On line hemodiafiltration: clinical evidence.

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the Netherlands
Willem Kolff (1911 – 2009)

First hemodialysis in 1943
Solute fluxes in different treatment modalities
Different forms of HDF

High-flux HD
with unknown convective removal

Classical HDF
with 50 ml/min convective removal

On-line HDF
with 90 ml/min convective removal

NDT Plus 2010; 3: 8-16
Solute removal with different therapies

N=23, 3 treatment / mode
Same $Q_B$, $Q_D$, $t$, $\Delta BW$ and filter size

Am J Kidney Dis 2002; 40: 582
## Hemodiafiltration and ongoing randomized clinical trials.

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Contr Nephrol 2010
Outline of presentation

• Biochemical data:
  – β2M
  – phosphate
  – ESA sensitivity
• Morbidity / Mortality
• Safety
• Perspectives and remaining questions
CONTRAST: hypothesis

Improvement in clearance of MMW solutes during online HDF

↓

Better correction of uremic environment

↓

Decrease cardiovascular damage

↓

Decrease cardiovascular morbidity and mortality

CONTRAST: design and present status

• Design
  – prospective, randomized multicenter trial
  – run-in period: low-flux dialysis, Kt/V > 1.2 per treatment
  – randomization: on-line HDF and low-flux HD (treatment time unchanged)
  – target ultrafiltration volume is 6 L/h
  – n = ± 700
  – minimum follow up: 1 year
  – Trial management by Julius Clinical Research (www.juliusclinical.com)

• Present status
  – 715 patients included by Dec 31, 2009
  – > 25 centers participating (Netherlands, Norway and Canada)
CONTRAST: objectives

• Primary:
  – all cause mortality
  – fatal and non-fatal cardiovascular events

• Secondary:
  – left ventricular mass, arterial stiffness, carotid intima-media thickness
  – laboratory assessments e.g. endothelial function, oxidative stress
  – nutritional state
  – quality of life

HEMO study: $\beta_2$m levels and mortality

JASN 2006; 17 546-555
β2m clearance in HDF

Q_D 600 mL/min, Q_B 300 mL/min

Lornoy et al, NDT 2000; 15 (suppl 1): 49-54
Predialysis β2M in relation to residual kidney function

![Graph showing serum β2M levels in different baseline GFR categories.](Clin J Am Soc Nephrol 2010; 5: 80-86)
Changes in predialysis β2M

* p<0.01

Changes in predialysis β2M in HDF related to residual kidney function

Convection volume 19 ± 4 L

The effect of dialysis modality on phosphate control: haemodialysis compared to haemodiafiltration. The Pan Thames Renal Audit

Andrew Davenport¹, Carrie Gardner², Michael Delaney³
and on behalf of the Pan Thames Renal Audit Group⁴

Nephrol Dial Transpl 2010; 25: 897-901
Residual kidney function ↔ predialysis phosphate

GFR (mL/min/1.73m²)

0 0 - 1.65 1.66 - 4.13 >4.13

% of patients

n=270 n=94 n=94 n=94

sPhos > 1.78 mmol/L
sPhos > 1.13 and ≤ 1.78 mmol/L
sPhos ≤ 1.13 mmol/L

N=552

Residual kidney function ⇔ phosphate binding agents
Short term effects of online HDF on phosphate

Convection volume 19 ± 4 L

Am J Kidney Dis 2010; 55: 77-87
Short term effects of online HDF on phosphate

![Graph showing proportion of patients using phosphate binders over time.](chart.png)

Proportion of patients using phosphate binders (%)

- **Baseline**
- **3 months**
- **6 months**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Calcium salts</th>
<th>Calcium-free phosphate binders</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDF</td>
<td>46</td>
<td>76</td>
</tr>
<tr>
<td>HD</td>
<td>44</td>
<td>76</td>
</tr>
<tr>
<td>HDF</td>
<td>49</td>
<td>75</td>
</tr>
<tr>
<td>HD</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>HDF</td>
<td>48</td>
<td>78</td>
</tr>
<tr>
<td>HD</td>
<td>42</td>
<td>81</td>
</tr>
</tbody>
</table>

N=493

Am J Kidney Dis 2010; 55: 77-87
Proportion of patients achieving phosphate treatment targets (5.5 mg/dL = 1.78 mmol/L) at baseline and after 3 or 6 months of follow-up. Numbers above bars represent percentages. a) $P < 0.05$ (vs baseline); b) $P < 0.05$ (difference in change between groups).

