Present evidence on online hemodiafiltration.

Peter J. Blankestijn
Department of Nephrology,
Center Circulatory Health, University Medical Center Utrecht,
The Netherlands
Outline of presentation

• Basic principle of HDF
• Meta-analysis of trials & pooling project
• Safety
• Mechanism(s) of effect
• Practical issues
• What next?
• Conclusions
Solute fluxes in different treatment modalities
Different forms of hemodiafiltration

High-flux HD with unknown convective removal

On-line HDF with 90 ml/min convective removal

Blood and dialysate flow in mL/min

Nephrol Dial Transplant 2013
Mortality risk for patients receiving high efficiency HDF vs. HD is reduced

European Results from DOPPS

n = 2165, adjusted for age, sex, time on dialysis, comorbidity, weight, catheter, Hb, alb, nPCR, lipids, Kt/V, EPO, QoL

Kidney Int 2006; 69:2087-2093
Randomized clinical trials in Europe evaluating HDF vs HD

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

Muriel P.C. Grooteman,† Marinus A. van den Dorpel,‡ Michel L. Bots,§ E. Lars Penne,‖ Neelke C. van der Weerd,† Albert H.A. Mazzaro,‡ Carla H. den Hoedt,‖ Ingeborg van der Tawel,‖ Renée Lévesque,‖ Menno J. Nijp,‖ Piet M. ter Wee,‡ and Peter J. Blankensteijn,‖ for the CONTRAST Investigators

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

Francisco Maduell,*, Francisco Moreno,§ Mercedes Pons,∥ Rosa Rambos,∥ Josep Mora-Macías,∥ Jordi Carreras,∥ Jordi Soler,** Ferran Torres,∥∥ Josep M. Campistol,* and Alberto Martinez-Castro,* for the ESHO Study Investigators

*Nephrology Department, Hospital Clinic, Barcelona, Spain; †Nephrology Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain; ‡CETIRS, Barcelona, Spain; §Hospital San Antonio Abad, Vilanova i la Geltrú, Spain; ††Nanovas Medical Care, Granollers, Spain; †‡Eunavus Max Llibreger, L’Hospitalet, Llibreger, Spain; †∥Nanovas Medical Care, Roses, Spain; ‡∥∥Biostatistics Unit, School of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; ‡∥∥∥Nephrology Department, Hospital Universitari Bellvitge, L’Hospitalet, Bellvitge, Spain.

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

Ercan Ok,‡ Gulay Asci,§ Hayeun Toz,¶ Ebru Sevinc Ok,† Fatih Kirciliar,† Mustafa Yılmaz,‡ Endar Hur,§ Mehmet Sırrı Demirel,‡ Cenk Demirci,‖ Sener Duman,‖ Ali Basınlı,∥ Siddig Morin Adam,∥ Ismet Onder Isık,∥ Murat Zengin,∥ Gökhan Suleymanlar,∥ Mehmet Emir Yılmaz,‡ and Mehmet Oralıly from the ‘Turkish Online Haemodiafiltration Study’

*Division of Nephrology, Ege University School of Medicine, Izmir, Turkey; †Division of Nephrology, Akdeniz University School of Medicine, Antalya, Turkey; ‡Division of Nephrology, Dicle University School of Medicine, Diyarbakir, Turkey.

Correspondence and offprint requests to: Ercan Ok; E-mail: ercan.ok@ege.edu.tr

Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly

Marion Morena,∗,†,‡, Audrey Jaussent,∗, Zofia Chalabi,∗, Hélène Leray-Moragues,§, Leila Cherine,§, Alain Debure,§, Damien Thibaudin,§, Lynda Azouz,¶, Laure Patier,¶, François Maurice,¶, Philippe Nicoud,¶, Claude Durand,¶, Bruno Seigneuric,¶, Anne-Marie Dupuy,¶, Marie-Christine Picot,¶, Jean-Paul Cristol,*,†, and Bernard Canaud,‡,‡, for the FRENCHIE Study Investigators

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HDF Pooling project

- **Aim**: compare effects of online HDF and standard HD on all cause and cause specific mortality in ESKD patients.
- Pooling all individual data of four published trials.
- For this analysis additional follow up data on all cause and cause specific mortality was collected.
- 2793 patients, median follow up 2.5 y.

