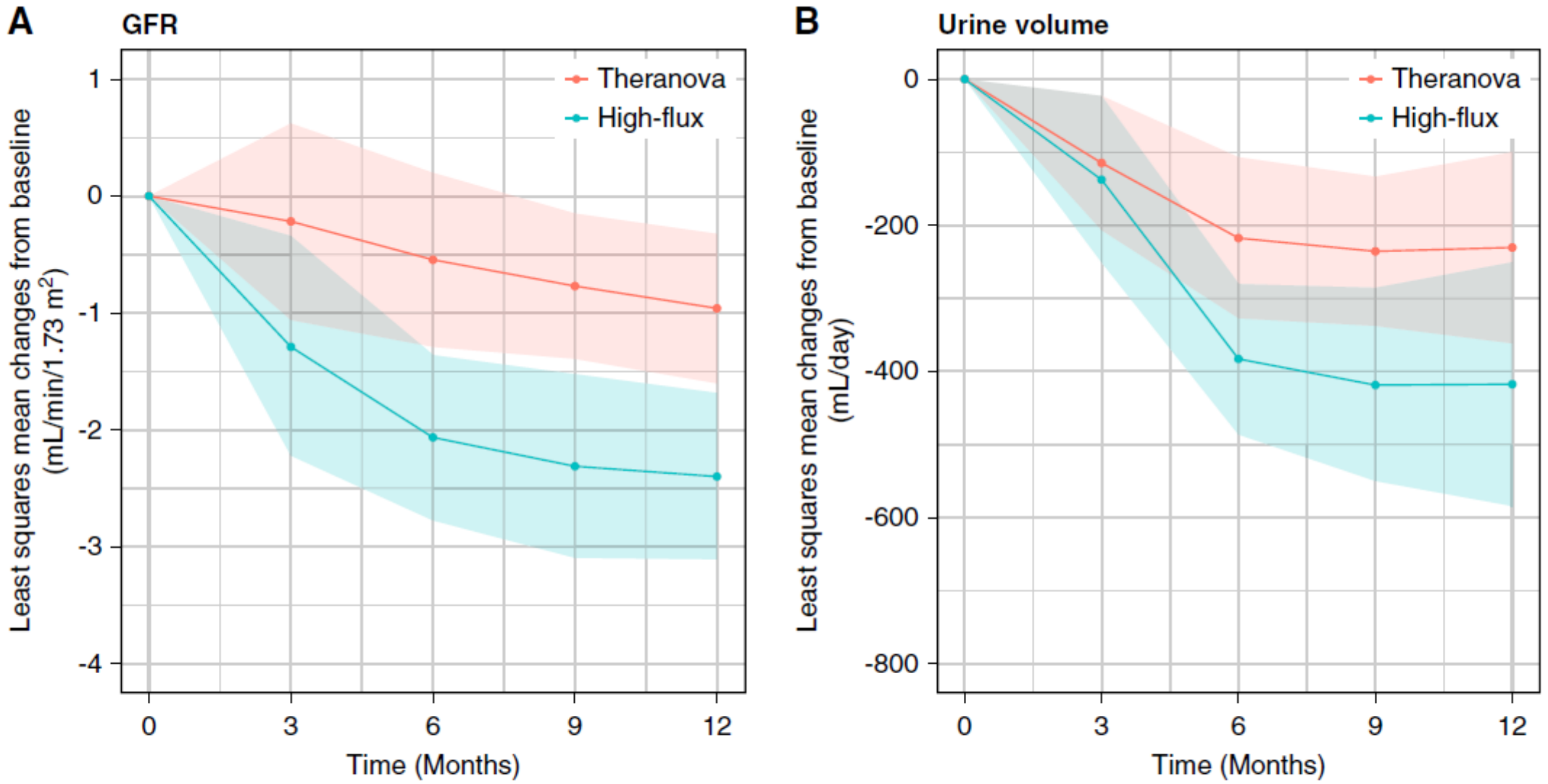
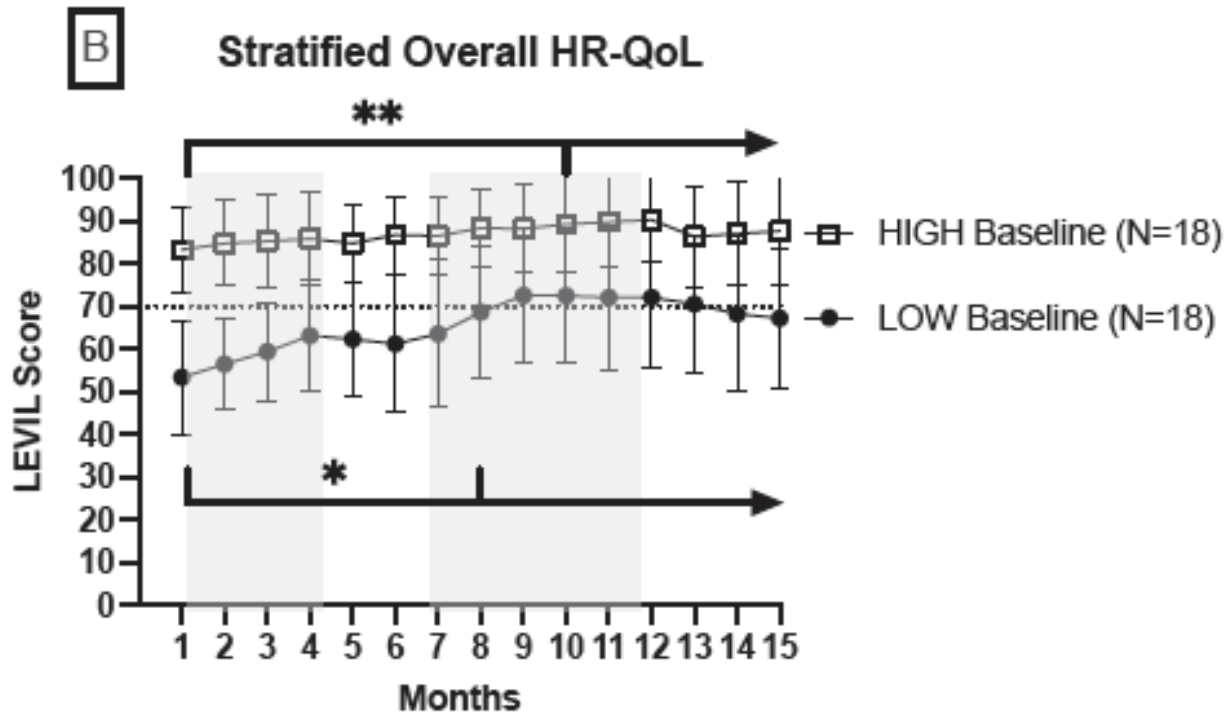


