On line Hemodiafiltration and Cardiovascular Outcomes

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Adequate sodium removal and cardiovascular stability

In clinically stable patients the amount of water and sodium accumulated during the interdialytic period has to be removed at each dialysis session to obtain zero balance

Locatelli et al. Kidney Int Suppl. 2000; 76: S89-95
Adequate sodium removal and cardiovascular stability

Adequate sodium removal:

- reduces intradialytic hypotension and the effects of sodium depletion
- prevents overhydration
- intra and interdialytic hypertension and pulmonary edema

Locatelli et al. Kidney Int Suppl. 2000; 76: S89-95
Convective Therapies: Outcomes

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

Sessions with hypotension (No. / month)

# Tolerance of CKD patients receiving HDF and HF versus HD


<table>
<thead>
<tr>
<th>Author, Year</th>
<th>HDF vs Comp</th>
<th>Type of study</th>
<th>β2-M</th>
<th>Survival</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locatelli F et al, 1996</td>
<td>LF-HD vs cuprophan-HD vs HF-HD vs HDF</td>
<td>RCT</td>
<td>↓ (HF-HD and HDF)</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Wizemann V et al, 2000</td>
<td>HDF vs LFHD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Bosch JP et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 45%</td>
<td>↑</td>
</tr>
<tr>
<td>Canaud B et al 2006</td>
<td>HDF+/- vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 35%</td>
<td>=</td>
</tr>
<tr>
<td>Jirka et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 36%</td>
<td>=</td>
</tr>
<tr>
<td>Schiffi H et al, 2007</td>
<td>HDF vs HFHD + UPD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Vinhas J et al, 2007</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>?</td>
<td>↑ 50%</td>
<td>↑</td>
</tr>
<tr>
<td>Panichi V et al. 2008</td>
<td>HDF+/- vs LFHD</td>
<td>Prospective controlled study</td>
<td>↓</td>
<td>↑ 15%</td>
<td>↑</td>
</tr>
<tr>
<td>Santoro A et al, 2008</td>
<td>HF vs HFHD</td>
<td>RCT</td>
<td>↓</td>
<td>↑ 18%</td>
<td>↑</td>
</tr>
<tr>
<td>Tiranathanagul K 2009</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>↓</td>
<td>=</td>
<td>↑</td>
</tr>
<tr>
<td>Vilar E et al, 2009</td>
<td>HDF vs HFHD</td>
<td>Historical prospective cohort</td>
<td>↓</td>
<td>↑ 34%</td>
<td>↑</td>
</tr>
<tr>
<td>Locatelli F et al, 2010</td>
<td>HDF &amp; HF vs LFHD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
<td>↑ ↑ ↑</td>
</tr>
</tbody>
</table>
Randomized clinical trials in Europe evaluating HDF vs HD

Dutch Trial
CONTRAST
LFHD vs HDF
350/350
CV events
Mortality
36 months

Italian Trial
CONVESTUDY
LFHD vs HF/HDF
150/75/75
Tolerance
Morbidity
Mortality
24 months

French Trial
HFHD vs HDF
> 65y
300/300
Tolerance
CV events
Mortality
24 months

Catalonian Trial
ESHOL
HFHD vs HDF
300/300
CV events
Mortality
24 months

Turkish Trial
HFHD vs HDF
300/300
CV events
Mortality
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, 2015

~900 patients; JASN 2013

~ 800 patients
NDT 2012

70 HD; 40 HDF & 36 HF patients
JASN 2010

410 patients; enrollment closed
Dec 31, 2010; Results by Dec, 2015

~900 patients; JASN 2013

~ 800 patients
NDT 2012
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***
The Italian Convective Study
Multicenter, prospective, controlled, randomised trial

Study Design

Randomisation

Run-in
Stabilization phase

2 months
3 months

Hemodialysis

Random

50% hemodialysis

50% convective therapy

Evaluatation phase

21 months

146 patients

Low flux HD n = 70
Hemofiltration n = 36
Hemodiafiltration n = 40

Primary end point
Cardiovascular stability and blood pressure control

Treatment parameters valid for all patients

- **Monitors** with use of ultra-pure dialysate and sterile non-pyrogen substitution fluid checked at monthly intervals.