- Financed by EUdial.
## Meta-analysis of all individual data of 4 RCTs

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Hemodialysis</th>
<th></th>
<th>On line HDF</th>
<th></th>
<th></th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events/100 PY</td>
<td>Events</td>
<td>Events/100 PY</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>All-cause mortality</strong></td>
<td>410</td>
<td>12.10</td>
<td>359</td>
<td>10.45</td>
<td></td>
<td>0.86 (0.75; 0.99)</td>
</tr>
<tr>
<td><strong>CVD mortality</strong></td>
<td>164</td>
<td>4.84</td>
<td>128</td>
<td>3.73</td>
<td></td>
<td>0.77 (0.61; 0.97)</td>
</tr>
<tr>
<td><strong>Infections</strong></td>
<td>77</td>
<td>2.27</td>
<td>73</td>
<td>2.13</td>
<td></td>
<td>0.94 (0.68; 1.30)</td>
</tr>
<tr>
<td><strong>Sudden death</strong></td>
<td>56</td>
<td>1.65</td>
<td>56</td>
<td>1.63</td>
<td></td>
<td>0.99 (0.68; 1.43)</td>
</tr>
</tbody>
</table>

EuDial Pooling Project, N=2793, median follow up 2.5 y
Nephrol Dial Transplant 2016; 31: 978-984
## Risk of mortality by achieved volume in 4 RCTs

<table>
<thead>
<tr>
<th></th>
<th>Online Hemodiafiltration Convection Volume, delivered BSA-standardized in L / 1.73 m² per treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hemodialysis &lt;19 19–23 &gt;23</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1 0.91 (0.74; 1.13) 0.88 (0.72; 1.09) 0.73 (0.59; 0.91)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1 0.83 (0.66; 1.03) 0.93 (0.75; 1.16) 0.78 (0.62; 0.98)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1 1.00 (0.71; 1.40) 0.71 (0.50; 1.01) 0.69 (0.48; 0.98)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1 0.92 (0.65; 1.30) 0.71 (0.49; 1.03) 0.69 (0.47; 1.00)</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1 1.50 (0.93; 2.41) 0.96 (0.56; 1.65) 0.56 (0.30; 1.08)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1 1.50 (0.92; 2.46) 0.97 (0.54; 1.74) 0.62 (0.32; 1.19)</td>
</tr>
<tr>
<td>Sudden Death</td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1 1.24 (0.80; 1.91) 0.91 (0.57; 1.47) 0.60 (0.35; 1.03)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1 1.09 (0.69; 1.74) 1.04 (0.63; 1.70) 0.69 (0.39; 1.20)</td>
</tr>
</tbody>
</table>

EuDial Pooling Project, N=2793, median follow up 2.5 y
Nephrol Dial Transplant 2016; 31: 978-984
Convection volume by body size, when aimed at 23L/session
Relative survival rate (95% CI) versus convection volume

...adjusted for age, gender, Charlson comorbidity index, vasc access, albumin, CRP, Kt/V

N=2293

Kidney Int 2015 88:1108-16
Outline of presentation

• Basic principle of HDF
• Meta-analysis of trials & pooling project
• Safety
• Mechanism(s) of effect
• Practical issues
• What next?
• Conclusions
Online haemodiafiltration: definition, dose quantification and safety revisited

James E. Tattersall¹
Richard A. Ward² on behalf of the EUDIAL group*

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²Department of Medicine, University of Louisville, Louisville, KY, USA

Keywords: haemodiafiltration, review, definition, safety

The details of the EUDIAL group are given in Appendix 2.
Results of CFU and endotoxin measurements