Figure 3. Changes in GFR and urine volume over the study period. LS mean changes from baseline to 12 months for GFR (A) and 24-hour urine volume (B). Data are presented as LS mean changes with 95% CIs, which were calculated using a constrained longitudinal data analysis model.

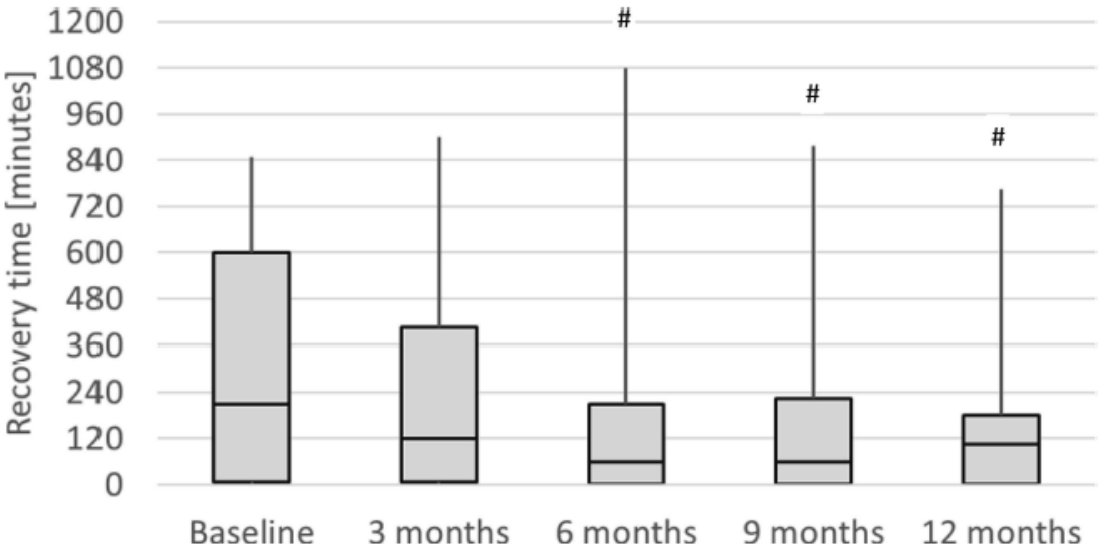
Pro for HDx (2): soft outcomes in quality of life

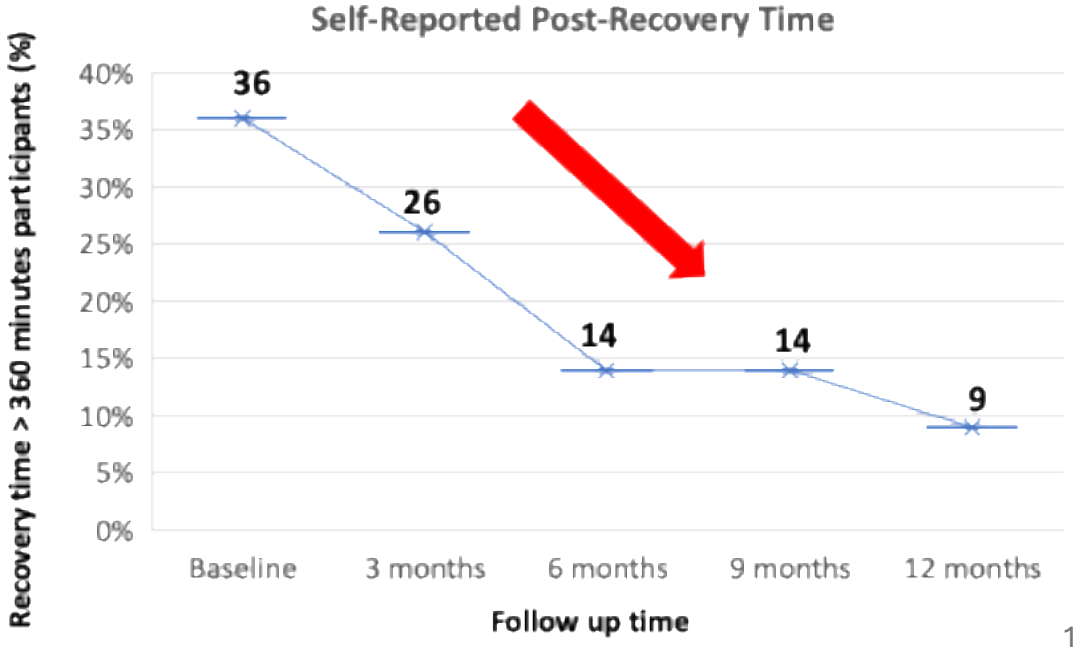
Study	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)	Key Finding
Penny 2025 (Canada)	Mai… p…			• LEVIL PROM …eing, …n	• Patients with low baseline QoL showed the greatest improvement after HDx
Mitchell 2023 (systematic review)	s… data…				• HDx improves pruritus, RLS, and physical QoL components



