The 20th Budapest Nephrology School

August, 30,2013

Online Haemodiafiltration

is it really the Technique of the Future?

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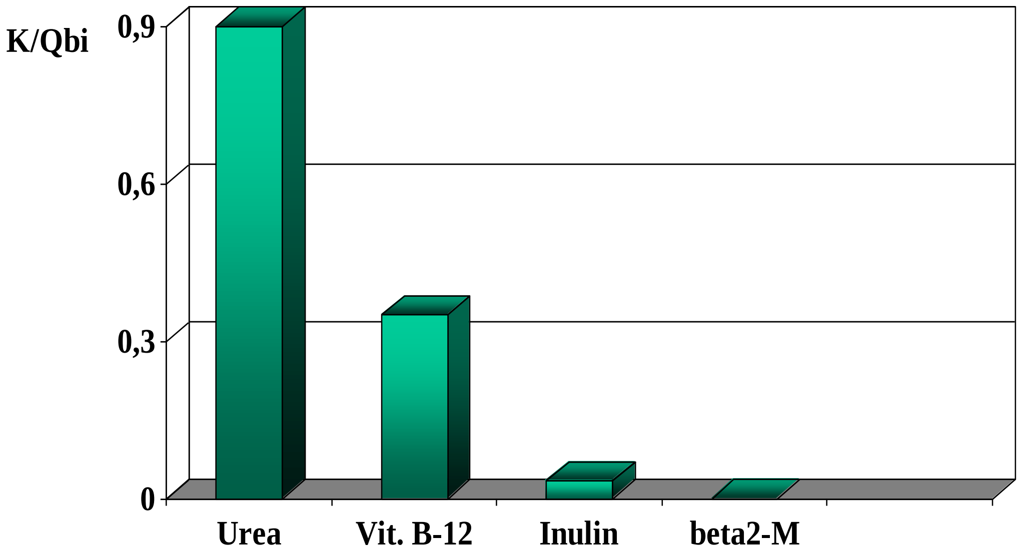
Standard Haemodialysis

3 times weekly, 4 h per session

low flux membranes

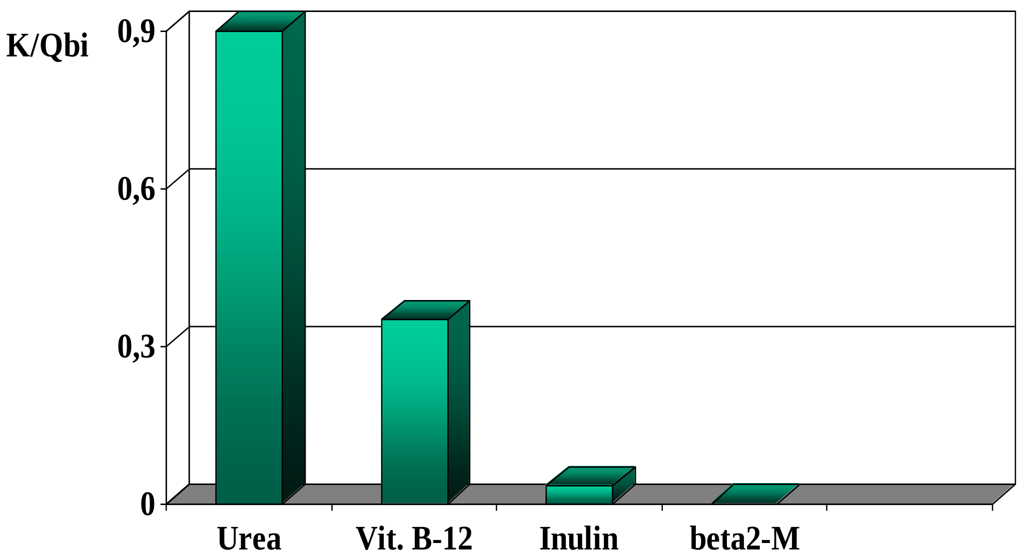
.... it is far from ideal in that it supports life but it fails to restore the patient to full functional normality and longevity

Standard Haemodialysis
"in vitro clearances"



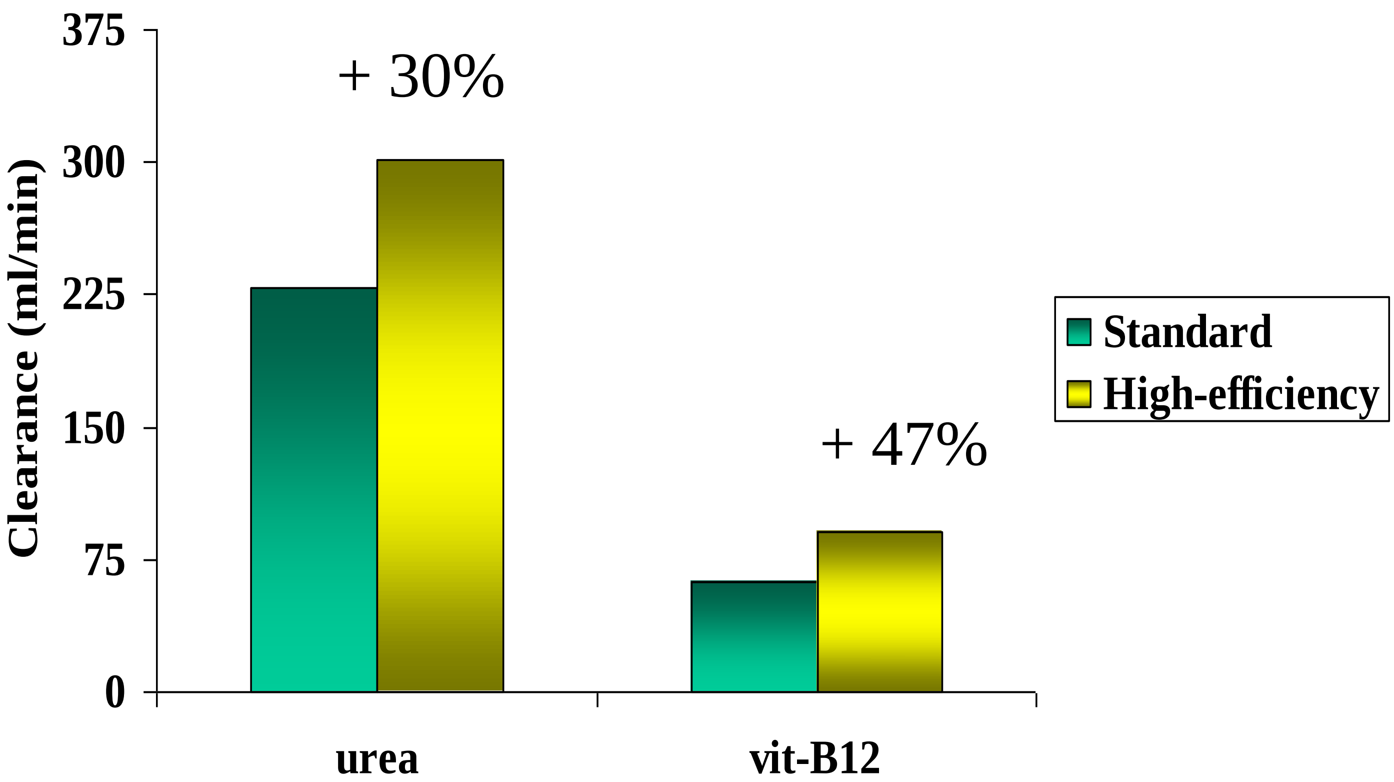
The low effectiveness of conventional HD is mainly referred to the hypothesis that high morbidity and mortality rates are associated with inadequate removal of "middle molecules"

Standard Haemodialysis "in vitro clearances"

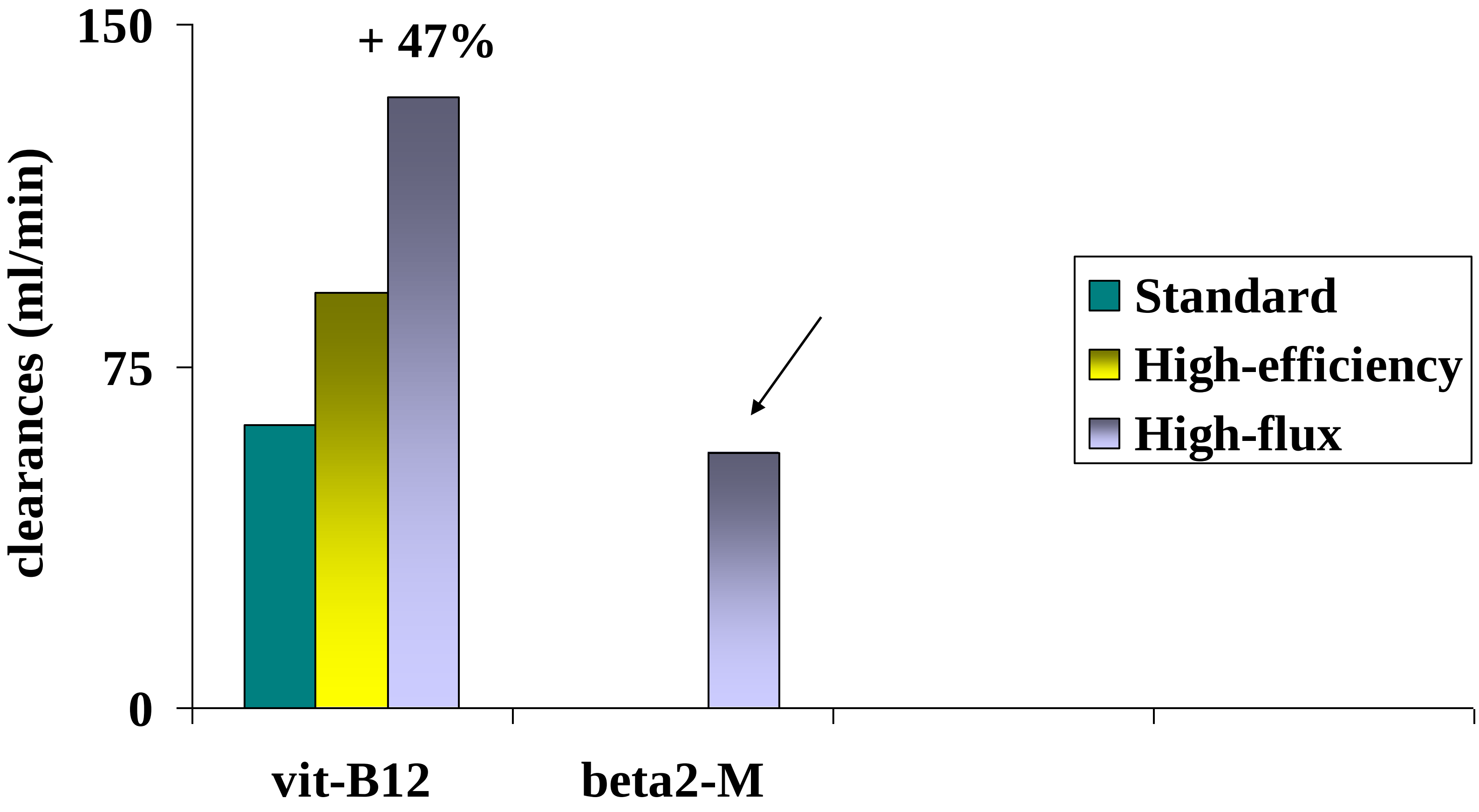


The low effectiveness of conventional HD is mainly referred to the hypothesis that high morbidity and mortality rates are associated with inadequate removal of "middle molecules"

High-efficiency vs Standard Haemodialysis



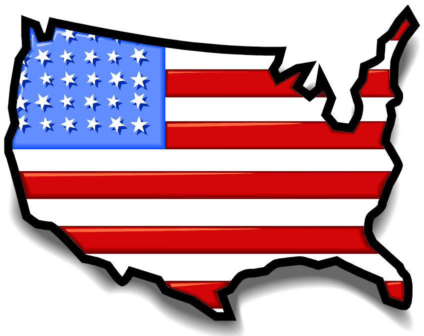
High-Flux vs High-Efficiency and Standard Haemodialysis



Early observational studies on the effect of high-flux HD on risk of mortality

	Design	High-flux or convective treatment	Sample size	% reduction in risk of death with high-flux	P value
Hornberger et al. 1992	Retrospective	HF-HD	253	76	<0.001
Koda et al. 1997	Retrospective	HF-HD	819	39	<0.05
Locatelli et al. 1999	Historical, prospective	HDF or HF	6,444	10	NS
Leypold et al. 1999	Retrospective	HF-HD	1,771	5	<0.0001
Woods et al. 1999	Retrospective	HF-HD	715	42	<0.01
Port et al. 2001	Prospective, observational	HF-HD	12,791	19	0.04