- **Dialysate/infusate conductivity**, **dialysate/infusate calcium and bicarbonate concentrations** and **the dialysate/infusate temperatures**, food ingestion habitude during the study and the use of anti-hypertensive drugs before the dialysis session were kept constant according to the Centre’s policy.

- **Blood flow** between 300 and 400 ml/min.

- **Treatment time** between 3 and 4.5 hours.

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Sessions with intradialytic hypotension (%)

HD
- Basal: 7.1%
- Evaluation phase: 7.9%

HF
- Basal: 9.8%
- Evaluation phase: 8.0%

HDF
- Basal: 10.6%
- Evaluation phase: 5.2%

P < 0.001

7.5%
Pre-dialytic systolic blood pressure (mmHg) repeated measures of analysis of variance

Increase of 4.2 mmHg of pre-dialysis systolic blood pressure values in HDF compared to the other groups

P = 0.038

Intradialytic changes of plasma sodium

HD  HF  HDF

Treatment

(mMol/L)

P 0.579

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.
Conclusions (2)

- The lower frequency of intradialytic symptomatic hypotension in HDF was associated with a significant increase in predialysis systolic blood pressure values.

- The beneficial effect of a 54% reduction of intradialytic symptomatic hypotensions should be balanced with a mean increase in predialysis systolic blood pressure of 4.2 mmHg.

Adequate sodium removal and cardiovascular stability

Hypernatric dialysate is more frequently used in order to avoid excessive sodium losses due to ultrafiltration and prevent cardio-vascular instability.

**HOWEVER**

- It may cause insufficient net sodium removal
- It favours the development of refractory hypertension and intradialytic hypertension
- It can trigger an intensive sense of thirst, causing high water intake

Adequate sodium removal and cardiovascular stability

- Sodium and water load varies from one uremic patient to another and from one dialytic session to another.

- Removal must be individualised by setting:
  - total ultrafiltration equal to interdialytic weight gain
  - end-dialysis plasma Na concentration as a “constant value”

Locatelli et al. Kidney Int Suppl. 2000; 76: S89-95
Conductivity kinetic model in HD

CKM may substitute sodium kinetic model

- to predict final plasma water conductivity when dialysate conductivity is known
- to determine dialysate conductivity needed to obtain a desired final plasma water conductivity
AIMS STUDY
Incidence of Symptomatic Hypotension during Dialysis Sessions

HFR Aeq vs Wash Out: $p < 0.05$  

HFR Aeq vs HFR: $p < 0.05$  

HFR vs Wash Out: $p = 0.061$

HFR Aequilibrium showed to be effective in stabilizing intradialytic haemodynamic (blood pressure and heart rate).

During HFR Aequilibrium treatment periods a reduction of intradialytic hypotension events was observed.

A reduction of all care intradialytic interventions was obtained with HFR Aequilibrium.

The clinical efficacy of HFR Aequilibrium resulted higher on more unstable patients.

HFR Aequilibrium induced a haemodynamic stabilizing effect on the following WO and HFR treatment periods (“carry – over” effect).
We called “Lag Phenomenon” the delay between the abrupt normalization of extracellular volume and the much more gradual decrease in the pre-dialysis MAP.
In order to maintain stable sodium balance, dry body weight and sodium plasma concentration should be kept constant.