Penny. Kidney Med. 2025;7(12): 101134
Mitchell. Semin Dial. 2023;36:86

Study	Population (P)	Intervention (I)	Comparator (C)	Outcomes (O)	Key Finding
Bolton 2021 (UK)	Maintenance HD patients switched to HDx; followed longitudinally (n=90)	HDx using medium cut-off (MCO) dialyzer	Prior period on high-flux HD	• Post-dialysis recovery time • Fatigue, leg pain, itching • KDQOL-36	• Recovery time shortened (patients needing >360 min dropped from 36% → 9% over 12 months). • Pruritus, fatigue, leg discomfort, KDQOL-36 improved.





Bolton. Patient Relat Outcome Meas. 2021;12:315

Pro for HDx (3): so… dication use

Study	Population (P)	Key Finding
Lim 2020 (Korea)		• ESA dose significantly ↓ in HDx group (p=0.006). • Weight-adjusted ESA dose ↓ (p=0.012). • ERI decreased (p=0.017).
Ariza 2021 (Colombia)		• HDx improves overall medication burden: declined across all categories.

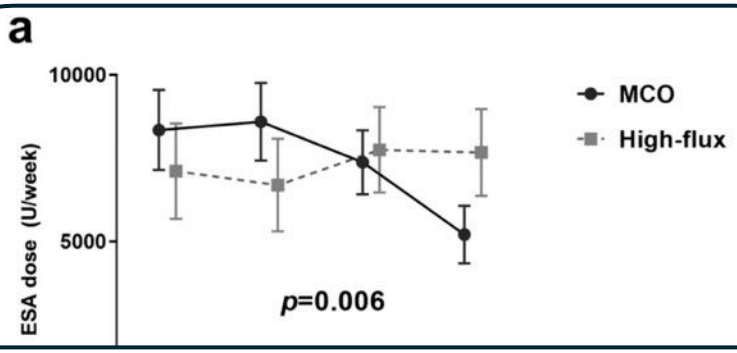
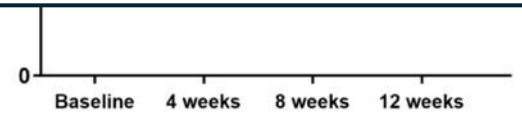


TABLE 3. Annual costs with HD HF and with HDx

Annual per patient cost category	Average Annual costs with HD HF	Average Annual costs with HDx	Percent change HDx vs. HD HF
Hospitalizations	$1822	$1394	−23.9%
ESA	$385	$357	−7.27%
Iron	$4.32	$3.42	−20.83%
Insulin	$242	$163	−32.64%
Antihypertensives	$189	$132	−30.16%



