Hemodiafiltration: Where are we ? Where are we going ?

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Limits of conventional hemodialysis

Maltolerance of dialysis sessions

- Intradialytic Hypotension
- Cardiac Stunning
- Stroke
- Poor Quality of Life
- Gut Ischemia - Translocation

Gut wall

- Bacteria or LPS
- LPS
- Thoracic Duct
- Portal Vein
- Monocytes
- Tissue Hypoxia

Release of:
- IL-1, IL-6, IL-8, IL-10
- IFN-γ, TGF-β, TNF
- Chemokines, adhesion molecules
Limits of conventional dialysis modalities

Dialysis-related pathology

- β2-Amyloidosis
- Tissular calcinosis

Annual crude mortality, %

- Japan: 6.6%
- Europe: 15.6%
- USA: 21.7%

Source: DOPPS
Outline of the presentation

- Definition
- Epidemio
- Regulatory
- Efficacy
- Safety
- Outcomes
- Future of HDF
Outline of the presentation

- Definition
- Future of HDF
- Outcomes
- Efficacy
- Safety
- Regulatory
- Epidemiology
HDF combines **diffusive**, **convective** and **adsorptive** clearances in the same module.
Hemodiafiltration enhances clearances of middle and large molecular weight solutes.
Total solute clearance in HDF is not the algebraic sum of solute transfer component

\[ K_T = K_D + K_C + K_{\text{Ads}} \]

\[ K_T = K_D + 0.43 Q_{\text{UF}} + 8.3 \cdot 10^{-3} Q_{\text{UF}}^2 + ? \]

\[ K_T = K_D + 0.50 Q_{\text{UF}} \]

Convective **dialysis dose** is a linear function of substitution volume

\[ \beta_2\text{-Microglobulin, Reduction Rate (\%)} \]

\[ \text{On-line HDF substitution volume (ml/min)} \]


*Postdilution HDF*
Outline of the presentation

Definition
Epidemie
Future of HDF
Outcomes
Efficacy
Safety
Regulatory
Prevalence of HDF in Europe in 2010

Percent of HDF treated patients, %

<table>
<thead>
<tr>
<th>Country</th>
<th>Germany</th>
<th>Italy</th>
<th>Turkey</th>
<th>France</th>
<th>Spain</th>
<th>Portugal</th>
<th>Greece</th>
<th>Belgium</th>
<th>Netherlands</th>
<th>Hungary</th>
<th>Czech Republic</th>
<th>Serbia</th>
<th>Austria</th>
<th>Sweden</th>
<th>Switzerland</th>
<th>Slovakia</th>
<th>Denmark</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD treated</td>
<td>0.13</td>
<td>0.16</td>
<td>0.18</td>
<td>0.13</td>
<td>0.14</td>
<td>0.18</td>
<td>0.48</td>
<td>0.29</td>
<td>0.30</td>
<td>0.42</td>
<td>0.33</td>
<td>0.26</td>
<td>0.27</td>
<td>0.28</td>
<td>0.67</td>
<td>0.55</td>
<td>0.20</td>
</tr>
<tr>
<td>Online HDF</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bag HDF</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Hemodiafiltration Trends by Country

DOPPS 1-4 Sample Patients* (1996-2010)

*Initial prevalent cross-sections who dialyzed 3 times/wk with vintage ≥3 months; DOPPS 4 data are preliminary; ANZ, BE and SW did not participate in DOPPS phase 1
Facility % of Patients on HDF, by Phase and Country

Facility % of Patients

Initial prevalent cross-sections who dialyzed 3 times/wk with vintage ≥3 months

* p-value <0.05 for test for trend for HDF use over time; †HDF was not used in Japan during DOPPS phases 1 and 2
Outline of the presentation

Definition
Future of HDF
Epidemio
Outcomes
Efficacy
Safety
Regulatory
Hemodialysis/Patient Interaction

Water treatment system

Water

Concentrate

HDF machine

Dialysate

Patient
Water treatment system to produce ultrapure water

- Tap Water
- Softener
- Activated Charcoal
- μFilter
- 0.1μ+
- RO
- RO
- μFilter
- 0.1μ+
- Pump
- Recirculating Loop
- Dialysis Station
Ultrapure dialysis fluid is now recognized as a new standard of contemporary dialysis.
INTERNATIONAL STANDARD