Dialysate and infusate sodium concentration should be personalized, and frequently checked, not only in patients with intradialytic hypotension, but also in patients with hypertension, especially those with residual renal function.
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
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

### Primary outcome

<table>
<thead>
<tr>
<th>Online Hemodiafiltration</th>
<th>Low-Flux Hemodialysis</th>
<th>HR (95% CI)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events</td>
<td>Person-Years of Follow-Up</td>
<td>Number of Events</td>
</tr>
<tr>
<td>131</td>
<td>1085</td>
<td>138</td>
</tr>
</tbody>
</table>

Primary outcome: all-cause mortality

\(^a\) Obtained through unadjusted Cox proportional hazards models

Risk of all-cause mortality by achieved convection volume
82 missing and 206 deaths instead of 269

<table>
<thead>
<tr>
<th>HD Online Hemodiafiltration Convection Volume Tertiles</th>
<th>$P$ for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td></td>
</tr>
<tr>
<td>crude</td>
<td></td>
</tr>
<tr>
<td>&lt;18.17 L</td>
<td>1.0</td>
</tr>
<tr>
<td>0.95 (0.66–1.38)</td>
<td>0.83 (0.57–1.22)</td>
</tr>
<tr>
<td>0.83 (0.57–1.22)</td>
<td>0.62 (0.41–0.93)</td>
</tr>
<tr>
<td>0.62 (0.41–0.93)</td>
<td>0.010</td>
</tr>
<tr>
<td>adjusted</td>
<td></td>
</tr>
<tr>
<td>&lt;18.17 L</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>0.79 (0.53–1.14)</td>
</tr>
<tr>
<td>0.79 (0.53–1.14)</td>
<td>0.77 (0.51–1.14)</td>
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<tr>
<td>0.77 (0.51–1.14)</td>
<td>0.65 (0.42–0.99)</td>
</tr>
<tr>
<td>0.65 (0.42–0.99)</td>
<td>0.012</td>
</tr>
<tr>
<td>adjusted</td>
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<tr>
<td>&lt;18.17 L</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>0.80 (0.52–1.24)</td>
</tr>
<tr>
<td>0.80 (0.52–1.24)</td>
<td>0.84 (0.54–1.29)</td>
</tr>
<tr>
<td>0.84 (0.54–1.29)</td>
<td>0.61 (0.38–0.98)</td>
</tr>
<tr>
<td>0.61 (0.38–0.98)</td>
<td>0.015</td>
</tr>
</tbody>
</table>

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

Echocardiography was used to assess LVM and EF in 342 patients followed for up to 4 years.

PWV was measured in 189 patients for up to 3 years.

Effect of HDF versus HD on LVM, EF, and PWV was valuated using linear mixed models.
Table 2. Changes of left ventricular mass, ejection fraction, and pulse-wave velocity in postdilution online hemodiafiltration and low-flux hemodialysis groups over time

<table>
<thead>
<tr>
<th>Variable per Duration of Follow-up</th>
<th>Mean Change in LVM or PWV per Year (95% CI)</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Change in LVM or PWV per Year (95% CI)</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HDF Group</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 year</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LVM (g)</td>
<td>2.48 (−17.89 to 22.85)</td>
<td>0.77</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>−3.06 (−6.94 to 0.82)</td>
<td>0.12</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PWV (m/s)</td>
<td>−0.41 (−1.21 to 0.40)</td>
<td>0.32</td>
<td></td>
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<tr>
<td>3 years</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM (g)</td>
<td>−2.04 (−10.12 to 6.03)</td>
<td>0.61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>−0.39 (−2.51 to 1.73)</td>
<td>0.72</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PWV (m/s)</td>
<td>−0.01 (−0.41 to 0.40)</td>
<td>0.98</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVM (g)</td>
<td>−0.86 (−8.85 to 7.71)</td>
<td>0.87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF (%)</td>
<td>−0.29 (−2.34 to 1.76)</td>
<td>0.78</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

P Value for Slope: HDF versus HD

Analyses were adjusted for baseline LVM/ PWV. P value comparing the slope to be different from zero. 95% CI, 95% confidence interval; EF, ejection fraction.
Ejection fraction significantly increased in patients treated with HDF. LVM and PWV do not differ in patients treated HDF or HD. Mostovaya, 2014
No differences related to the convective volumes
Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study