…0(1):16062
Ariza. Ther Apher Dial. 2021;25(5):621

Pro for HDx (4): hard outcomes in hospitalization, mortality, and costs

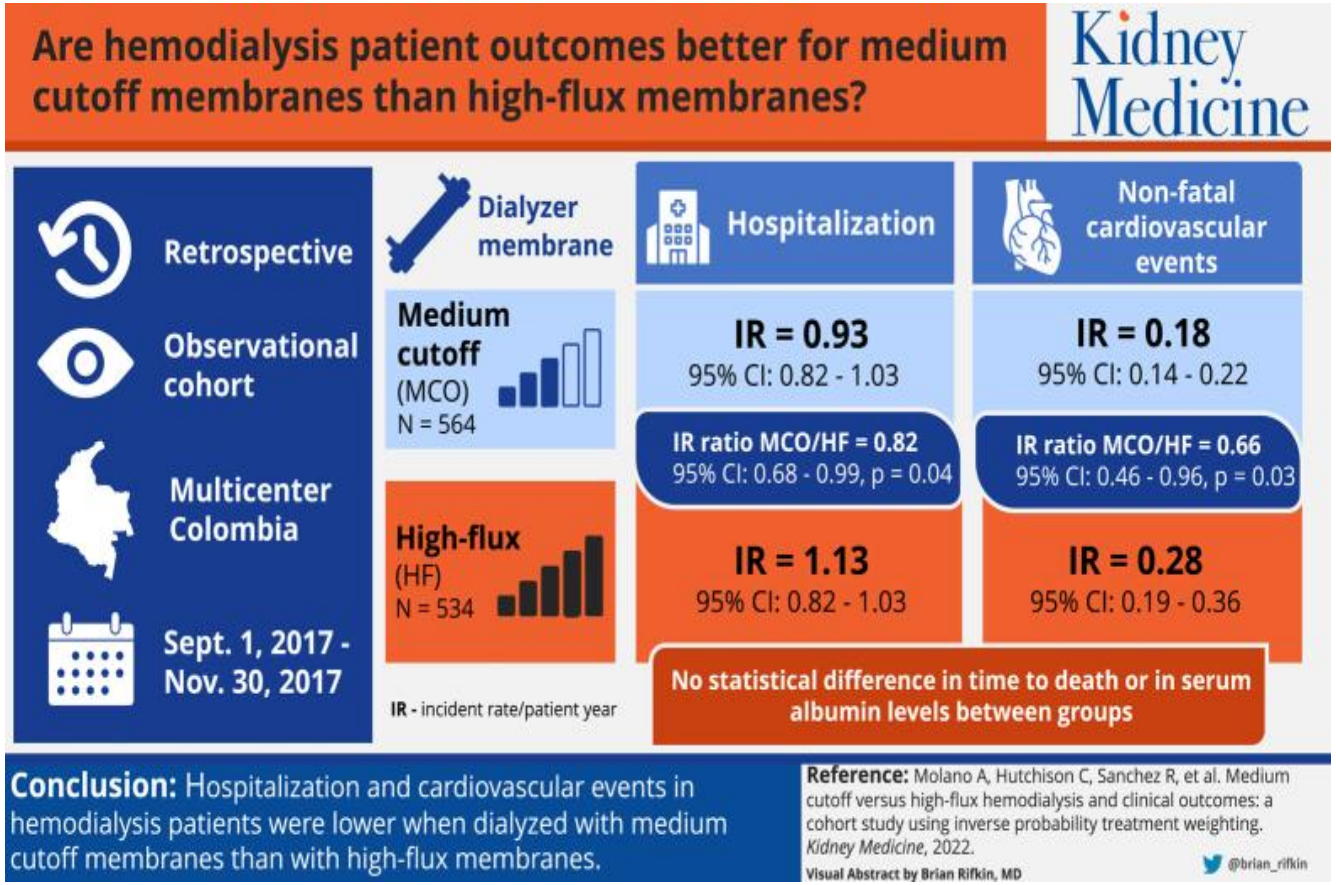
Original Research — Kidney Medicine

Medium Cutoff Versus High-Flux Hemodialysis Membranes and Clinical Outcomes: A Cohort Study Using Inverse Probability Treatment Weighting

Alejandra P. Molano, Colin A. Hutchison, Ricardo Sanchez, Angela S. Rivera, Giancarlo Buitrago, María P. Dazzarola, Mario Munevar, Mauricio Guerrero, Jasmín I. Vesga, and Mauricio Sanabria

Lower hospitalization rate:
Hospitalization and non-fatal cardiovascular events were lower with HDx vs high-flux HD

Study design (Colombia)	Chronic HD patients, Colombia. Cohort inception 2017/9~2017/11, followed until 2019/11 (2+ years).
Participants	Total n = 1,098: 564 in the HDx group; 534 in the HF-HD group.
Intervention	Expanded hemodialysis (HDx)
Comparator	Conventional high-flux hemodialysis (HF-HD)
Outcomes	hospitalization rate from any cause; hospital days per patient-year
Key results	HDx group had lower all-cause hospitalization incidence rate (IR = 0.93 per patient-year; 95% CI 0.82-1.03) vs HF-HD group (IR = 1.13; 95% CI 0.96-1.30). The incident rate ratio (IRR HDx/HF-HD) was 0.82 (95% CI 0.68-0.99; p = 0.04)



Molano. Kidney Med. 2022;4(4): 100431

Survival Differences in Patients with High-Flux Hemodialysis versus Expanded Hemodialysis: A Cohort Study

Juan C. Castillo[a] Jasmin Vesga[b] Angela Rivera[c] Peter Rutherford[d]
Ricardo Sanchez[e] Henry Oliveros[f] Bengt Lindholm[f,g] Mauricio Sanabria[h]
On behalf of the Colombian Registry of Expanded Hemodialysis Investigators

[a]Renal Care Services Soacha, Bogota DC, Colombia; [b]Renal Care Services Colombia, Bucaramanga, Colombia;