adapted from Pozzoni and Locatelli J Nephrol 17: S87-S95, 2004

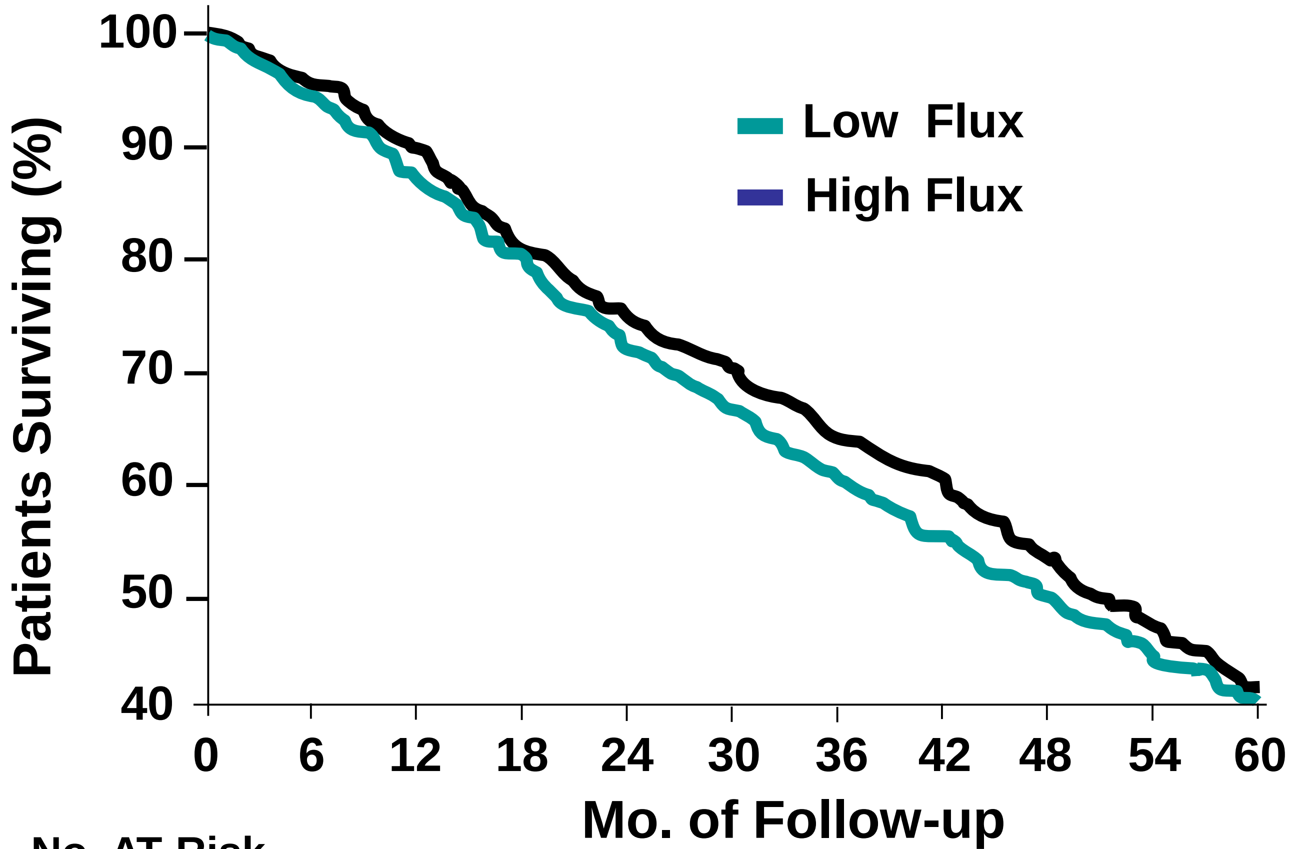


The HEMO Study in the US

The MPO Study in Europe

HEMO Study

Effect of Membrane Flux on All-cause Mortality

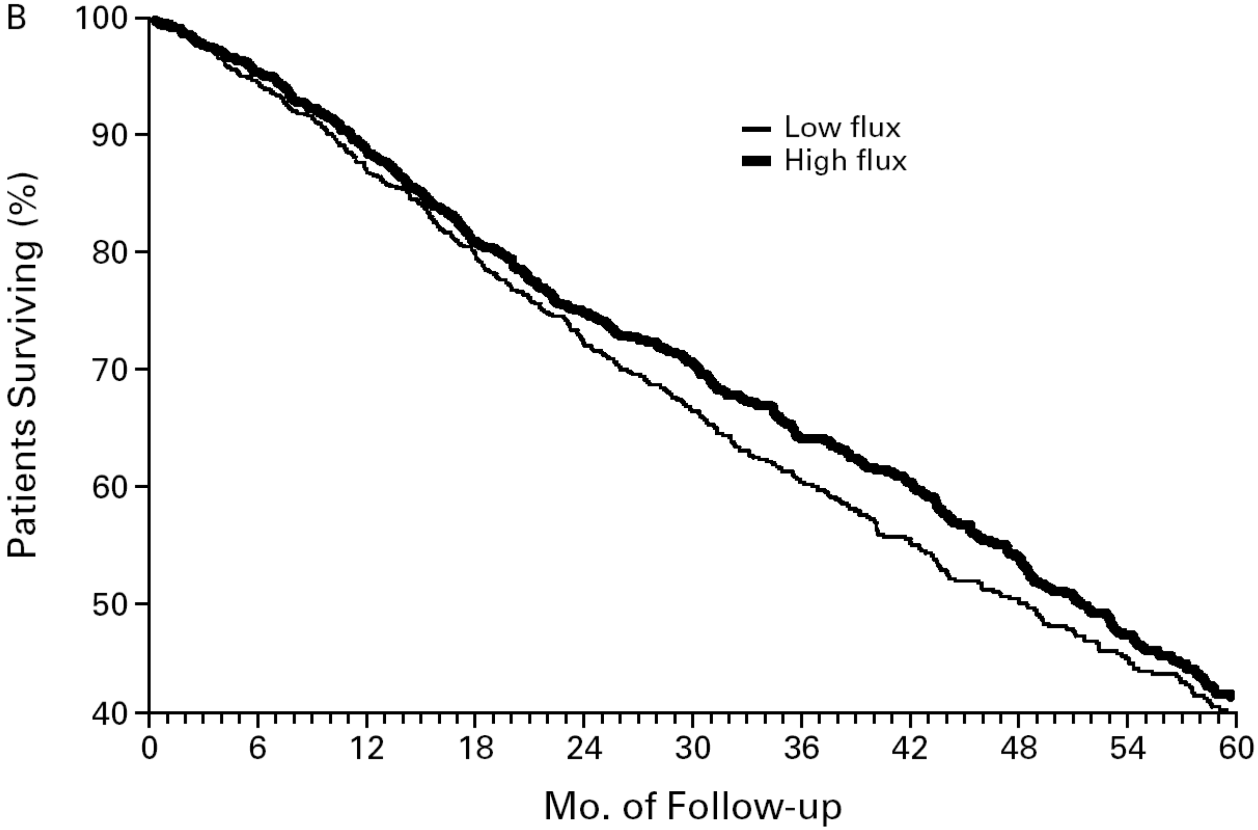


No. AT Risk

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 et al. New Eng J Med 347: 2010-2019, 2002

After adjustment for the base-line factors, mortality in the high-flux group was 8 percent lower (P=0.23) than that in the low-flux group



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High flux	860	761	635	537	473	399	335	269	212	160

Eknoyan G et al N Engl J Med Vol 347, 2002

CLINICAL RESEARCH www.jasn.org

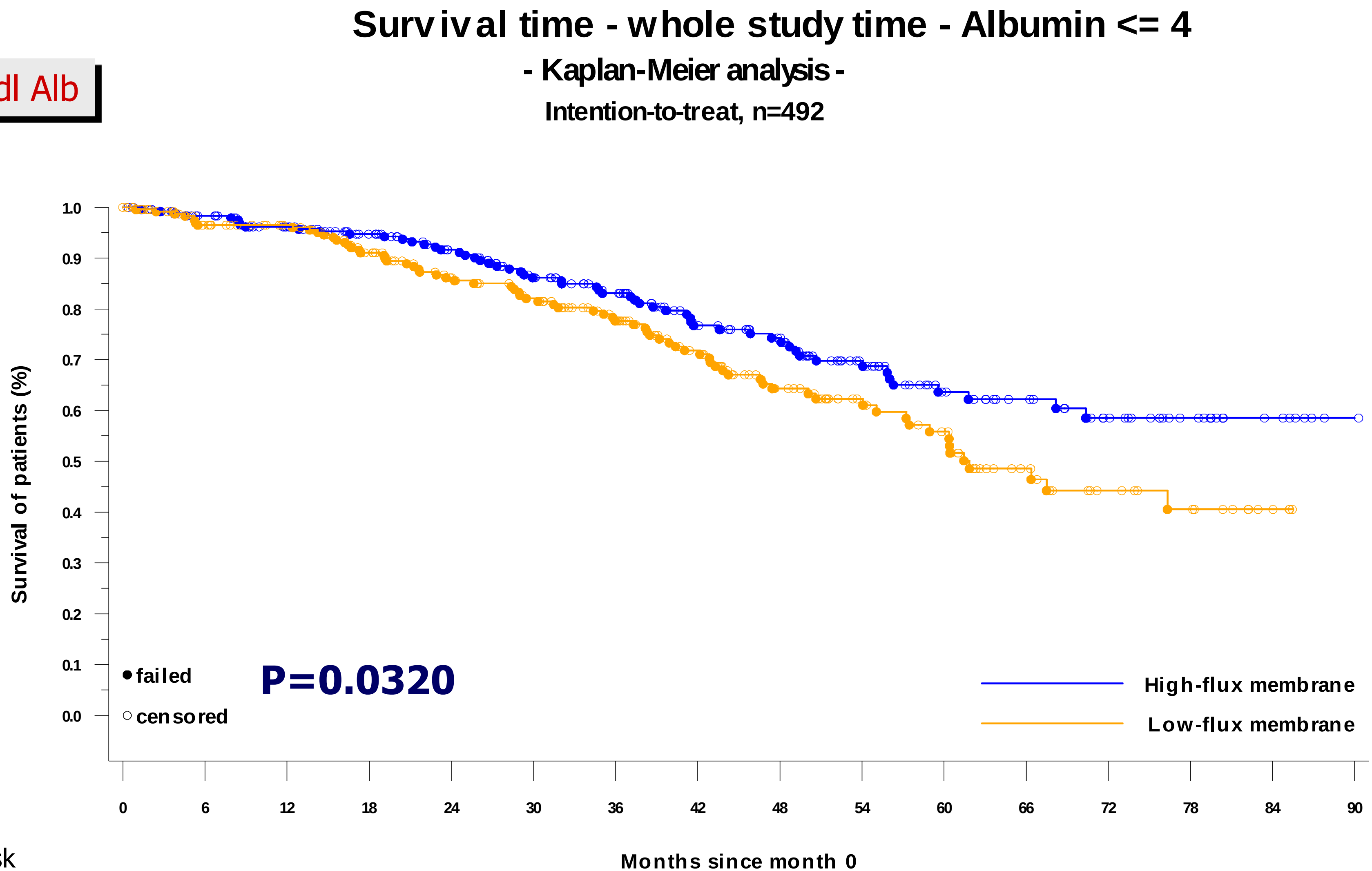
Effect of Membrane Permeability on Survival of Hemodialysis Patients

Francesco Locatelli,* Alejandro Martin-Malo,† Thierry Hannedouche,‡ Alfredo Loureiro,§ Menelaos Papadimitriou,|| Volker Wizemann,¶ Stefan H. Jacobson,** Stanislaw Czekalski,†† Claudio Ronco,‡‡ and Raymond Vanholder,§§
for the Membrane Permeability Outcome (MPO) Study Group

J Am Soc Neprol 20: 645 – 654, 2009

MPO : Kaplan-Meier Survival Analysis

≤ 4g/dl Alb

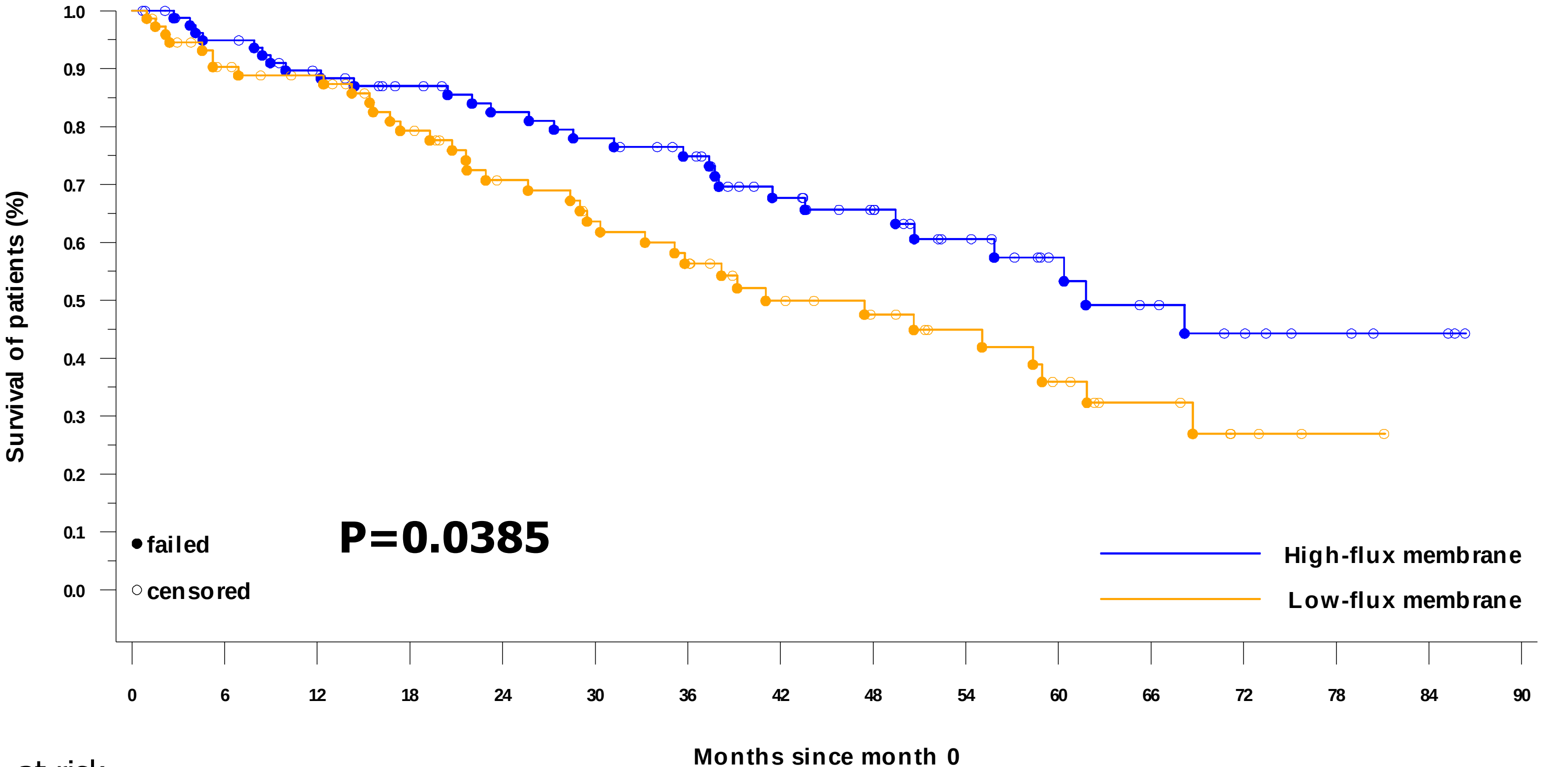


No. at risk								
High-flux	250	212	173	134	85	44	26	7
Low-flux	243	202	152	117	67	41	15	3

Locatelli F et al. J Am Soc Nephrol. 2009 Mar; 20 (3): 645-54

MPO : Kaplan-Meier Survival Analysis
Subgroup Analysis – Diabetics*

Fi *Pts. with both serum albumin ≤ 4 and > 4 g/dl albumin



No. at risk								
High-flux	83	67	55	46	27	14	7	3
Low-flux	74	59	40	29	19	11	3	0

Locatelli F et al. J Am Soc Nephrol. 2009 Mar; 20 (3): 645-54

Randomised studies on the effect of High-Flux Haemodialysis on mortality risk

	Design	Treatment (patients)	Sample size	% relative risk reduction	P value
Locatelli et al. 1996	**Randomised, prospective**	Cuprophan-HD (132) LF-HD (147) HF-HD (51) HDF (50)	**380**		**NS**
Eknoyan et al. 2002	**Randomised, prospective**	HF-HD (921) LF-HD (925)	**1,846**	**8**	**NS**
Locatelli et al. 2009	**Randomised, prospective**	**Albumin ≤ 4 g/dl** HF-HD (279) LF-HD (283)	**562**	**37**	**0.032**
	Randomised, prospective	**Albumin > 4 g/dl** HF-HD (84) LF-HD (92)	**176**		**NS**
	Randomised, prospective, post-hoc analysis	**Diabetics** HF-HD (83) LF-HD (74)	**157**	**38**	**0.039**

LF-HD: low-flux haemodialysis; HF-HD: high-flux haemodialysis; HDF:haemodialfiltration

Locatelli F et al. Contrib Nephrol 2011; 168: 5-18

Editorial Comment to MPO Study:

Locatelli F et al. J Am Soc Neprol 20: 645 – 654, 2009

The results of the MPO Study can be interpreted as a supporting rationale for the use of high-flux dialysis membranes if they are financially affordable.

A K Cheung T Green J Am Soc Nephrol 20: 462-464, 2009

ERBP

European Renal Best Practice

High-flux or low-flux dialysis: a position statement following publication of the MPO study

- MPO study provides sufficient evidence to upgrade the strength of guideline 2.1 to a level 1A (strong recommendation, based on high-quality evidence): high-flux HD should be used to delay long-term complications of hemodialysis in the case of high-risk patients (comparable to the low-albumin group of the MPO study)

- Because the substantial reduction of an intermediate marker (beta2-microglobulin) in the high-flux group of the MPO study, synthetic high-flux membranes should be recommended even in low-risk patients (level 2b: weak recommendation, low quality evidence)

Tattersal J et al. Nephrol Dial Transplant 2010; 25(4):1230-1232

Quality of dialysis procedure

HDF

- Water quality and distribution system
- Dialysate
- Extracorporeal circuit
- Dialysis dose and frequency
- Membranes and convective treatments
- Online treatments

Observational studies on the effect of Haemofiltration and/or Haemodiafiltration on mortality risk

	Design	Treatments (patients)	Sample size	Relative risk reduction	P value
Locatelli et al. 1999	Historical, prospective	HDF or Haemofiltration (188) HD (6,256)	6,444	10%	NS
Canaud et al. 2006	Historical, prospective	LF-HD (1,366) HF-HD (546) Low-efficiency HDF (156) High-efficiency HDF (97)	2,165	35% (High-efficiency HDF vs LF-HD)	0.01
Panichi et al. 2008	Prospective	Bicarbonate-HD* (424) HDF (204) On-line HDF (129)	757	22% (HDF and On-line HDF vs Bicarbonate-HD)	0.01

LF-HD: low-flux haemodialysis; HF-HD: high-flux haemodialysis; HDF: haemodiafiltration; * Including LF-HD (403 patients) and HF-HD (21 patients)

Locatelli F et al. Contrib Nephrol. 2011

Randomised studies on the effect of Hemofiltration and/or Hemodiafiltration on mortality risk

	Design	Treatments (patients)	Sample size	Relative risk reduction	P value
Locatelli et al. 1996	Randomised, prospective	Cuprophan-HD (132) LF-HD (147) HF-HD (51) HDF (50)	380		NS
Wizemann et al. 2000	Randomised, prospective	HDF (23) LF-HD (21)	44		NS
Santoro et al. 2008	Randomised, prospective	On-line Hemofiltration (32) LF-HD (32)	64	55%	0.05
Locatelli et al. 2010	Randomised, prospective	LF-HD (70) On-line Hemofiltration (36) On-line HDF (40)	146		NS

LF-HD: low-flux hemodialysis; HF-HD: high-flux hemodialysis; HDF: hemodiafiltration

