Effect of Membrane Permeability on Survival of Hemodialysis Patients

Francesco Locatelli,* Alejandro Martin-Malo,† Thierry Hannedouche,‡ Alfredo Loureiro,§ Menelaos Papadimitriou,‖ Volker Wizemann,¶ Stefan H. Jacobson,** Stanislaw Czekalski,†† Claudio Ronco,‡‡ and Raymond Vanholder,§§
for the Membrane Permeability Outcome (MPO) Study Group

*Department of Nephrology, Dialysis and Renal Transplantation, A. Manzoni Hospital, Lecco, Italy; †Department of Nephrology, University Hospital Reina Sofia, Cordoba, Spain; ‡Department of Nephrology, University Hospital, Strasbourg, France; §Department of Nephrology, Portuguese Institute of Oncology, Porto, Portugal; ‖Department of Nephrology, Hippokration General Hospital, Thessaloniki Greece; ¶Georg-Haas-Dialysis Centre, Giessen, Germany; **Department of Nephrology, Danderyd University Hospital, Karolinska Institute, Stockholm, Sweden; ††Department of Nephrology, Transplantology and Internal Diseases, Poznań University of Medical Sciences, Poznań, Poland; ‡‡Department of Nephrology and Intensive Care, St. Bortolo Hospital, Vincenza, Italy; and §§Department of Internal Medicine, Nephrology Section, University Hospital, Ghent, Belgium

ABSTRACT

The effect of high-flux hemodialysis membranes on patient survival has not been unequivocally determined. In this prospective, randomized clinical trial, we enrolled 738 incident hemodialysis patients, stratified them by serum albumin ≤4 and >4 g/dl, and assigned them to either low-flux or high-flux membranes. We followed patients for 3 to 7.5 yr. Kaplan-Meier survival analysis showed no significant difference between high-flux and low-flux membranes, and a Cox proportional hazards model concurred. Patients with serum albumin ≤4 g/dl had significantly higher survival rates in the high-flux group compared with the low-flux group ($P = 0.032$). In addition, a secondary analysis revealed that high-flux membranes may significantly improve survival of patients with diabetes. Among those with serum albumin ≤4 g/dl, slightly different effects among patients with and without diabetes suggested a potential interaction between diabetes status and low serum albumin in the reduction of risk conferred by high-flux membranes. In summary, we did not detect a significant survival benefit with either high-flux or low-flux membranes in the population overall, but the use of high-flux membranes conferred a significant survival benefit among patients with serum albumin ≤4 g/dl. The apparent survival benefit among patients who have diabetes and are treated with high-flux membranes requires confirmation given the *post hoc* nature of our analysis.

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Patients who have stage 5 chronic kidney disease (CKD) and are on dialysis therapy have a high mortality rate, estimated between 14 and 26% in Europe and at 24% per year in the United States.[1] The accumulation of various retention solutes over a broad range of molecular weights and chemical composition is involved in the complex pathophysiology of uremia and, among other factors, implicated in the high mortality observed in CKD.[2]

Because of their higher porosity, high-flux hemodialysis (HD) membranes have the capacity to remove retention solutes of higher molecular weight than do low-flux membranes,[3] which contain smaller pores. Whether this enhanced solute elimination of high-flux membranes translates

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Correspondence: Prof. Francesco Locatelli, Department of Nephrology, Dialysis and Renal Transplantation, A. Manzoni Hospital, Via dell'Eremo 9/11, I-23900 Lecco, Italy. Phone: +39-0341-489850; Fax: +39-0341-489860; E-mail: f.locatelli@ospedale.lecco.it

into long-term benefits in terms of survival of long-term HD patients has not been backed by sound clinical data, although epidemiologic studies suggested a benefit for patients who were treated with high-flux compared with low-flux membranes.[4,5]

Results of a previous controlled, randomized study that compared dialysis membranes of different permeability could not find any difference in terms of morbidity or mortality[6]; however, that study lacked statistical power because it was not designed to evaluate these hard end points. From the observed cumulative 2-yr survival rate in that study,[6] it was concluded that further studies should involve a sicker patient population to provide enough statistical power to demonstrate differences in patient survival and should include incident patients to avoid any carryover effect from the previous treatment modality and the selection bias toward survivors.

The Hemodialysis (HEMO) Study, published while our trial was ongoing, was a randomized, four-arm, controlled clinical study that enrolled, in contrast to this study, prevalent patients to investigate patient survival. It showed no significant survival difference between the high-flux and the low-flux membrane types at primary analysis,[7] although secondary analyses pointed to an advantage for high-flux membranes in subgroups of patients.[8,9] This prospective, randomized Membrane Permeability Outcome (MPO) study was designed to compare the impact of membrane permeability on survival in incident HD patients who had either low (≤4 g/dl) or normal albumin (>4 g/dl) and were treated with a minimum dialysis dose (single-pool Kt/V [spKt/V]) of 1.2.