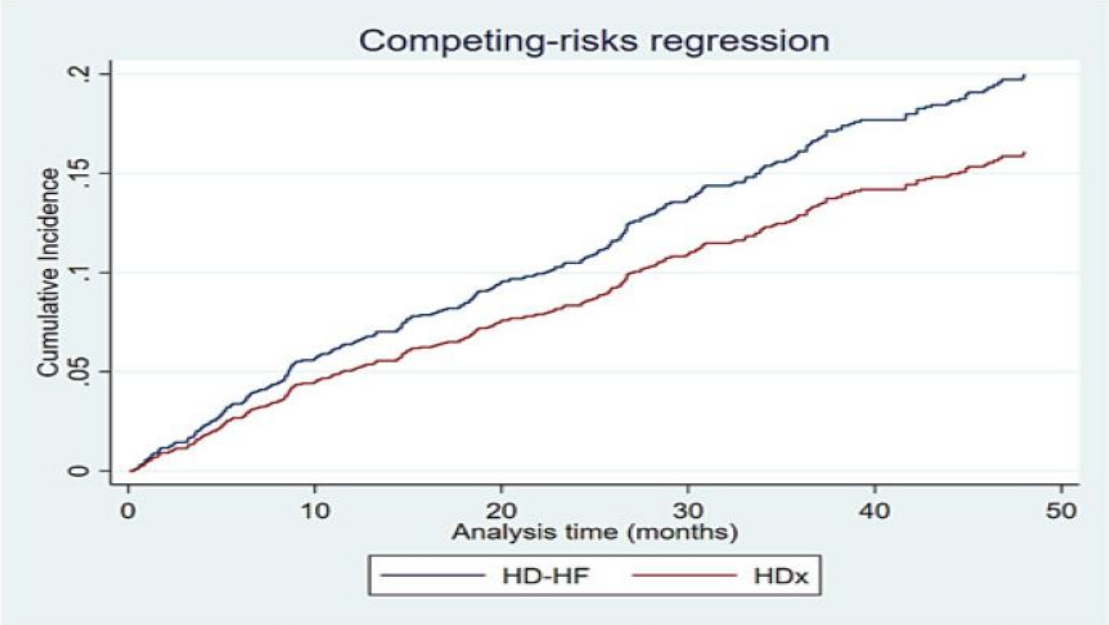


Fig. 2. Cumulative incidence functions for all-cause mortality were analyzed based on dialyzer type high-flux hemodialysis (HF-HD) or expanded hemodialysis (HDx) over a follow-up period of up to 48 months. A statistically significant difference in the cumulative incidence curves was observed ($p = 0.014$).

Lower mortality

Study design	Multicenter observational cohort at Colombia; enrollment 2017/9~2017/11; follow-up 48 months.
Participants	Total n=1,092 (HF-HD 533, HDx 559); mean age 61; 42% diabetes; 19% cardiovascular disease.
Intervention	Expanded hemodialysis (HDx)
Comparator	Conventional high-flux hemodialysis (HF-HD)
Outcomes	Time to death (all-cause mortality adjusted for competing risk [COVID-19] and clinical covariates) up to 48 months
Key results	HDx associated with lower mortality vs HF-HD Fine-Gray sHR 0.79 (95% CI 0.62–0.98)

Castillo. Blood Purif. 2025 published online, DOI: 10.1159/000548158

Received: 23 June 2021 | Revised: 21 January 2022 | Accepted: 25 March 2022

DOI: 10.1111/hdi.13015

ORIGINAL ARTICLE

Quality of Life, Outcomes

Economic evaluation of expanded hemodialysis with the Theranova 400 dialyzer: A post hoc evaluation of a randomized clinical trial in the United States

Michael J. Blackowicz[1] | Luke Falzon[2] | Werner Beck[3] | Ha Tran[1] | Daniel E. Weiner[4]

Study design	A post-hoc economic/clinical analysis of hospitalization and costs during 24 weeks in the US
Participants	Theranova n=86 (389 patient-months) vs high-flux n=85 (366 patient-months)
Intervention	Expanded hemodialysis (HDx)
Comparator	Conventional high-flux hemodialysis (HF-HD)
Outcomes	All-cause hospitalization rate, total hospital days, length of stay, and estimated costs
Key results	Estimated annual hospitalization cost lower with Theranova (≈ $6,098 less per patient; total annual cost ≈ $4,772 less per patient, dialyzer costs taken into account) driven by fewer hospitalizations.

Lower costs:
from lower hospitalization rate and length of stay as the main drivers

TABLE 2 Clinical outcomes

Health resource utilization	Theranova ($n = 86$)	High-flux HD ($n = 85$)[a]	p-value
Hospitalization events	18	31	–
Total hospital days	74	139	–
Total patient-years	32.4	30.5	–
Hospitalization rate per PY (SE)	0.56 (0.13)	1.02 (0.12)	0.042
Hospital length of stay (mean days [SE])	4.11 (0.57)	4.63 (0.58)	0.406

Abbreviation: HD, hemodialysis.

[a]One high-flux HD randomized participant did not complete baseline.

Blackowicz MJ, Falzon L, Beck W, Tran H, Weiner DE. Economic evaluation of expanded hemodialysis with the Theranova 400 dialyzer: A post hoc evaluation of a randomized clinical trial in the United States. Hemodial Int. 2022 Jul;26(3):449-455. doi: 10.1111/hdi.13015. Epub 2022 Apr 19. PMID: 35441486; PMCID: PMC9544662. https://onlinelibrary.wiley.com/doi/10.1111/hdi.13015

Blackowicz. Hemodial Int. 2022;26(3):449.

Pro for HDx (5): Eco-friendly
HDx uses less water, energy, and equipment than HDF

Modality	Clearance	Complexity	Machine Need	Fluid Replacement
HD	Low	Simple	Basic HD	No
HDF	High	Complex	Specialized	Yes
HDx	High	Simple	Basic HD	No

Still Waiting: Randomized controlled trial (RCT) comparing HDx and OL-HDF

Clinical Kidney Journal

Trial design of MOTheR HDx study: a multicenter, open-label, prospective, randomized study to explore the morbidity and mortality in patients dialyzed with the Theranova HDx in comparison to online hemodiafiltration

Methods

Multicenter

Participants:
- Adults
- 3 m < HD time > 2 y

Composite primary endpoint:
- HDx is non inferior to post OL-HDF

Global mortality
CV mortality
CV events

Follow up period: 24 months

Study design	Designed to test non-inferiority of HDx vs OL-HDF for major morbidity/mortality in Spanish dialysis centers.
Participants	multicenter, open-label RCT 469 randomized (HDx 229, OL-HDF 240).
Intervention	HDx using Theranova (MCO) dialyzer.
Comparator	Post-dilution OL-HDF (minimum convection dose 23L/session)
Outcomes	Testing non-inferiority of HDx vs OL-HDF for all-cause death, stroke (ischemic/hemorrhagic), acute coronary syndrome, peripheral arterial disease, and ischemic colitis over ≤36 months.
Preliminary results in interim analysis	all-cause mortality: 12.7% (29/229) vs 12.9% (31/240), HR 0.89 (0.54–1.48)—supporting non-inferiority of HDx for mortality in interim analysis.