Locatelli F et al. Contrib Nephrol. 2011

Potential strategies to improve hemodialysis efficiency

Strategies	Variables			
	> Duration (T)	> Frequency	> TBK (S & M)	< V
Nocturnal HD	Yes	No	Yes	Yes
Daily HD	No	Yes	Yes	Yes
Extended: >6 hrs	Yes	No	Yes	Yes
Hemodiafiltration	Yes / No	Yes / No	Yes (small/middle molecules)	Yes
Hemofiltration	Yes / No	Yes / No	Yes (middle molecules)	Yes

Francesco Locatelli and Bernard Canaud Nephrol.Dial Transpl. 2012

Convective Therapies: Outcomes

- Intradialytic Cardiovascolar Stability
- Beta2 microglobulin
- Phosphataemia
- Anaemia and ESA Dose
- Inflammation

  Mortality

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  Mortality

CLINICAL RESEARCH www.jasn.org

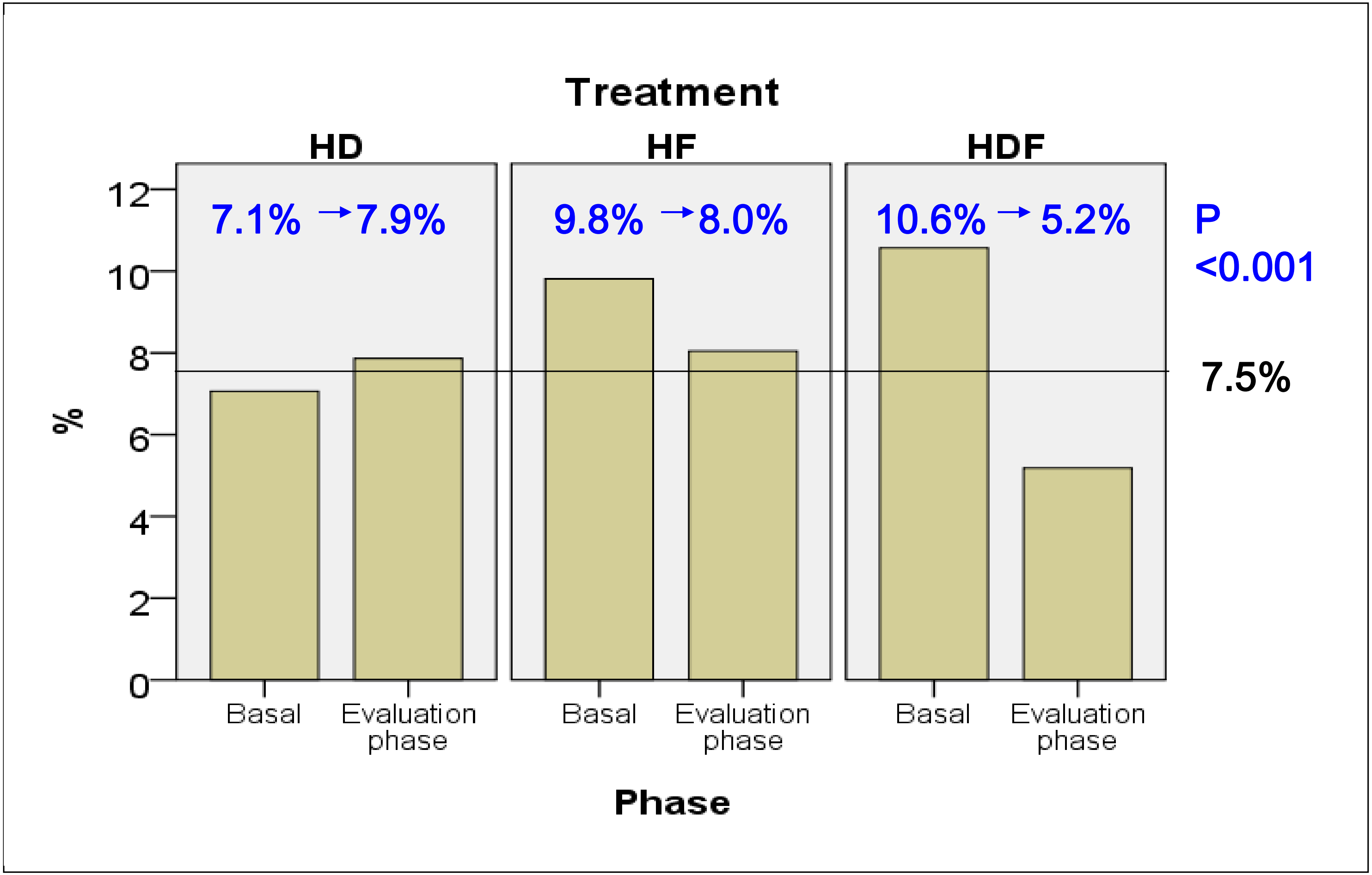
JASN® Journal of the American Society of Nephrology

Hemofiltration and Hemodiafiltration Reduce Intradialytic Hypotension in ESRD

Francesco Locatelli,* Paolo Altieri,† Simeone Andrulli,* Piergiorgio Bolasco,‡ Giovanna Sau,† Luciano A. Pedrini,§ Carlo Basile,‖ Salvatore David,¶ Mariano Feriani,** Giovanni Montagna,†† Biagio Raffaele Di Iorio,‡‡ Bruno Memoli,§§ Raffaella Cravero,‖‖ Giovanni Battaglia,¶¶ and Carmine Zoccali***

J Am Soc Nephrol 2010 21:1798-807

Sessions with intradialytic hypotension (%)



Locatelli et al. J Am Soc Nephrol. 2010; 21(10):1798-807

Intradialytic symptomatic hypotension

Logistic Regression

	B	Sig	ODDS ratio	95% CI for ODDS ratio	
Diabetes	0.517	<0.001	1.68	1.48	1.90
Age (years)	0.024	<0.001	1.02	1.02	1.03
Systolic blood pressure (mmHg)	-0.025	<0.001	0.975	0.972	0.978
Diastolic blood pressure (mmHg)	0.007	0.011	1.01	1.002	1.012
Ischemic cardiopathy	0.493	<0.001	1.64	1.47	1.83
Chronic ischemic arteriopathy	0.430	<0.001	1.54	1.34	1.77
Previous transient ischemic attack	0.715	<0.001	2.04	1.80	2.32
Ultrafiltration rate (hg/hour)	0.130	<0.001	1.14	1.12	1.16
Experimental treatment:		<0.001			
HF	-0.378	**0.011**	**0.69**	0.51	0.92
HDF	0.782	**<0.001**	**0.46**	0.33	0.63

Number needed to treat

	Expected Hypotensions (patient*/year) from run-in phase	RRR (relative risk reduction, %)	ARR (absolute risk reduction, %)	Avoided Hypotensions (patient*/year)	NNT (number needed to treat) dialysis sessions
Dialytic Modality					
Hemofiltration	14.9	18	1.8	**2.74** (156/57)	**57**
Hemodiafiltration	16.1	51	5.4	**8.21** (156/19)	**19**

***Patient performing 3 dialytic treatments/week**

from Locatelli et al. J Am Soc Nephrol. 2010; 21(10):1798-807

Italian Study Conclusions

- **This is the first multicenter randomized controlled trial simultaneously comparing three extracorporeal treatments with different levels of convection and diffusion on intra-dialytic cardiovascular stability of chronic hemodialysis patients**

- **The main finding is the demonstration of a lower frequency of intradialytic symptomatic hypotension in patients treated with pure (HF) or mixed (HDF) convection in comparison with patients treated with a diffusive technique (low flux HD)**

- **This effect was more pronounced in online pre-dilution HDF**

Locatelli et al. J Am Soc Nephrol. 2010; 21(10):1798-807

Tolerance of CKD patients receiving HDF and HF versus HD

F.Locatelli B. Canaud, Nephrol Dial Transplant. 2012 Aug;27(8):3043-8

Author, Year	HDF vs Comp	Type of study	β2-M	Survival	Tolerance
Locatelli F et al, 1996	LF-HD vs cuprophan-HD vs HF-HD vs HDF	RCT	↓ (HF-HD and HDF)	=	=
Wizemann V et al, 2000	HDF vs LFHD	RCT	↓	=	=
Bosch JP et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 45%	↑
Canaud B et al 2006	HDF+/- vs LFHD vs HFHD	Historical prospective cohort	?	↑ 35%	=
Jirka et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 36%	=
Schiffl H et al, 2007	HDF vs HFHD + UPD	RCT	↓	=	=
Vinhas J et al, *2007*	HDF vs HFHD	Prospective controlled study	?	↑ 50%	↑
Panichi V et al. 2008	HDF+/- vs LFHD	Prospective controlled study	↓	↑ 15%	↑
Santoro A et al, 2008	HF vs HFHD	RCT	↓	↑ 18%	↑
Tiranathanagul K 2009	HDF vs HFHD	Prospective controlled study	↓	=	↑
Vilar E et al, 2009	HDF vs HFHD	Historical prospective cohort	↓	↑ 34%	↑
Locatelli F et al, 2010	HDF & HF vs LFHD	RCT	↓	=	↑ ↑

Convective Therapies: Outcomes

- Intradialytic Cardiovascolar Stability
- Beta2 microglobulin
- Phosphataemia
- Anaemia and ESA Dose
- Inflammation

  Mortality

Long-term effects of high-efficiency on-line HDF on uraemic toxicity

Multicentre prospective randomized cross-over study

Laboratory values and dialysis adequacy parameters at the end of the 2 periods

6 months x 2	LF-HD (n=62)	Ol-HDF (n=62)	P-value
eKt/V urea	**1.44±0.26**	**1.60±0.31**	**< 0.0001**
Urea, basal, mg/dL	143 ± 25	133 ± 23	0.004
End session, mg/dL	36 ± 12	29 ± 10	<0.0001
Beta2-m	**33.5±11.8**	**22.2±7.8**	**< 0.0001**
tHcy, μmol/L	18.7 ± 8.2	15.4 ± 5.0	0.003*
ADMA, μmol/L	0.97 ± 0.40	0.84 ± 0.37	0.2
P	**5.0±1.4**	**4.6±1.3**	**0.008**
iPTH	**228±177**	**203±154**	**0.03**
Triglycerides, mg/dL	167 ± 87	148 ± 77	0.008*
Total cholesterol, mg/dL	175 ± 45	176 ± 45	0.9
Albumin	**4041±391**	**3919±393**	**0.004**
Albumin, g/dL	4041 ± 391	3919 ± 393	0.004*
CRP	**6.65±6.07**	**5.49±5.46**	**0.03**
Potassium, mmol/L	5.2 ± 0.6	5.2 ± 0.7	0.8
Bicarbonate, mmol/L	21.8 ± 2.1	21.7 ± 1.9	0.6

Pedrini LA et al. Nephrol Dial Transplant. 2011 Apr;26(4):1445-6

β2-M of CKD patients receiving HDF and HF versus HD

F.Locatelli B. Canaud, Nephrol Dial Transplant. 2012 Aug;27(8):3043-8

Author, Year	HDF vs Comp	Type of study	β2-M	Survival	Tolerance
Locatelli F et al, 1996	LF-HD vs cuprophan-HD vs HF-HD vs HDF	RCT	↓ (HF-HD and HDF)	=	=
Wizemann V et al, 2000	HDF vs LFHD	RCT	↓	=	=
Bosch JP et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 45%	↑
Canaud B et al 2006	HDF+/- vs LFHD vs HFHD	Historical prospective cohort	?	↑ 35%	=
Jirka et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 36%	=
Schiffl H et al, 2007	HDF vs HFHD + UPD	RCT	↓	=	=
Vinhas J et al, *2007*	HDF vs HFHD	Prospective controlled study	?	↑ 50%	↑
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Tiranathanagul K 2009	HDF vs HFHD	Prospective controlled study	↓	=	↑
Vilar E et al, 2009	HDF vs HFHD	Historical prospective cohort	↓	↑ 34%	↑
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6 months x 2	LF-HD (n=62)	Ol-HDF (n=62)	P-value
eKt/V urea	**1.44±0.26**	**1.60±0.31**	**< 0.0001**
End session, mg/dL	36 ± 12	29 ± 10	<0.0001
Creatinine, mg/dL	9.8 ± 2.2	9.1 ± 2.2	<0.0001
Beta2-m	**33.5±11.8**	**22.2±7.8**	**< 0.0001**
ADMA, μmol/L	0.97 ± 0.40	0.84 ± 0.37	0.2
Calcium, mg/dL	9.6 ± 0.8	9.7 ± 0.7	0.3
P	**5.0±1.4**	**4.6±1.3**	**0.008**
Ca × P product	47.6 ± 15.1	44.4 ± 13.0	0.05
iPTH	**228±177**	**203±154**	**0.03**
Total cholesterol, mg/dL	175 ± 45	176 ± 45	0.9
HDL, mg/dL	44.7 ± 12.4	49.2 ± 12.7	<0.0001*
Albumin	**4041±391**	**3919±393**	**0.004**
CRP, mg/L	6.65 ± 6.07	5.49 ± 5.46	0.03*
CRP	**6.65±6.07**	**5.49±5.46**	**0.03**
Potassium, mmol/L	5.2 ± 0.6	5.2 ± 0.7	0.8
Bicarbonate, mmol/L	21.8 ± 2.1	21.7 ± 1.9	0.6

Pedrini LA et al. Nephrol Dial Transplant. 2011 Apr;26(4):1445-6

Long-term effects of high-efficiency on-line HDF on uraemic toxicity

Multicentre prospective randomized cross-over study

Phosphate binders and 1-25 OH Vit D

	Low Flux-HD	On line-HDF	P-value
Ca (acetate/carbonate), g/day	$n = 35$	$n = 34$	
	2.54 ± 1.36	2.67 ± 1.45	0.6
Al hydroxide, g/day	$n = 16$	$n = 16$	
	2.98 ± 1.99	3.10 ± 1.97	0.9
Sevelamer, mg/day	**5120±2001**	**3947±2016**	**0.04**
1-25 OH cholecalciferol, μg/week	$n = 38$	$n = 38$	
	2.25 ± 1.64	2.38 ± 1.83	0.8

Pedrini LA et al. Nephrol Dial Transplant. 2011 Apr;26(4):1445-6

Effect of post-dilutional on-line HDF on serum calcium, phosphate and PTH in uraemic patients

Prospective trial

30 pts → Lf-HD → Ol-HDF

	Baseline	6 Months	12 Months	Period 1 P:Baseline versus 6 months	Period 2 P:Baseline versus 12 months
Study group: *n*=30					
Calcium (mg/dl)	8.9 ± 0.8	9.1 ± 0.7	8.9 ± 0.6	NS	NS
Serum phosphate (mg/dL)	5.3 ± 0.7	5.1 ± 1.0	4.0 ± 0.7	NS	<0.0001
PTHint (ng/mL)	319 ± 163	307 ± 167	194± 98	NS	<0.0001
Controls: *n*=35 (Lf-HD)					
Calcium (mg/dl)	9.1 ± 0.6	9.2 ± 0.6	9.2 ± 0.5	NS	NS
Serum phosphate (mg/dL)	5.0 ± 0.5	5.1 ± 0.4	5.2 ± 0.5	NS	NS
PTHint (ng/mL)	276 ± 182	242 ± 149	294 ± 189	NS	NS

Movilli E et al. Nephrol Dial Transplant. 2011 Dec;26(12):4032-7

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Anaemia and dialysis procedure

HDF

- Water quality and distribution system
- Dialysate
- Extracorporeal circuit
- Dialysis dose and frequency
- Membranes and convective treatments
- Online treatments

Observational studies on the effect of Convective Treatments on Anaemia correction

	Design	Treatments	Sample size	Haemoglobin Haematocrit	Epo dose
Kawano et al. 1994	Prospective	LF-HD to HF-HD	10	NA	↓
Villaverde et al. 1999	Prospective	Cellulose-HD to polysulphone-HD	31	=	↓
Maduell et al. 1999	Prospective	Conventional HDF to On-line HDF	37		↓
Lin et al. 2002	Prospective	Conventional HD to On-line HDF	92		↓
Bonforte et al. 2002	Prospective	Cuprophan HD to On-line HDF	32	*	↓#
Yokoyama et al. 2008	Historical, prospective	HF-HD vs LF-HD And Cellulose vs Biocompatible	1,207	=	=

LF-HD: low-flux haemodialysis; HF-HD: high-flux haemodialysis; HDF: haemodiafiltration; NA: not available;