ISO/FDIS 2009 11663

Quality of dialysis fluid for haemodialysis and related therapies

Qualité des fluides de dialyse pour hémodialyse et thérapies annexes

ISO/FDIS 2009-11663
3.18 non-pyrogenic
less than 0.03 EU/ml

NOTE Historically, the threshold pyrogenic dose of 5 EU/kg/h (the minimum dose that produces fever) has been used to set endotoxin limits of devices and injectable medications.

3.19 sterile
free from viable microorganisms with a sterility assurance level (SAL) of 6

NOTE 1 “sterile” can be used to describe a packaged solution that was prepared using a terminal sterilization process that has been demonstrated to achieve a $10^{-6}$ microbial survivor probability, i.e., assurance of less than one chance in one million that viable microorganisms are present in the sterilized article.

NOTE 2 Alternatively, “sterile” can be used to describe a solution prepared for immediate use by a continuous process that has been validated to produce a solution free from viable microorganisms with a SAL of at least 6. This SAL applies to the total volume of solution used in a single application.

ISO/FDIS 2009-11663
3.21 Ultrapure dialysis fluid

highly purified dialysis fluid that can be used in place of conventional dialysis fluid or as feed solution for possible further processing to create fluid intended for infusion directly into the blood

NOTE A widely accepted specification of ultrapure dialysis fluid is < 0.1 CFU/ml and < 0.03 EU/ml.

3.20 Substitution fluid

fluid used in haemofiltration and haemodiafiltration treatments which is infused directly into the patient's blood as a replacement for the fluid that is removed from the blood by filtration

NOTE 1 Substitution fluid is also referred to as substitution solution or replacement solution.

NOTE 2 Substitution fluid may also be used for bolus administration, for priming of extracorporeal blood circuit and for returning blood to the patient at the end of a treatment.
Water and dialysis fluid tend to the same degree of microbiological purity

<table>
<thead>
<tr>
<th>International standards of water and dialysis fluid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum levels</td>
</tr>
<tr>
<td>Microbial contamination (CFU/ml) Sensitized methods</td>
</tr>
<tr>
<td>Bacterial endotoxins (IU/ml) LAL</td>
</tr>
</tbody>
</table>

Water Treatment System, Contamination Levels

- **High contamination**
  - Activated Carbon
  - Reverse Osmosis
- **Low contamination**
  - Storage Tank
  - Pump
  - Distribution loop
  - HDF machine

- **Tap Water**
  - Softener
  - Waste

- **Concentrates**
  - µF
  - UF
Basic concept of online production of substitution fluid (infusate)

Patient

Ultrafilter

Direct connection

No dead space

Ultrafilter

Frequent disinfection

(Heat, Chemical)
Online HDF, Modalities of substitution

Post-dilution on-line HDF
Volume of substitution ≈ 25 l/ses

Pre-dilution on-line HDF
Volume of substitution ≈ 50 l/ses
On-Line HDF machines approved and labeled with CE mark

- Bellco Formula
- B.Braun Dialog
- Gambro AK 200S/ Ultra™
- Nikkiso DBB-05
- FMC 4008
- FMC 5008
- Gambro Innova

IEC  ISO
Outline of the presentation

- Definition
- Future of HDF
- Epidemiology
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- Outcomes
Safety and efficacy on long term use (1994-1997)

Canaud B et al, Nephrol Dial Transplant 2000; 15[S1]:60-67

19200 HDF sessions
Total production of substitution fluid 533 594 liters
Infusate bacteriometry (1994-1997)

19200 HDF sessions – Mean volume filtrate 24 liters
Total production of substitution fluid 533 594 liters


<table>
<thead>
<tr>
<th>Membranes cultured</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDF sessions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>18465</td>
<td>96.2</td>
</tr>
<tr>
<td>Positive</td>
<td>735</td>
<td>3.8</td>
</tr>
<tr>
<td>Total</td>
<td>19200</td>
<td>100.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Positive membranes</th>
<th>n cfu</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–9</td>
<td>663</td>
<td>90.2</td>
</tr>
<tr>
<td>10–99</td>
<td>48</td>
<td>6.5</td>
</tr>
<tr>
<td>100</td>
<td>24</td>
<td>3.3</td>
</tr>
<tr>
<td>Total</td>
<td>735</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Microbiological quality of purified water and ultrapure dialysis fluids for online HDF in clinical routine practice

