Dose of dialysis, convection and haemodialysis patients outcome—what the HEMO study doesn’t tell us: the European viewpoint

Francesco Locatelli

Department of Nephrology and Dialysis, A. Manzoni Hospital, Lecco, Italy

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The main aims of dialysis treatment are to prolong patient survival, reduce morbidity and improve quality of life. However, despite many technical advances made over the last few years, morbidity and mortality of dialysis patients remain unacceptably high [1] and their quality of life is often poor.

The delivered dose of dialysis can affect morbidity and mortality of dialysis patients [2]. Moreover, in the last decade, several epidemiological studies, based mainly on longitudinal database registries, have suggested a possible superiority of convective dialysis treatments in improving patient outcome [3–7]. Thus, in addition to the dose of dialysis delivered, the size of molecules removed can also be of importance. In a randomized controlled study of 380 patients, Locatelli et al. [8] compared four dialysis modalities (cuprophan dialysis, low- and high-flux polysulfone dialysis, and high-flux polysulfone haemodiafiltration). While there was no difference in treatment tolerance and nutritional status, a statistically significant difference in pre-dialysis plasma $\beta$-microglobulin levels between convective and diffusive treatments (high vs low flux) was found. No difference in morbidity and mortality was found; however, this study was not designed to detect such a difference.

Given the importance of these issues, it is not surprising that the primary aim of the HEMO study, the largest clinical trial on outcome of chronic haemodialysis (HD) patients reported to date, was to evaluate the effect of dialysis dose and convection on patient survival [9].

The HEMO study was thus designed to answer two basic questions: (i) should we increase dialysis dose above the currently recommended minimum dose [a single-pool (sp) $Kt/V$ of 1.3], and (ii) should the concept of dialysis adequacy be widened to include, in addition to urea removal, medium and large-size molecule clearance in order to improve the outcome of dialysis patients?

Dialysis dose

Dialysis adequacy is not easy to quantify. Clinically, several parameters must be considered to provide adequate dialysis, such as control of fluid overload and electrolytes disturbance, correction of metabolic acidosis and dialysis dose.

The most commonly used parameter to evaluate delivered dialysis dose is the sp$Kt/V$ index, where $K$ is the dialyzer urea clearance, $t$ is the duration of dialysis session and $V$ is the patient’s urea distribution volume. The sp$Kt/V$ is derived from a mathematical model formulated 20 years ago [10] that assumes that urea is removed from a single, well-mixed pool. However, due to technical advances, dialysis efficiency has substantially increased over the last 10 years, and post-dialysis urea rebound observed with such treatments shows that urea removal follows double-pool kinetics. Thus, at the end of the dialysis session, urea levels in the blood compartment may be lower than urea levels in the peripheral compartments (such as muscle and skin) and in the intracellular environment. Therefore, delivered dialysis dose calculated on the basis of sp$Kt/V$ may be overestimated. Hence, equilibrated Kt/V (eKt/V), a two-pool approximation derived from sp$Kt/V$, was proposed to assess the dose of dialysis more adequately [11].

Unfortunately, this parameter considers clearance and time as a product, thus failing to evaluate the relative importance of each factor. The importance of time on dialysis, not only in relation to increased dialysis dose, should be emphasized. Duration of each dialysis treatment must be long enough to minimize the clinical effect of ultrafiltration and to ensure that correct ‘dry weight’ is maintained by removing sodium and water excess. This leads not only to a decrease in the incidence of intradialytic hypotension, but also to an improvement of blood pressure control, the strongest predictor of survival. In fact, it is worth noting that cardiovascular mortality represents more
than 40% of total mortality of dialysis patients. When trying to define dialysis adequacy, these two aspects of treatment time must obviously be taken into account.

Dialysis dose and treatment failure: the National Cooperative Dialysis Study

The National Cooperative Dialysis Study (NCDS) was the first multicentric, randomized and controlled trial to investigate the impact of dialysis dose (in terms of small and middle molecule removal) on patients’ outcome [12]. Using a two-by-two factorial design, 160 patients were randomized to two different urea time-averaged concentrations (TAC; 100 vs 50 mg/dl) and to two different treatment times (2.5–3.5 vs 4.5–5.5 h) and followed-up for 6 months. TAC urea was inversely associated with treatment failure. Of interest, although not statistically significant, a trend towards a longer follow-up would have led to more clear-cut results.

