EFFECT OF ONLINE HEMODIAFILTRATION ON ALL-CAUSE MORTALITY AND CARDIOVASCULAR OUTCOMES

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Slide 1

Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes

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Dear Chairman, dear colleagues good afternoon everybody.

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As everybody knows, there is quite a high cardiovascular mortality rate in dialysis patients. It is around a 10-fold increase compared to the general population.

There are some prediction risk factors in dialysis patients, some of them modifiable, some of them non-modifiable but dialysis patients have also some untraditional risk factors such as increased β2-microglobulin, hyperphosphatemia, inflammation, anaemia and finally, fluid overload.
Middle-molecules are associated with different situations such as dialysis-associated amyloidosis, inflammation, mortality, hospitalization, atherosclerosis, malnutrition and anaemia.

If you increase the surface of dialysate, you will have 22% increase of β2-microglobulin clearance. When you increase blood flow from 300 mL/min to 500 mL/min, you will obtain a 16% increase in β2-microglobulin clearance. But if you switch this patient to HDF, there is a huge increase in β2-microglobulin clearance.
Hemodiafiltration combines haemodialysis and hemofiltration, so there is a combination of diffusion and also of convection.

There are two main types of HDF. The first is pre-dilution HDF and in this model replacement fluid is given at the beginning of dialysis. In this situation, it is quite easy to reach a very high convection volume with low coagulation rates but there is a disadvantage, it provides relatively low small molecule clearance. Regarding post-dilution HDF there is no loss in small molecule clearance compared to pre-dilution HDF. It provides 15% more clearance but there is coagulation risk so it is not easy to reach a very high convection volume.
This slide illustrates production of on-line sterile fluid. Dialysate will pass one filter and you obtain ultrapure dialysate after the second filter it produces sterile infusion fluid.

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Safety of on-line replacement fluid production

- Cross-over study
- on-line HDF vs. LF-HD
- Pre- and post-treatment IL-1Ra and TNF-α levels

- On-line HDF is not associated with increased production of cytokines

This is crossover study to document the safety of on-line HDF. On-line HDF is not associated with increased production of cytokines.

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What are the prerequisites for successful on-line HDF? High volume substitution to achieve highly efficient dialysis. There are some technical prerequisites. Dialysis machine should be suitable for On-line HDF. On-line preparation of high volume dialysis and substitution fluid, preparation of fluid with highest microbiological purity, a suitable high flux membrane and automatic optimisation of substitution volume.

Those are clinical pre-requisite units, high extracorporeal blood flow to reach high convection volume and it is necessary to have a good vascular access to achieve high convection volume and also the highest possible needle diameter.
In this slide we see the clearance of urea, creatinine, vitamin B12 and β2-microglobulin. As you see, the clearance of urea is not different between high flux, low flux and even HDF although HDF provides a little better clearance of small molecules but if you look at middle-molecules the difference between low flux and high flux and also between high flux and HDF is quite clear.

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In this slide we see the correlation between the amount of substitution volume and the β2-microglobulin clearance. As substitution volume increases β2-microglobulin clearance increases.

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In this study urea, creatinine and phosphate clearance were compared in HD, pre-dilution HDF and post-dilution HDF. As you see, post-dilution HDF provides the highest urea, phosphate and creatinine clearance compared to other treatment modalities.

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Higher urea, creatinine and phosphate clearance with post-dilution of HDF

Here we see β2-microglobulin clearance in case of HD, pre-dilution On-line-HDF and post-dilution On-line-HDF, again post-dilution On-line-HDF is associated with β2-microglobulin clearance.

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β-2 microglobulin clearance with HDF

*β-2 microglobulin clearance: post-dilution HDF > pre-dilution HDF > HD


Almost every study reported a higher reduction rate of β2-microglobulin by implementation of HDF. This prospective randomised controlled trial showed no difference regarding pre-dialysis β2-microglobulin level in HD and HDF. This phenomenon is explained by slow intercompartmental transfer of β2-microglobulin.

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Doctor Locatelli nicely showed a 42% less frequency of carpal tunnel syndrome in patients treated with HDF compared to HD patients.

Slide 18
This study evaluated hemoglobin level and Epo dose after switching 37 HD patients to HDF. There is an increase in Hb levels and also a decrease in Epo dose during a one year follow-up.

This study evaluated hemoglobin level and Epo dose after switching 37 HD patients to HDF. There is an increase in Hb levels and also a decrease in Epo dose during a one year follow-up.

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In this study the effect of hemodiafiltration on intradialytic complications, intradialytic hypotension episodes, has been evaluated HD hemofiltration and hemodiafiltration. This study showed clearly a significant reduction in the frequency of the intradialytic hypotension by HDF treatment.