A new generation of membranes, medium cut off (MCO) allow the removal of a greater number of medium-sized molecules and generated a new concept of therapy called expanded HD (HDx). Until now, online hemodiafiltration (OL-HDF) has demonstrated its superiority, in terms of survival, compared to HF-HD. But the comparison between OL-HDF and HDx is a question not solved.

De Sequera, P. et al.
Clinical Kidney Journal (2023)
psequerao@senefro.org
@CKJsocial

Interim analysis:
as good as OL-HDF

Volume 38, Issue Supplement_1
June 2023

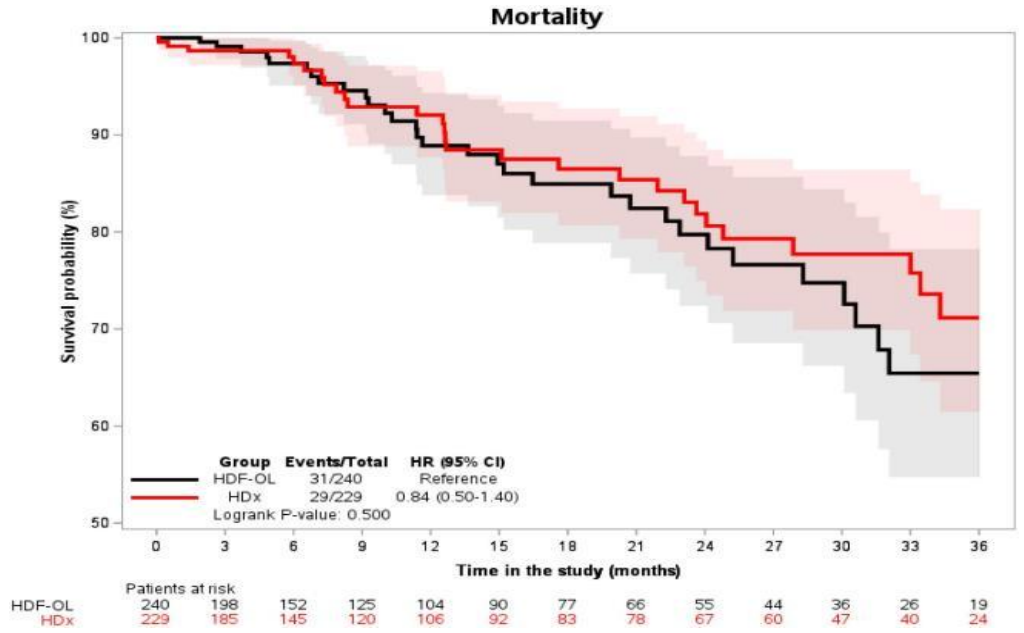
JOURNAL ARTICLE

#3472 PRELIMINARY DATA FROM MOTHER HDX STUDY: A MULTICENTRE OPEN-LABEL RCT STUDY TO EXPLORE THE MORBIMORTALITY WITH THE THERANOVA HDX VS OL-HDF FREE

Patricia De Sequera Ortiz, Rafael Pérez García, Almudena Vega, Francisco Maduell

Nephrology Dialysis Transplantation, Volume 38, Issue Supplement_1, June 2023, gfad063c_3472, https://doi.org/10.1093/ndt/gfad063c_3472

Published: 14 June 2023



#3472

PRELIMINARY DATA FROM MOTHER HDX STUDY: A MULTICENTRE OPEN-LABEL RCT STUDY TO EXPLORE THE MORBIMORTALITY WITH THE THERANOVA HDX VS OL-HDF

Patricia De Sequera Ortiz[1], Rafael Pérez García[1], Almudena Vega[2] and Francisco Maduell[3]

[1]Hospital Universitario Infanta Leonor, Nephrology, Madrid, Spain, [2]Hospital General Universitario Gregorio Marañon, Nephrology, Madrid, Spain and [3]Hospital Clinic, Nephrology, Barcelona, Spain

Background and Aims: Dialysis patients have a high rate of cardiovascular morbidity and mortality. For this reason, new technical advances are necessary to be introduced in clinical practice. Medium cut-off (MCO) membranes are a new generation of membranes that allow the removal of a greater number of medium-sized molecules compared to high-flux hemodialysis (HF-HD) but retaining albumin. Theranova, a MCO membrane has an increased permeability and also produces high convective volume in the form of internal filtration. For these special properties, MCO generated a new concept of therapy called expanded HD (HDx). Until now, online hemodiafiltration (OL-HDF) has demonstrated its superiority, in terms of survival, compared to HF-HD. But the comparison between OL-HDF and HDx is a question not solved.

Method: The MOTheR HDx study trial (NCT03714386) is an open-label, multicentric, prospective, 1:1 randomized, parallel-group trial designed to evaluate the efficacy and safety of HDx compared to OL-HDF in incident HD patients in Spain for up to 36 months. The main endpoint is to determinate if HDx is non inferior to OL-HDF at reducing the combined outcome of all-cause dead and stroke (ischemic or hemorrhagic), acute coronary syndrome (angina and myocardial infarction), peripheral arterial disease (amputation or revascularization) and ischemic colitis (mesenteric thrombosis).