Ercan Ok¹, Gulay Asci¹, Huseyin Toz¹, Ebru Sevinc Ok¹, Fatih Kircelli¹, Muntaz Yilmaz¹, Ender Hur¹, Meltem Sezis Demirci¹, Cenk Demirci¹, Soner Duman¹, Ali Basci¹, Siddig Momin Adam², Ismet Onder Isik², Murat Zengin², Gultekin Suleymanlar³, Mehmet Emin Yilmaz⁴ and Mehmet Ozkahya¹ and On behalf of the ‘Turkish Online Haemodiafiltration Study’

¹Division of Nephrology, Ege University School of Medicine, Izmir, Turkey, ²Fresenius Medical Care Dialysis Clinics, Turkey, ³Division of Nephrology, Akdeniz University School of Medicine, Antalya, Turkey and ⁴Division of Nephrology, Dicle University School of Medicine, Diyarbakir, Turkey

Correspondence and offprint requests to: Ercan Ok; E-mail: ercan.ok@ege.edu.tr
Composite event-free survival in patients treated with OL-HDF and high-flux HD

## Mortality

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 782)</th>
<th>OL-HDF (n = 391)</th>
<th>High-flux HD (n = 391)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mortality (n, %)</td>
<td>117 (15.0)</td>
<td>52 (13.3)</td>
<td>65 (16.6)</td>
</tr>
<tr>
<td>Cardiovascular mortality (n, %)</td>
<td>76 (9.7)</td>
<td>32 (8.1)</td>
<td>44 (11.2)</td>
</tr>
<tr>
<td>Noncardiovascular mortality (n, %)</td>
<td>41 (5.2)</td>
<td>20 (5.1)</td>
<td>21 (5.3)</td>
</tr>
</tbody>
</table>
Overall (A) and cardiovascular survival (B) among the treatment groups

A: Overall Survival
- OL-HDF > 17.4 L
- OL-HDF ≤ 17.4 L
- High-flux HD

B: Cardiovascular Survival
- OL-HDF > 17.4 L
- OL-HDF ≤ 17.4 L
- High-flux HD

p=0.03
p=0.002

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

36 months survival in the intention to treat population (p=0.001 by the long rank test)
Analyses for the main outcome showing HRs (95% CIs) for the intervention based on relevant variable that were found to be independent predictors for all-cause mortality.

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)
### Outcome data: Hospitalizations and intradialysis symptoms

<table>
<thead>
<tr>
<th>Event</th>
<th>Hemodialysis Group (n=450) (867.3 Patient-Years at Risk)</th>
<th>OL-HDF Group (n=456) (863.1 Patient-Years at Risk)</th>
<th>Rate Ratio (95% CI)</th>
<th>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Events</td>
<td>No. of Events/100 Patient-Years</td>
<td>No. of Events</td>
<td>No. of Events/100 Patient-Years</td>
</tr>
<tr>
<td>All-cause hospitalizations</td>
<td>412</td>
<td>47.5</td>
<td>317</td>
<td>36.7</td>
</tr>
<tr>
<td>Infections</td>
<td>73</td>
<td>8.4</td>
<td>72</td>
<td>8.3</td>
</tr>
<tr>
<td>Vascular access</td>
<td>98</td>
<td>11.3</td>
<td>56</td>
<td>6.5</td>
</tr>
<tr>
<td>Heart failure</td>
<td>28</td>
<td>3.2</td>
<td>15</td>
<td>1.7</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>25</td>
<td>2.9</td>
<td>16</td>
<td>1.9</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>26</td>
<td>3.0</td>
<td>28</td>
<td>3.2</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>10</td>
<td>1.2</td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td>Other reasons</td>
<td>152</td>
<td>17.5</td>
<td>126</td>
<td>14.6</td>
</tr>
<tr>
<td>Symptomatic hypotension episodes</td>
<td>8133</td>
<td>937.7</td>
<td>5862</td>
<td>679.2</td>
</tr>
<tr>
<td>Dysrhythmia</td>
<td>444</td>
<td>51.2</td>
<td>477</td>
<td>55.3</td>
</tr>
<tr>
<td>Thoracic pain</td>
<td>327</td>
<td>37.7</td>
<td>318</td>
<td>36.8</td>
</tr>
</tbody>
</table>

