Randomized clinical trials in Europe evaluating HDF and HD.

Peter J. Blankestijn
Department of Nephrology
University Medical Center Utrecht
the Netherlands

Overall hypothesis of RCTs

Improvement in clearance of MMW solutes during online HDF

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Better correction of uremic environment

↓

Decrease cardiovascular damage

↓

Decrease cardiovascular morbidity and mortality

Randomized clinical trials in Europe evaluating HDF vs HD

Italian Trial	Turkish Trial	Dutch Trial	Catalonian Trial	French Trial
LFHD vs HF/HDF	HFHD vs HDF	CONTRAST	ESHOL	HFHD vs HDF
150/75/75	300/300	LFHD vs HDF	HFHD vs HDF	> 65 y
Tolerance	CV events	350/350	400/400	300/300
Morbidity	Mortality	CV events	CV events	Tolerance
Mortality	24 months	Mortality	Mortality	CV events
24 months		36 months	36 months	Mortality
				24 months
70 HD; 40 HDF & 36 HF patients; published JASN 2010	~ 800 patients, closed 2010, Results presented yesterday	715 enrolled; study closed Dec 31, 2010; Results presented yesterday	906 patients; followed for 3 yrs; Study ends late 2011	420 patients; enrollment closed Feb 2011

Contr Nephrol 2011; 168: 39-52

Turkish study, presented yesterday

Main objective: Composite of all-cause mortality and new non-fatal cardiovascular events (myocardial infarction, stroke, revascularization, unstable angina pectoris requiring hospitalization)

- Secondary endpoints: cardiovascular mortality, hospitalization rate, Intra-dialytic complications, changes in various variables
- In- and exclusion criteria: prevalent patients, KtV ≥ 1.2, UP < 250 mL/day
- Target substitution volume > 15 L/session post-dilution
- Follow up: 24 m

Courtesy of Prof E. Ok

Turkish study, presented yesterday

N = 782

Baseline characteristics: age 56 y, no residual kidney function, dialysis vintage approx 4½ y, 95% native AVF, 26 % history CV disease

Baseline already on HF dialyzers (?)

Lab: β2M = 26 mg/L

Follow up: mean 23 months, range 1.2 – 38.5.

Mean substitution volume: 17.2 L (9.8 – 20.3), 93% > 15 L/session

Courtesy of Prof E. Ok

CONTRAST, presented yesterday

Main objective: all cause mortality

- Secondary endpoints: fatal and non-fatal cardiovascular events, left ventricular mass, arterial stiffness, carotid intima-media thickness, laboratory assessments, nutritional status, quality of life
- randomization: on-line HDF and low-flux HD (treatment time unchanged)
- In- and exclusion criteria: prevalent patients, KtV ≥ 1.2
- Target substitution volume > 6 L/h post-dilution
- Event driven

Sem Dial 2005; 18: 47-51, Curr Control Trials Cardiovasc Med. 2005 May 20;6(1):8

CONTRAST, presented yesterday

N = 714

Baseline characteristics: age 64 y, vintage approx 2.9 y, 81% native AVF, eGFR 3.2 mL/min, 44% CV disease

Baseline already on LF dialyzers

Lab: β2M = 31 mg/L, KtV 1.4

Follow up: mean 3.03 y, range 0.4 – 6.6

Mean substitution volume: 19.1 L (90% session delivered as HDF)

ESHOL, Catelonian HDF study

Main objective : study effect on all cause mortality of on line HDF versus HF dialysis

Secondary objectives: intra-dialytic morbidity, nutrition, hospitalization, various laboratory values

Post-dilution HDF, target replacement volume ≥ 18 L/session

Design:

Inclusion: May 2007 – September 2008

Inclusion criteria: Kt/V ≥ 1.3 / session

Study end: October 2011

J Nephrol 2011; 24: 196-201

TABLE I
DEMOGRAPHIC CHARACTERISTICS AND DIALYSIS PARAMETERS IN RANDOMIZED PATIENTS

Characteristics	All patients (n=906)	Hemodialysis (n=450)	Online HDF (n=456)
Age, years	65.4 ± 14	66.3 ± 14	64.5 ± 14
Male sex, no. (%)	606 (66.9%)	289 (64.2%)	317 (69.5%)
Diabetes, no. (%)	226 (24.9%)	122 (27.1%)	104 (22.8%)
Charlson comorbidity Index score	6.6 ± 2.3	6.7 ± 2.3	6.4 ± 2.4
Time on dialysis, months	48.8 ± 64	50.3 ± 71	47.4 ± 55
Vascular access, no. (%)			
Fistula	777 (85.8%)	375 (83.3%)	402 (88.1%)
Graft	33 (3.6%)	18 (4.0%)	15 (3.3%)
Catheter	95 (10.5%)	56 (12.4%)	39 (8.5%)
Dialysis time, minutes	235 ± 19	234 ± 21	236 ± 18
Qb, ml/min	387 ± 64	381 ± 66	393 ± 60*
Qd, ml/min	541 ± 125	529 ± 120	552 ± 128*
Body weight, kg	67.4 ± 14	66.8 ± 13	67.9 ± 14
High-flux membrane, no. (%)	848 (93.7%)	412 (91.8%)	436 (95.6%)
Kt/V	1.66 ± 0.36	1.66 ± 0.40	1.67 ± 0.31
URR, %	74.3 ± 17	74.2 ± 14	74.3 ± 20
nPCR, g/kg	1.09 ± 0.23	1.09 ± 0.22	1.10 ± 0.24

Values are means ± SD of the data, unless specified otherwise.
HDF = hemodiafiltration; nPCR = normalized protein catabolic rate; Qb = blood flow; Qd = dialysate flow; URR = urea reduction ratio.
*$p<0.05$.

J Nephrol 2011; 24: 196-201

TABLE II
PREDIALYSIS BIOCHEMICAL PARAMETERS AT ENROLLMENT

Characteristics	All patients (n=906)	Hemodialysis (n=450)	Online HDF (n=456)
C-reactive protein, mg/L	6.3 (4.9-13.0)	5.7 (4.9-12.3)	7.0 (4.3-13.7)
Blood urea nitrogen, mg/dL	61.0 (50-73)	61.0 (51-75)	61.1 (50-71)
Creatinine, mg/dL	7.8 (6.3-9.6)	7.7 (6.2-9.6)	8.0 (6.4-9.7)
Bicarbonate, mmol/L	21.5 (20-24)	21.5 (20-24)	21.5 (20-24)
Sodium, mmol/L	139 (137-141)	139 (136-141)	139 (137-141)
Potassium, mmol/L	5.3 (4.7-5.8)	5.4 (4.8-5.9)	5.2 (4.67-5.8)
Uric acid, mg/dL	5.6 (4.9-6.2)	5.6 (4.8-6.2)	5.6 (4.9-6.3)
Albumin, g/dL	4.1 (3.8-4.4)	4.1 (3.8-4.4)	4.1 (3.8-4.4)
Calcium, mg/dL	9.0 (8.6-9.5)	9.0 (8.6-9.5)	9.0 (8.6-9.5)
Phosphorus, mg/dL	4.5 (3.6-5.5)	4.4 (3.5-5.4)	4.6 (3.7-5.6)
Intact parathyroid hormone, pg/mL	209 (113-360)	209 (122-359)	209 (105-362)
β_2-Microglobulin, mg/L	22.7 (19-28)	22.8 (19-29)	22.1 (18-28)

Values are medians (interquartile range).
HDF = hemodiafiltration.

J Nephrol 2011; 24: 196-201

HEMATOLOGICAL PARAMETERS AND BLOOD PRESSURE FINDINGS AT ENROLLMENT

Characteristics	All patients (n=906)	Hemodialysis (n=450)	Online HDF (n=456)
Hemoglobin, g/dL	12.0 (11.0-13.0)	12.0 (11.0-12.8)	12.1 (11.0-13.0)
Hematocrit, %	37.5 (35-41)	37.1 (35-40)	37.7 (35-40)
Transferrin saturation, %	26.0 (19-37)	27.0 (20-38)	25.5 (19-35)
Ferritin, ng/mL	336 (210-499)	360 (231-500)	322 (189-494)
Iron doses, mg/week	25.0 (10-50)	25.0 (0-50)	25.0 (12.5-50)
ES agents, no. (%)			
EPO	413 (45.6%)	209 (46.2%)	204 (44.7%)
Darbepoetin	409 (45.1%)	206 (45.8%)	203 (44.5%)
CERA	11 (1.2%)	5 (1.1%)	6 (1.3%)
EPO dosage, IU/kg per week	6,000 (4,000-12,000)	6,000 (4,000-11,000)	6,000 (4,000-12,000)
Systolic blood pressure, mm Hg	136 (120-152)	137 (120-152)	134 (120-152)
Diastolic blood pressure, mm Hg	70 (62-80)	70 (60-80)	71 (64-84)
Patients on antihypertensive therapy, no. (%)	530 (58.6%)	260 (57.9%)	270 (59.2%)
Phosphate binding, pills/day	3 (2-5)	3 (2-5)	3 (2-5)

Values are number (%) or median (interquartile range) where appropriate.
CERA = continuous erythropoietin receptor activator; EPO = epoetin-alpha or epoetin-beta; ES = erythropoiesis-stimulating; HDF = hemodiafiltration.