A quantification of dialysis dose using spKt/V was first proposed by Gotch [13] in a secondary analysis of NCDS data. In his analysis, probability of dialysis failure was a constant step function of Kt/V: it was higher for Kt/V ≤ 0.8 and abruptly decreased for Kt/V > 0.9. However, in a subsequent analysis of the same NCDS data Keshaviah [14] demonstrated an exponential decrease in probability of failure as Kt/V increased and also suggested a benefit of spKt/V > 1.2.

Dialysis dose and mortality

Thus, according to NCDS conclusions, patient morbidity and treatment failure are related to the dialysis dose [15].

Subsequently, a correlation of lower mortality with higher dose of dialysis has been suggested. In the US, this correlation was evaluated by a historical prospective study of a national random sample of over 2300 Medicare ESRD patients [15]. After adjustment for an extensive list of co-morbidity and other risk factors, there was a strong indication that higher doses of dialysis were associated with lower mortality. The risk of mortality was 7% lower (P = 0.001) with each 0.1 increase of delivered dialysis dose.

Dialyzer flux

A major improvement in dialysis membranes over the last few years has been the introduction of high-flux membranes, characterized by high permeability for water, low and middle molecular weight solutes and high ‘biocompatibility’. While transport of solutes through low-flux membranes is mainly mediated by diffusion, convection represents an important additional mechanism for high-flux membranes. Published data on the magnitude of the impact of high-flux membranes on decreasing patients’ mortality are controversial (Table 1), although all of them support favourable effects. A decreased relative risk of mortality [relative risk (RR) 0.24, 95% confidence interval (CI) 0.12–0.49] was reported by Hornberger et al. [3] for patients treated with high-flux membranes compared with standard HD. In another retrospective analysis, Woods et al. [4] demonstrated lower mortality (21 vs 36 per 1000 years, P < 0.01) and increased 5-year survival (90 vs 60%, P = 0.029) among patients treated with high-flux polysulfone vs patients treated with low-flux polysulfone. In a Cox proportional hazards model, high-flux dialysis was associated with a 70% reduction in death risk compared with high-flux dialysis [4]. In a large retrospective study of almost 13 000 patients, Port et al. [5] reported an 18% reduction in mortality for patients treated with high- vs low-flux membranes. Koda et al. [7] reported that the use of high-flux membranes was associated with improved survival of dialysis patients (RR of mortality 0.613; P < 0.05). Conversely, analyzing data from 6640 patients treated in Lombardy between 1983 and 1995, Locatelli et al. [6] found a 10% reduction in patients treated with convective treatments (RR 0.90, 95% CI 0.76–1.06), which however was not statistically significant as to the relative risk of death.

Table 1. Decrease in mortality among patients treated with high-flux membranes

<table>
<thead>
<tr>
<th>Source</th>
<th>Mortality decrease (%)</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Hornberger et al. [3]</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Koda et al. [7]</td>
<td>39</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Locatelli et al. [6]</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Woods et al. [4]</td>
<td>42</td>
<td>0.03</td>
</tr>
<tr>
<td>Port et al. [5]</td>
<td>19</td>
<td>0.04</td>
</tr>
<tr>
<td>Eknoyan et al. [9]</td>
<td>8</td>
<td>0.23</td>
</tr>
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</table>

NS, not significant.

The HEMO study

Design and methods

The results of the HEMO study, conducted between 1995 and 2001 in the US, have been published recently [9]. The aim of the study was to evaluate morbidity and mortality of patients randomized to standard- or high-dose dialysis and to low- or high-flux membranes, respectively. Dose of dialysis was estimated by spKt/V and eKt/V [11]. High- and low-flux membranes were defined according to β2-microglobulin clearance (β2-μ cl). Exclusion criteria were: urea clearance > 1.5 ml/min per 35.1 of urea, serum albumin < 2.6 g/dl and inability to achieve an eKt/V > 1.3 within 4.5 h during two out of three dialysis sessions.
Primary outcome was death from any cause. Main secondary outcomes included first hospitalization for cardiac cause or death from any cause, first hospitalization for infection or death from any cause and decline of > 15% from baseline in serum albumin or death from any cause. Using a two-by-two factorial design, a total of 1846 patients were randomized to standard- or high-dose dialysis and to low- or high-flux dialyzers.