Prospective, randomized study

42 ESRD patients

n = 22 switch from high-flux HD to high-efficiency on-line HDF (\( > 22 \text{ L} \))
n = 20 continue high-flux HD

Ultrapure fluid, polysulfone membrane

Convection volume \(26.6 \pm 2.9 \text{ L} \), with a value \( > 22 \text{ L} \) reached in 91\% of the patients
Flow-mediated dilatation and carotid distensibility in HDF on-line
High-efficiency on-line haemodiafiltration improves conduit artery endothelial function compared with high-flux haemodialysis in end-stage renal disease patients

Table 4. Markers of oxidative stress, inflammation and NO pathway

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Change after 4 months</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HD</td>
<td>HDF</td>
<td>HD</td>
</tr>
<tr>
<td><strong>Oxidative stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBARs (μmol/L)</td>
<td>0.24 (0.19–0.32)</td>
<td>0.22 (0.16–0.45)</td>
<td>0.02 (−0.1 to 0.2)</td>
</tr>
<tr>
<td>ROS (μmol/L)</td>
<td>34.7 (29.5–50.0)</td>
<td>38.3 (30.0–49.5)</td>
<td>−3 (−11 to 2)</td>
</tr>
<tr>
<td>TAS (mmol/L)</td>
<td>1.55 ± 0.22</td>
<td>1.58 ± 0.26</td>
<td>−0.16 ± 0.29</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>4.4 (1.8–16)</td>
<td>4.7 (2.1–13.5)</td>
<td>1 (−2 to 4)</td>
</tr>
<tr>
<td><strong>NO pathway</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PKCε mRNA to 18S rRNA ratio</td>
<td>0.59 (0.56–0.70)</td>
<td>0.48 (0.36–0.59)</td>
<td>0.12 (0.03 to 0.31)</td>
</tr>
<tr>
<td>P85β mRNA to 18S rRNA ratio</td>
<td>0.80 (0.58–1.12)</td>
<td>0.77 (0.60–1.00)</td>
<td>−0.04 (−0.27 to −0.03)</td>
</tr>
</tbody>
</table>

HD, high-flux haemodialysis; HDF, high-efficiency on-line haemodiafiltration; TBARs, thiobarbituric acid reactive substances; ROS, reactive oxygen species; TAS, total antioxidant status; hs-CRP, high-sensitivity C-reactive protein; PKC, protein kinase C; IQR, interquartile range.

Values are expressed as mean ± SD, if not specified.
Clinical Evidence on Hemodiafiltration: A Systematic Review and a Meta-analysis

Ira M. Mostovaya,* Peter J. Blankestijn,* Michiel L. Bots,† Adrian Covic,‡ Andrew Davenport,§ Muriel P.C. Grooteman,¶** Jörgen Hegbrant,†† Francesco Locatelli,‡‡ Raymond Vanholder, §§ Menso J. Nubé,¶** and on behalf of the EUDIAL¹ – an official ERA-EDTA Working Group

**Meta-analysis of all RCTs comparing **MORTALITY** in patients treated with HD or HDF**
Clinical Evidence on Hemodiafiltration: A Systematic Review and a Meta-analysis

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Meta-analysis of all RCTs comparing **CARDIOVASCULAR MORTALITY** in patients treated with HD or HDF