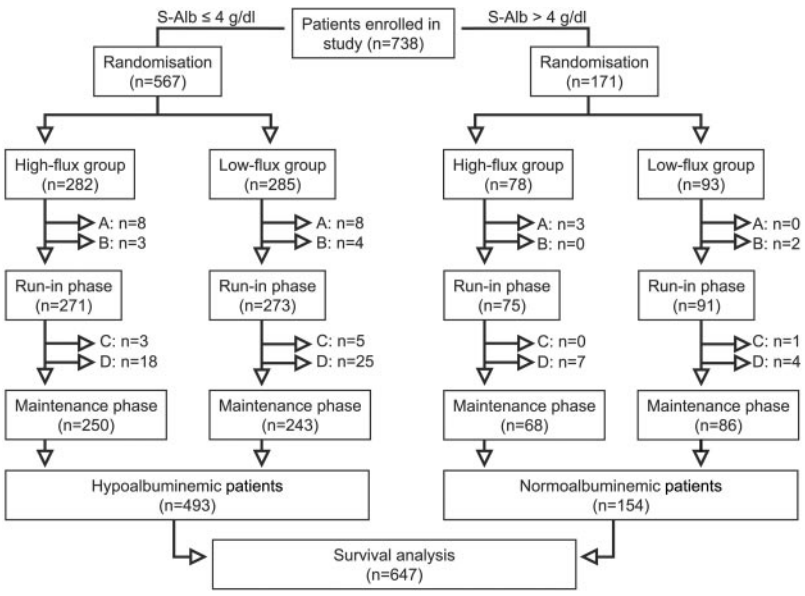

Figure 1. Number of patients enrolled in the study, allocated to the strata of serum albumin, randomized to the study groups, and included in the analysis populations. Patients not included in the survival analysis population: A, no study treatment started; B, major protocol violations at enrollment; C, premature termination or death before month 0; D, Kt/V <1.2 (end of run-in phase or month 3).

RESULTS

Baseline Patient Characteristics

During the recruitment period of 4.5 yr from December 1998 through June 2003, 738 HD patients were enrolled in 59 European study centers; 567 of them had serum albumin ≤4 g/dl, and 171 had serum albumin >4 g/dl (Figure 1). The following patients were not included in the survival analysis population: 19 patients in whom no study treatment was started, nine patients because of major protocol violations at inclusion, and nine patients because of death or a reason for premature termination before entering the maintenance phase. Furthermore, 54 patients were ineligible to enter the maintenance phase because they failed to reach the minimum dialysis dose (Kt/V) of 1.2. Thus, 647 patients were eligible to be included in the analysis population (Figure 1).

Patient characteristics at baseline were comparable for the two groups of membrane permeability in the population as a whole (Tables 1 and 2) as well as in the patients with serum albumin either ≤ or >4 g/dl (data not shown). Vascular access was an arteriovenous fistula in the majority of patients. Overall, 15% of the patients were treated *via* a central venous catheter, with a slightly higher percentage found in the high-flux group.

Dialysis Treatment Parameters

Membrane flux was clearly separated between the study groups as demonstrated by the mean ultrafiltration coefficient of the dialyzers of 44.7 ± 9.1 ml/mmHg per h of all patients who were treated with high-flux membranes and of 9.8 ± 3.5 ml/mmHg per h in those who were treated with low-flux membranes ($P < 0.0001$). All other treatment parameters (blood flow rate, dialysis fluid flow rate, treatment time, and dialysis membrane surface area) were not different between the two groups. The applied treatment parameters resulted in a mean dialysis dose in all patients of spKt/V of 1.36 ± 0.3 at month 0, with no significant difference between the groups. Throughout the study, further adjustments of treatment parameters were made when Kt/V fell below 1.2 or when indicated otherwise.

Primary Outcomes

Mortality.

The patient observation period considered for the outcome analysis started with entering the maintenance phase (month 0). Patients were observed until the last enrolled patient reached 3 yr of observation time, until premature termination occurred, or until death. The resulting mean observation time in the study was 3.0 ± 1.9 yr; the maximum was 7.5 yr. During the observa-

Table 1. Patient characteristics at enrollment

Characteristic	All Patients (n = 647)	High-Flux (n = 318)	Low-Flux (n = 329)
Age (yr; mean ± SD)	59.8 ± 13.6	59.4 ± 14.5	60.2 ± 12.7
Male gender (n [%])	415 (64.1)	200 (62.9)	215 (65.3)
Diabetes (n [%])	157 (24.2)	83 (26.1)	74 (22.5)
Cardiovascular diseases (n [%])	174 (26.9)	81 (25.5)	93 (28.3)
Charlson comorbidity index (mean ± SD)[a]	4.6 ± 2.1	4.5 ± 2.2	4.6 ± 2.0
Time on dialysis (d; mean ± SD)	30 ± 18	31 ± 18	29 ± 19
Body mass index (kg/m^2; mean ± SD)	25.3 ± 4.3	25.2 ± 4.3	25.3 ± 4.3
Urine volume >100 ml/24 h (n [%])	465 (71.9)	222 (69.8)	243 (73.9)
Vascular access (n [%])			
fistula	518 (80.1)	246 (77.3)	272 (82.7)
graft	30 (4.6)	13 (4.1)	17 (5.2)
catheter	99 (15.3)	59 (18.6)	40 (12.2)
spKt/V (mean ± SD)[b]	1.36 ± 0.30	1.36 ± 0.30	1.35 ± 0.30
Serum albumin (g/dl; mean ± SD)[b]	3.8 ± 0.5	3.9 ± 0.5	3.8 ± 0.5

[a]Charlson comorbidity index was calculated excluding diabetes.
[b]Month 0.

