Hemodiafiltration in children and long-term outcomes

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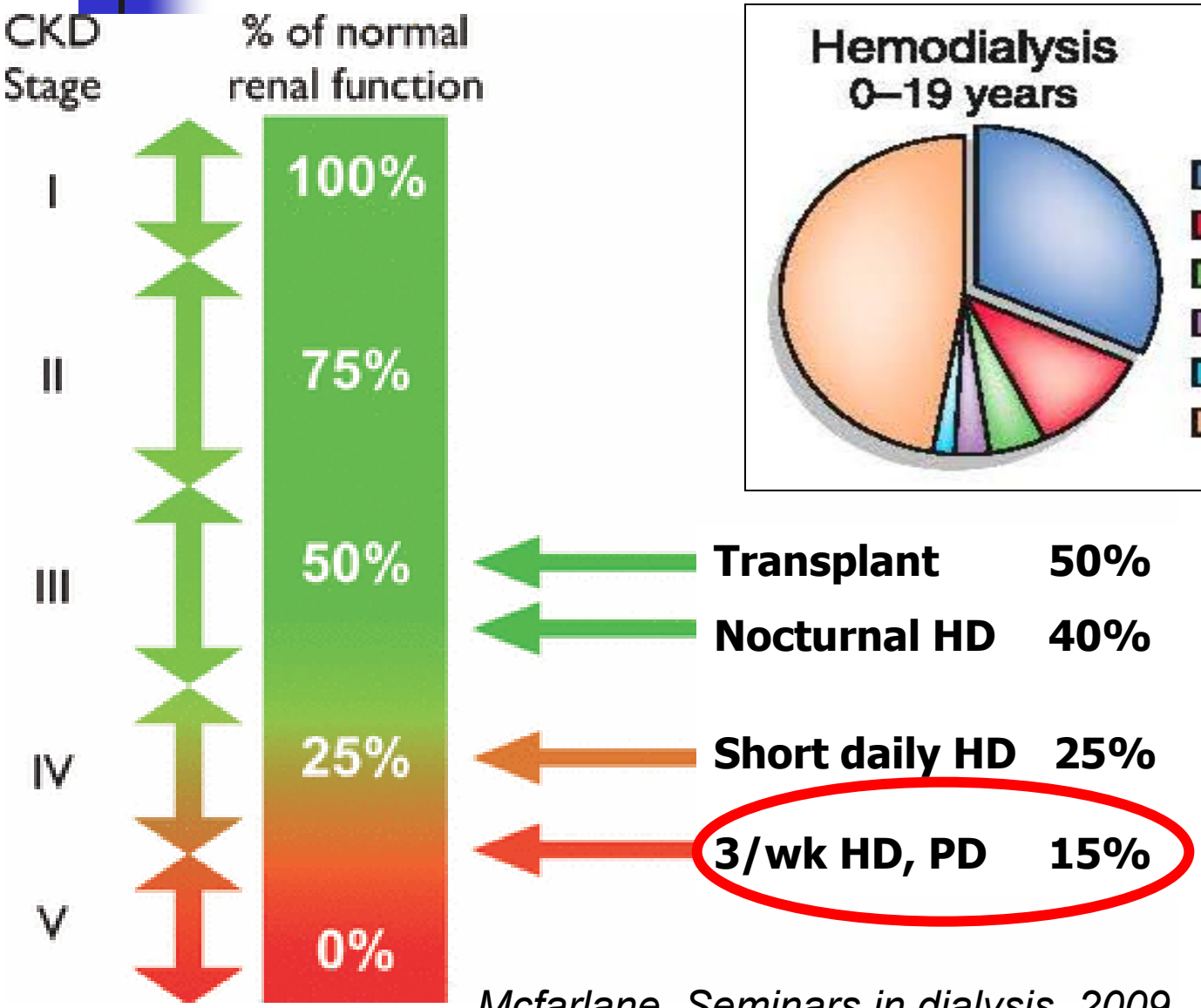
Outline

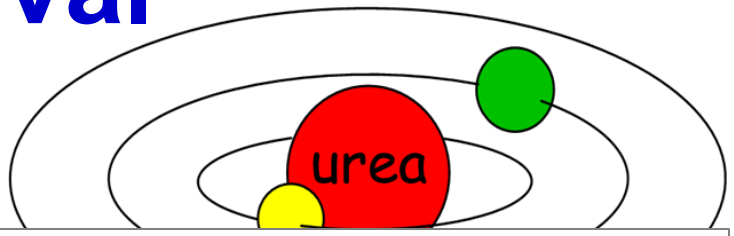
- What is HDF – adding convection to diffusion based treatments
- Learning from adult RCTs
- Paediatric studies
- Effects of HDF on:
  - survival
  - cardiovascular outcomes & BP
  - bone disease and growth
  - health related quality of life measures