<table>
<thead>
<tr>
<th>Study name</th>
<th>Weight</th>
<th>HDF (Events/Pat)</th>
<th>HD (Events/Pat)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grooteman et al. (12)</td>
<td>0.30</td>
<td>37/358</td>
<td>46/356</td>
<td>0.80</td>
<td>0.53 – 1.20</td>
</tr>
<tr>
<td>Ok et al. (13)</td>
<td>0.26</td>
<td>32/391</td>
<td>44/391</td>
<td>0.73</td>
<td>0.47 – 1.12</td>
</tr>
<tr>
<td>Maduell et al. (14)</td>
<td>0.44</td>
<td>37/456</td>
<td>55/450</td>
<td>0.66</td>
<td>0.57 – 0.92</td>
</tr>
<tr>
<td>Pooled</td>
<td>1.00</td>
<td>106/1205</td>
<td>145/1197</td>
<td>0.73</td>
<td>0.57 – 0.92</td>
</tr>
</tbody>
</table>

[Diagram showing relative risk with favours HDF and favours HD on the x-axis]
In This Issue

869 & 892-905
Blood Pressure Management

906
Nephrology Objectively Structured Clinical Examinations

945 & 1022
Drug Abuse and Kidney Disease

954, 968, & 888
Convective Versus Diffusive Dialysis Therapies
Convective Versus Diffusive Dialysis Therapies for Chronic Kidney Failure: An Updated Systematic Review of Randomized Controlled Trials

Ionut Nistor, MD,1,2,* Suetonia C. Palmer, MBChB, PhD,3,*
Jonathan C. Craig, MBChB, DCH, MM, PhD,4 Valeria Saglimbene, MSc, Valeria Saglimbene, MSc,
Mariacristina Vecchio, MSc,6 Adrian Covic, MD, PhD,1 and Giovanni F.M. Strippoli, MD, PhD, MM, MPH4,5,6

Cochrane review 2006
2341 titles and abstracts identified through database searching
639 Medline (1966 to 2006)
1296 Embase (1980 to 2006)
410 Cochrane Central Registry of Controlled Trials (issue 2, 2006), CDSR, and CINAHL (1872-2006)

2260 excluded
Not RCTs, not appropriate interventions, not dialysis population, or not relevant outcomes

81 Full text articles for detailed assessment

61 excluded
47 Not RCTs
6 Outcomes not relevant to review
5 RCTs of other interventions
3 Reviews

17 RCTs (20 publications) identified
600 participants

Included in systematic review
35 RCTs
4039 participants

Cochrane review 2013
180 titles and abstracts identified through searching of Cochrane Renal Groups’ Specialized Register (February 2012)

31 citations excluded in 44 publications
6 Not RCT
6 Not relevant outcome
19 Not relevant intervention

136 Full text articles for detailed assessment

75 excluded or new reports of included studies
27 No relevant intervention
14 Not RCT
10 No relevant outcome
19 other publication/new reports of trials already included in original review
5 ongoing studies

18 new RCTs (61 publications identified)
3439 participants

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3439 participants
Convective Versus Diffusive Dialysis Therapies for Chronic Kidney Failure: An Updated Systematic Review of Randomized Controlled Trials