* Only in patients not receiving Epo therapy; # Only in patients receiving Epo therapy

Locatelli F et al. Contrib Nephrol 2011; 168: 162-72

Randomised studies on the effect of Convective Treatments on Anaemia correction

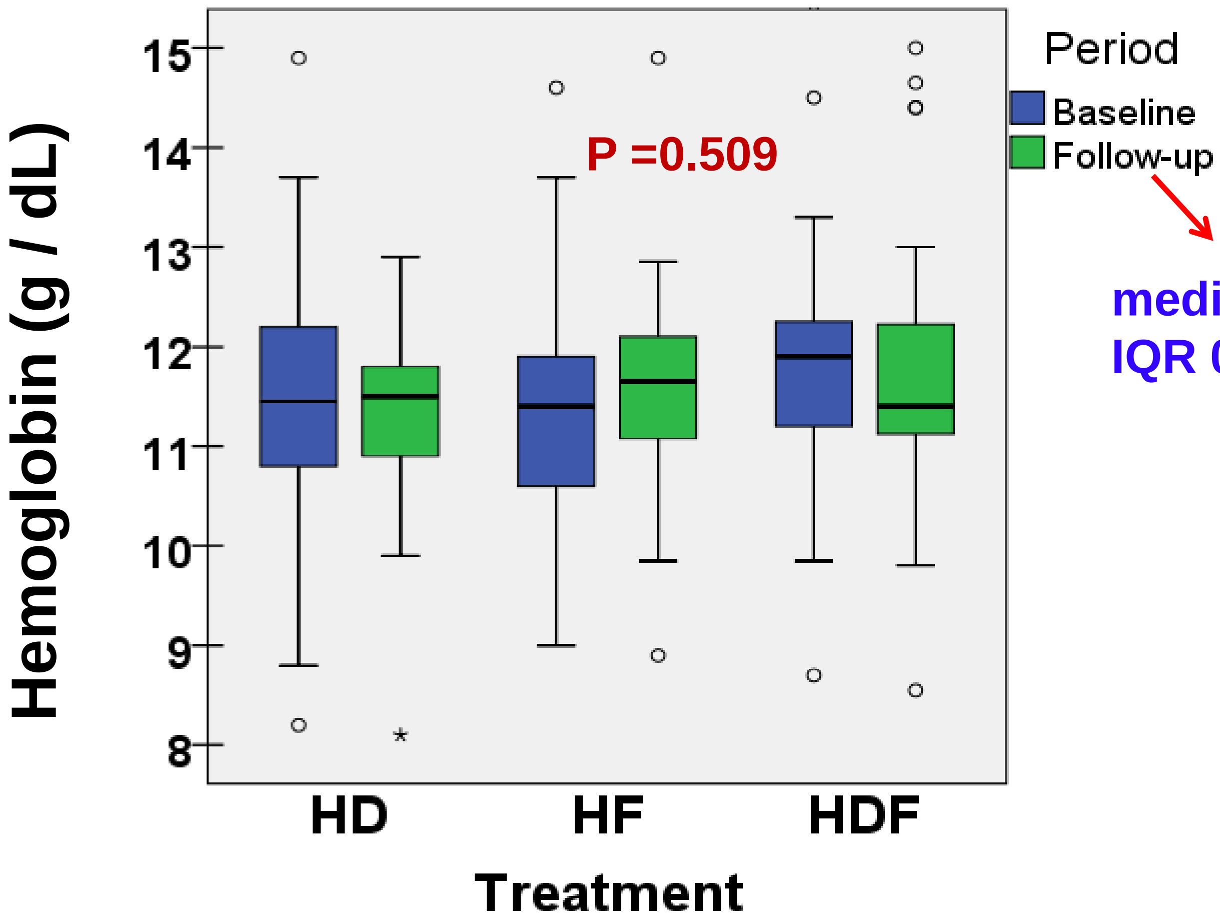
	Analysis	Treatments (patients)	Sample size	Haemoglobin Haematocrit	Epo dose
Locatelli et al. 1996	Secondary	Cuprophan-HD (132) LF – Ps HD (147) HF – Ps HD (51) HDF Ps (50)	380	(HF-HD vs LF-HD)	NA
Locatelli et al. 2000	Primary	HF-PMMA HD (42) Cellulose-HD (42)	84	=	=
Ward et al. 2000	Primary	On-line HDF vs HF-HD	44	=	
Wizemann et al. 2000	Primary	LF-HD (21) On-line HDF (23)	44	=	=
Ayli et al. 2004	Primary	HF-HD vs LF-HD	48		↓
Vaslaki et al. 2006	Primary (cross-over)	On-line HDF vs HD	70		↓
Locatelli et al. 2009	Secondary	LF–HD (375) HF–HD (363)	738	=	=
Andrulli.. and Locatelli 2010	Primary	HF-HD+**Vit. E coated membranes** vs HF-HD	20	=	=
	Secondary			=	↓

LF-HD: low-flux haemodialysis; HF-HD: high-flux haemodialysis; HDF: haemodiafiltration; NA: not available; Ps: Polysulphone; BK-F polymethylmetacrylate

Locatelli F et al. Contrib Nephrol 2011; 168: 162-72

Baseline and follow-up haemoglobin values in online HF and online HDF vs low-flux HD

A total of 146 patients were centrally randomized to HD (70 patients), HF (36 patients) or HDF (40 patients)



median of 1.5 years
IQR 0.8-2.2

Locatelli F. et al - Nephrol Dial Transplant 2012 Sep 27 (9): 3594-600

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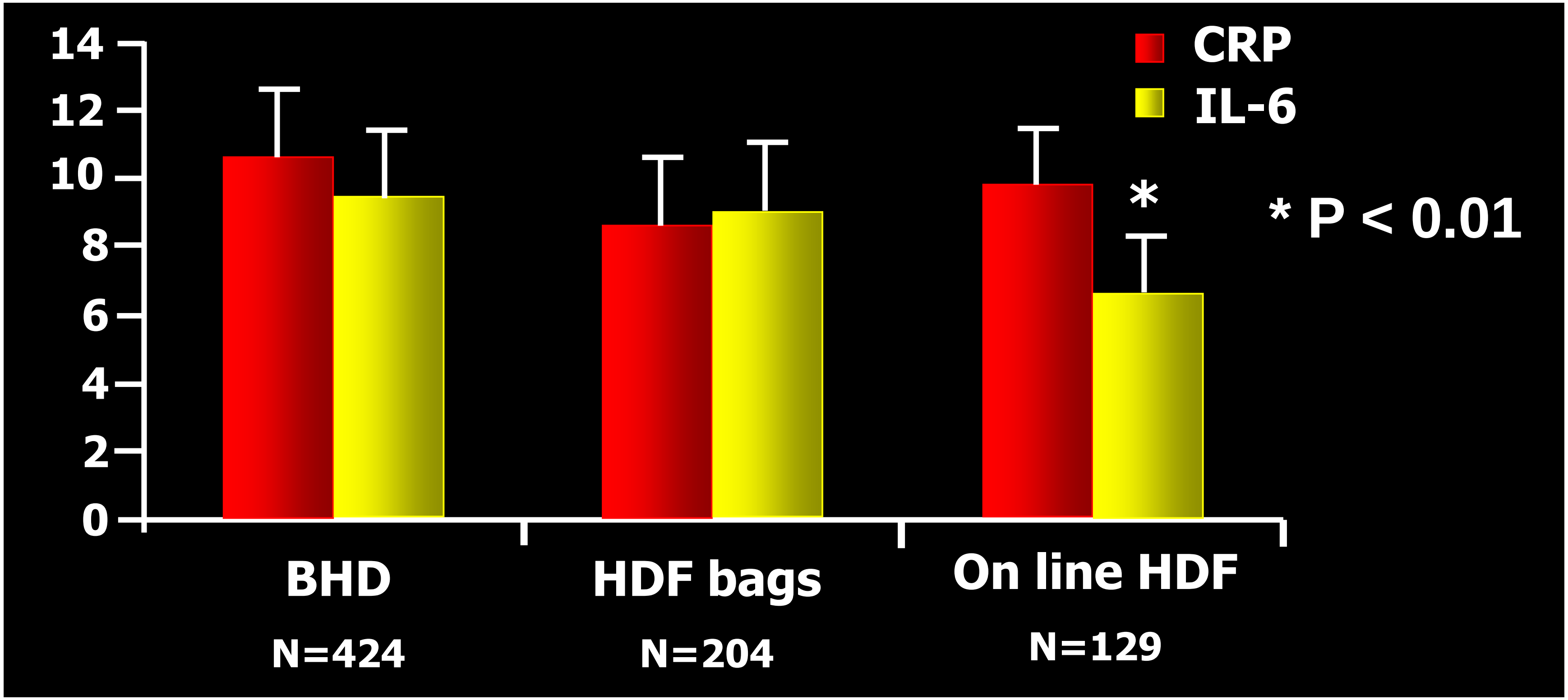
  Mortality

Chronic inflammation and mortality in HD: effect of different renal replacement therapies. Results from the RISCAVID study

Prospective observational trial

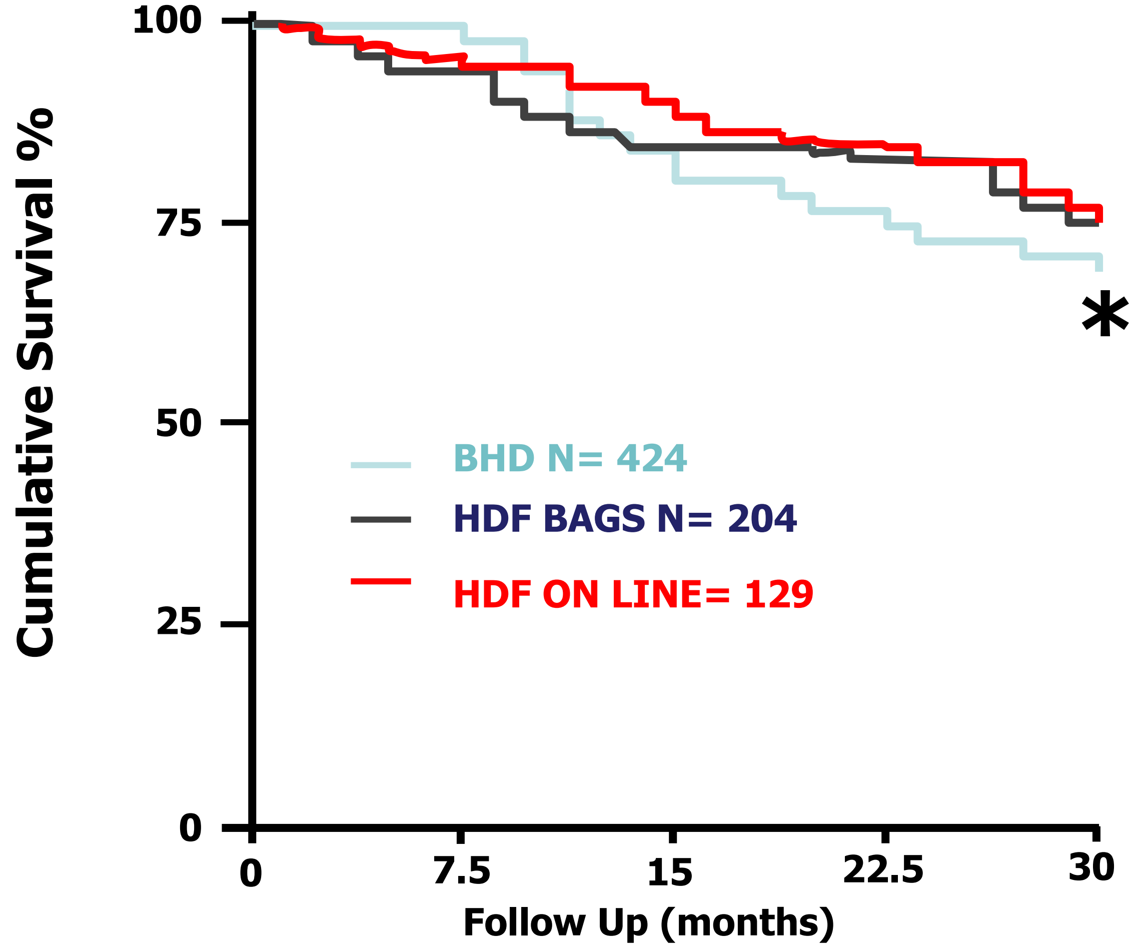
Inflammatory markers and dialytic techniques



Panichi V et al. Nephrol Dial Transplant 2008; 23: 2337-2343

Chronic inflammation and mortality in HD: effect of different renal replacement therapies. Results from the RISCAVID study

Prospective observational trial



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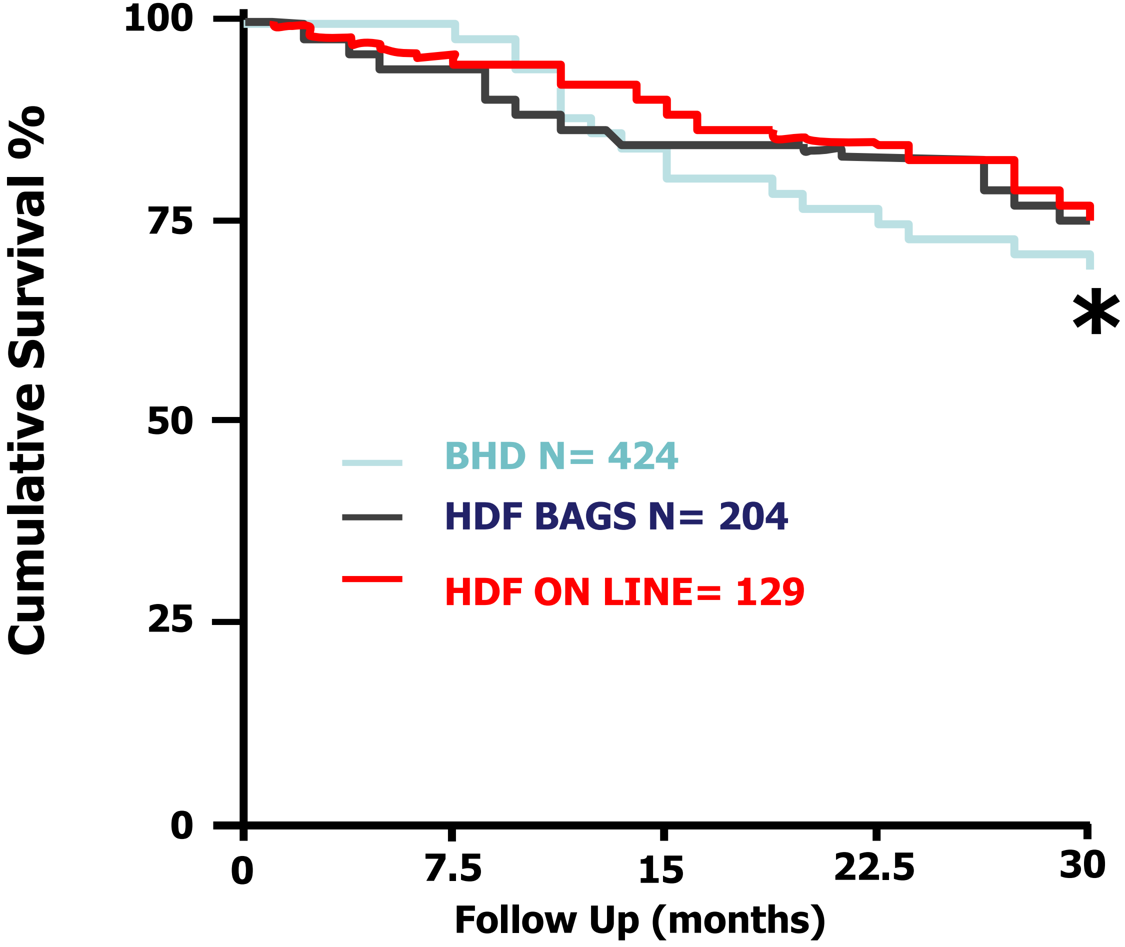