Table 2. Clinical and biochemical parameters at month 0, major concomitant medication at enrollment

Parameter	All Patients (n = 647)	High-Flux (n = 318)	Low-Flux (n = 329)
Predialysis BP (mmHg; mean ± SD)			
systolic	143 ± 21	142 ± 21	143 ± 22
diastolic	79 ± 12	79 ± 12	79 ± 12
Hematocrit (%; mean ± SD)	33.3 ± 4.6	33.6 ± 4.7	33.0 ± 4.6
Iron (μg/dl; mean ± SD)	65.1 ± 31.1	67.7 ± 33.8	62.7 ± 28.1
Total cholesterol (mg/dl; mean ± SD)	189.8 ± 46.3	185.9 ± 41.1	193.5 ± 50.6
LDL (mg/dl; mean ± SD)	113.5 ± 40.1	111.2 ± 36.9	115.8 ± 43.0
HDL (mg/dl; mean ± SD)	44.4 ± 13.9	45.1 ± 13.2	43.8 ± 14.5
Triglycerides (mg/dl; mean ± SD)	174.6 ± 127.5	165.9 ± 99.7	182.7 ± 148.9
Patients on antihypertensive therapy (%)	85.3	85.2	85.4
Patients on erythropoietin (%)	84.5	83.6	85.4
Patients on lipid-lowering agents (%)	13.3	10.7	15.8

tion period, 270 patients prematurely terminated the study because of kidney transplantation (n = 170); change of dialysis center (n = 58); withdrawal of patient's consent to participate in the study (n = 15); change to peritoneal dialysis for >60 d (n = 7); recovery of renal function (n = 1); or to other, not predefined reasons (n = 19). In the Kaplan-Meier survival analysis, these patients were censored at the time when premature termination occurred.

There were 162 deaths for all causes, which is equivalent to a crude mortality rate of 8.2% with a nonsignificant difference between the two study groups (Table 3). Main causes of death were cardiovascular diseases (46.3% of all deaths) and infectious diseases (21.6% of all deaths). Number of deaths and crude mortality rates are given in Table 3.

The 3-yr mortality was 17.5 and 20.7% and the 4-yr mortality 26.9 and 31.0% in the high-flux and the low-flux group, respectively. The Kaplan-Meier analysis showed a slightly better survival in the high-flux group than in the low-flux group, which did not, however, reach statistical significance (P = 0.214; Figure 2). The treatment efficacy analysis revealed comparable results.

Analysis with the Cox proportional hazards model is shown in Table 4. Membrane permeability caused a nonsignificant 24% relative risk (RR) reduction of mortality (hazard ratio [HR] 0.76; 95% confidence interval [CI] 0.56 to 1.04; P = 0.091). Age, diabetes, and comorbidity index were shown to be independent predictors of death.

Following the initial rationale of the study to enroll patients at risk, we then analyzed the patients separately according to their serum albumin. In the group with serum albumin ≤4 g/dl (n = 493), 132 deaths occurred. The crude mortality rate for these patients was 8.8%, with a more pronounced difference between the high-flux and the low-flux groups (7.3 *versus* 10.4%; P = 0.04). We found a 3-yr mortality of 16.9 and 22.3% and a 4-yr mortality of 26.6 and 35.7% in the high-flux and the low-flux groups, respectively. The mortality as shown in the Kaplan-Meier analysis was significantly lower in the high-flux group than in the low-flux group (P = 0.032; Figure 3). In the Cox proportional hazards model, membrane permeability showed a significant 37% RR reduction of mortality (HR 0.63; 95% CI 0.45 to 0.90; P = 0.010).

In the patients with normal serum albumin (>4 g/dl; n =

Table 3. Outcome data: Mortality and morbidity[a]

Parameter	All Patients (n = 647)	High-Flux (n = 318)	Low-Flux (n = 329)
Patient years at risk	1967.0	991.9	975.1
All-cause death	162 (8.2)	74 (7.5)	88 (9.0)
Cardiovascular death	75 (3.8)	34 (3.5)	41 (4.2)
Infectious death	35 (1.8)	15 (1.5)	20 (2.0)
All-cause hospitalizations	1045 (53.1)	527 (53.1)	518 (53.1)
Hospitalization for infections	156 (7.9)	74 (7.5)	82 (8.4)
Hospitalization for vascular access problems	214 (10.9)	114 (11.5)	100 (10.3)

[a]Data are no. of events for deaths and hospitalizations (deaths per 100 patient-years and hospital admissions per 100 patient years for mortality and hospitalization rate, respectively).