Results: Now we have enrolled 513 patients, 44 excluded and 469 were randomized. 229 were allocated to HDx and 240 to OL-HDF. No differences were found in neither baseline characteristics, hemodialysis or pharmacological treatment, nor laboratory parameters. Follow up time was similar in both groups: 15.06 (12.8) vs 13.73 (11.51) months [HR 0.84 (0.50-1.40)] without differences in mortality: 29 (12.7%) vs 31 (12.9%) [HR 0.89 (0.54-1.48)] in HDx and HDF respectively (Figure 1).

Conclusion: These preliminary results from Mother study support that HDx is not inferior to OL-HDF in reducing the all-cause mortality outcome.

Nephrology Dialysis Transplantation, Volume 38, Issue Supplement_1, June 2023, gfad063c_3472, https://doi.org/10.1093/ndt/gfad063c_3472

So far so good:
Ready for HDx for all?

Rebuttal?

Universal HDx adoption for all hemodialysis patients?

- Outcomes are so good, why not for all patients?
- HDx is a promising innovation but does not yet warrant replacing standard HD for all patients
- Meta-analyses and cohort studies for hard clinical outcomes: not all are positive (some results are neutral)
- Guideline & expert positions – No consensus for HDx for all

Aktas. Int Urol Nephrol 2025; 57: 3761

Con for HDx for all

- Patient heterogeneity
  - Not all patients benefit equally
  - Tailored therapy, not a one-size-fits-all approach
- Potential safety concerns
  - Albumin loss (1.5–2.5 g/session): concerns in malnourished or elderly patients.
  - Long-term safety: Probably not all the large middle molecules are harmful

Maduell. Clin Kidney J. 2022;15(12): 2292
Castillo. Hemodial Int. 2025;29(3):327

Clinical Kidney Journal

Super high-flux membrane dialyzers reduce mortality in patients on hemodialysis: a 3-year nationwide cohort study

In Japan, dialyzers are classified according to their β2-microglobulin clearance: type I dialyzers are classified as low-flux, type II and III as high-flux, and type IV and V as super high-flux dialyzers

Aim

To assess the association of each dialyzer type with 3-year all-cause mortality

Methods

Nationwide prospective cohort study
Dialysis Therapy Renal Data Registry
2008–2011

Low-flux
(< 10 mL/min clearance)

High-flux
(10–30 and 30–50 mL/min clearance)

Super high-flux
(50–70 and ≥ 70 mL/min clearance)

Results

242 467 patients

R.I.P.
53 172 (21.9%)

	Low-flux	High-flux	Super high-flux
	Type I 1.3%	Type II 1.0% Type III 4.2%	Type IV 81.2% Type V 12.3%
Unadjusted HR	**2.43**		
Type II HR		**1.74**	
Type III HR		**1.21**	
Type IV			(reference)
Type V HR			**0.65**

Adjusted HR for (1) basic factors; (2) basic factors + dialysis-related factors; (3) basic factors + dialysis-related factors + nutrition- and inflammation-related factors; type I maintained a higher HR and type V a lower HR

Conclusion: Hemodialysis using super high-flux dialyzers might reduce mortality. Randomized controlled trials are warranted to clarify whether these type V dialyzers can improve prognosis.

Abe M., et al
Clinical Kidney Journal (2021)
@CKJsocial

Abe. Clin Kidney J, 2022; 15(3): 473. https://doi.org/10.1093/ckj/sfab177

Con for HDx for all

- Lack of long-term outcome data
  - Most existing studies are small-scale or observational: 3~48 months
  - Large-scale RCTs comparing HDx with high-flux HD or hemodiafiltration (HDF) are needed before making it standard of care (SOC) for all.
- Cost-effectiveness concerns
  - MCO membranes are more expensive
  - Budget impact: Universal implementation of HDx could endanger other options of therapy in a strained-budget health system

Summary:

- Expanded hemodialysis (HDx), by enhancing the removal of large middle molecules, addresses:
  - Improves patient-reported outcomes (pruritus, restless leg syndrome, fatigue, recovery time).
  - Reduces hospitalization and mortality.
  - Eco-friendly compared to HDF.
- HDx should be individualized, considering each patient's clinical status and local operational factors.
  - Certain patients may benefit equally from high-flux HD or HDF
- Whether HDx is intended for all hemodialysis patients: it's too early to say, but it's *not whether, but when; not for all, but for most*
  - Waiting for large-scale long-term outcome data—especially randomized trials

Thank you for your attention!

Meta-analysis: HDx vs OL-HDF

Population	**Adults with end-stage kidney disease (ESKD) receiving maintenance HD; 8 studies, total 614 patients.**
Intervention	Expanded hemodialysis (HDx) using medium cut-off (MCO) membranes.
Comparison	Online hemodiafiltration (online HDF).
Primary Outcome	All-cause mortality: No difference (RR 0.97; 95% CI 0.62–1.53; p = 0.91; I^2 = 0%).
Middle Molecule Clearance	β2-microglobulin: Favored online HDF (Hedges' g −0.61; p = 0.01).Prolactin: Trend favoring HDF but not significant; high heterogeneity (I^2 = 90.9%).
Small Solute Clearance	Creatinine, urea, phosphate: No significant differences between HDx and HDF.
Other Biochemical Outcomes	Uncertain effects on myoglobin clearance and albumin loss due to high heterogeneity and inconsistent reporting.
Conclusion	Both HDx and HDF are effective. Online HDF shows superior clearance of some middle molecules, but no mortality advantage. More standardized RCTs are needed.