- Subgroup analysis after enrolment
- 10 centers - One year follow-up
- 97 patients - 11258 HDF sessions
- 3961 samples

Clinical safety is confirmed on a routine basis and large scale

- One year follow-up
- 97 patients
- 11258 HDF sessions
- No febrile reactions
- No clinical adverse events

Ultrapurity of dialysis fluid is confirmed in 85 to 98% of samples

10 centers
One year follow-up
11258 HDF sessions
97 patients – 3961 samples

CONTRAST Dutch Convective Transport Study

Ultrapurity of infusate is confirmed in 99 to 100% of samples

CONTRAST Dutch Convective Transport Study

Penne EL et al, Kidney Int. 2009; 76: 665-672
Effects of OL-HDF & r-HDF on inflammatory & nutritional markers

Cross-over, randomized multicentre trial

Effects of OL-HDF and r-HDF on inflammatory and nutritional markers

Cross-over, randomized multicentre trial

Effect of HD and HDF on CD14^+CD16^+ monocytes, TNFα, IL6 and inflammatory markers

Cross-over, randomized study (31 HD patients)

- Polysulfone membrane
- Ultrapure dialysate
- Same dialysis conditions

OL-HDF reduces proinflammatory CD14<sup>+</sup>CD16<sup>+</sup> monocyte-derived dendritic cells
Outline of the presentation
High-Efficiency on-line HDF. What does it means?

- Treatment schedule
  - 3 sessions of 4 hours weekly (minimum)
  - Longer or more frequent (possible)
- Highly permeable synthetic membrane
- Large surface area > 1.8 m²
- Ultrapure bicarbonate dialysis fluid
- High blood flow (effective QB: 350 - 400 ml/min)
- High dialysate flow (500-700 ml/min) ⇒ diffusive dose
- Large volume of substitution ⇒ convective dose
  - Post-dilution (Qsub : 100 ml/min, 24 l / session)
  - Pre-dilution (Qsub : 200 ml/min, 48 l / session)
  - Mixed dilution (Qsub : 150ml/min, 36 l/session)
Distribution of Mean Replacement Fluid Volume for Patients on HDF, by Country

Volume of replacement fluid (Liters)

Country across phase 1 - 3

ANZ 50
BE 86
FR 184
GE 142
IT 270
JP 73
SP 56
SW 129
UK 69
All 1059

Initial prevalent cross-sections who dialyzed 3 times/wk with vintage ≥3 months; HDF not used in the US and Canada
Middle molecules removal in ol-HDF vs LF-HD vs HF-HD

Percent reduction per session (%)

Urea, 60d  Creat, 113d  Osteoc, 5.8kd  B2M, 11.8kd  Myogl, 16kd

LF-HD  HF-HD  Ol-HDF

Mean dialysis dose and nPCR in HDF treated patients with direct dialysis quantification method


Urea Monitoring, BioStat 1000

HDF vs HFHD: modest increase of urea Kt/V but significant reduction of circulating β2M

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>Period 1 p: baseline versus 6 months</th>
<th>Period 2 p: 6 months versus 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study group: n = 30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ol-HDF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eKt/V</td>
<td>1.20 ± 0.08</td>
<td>1.21 ± 0.08</td>
<td>1.34 ± 0.11</td>
<td>NS</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Beta₂ microglobulin (mg/dL)</td>
<td>35.0 ± 9.6</td>
<td>34.9 ± 9.2</td>
<td>24.5 ± 9.0</td>
<td>NS</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Controls: n = 35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LFHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eKt/V</td>
<td>1.22 ± 0.06</td>
<td>1.23 ± 0.07</td>
<td>1.22 ± 0.06</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Beta₂ microglobulin (mg/dL)</td>
<td>36 ± 12</td>
<td>37 ± 13</td>
<td>37 ± 11</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Movilli E et al, Nephro Dial Transplant. 2011; 0:1-6 ePub May 2011
β2-M concentrations is reduced after switching from HFHD to ol-HDF