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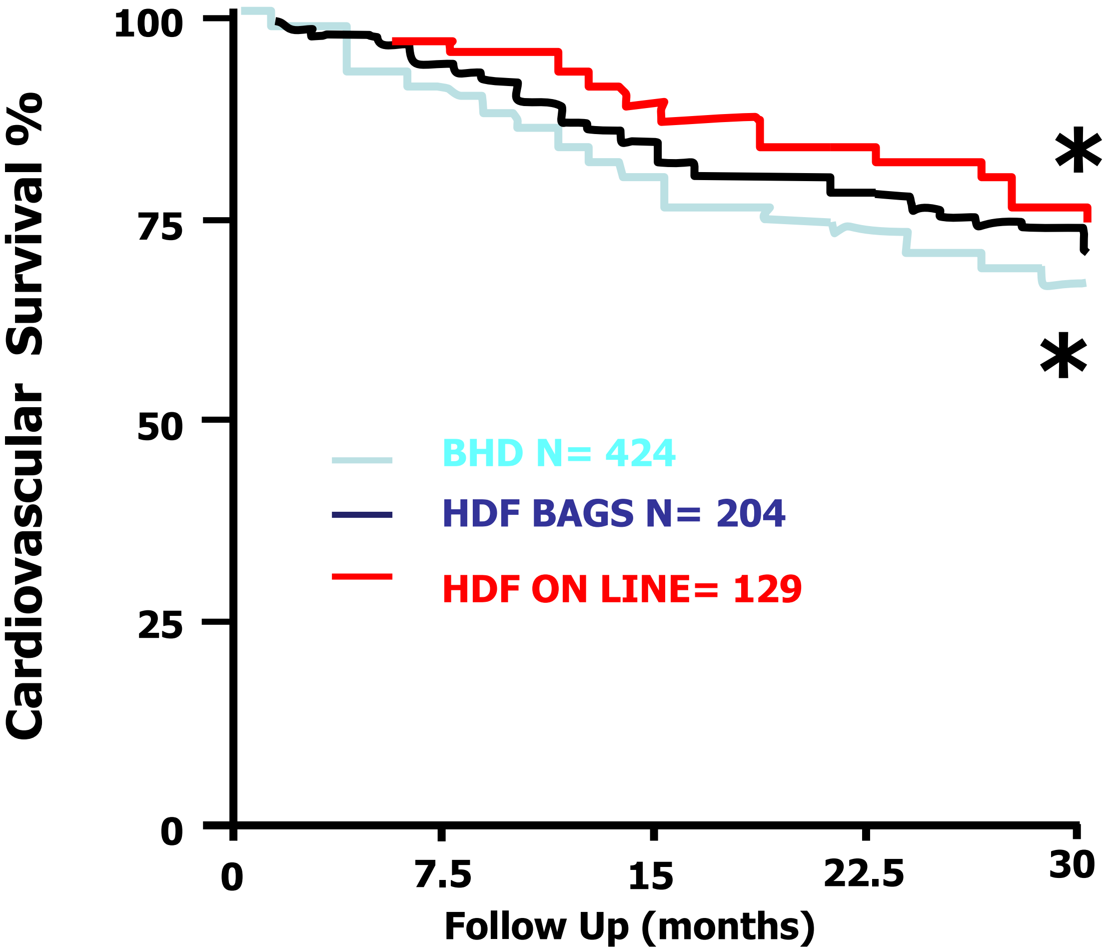


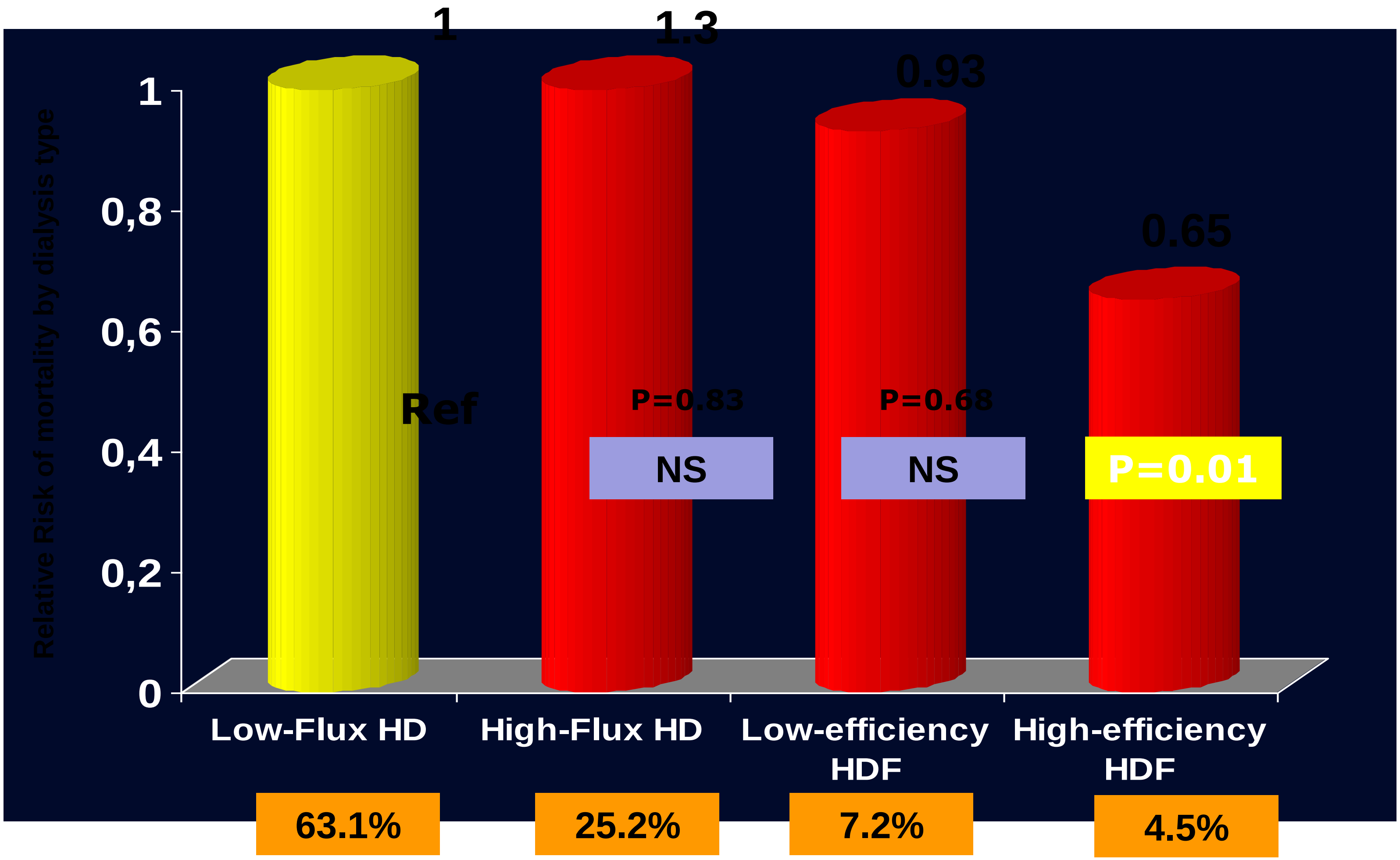
Panichi V et al. Nephrol Dial Transplant 2008; 23: 2337-2343

Convective Therapies: Outcomes

- Intradialytic Cardiovascolar Stability
- Beta2 microglobulin
- Phosphataemia
- Anaemia and ESA Dose
- Inflammation

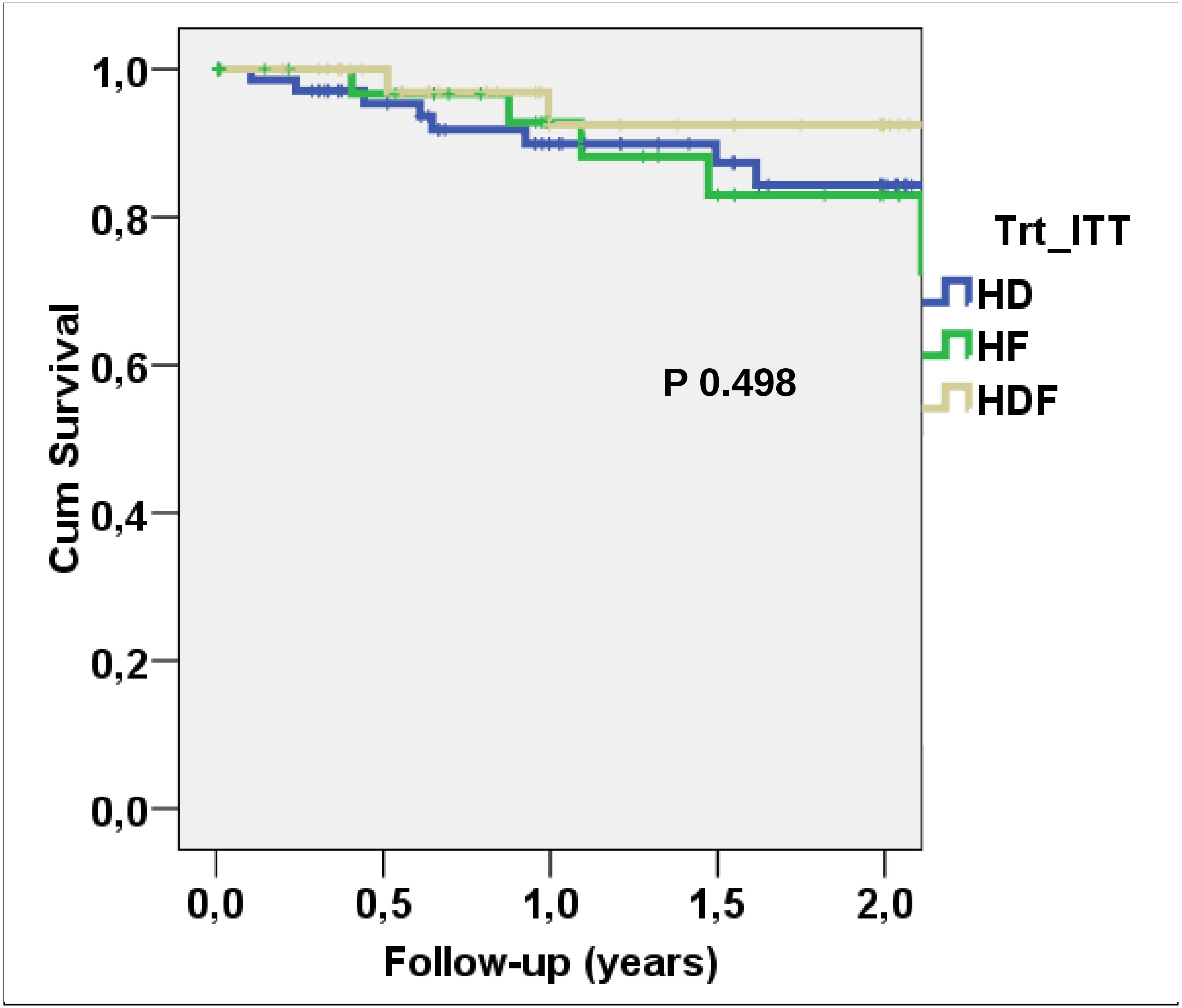
Mortality

Mortality risk for patients receiving HDF versus HD: European results from the DOPPS



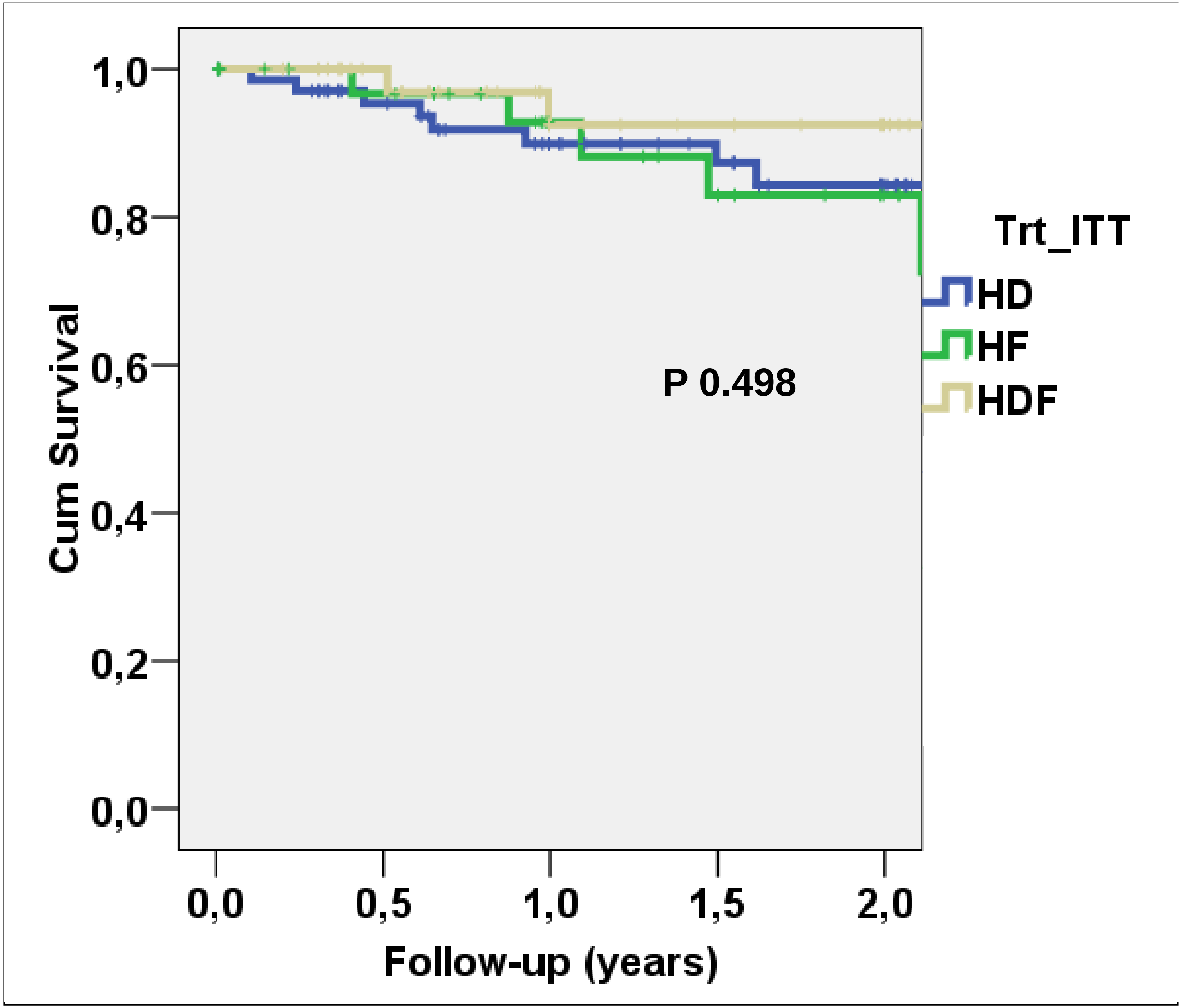
Canaud B et al. Kidney Int 2006; 69: 2087-2093

Patient survival



Locatelli et al. J Am Soc Nephrol. 2010; 21(10):1798-807

Patient survival



Locatelli et al. J Am Soc Nephrol. 2010; 21(10):1798-807

Survival of CKD patients receiving HDF and HF versus HD

Locatelli F. and Canaud B. Nephrol.Dial Transpl. 2012

Author, Year	HDF vs Comp	Type of study	β2-M	Survival	Tolerance
Locatelli F et al, 1996	LF-HD vs cuprophan-HD vs HF-HD vs HDF	RCT	↓ (HF-HD and HDF)	=	=
Wizemann V et al, 2000	HDF vs LFHD	RCT	↓	=	=
Bosch JP et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 45%	↑
Canaud B et al 2006	HDF+/- vs LFHD vs HFHD	Historical prospective cohort	?	↑ 35%	=
Jirka et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 36%	=
Schiffl H et al, 2007	HDF vs HFHD + UPD	RCT	↓	=	=
Vinhas J et al, *2007*	HDF vs HFHD	Prospective controlled study	?	↑ 50%	↑
Panichi V et al. 2008	HDF+/- vs LFHD	Prospective controlled study	↓	↑ 15%	↑
Santoro A et al, 2008	HF vs HFHD	RCT	↓	↑ 18%	↑
Tiranathanagul K 2009	HDF vs HFHD	Prospective controlled study	↓	=	↑
Vilar E et al, 2009	HDF vs HFHD	Historical prospective cohort	↓	↑ 34%	↑
Locatelli F et al, 2010	HDF & HF vs LFHD	RCT	↓	=	↑ ↑

Outcomes of CKD patients receiving HDF versus HD

Locatelli F. and Canaud B. Nephrol.Dial Transpl. 2012

Author, Year	HDF vs Comp	Type of study	β2-M	Survival	Tolerance
Locatelli F et al, 1996	LF-HD vs cuprophan-HD vs HF-HD vs HDF	RCT	↓ (HF-HD and HDF)	=	=
Wizemann V et al, 2000	HDF vs LFHD	RCT	↓	=	=
Bosch JP et al, 2006	HDF vs LFHD vs HFHD	Historical prospective cohort	?	↑ 45%	↑
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Schiffl H et al, 2007	HDF vs HFHD + UPD	RCT	↓	=	=
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KDIGO Controversies Conference

Novel techniques and innovation in blood purification:
How can we improve clinical outcomes in hemodialysis?