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<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>No. of events/No. of participants</th>
<th>Relative risk (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Convection</td>
<td>Diffusion</td>
<td>Random effects model</td>
</tr>
<tr>
<td>Beerathout et al, 2005</td>
<td>1/20</td>
<td>1/20</td>
<td>1.00 (0.07 to 14.9)</td>
</tr>
<tr>
<td>Schiff, 2007</td>
<td>1/38</td>
<td>2/38</td>
<td>0.50 (0.04 to 5.28)</td>
</tr>
<tr>
<td>Wizemann et al, 2000</td>
<td>1/23</td>
<td>2/21</td>
<td>0.46 (0.04 to 4.68)</td>
</tr>
<tr>
<td>PROFIL study, 2011</td>
<td>2/27</td>
<td>3/21</td>
<td>0.52 (0.10 to 2.83)</td>
</tr>
<tr>
<td>Locatelli et al, 1996</td>
<td>7/50</td>
<td>6/155</td>
<td>3.62 (1.27 to 10.26)</td>
</tr>
<tr>
<td>Locatelli et al, 2010</td>
<td>7/76</td>
<td>8/70</td>
<td>0.81 (0.31 to 2.11)</td>
</tr>
<tr>
<td>Santoro et al, 2008</td>
<td>7/32</td>
<td>12/32</td>
<td>0.58 (0.26 to 1.29)</td>
</tr>
<tr>
<td>TURKISH OL-HDF study, 2013</td>
<td>52/391</td>
<td>65/391</td>
<td>0.80 (0.57 to 1.12)</td>
</tr>
<tr>
<td>Tessitore et al, 2012</td>
<td>65/177</td>
<td>69/194</td>
<td>1.03 (0.79 to 1.35)</td>
</tr>
<tr>
<td>ESHOL study, 2013</td>
<td>85/456</td>
<td>122/450</td>
<td>0.69 (0.54 to 0.88)</td>
</tr>
<tr>
<td>CONTRAST study, 2012</td>
<td>131/358</td>
<td>138/356</td>
<td>0.94 (0.78 to 1.14)</td>
</tr>
<tr>
<td>Total</td>
<td>359/1648</td>
<td>428/1748</td>
<td>0.87 (0.70 to 1.07)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2_{10}= 15.1$; $P = 0.1$; $I^2 = 34\%$
Cardiovascular outcomes

Dialysis parameters

Dialysis type in comparator group
- High flux membranes
- Low flux membranes
- Combination of High & Low flux membranes

RR (95% CI)  Heterogeneity p-value
- 0.81 (0.58, 1.13)  0.44
- 1.03 (0.83, 1.28)
- 0.66 (0.45, 0.99)

Study quality parameters

Sequence generation description
- Low risk
- Unclear risk

- 0.83 (0.55, 1.27)  0.90
- 0.82 (0.58, 1.15)

Trial analysis method
- Intention to treat
- Per protocol

- 0.93 (0.42, 2.05)  0.21
- 0.75 (0.58, 0.97)
Effect of Hemodiafiltration or Hemofiltration Compared With Hemodialysis on Mortality and Cardiovascular Disease in Chronic Kidney Failure: A Systematic Review and Meta-analysis of Randomized Trials

Amanda Y. Wang, MBBS, FRACP, Toshiharu Ninomiya, MD, PhD, Anas Al-Kahwa, BSc(Med), VLado Perkovic, MBBS, PhD, FRACP, Martin P. Gallagher, MBBS, PhD, FRACP, Carmel Hawley, MBBS (Hons), M Med Sci, FRACP, and Meg J. Jardine, MBBS, PhD, FRACP.

### All-cause mortality

<table>
<thead>
<tr>
<th>Dialysis parameters</th>
<th>RR (95% CI)</th>
<th>Heterogeneity p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Filtration type in intervention group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemodiafiltration</td>
<td>0.88 (0.66, 1.17)</td>
<td>0.67</td>
</tr>
<tr>
<td>Haemofiltration</td>
<td>0.55 (0.27, 1.16)</td>
<td></td>
</tr>
<tr>
<td>Combination of HDF &amp; HF</td>
<td>0.81 (0.31, 2.11)</td>
<td></td>
</tr>
<tr>
<td><strong>Dialysis type in comparator group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High flux membranes</td>
<td>0.79 (0.57, 1.11)</td>
<td>0.69</td>
</tr>
<tr>
<td>Low flux membranes</td>
<td>0.91 (0.76, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Combination of high &amp; low flux membranes</td>
<td>1.45 (0.29, 7.35)</td>
<td></td>
</tr>
<tr>
<td><strong>Study quality parameters</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sequence generation description</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0.82 (0.65, 1.03)</td>
<td>0.39</td>
</tr>
<tr>
<td>High risk</td>
<td>0.61 (0.34, 1.09)</td>
<td></td>
</tr>
<tr>
<td>Unclear risk</td>
<td>1.56 (0.36, 6.80)</td>
<td></td>
</tr>
<tr>
<td><strong>Free of selective outcome reporting</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>0.64 (0.65, 1.09)</td>
<td>0.59</td>
</tr>
<tr>
<td>High risk</td>
<td>0.48 (0.09, 2.50)</td>
<td></td>
</tr>
<tr>
<td><strong>Trial analysis method</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention to treat</td>
<td>0.91 (0.76, 1.09)</td>
<td>0.87</td>
</tr>
<tr>
<td>Per protocol</td>
<td>0.87 (0.55, 1.37)</td>
<td></td>
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Symptomatic hypotension

