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The Membrane Permeability Outcome Study

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Abstract

Many observational studies have consistently shown that high-flux hemodialysis has positive effects on the survival and morbidity of uremic patients when compared with low-flux hemodialysis. However, the HEMO study, a randomized trial designed to evaluate the effect of membrane permeability on patient survival, showed only an 8% non-statistically significant reduction of mortality, albeit a secondary analysis suggested an advantage for high-flux membranes in certain patient subgroups. The prospective, randomized Membrane Permeability Outcome (MPO) study investigated the impact of membrane permeability on survival in incident hemodialysis patients who had low albumin (≤4 g/dl) and normal albumin (>4 g/dl) as separate randomization groups. Patients with serum albumin ≤4 g/dl had significantly better survival rates in the high-flux group compared with the low-flux group ($p = 0.032$). Moreover, a post-hoc secondary analysis showed that high-flux membranes may significantly improve survival in diabetic patients. No difference was found in patients with normal albumin levels. Considering the increasing number of dialysis patients with low serum albumin levels and with diabetes, the relevance of the MPO study led to the publication of a position statement by the European Renal Best Practice Advisory Board. This board strongly recommended that high-flux hemodialysis should be used for high-risk patients and, with a lower degree of evidence, even also for low-risk subjects due to the substantial reduction in β_2-microglobulin levels observed in the high-flux group.

The aims of hemodialysis (HD) are to control fluid overload, to correct metabolic acidosis and electrolyte imbalance and to remove the solutes that are normally excreted by the kidneys. However, patient morbidity and mortality rates are still very high today (15–25% per year) [1]. The use of high-flux HD (HF-HD) as an alternative and efficient dialysis technique was proposed more

than 20 years ago. It was then believed that the extremely high morbidity and mortality rates were associated with inadequate removal of middle molecular weight solutes and that standard low-flux HD (LF-HD) is not very efficacious in this respect [2]. HF-HD is characterized by the use of membranes of high permeability and increased in vitro clearance of vitamin B_{12} (molecular weight 1,355 daltons), which is considered a marker of middle molecules. Moreover, these membranes remove solutes with molecular weights in excess of that of β_2-microglobulin (11.8 kDa). Good biocompatibility is another key characteristic of high-flux membranes since, during conventional HD with 'bioincompatible' membranes, several cellular mechanisms and biological systems are activated, leading to chronic inflammation and oxidative stress. In uremia, chronic inflammation, together with malnutrition and anemia [3], are considered independent risk factors for accelerated atherosclerosis, cardiovascular complications and death [4]. There are several reasons why chronic inflammation affects uremic patients; here the type of the dialysis membrane and microbial contamination of the dialysate can add to the pro-inflammatory state [5].

What Was the Rationale for the Membrane Permeability Outcome Study?

High-flux membranes are characterized by enhanced removal of middle and high molecular weight solutes that are believed to be involved in the genesis of many complications of HD. After the introduction of HF-HD into clinical practice, several epidemiological and observational studies published since the early 1990s showed an association with an improvement in several aspects of chronic HD-related morbidity. These improvements include a reduction of β_2-microglobulin, a lower incidence of dialysis-related amyloidosis, a slower decrease of residual renal function and a better lipid profile. Furthermore, possible positive effects were also reported for anemia, nutritional status, susceptibility to infection, peripheral nerve conductivity and, above all, long-term survival [6].

Using a data subset from the US Renal Data System (USRDS) registry, Leypoldt et al. [7] showed a clear correlation between death rate and in vitro vitamin B_{12} dialyzer clearance, thus supporting the importance of middle molecules in uremic toxicity. Moreover, recent experimental data has revived interest in middle molecules toxicity [8]. Running parallel to the Membrane Permeability Outcome (MPO) study, the impact of HF-HD on mortality was evaluated in many epidemiologic and observational studies. In an analysis of a sample of the USRDS including nearly 14,000 HD patients, the effect of reuse practice and type of dialyzer membrane were investigated. The results showed that the relative risk for mortality was 24% higher in patients treated with LF-HD than in those receiving HF-HD [9]. A similar reduction (38%) was found in patients on LF-HD versus HF-HD in a European observational cohort of 650 patients [10].

However, no adequately controlled, randomized trials specifically designed to evaluate such benefits have been available for a long time. In 1996, results of a randomized controlled study evaluating the effects of different membrane permeabilities on patient treatment tolerance and nutritional parameters were published [11]. This study did not identify any differences in terms of morbidity or mortality (although it should be underlined that the study was not designed to investigate mortality) [12]. However, this trial was extremely important since it revealed the need to enroll a sicker patient population in future trials in order to adequately address patient mortality. Of note, the conclusions of that study were the basis for the rationale behind the MPO study, which started in 1998.