Dialysis dose and dialyzers flux targets for each of the two arms are shown in Table 2.

### Results

Despite the large sample, the HEMO study failed to demonstrate any benefit on survival of either high-dose dialysis or high-flux membranes. The RR of death in the high-dose arm when compared with the standard-dose arm was 0.96 (95% CI 0.84–1.1, \( P = 0.53 \)), with a 4% reduction in RR of death in the high-dose patient group. Similarly, the RR of death in the high-flux arm when compared with the low-flux arm was 0.92 (95% CI 0.81–1.05, \( P = 0.23 \)), with an 8% reduction in the RR of death in the high-flux group. No significant difference in main secondary outcomes was observed. Surprisingly, however, a secondary analysis suggested a benefit of high-flux membranes in patients treated for > 3.7 years. These findings should be interpreted with caution because they are the results of a secondary analysis.

In our opinion, these disappointing results are not fully unexpected and could be partially explained by demographic and dialytic characteristics of participants.

#### Study sample selection bias

Participants in the HEMO study were not fully representative of the US composite HD population. In fact, in the HEMO study sample, mean age was lower (57.6 ± 14.0 years) and percentage of blacks was much higher (63% of study participants) than in the US HD population at large [1]. Due to the study exclusion criteria, very heavy weight patients (97% of patients who underwent randomization weighed less than 100 kg) and severely malnourished patients were excluded (mean serum albumin 3.6 ± 0.4 g/dl). A selection bias was also evident when considering some dialysis-related parameters. At baseline, the dose of dialysis delivered was high (mean eKt/V 1.43 ± 0.21) and high-flux dialyzers were used in 60.2% of participants. Furthermore, time on dialysis at baseline was relatively long (3.7 ± 4.4 years), indicating a selection of fitter patients and longer survivors.

Hence, overall the HEMO study sample was not representative of the US HD population as a whole and, by definition, of the European dialysis population.

#### Dialysis parameters

Considering patient characteristics at baseline (high mean Kt/V and high proportion of patients treated with high-flux dialyzers), it is likely that a carryover effect occurred after randomization. Some of the patients who were previously treated with high-flux membranes were likely randomized to the low-flux arm. Similarly, some of those who had high Kt/V at baseline were randomized to the standard-dose group. This might have led to a confounding effect and to a bias in the final results.

Another factor that might have led to a misinterpretation in the comparison of high- vs low-flux membranes is the reuse of dialyzers. In fact, while commonly practiced in the US, reuse affects high-flux membrane performance. For instance, in a cohort of HEMO study participants treated with high-flux membrane (CT190) a decrease of \( \beta_2 \)-microglobulin clearance from 42 to 12 ml/min with reuse was reported [16]. Thus, practice of reuse might have led to loss in permeability of high-flux membranes, that could in a final analysis have been similar to low-flux dialyzers.

Moreover, a possible beneficial effect of convection could have been attenuated by the fact that its level in the high-flux arm was low. In fact, solute transport obtained by internal filtration in high-flux HD is lower than that expected by convection in haemodiafiltration or haemofiltration, which provide a high dose of convection together with a powerful clearance of low-molecular weight substances [17].

An interim analysis of HEMO study patients demonstrated that dose of dialysis delivered in the standard- and high-dose arms was tightly controlled and fulfilled the study design targets. Therefore, patients randomized to the standard dose were protected from underdialysis [11]. However, it is possible that the dose separation between the high-dose arm (mean eKt/V 1.53 ± 0.09) and the standard-dose arm (mean eKt/V 1.16 ± 0.08) was not marked enough to detect any effect on patient mortality. Thus, it cannot be excluded that a higher dialysis dose target for the high-dose arm might have led to beneficial effects on survival. However, it is almost impossible to increase dialysis dose further without modifying dialysis frequency. At present, daily dialysis,

### Table 2. Dialysis dose and flux targets in the HEMO study

<table>
<thead>
<tr>
<th>Dialysis dose</th>
<th>Standard</th>
<th>High</th>
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<tbody>
<tr>
<td>spKt/V</td>
<td>1.25</td>
<td>1.65</td>
</tr>
<tr>
<td>eKt/V</td>
<td>1.05</td>
<td>1.45</td>
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<tr>
<td>Dialyzers flux</td>
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<tr>
<td>Low</td>
<td>Mean ( \beta_2 )-ul &lt; 10 ml/min</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Mean ( \beta_2 )-ul &gt; 20 ml/min and ultrafiltration coefficient &gt; 14 ml/h per mmHg</td>
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aCurrent DOQI guidelines target: spKt/V > 1.2.
be it short [18] or long (nocturnal) [19], has limited diffusion although the results are impressive. The general applicability of this approach is questionable without solving the problem of the ‘one button machine’, vascular access and reimbursement.