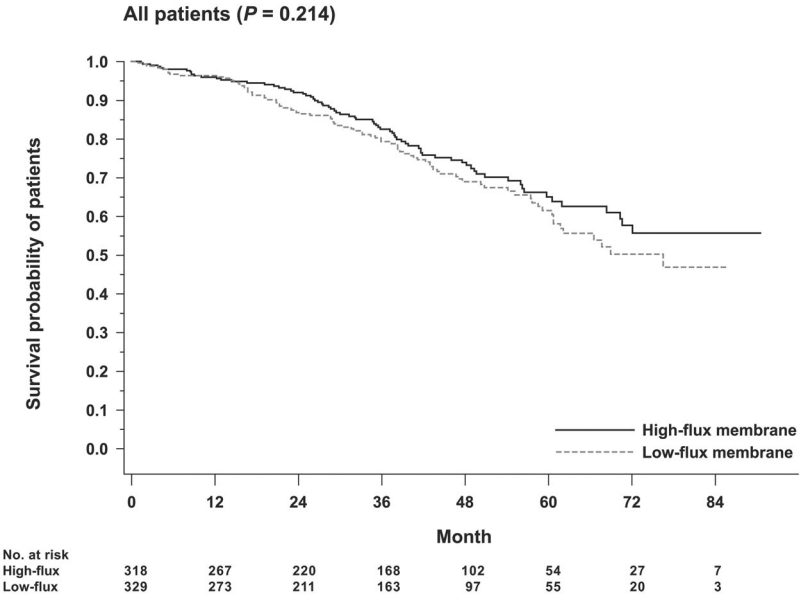

Figure 2. Kaplan-Meier survival curves for the complete intention-to-treat population (Log-rank test $P = 0.214$).

154), only 30 deaths occurred. The 3-yr mortality was 19.7 and 16.1% and the 4-yr mortality was 27.3 and 18.0% in the high-flux and the low-flux groups, respectively. No significant survival difference between the two groups could be observed in the Kaplan-Meier analysis ($P = 0.211$). The HR from the Cox proportional hazards model was 1.82 (95% CI 0.86 to 3.82; $P = 0.117$).

Subgroup Analysis: Patients with Diabetes.
All patients ($n = 157$) with diabetes either of type 1 (12%) or 2 (88%) were included in a subgroup analysis of survival. The crude mortality rate was 11.3% in the high-flux and 18.9% in the low-flux groups ($P = 0.037$). A Kaplan-Meier survival analysis showed a significantly higher survival rate in the group of high-flux dialysis as compared with low-flux dialysis ($P = 0.039$; Figure 4). In the Cox proportional hazards model adjusted for age, gender, comorbidity index, and vascular access, the RR reduction for mortality was 38% (HR 0.62; 95% CI 0.38 to 1.01; $P = 0.056$).

We found an interaction between the effect of membrane flux and serum albumin levels ($P = 0.009$) but not with the presence of diabetes ($P = 0.216$); however, we analyzed whether the effect of high-flux membranes on the RR for mortality in patients with serum albumin $\leq$4 g/dl was related to diabetes status. For patients with serum albumin $\leq$4 g/dl, the RR for mortality with high-flux *versus* that with low-flux dialysis was 0.49 (95% CI 0.28 to 0.87; $P = 0.014$) in patients with diabetes ($n = 127$) and 0.81 (95% CI 0.52 to 1.26; $P = 0.350$) in patients without diabetes ($n = 366$); there was only a borderline significance for the difference between these HRs ($P = 0.099$). For patients with serum albumin $>$4 g/dl, the RR for mortality with high-flux *versus* that with low-flux dialysis was 2.02 (95% CI 0.67 to 6.04; $P = 0.209$) in patients with diabetes ($n = 30$) and 1.47 (95% CI 0.47 to 4.60; $P = 0.511$) in patients without diabetes ($n = 124$; $P = 0.862$ for the difference between the HRs).

Secondary Outcomes

Morbidity.
The rate of hospital admissions was comparable in the high-flux and the low-flux groups, whether considered for all causes, for infections, or for problems associated to vascular access (Table 3).

β_2-Microglobulin.
High-flux dialysis resulted in a lower accumulation of β_2-microglobulin than low-flux dialysis. It increased from month 0 to month 36 to a significantly lesser extent ($P < 0.05$) in the high-flux group (by 4.4 $\pm$ 7.8 mg/L) than in the low-flux group (by 8.0 $\pm$ 12.3 mg/L).

DISCUSSION

The aim of this study was to investigate the effect of membrane permeability on survival in HD patients, with focus on patients at risk defined by serum albumin $\leq$4 g/dl.[10] Many studies have shown a mortality risk inversely proportional to serum albumin levels,[11,12] thereby supporting the rationale of our initial study design to enroll a sicker patient population than enrolled in a previous study to increase the power of the study.[6]

In this study, no significant effect of membrane permeability on survival was found in the population as a whole, including the patients with normal serum albumin levels; however, high-flux dialysis showed a significant survival benefit in pa-

Table 4. Cox regression analysis of mortality[a]

Parameter	RR for Death (95% CI)	*P*
High-flux membrane (*versus* low-flux)	0.76 (0.56 to 1.04)	0.0910
Age (per 1-yr increment)	1.04 (1.02 to 1.06)	0.0010
Gender (male *versus* female)	0.80 (0.57 to 1.13)	0.2110
Diabetes (presence *versus* absence)	1.97 (1.43 to 2.72)	<0.0001
Charlson comorbidity index (per 1-U increment)	1.18 (1.08 to 1.29)	0.0004
Vascular access (catheter *versus* fistula)	1.26 (0.82 to 1.93)	0.2840

[a]Charlson comorbidity index was considered excluding diabetes.