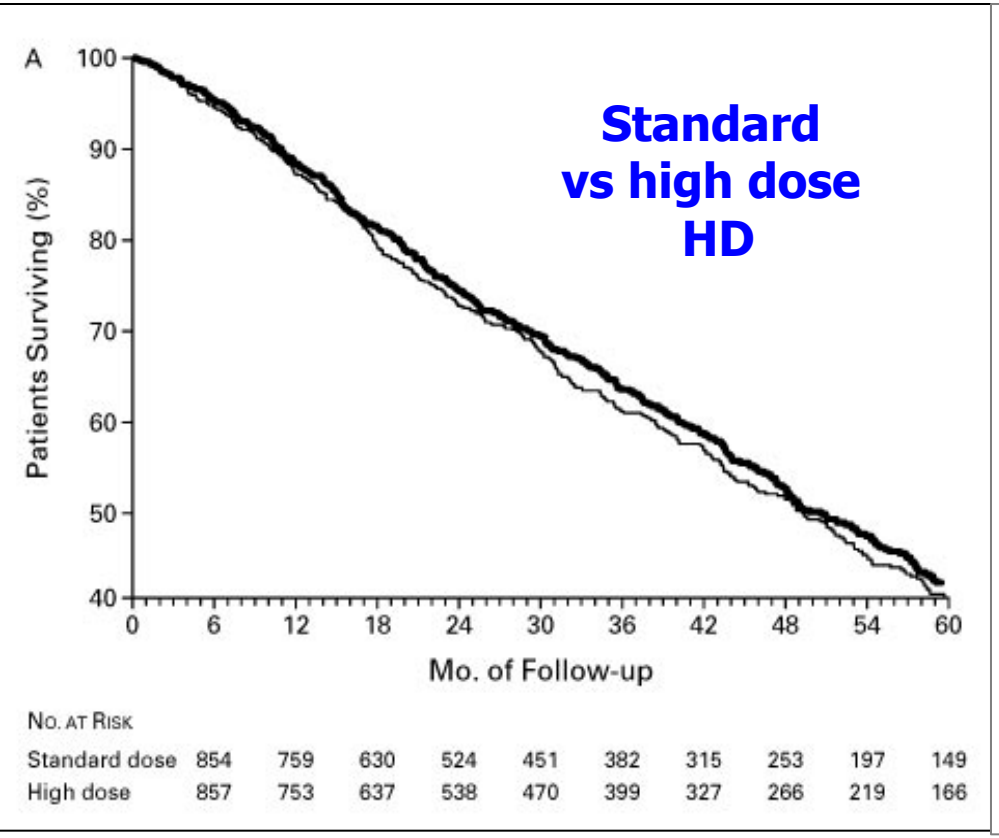
Effectiveness of treatment types

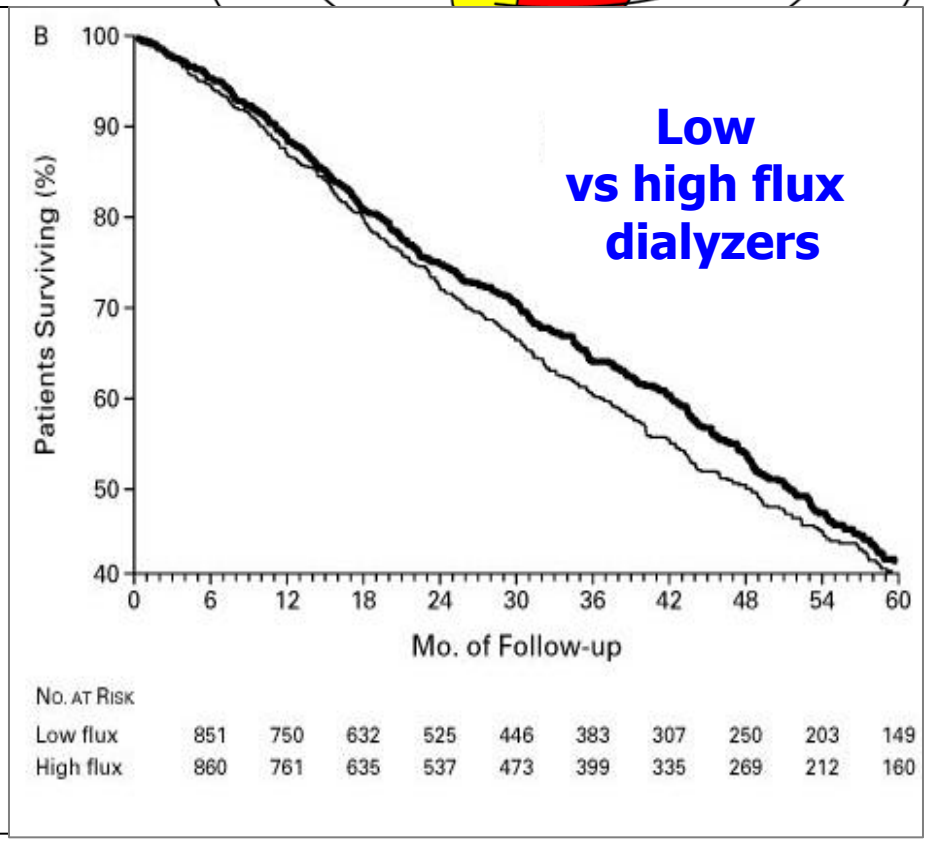


Mcfarlane, Seminars in dialysis, 2009

A ‘urea-centric’ approach does not improve survival

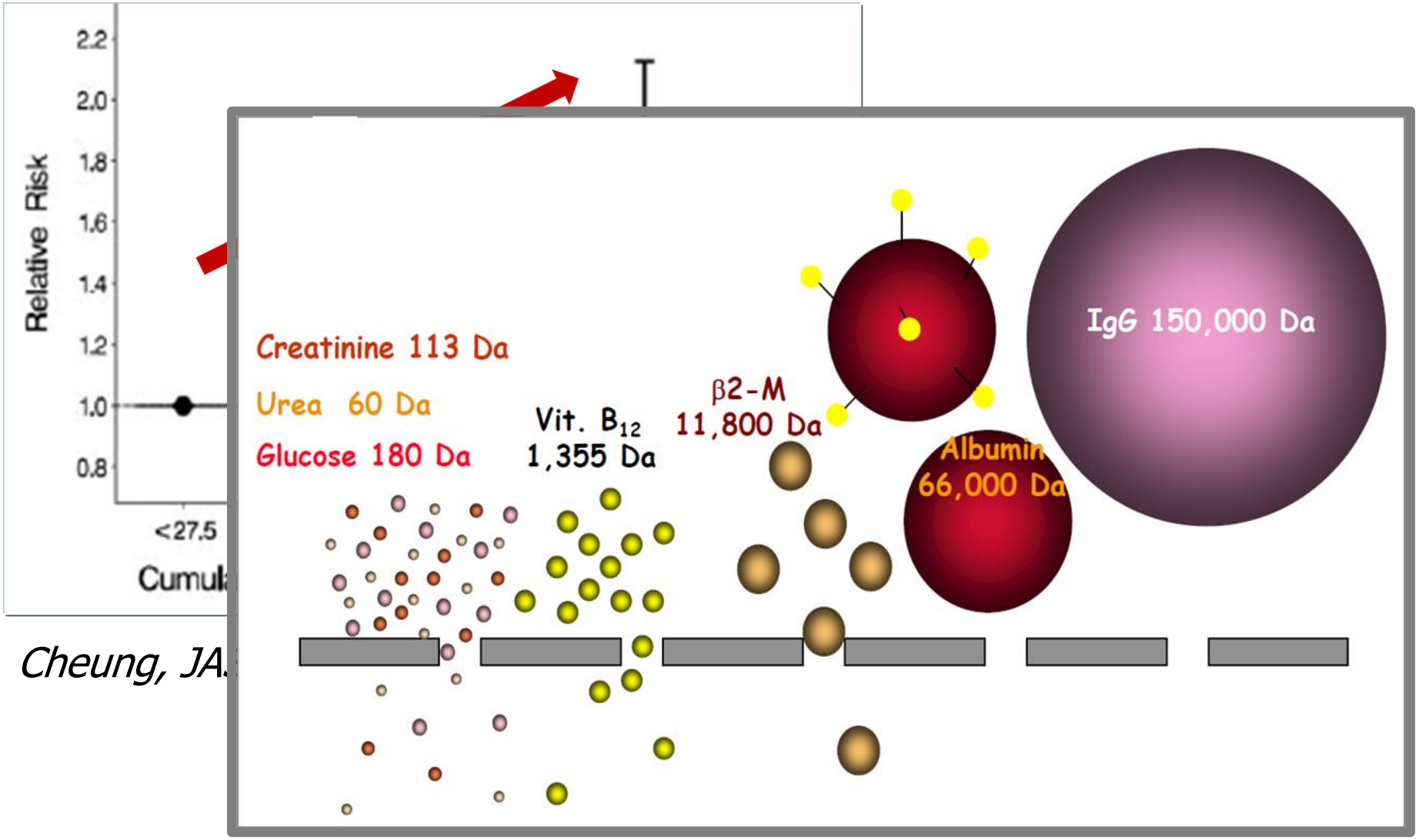






HEMO study, NEJM, 2002

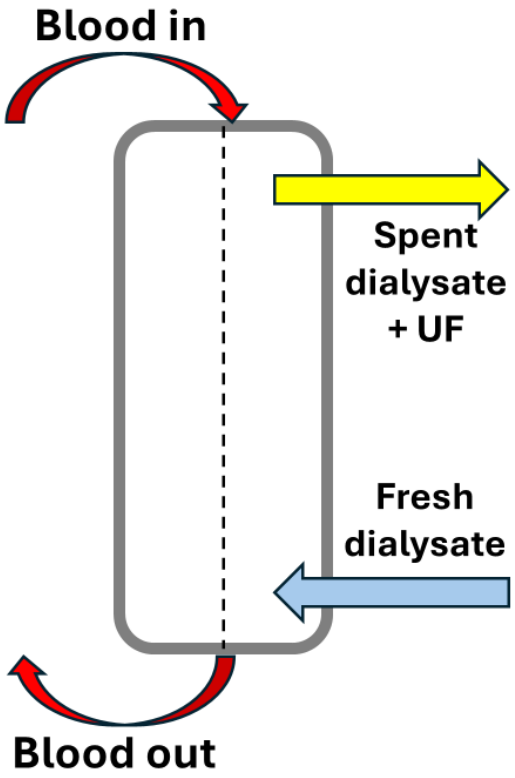
Changing the hemodialysis paradigm



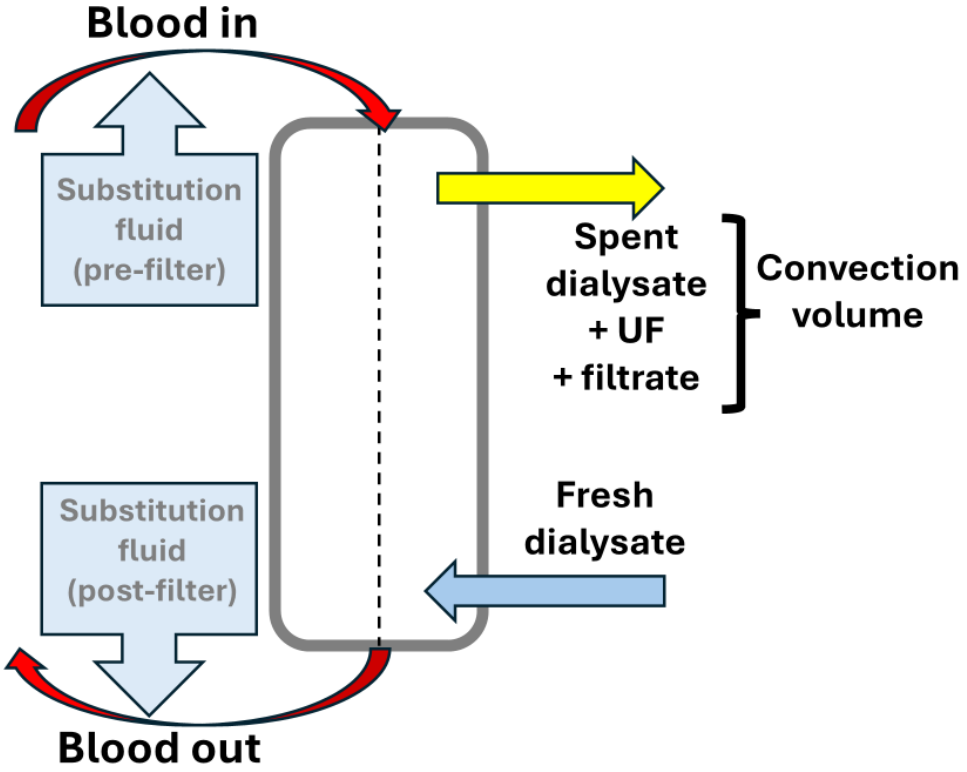
Cheung, JA.

Technical differences

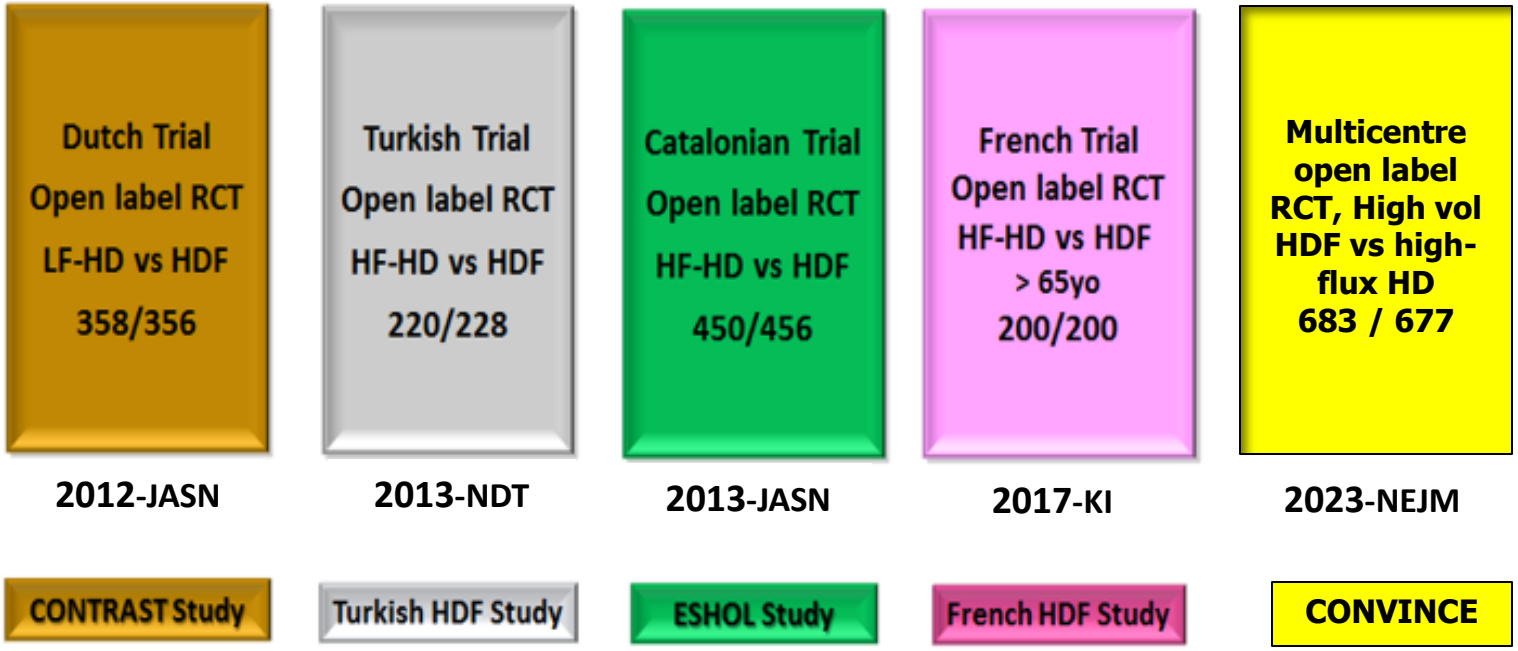
Conventional haemodialysis (HD)



Haemodiafiltration (HDF)

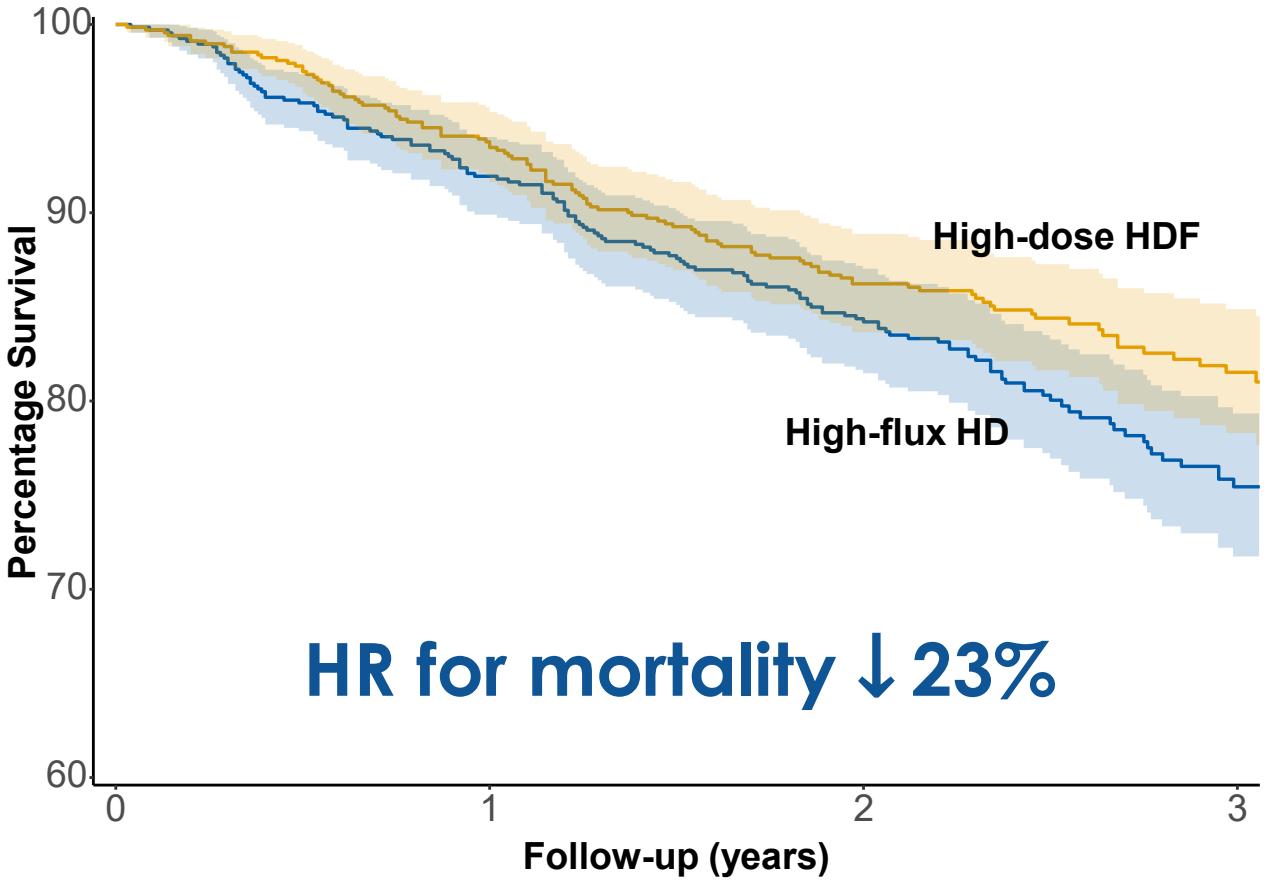


Randomized trials and meta-analyses



***A priori* benefit of HDF over high-flux HD**

Improved survival on HDF compared to HD



HR for mortality ↓ 23%

No. at Risk				
High-dose hemodiafiltration	683	625	519	194
High-flux hemodialysis	677	612	501	170
No. of Events				
High-dose hemodiafiltration	0	44	92	110
High-flux hemodialysis	0	54	105	140

Funded by the European Union

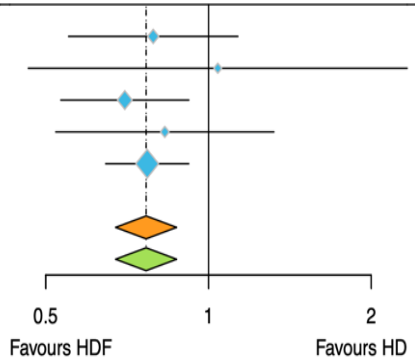
CONVINCE

Meta-analysis – HDF vs. high flux HD

Overall mortality

Author & Year	Log Estimate Effect	Log SE	n/N in HD group	n/N in HDF group	HR	95% CI	W(common)	W(random)
Ok E 2012	−0.2357	0.1841	65/391	52/391	0.79	[0.55; 1.13]	13.0	13.0
Kang A 2012	0.0392	0.4119	15/61	16/63	1.04	[0.46; 2.33]	2.6	2.6
Maduell F 2012	−0.3567	0.1393	122/450	85/456	0.70	[0.53; 0.92]	22.7	22.7
Morena M 2017	−0.1863	0.2371	43/191	36/190	0.83	[0.52; 1.32]	7.8	7.8
Blankestijn PJ 2023	−0.2614	0.0905	148/677	118/683	0.77	[0.64; 0.92]	53.8	53.8
Total (95% CI), common					0.77	[0.67; 0.87]	100.0	.
Total (95% CI), random					0.77	[0.67; 0.87]	.	100.0