Thus evidence supporting the clinical superiority of HF-HD was far from being conclusive – there was a clear need for adequate randomized controlled clinical trials to possibly confirm data coming from previous epidemiological studies. For these reasons, two large, randomized and controlled clinical trials were specifically designed to better evaluate the effect of high-flux membranes on morbidity and mortality in HD patients: the Hemodialysis (HEMO) study [12] and the MPO study [13]. The HEMO study, which took place in the United States between 1995 and 2001, evaluated 1,846 mainly prevalent HD patients who were randomized to different membranes and different dialysis doses in a two-by-two factorial design. The aim of the study was to analyze the effect on morbidity and mortality of standard versus high dialysis dose and of low-flux versus high-flux membranes (the latter being defined as having an ultrafiltration coefficient >14 ml/mm Hg per hour) [13]. The trial did not reveal a significant difference in the outcome between the two types of membranes: the adjusted relative risk of all-cause death was with 8% not statistically significantly lower when using high-flux membranes ($p = 0.24$) [13]. A secondary analysis of the study considering only cardiac death or patients receiving HD for more than 3.7 years suggested a better survival in the high-flux group [13]. However, it has to be underlined that the HEMO study, although it is the best trial in the field of dialysis published to date, has some drawbacks, including the following: the relatively low mean age of the patients at inclusion (58 years); the exclusion of patients with low plasma albumin and high body weight; the possible presence of a carry-over effect; the practice of dialyzer reuse, and, above all, the high number of prevalent patients enrolled (selection bias of long survivors). These limitations clearly affect the quality and the general applicability of the HEMO study results [14, 15].

The MPO study was designed to evaluate the long-term effects of membrane permeability on multiple clinical outcomes, including mortality, morbidity, vascular access survival and nutritional status [16]. It is a prospective, randomized, controlled, multicenter clinical trial performed in several European countries. Only incident patients were enrolled (defined as subjects receiving dialysis for no longer than 2 months) to avoid any possible confounding effect of previous treatment schedules and a selection bias towards long survivors [14]. High-flux and low-flux dialyzers were distinguished by their β_2-microglobulin sieving

coefficients (>0.6 for HF-HD and 0 for LF-HD) and by their ultrafiltration coefficients (≥20 ml/mm Hg per hour for HF-HD and ≤10 ml/mm Hg per hour for LF-HD). Dialyzer reuse was not allowed [13]. Moreover, the study was specifically designed to include a sicker patient population which, according to the study rationale, is more susceptible to the advantages of HF-HD and in order to provide sufficient statistical power (increased number of events) to possibly demonstrate differences in survival [16]. A serum albumin of ≤4 g/dl was chosen as a marker for increased mortality risk and as an inclusion criterion [16]. However, since the recruitment rate was lower than expected after about 11 months of the enrolment period, and the low albumin requirement was perceived to be the major reason for this, a study amendment was made that also allowed the inclusion of subjects with serum albumin >4 g/dl. A separate randomization list was maintained for these patients to ensure balanced patient distribution and, above all, to facilitate the performance of separate and combined data analysis, thereby avoiding jeopardizing the original study hypothesis.

The trial of Locatelli et al. [11], which provided the basis for the rationale of the MPO study, suggested that dialysis dose is not so relevant for outcome when the dose is higher than a minimum adequate value. Therefore, in order to exclude dialysis dose as a confounding factor in the MPO study, a monitored single pool Kt/V of at least 1.2 was required for patients at randomization and throughout the study. It was thus possible to avoid stratifying the patients and, as a consequence, reducing the statistical power of the study [13]. It is worth noting that the HEMO study was not able to confirm the hypothesis that higher HD dose (Kt/V >1.2) was superior to the standard dose in reducing patient mortality. Thus, the HEMO study proved that CKD-5D patient mortality does not depend on small molecule clearances, provided a threshold minimum dialysis dose is delivered (single pool Kt/V ≈1.3) [12]. Apart from dialysis duration and a minimum dialysis dose, no exclusion criteria were applied in the selection of patients for the MPO study. Thus it was possible to avoid the possibility that the exclusion of high-risk patients could interfere with the results of the study, making the MPO study the first randomized trial evaluating the independent effect of flux on mortality in incident HD patients (table 1).