J Nephrol 2011; 24: 196-201

French study

- Main objective:To appreciate the tolerance of "on line" HDF treatment versus conventional high flux hemodialysis in terms of adverse events occuring during dialysis sessions between day 30 and day 120 of treatment.
- Secondary analyses:

  To evaluate:
  - Quality of life evaluated with the KDQOL questionnaire
  - Incidence of cardiovascular events
  - Influence of the technique on cardiovascular, inflammation and infection risk factors
  - Mortality
- Design: Multicenter, prospective, randomized and comparative study

French study

Inclusion criteria

- Patient who has signed the written consent form
- Patient aged ≥ 65 and ≤ 90 years
- With creatinine clearance < 10 mL/min
- On dialysis for a minimum of 3 months, with 3 times a week hemodialysis sessions
- Erythropoietin dosage needed to maintain hemoglobin at a constant level (range of hemoglobin: 9-13 g/dL without any variation of more than 2g/dL for less than 3 months)
- Without any problem of vascular access

Present status: inclusion ended Feb 2011, n=420

Some differences in RCTs in Europe

	modalities	Age at baseline	B2M at baseline	Convection volume	Follow up	Primary End points	Sec. End points
Turkish	HF ⇔ olHDF	Mean 56 y	26 mg/L	Target > 15 L Mean 17.4 L Subst vol	Mean 23 m Range 1.2 – 38.5 m	Composite All cause mort and non fetal CV events	Hemodynamic tolerance
CONTRAST	LF ⇔ olHDF	Mean 64 y	31 mg/L	Target 6 L/h Mean 19 L/session	Min 1 y Mean 3.03 y Range 0.4 – 6.6y	All cause mortality	CV Morbidity QoL Cost utility
Catalonian	HF ⇔ olHDF	Mean 65 y	23 mg/L	Target > 18 L session	Min 3 y	All cause mortality	Hemodynamic tolerance QoL
French	HF ⇔ olHDF	> 65 y	?		Min 2 y	Hemodynamic tolerance	QoL CV morbidity / mortality

Determinants of convective volume

	Univariable model		Multivariable model	
Determinant	**B**	**95% CI**	**B**	**95% CI**
Sex (Male)	1.8	0.7 to 2.8†	0.47	-0.16 to 1.1
Age (years)	0.0	-0.04 to 0.03		
BMI (kg/m^2)	0.14	0.03 to 0.25†	0.028	-0.04 to 0.09
History of CVD	-0.14	-1.2 to 0.90		
DM	0.67	-0.50 to 1.8		
Time on RRT (years)	0.01	-0.1 to 0.1		
SBP (mmHg)	0.0	-0.03 to 0.02		
DBP (mmHg)	0.01	-0.03 to 0.06		
Vascular access (Fistula)	-0.3	-1.5 to 1.0		
Hemoglobin (mmol/L)	-0.89	-1.5 to -0.28†		
Hematocrit (%)	-0.18	-0.30 to -0.06†	-0.14	-0.22 to -0.07†
Thrombocytes (x 109/L)	-0.003	-0.01 to 0.004		
Serum albumin (g/L)	0.19	0.07 to 0.3†	0.10	0.02 to 0.18†
Treatment time (min)	0.09	0.07 to 0.10†	0.09	0.07 to 0.10†
Blood flow rate (mL/min)	0.05	0.04 to 0.06†	0.04	0.03 to 0.05†

N = 256

Nephrol Dial Transplant 2009; 24: 3493-99

Interaction between bloodflow and filtration fraction in HDF

Blood flow (Q_B)	UF volume (FF 25%)	UF volume (FF 30%)
200 ml/min	3 L/h	3.6 L/h
300 ml/min	4.5 L/h	5.4 L/h
350 ml/min	5.25 L/h	6.3 L/h
400 ml/min	6 L/h	7.2 L/h

Filtration fraction = UF volume / bloodflow

Nephrol Dial Transplant 2009; 24: 3579-81

Present situation

- Data of RCT on hemodynamic stability published in JASN (Locatelli et al), presently running studies addressing this subject as well.
- First results on survival and hard clinical endpoints show overall no benefit.
- However: studies give strong suggestion of a dose ⇔ effect relation
- Other end points might be of relevance as well: especially QoL and cost utility.
- Presented and still running studies show differences in design and base line patient characteristics, which might be of relevance.
- EDTA Working Group on Dialysis Therapies (EuDial). First objective: address convective therapies and integrate and summarize present knowledge.

Next questions

- Combining data:
  - Are there subgroups of patients especially benefiting from online HDF therapy? Predictors of outcome?
  - Effects on relevant secondary outcomes?
  - What is the best variable to guide convective therapy?
  - Statement on safety.
- What is the most effective form of HDF?
- How to achieve an “adequate” dosage without machine alarms?