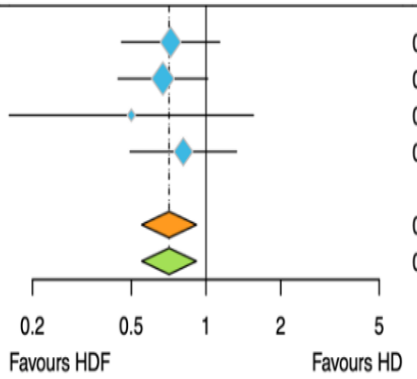
Heterogeneity: $\tau^2=0$; $\chi^2=1.12$, df=4, P=0.89; $I^2=0\%$



CVD mortality

Author & Year	Log Estimate Effect	Log SE	n/N in HD group	n/N in HDF group	HR	95% CI	W(common)	W(random)
Ok E 2012	−0.3285	0.2325	44/392	32/392	0.72	[0.46; 1.14]	31.1	31.1
Maduell F 2012	−0.4005	0.2123	69/450	51/456	0.67	[0.44; 1.02]	37.3	37.3
Kang A 2017	−0.6931	0.5783	9/61	5/63	0.50	[0.16; 1.55]	5.0	5.0
Blankestijn PJ 2023	−0.2107	0.2522	37/677	31/683	0.81	[0.49; 1.33]	26.5	26.5
Total (95% CI), common					0.71	[0.55; 0.92]	100.0	.
Total (95% CI), random					0.71	[0.55; 0.92]	.	100.0

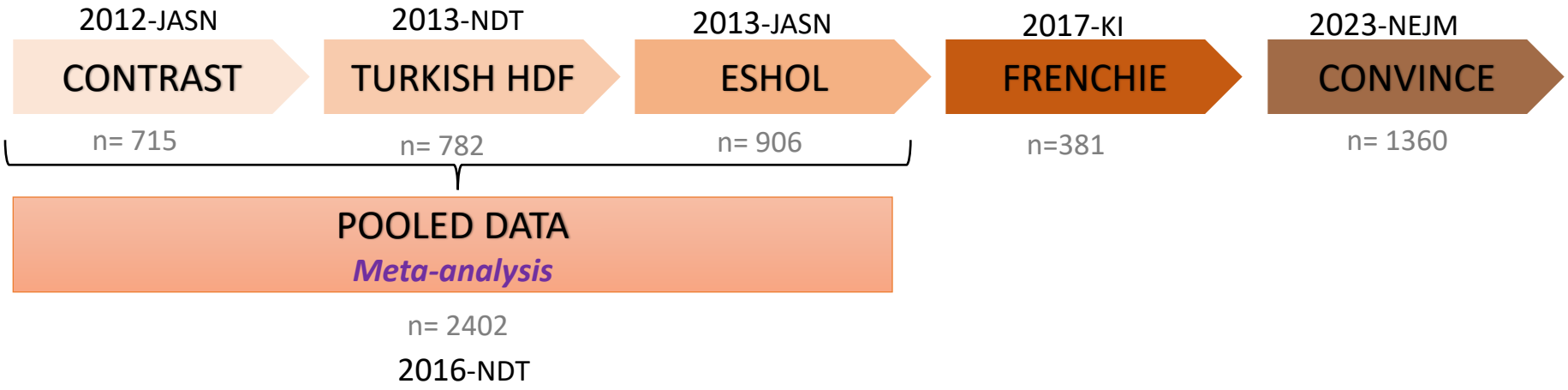
Heterogeneity: $\tau^2=0$; $\chi^2=0.72$, df=3, P=0.87; $I^2=0\%$



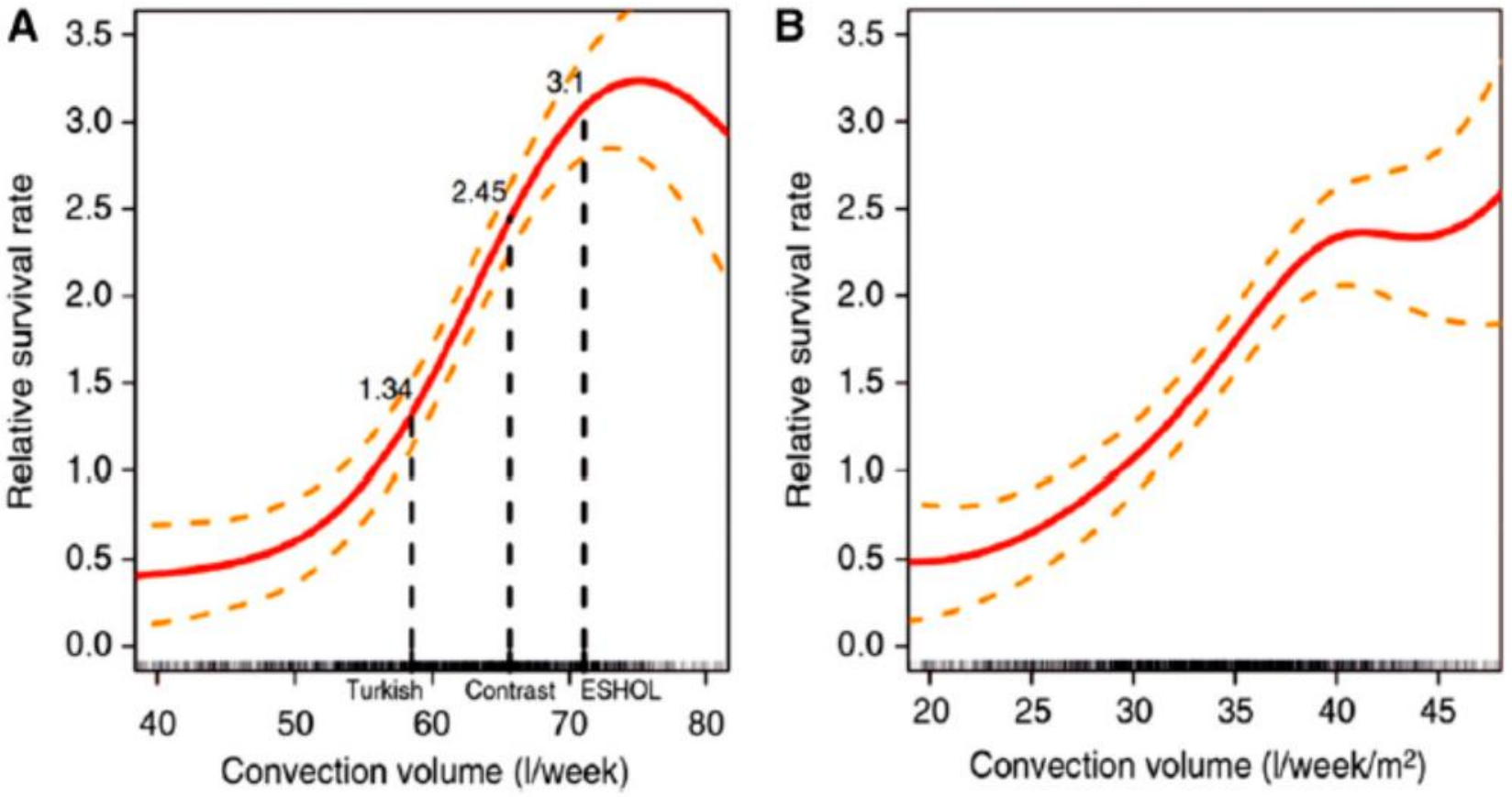
The beneficial effects of HDF are dose dependent

- Efficient dose→ High volume→ **>23 L / session,** post-dilution HDF
- Adjusted from adult data → **12-15 L / m² BSA/ session** for children

Randomized controlled trials, hF-HD vs HDF, in adults



Convection volume – the holy grail of HDF treatment



Canaud et al; KI 2015

Steps to Increase the Convection Vol

Treatment time	Blood flow (Qb)	Dialyzer	Machine setting
• Increase time up to ≥4 h	• Check access / needle size • Slow increase of blood flow rate* by 50 mL/min per session or less	• Optimal surface area to match BSA • In case of clotting, review heparin dose	• Manual technique with filtration fraction FF <30 % • Increase FF in steps of 2 % per session

*While not exceeding access flow and within pressure limits for arterial and venous pressure, as specified

Convection volume target in post-dilution HDF ≥23 L/session, 3x /week

van Zuijdewijn et al, Clin Kidney J. 2017;
Basile C et al. J Nephrol. 2017

3H (HDF, Hearts and Height) study

Hypothesis

Children on HDF compared with HD have improved:

- Cardiovascular risk profile
- Growth and nutritional status
- Quality of life

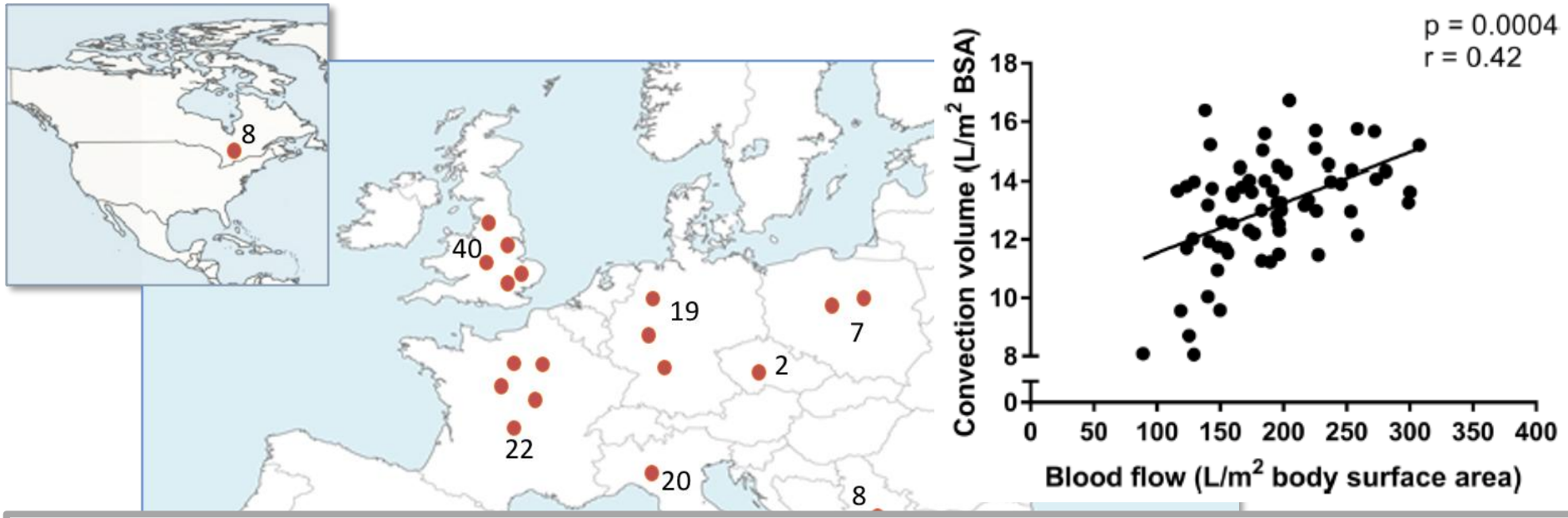
Shroff et al; BMC Neph 2018
Shroff et al; JASN 2019
Snauwaert et al; NDT 2020
De Zan et al; Ped Nephrol 2021
Fischer et al; Kidney Int Reports 2021
De Zan et al; Semin Daily 2022
Paglialonga et al; J Ren Nutr 2023

Recruitment

29 centres in 10 countries

190 children recruited

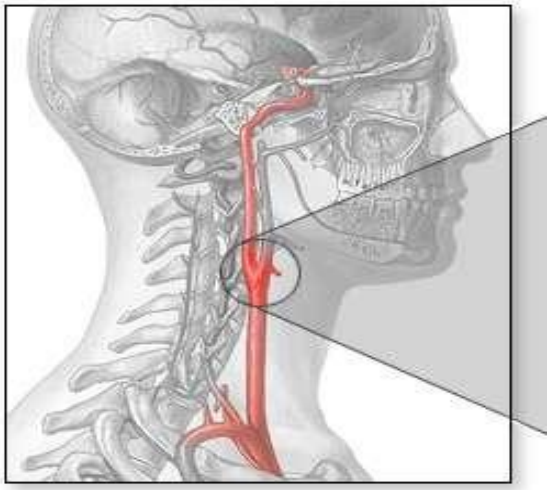
78 on HD and 55 on HDF completed 1-year follow-up