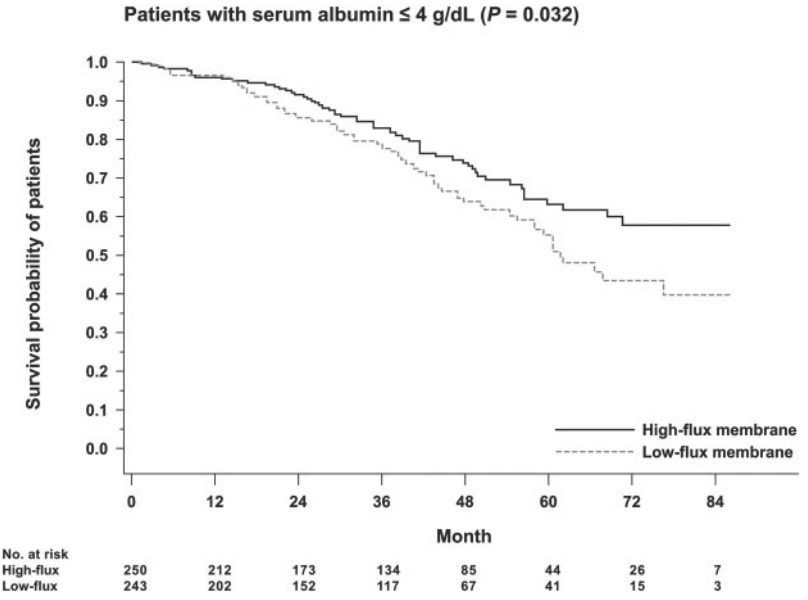

Figure 3. Kaplan-Meier survival curves for the population of patients with serum albumin ≤4 g/dl (Log-rank test $P = 0.032$).

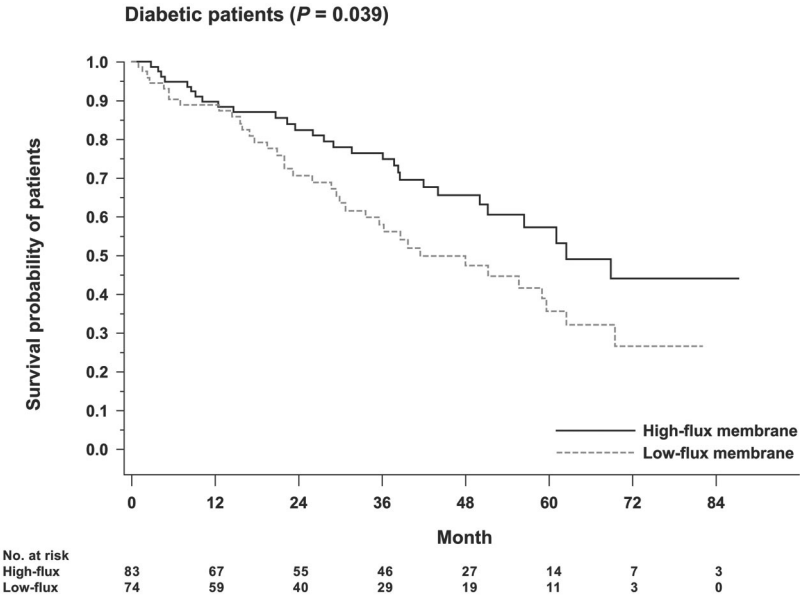

Figure 4. Kaplan-Meier survival curves for the subpopulation of patients with diabetes (Log-rank test $P = 0.039$).

tients at risk for worse outcome, defined by serum albumin ≤4 g/dl according to our initial study design. The RR reduction of mortality in this patient population, after adjustment for confounding factors, was 37%.

The total number of deaths observed in this study was 162, 132 of them in the stratum with serum albumin ≤4 g/dl. The resulting mortality rate of 8.2% is lower than that reported from registries[1] or in the patient cohort of the worldwide observational Dialysis Outcomes and Practice Patterns Study (DOPPS), possibly as a result of a different comorbidity profile as found in a preliminary analysis comparing the population of our study with a population of incident patients from the DOPPS.[13,14]

During the course of the MPO study, the impact of high-flux dialysis on mortality was addressed in a number of epidemiologic studies and in one randomized clinical trial.[7] In an analysis of a sample of the US Renal Data System registry including nearly 14,000 HD patients, the effects of reuse practice and type of dialyzer membranes were addressed. A specific analysis including only synthetic membranes revealed the RR for mortality to be 24% higher in patients treated with low-flux than in those treated with high-flux membranes.[15] Similarly, a reduction of the RR for mortality by 38% in the patients on high-flux dialysis *versus* those on low-flux dialysis was found in a European observational cohort of 650 patients.[16] In contrast to these two studies, the HEMO study was a prospective, randomized, controlled clinical trial published while our study was ongoing.[7] This landmark study had a two-factorial design with membrane flux and dialysis dosage as applied interventions. In the primary analysis of the HEMO study, no significant effect of membrane flux on outcome was demonstrated.

