1. Is there any new evidence about the effectiveness of HVHDF therapy?

Two recent meta-analyses, including 3 main randomized clinical trials (RCT), (CONTRAST, Turkish and ESHOL studies)\(^1\)\(^-\)\(^3\), have confirmed that on-line hemodiafiltration (OL-HDF) decrease in overall and cardiovascular mortality. In Nistor et al meta-analysis\(^4\) OL-HDF was associated with a 13% reduction in all-cause mortality (no statically significant) and 25% in cardiovascular mortality. Similar, in EUDIAL systematical review and meta-analysis\(^5\), OL-HDF reduce all-cause and cardiovascular mortality risk in 16% and 27% respectively.

A large-scale pooled individual participant data analytic approach\(^6\) (including 3 main RCTs\(^1\)\(^-\)\(^3\) and French study\(^7\)), 2797 patients included; on the effects of online HDF compared with conventional HD indicates that online HDF reduces a significant 14% and 23% the risk of all-cause and cardiovascular mortality.

Several multicentre, epidemiological studies in incident patients supported the generalizability of previous studies findings regarding the survival benefit of HV-HDF over HD. Three incident patients’ studies have been recently published. Imamovic et al\(^8\), in an epidemiological cohort study in 442 incident hemodialysis patients in three countries (Bosnia and Herzegovina, Serbia and Slovenia), observed that high-volume OL-HDF (>20.4 L replacement volume session) was associated with improved survival (HR 0.29; CI 0.13-0.68) compared with high-flux dialysis. Siriopol et al\(^9\), in a retrospective analysis of the Romanian dialyzed population from the EUCLID database, evaluated an incident cohort. After propensity score matching, 265 HDF-treated patients were matched to 530 HD-treated patients; OL-HDF was associated with improved survival (HR 0.24; CI 0.13-0.46). Canaud et al\(^10\), in study population extracted from database of patients on dialysis treatment in 369 NephroCare centres throughout 12 European countries. After propensity score matching 795 high-volume HDF-treated patients (>21 L replacement volume /session) were matched to 795 high-flux HD-treated patients and inverse probability of censoring weighting were applied to reduce bias by indication and consider modality crossover. Again, high-volume OL-HDF was associated with improved survival (HR 0.50; CI 0.37-0.68).

Finally, French REIN Registry\(^11\) showed that patients treated exclusively with HDF therapy compared to standard HD, reduced all-cause mortality in 23% and cardiovascular mortality in a 34% from 2008 through 2012.

2. Can you confirm the initial Catalanian study data, regarding risk reduction in all-cause mortality, risk reduction in mortality from stroke and risk reduction in mortality from infection by any new results?

In the original study, patients were observed until each enrolled patient completed 3 years of follow-up, until premature termination, or until death. In the original study, 355 out of 906 patients (39.2%) with premature termination were censored before completing the 3-year follow-up. The results of a reanalysis of the ESHOL trial\(^12\), which considered all-cause mortality in the ITT population without censures, confirm that high efficiency postdilution OL-HDF reduces all-cause mortality versus conventional hemodialysis in prevalent patients. These results are consistent independently of the statistical analysis employed. The original results observed in the ESHOL study, which censored patients discontinuing the study for any reason, showed reduction risk all-cause mortality in 30% (HR 0.70; CI 0.53-0.92). These data were confirmed in the reanalysis study, which considered all-cause mortality in the ITT population without censures with a 24% reduction risk all-cause mortality (HR 0.76; CI 0.58-0.98). In this reanalysis the risk reduction in mortality from stroke and infection were lower,
HR 0.57 and HR 0.56 respectively, but statistical significance observed in the original analysis was not sustained, p value 0.122 and 0.065 respectively.

3. Are there any studies running or being prepared, to confirm the initial results of the Catalanian Study?
   
   To my knowledge, there are no large RCT ongoing, but a study to evaluate the association between survival and convective volume is being prepared. In all large, randomized studies the convective volume seemed to be an important issue. A post hoc analysis of the CONTRAST study showed in the group of patients with the highest delivered convection volume (upper tertile >21.95 L) mortality was considerably lower than in patients randomized to LF-HD, a 39% mortality risk reduction in patients receiving high convection volumes. In a Turkish study, the median value of substitution volume in the OL-HDF group was 17.4 L. In a secondary analysis, stratifying patients according to this threshold, those in the low-efficiency OL-HDF group were more likely to have diabetes, higher phosphate levels, lower albumin levels, higher hemoglobin levels compared with the high-efficiency OL-HDF and HF-HD groups. The patients treated with high-efficiency OL-HDF were associated with a 46% risk reduction for overall mortality and a 69% risk reduction for cardiovascular mortality. In post hoc analyses of the ESHOL study mortality in the intermediate tertile (23.1–25.4 L per session) and upper tertile (>25.4 L) was significantly lower than that in patients randomized to HD, 40% and 45% risk reduction for overall mortality respectively.
   