**HDF**
- Lin (2001)
- Schiffi (2007)
- Maduell (2013)
- Subtotal ($I^2 = 86.1\%, p = 0.001$)

**HF**
- Santoro (2008)
- Subtotal

**HDF or HF**
- Locatelli (2010)
- Subtotal

Overall ($I^2 = 76.7\%, p = 0.002$)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDF</td>
<td>0.39 (0.18, 0.86)</td>
</tr>
<tr>
<td></td>
<td>0.36 (0.25, 0.53)</td>
</tr>
<tr>
<td></td>
<td>0.72 (0.68, 0.77)</td>
</tr>
<tr>
<td></td>
<td>0.49 (0.28, 0.86)</td>
</tr>
<tr>
<td>HF</td>
<td>0.11 (0.01, 1.04)</td>
</tr>
<tr>
<td></td>
<td>0.11 (0.01, 1.04)</td>
</tr>
<tr>
<td>HDF or HF</td>
<td>0.84 (0.26, 2.68)</td>
</tr>
<tr>
<td></td>
<td>0.84 (0.26, 2.68)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.49 (0.30, 0.81)</td>
</tr>
</tbody>
</table>
# Outcomes of CKD patients receiving HDF versus HD

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

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>HDF vs Comp</th>
<th>Type of study</th>
<th>β2-M</th>
<th>Survival</th>
<th>Tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locatelli F et al, 1996</td>
<td>LF-HD vs cuprophan-HD vs HF-HD vs HDF</td>
<td>RCT</td>
<td>↓ (HF-HD and HDF)</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Wizemann V et al, 2000</td>
<td>HDF vs LFHD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Bosch JP et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 45%</td>
<td>↑</td>
</tr>
<tr>
<td>Canaud B et al, 2006</td>
<td>HDF +/- vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 35%</td>
<td>=</td>
</tr>
<tr>
<td>Jirka et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>↑ 36%</td>
<td>=</td>
</tr>
<tr>
<td>Schiffl H et al, 2007</td>
<td>HDF vs HFHD + UPD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Vinhas J et al, 2007</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>?</td>
<td>↑ 50%</td>
<td>↑</td>
</tr>
<tr>
<td>Panichi V et al, 2008</td>
<td>HDF +/- vs LFHD</td>
<td>Prospective controlled study</td>
<td>↓</td>
<td>↑ 15%</td>
<td>↑</td>
</tr>
<tr>
<td>Santoro A et al, 2008</td>
<td>HF vs HFHD</td>
<td>RCT</td>
<td>↓</td>
<td>↑ 18%</td>
<td>↑</td>
</tr>
<tr>
<td>Tiranathanagul K 2009</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>↓</td>
<td>=</td>
<td>↑</td>
</tr>
<tr>
<td>Vilar E et al, 2009</td>
<td>HDF vs HFHD</td>
<td>Historical prospective cohort</td>
<td>↓</td>
<td>↑ 34%</td>
<td>↑</td>
</tr>
<tr>
<td>Locatelli F et al, 2010</td>
<td>HDF &amp; HF vs LFHD</td>
<td>RCT</td>
<td>↓</td>
<td>=</td>
<td>↑ ↑ ↑</td>
</tr>
</tbody>
</table>
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.
HDF Trends by Country
– DOPPS 2-5 (2002-2013) –

Non-European Countries

European Countries

HDF (%)

Study Year

Study Year
there is no support for the recommendation of the routine use of hemodiafiltration

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