Am J Kidney Dis 2010; 55: 77-87
Residual kidney function ↔ ESA

![Graph showing the relationship between residual kidney function and ESA index.](image)

- **n=270**
- **n=94**

**ESA index (DDD/kg/Htx100%)**

- 0.05
- 0.06
- 0.07
- 0.08
- 0.09

**rGFR (mL/min/1.73m2)**

- 0
- 0 - 1.65
- 1.66 - 4.13
- > 4.13

submitted
Change in ESA index after 12 months

Mean ΔESA index (DDD/kg/Hct/week)

 ESA index at baseline in tertiles

N=448

submitted
Outline of presentation

• Biochemical data:
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  – phosphate
  – ESA sensitivity

• Morbidity
• Mortality
• Safety
• Perspectives and remaining questions
### Retrospective analysis of intradialytic symptoms

<table>
<thead>
<tr>
<th>Episodes per session</th>
<th>On-line HDF 152 043 sessions</th>
<th>High-flux HD 291 222 sessions</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>intradialytic hypotension</td>
<td>0.03</td>
<td>0.05</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>saline bolus administration</td>
<td>0.02</td>
<td>0.03</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>cramping</td>
<td>0.01</td>
<td>0.01</td>
<td>ns</td>
</tr>
<tr>
<td>UF rate (ml/h)</td>
<td>700-800</td>
<td>500-600</td>
<td>0.003 - &lt;0.001</td>
</tr>
</tbody>
</table>

Study design

Randomization

Run-in: 2 months
Adaptation phase: 3 months
Evaluation phase: 21 months

50% hemodialysis
50% convectives therapies
25% HF
25% HDF

J Am Soc Nephrol 2010
RCT showing decrease of intradialytic hypotension with convective therapies

% of 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>
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* p<0.001

J Am Soc Nephrol 2010
DOPPS: risk of mortality

- **Reference**: relative risk of mortality 1.00, adjusted for age, sex, time on dialysis, comorbidity, weight, catheter, Hb, alb, nPCR, lipids, Kt/V, EPO, QoL
- **Low-flux HD**: 1.03, p=0.68
- **High-flux HD**: 0.93
- **Low-ef fic HIF**: 0.65
- **High-ef fic HIF**: 0.65

**Note**: The sample size for each group is as follows:
- Low-flux HD: 1366
- High-flux HD: 546
- Low-ef fic HIF: 156
- High-ef fic HIF: 97

Kidney Int 2006; 69:2087-2093
Survival differences between patients in whom the predominant treatment modality was HDF and high-flux HD

152,000 sessions of on-line HDF in 232 patients compared to 291,000 sessions on hfHD in 626 patients

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- Mortality
- Safety
- Perspectives and remaining questions
Schematic representation of the production of substitution fluid

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<tr>
<th>Quality level</th>
<th>Bacteria CFU/mL</th>
<th>Endotoxins EU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>standard</td>
<td>&lt; 100 - 200</td>
<td>&lt; 0.1 – 1.0</td>
</tr>
<tr>
<td>ultrapure</td>
<td>&lt; 0.1</td>
<td>&lt; 0.03</td>
</tr>
<tr>
<td>sterile</td>
<td>&lt; 10 (^{-6})</td>
<td>&lt; 0.03</td>
</tr>
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NDT Plus 2010; 3: 8-16
Results of CFU and endotoxin measurements

Ultrapure dialysate

<table>
<thead>
<tr>
<th>CFU/mL</th>
<th>n=1185</th>
<th>EU/mL</th>
<th>n=1058</th>
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<tbody>
<tr>
<td>≥100</td>
<td>0.7%</td>
<td>≥0.3</td>
<td>0.4%</td>
</tr>
<tr>
<td>≥1 - &lt;100</td>
<td>12.1%</td>
<td>≥0.03 - &lt;0.3</td>
<td>0.9%</td>
</tr>
<tr>
<td>≥0.1 - &lt;1</td>
<td>87.3%</td>
<td>&lt;0.03</td>
<td>1.2%</td>
</tr>
<tr>
<td>&lt;0.1</td>
<td></td>
<td>BDL</td>
<td>97.4%</td>
</tr>
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Reference quality level

8 centers, 12 months
11258 HDF sessions in 97 patients

Kidney Int 2009; 76: 665-72
Biochemical data:
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Morbidity

Mortality

Safety

Perspectives and remaining questions
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CONCLUSIONS

On line HDF as compared to standard HD:

- Short term results indicate that changes occur in potentially relevant substances / variables
- Effects most pronounced in patients without residual kidney function
- Better intradialytic hemodynamic stability
- Uncontrolled studies suggest (substantial) survival benefit
- Results on primary endpoints of RCTs will be available in near future