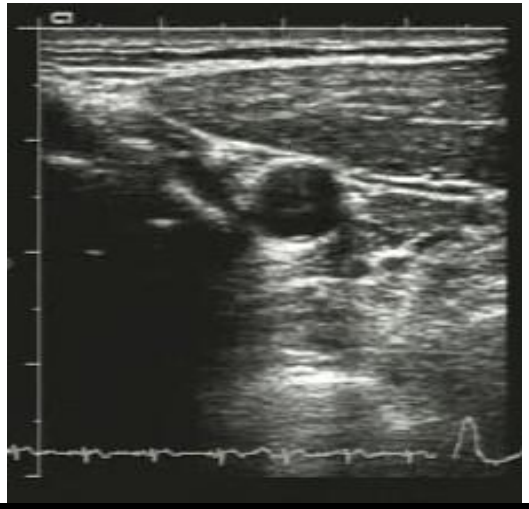


Median convective volume 13.2 (12.1 - 14.3) L/m^2/session
corresponds to 23L/m^2 BSA in adults

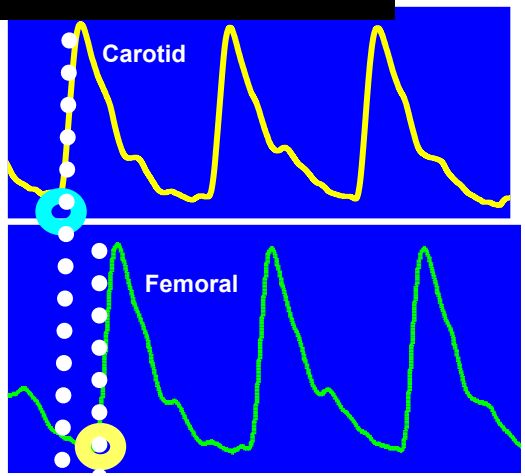
Surrogate measures of vascular disease

Carotid intima-media thickness (cIMT)

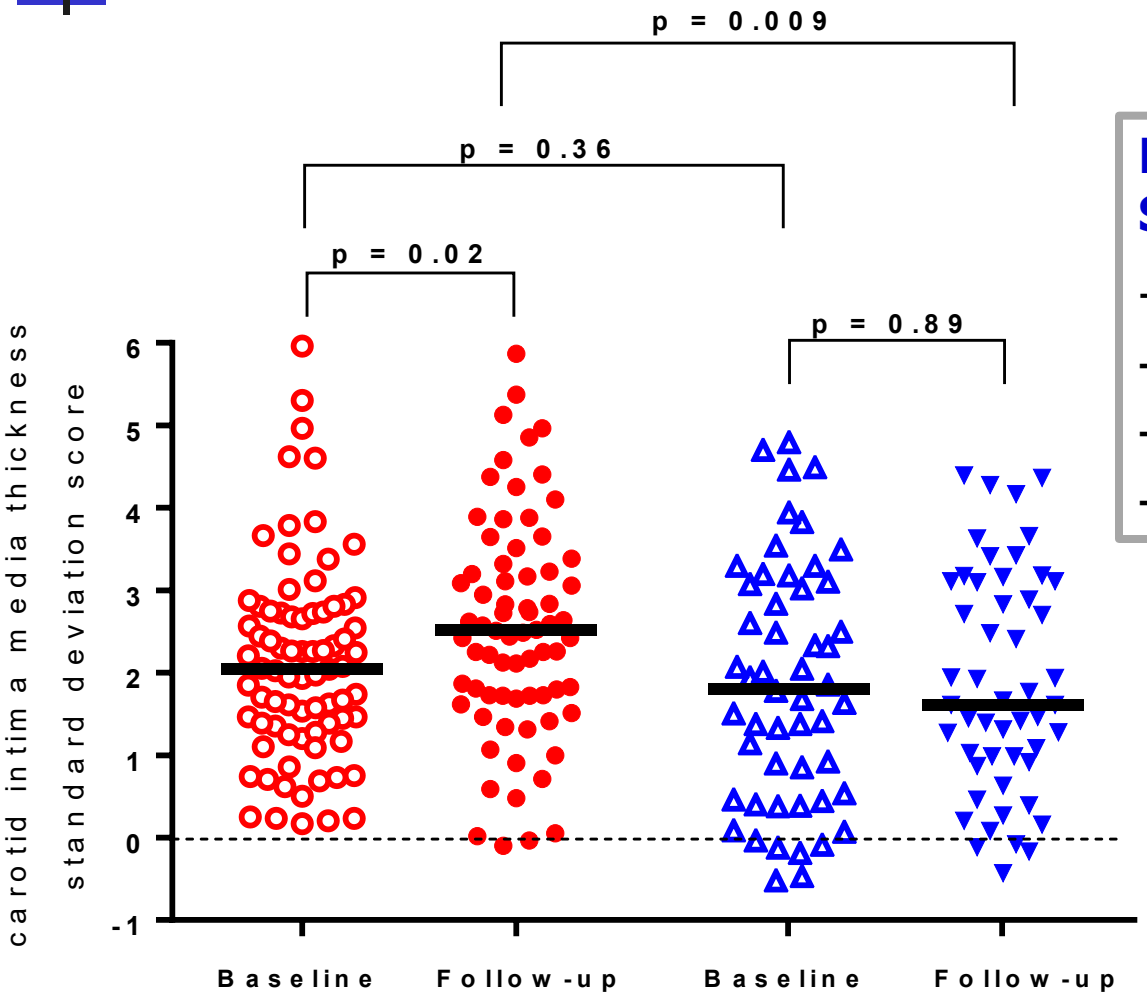




Pulse wave velocity (PWV)



cIMT SDS at baseline and 1-year

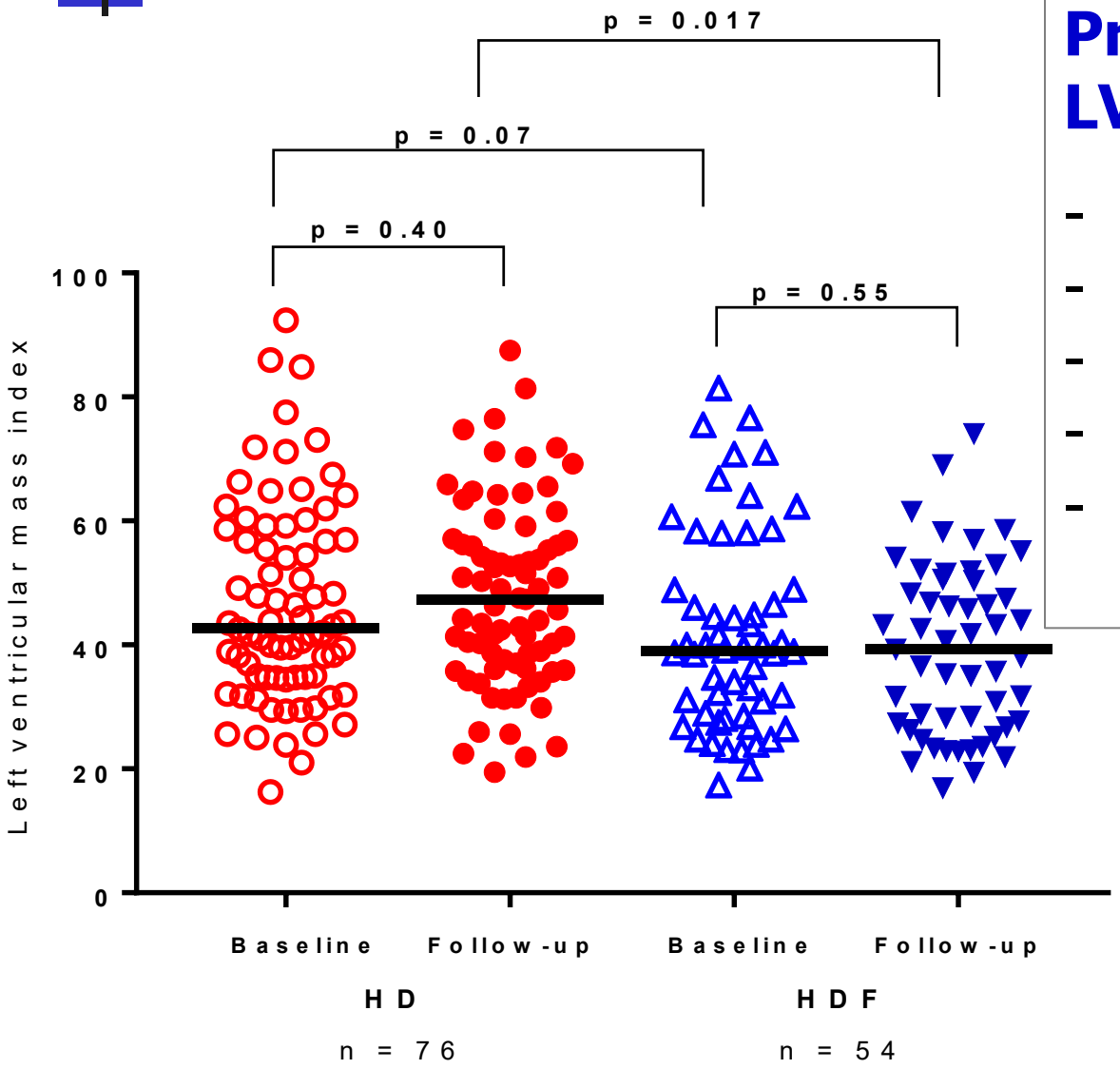


Predictors of higher cIMT-SDS at 12-months

- HD group
- Higher IDWG% and UF rate
- Higher systolic BP
- higher β2-microglobulin

HDF halts the progression of cIMT

LVMI at baseline and 1-year



Predictors of higher LVMI at 12-months

- higher IDWG%
- higher MAP-SDS
- Low Hb
- higher PTH
- Higher BMI SDS

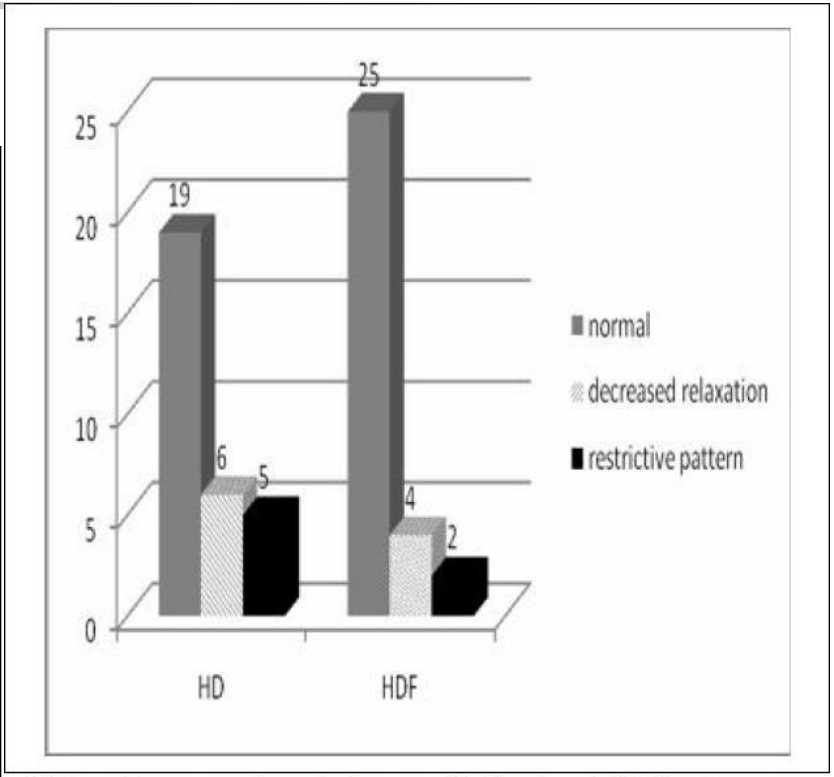
Improvement in cardiac function

N = 30 children

Converted from HD to HDF

At 6-months:

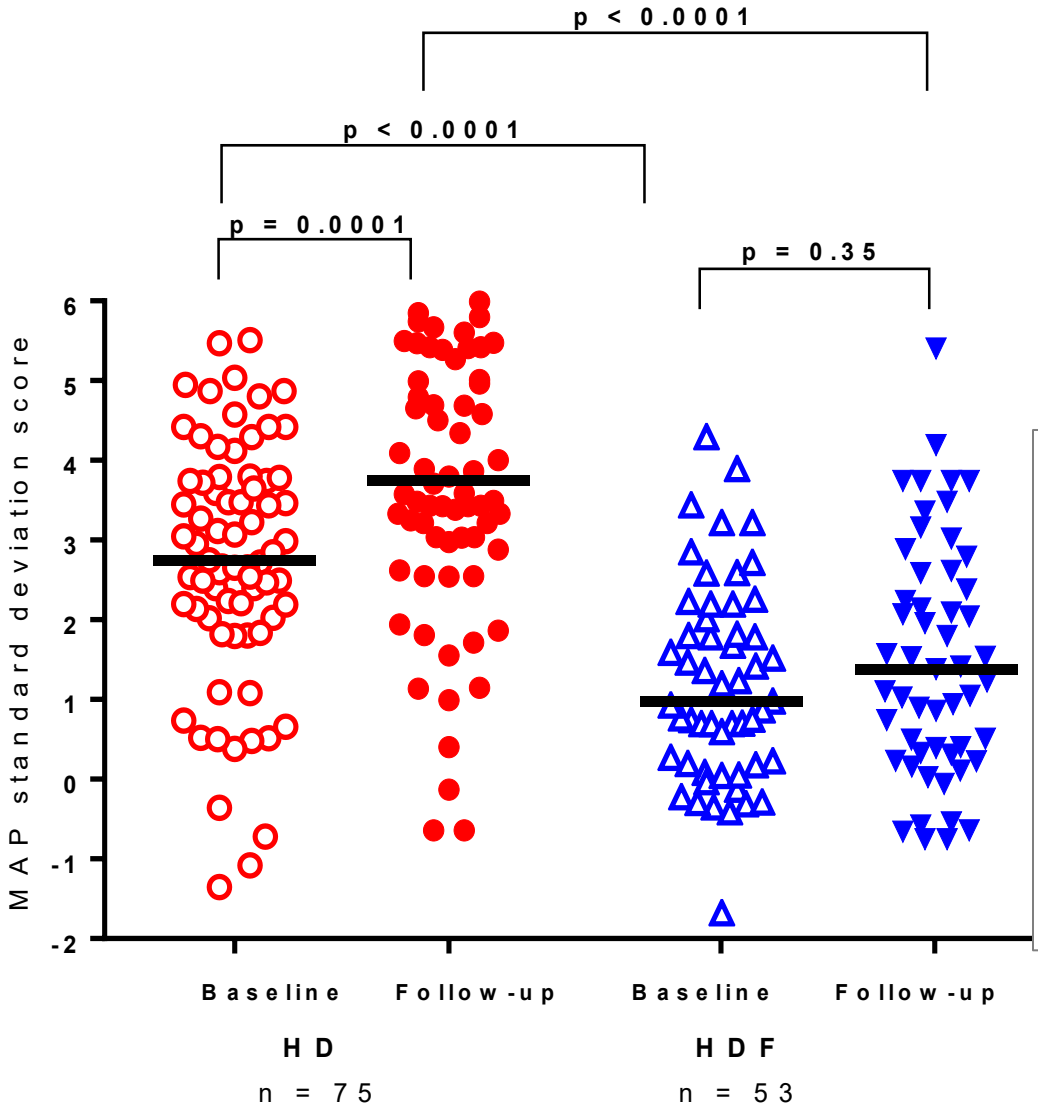
- ✓ decrease in frequency of diastolic dysfunction
- ✓ *improvement in systolic function (FS and EF)*
- ✓ *L*VMI did not change



HD: Conventional hemodialysis, HDF: hemo-diafiltration.

Fadel et al., Saudi J Kidney Dis Transplant 2015

MAP-SDS at baseline and 1-year



At 12-months MAP > 2SD in

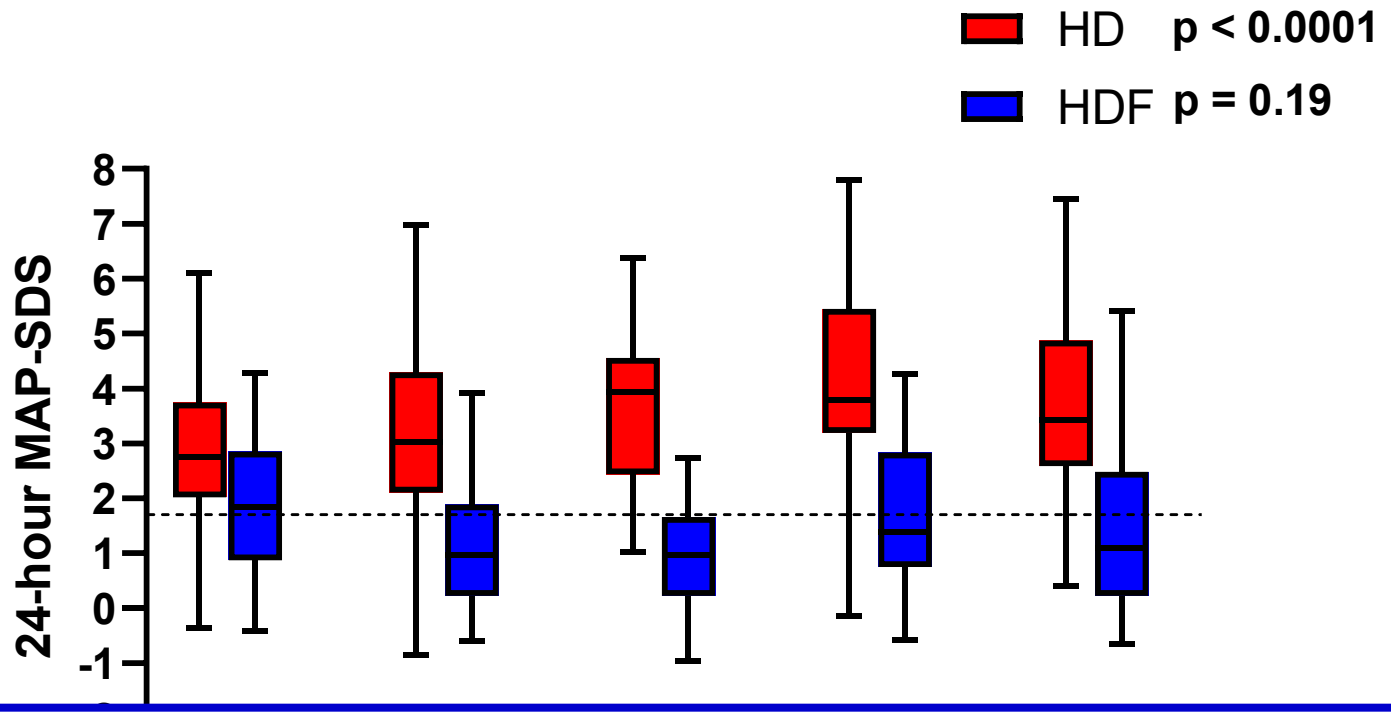
HD 81%
HDF 37%

Predictors of higher MAP-SDS at 12-months

- higher IDWG%
- higher β2-MG
- higher PTH

(no correl with dNa)

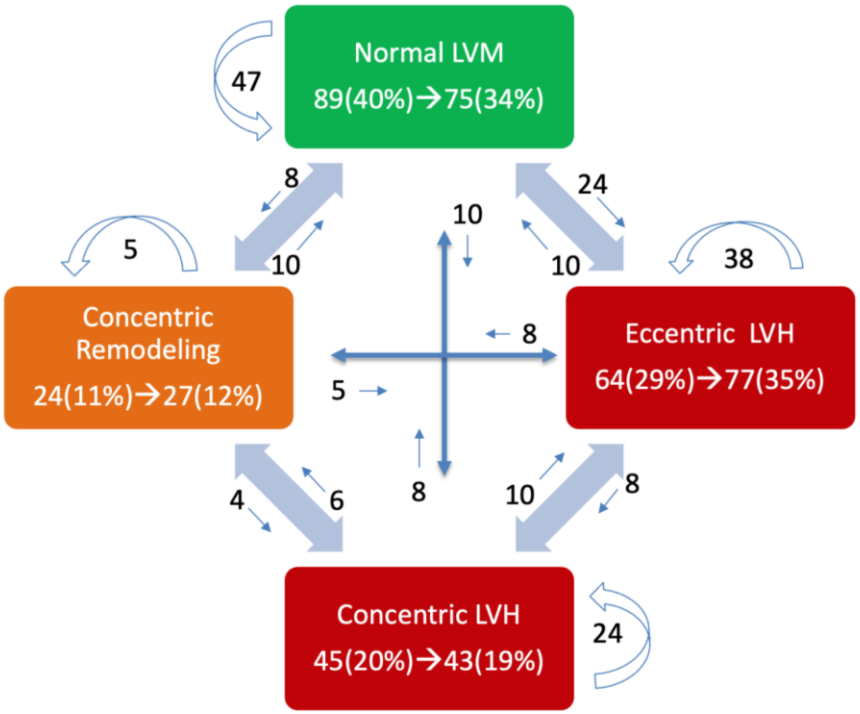
Sustained improvement in BP on HDF compared to HD

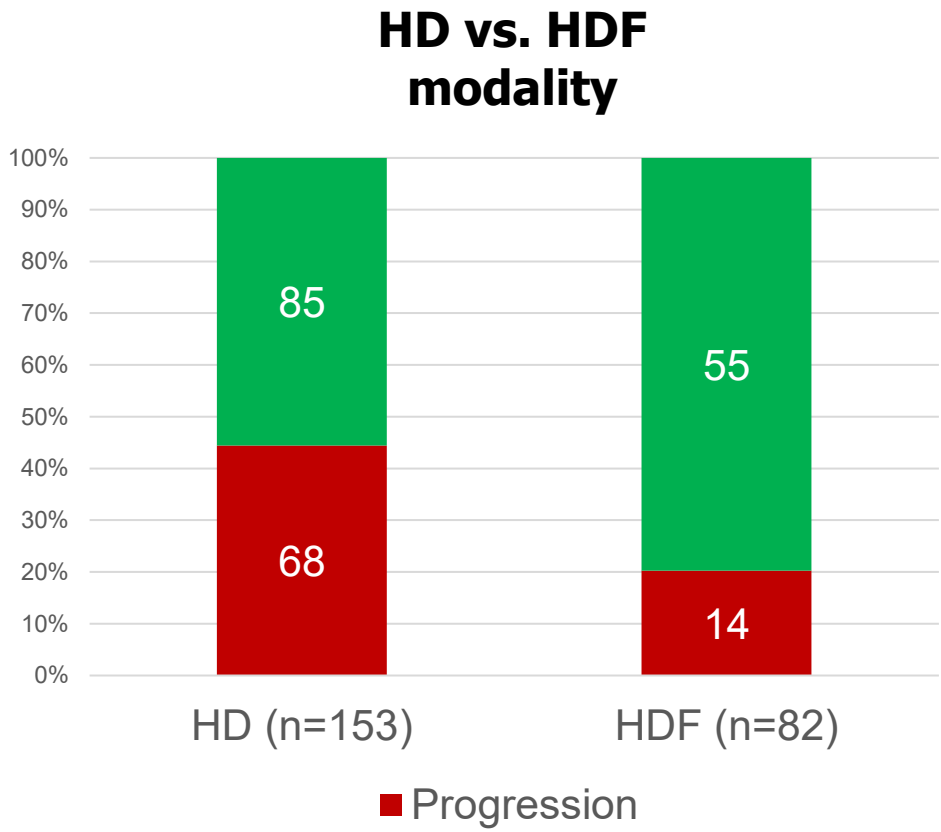


Over a 1-year follow-up the MAP-SDS increased by 1 SDS in HD patients and 0.2 SDS in HDF patients.

HD modality and higher IDWG% are risk factors for a higher MAP-SDS over the one year follow up.