What Are the Results of the MPO Study?

The MPO study recruitment period lasted 4.5 years, from December 1998 to June 2003, enrolling 738 HD patients from 59 centers in 9 European countries. The number of patients with serum albumin ≤4 g/dl was 567, while 171 patients had serum albumin >4 g/dl. A total of 647 patients were included in the survival analysis (91 subjects could not be considered). Patients in the low-flux and high-flux groups and patients with low and high serum albumin level had similar baseline characteristics [13].

Table 1. Comparison between the HEMO study and the MPO study

	HEMO study	MPO study
Primary outcome	All-cause mortality	All-cause mortality
Study groups and intervention	4 groups 2 × 2 factorial design Membrane flux and dialysis dose	2 groups Membrane flux
Randomization	Stratified by center, diabetic status and age	Stratified by center and serum albumin
Target sample size	900 patients	666 patients
Follow-up	1.5–6.5 years	3–7.5 years
Study sites	USA	9 European countries
Patients	Prevalent patients (≥3 months on HD) Age 18–80 years ≥2.6 g/dl albumin	Incident patients (≤2 months on HD) Age 18–80 years (initially ≤4 g/dl albumin)
Dialyzer	Reuse up to 20 times Synthetic or substituted cellulose	No reuse
		Synthetic or substituted cellulose (in low-flux group also cellulose)
Results (primary outcome)	Non-statistically significant benefit of high-flux membranes (8% relative risk reduction of mortality)	– Statistically significantly benefit of high-flux membranes for patients with serum albumin ≤4 g/dl (37% relative risk reduction of mortality)
		– Non-statistically significant benefit of high-flux membranes in the population as a whole (24% relative risk reduction of mortality)
Results (secondary analysis)	Better survival in high-flux group for patients on dialysis for more than 3.7 years or considering cardiac death (22% relative risk reduction)	Better survival in high-flux group for diabetic patients (40.4% relative risk reduction)

Apart from membrane flux, there were no differences between the two groups regarding the dialysis treatment parameters (i.e. blood flow rate, dialysis fluid flow rate, treatment time and dialysis membrane surface area). Membrane flux was clearly different: for patients receiving HF-HD and LF-HD, the mean ultrafiltration coefficient of the dialyzers was 44.7 ± 9.1 and 9.8 ± 3.5 ml/mm Hg per hour, respectively ($p < 0.0001$). The mean dialysis dose was a spKt/V of 1.36 ± 0.3 at month 0 (with no significant difference between the groups);

adjustments to treatment parameters were made during the study course when Kt/V fell below 1.2 or when otherwise indicated [13].

The primary outcome of the MPO study was the effect of membrane permeability on survival in HD patients. This was observed until the last enrolled patient reached 3 years of observation time, until premature termination occurred or until death. The mean study follow-up was 3.0 ± 1.9 years, while the maximum was 7.5 years. During the study, 270 patients prematurely terminated the study: reasons were kidney transplantation, change of dialysis center, withdrawal of patient's consent, change to peritoneal dialysis for >60 days, recovery of renal function or other, not predefined reasons [13].

The initial aim of the study, according to the rationale [11], was to enroll patients at risk. Thus the patients were analyzed separately, according to their serum albumin values. A total of 132 deaths occurred in the group with serum albumin ≤4 g/dl (n = 493) and the crude mortality rate was 8.8%. The difference between the high-flux and the low-flux groups was statistically significant (7.3 vs. 10.4%; p = 0.04). Three- and 4-year mortality rates were 16.9 and 22.3 and 26.6 and 35.7% in the high-flux and the low-flux groups, respectively. A Kaplan-Meier analysis showed that mortality was significantly lower in the high-flux group than in the low-flux group (p = 0.032). The Cox proportional hazards model revealed that membrane permeability reduced the relative risk of mortality by a statistically significant 37% (HR 0.63; 95% CI 0.45–0.90; p = 0.010) [13]. Only 30 patients died in the group with normal serum albumin (>4 g/dl; n = 154). In this set, the 3-year mortality was 19.7% in the high-flux and 16.1% in the low-flux group; the corresponding 4-year mortality was 27.3 and 18.0%, respectively. The survival difference was not statistically significant in the Kaplan-Meier analysis (p = 0.211) [13].