Ultrapure dialysate

CFU/mL

- ≥100: 0.7%
- ≥1 - <100: 0.7%
- ≥0.1 - <1: 12.1%
- <0.1: 87.3%

EU/mL

- ≥0.3: 0.4%
- ≥0.03 - <0.3: 0.9%
- <0.03: 1.2%

Reference quality level

n=1185

n=1058

8 centers, 12 months

11258 HDF sessions in 97 patients

Kidney Int 2009; 76: 665-72
## Risk of mortality by achieved volume in 4 RCTs

<table>
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EuDial Pooling Project, N=2793
Nephrol Dial Transplant 2016; 31: 978-984
Outline of presentation

• Basic principle of HDF
• Meta-analysis of trials & pooling project
• Safety
• Mechanism(s) of effect
• Practical issues
• What next?
• Conclusions
Annualized all cause and CVD mortality/100 patient years in the complete online HDF cohort and in thirds of the convection volume. The HD group is used as reference.

<table>
<thead>
<tr>
<th></th>
<th>HD</th>
<th>Online HDF: BSA adjusted convection volume (L/session)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n.a.</td>
<td>Mean 22</td>
</tr>
<tr>
<td><strong>All cause/100 PY</strong></td>
<td>12.10</td>
<td>10.45</td>
</tr>
<tr>
<td><strong>CVD/100 PY</strong></td>
<td>4.84</td>
<td>3.73</td>
</tr>
</tbody>
</table>
Annualized CVD mortality per 100 patient-years in the HD and online HDF groups (Pooling Project)

N=2793

HD

- unclassified CVD: 1.2
- non-cardiac: 1.2
- cardiac: 2.4

HDF

- unclassified CVD: 1.1
- non-cardiac: 1.1
- cardiac: 1.6

What could be the mechanism(s)

- Better removal of toxins
- Improved hemodynamic stability
- Less inflammatory status
- Yet other factors??
Original Hypothesis

improvement in clearance of MMW solutes during online HDF
↓
better correction of uremic environment
↓
less cardiovascular damage
↓
lower cardiovascular morbidity and mortality

HEMO study: $\beta_2m$ levels and mortality

Relative Risk

Cumulative mean predialysis serum $\beta_2m$ (mg/L)

N=1704
ONLINE HDF: Substitution Volume

Achieving high substitution volumes, more effective elimination of middle molecules and may improves patient outcomes

Nephrol Dial Transplant 2000; 15: 49-54
Pre-dialysis β2-microglobulin levels

![Graph showing the change in β2-microglobulin levels over time (months) for lowflux HD and online HDF, with a p value of less than 0.001.]

N=714

*J Am Soc Nephrol 2012*
## Results on CRP and IL-6

<table>
<thead>
<tr>
<th></th>
<th>HDF (N=201)</th>
<th>HD (N=204)</th>
<th>HDF versus HD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Δ/yr</td>
<td>P</td>
<td>Δ/yr</td>
</tr>
<tr>
<td>LnCRP (mg/L)</td>
<td>0.03</td>
<td>0.61</td>
<td>0.17</td>
</tr>
<tr>
<td>LnIL-6 (pg/mL)</td>
<td>0.04</td>
<td>0.21</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Results from a linear mixed effect model, measurements until 36 months

N = 1295 samples

Kidney Int 2014
RCT showing decrease of intradialytic hypotension with convective therapies

dialysis sessions with symptomatic intradialytic hypotension

<table>
<thead>
<tr>
<th></th>
<th>at baseline</th>
<th>at 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HD, n=70</strong></td>
<td>7.1</td>
<td>7.9</td>
</tr>
<tr>
<td>low-flux</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDF, n=40</strong></td>
<td>10.6</td>
<td>5.2 *</td>
</tr>
<tr>
<td>predilution, 40L</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HF, n=36</strong></td>
<td>9.8</td>
<td>8.0 *</td>
</tr>
<tr>
<td>predilution, 60L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<0.001

### Intra-dialytic hemodynamic instability (mean CV 23L)

<table>
<thead>
<tr>
<th>Condition</th>
<th>hf-HD (no events /100 patient years)</th>
<th>HDF (no events /100 patient years)</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypotension</td>
<td>938</td>
<td>697</td>
<td>0.72 (0.68-0.77)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

How could these mechanisms result in a reduction in CV mortality?