Tiranathanagul K et al. Ther Apher Dial 2009; 13: 56-62
High efficiency HDF increases the erythropoietic response to ESA

High efficiency HDF increases the phosphate mass removal


4hrs x 3wk
HF80 - QD800
Direct dialysate quantification

22 HD pats
Hemodynamic tolerance is improved in HDF

<table>
<thead>
<tr>
<th>Condition</th>
<th>HFHD (Baseline)</th>
<th>On-line HDF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Hypotension</td>
<td>20.2 ± 17.1</td>
<td>10.4 ± 17.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.9 ± 4.7</td>
<td>2.2 ± 7.7</td>
</tr>
<tr>
<td>Muscle cramp</td>
<td>7.8 ± 9.5</td>
<td>5.3 ± 7.7</td>
</tr>
<tr>
<td>Headache</td>
<td>1.7 ± 2.6</td>
<td>1.3 ± 3.2</td>
</tr>
</tbody>
</table>

ol-HDF in Southeast Asia: 3 years experience
22 HD patients HFHD → ol-HDF

Tiranathanagul K et al. Ther Apher Dial 2009; 13: 56-62
Convective therapies (HF, HDF) reduce intradialytic symptomatic hypotension (ISH)

Total incidence of ISH 7.5% 28950 sessions

Italian Multicentric Study RCT LFHD, HF, HDF Ratio 2/1/1

### Daily online HDF promotes catch-up growth in CKD children

<table>
<thead>
<tr>
<th>Patient (n = 15)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height (SDS)</strong></td>
<td></td>
</tr>
<tr>
<td>Start of D-OL-HDF</td>
<td>$-1.5 \pm 0.3$</td>
</tr>
<tr>
<td>End of D-OL-HDF (1)</td>
<td>$+0.2 \pm 1.1^*$</td>
</tr>
<tr>
<td>Mid-parental target height (2)</td>
<td>$-0.3 \pm 0.7$</td>
</tr>
<tr>
<td>(1) - (2) (SDS)</td>
<td>$+0.3 \pm 0.7$</td>
</tr>
<tr>
<td><strong>Growth velocity (centimetres per year)</strong></td>
<td></td>
</tr>
<tr>
<td>The year before daily</td>
<td>$3.8 \pm 1.1$</td>
</tr>
<tr>
<td>First year of daily</td>
<td>$14.3 \pm 3.8$</td>
</tr>
<tr>
<td>Mean over daily</td>
<td>$8.9 \pm 2.2$</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>kg/cm²</td>
</tr>
<tr>
<td>At start of daily</td>
<td>$16.5 \pm 2.0$</td>
</tr>
<tr>
<td>End of daily</td>
<td>$18.0 \pm 2.4$</td>
</tr>
</tbody>
</table>

Normalization of growth curve in children treated by daily ol-HDF

Nocturnal, every-other-day, ol-hemodiafiltration

Randomized Patients (n=26)
Td: 4 – 5 h
3 sessions/week
OL-HDF with 25-30 L convective volume

Group A (n=12)
Td: 7 – 8 h
Every-other-day dialysis
6 months OL-HDF
20-30 L convective volume
(n = 12)

Group B (n=14)
Td: 7 – 8 h
Every-other-day dialysis
6 months OL-HDF
35-50 L convective volume
(n = 14)

Dropout (n=2)

6 months OL-HDF
20-30 L convective volume
(n = 12)

6 months OL-HDF
35-50 L convective volume
(n = 12)

Time & Frequency

Intracorporeal resistance

Volume substitution

Convective dose

Remarkable effect on phosphate control

Considerable reduction of phosphate binders consumption

Significant beneficial effect on nutritional status

Maduell F et al, Nephro Dial Transplant. 2011; 0:1-13 ePUB 13Sep2011
Outline of the presentation