Considering the population as a whole, there were 162 deaths for all causes and a mortality rate of 8.2% during the follow-up of the study; the difference between the two study groups was not statistically significant. Cardiovascular diseases accounted for almost one half of deaths (46.3%), followed by infectious diseases (21.6% of all deaths). The 3-year mortality was 17.0% in the high-flux group and 20.7% in the low-flux group; the corresponding 4-year mortality rates were 26.9 and 31.0%, respectively. Although the Kaplan-Meier analysis showed a slightly better survival in the high-flux group than in the low-flux group, this difference was not statistically significant (p = 0.214). The treatment efficacy analysis revealed comparable results between the two study arms [13]. A Cox proportional hazards model showed that membrane permeability caused a non-statistically significant 24% relative risk reduction of mortality (hazard ratio 0.76; 95% confidence interval 0.56–1.04; p = 0.091). Age, diabetes and comorbidity index were independent predictors of death [13].

Seeing as the number of events is very low in patients with serum albumin >4 g/dl, one can say that the power of the study derives from the initial aim of the trial, which focused only on patients at risk. A secondary post-hoc analysis of survival

Table 2. MPO Study – number needed to treat

	Incidence of events per patient year (×100)		Relative risk reduction	Absolute risk reduction	Number needed to treat
	high-flux	low-flux			
Total patients					
All patients (n = 647)	7.5	9.0	17.3	1.6	63.9
≤4 g/dl albumin (n = 493)	7.3	10.4	30.2	3.2	31.7
Diabetics					
All patients (n = 157)	11.3	18.9	40.4	7.7	13.1
≤4 g/dl Albumin (n = 127)	9.3	20.0	53.3	10.7	9.4

took diabetic patients into consideration (n = 157) and found a higher crude mortality rate in the low-flux group (18.9%) compared to the high-flux group (11.3%): this difference was statistically significant (p = 0.037). In diabetic patients with serum albumin ≤4 g/dl (n = 127), the use of HF-HD resulted in a 53.3% relative risk reduction in mortality and an absolute risk reduction of 10.7% compared to LF-HD (table 2). The Kaplan-Meier survival analysis of diabetic patients as a whole showed a statistically significant higher survival rate in high-flux dialysis compared to low-flux dialysis (p = 0.039). The Cox proportional hazards model (adjusted for age, gender, comorbidity index and vascular access) revealed a 38% relative risk reduction for mortality (hazard ratio 0.62; 95% confidence index 0.38–1.01; p = 0.056) [13]. An interaction was found between the effect of membrane flux and serum albumin levels (p = 0.009) but not with the presence of diabetes (p = 0.216) [13]. This is in contrast to the results of the HEMO study [12].

The MPO secondary outcomes were morbidity and β_2-microglobulin levels. There were no differences in the rate of hospital admissions between the two groups for all causes, for infections or for problems associated to vascular β_2-microglobulin access. β_2-Microglobulin levels were lower in high-flux dialysis than in the low-flux counterpart, with a 3-year increase being statistically significantly different between the study arms (4.4 ± 7.8 vs. 8.0 ± 12.3 mg/l; p < 0.05) [13]. These results are of paramount importance considering that the HEMO study reported an association between mortality and β_2-microglobulin levels [17], including mortality for infections [18].

What Is the Clinical Impact of the MPO Study?

In the MPO study, according to the initial study design, high-flux dialysis resulted in a significant lower mortality rate (37% relative risk reduction after

adjustment for confounding factors) in patients with serum albumin ≤4 g/dl, i.e. patients considered at risk for poor outcome. However, considering the population as a whole (i.e. including patients with normal and low serum albumin levels), the MPO study did not show a significant effect of membrane permeability on survival [13] – as in the primary analysis of the HEMO study [12]. The authors underlined that the mortality rate of 8.2% is lower than that reported in registries and observational trials, and considered this result to be due to a different patient comorbidity profile (as found in a preliminary study analysis) [19]. It is important to remember that the secondary analysis of HEMO study showed that patients receiving HD for >3.7 years had a relative mortality risk reduction by 32% when treated with HF-HD [12].

The MPO post-hoc analysis, evaluating the effect of membrane permeability in diabetic patients, showed a higher survival rate associated with HF-HD compared to LF-HD, with an adjusted risk reduction of 38%. Although it is important to keep in mind that these results come from a secondary analysis, such data are in line with the rationale of the MPO study [13]. Moreover, a post-hoc analysis of the 4D study [20], which considered only patients receiving HD with the same membrane type during the entire follow-up period, showed that diabetic patients treated with LF-HD had a 59% increase in the hazard ratio for mortality when compared with HF-HD. This further supports the MPO results for diabetic patients.