This is in line with the results of our study taking the entire patient cohort into account, although the two studies have some substantial differences in the study design and patient population. The MPO study addressed a single intervention, namely membrane flux, while maintaining a minimum dialysis dosage throughout the study. Whereas the HEMO study included prevalent patients who were on dialysis an

average of 3.7 yr and 60% of the patients were treated with high-flux dialysis before entry in the study, the MPO study enrolled incident patients only to avoid early mortality bias (so-called selection of survivors) and a carryover effect of the previous treatment to the actual intervention phase. Although the HEMO study could not show a significant survival difference in the primary analysis, results of secondary analyses, namely of patients who were on renal replacement therapy for >3.7 yr, showed a significant survival benefit in the high-flux group with a reduction of the relative mortality risk by 32%.[8]

In a secondary analysis of our study, we found a higher survival rate in patients who had diabetes and were treated with high-flux compared with low-flux dialysis, with an adjusted risk reduction of 38%. Although this *post hoc* analysis was initially not planned, the results are in line with the rationale of our study design and with a *post hoc* analysis from the 4D-study.[17] This analysis of the 4D-study considered only patients who were treated with the same membrane type during the entire follow-up period. Here, the HR for mortality in patients who had diabetes and were treated with synthetic low-flux membranes was 59% greater than in those who were treated with synthetic high-flux membranes. Still, because the patients were not randomly assigned to these membrane types, this *post hoc* analysis should be carefully interpreted.

In the HEMO study, no interaction of membrane flux and either low serum albumin or diabetes status was found.[8] An explanation for this could be a "selection of survivors" that was unavoidable when enrolling prevalent patients, in contrast to the MPO study, in which only incident patients were recruited. Here, an interaction of serum albumin with the effect of membrane flux was seen. Because of the only borderline significantly higher effect of membrane flux in patients with than without diabetes in the group with serum albumin ≤4 g/dl, we cannot completely exclude that the risk reduction with high-flux dialysis in patients with low serum albumin is to some degree related to diabetes status; however, the different and, in part, small samples sizes of these subgroups may preclude final conclusions.

The general applicability of our results found in patients with hypoalbuminemia and diabetes should be seen against the background of an increasing proportion of dialysis patients with inflammation and/or malnutrition and of diabetic nephropathy as primary renal disease or diabetes as comorbidity.[18] Serum albumin is a strong predictor of mortality[11,12] and related to nutritional and inflammatory status.[19] Epidemiologic studies have confirmed that low serum albumin levels are frequent in HD patients, the prevalence being nearly unchanged in the past decade. Owen *et al.*[12] reported 60% of the patients with serum albumin <4.0 g/dl, which is similar to the more recent figures from the DOPPS study, with 57 to 86% of the patients with serum albumin below this level.[20]

The causal relation between treatment with high-flux dialysis and survival could lie in the eliminative capacity of high-flux membranes. As shown previously and also in this study, high-flux membranes have a significant removal capacity for β_2-microglobulin, the acknowledged surrogate of the middle molecules, and positively affect serum levels in the long term, which in turn are related to mortality.[21,22] A confounding effect of residual renal function on outcome in our study is unlikely, because there were no differences between the high-flux and the low-flux groups in the absolute values of GFR at baseline and of the decrease over time.

In summary, the results of this study demonstrate no significant difference in survival between the patients treated with either low-flux or high-flux dialysis in the population as a whole; however, the patients with serum albumin levels ≤4 g/dl as a recognized marker of comorbidities, including malnutrition and inflammation, had a significantly better survival in the group treated with high-flux than in that treated with low-flux membranes. In addition, patients with diabetes, also a disease known to be associated with a worse prognosis, showed a survival benefit with high-flux dialysis; however, because the study was not designed for this specific patient group, the results of this *post hoc* analysis have to be interpreted with caution. The clinical implications of these findings are underlined by the high prevalence of dialysis patients with low serum albumin and the increasing proportion of patients who have diabetes and begin renal replacement therapy worldwide.

CONCISE METHODS

Study Design

The primary objective of the study was to examine the mortality rates in incident patients with CKD when being treated with either high-flux or low-flux HD.[10] This open, prospective, randomized, controlled clinical trial was implemented in 59 HD centers from nine European countries. The study adhered to the Declaration of Helsinki and was approved by national or local ethics committees of all participating centers according to national legislation. All patients gave informed consent before being enrolled in the study.

Patients could be enrolled in the study when they fulfilled the inclusion criteria of being between 18 and 80 yr of age, having been on renal replacement therapy for up to 2 mo, and having a serum albumin level ≤4 g/dl (measured within the 2 mo before inclusion). Major exclusion criteria were being scheduled for renal transplantation from a living donor within the period of the study, on HD after renal transplantation, and serious clinical conditions potentially confounding the effect of the intervention (proteinuria >6 g/24 h per 1.73 m^2, active malignancies, current therapy with immunosuppressive agents, severe congestive heart failure despite maximal therapy [New York Heart Association class IV], unstable angina pectoris, active systemic infections [*e.g.*, tuberculosis, systemic fungal infection, AIDS, hepatitis), chronic pulmonary disease requiring supplementary oxygen, and cirrhosis with encephalopathy).