Possible pathways include:

• less vascular damage

• better haemodynamic stability during treatment and as a consequence fewer periods of cardiac/tissue ischemia, fewer myocardial infarctions, resulting in a less arrhythmogenic milieu.
Overall conclusion: no difference in cardiovascular response between the two modalities.

Intradialytic Cardiac Magnetic Resonance Imaging to Assess Cardiovascular Responses in a Short-Term Trial of Hemodiafiltration and Hemodialysis

Charlotte Buchanan,* Azharuddin Mohammed,† Eleanor Cox,* Katrin Köhler,* Bernard Canaud,‡ Maarten W. Taal,† Nicholas M. Selby,† Susan Francis,* and Chris W. McIntyre*;

*Sir Peter Mansfield Imaging Centre and †Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, University of Nottingham, Nottingham, United Kingdom; ‡Center of Excellence Medical Europe, Middle East and Africa, Fresenius Medical Care, Bad Homburg, Germany; and Departments of †Medicine and *Biophysics, Schulich School of Medicine and Dentistry, Western University, London, Canada

JASN 2017;28:1269-1277
All cause mortality in patients on HD and pre-OL HDF by substitution volume

Presentation at 53rd annual ERA-EDTA meeting 2016, Vienna
Registry of JSDT, courtesy K. Kikushi, I. Masakane et al
Contrib Nephrol 2017 189; 17-23
Outline of presentation

• Basic principle of HDF
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Convection volume distribution in 4 RCTs
Convection volume over time: “Spaghetti plot”

Over time $\Delta CV$: 0.36 L/treatment per yr (0.12 – 0.60, p=0.003)
### Factors affecting convection volume: multivariable analysis

**Table 3. Determinants of convection volume: univariable and multivariable linear regression analyses**

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Univariable model</th>
<th>Multivariable model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>95% CI</td>
</tr>
<tr>
<td>Male gender</td>
<td>1.97</td>
<td>0.99 to 2.94</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>-1.72</td>
<td>-3.04 to -0.39</td>
</tr>
<tr>
<td>Age (year)</td>
<td>-0.02</td>
<td>-0.06 to 0.02</td>
</tr>
<tr>
<td>Clinical charact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cardiovascu</td>
<td>-0.37</td>
<td>-1.36 to 0.62</td>
</tr>
<tr>
<td>Diabetes melitus</td>
<td>0.24</td>
<td>0.67 to 1.34</td>
</tr>
<tr>
<td>Dialysis vintage (year)</td>
<td>0.19</td>
<td>0.03 to 0.95</td>
</tr>
<tr>
<td>BSA (cm²)</td>
<td>0.04</td>
<td>0.02 to 0.06</td>
</tr>
<tr>
<td>Pre-dialysis systolic blood pressure (mmHg)</td>
<td>-0.01</td>
<td>-0.02 to 0.02</td>
</tr>
<tr>
<td>Residual kidney function*</td>
<td>-0.77</td>
<td>-1.74 to 0.21</td>
</tr>
<tr>
<td>Fistula (versus all other access types)</td>
<td>-0.26</td>
<td>-1.46 to 0.94</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>-0.19</td>
<td>-0.30 to -0.08</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>0.27</td>
<td>0.13 to 0.40</td>
</tr>
<tr>
<td>Treatment charact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment time (minute)</td>
<td>0.05</td>
<td>0.05 to 0.10</td>
</tr>
<tr>
<td>Blood flow rate (mL/min)</td>
<td>0.06</td>
<td>0.05 to 0.07</td>
</tr>
</tbody>
</table>

*Residual kidney function defined as diuresis of ≥100 mL/day.