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There are several observational studies in the literature suggesting survival benefits with on-line HDF. In the first study from DOPPS data doctor Canaud showed that if you reach over 15 L of convection volume by HDF, mortality risk reduces by 35%. Another study compared survival of patients treated predominantly with HDF and those treated predominantly with high flux HD and HDF is associated with better survival.

Reported benefits by hemodiafiltration are those: enhanced small, middle and larger protein-bound uremic solute clearance, better intradialytic hemodynamic stability, reduced inflammatory markers, improved phosphate control, increased erythropoietin responsiveness, better beta-2 microglobulin removal and lower risk of carpal tunnel syndrome. Regarding effect on survival, retrospective studies indicate survival advantage.
Regarding effects on survival so far there have been some retrospective studies to indicate survival advantage.

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**CONTRAST (Dutch HDF Study)**

- Netherlands, Canada, Norway
- Randomized controlled study, 714 prevalent HD patients
- Online-HDF compared with low-flux HD
- Primary outcome measure all-cause mortality
- Mean follow-up 3.04 years
- Shorter session duration and higher blood flow in HDF group during follow-up


This is the first randomised controlled study. It’s from the Netherlands and they compared On-line-HDF with low flux HD primary outcome measure was all-cause mortality, mean follow-up was 3 years and there was shorter session duration in high blood flow in the HDF group during follow-up.

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**CONTRAST (Dutch HDF Study)**

- Target convection volume 24 L, achieved median level 19.8 L (target reached only in 33% of patients) (substitution volume 17.9 L)
- No significant difference between groups regarding overall survival
- Posthoc analysis showed a 39% survival benefit in patients treated with a convection volume over 21.95 L (HR 0.61, 95%CI 0.38-0.98, p=0.015 in adjusted model)


Target convection volume in the Dutch study was 24L but the achieved median level was only 90.8 L a target reached only in 33% of patients. There was no significant
difference between groups regarding overall survival. Post-hoc analyses showed a 39% survival benefit in patients treated with a convection volume over 22 L.

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**CONTRAST (Dutch HDF Study)**

- Higher Hb levels and spKt/V, lower levels of PO₄ in the HDF group

- Lower beta-2 microglobulin levels in HDF group (26.4 vs 35.4 mg/L (p<0.001)

The CONTRAST study also reported high Hb levels and Kt/v in HDF patients and lower levels of phosphate compared to low flux HD in the HDF group. In the graph you see a huge difference between low flux HD and HDF regarding predialysis β2-microglobulin levels.

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**Turkish HDF Study**

- Randomized controlled study, 782 prevalent HD patients
- Online-HDF compared with high-flux HD
- Primary outcome: composite of all-cause mortality and new non-fatal cardiovascular events (myocardial infarction, stroke, revascularization, unstable angina pectoris requiring hospitalization)
- Secondary outcomes overall and CV mortality, intradialytic complications, changes in clinical-laboratory parameters and medications


This is a Turkish HDF study. We randomised 782 prevalent HD patients to On-line-HDF and high flux HD.
The primary outcome was a composite of all-cause mortality and near non-fatal cardiovascular events. Secondary outcomes were overall and cardiovascular mortality, intradialytic complications, changes in clinical-laboratory parameters and medications.

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**Turkish HDF Study**

- Mean follow-up 22.7 months
- Higher blood flow in the HDF group during follow-up
- Target substitution volume over 15 L per session
- Target achieved in 96.7% of patients
- Mean substitution volume 17.2 ± 1.2 L, mean convection volume 19.6 L per session

*Ok E et al. Nephrol Dial Transplant 2013; 28: 192-202*

Target substitution volume over 15 L per session. Target achieved in 96.7% of patients. Mean follow-up was close to 3 years. Higher blood flow in the HDF group during follow-up was observed. Mean substitution volume was 17.2 L and mean convection volume was close to 20 L.

**Slide 27**

<table>
<thead>
<tr>
<th></th>
<th>On-line HDF (n=391)</th>
<th>High-flux HD (n=391)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eKt/V</td>
<td>1.44 ± 0.19</td>
<td>1.33 ± 0.19</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**OL-HDF ➔ BETTER DIALYSIS ADEQUACY**

|                          | 129 ± 13            | 126 ± 13             | <0.001  |
| Systolic BP (mmHg)       |                     |                      |
| IDWG (% body weight)     | 3.5 ± 1.9           | 3.2 ± 1.5            | 0.01    |

**OL-HDF ➔ HIGHER SBP AND IDWG**

|                          | 11.5 ± 1.2          | 11.5 ± 1.2           | 0.86    |
| Hemoglobin (g/dl)        |                     |                      |
| ESA dose (U/week)        | 2282 ± 2121         | 2852 ± 2706          | 0.001   |

**OL-HDF ➔ 20% REDUCTION IN EPO DOSE**
Here you see Kt/V, systolic blood pressure, intradialytic weight gain, Hb and Epo dose. HDF was associated with better dialysis adequacy reflected by higher Kt/V urea reduction ratio. In the HDF groups systolic blood pressure and intradialytic weight gain were a little bit higher compared to the HD group. Haemoglobin levels were exactly the same in the two groups but Epo dose was 20% lower in patients treated with HDF.