14-15 October, 2011
Paris, France

CONFERENCE LEADERS

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Is hemodiafiltration the future?

Barriers to its large use

Chan CT… Locatelli F. et al Kidney Int. 2013 Jan 16

Barriers to larger use of Hemodiafiltration

- Lack of convincing evidence of survival benefit
- Lack of convincing cost saving – varies from country to country
- Safety concerns using large volume of on-line prepared substitution fluid
- Regulatory issues regulation of on-line fluid preparation (cumbersome and costly)
- Inadequate vascular access for Qb requirements
- Education and training
- Cost of OL-HDF machine

Chan CT… Locatelli F. et al Kidney Int. 2013 Jan 16

Lessons from recent trials in hemodialysis

The solution…

- **Randomised controlled studies in dialysis are welcomed**
- **The HEMO and MPO studies comparing High flux and low flux hemodialysis, the Italian Convective Study comparing hemodialysis, hemodiafiltration and hemofiltration gave important information on how to improve the management of dialysis patients**

Locatelli F et al. Contrib Nephrol 2011

Randomized clinical trials in Europe evaluating HDF vs HD

Dutch Trial	Italian Trial	French Trial	Catalonian Trial	Turkish Trial
CONTRAST	CONVESTUDY		ESHOL	
LFHD vs HDF	LFHD vs HF/HDF	HFHD vs HDF	HFHD vs HDF	HFHD vs HDF
		> 65y		
350/350	150/75/75	300/300	300/300	300/300
	Tolerance	Tolerance		
	Morbidity			
CV events		CV events	CV events	CV events
Mortality	Mortality	Mortality	Mortality	Mortality
36 months	24 months	24 months	24 months	24 months
715 enrolled JASN 2012	70 HD; 40 HDF & 36 HF patients JASN 2010	410 patients; enrollment closed Dec 31, 2010; Results by Dec , 2013?	~900 patients; JASN 2013	~ 800 patients NDT 2012

CLINICAL RESEARCH www.jasn.org

JASN® Journal of the American Society of Nephrology

Hemofiltration and Hemodiafiltration Reduce Intradialytic Hypotension in ESRD

Francesco Locatelli,* Paolo Altieri,† Simeone Andrulli,* Piergiorgio Bolasco,‡ Giovanna Sau,† Luciano A. Pedrini,§ Carlo Basile,|| Salvatore David,¶ Mariano Feriani,** Giovanni Montagna,†† Biagio Raffaele Di Iorio,‡‡ Bruno Memoli,§§ Raffaella Cravero,|||| Giovanni Battaglia,¶¶ and Carmine Zoccali***

J Am Soc Nephrol 2010 21:1798-807

CONTRAST Study

JASN

CLINICAL RESEARCH www.jasn.org

Effect of Online Hemodiafiltration on All-Cause Mortality and Cardiovascular Outcomes

Muriel P.C. Grooteman,[*†] Marinus A. van den Dorpel,[‡] Michiel L. Bots,[§] E. Lars Penne,[*‖] Neelke C. van der Weerd,[*] Albert H.A. Mazairac,[‖] Claire H. den Hoedt,[‡‖] Ingeborg van der Tweel,[§] Renée Lévesque,[¶] Menso J. Nubé,[*†] Piet M. ter Wee,[*†] and Peter J. Blankestijn,[‖] for the CONTRAST Investigators

[*]Department of Nephrology, VU University Medical Center, Amsterdam, The Netherlands; [†]Institute for Cardiovascular Research, VU Medical Center, Amsterdam, The Netherlands; [‡]Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands; [§]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; [‖]Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands; and [¶]Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

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

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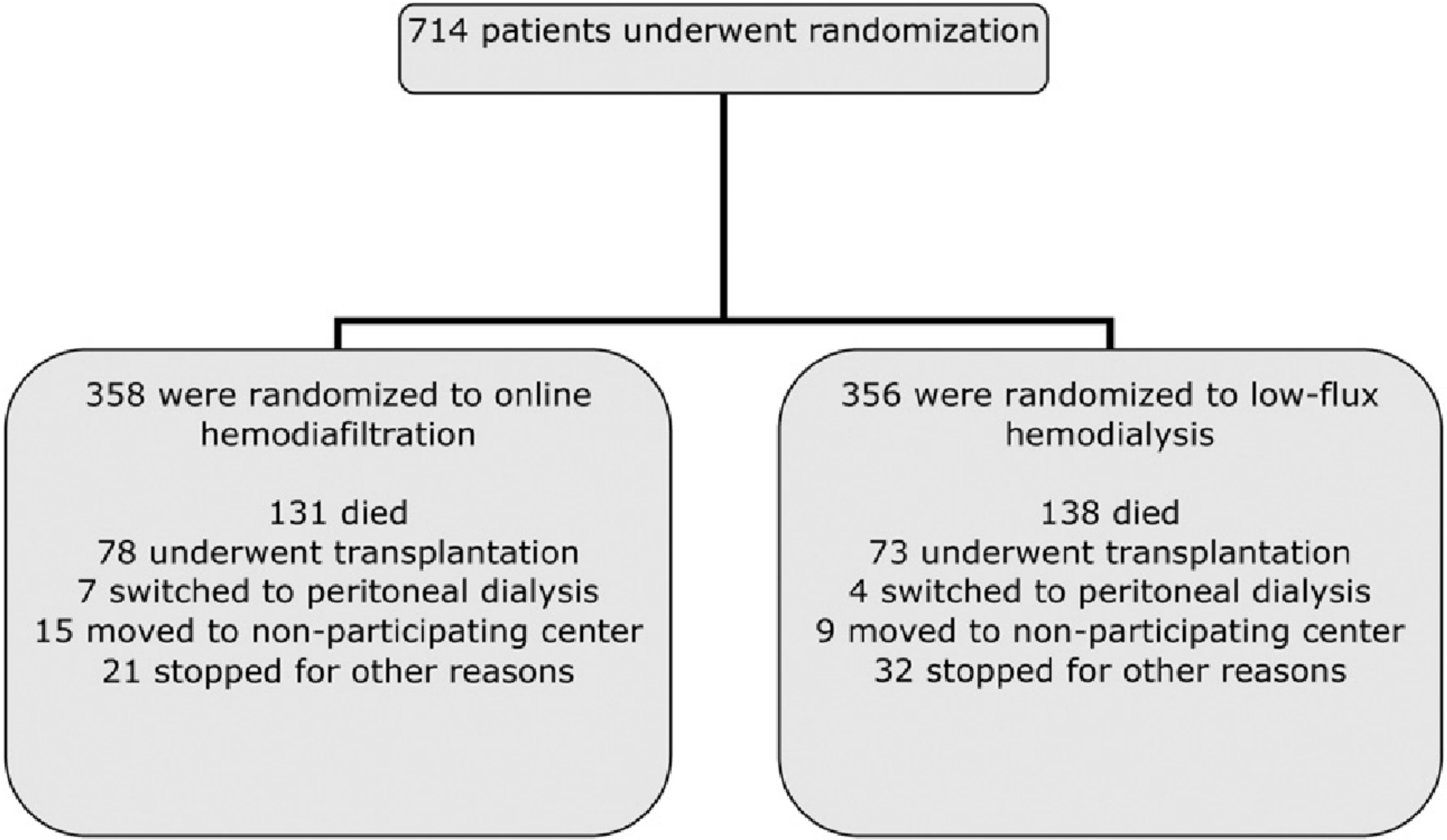

Figure 1. Enrollment, randomization, and follow-up of study participants. For mortality and cardiovascular events, all patients were followed until the end of the study.

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

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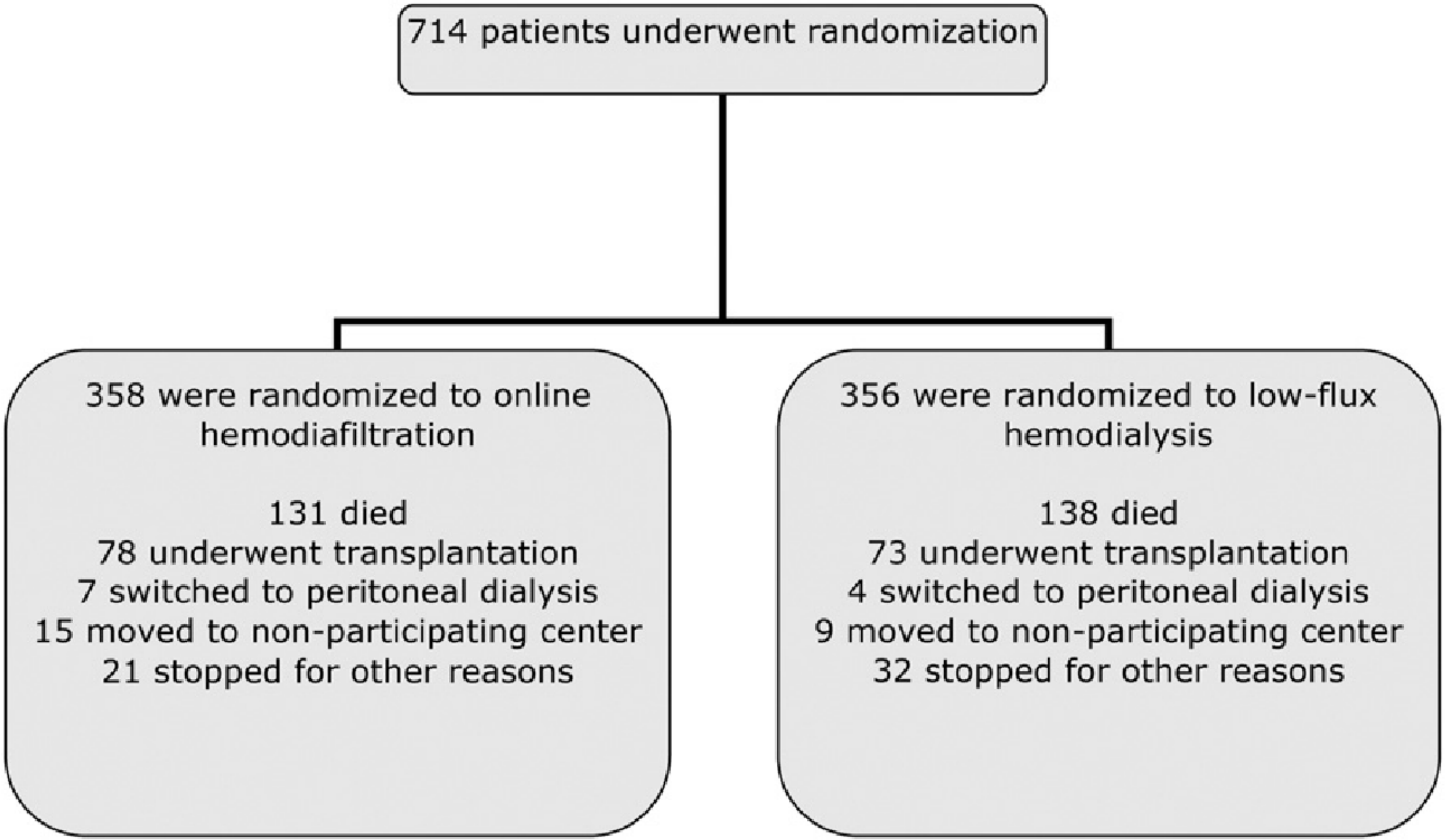


Figure 1. Enrollment, randomization, and follow-up of study participants. For mortality and cardiovascular events, all patients were followed until the end of the study.

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

Primary outcome

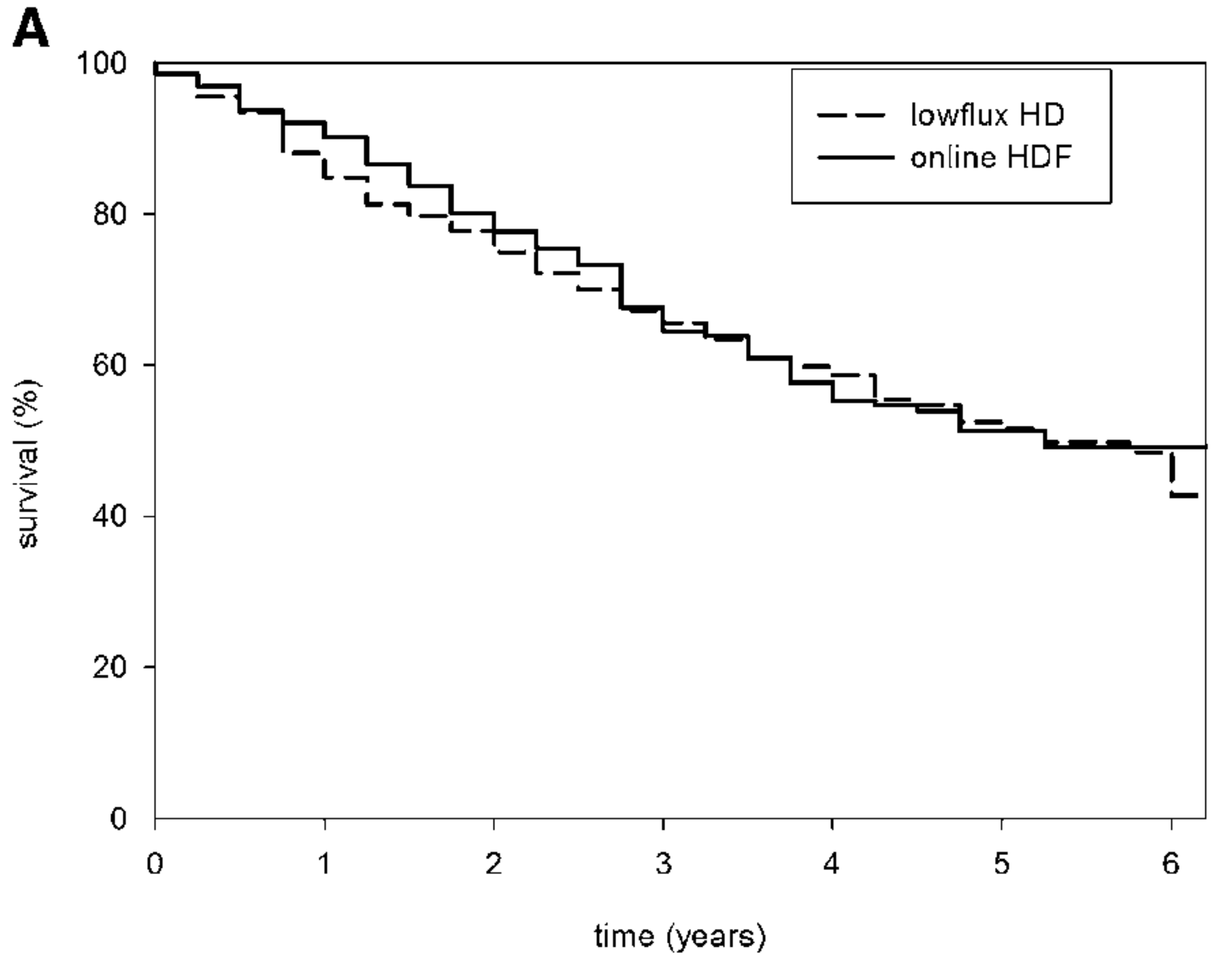
	Online Hemodiafiltration		Low-Flux Hemodialysis		HR (95% CI)[a]
	Number of Events	Person-Years of Follow-Up	Number of Events	Person-Years of Follow-Up	
Primary out-come: all-cause mortality	131	1085	138	1085	0.95 (0.75–1.20)

[a] Obtained through unadjusted Cox proportional hazards models

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

All-cause mortality was not affected by treatment

Survival curves for time to death from any cause based on life table analyses using 3-month time periods