During the course of the study protocol amendments were introduced. After 11 of the planned 24 mo of the recruitment period, only 114 patients had been enrolled; therefore, the study protocol was amended by prolonging the recruitment period to 4.5 yr and including also patients with serum albumin >4 g/dl before enrollment, ran-

domly assigned as a separate stratum so as not to jeopardize the original protocol. Central block randomization in a 1:1 ratio to either the high-flux or the low-flux group was performed directly after enrollment in the study and stratified by study center and serum albumin.

For exclusion of inadequate dialysis therapy as a confounding factor, spKt/V delivered by HD (without considering residual renal function) and determined according to Daugirdas *et al.*[23] had to be maintained at a minimum of 1.2. This level had to be reached at the end of the 4-wk run-in phase, which followed the randomization; otherwise, the patient terminated the study. After 11 of the planned 24 mo of the recruitment period, it was also noted that an unexpected 10% of the patients failed to reach the Kt/V of 1.2 within these 4 wk, which was therefore considered too short. In consequence, the protocol was amended so that patients who had not reached the target Kt/V at the end of the run-in phase could remain in the study, with monthly evaluation of Kt/V until month 3 of the maintenance phase. When the Kt/V at month 3 still was <1.2, those patients terminated the study and no further follow-up of them was performed.

Study Procedures

Patients who met the inclusion and exclusion criteria were enrolled after giving their informed consent. Demographic data, medical history, concomitant medication, current dialysis treatment parameters, and residual renal function at study entry were recorded at the baseline visit. Then patients were randomly assigned to either the high-flux or the low-flux group. Serum albumin levels determined within 2 mo before enrollment were used to allocate the patients to the hypo- or the normoalbuminemic group.

The dialyzer type was selected by the investigator according to predefined criteria for high-flux (sieving coefficient for β_2-microglobulin >0.6 and ultrafiltration coefficient ≥ 20 ml/mmHg per h) and for low-flux membranes (sieving coefficient for β_2-microglobulin 0 and ultrafiltration coefficient ≤ 10 ml/mmHg per h). The dialysis membrane material could be synthetic or substituted cellulose for the high-flux dialyzer group and synthetic, substituted, or unsubstituted cellulose for the low-flux dialyzer group. In the high-flux group, 99% of the dialyzers contained synthetic membranes, whereas in the low-flux group, 75% contained synthetic membranes and 22% contained substituted cellulose. Dialyzer reuse was not allowed. Patients had to be treated three times per week with bicarbonate HD for a minimum treatment time of 180 min. Water and dialysate quality had to comply with the criteria specified in the European Pharmacopoeia of 1997 and adopted by the European Best Practice Guidelines.[24]

To achieve the minimum spKt/V of 1.2, the patients first underwent the run-in phase of 4 wk, in which Kt/V was controlled weekly and the treatment parameters (treatment time, blood flow rate, dialysis fluid flow rate, and dialyzer surface area) were adjusted locally by the investigator to reach this target. Patients who reached the specified minimum Kt/V then entered the maintenance phase (*i.e.*, actual study observation) with the starting point defined as month 0. As specified in the study protocol, all patients were observed until the latest enrolled patients reached a maintenance period of 3 yr. Premature termination of the study was defined as kidney transplantation, change of dialysis center, withdrawal of patient's consent, change to peritoneal dialysis for >60 d, or recovery of renal function. Nevertheless, conforming patients were included in the survival analysis and censored at the date of premature termination. No further follow-up of these patients within the study was performed.

At month 0, the first serum samples were taken to determine various biochemical parameters. Clinical data were collected every 3 mo; serum samples for analysis of biochemical parameters and urine collection to determine residual renal function were performed at 6-mo intervals. Kt/V was controlled monthly in the first 3 mo of the maintenance period, then every 3 mo throughout the study. Treatment parameters were to be adjusted if Kt/V fell below 1.2. In contrast to the run-in phase, the patient continued the study when this happened during the maintenance phase.

Parameters

End points (deaths) and hospitalizations were documented as and when they occurred. The classification of the cause of death as given by the investigator together with information on primary renal disease and comorbidities were reviewed by an independent safety review committee. Hospitalizations were documented by the investigator and included information on the cause, allocation to predefined groups for infection or for vascular access problems, and the date of admission and discharge.

Central laboratory analysis was performed for β_2-microglobulin by a microparticle enzyme immunoassay with the Abbott IMx system (Abbott GmbH & Co KG, Wiesbaden, Germany). All other parameters were determined at local clinical laboratories.