IPHN Registry - Greater progression of LVMI in HD vs HDF

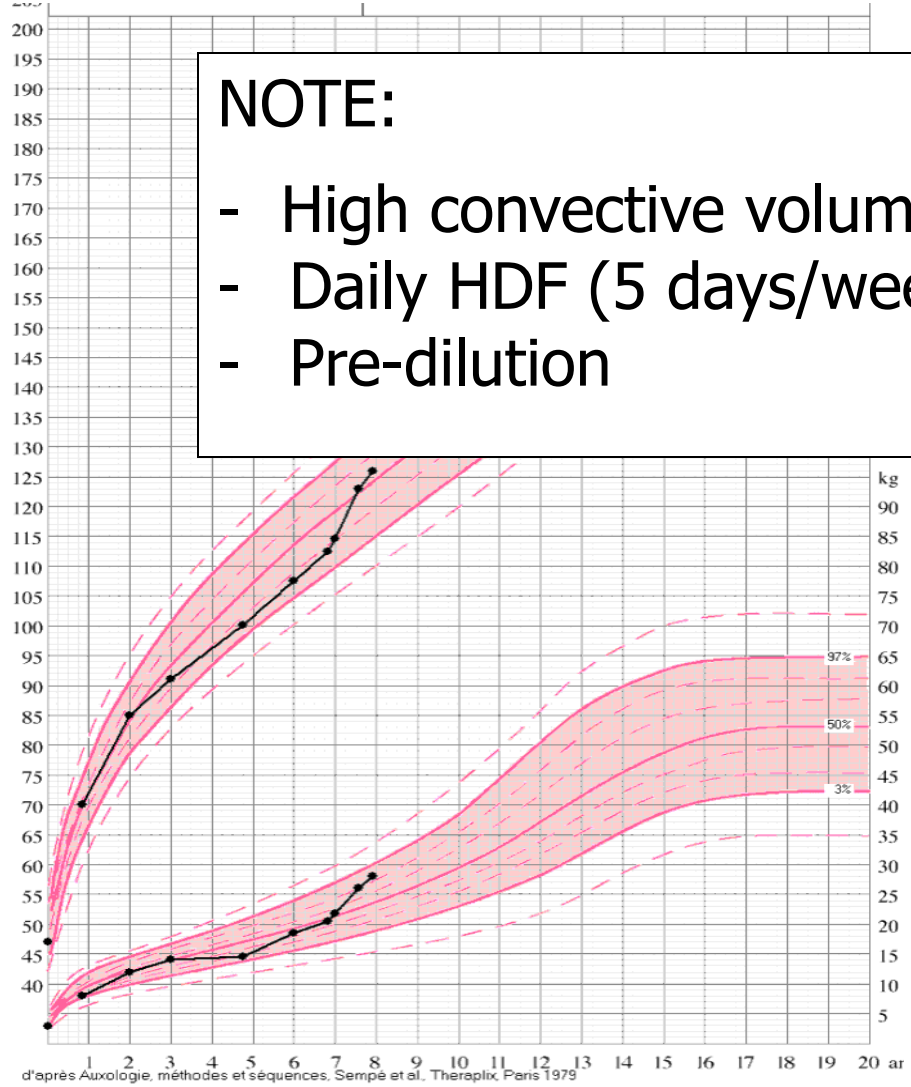


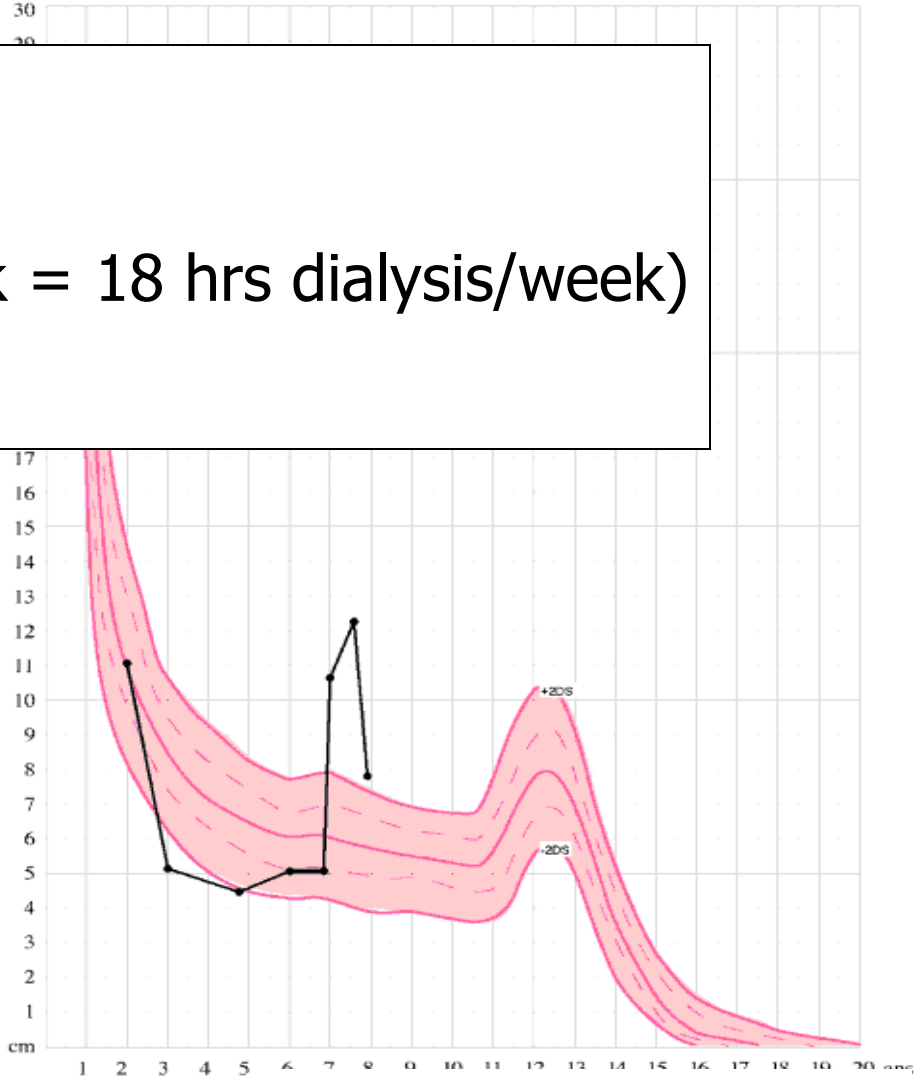


Improved growth on HDF

NOTE:

- High convective volume
- Daily HDF (5 days/week = 18 hrs dialysis/week)
- Pre-dilution





Fischbach et al; NDT, 2010

Dialysis dose and growth

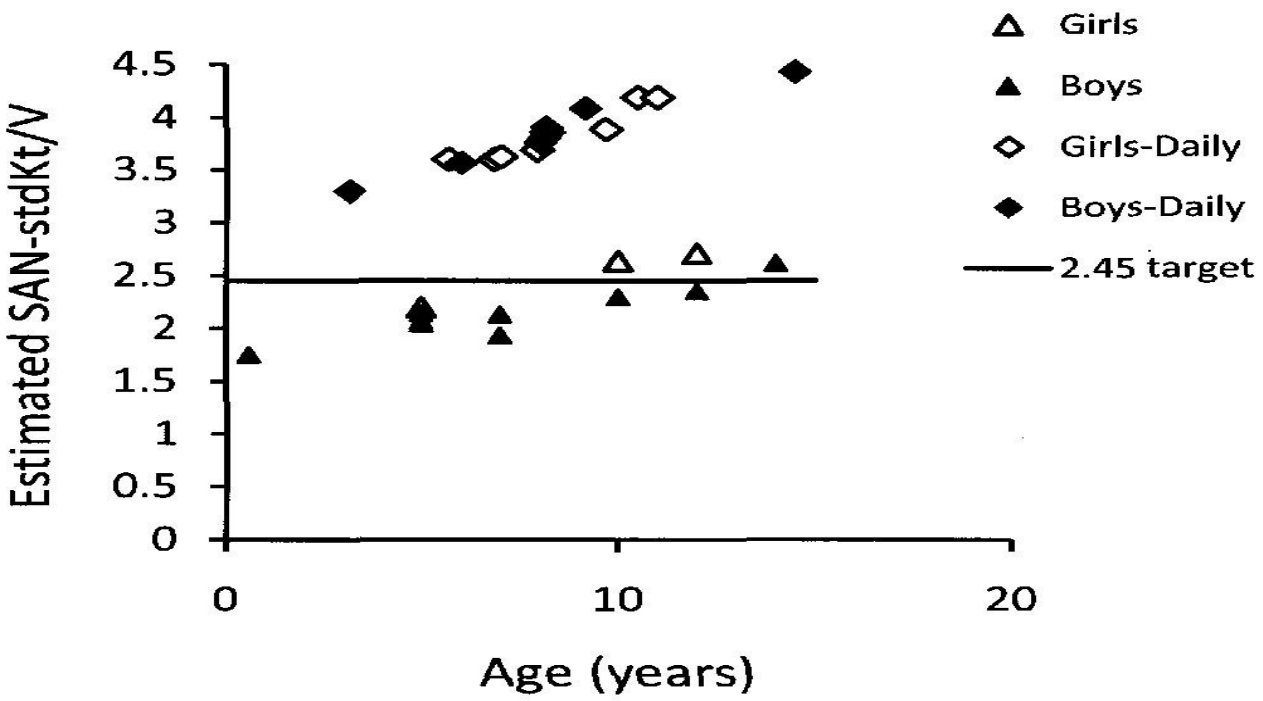
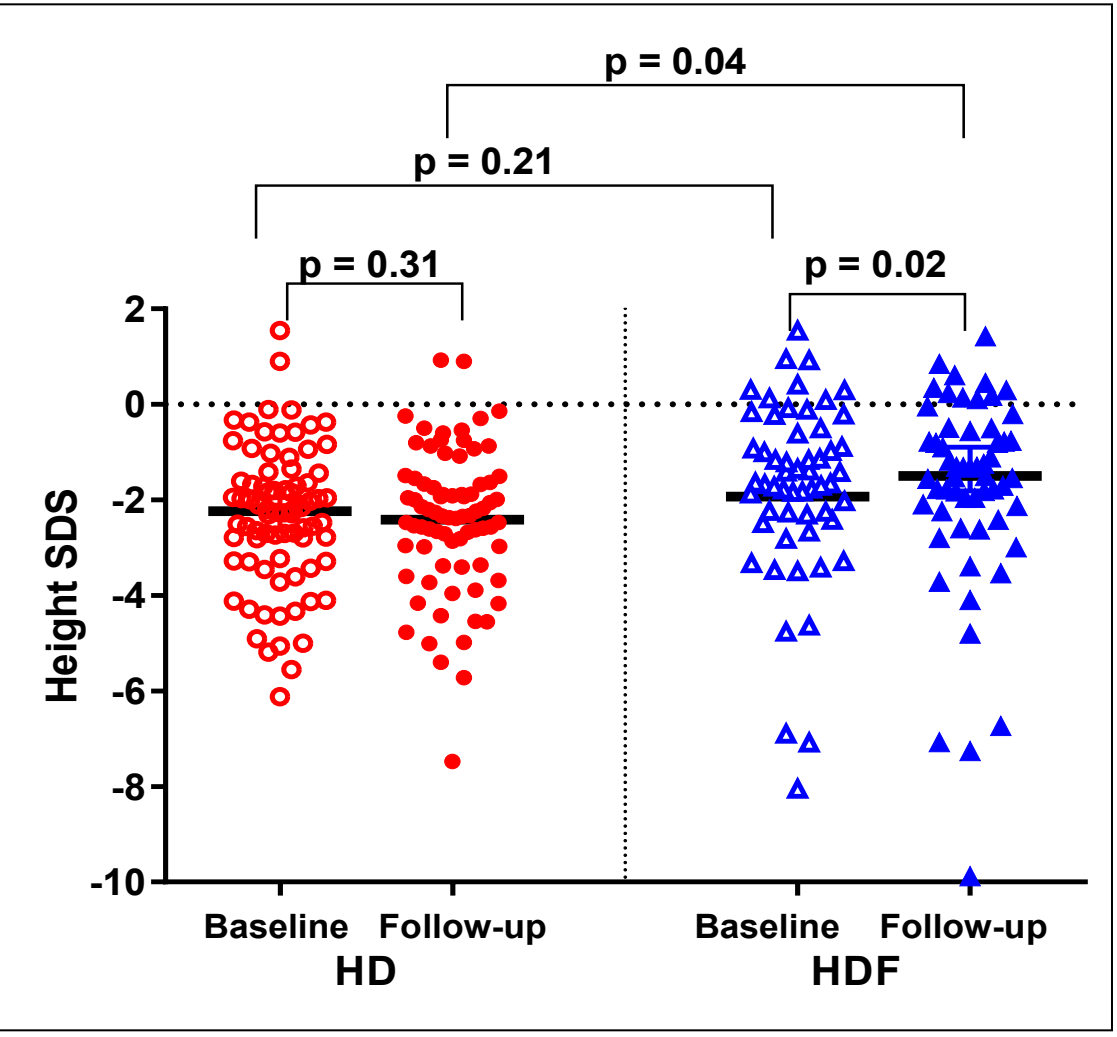


Figure 6. Estimated SAN-stdKt/V *versus* age in two studies in which increased growth rates were linked to intensified dialysis regimens, one with hemodialysis treatments given 3 times/wk by Tom *et al.* (10) and one using 6-times/wk hemodiafiltration by Fischbach *et al.* (11).

Daugirdas et al; Clin JASN 2010

Change in Height SDS



15% on HD and 25% on HDF on growth hormone treatment

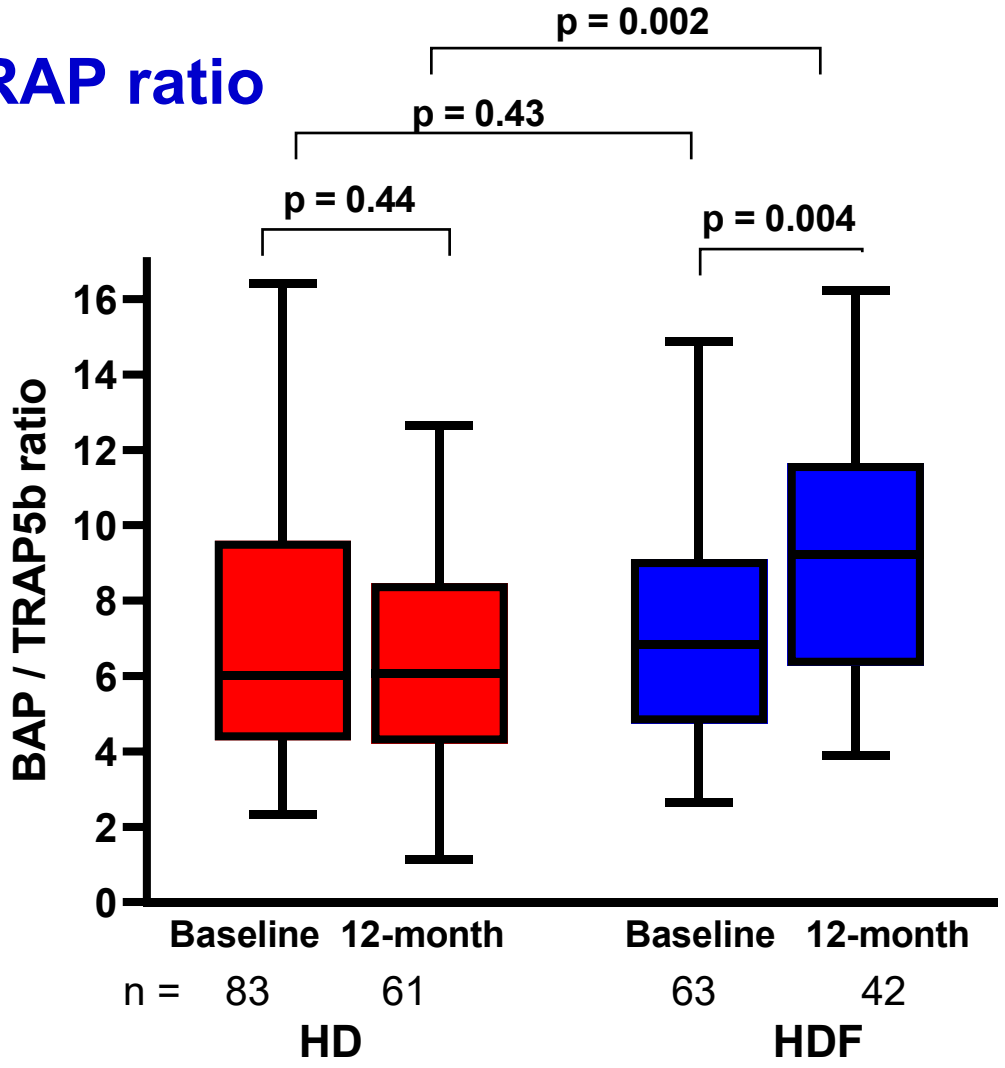
No difference in height-SDS in GH-Rx HDF vs HD patients (p = 0.08).