Aktas. Comparative efficacy of expanded hemodialysis and online hemodiafiltration: a systematic review and meta-analysis. Int Urol Nephrol 57, 3761–3772 (2025). https://doi.org/10.1007/s11255-025-04559-2

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ORIGINAL ARTICLE

Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure

Peter J. Blankestijn, M.D., Robin W.M. Vernooij, Ph.D., Carinna Hockham, Ph.D., Giovanni F.M. Strippoli, M.D., Bernard Canaud, M.D., Jörgen Hegbrant, M.D., Claudia Barth, M.D., Adrian Covic, M.D., Krister Cromm, M.Sc., Andrea Cucui, M.D., Andrew Davenport, M.D., Matthias Rose, M.D., Marietta Török, M.D., Mark Woodward, Ph.D., and Michiel L. Bots, M.D., for the CONVINCE Scientific Committee Investigators*

Not an easy task! Convection 100mL/min in 4-hr HDF

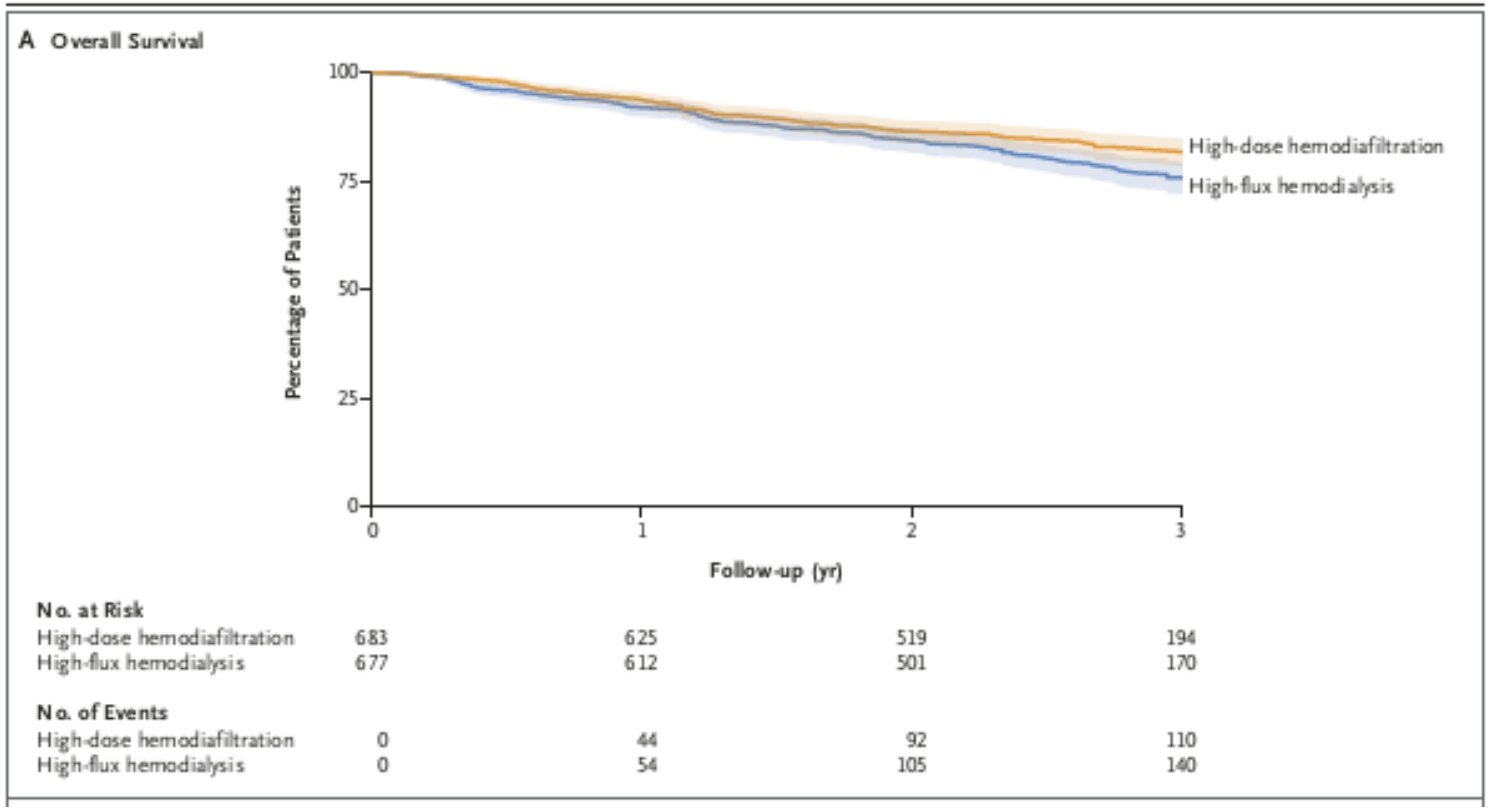

Figure 2 (facing page). Overall Survival and Subgroup Analysis.

Panel A shows Kaplan–Meier curves for overall survival as calculated with the use of data regarding death from any cause (the primary outcome) among the patients who had received either high-dose hemodiafiltration or high-flux hemodialysis. Panel B shows a forest plot with hazard ratios for death from any cause and from cardiovascular causes among prespecifiied subgroups. No adjustment for multiplicity was made, so the 95% confidence intervals should not be used in place of hypothesis testing.

Results:

- The target vol. of at least 23±1 L/session was achieved in 92% of HDF sessions, whereas the mean convection vol. (25.3L) was stable over the course of trial
- All-cause mortality: 118/683 (17.3%) in HDF & 148/677 (21.9%) in HD (HR: 0.77 [0.65 to 0.93], p=0.005)

Blankestijn. N Engl J Med 2023; 389:700-709