- Definition
- Future of HDF
- Outcomes
- Epidemiology
- Regulatory
- Efficacy
- Safety
## Outcomes of HDF versus HD

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>HDF vs Comparator</th>
<th>Type of study</th>
<th>Grading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wizemann V et al, 2000</td>
<td>HDF vs LFHD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
<tr>
<td>Bosch JP et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>IIb</td>
</tr>
<tr>
<td>Canaud B et al 2006</td>
<td>HDF± vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>Ila</td>
</tr>
<tr>
<td>Jirka et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>Ila</td>
</tr>
<tr>
<td>Schiffl H et al, 2007</td>
<td>HDF vs HFHD + UPD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
<tr>
<td>Vinhas J et al, 2007</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>IIb</td>
</tr>
<tr>
<td>Panichi V et al. 2008</td>
<td>HDF+/− vs LFHD</td>
<td>Prospective controlled study</td>
<td>Ila</td>
</tr>
<tr>
<td>Santoro A et al, 2008</td>
<td>HF vs HFHD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
<tr>
<td>Tiranathanagul K 2009</td>
<td>HDF vs HFHD</td>
<td>Prospective controlled study</td>
<td>Ila</td>
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<tr>
<td>Vilar E et al, 2009</td>
<td>HDF vs HFHD</td>
<td>Historical prospective cohort</td>
<td>IIb</td>
</tr>
<tr>
<td>Locatelli F et al, 2010</td>
<td>HDF vs HD vs LFHD</td>
<td>RCT</td>
<td>Ia</td>
</tr>
</tbody>
</table>
Distribution of dialysis modality for prevalent patients

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
<th>Low-efficiency HDF&lt;sup&gt;a&lt;/sup&gt;</th>
<th>High-efficiency HDF&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Low-flux HD</th>
<th>High-flux HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>460</td>
<td>5.4</td>
<td>8.9</td>
<td>45.9</td>
<td>39.8</td>
</tr>
<tr>
<td>Germany</td>
<td>440</td>
<td>11.1</td>
<td>4.8</td>
<td>50.5</td>
<td>33.6</td>
</tr>
<tr>
<td>Italy</td>
<td>443</td>
<td>14.7</td>
<td>5.4</td>
<td>74.9</td>
<td>5.0</td>
</tr>
<tr>
<td>Spain</td>
<td>383</td>
<td>1.8</td>
<td>0.0</td>
<td>61.4</td>
<td>36.8</td>
</tr>
<tr>
<td>UK</td>
<td>439</td>
<td>2.3</td>
<td>2.5</td>
<td>83.4</td>
<td>11.8</td>
</tr>
<tr>
<td>All</td>
<td>2165</td>
<td>7.2</td>
<td>4.5</td>
<td>63.1</td>
<td>25.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>Low-efficiency HDF includes replacements of 5-14.91, while high-efficiency HDF includes replacement of 15-24.91. HD, hemodialysis; HDF, hemodiafiltration.

Mortality risk for patients receiving high efficiency HDF vs. HD is reduced

European Results from DOPPS

- Low-flux HD: Relative risk 1.00 (p = 0.83, Ref)
- High-flux HD: Relative risk 1.03 (p = 0.68)
- Low-efficiency HDF (5-14.9 l): Relative risk 0.93 (p = 0.68, ↓7% ns)
- High-efficiency HDF (15-24.9 l): Relative risk 0.65 (p = 0.01, ↓35% hs)

Canaud B et al, Kidney Int 2006; 69: 2087-2093
Cardiovascular mortality is reduced in ol-HDF