There was an inverse association between final height-SDS and β2-MG

(beta = -0.07 per 10 mg/L higher level; 95%CI = -0.14 to 0; p = 0.05).

Bone formation vs resorption ratios

BAP/ TRAP ratio

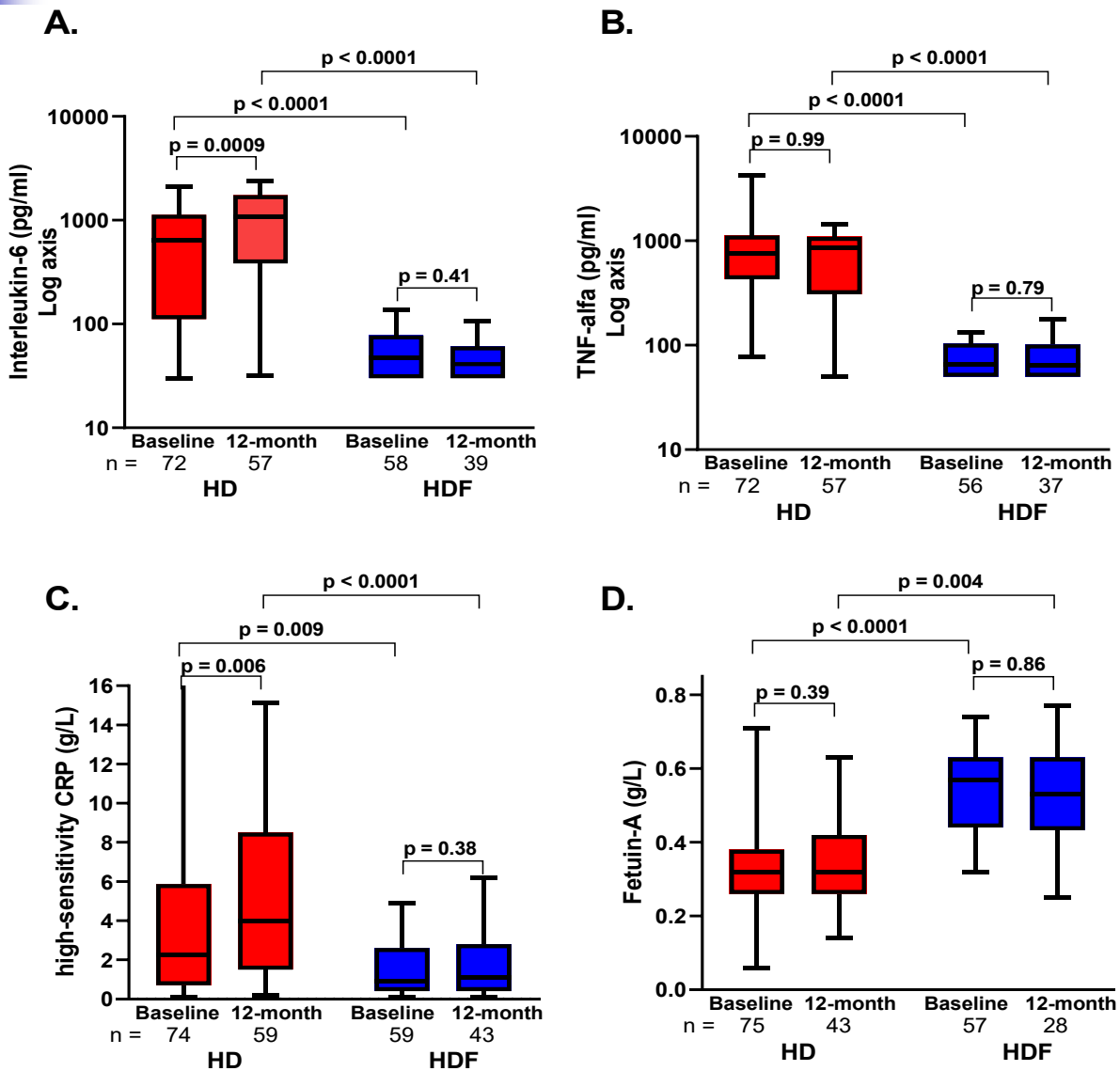


Anabolic effect of daily HDF

- Stimulates appetite - removal of circulating satiety factors (leptin, cholecystokinin, tryptophan)
- Correction of metabolic acidosis. Acidosis can:
  - activate the ubiquitin-proteosome pathway & increase protein degradation
  - suppresses endogenous GH secretion
- Minimises inflammatory cytokine release
- ? Removal of somatomedin and gonadotropin inhibitors by HDF
- ? reverses rhGH resistance

Schaefer et al, NDT 2010

Reduced systemic inflammation in HDF



Fischer et al;
Kidney Int Reports 2021

Improved anaemia control on HDF

Hemoglobin values and need for transfusions

	HD (12 months)	HDF (12 months)
Hb g/dl	7.4	8.3
Number of transfusions for the whole group	32 (mean 5)	12 (mean 2)
Membrane	Cuprophane	Polyacrylonitrile
Duration (sessions)	3x5 h	3x3 h

Fischbach et al; Ped Nephrol 1984

SWITCH study

Hypothesıs

HDF is associated with less inflammation and endothelial dysfunction compared to HD

To compare:

Hıgh flux HD vs HDF

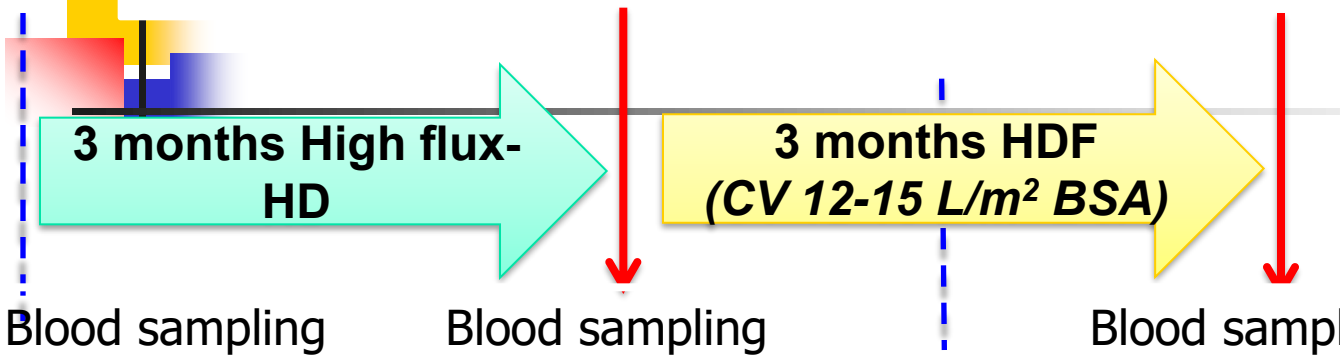
3-months on each modality

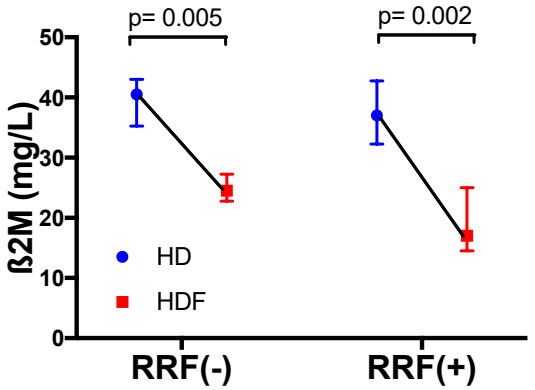
Recruitment:

Istanbul (n = 9), London (n = 13)

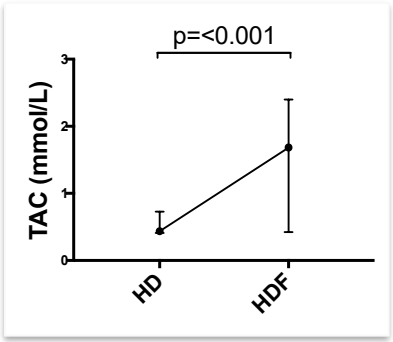
Agbas and Shroff; Plos One 2018

HD → HDF - SWITCH STUDY

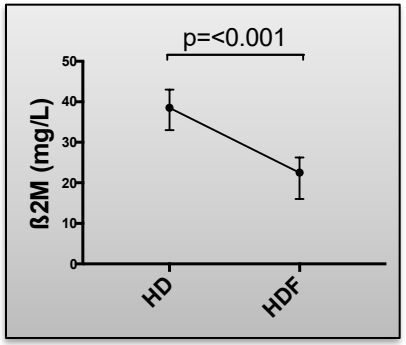


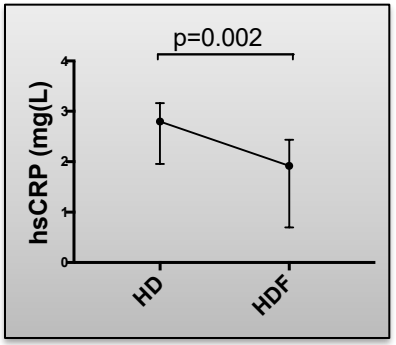


✓**Higher** antioxidant capacity

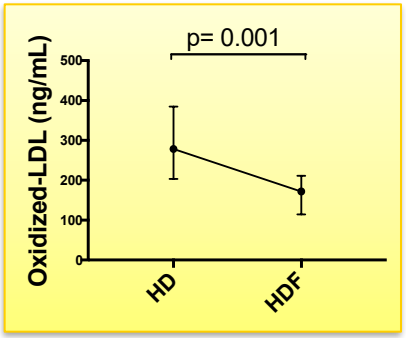


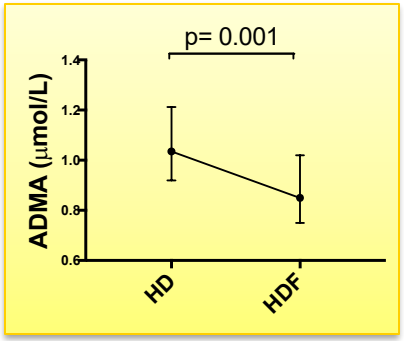
✓**Lower** inflammation (**ß2M, hsCRP**)