The MPO study pointed out an interaction of serum albumin with membrane flux. The importance of the results of the MPO study stays in the general applicability of the data found in patients with hypoalbuminemia and diabetes, considering the fact that many dialysis patients have diabetes, inflammation and/or malnutrition [21, 22] (table 2). The causal relation between treatment with HF-HD and improved survival could lie in the eliminative capacity of high-flux membranes, in particular their ability to significantly remove β_2-microglobulin (an acknowledged surrogate of middle molecules) and to reduce its serum levels in the long term, which in turn are related to mortality [17, 18]. Of course, these findings could be related to many factors, including a better volume control as this is more easily achieved with these dialysis techniques (table 3).

The associated editorial comment to MPO study publication by Cheung and Greene [26] underlines the value and insight provided by the MPO study concerning the benefits of HF-HD compared to LF-HD. A key aspect is that the MPO study provided relevant results in a setting that was different from that of the HEMO study. It is noteworthy that, in comparison with the HEMO study, MPO patients were more likely to be white, to use a native fistula and to have less comorbidities. Cheung and Greene [26] pointed out that the fact that subgroup analyses based on serum albumin level were preplanned gives strength to the study findings, reducing possible interferences coming from multiple comparisons. They also suggested that joint analyses of the HEMO and MPO databases should be conducted in order to elucidate any possible combined evidence from

Table 3. Randomized and observational studies evaluating the role of HF-HD on patient mortality

Group (first author)	Design	Treatments	Sample size	Relative risk reduction	p value
Hornberger 1992 [23]	Historical, prospective	HF-HD (107) LF-HD (146)	253	76%	<0.001
Locatelli 1996 [11]	Randomized, prospective	Cuprophan-HD (132) LF-HD (147) HF-HD (51) HDF (50)	380		NS
Koda 1997 [24]	Historical, prospective	HF-HD (248) LF-HD (571)	819	39%	<0.05
Leypoldt 1999 [7]	Historical, prospective	HF-HD LF-HD	1,171	5%	<0.0001
Eknoyan 2006 [12]	Randomized, prospective	HF-HD (921) LF-HD (925)	1,846		NS
Woods, 2000 [25]	Historical, prospective	HF-HD (463) LF-HD (252)	715	42%	<0.01
Port 2001 [9]	Historical, prospective	HF-HD (3,751) LF-HD (9,040)	12,791	19%	0.04
Chauveau 2005 [10]	Historical, prospective	HF-HD (299) LF-HD (351)	650	38%	0.01
Krane 2007 [20]	Post-hoc analysis of prospective randomized study	HF-HD (241) LF-HD (407)	648	59%	0.0006
Locatelli 2009 [13]	Randomized, prospective	Albumin ≤4 g/dl HF-HD (279) LF-HD (283)	562	37%	0.032
	Randomized, prospective	Albumin >4 g/dl HF-HD (84) LF-HD (92)	176		NS
	Randomized, prospective, post-hoc analysis	Diabetics HF-HD (83) LF-HD (74)	157	38%	0.039

the two studies or any new hypotheses that should be tested in new randomized clinical trials. Cheung and Greene [26] finally comment that the results of the MPO study represent the basis for the use of high-flux membranes, with the only limitation being a possible economic burden.

Conclusions

The current European Best Practice Guidelines (EBPG) on dialysis strategies published in 2007 recommend in Guideline 2.1 that 'The use of synthetic high-flux membranes should be considered to delay long-term complications of hemodialysis therapy. Specific indications include: to reduce dialysis-related amyloidosis (evidence level III); to improve control of hyperphosphatemia (level II); to reduce the increased cardiovascular risk (level II), and to improve control of anemia (level III)' [27]. It should be noted that, at the time the guideline was prepared, no sufficient evidence was available to link membrane permeability with survival. The European Renal Best Practice (ERBP) Advisory Board, in the light of the MPO results, recently published a position statement [28] to change the existing Guideline 2.1. The board considered that the MPO study provided sufficient evidence to upgrade the strength of the guidance to a level 1A (strong recommendation, based on high-quality evidence) and recommend that HF-HD should be used in the case of high-risk patients (comparable to the low-albumin group of the MPO study). Because of the substantial improvement in an intermediate marker (β_2-microglobulin) in the high-flux group of the MPO study, the ERBP Advisory Board also recommended that synthetic high-flux membranes should used even in low-risk patients (level 2b: weak recommendation, low quality evidence) [28].

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