Survival is significantly higher in HDF treated patients

# Outcomes of HDF versus HD up to 2011

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>HDF vs Comparator</th>
<th>Type of study</th>
<th>β2-M</th>
<th>Annual Mortality HD/HDF</th>
<th>Survival Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wizemann V et al, 2000</td>
<td>HDF vs LFHD</td>
<td>RCT</td>
<td>↓</td>
<td>9.5/4.3</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>↑ 45%</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>12.7/8.9</td>
<td>↑ 35%</td>
</tr>
<tr>
<td>Jirka et al, 2006</td>
<td>HDF vs LFHD vs HFHD</td>
<td>Historical prospective cohort</td>
<td>?</td>
<td>14.8/8.2</td>
<td>↑ 36%</td>
</tr>
<tr>
<td>Schiffl H et al, 2007</td>
<td>HDF vs HFHD + UPD</td>
<td>RCT</td>
<td>↓</td>
<td>4.1/4.2</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>19.9/8.9</td>
<td>↑ 50%</td>
</tr>
<tr>
<td>Panichi V et al. 2008</td>
<td>HDF+/− vs LFHD</td>
<td>Prospective controlled study</td>
<td>↓</td>
<td>13.2/10</td>
<td>↑ 15%</td>
</tr>
<tr>
<td>Santoro A et al, 2008</td>
<td>HF vs HFHD</td>
<td>RCT</td>
<td>↓</td>
<td>13.3/12</td>
<td>↑ 18%</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>9/6</td>
<td>↑ 34%</td>
</tr>
<tr>
<td>Locatelli F et al, 2010</td>
<td>HDF vs HD vs LFHD</td>
<td>Prospective randomized controlled study</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
- Completed
- Reported at ERA-EDTA

**Italian Trial**
- LFHD vs HF/HDF
- 150/75/75
- Tolerance
- Morbidity
- Mortality
- 24 months
- Reported & Published

**French Trial**
- HFHD vs HDF
- > 65yo
- 300/300
- Tolerance
- CV events
- Mortality
- 24 months
- Ongoing

**Catalonian Trial**
- HFHD vs HDF
- 300/300
- CV events
- Mortality
- 24 months
- Ongoing

**Turkish Trial**
- HFHD vs HDF
- 300/300
- CV events
- Mortality
- 24 months
- Completed
- Reported at ERA-EDTA
Outline of the presentation

Definition

Epidemiology

Future of HDF

Regulatory

Safety

Efficacy

Outcomes
Focusing on middle molecules...Convective dialysis dose

Small water soluble solutes
- Asymmetric dimethylarginine
- Benzylalcohol
- β-Guanidinopropionic acid
- β-Lipotropin
- Creatinine
- Cytidine
- Guanidine
- Guanidinoacetic acid
- Guanidinosuccinic acid
- Hypoxanthine
- Malondialdehyde
- Methylguanidine
- Myo-inositol
- Orotic acid
- Orotidine
- Oxalate
- Pseudouridine
- Symmetric dimethylarginine
- Urea
- Uric acid
- Xanthine

Protein-bound solutes
- 3-Deoxyglucosone
- CMPF*
- Fructoselysine
- Glyoxal
- Hippuric acid
- Homocysteine
- Hydroquinone
- Indole-3-acetic acid
- Indoxyl sulfate
- Kinurenic acid
- Kynurenic acid
- Methylglyoxal
- N-carboxymethyllysine
- P-cresol
- Phenol
- P-OHhippuric acid
- Quinolinic acid
- Spermidine
- Spermine

Middle molecules
- Adrenomedullin
- Atrial natriuretic peptide
- B2-Microglobulin
- β-Endorphin
- Cholecystokinin
- Clara cell protein
- Complement factor D
- β2-Microglobulin
- Interleukin 1β
- Interleukin 6
- Kappa-Ig light chain
- Lambda-Ig light chain
- Leptin
- Methionine-enkephalin
- Neuropeptide Y
- Parathyroid hormone
- Retinol binding protein
- Tumor necrosis factor alpha

*CMPF is carboxy-methyl-propyl-furanpropionic acid

HDF vs Daily HDF, β2-M Kinetic

8 patients (6M, 2F)
4-5 hrs x 3 to 2-2.5 hrs x 6 per week for 6 months

Online HDF provides a platform for developing new RRT options

Flexible HDF
- Blood volume controlled machine
- Manual infusion
- Biofeedback system
- Cleansing
- Priming
- Rinsing
- Suppressing saline requirement
- Reducing manual handling
- Save money
- Self Care or Home therapy

Automated dialysis procedure

Internal HDF
If you want to know more register to eudial@era-edta.org

European Dialysis Working Group dedicated to improve dialysis outcomes focusing on online convective therapies