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*Chapdelaine et al. Blood Purif 2014; 37; 229-237*
Key requirements for performing high volume post-dilution HDF

Table 4. Summary of the technical and practical aspects to optimize convection volume in online post-dilution HDF

- Ensure adequate dialysis time
- Ensure adequate blood flow
  o Select a vascular access able to deliver high blood flow rate; a central venous catheter should not be automatically considered a contra indication
  o Tailor the needle size to the desired blood flow rate (usually 15G-needle), not the opposite
  o Recognize the difference between steel and plastic needles in terms of size of the lumen
  o Monitor for access recirculation
  o Consider discrepancy between set and real values for blood flow rate
- Optimize filtration fraction on an individualized basis
  o Become acquainted with the specificities of the dialysis machine(s) employed in your HDF unit; read user manual thoroughly
  o If automatic regulation of substitution flow is chosen, know which factors are involved
  o Establish pre-specified and optimal safety thresholds for system pressures and filtration fraction
  o Learn how to manage the various safety alarms
  o Appreciate the influence of high haematocrit on plasma water filtration fraction; if needed adjust anti-coagulation
- Chose a haemodiafilter with a high hydraulic permeability, a large surface area and short fibres with large internal radius
- Avoid single-needle circuit configuration
- Perform regular teaching and feedback for the nursing staff
- Re-evaluate on a frequent basis that the convection volume goals are met and sustained
Summary present knowledge

Online hemodiafiltration in post-dilution mode:

Present knowledge:

– Suggestion of a reduction in all cause mortality, in particular CV mortality
– Especially when convection volume > 23 L/session (i.e. 69 L/week)
– In previous studies convection volume > 23 L/4h only in minority of patients
– No clear side effects, no clear safety issues
– Mechanism(s): not fully clear
Outline of presentation

- Basic principle of HDF
- Meta-analysis of trials & pooling project
- Safety
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Call text of HORIZON 2020 program

HORIZON 2020 - Work Programme 2016 - 2017
Health, demographic change and well-being

Type of Action: Research and Innovation action

The conditions related to this topic are provided at the end of this call and in the General Annexes.

SC1-PM-10-2017: Comparing the effectiveness of existing healthcare interventions in the adult population

Specific Challenge: Effective health care and prevention may be improved by additional evidence as to the most effective health interventions. Growing numbers of patients affected by chronic diseases also call for efficiently managing co-morbidities.

Scope: Proposals should compare the use of currently available preventative or therapeutic (pharmacological as well as non-pharmacological) healthcare interventions in adults. While there is no restriction on the diseases or interventions to be the focus of proposals, preference will be given to proposals focusing on interventions with high public health relevance and socio-economic impact, i.e. interventions addressing conditions that are particularly frequent, may lead to co-morbidities, have a high negative impact on the quality of life of the individual and/or are associated with significant costs or where savings can be achieved. A cost effectiveness analysis must be included. Given the focus on existing interventions, proposals will aim to contribute to improve interventions, take decisions about the discontinuation of interventions that are less effective or less cost-effective than others, and make recommendations on the most effective and cost-effective approaches. A comprehensive array of clinical and safety parameters, as well as health and socio-economic outcomes (e.g. quality
CONVINCE

• Hypothesis: treatment with HDF, when consistently delivered in high dose, results in an improvement in clinical outcome.
• End points:
  – All cause and cause specific mortality, CV morbidity
  – Patients perspectives
• Prospective randomized clinical trial, n=1800
• Funded by EC HORIZON 2020
Impact of CONVINCE

• If magnitude of an effect is in the range of the pooled analysis, then the study is of high clinical relevance and identifies an unparalleled improvement in the overall treatment of ESKD patients within the same treatment environment (logistic and infrastructure) as standard HD.

• Study provides highest level of evidence (level A). Guidelines will change. Daily practice will change globally.

• Patients perspectives: also in the absence of difference in the primary outcome, any difference in domains of patient perspectives, may be meaningful and (highly) clinically relevant
## CONVINCE

<table>
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<tr>
<th>Participant No</th>
<th>Participant organisation legal name</th>
<th>Country</th>
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Conclusions

Online hemodiafiltration in post-dilution mode:

Present knowledge:
- Suggestion of a reduction in all cause mortality, in particular CV mortality
- Especially when convection volume > 23 L/session (i.e. 69 L/week)
- In previous studies convection volume > 23 L/4h was only delivered in minority of patients
- No clear side effects, no clear safety issues
- Mechanism(s): not fully clear

CONVINCE will deliver definite proof of superiority yes/no.
Adapted from figure by Bernard Canaud