### Follow-up: Laboratory Data

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Albumin (g/dl)</td>
<td>3.93 ± 0.24</td>
<td>3.99 ± 0.27</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>170 ± 37</td>
<td>170 ± 39</td>
<td>0.91</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>173 ± 97</td>
<td>191 ± 107</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>37 ± 11</td>
<td>34 ± 9</td>
<td>0.007</td>
</tr>
<tr>
<td>LDL (mg/dl)</td>
<td>99 ± 29</td>
<td>97 ± 30</td>
<td>0.52</td>
</tr>
</tbody>
</table>

**OL-HDF → LOWER ALBUMIN, BETTER LIPID CONTROL**

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<tr>
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<th>High-flux HD (n=391)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hs-CRP (mg/dl)</td>
<td>1.48 ± 1.63</td>
<td>1.47 ± 1.52</td>
<td>0.88</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>22.5 ± 1.8</td>
<td>21.9 ± 2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β2-microglobulin (mg/L)</td>
<td>27.4 ± 6.0</td>
<td>27.4 ± 5.8</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**OL-HDF → LESS ACIDOSIS, NO DIFFERENCE IN CRP AND BETA-2 MG**

Serum albumin level recorded during the study period was lower in the HDF group. The HDF group also showed a better liquid profile by lower triglyceride levels and higher HDL cholesterol levels. There was no difference in Crp and β2 - microglobulin between groups. Bicarbonate level was higher in the HDF group.
Here you see the primary outcome. Ol-HDF was associated with an 18% global risk of primary endpoint. The difference did not reach statistical significance.

Overall mortality was 20% lower in the HDF group but not statistically significant (HR 0.80, 95%CI 0.55-1.14, p=0.21).

CV mortality was 28% lower in the HDF group (not statistically significant) (HR 0.72, 95%CI 0.45-1.13, p=0.15).

Statistical power lower than hypothesized
- anticipated event-free survival in HD group 64%, observed 74.8%
- anticipated risk reduction with HDF 35%, observed 18%

Overall mortality was 20% lower in the HDF group but it was not statistically significant.
Cardiovascular mortality was also 28% lower in the HDF group but again statistically not significant.
The statistical power of this study was lower than hypothesised because anticipated event-free survival in the HD group was 64% but observed rate was 74.8%.
In addition, an anticipated risk reduction used for power analysis was 35% and observed benefit was 18%.
Target substitution volume was chosen as >15 L per session on the basis of DOPPS data (35% higher survival with a substitution volume over 15 L). We investigated whether survival benefit with HDF is more pronounced with higher volumes.

1) High volume HDF group (substitution volume >17.4 L)
2) Low volume HDF group (substitution volume ≤17.4 L)


There was significantly better overall survival and cardiovascular survival in the high volume HDF group compared to HD.
In the low volume group, there were more diabetics; albumin was lower, phosphate and Hb were higher.

In the high volume group, blood flow rate was higher.

In adjusted Cox regression analysis, high volume HDF was associated with reduced rate of both overall (HR 0.54, 95% CI 0.31-0.93, p=0.02) and cardiovascular mortality (HR 0.29, 95% CI 0.12-0.65, p=0.003) compared to HD and low volume HDF groups.

(variables age, sex, DM, CVD, time on HD, vascular access, blood flow rate, IDWG, hemoglobin, albumin, phosphate and urea reduction rate)

The study demonstrates that On-line HDF provides better dialysis adequacy, lipid profile and acidosis control.

ol-HDF reduces erythropoietin requirement.

Despite better survival trends in the HDF group, the difference did not reach statistical significance in the whole group.
Our study demonstrates that On-line HDF provides better dialysis adequacy, lipid profile and acidosis control. In addition, Online-HDF treatment reduces Epo requirement by 20%. Despite better survival trends in the HDF group, the difference did not reach statistical significance in the whole group.

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- Significantly better cardiovascular and overall survival in patients treated with a substitution volume over 17.4 L (but the target was over 15 L in the study in the design of the study)

- Although there were differences between baseline characteristics of the groups (HD, low volume HDF and high volume HDF), survival benefit by high volume HDF persisted after correction with all of these confounding factors

Significantly better cardiovascular overall survival in patients treated with a substitution volume over 17.4 L. Although there were differences between the baseline characteristics of the groups, survival benefit by high volume HDF persisted after correction with all of these confounding factors.