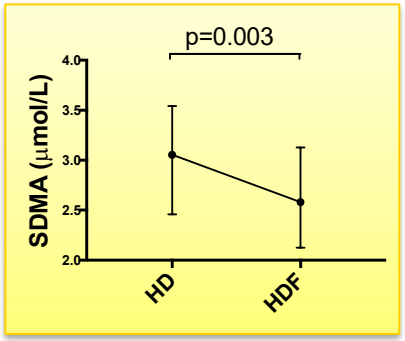


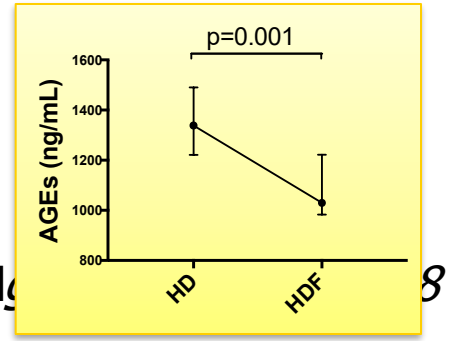


✓ **Lower** endothelial dysfunction markers (**ox-LDL,ADMA, SDMA, AGEs)**



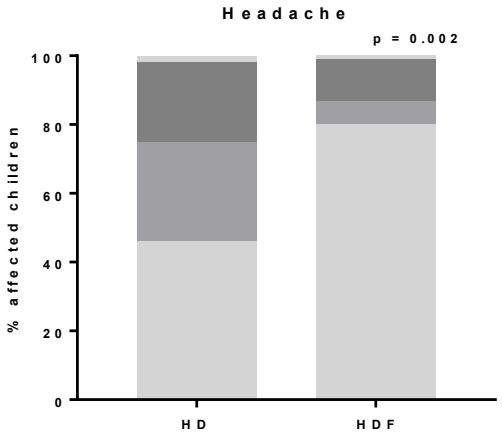


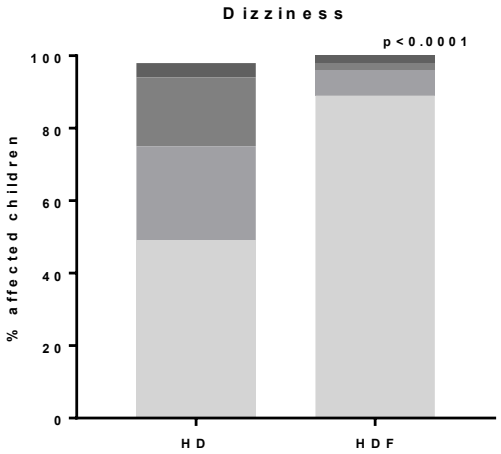


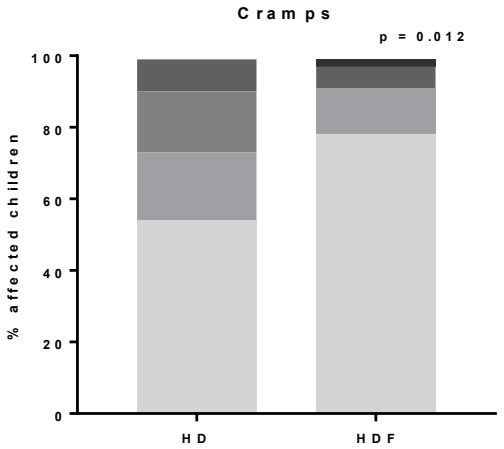


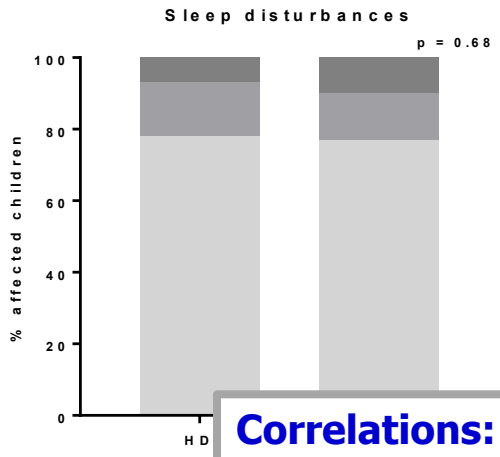
Patient related outcomes

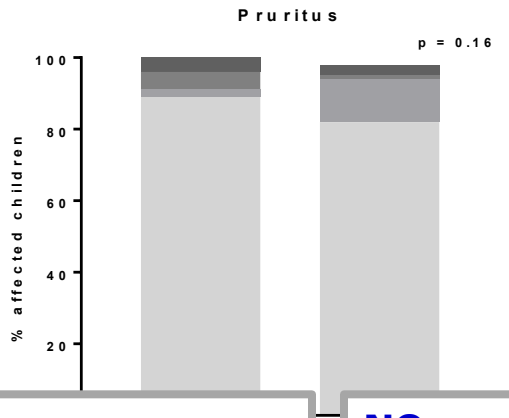
Self-reporting on 6-monthly questionnaires











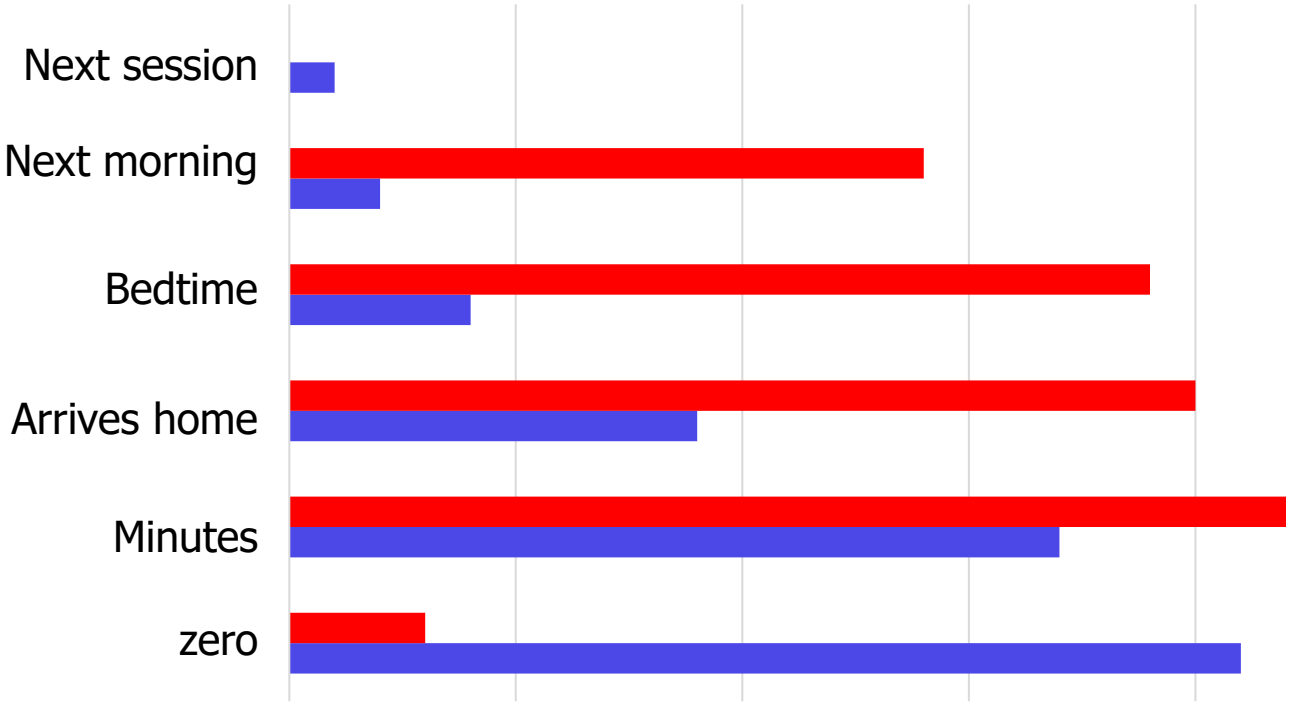
Correlations:

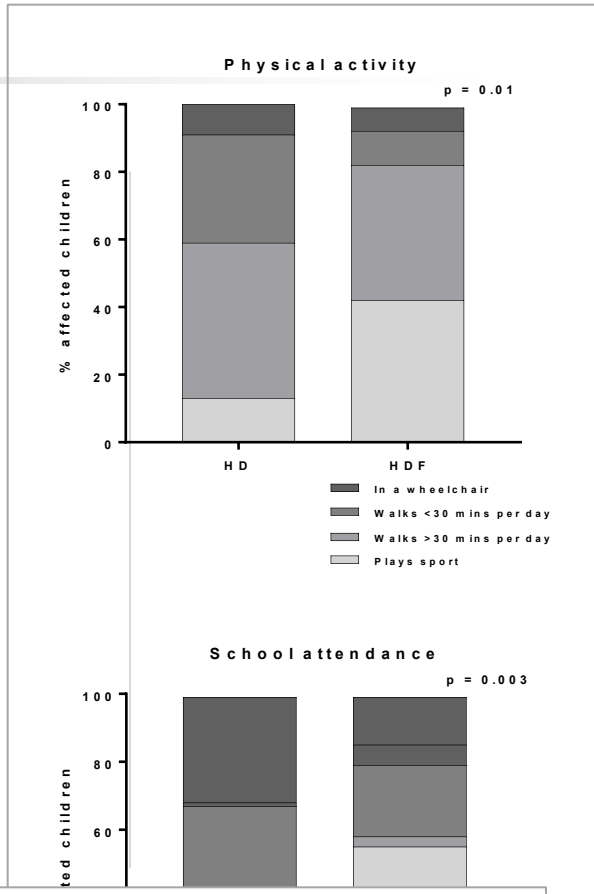
- ultrafiltration volume per session
- hemoglobin

NO correlations with:

- 24-hr ABPM / systolic or diastolic BP
- Residual renal function

PROMs – post-dialysis recovery time



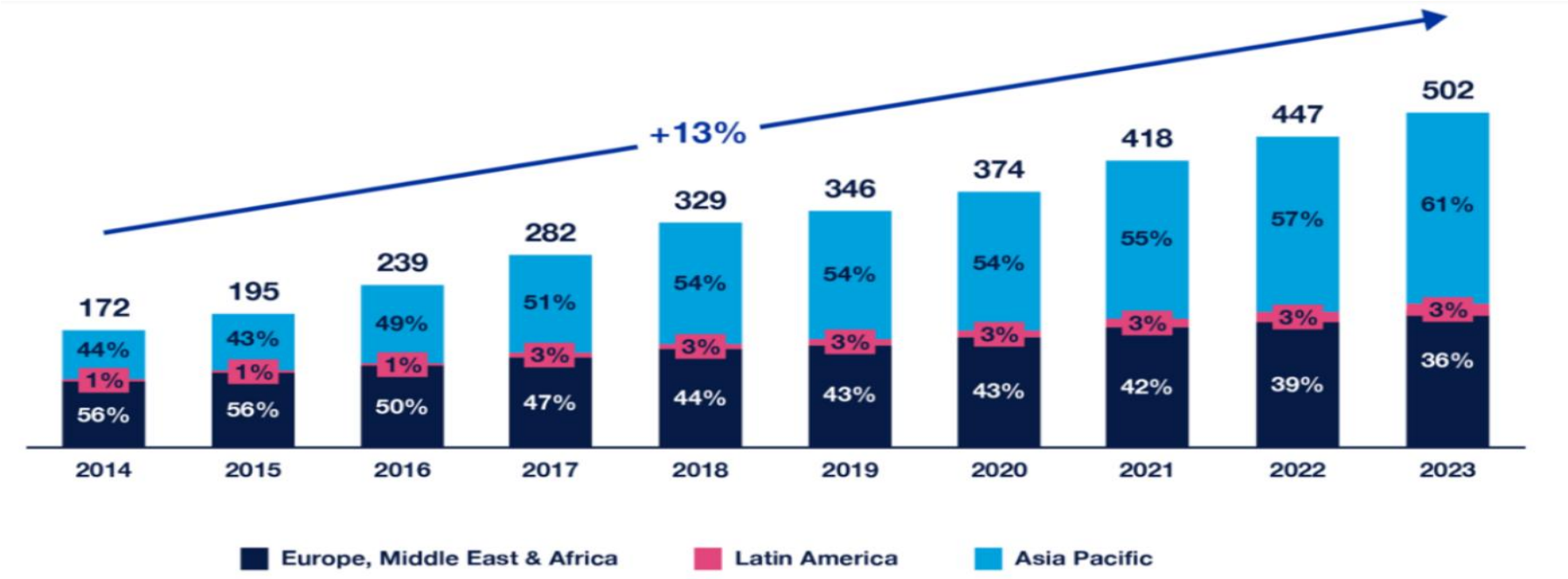


Improved outcomes on HDF:

- fewer symptomatic intradialytic hypotensive episodes and muscle cramps (FRENCHIE, in elderly dialysis patients)
- lower risk of stroke (ESHOL) attributed to improved intra-dialytic hemodynamic stability
- SONG-HD - fatigue is a highly prioritized outcomes for dialysis patients

HDF Uptake globally

- 13%/yr average increase in HDF worldwide (2014 to 2023)
- Rapid increase in Asia region (Japan & China)



https://freseniusmedicalcare.com/en/media/multimedia/publications/amr/2024-amr-hemodiafiltration/

Adopting HDF in low-resource settings

- **Thailand** - recommend HDF for:
  - Dialysis related amyloidosis
  - Cardiovascular instability & intra-dialytic hypotension
  - Unexplained anaemia & ESA hyporesponsiveness
  - Unexplained malnutrition with high β2 microglobulin levels (> 27.5 µg/L)

- **Brazil** - recommend HDF for:
  - Growing children with kidney transplant restrictions
  - Cardiovascular disease and complications of β2 microglobulin

- **China** - the government covers the cost of 10 HD + 1 HDF session per month, but prevalence of HDF use is increasing.

Dialyzer re-use did not impact clearance

Jung et al, Am J Kidney Dis. 2020

Conclusions (for HDF)

- In children, HDF halts the progression of vascular changes compared to conventional HD
- HDF is associated with an early and sustained improvement in:
  - fluid status and BP
  - Bone health and growth
  - Reduced inflammation and oxidative stress
  - Improved patient outcomes
- Frequent / daily HD improves growth and QoL

HDF for all in-centre patients?

- We need a randomised trial….. but until this is done, HDF could be used in children based on:
  - Safe and well tolerated
  - Biological plausibility
  - Data from adult RCTs
  - 3H study in children

- Early benefits of HDF – use even if short period on dialysis anticipated
- HDF is beneficial even in those with residual renal function

Thank you!

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