   So, in secondary analyses all 3 RCT provide the evidence of the need to deliver high convection volume to reduce mortality. Current recommendation for high-volume OL-HDF would be > 21 L per session of replacement volume. But you should have in mind that this recommendation is based in secondary analysis, and therefore there could be a selection bias because patients getting greater convective volume are those in better overall, having good vascular access, less diabetes or cardiovascular disease. For these reasons new RCT are needed to evaluate what is the threshold volume for increasing survival.

4. In your opinion, what are the main benefits of the method HVHDF?
   
   High-volume hemodiafiltration techniques mark a new step towards mimicking the blood purification of the native kidney. These techniques offer superior uremic substance removal over a wider range of molecular sizes, yet require the use of biocompatible membranes and ultrapure dialysate, which has been related to additional clinical benefits. The above mentioned studies have shown an association of a lower mortality risk with hemodiafiltration. A number of studies have addressed the potential role played by larger solutes or low-molecular-weight proteins in dialysis-related complications and the potential clinical advantages offered by high-convection therapies. Specific indications should be considered because hemodiafiltration has been reported to be effective against hyperphosphatemia, malnutrition, insomnia, irritability, restless-leg syndrome, polyneuropathy, anemia, itching and joint pain, and may prevent dialysis-associated amyloidosis.

5. What would be your message to Czech dialysis patients?
   
   High efficiency postdilution OL-HDF reduces all-cause mortality vs hemodialysis in prevalent and incident patients. Furthermore, the main causes of mortality, cardiovascular and infectious diseases, were significantly reduced by OL-HDF. In view of these results, OL-HDF may become the first-line option in hemodialysis patients.
Based on the results of secondary analyses of the main clinical trials, current recommendation for high-volume OL-HDF would be >23 L per session of the total convective volume (replacement volume plus interdialysis weight gain). But you should have in mind that this recommendation is based in secondary analysis, and therefore there could be a selection bias. In the absence of more conclusive scientific evidence, it seems a reasonable and affordable recommendation that should be confirmed with future clinical trials.

The main limitation to achieving a high convective volume lies in blood flow (Qb) and haemoconcentration. In this regard, the new generation of dialysis machines has improved the software in terms of increasing the total convective volume, optimising infusion flows (QI) in relation to intradialisis changes. The ultracontrol system in the Gambro machines or the Fresenius 5008 CorDiax automated replacement system are technological advances that attempt to maximize the convective volume administered automatically. The change of software in the 5008 dialysis monitor has meant a 13% increase in the total convective volume. The effective convective volume percentage of total processed blood increased by 3.5%. These results were achieved without differences in arterial, venous or transmembrane pressure. This technological advancement has allowed an increase in the convective volume per session, which could lead to optimum volumes being achieved in a greater number of patients.13

Increasing Qb is probably the best option for achieving the highest convective volume. For every 50 ml/min increased, the convective volume increases more than half a litre per hour. The auto-substitution system boosts the percentage of total purified blood at lower Qb. Qb increases the capacity to clear small molecules, it favours that of β2 -microglobulin and myoglobin, and does not influence larger molecules.14

With the currently available high-flow dialysers for OL-HDF modalities, it is necessary to assess the selection of the dialyser surface area considering the cost-effectiveness ratio. A smaller surface area may reduce side effects and decrease the immunological and inflammatory response that is always present in haemodialysis. In our experience, the full use of the convective capacity ranging from 57% to 95% has been observed among the dialysers used, showing minimal differences both in convective volume and clearance capacity when the UFC is greater than 45 mL/h/mmHg. It is advisable to optimize dialyser output to the minimum surface area possible, adapting the treatment prescription, particularly of the Qb and the duration.15

Dialysate flow in OL-HDF does not affect convective volume. A higher Qd results in a slight increase in clearance capacity for urea (diffusion dependent), with no changes for medium and large molecules (convection dependent). It is recommended that Qd to be optimised to the minimum possible that guarantees an adequate dialysis dose (Kt or Kt/V) and allows rationalization of water and dialysis concentrate consumption.16

In the 20 years of treatment with OL-HDF, there is still no a study or case reports published with negative clinical outcomes. We consider that there is enough scientific evidence to sustain that OL-HDF compared with hemodialysis reduces all-cause and cardiovascular mortality. Accept the evidence where it exists, it should not be so difficult.
References


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