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- What are the factors to determine convection volume?
  - Patient-related: high blood flow, high albumin, low Htc
  - Medical staff-related: might not be willing to increase convection volume to avoid annoying high-pressure alarms of machines related to excessive hemoconcentration during treatment

- Is it possible to reach a substitution volume over 17.4 L in all patients by using new generation machines and by overcoming medical staff-related factors?
This is the question; can reaching higher convection volume provide survival benefits? Yes, but is it possible to reach higher convection volumes in all patients? What are the factors to determine convection volume? There are some patient-related factors such as high blood flow, high albumin, low haematocrit, high albumin and low haematocrit associated with high convection volumes. There are some medical studies related to factors especially in old machines. Medical staff might not be willing to increase convection volume to avoid annoying high pressure alarms of the machines related to excessive hemoconcentration during treatment. Is it possible to reach a substitution volume over 17.4 L in all patients by using new generation machines and by overcoming medical staff-related factors?

A recent retrospective analysis (Turkey database, 2009-2011)

- 4324 patients followed between April 2009 and March 2011 in 42 clinics, exclusion of patients younger than 18 years old (n=17) and patients on dialysis less than 3 months (n=266)
- Comparison of 2-year survival in 4041 patients treated with HDF (31.1%) and HD (68.9%)
- New generation machines, encouragement of high volumes
- MEAN SUBSTITUTION VOLUME 21.0 ± 9.2 L/SESSION, which is much higher than that achieved in Turkish HDF Study (17.2 L)

Recently we performed a retrospective analysis in 30 databases. We evaluated over 4,000 patients. After completion of our trial we encouraged medical staff to increase convection volume as much as possible and also new generation machines have been started to be used with this machine called --- alarm and we compared 2-year survival in these patients. 31% of 4,000 patients have been treated by HDF and 69% by HD. Mean substitution volume was 17.4 L in our randomised controlled trial but now mean substitution volume is 21 L per session, which is much higher than the randomised controlled trial.
Here you see in this retrospective study Kaplan-Meier analysis On-line HDF provides much better overall survival. 2-year survival rate 88.5% in OL-HDF and 79.6% in HD.

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In adjusted Cox-regression analysis including age, gender, presence of diabetes, time on HD, vascular access and blood flow rate

- on-line HDF treatment was associated with a 37% risk reduction for overall mortality compared to the HD treatment (RR: 0.63, 95% CI 0.51-0.76, p<0.001).

In adjusted Cox regression analysis including age, gender, presence of diabetes, time on HD, vascular access and blood flow rate OL-HDF treatment was associated with 37% risk reduction for overall mortality.

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What about the current situation in Turkey in HDF clinics and HD clinics? We evaluated annual mortality rate in 13 clinics where HDF treatment is practised and 38 clinics where HD is practised. Mean annual mortality rate in HD clinics was 11.3 and in HDF clinics, it was 8.1. It reflects a 28% lower mortality. However, these are retrospective data of course.

What would be the result of a randomized controlled study to achieve a substitution volume over 17.4 L?
The ESHOL study from Spain Cataluña is a randomised controlled trial. They randomised 906 patients to On-line HDF and high flux HD. Primary endpoint was overall mortality, mean follow-up was close to 2 years, acute mean substitution volume was much higher compared to previous randomised controlled trials and it changed between 20.8 L and 21.8 L per session.

There was higher blood flow and dialysate flow in the HDF group.

Here you see survival analysis in OL-HDF and HD group. Significantly better overall survival with high volume OL-HDF.

30% risk reduction in mortality with high volume HDF (HR 0.70, 95%CI 0.53-0.92, p=0.01)
Secondary outcomes

- 33% lower risk of CV mortality in the HDF group (HR 0.67, 95%CI 0.44-1.02, p=0.06)
- 61% lower risk of stroke-related mortality in the HDF group (HR 0.39, 95%CI 0.16-0.93, p=0.03)
- 55% lower risk of infection-related mortality in high volume HDF group (HR 0.45, 95%CI 0.21-0.96, p=0.03)


Secondary outcomes. This study reported a 33% lower risk of cardiovascular mortality in the HDF group and a 61% lower risk of stroke-related mortality in the HDF group. A 55% lower risk of infection-related mortality.

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Secondary outcomes

- A relative risk reduction of 22% for hospitalization in the HDF group (HR 0.78, 95%CI 0.67-0.90, p=0.001)
- 28% lower risk of intradialytic hypotension in the HDF group (HR 0.72, 95%CI 0.68-0.77, p<0.001)


A relative risk reduction of 22% for hospitalization in the HDF group. A 28% lower risk of intradialytic hypotension in the HDF group.
Therefore, I think we can say high volume hemodiafiltration is the first intervention capable to improve survival in conventional hemodialysis patients.

Therefore, I think we can say high volume hemodiafiltration is a first intervention capable to improve survival in patients treated with three times per hour dialysis.

Thank you for your attention.