Patients at risk

HD	356	337	307	269	230	201	169	140	102	83	65	52	32
HDF	358	346	324	287	237	203	160	131	103	77	57	44	18

Grooteman M P et al. JASN 2012;23:1087-1096

Patient characteristics during follow-up

Characteristic	Online Hemodiafiltration	Low-Flux Hemodialysis	Mean Difference (SEM)	P Value for Difference
Duration of dialysis session (h)	3.77 (0.01)	3.81 (0.01)	−0.04 (0.02)	0.02
Blood flow (ml/min)	332 (2.6)	312 (2.3)	20 (3.4)	0.001
Sessions/wk (n)	2.99 (SD 0.6)	2.99 (SD 0.7)	0.002 (0.02)	0.25
Online hemodiafiltration				
number of sessions/wk	2.71 (SD 0.35)	NA		
convection volume (L) / treatment	**20.7** (SD **6.0**)	NA		
Single-pool Kt/V_{urea}	1.63 (0.02)	1.45 (0.02)	0.18 (0.03)	<0.001
β-2-microglobulin (mg/L)	26.4 (0.37)	35.4 (0.54)	−8.9 (0.7)	<0.001
Albumin (g/L)	39.4 (0.14)	39.7 (0.15)	−0.30 (0.20)	0.14
CRP (mg/L)	11.9 (1.4)	11.4 (1.2)	0.52 (1.9)	0.77
Hemoglobin (g/dl)	11.8 (0.03)	11.6 (0.03)	0.11 (0.05)	0.03
Phosphorus (mg/dl)	4.80 (0.06)	4.95 (0.06)	0.19 (0.06)	0.02
Cholesterol (mg/dl)	143 (2)	139 (2)	2 (2)	0.28
Predialysis systolic pressure (mmHg)	146 (1)	145 (1)	0.9 (0.5)	0.49
Interdialytic weight change, pre − post (kg)	1.91 (0.05)	1.85 (0.05)	0.05 (0.07)	0.51

Risk of all-cause mortality by achieved convection volume

82 missing and 206 deaths instead of 269

	HD	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

[a] Adjusted for age, sex, previous vascular disease, diabetes, previous transplantation, spKt/V, baseline eGFR, baseline albumin, baseline creatinine, baseline hematocrit, and use of α- and β-blockers, calcium antagonists, and angiotensin converting inhibitors at baseline

[b] Adjusted for the above-mentioned determinates as well as for center differences

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

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ABSTRACT

In patients with ESRD, the effects of online hemodiafiltration on all-cause mortality and cardiovascular events are unclear. In this prospective study, we randomly assigned 714 chronic hemodialysis patients to online postdilution hemodiafiltration (n=358) or to continue low-flux hemodialysis (n=356). The primary outcome measure was all-cause mortality. The main secondary endpoint was a composite of major cardiovascular events, including death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, therapeutic coronary intervention, therapeutic carotid intervention, vascular intervention, or amputation. After a mean 3.0 years of follow-up (range, 0.4–6.6 years), we did not detect a significant difference between treatment groups with regard to all-cause mortality (121 versus 127 deaths per 1000 person-years in the online hemodiafiltration and low-flux hemodialysis groups, respectively; hazard ratio, 0.95; 95% confidence interval, 0.75–1.20). The incidences of cardiovascular events were 127 and 116 per 1000 person-years, respectively (hazard ratio, 1.07; 95% confidence interval, 0.83–1.39). Receiving high-volume hemodiafiltration during the trial associated with lower all-cause mortality, a finding that persisted after adjusting for potential confounders and dialysis facility. In conclusion, this trial did not detect a beneficial effect of hemodiafiltration on all-cause mortality and cardiovascular events compared with low-flux hemodialysis. On-treatment analysis suggests the possibility of a survival benefit among patients who receive high-volume hemodiafiltration, although this subgroup finding requires confirmation.

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

On-line hemodiafiltration not a self-fulfilling prophecy

- HDF needs to be applied in an educated and well defined manner
- Ongoing studies in this field will help to define future treatment standards
- On-line HDF is not a self-fulfilling prophecy; it must be used wisely

Kuhlmann MK J Am Soc Nephrol. 2012 Jun;23(6):974-5

NDT
Nephrology Dialysis Transplantation

http://ndt.oxfordjournals.org/

Nephrol Dial Transplant (2013) 28: 192–202
doi: 10.1093/ndt/gfs407
Advance Access publication 9 December 2012

Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study

Ercan Ok[1], Gulay Asci[1], Huseyin Toz[1], Ebru Sevinc Ok[1], Fatih Kircelli[1], Mumtaz Yilmaz[1], Ender Hur[1], Meltem Sezis Demirci[1], Cenk Demirci[1], Soner Duman[1], Ali Basci[1], Siddig Momin Adam[2], Ismet Onder Isik[2], Murat Zengin[2], Gultekin Suleymanlar[3], Mehmet Emin Yilmaz[4] and Mehmet Ozkahya[1] and On behalf of the 'Turkish Online Haemodiafiltration Study'

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Ok E et al: NDT 2013 28: 192-202

Flow chart of study participation.

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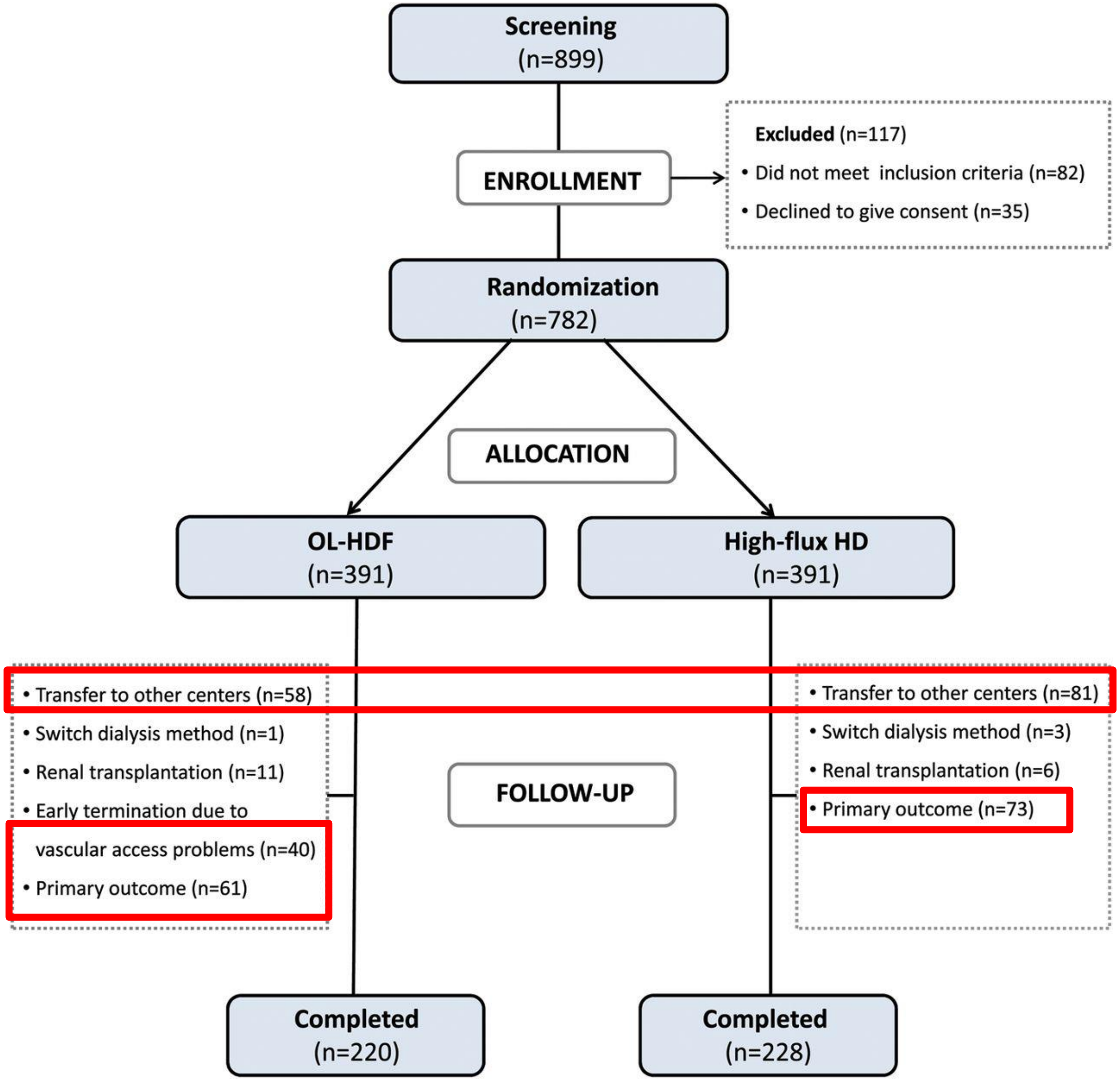


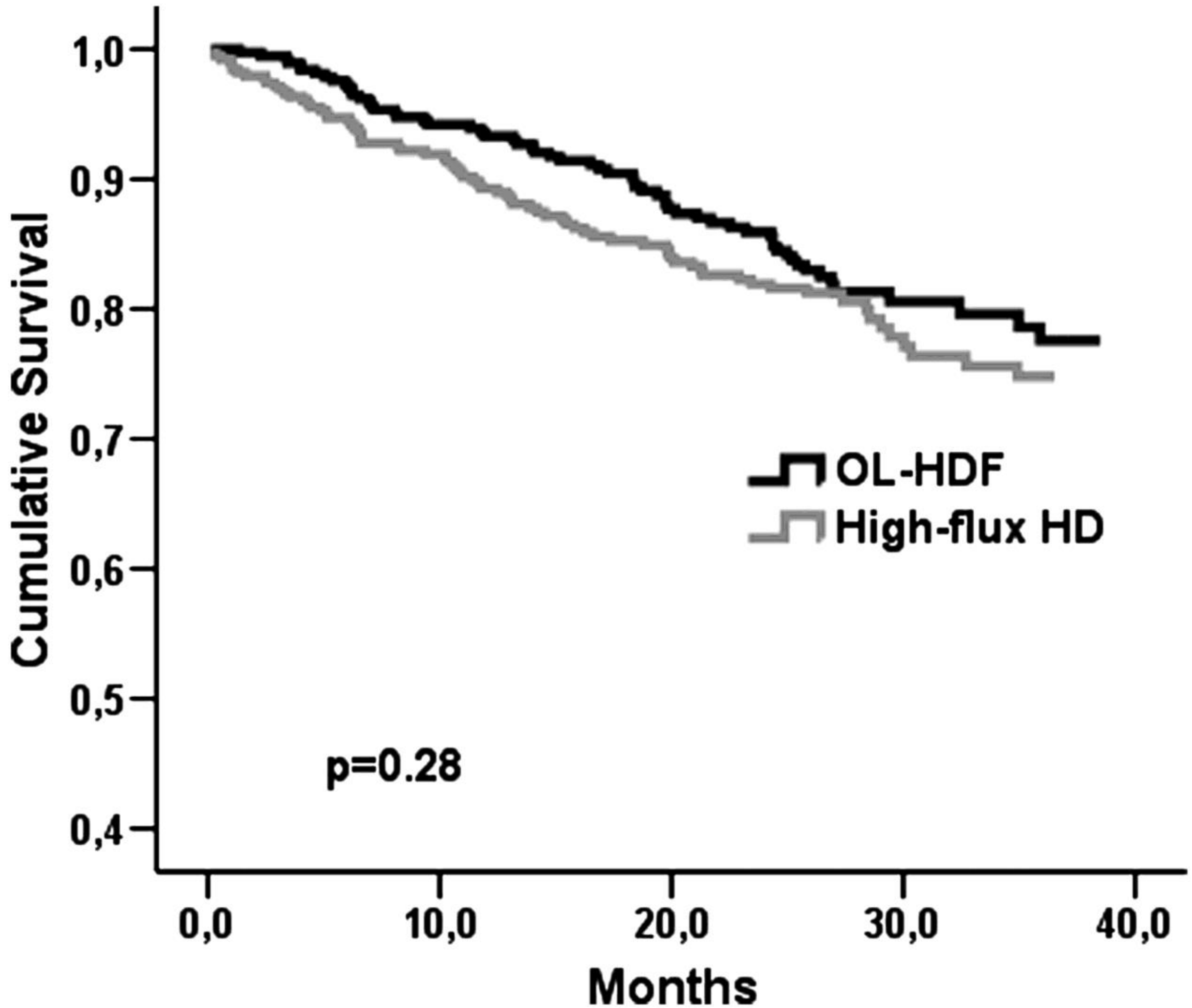
Ok E et al. Nephrol. Dial. Transplant. 2013;28:192-202

Mortality

	All patients ($n = 782$)	OL-HDF ($n = 391$)	High-flux HD ($n = 391$)
Overall mortality (n, %)	117 (15.0)	52 (13.3)	65 (16.6)
Cardiovascular mortality (n, %)	76 (9.7)	32 (8.1)	44 (11.2)
Noncardiovascular mortality (n, %)	41 (5.2)	20 (5.1)	21 (5.3)

Ok E et al: NDT 2013 28: 192-202

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



Ok E et al. Nephrol. Dial. Transplant. 2013;28:192-202

NDT Nephrology Dialysis Transplantation

Multivariate analysis for Mortality secondary endpoint

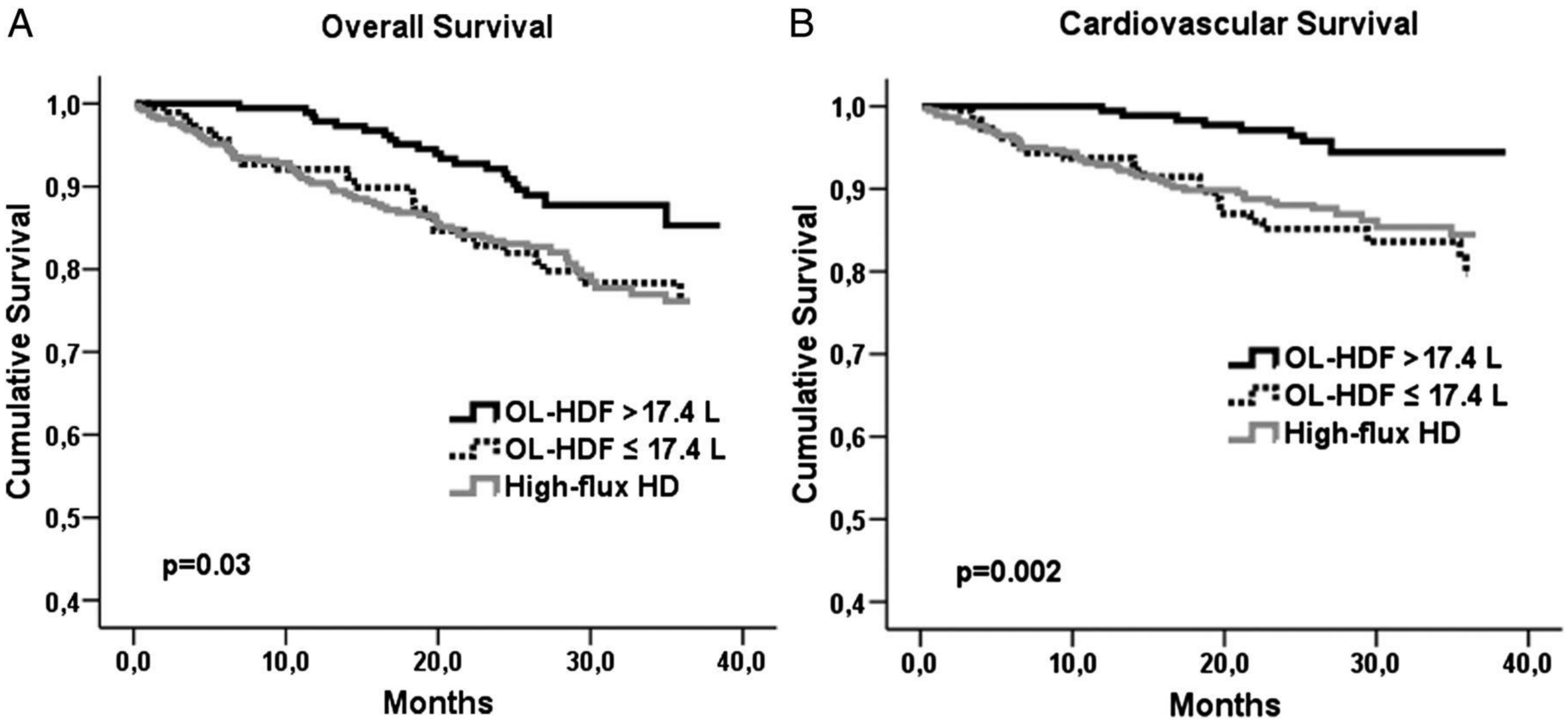
Table 6. Unadjusted and adjusted multivariate analysis for predictors of overall and cardiovascular mortality

	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Overall mortality			
High-flux HD	Reference	Reference	Reference
HDF with RF ≤ 17.4 L	0.99 (0.64–1.53), P = 0.54	1.17 (0.73–1.88), P = 0.36	1.10 (0.68–1.76), P = 0.69
HDF with RF > 17.4 L	0.54 (0.33–0.88), P = 0.01	0.57 (0.33–0.96), P = 0.04	0.54 (0.31–0.93), P = 0.02
Age (per year)		1.05 (1.03–1.07), P < 0.001	1.05 (1.03–1.07), P < 0.001
Presence of diabetes		1.73 (1.15–2.60), P = 0.007	1.88 (1.25–2.84), P = 0.002
Albumin (per g/dL)		–	0.49 (0.28–0.85), P = 0.01
Cardiovascular mortality			
HDF with RF ≤ 17.4 L	1.18 (0.72–1.94), P = 0.50	1.27 (0.75–2.16), P = 0.36	1.28 (0.75–2.19), P = 0.35
HDF with RF > 17.4 L	0.31 (0.14–0.65), P = 0.002	0.29 (0.13–0.65), P = 0.003	0.29 (0.12–0.65), P = 0.003
Age (per year)		1.05 (1.03–1.08), P < 0.001	1.05 (1.03–1.08), P < 0.001
Presence of diabetes		2.03 (1.24–3.34), P = 0.005	2.24 (1.35–3.73), P = 0.002

Model 1: Adjusted for age, gender, diabetes, cardiovascular disease, time on haemodialysis, vascular access, interdialytic weight gain, blood flow rate.
Model 2: Model 1+ haemoglobin, albumin, phosphate and eKt/V.