Body water volume
In the HEMO study, urea clearance was normalized by urea distribution volume. The use of $\text{Kt/V}$ as a measure of outcome has been criticized since $V$ independently predicts mortality when used as a surrogate for body mass and nutritional status. This could represent a drawback in the HEMO study design. However, among the HEMO study participants body water volume after dialysis did not significantly differ in any of the four arms. Therefore, from a practical point of view, this problem does not exist for the interpretation of the study results.

Prevalent patients
Participants in the HEMO study were prevalent HD patients. Thus, dialysis history prior to the time of randomization and selection of long survivors might have affected the results. As the aim of the study was to evaluate strictly the effect of treatment modality to which patients were randomized, any effect from previous dialysis schedules should have been ruled out. This would have been easily achieved if only incident patients had been included. The magnitude of the problem is of clinical relevance considering that mean time on dialysis was 3.7 years and that mean follow-up time was definitively shorter (2.84 years).

Statistical evaluation
Compared with other important two-by-two factorial design studies, results of the HEMO study were presented in an unusual way. In fact, only composite results by dose and flux but not individual results for each of the four arms were reported in the tables and figures. Given that no interaction between dialysis dose and membrane flux was found ($P = 0.30$), we can assume that RR for patients randomized to high dose and high flux compared with those randomized to standard dose and low flux is the sum of the two main effects (i.e. RR 0.88). Thus, a 12% reduction in mortality relative risk, resulting from the additional effects of high dose (4% reduction) and high flux (8% reduction) could potentially be achieved. While this reduction may not reach statistical significance, it could be clinically relevant for thousands of HD patients.

Membrane Permeability Outcome study
The Membrane Permeability Outcome (MPO) study that we are presently conducting in Europe [20] has been designed to evaluate prospectively the long-term effect of membrane permeability on clinical outcomes (including mortality, morbidity, vascular access survival and nutritional status). Duration of follow-up will be 3–6 years. Only patients on dialysis for no longer than 2 months (incident patients) are included. This policy was chosen to rule out any effect from previous treatment schedules and to allow the investigators to evaluate only the effect of flux on outcome. The comparison between HEMO and MPO studies is reported in Table 3.

Conclusions
The HEMO results demonstrate that an increase of the dialysis dose above the currently recommended minimum dose ($\text{spKt/V}$ of 1.3) or the use of high-flux membranes do not improve patient outcomes. However, each of these high dose and high-flux dialysis were associated with a trend towards a decrease in mortality. While this did not reach statistical significance, the trend could be relevant in clinical practice. The lack of a statistically significant difference does not imply equivalence; rather, there was not enough evidence to conclude for high-dose and/or high-flux superiority. Therefore, we should try to avoid making the same mistake we made in interpreting the NCDS results: as time of dialysis was not significantly

<table>
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<th>Table 3. MPO–HEMO study comparison</th>
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<td>Primary objective</td>
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<td>Design</td>
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<td>Study groups</td>
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<td>Dialyser</td>
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associated with an improved outcome, its importance was neglected and time on dialysis was shortened, without considering the associated risks (difficulties in reaching ‘dry body weight’ and blood pressure control with related potential increase in cardiovascular morbidity and mortality). Therefore, the HEMO study results should not be used to justify reducing dose of dialysis; after our experience in interpreting the NCDS study results we should avoid P-values being used to kill more patients!

It is possible that a much higher dose of dialysis and higher convection may improve outcome; on the other hand, it is very difficult to further increase dialysis dose without modifying the frequency. However, daily dialysis is far from being a routine treatment. As far as convection is concerned, a solution for improving it and nevertheless containing cost could be represented by on-line convective treatments (haemofiltration and haemodiafiltration); on-line preparation also improves quality of the currently used dialysate. In order to test this intriguing hypothesis according to evidence-based medicine, further well designed and adequately sized trials on these modalities are needed.

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References