PROGRESS WITHOUT EVIDENCE

Evidence-based medicine requires results from randomized controlled trials (RCT), ideally more than one, showing significant beneficial effect on mortality of a well-defined intervention in order for this mode of therapy to be considered superior and qualify for inclusion in clinical guidelines and reimbursement regulations. In the dialysis world, few RCT have provided clinical evidence for the three-times-weekly four-hour hemodialysis (HD) sessions with high-flux, biocompatible membranes and bicarbonate-containing, ultrapure dialysis fluid used by the majority today. Still, most steps on the development path have been perceived as going in the right direction, improving the quality of dialysis for the patients, and when technology has provided a cost-effective way forward, they have been implemented without the support of RCT. In retrospect, nobody would change back and everybody agrees that making dialysis more physiological is a logical development towards renal function, although with still a long way to go.

BENEFITS OF HDF

The HEMO study provided support for HD with high-flux membranes only in subgroup and secondary analyses, while the MPO study showed improved survival for high-flux HD treated patients with albumin levels ≤ 40 g/l as a primary outcome \(^{1, 2}\). Based on this evidence, the European Renal Best Practice Advisory Board is now recommending high-flux membranes for all HD patients \(^{3}\). The same high-flux membranes are used in hemodiafiltration (HDF) which is characterized by larger convective removal compared to high-flux HD. But what evidence is available to support the use of HDF? Numerous studies confirm the improved clearance of solutes in the middle and large molecular weight range that can be anticipated from increased convective transport through an open membrane \(^{4}\). This is particularly noteworthy for solutes such as phosphate, β2-microglobulin (β2m) and factor D for which reduced levels are directly associated with improved outcome in dialysis patients (reviewed in \(^{5}\)). Other studies show improved management of anemia, mineral metabolism and nutrition, less inflammation and better hemodynamic stability \(^{(5)}\). Outcome data with significantly improved survival for patients treated with HDF are available from observational studies. Analyses of large databases show that patients treated with on-line HDF have superior survival compared to those treated with HD, after compensating for demographic and co-morbidity-related differences between
the groups (6, 7, 8). Presently, several prospective, controlled trials are documenting various outcome parameters for patients randomized to on-line HDF or HD and within a year or two, more results should hopefully be available (Table 1) (5).

DOSE OF CONVECTION

In comparison with HD, HDF is characterized by ultrafiltration volumes exceeding the necessary weight loss, the difference being replaced by a substitution solution. Different forms of HDF can be defined depending on how the substitution solution is generated and added. Most commonly used is on-line HDF in which the substitution solution is prepared in a controlled and validated process and added before or after the filter (4). The substitution fluid can also be generated and added inside the filter, e.g. in push-pull HDF (9), a process which takes place also in high-flux HD, although uncontrolled and to less extent. High-flux HD can therefore be considered as a low-efficiency form of HDF (4). Using the volume of convection as a measure of dose, the difference between high-flux HD and HDF becomes a matter of a low-dose version compared to a high-dose version of the same therapy. Looking for studies indicating that a difference in convection dose might be related to a difference in outcome takes us back to the HEMO study. Secondary analysis showed that mortality correlated directly with predialysis levels of β2m, the lower the better. Every 10 mg/L increase in mean predialysis β2m levels increased the risk of all-cause-mortality by 11% and of infectious mortality by 21% (10, 11). However, the lowest β2m levels achieved among the HEMO patients were modest but corresponded to what can be expected in HD mode with reused filters. Patients treated with a higher dose of convection, such as in on-line HDF, achieve significantly lower predialysis plasma levels of β2m than the patients in the HEMO study and further benefits could be hypothesized from this fact (12). Another indication of the impact of convection dose on outcome can be found among DOPPS patients treated with different modes of HDF (7). The survival benefit of HDF over HD was significant only for patients treated with the higher dose of convection, in this case 15-25 L of substitution solution.

CONCLUSION

Hemodiafiltration can provide the largest removal of solutes over the widest range of sizes among all modes of dialysis. Clinical benefits associated with the enhanced blood purification have been documented in numerous studies. Outcome data showing improved survival is available from observational studies. Extrapolation of outcome data for high-flux dialysis, which is a low-dose version of HDF, can also be used to hypothesize about such benefits. In anticipation of result from ongoing RCTs, HDF should be considered the future direction of dialysis. Frequent application of HDF constitutes the most physiological form of dialysis therapy available today (13).
Références


**Table 1**

*Ongoing randomized controlled trials with hemodiafiltration*

<table>
<thead>
<tr>
<th>Country</th>
<th>n</th>
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