Ok E et al: NDT 2013 28: 192-202

Overall (A) and cardiovascular survival (B) among the treatment groups



Ok E et al. Nephrol. Dial. Transplant. 2013;28:192-202

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CLINICAL RESEARCH

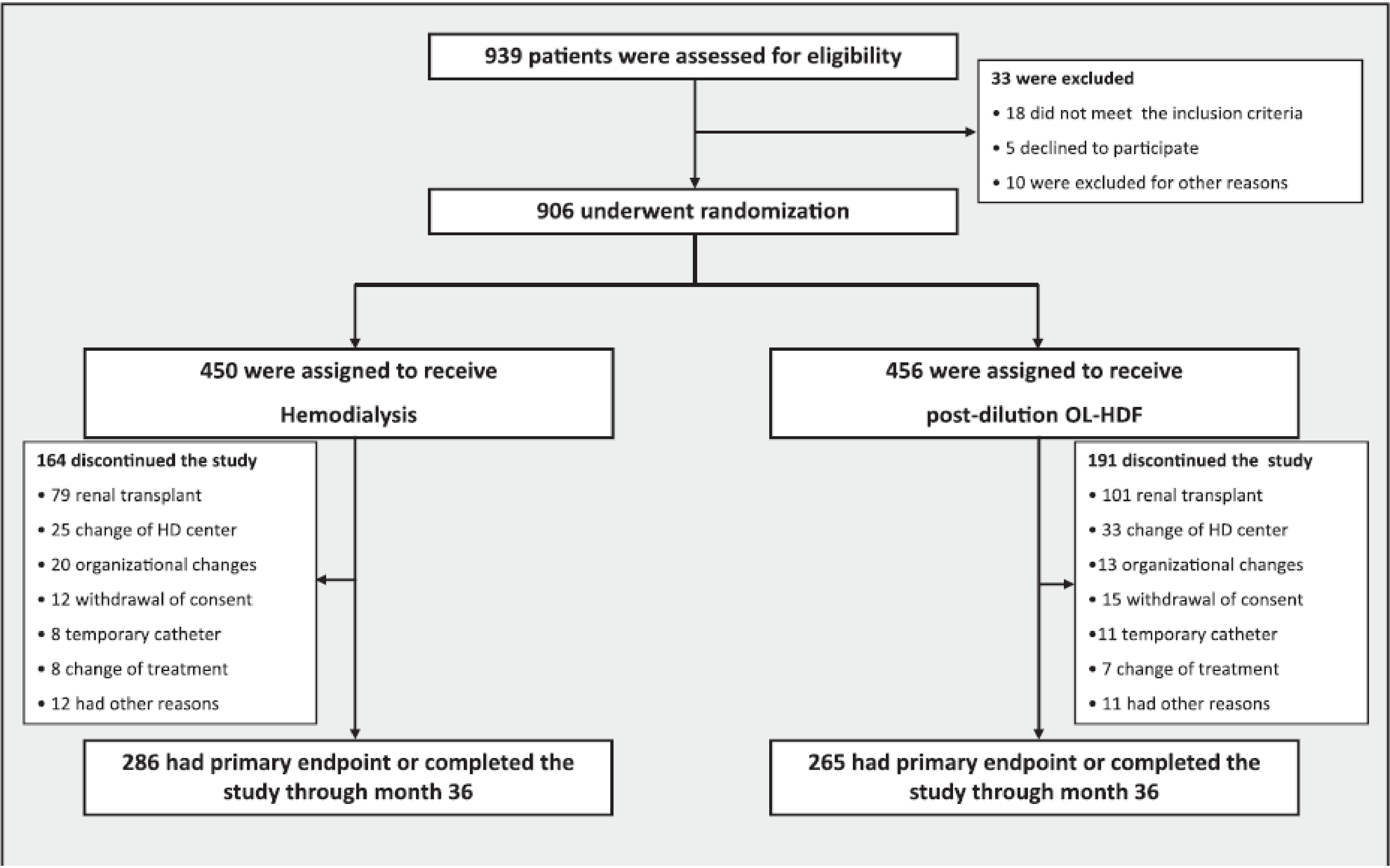
JASN® Journal of the American Society of Nephrology

High-Efficiency Postdilution Online Hemodiafiltration Reduces All-Cause Mortality in Hemodialysis Patients

Francisco Maduell,* Francesc Moreso,† Mercedes Pons,‡ Rosa Ramos,§ Josep Mora-Macià,‖ Jordi Carreras,¶ Jordi Soler,** Ferran Torres,††‡‡ Josep M. Campistol,* and Alberto Martinez-Castelao,§§ for the ESHOL Study Group

J Am Soc Nephrol 24: ●●●–●●●, 2013. doi: 10.1681/ASN.2012080875

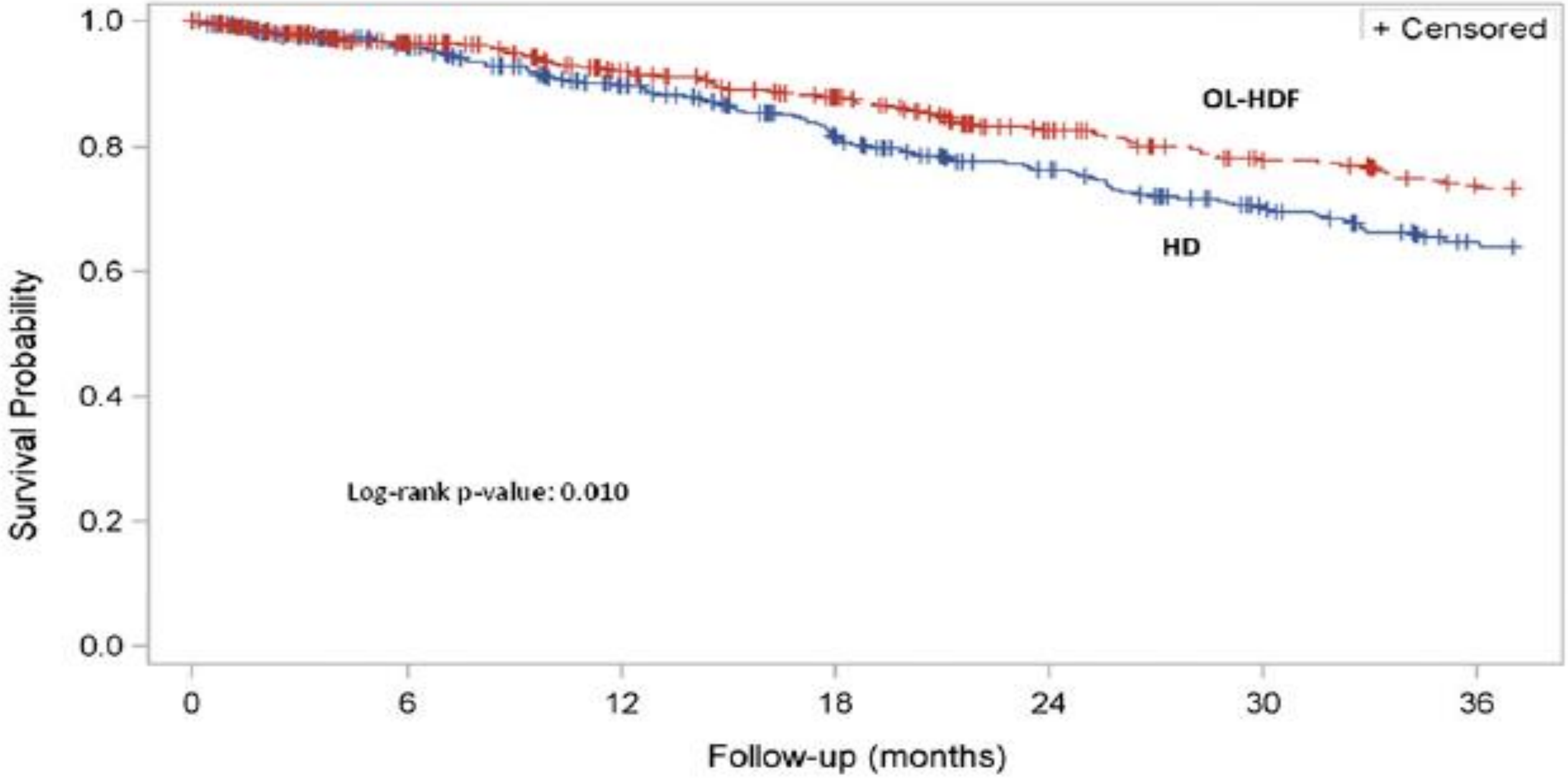
Study Populations



F. Maduell et al. J Am Soc Nephrol 24: 2013

36 months survival in the intention to treat population

(p=0,001 by the long rank test)

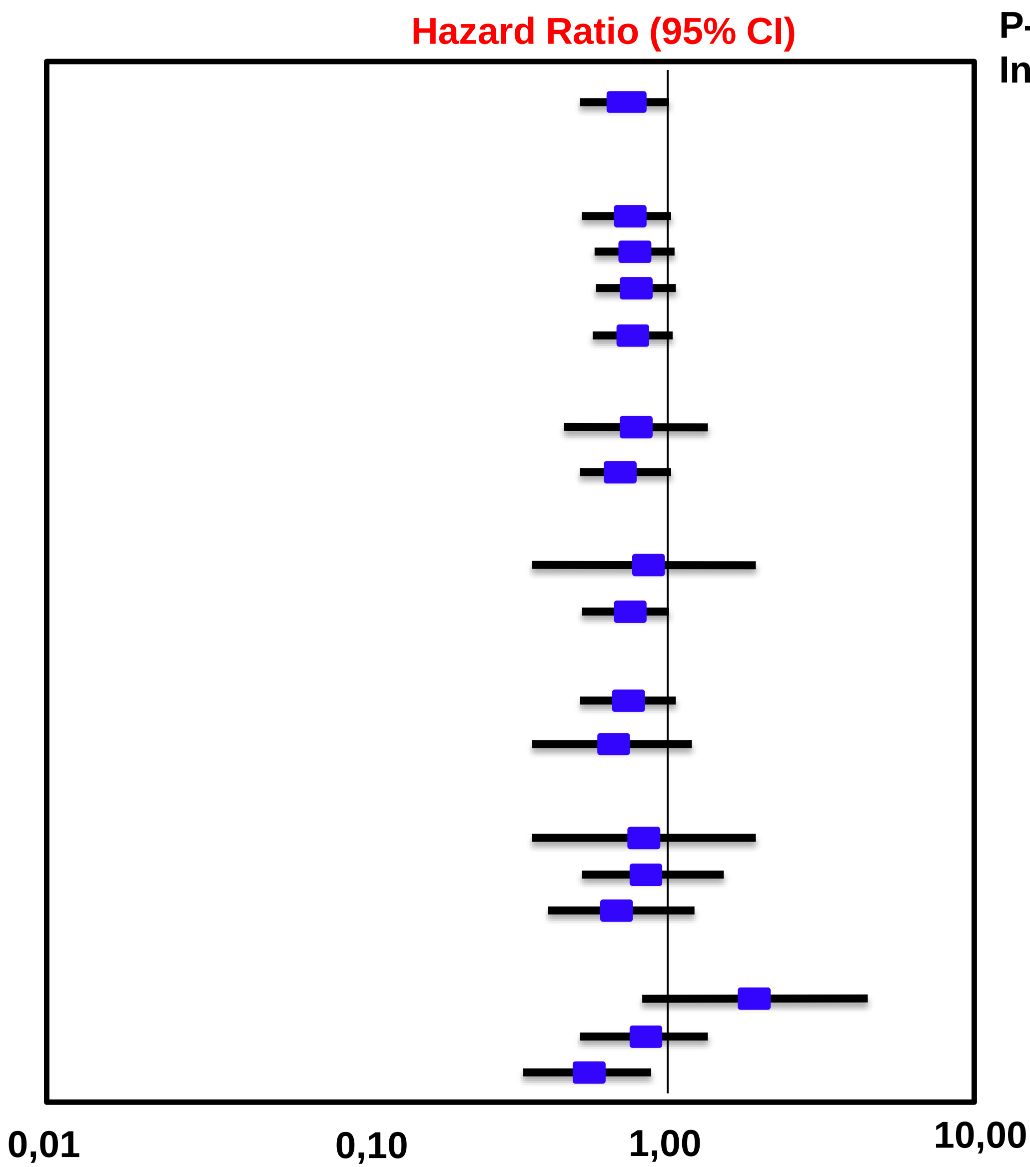


HD	450	388	327	275	235	196	165
OL-HDF	456	367	318	284	232	200	179

F. Maduell et al. J Am Soc Nephrol 24: 2013

Analyses for the main outcome showing HRs (95%Cis) for the intervention based on relevant variable that were found to be indipendent predictors for all-cause mortality

		P-Value for Interaction
Univariate	0,70 (0,53 to 0,92)	
Multivariate		
I	0,73 (0,55 to 0,96)	
II	0,72 (0,55 to 0,95)	
III	0,74 (0,56 to 0,98)	
IV	0,72 (0,55 to 0,96)	
Diabetes		
Y	0,75 (0,46 to 1,21)	
N	0,68 (0,48 to 0,95)	
Vascular Access		
Cath	0,83 (0,38 to 1,79)	
Fist	0,72 (0,53 to 0,97)	
Gender		
M	0,70 (0,51 to 0,96)	
F	0,64 (0,36 to 1,11)	
Age		
T1	0,81 (0,36 to 1,81)	
T2	0,82 (0,51 to 1,33)	
T3	0,63 (0,43 to 0,92)	
Charlson Index		
T1	1,83 (0,79 to 4,23)	
T2	0,78 (0,51 to 1,20)	
T3	0,54 (0,35 to 0,83)	



F. Maduell et al. J Am Soc Nephrol 24: 2013

Suggestions for future randomized studies

- Only incident patients
- Multicentre and multinational
- Large sample size
- Long follow-up
- Maximization and randomization of convective volumes

CONCLUSIONS

- Online Haemodiafiltration, is an established RRT modality in routine clinical practice for over two decades.

- Several clinical studies have reported upon the improved patient outcomes with Online Haemodiafiltration.

- Ever since the DOPPS data indicating that patient high-efficiency Online Haemodiafiltration improves outcomes, the focus has been on randomised controlled trials examining the impact of high convective volumes on patient survival.

CONCLUSIONS

- OL-HDF currently represents the most technically advanced dialysis treatment available.
- Widespread clinical experience with this RRT modality for ~ 3 decades has confirmed its safety and efficacy.
- Widespread implementation of this technique has been delayed pending conclusive evidence of its benefits from randomized studies.

The results of the ESHOL Study should be considered as an important step towards making
OL-HDF a gold standard treatment for patients with CKD.

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