Statistical Analysis

The sample size estimation was based on the hypothesis to reduce mortality with high-flux dialysis by approximately 10% at the end of the minimum 3-yr follow-up, if the 3-yr mortality of the control group was approximately 30 to 50% (type 1 probability of error of 0.05, power of 0.80, and one-sided test based on the hypothesis to reduce mortality). A sample size of approximately 300 patients per group was estimated to be adequate to detect this reduction of mortality with high-flux dialysis. This number was increased to 333 patients per group to allow for an expected rate of 10% of patients terminating the study prematurely. The target sample size of at least 666 patients was planned to be enrolled and randomly assigned during a period of 24 mo. Because the recruitment rate of incident patients turned out to be slower than expected, 11 mo after the start of patient enrollment, the recruitment period was prolonged to a total of 4.5 yr and opened also to patients with serum albumin >4 g/dl as a separate stratum so as not to jeopardize the original study design. A new sample size estimation for the group with serum albumin ≤ 4 g/dl was performed on the basis of the longer recruitment and thus observation period with an extrapolation of the postulated mortality difference of 10% after 3 yr to 13% after 4 yr and of the mortality in the control group at 4 yr to 40 to 66%. This resulted in a total patient number of at least 390 patients with low serum albumin (including a possible 10% of premature study termination) with a type 1 probability of error of 0.05, a power of 0.80, and a one-sided test.

The Charlson comorbidity index was calculated as described pre-

viously,[25] with the modifications proposed by Beddhu *et al.*,[26] not including diabetes, which is considered separately.

All patients who entered the maintenance phase of the study with a minimum Kt/V of 1.2 were included in the population for survival analysis. This analysis included the population as a whole and, according to the predefined strata of patients with serum albumin $\leq$4 g/dl and $>$4 g/dl, a survival analysis for these two patient groups. The survival analysis of patients with diabetes was a *post hoc* analysis.

We performed Kaplan-Meier survival analyses. Patients were censored at the time of premature study termination for the defined reasons. We calculated statistical significance of the difference between the survival curves with the log-rank test. According to the protocol, an additional treatment efficacy analysis was performed in which patients were censored at the time the membrane flux type was changed ($n = 8$) or when spKt/V was $<$1.2 at three consecutive study visits ($n = 28$). Statistical significance of the crude mortality and the hospitalization rate was calculated on the basis of a Poisson regression.

In a Cox proportional hazards model, besides membrane permeability, adjustments for baseline parameters (age, gender, presence of diabetes, comorbidity as scored by the Charlson comorbidity index [excluding diabetes], and type of vascular access) were included to assess the RR for mortality. The same baseline parameters were considered in the analysis of interactions.

All data are given, unless stated otherwise, as means $\pm$ SD. Statistical significance was assumed at $P < 0.05$. The study is registered with Current Controlled Trials no. ISRCTN43474447 and with Cochrane Renal Group trial no. CRG 090500013.

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Spain

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Portugal

Instituto Portugues De Oncologia Porto: A. Loureiro, A. Paiva; Centro Medico Nacional Amadora: J. Cruz, D. Carvalho, F. Buinho, J.P. Santos, K. Sotto, S. Sousa; Fresenius Medical Care Dialysis Centre Lisboa: L. da Cruz; Fresenius Medical Care Dialysis Centre Braga: C. Henriques, J. Santos; Fresenius Medical Care Dialysis Centre, Setúbal: J. Vinhas, J. Assunçao.

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Safety Review Committee

J. Bommer (Heidelberg, Germany), N.A. Hoenich (Newcastle, United Kingdom), K.L. M. Leunissen (Maastricht, Netherlands).

Statistical Analysis

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REFERENCES

1. Yoshino M, Kuhlmann MK, Kotanko P, Greenwood RN, Pisoni RL, Port FK, Jager KJ, Homel P, Augustijn H, de Charro FT, Collart F, Erek E, Finne P, Garcia-Garcia G, Gronhagen-Riska C, Ioannidis GA, Ivis F, Leivestad T, Lokkegaard H, Lopot F, Jin DC, Kramar R, Nakao T, Nandakumar M, Ramirez S, Van der Sande FM, Schon S, Simpson K, Walker RG, Zaluska W, Levin NW: International differences in dialysis mortality reflect background general population atherosclerotic cardiovascular mortality. *J Am Soc Nephrol* 17: 3510–3519, 2006
2. Boure T, Vanholder R: Biochemical and clinical evidence for uremic toxicity. *Artif Organs* 28: 248–253, 2004
3. Weissinger EM, Kaiser T, Meert N, De Smet R, Walden M, Mischak H, Vanholder RC: Proteomics: A novel tool to unravel the patho-physiology of uraemia. *Nephrol Dial Transplant* 19: 3068–3077, 2004
4. Hornberger JC, Chernew M, Petersen J, Garber AM: A multivariate analysis of mortality and hospital admissions with high-flux dialysis. *J Am Soc Nephrol* 3: 1227–1237, 1992
5. Bloembergen WE, Hakim RM, Stannard DC, Held PJ, Wolfe RA, Agodoa LY, Port FK: Relationship of dialysis membrane and cause-specific mortality. *Am J Kidney Dis* 33: 1–10, 1999
6. Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G, Orlandini G: Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. *Kidney Int* 50: 1293–1302, 1996
7. Eknoyan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347: 2010–2019, 2002
8. Cheung AK, Levin NW, Greene T, Agodoa L, Bailey J, Beck G, Clark W, Levey AS, Leypoldt JK, Ornt DB, Rocco MV, Schulman G, Schwab S, Teehan B, Eknoyan G: Effects of high-flux hemodialysis on clinical outcomes: Results of the HEMO study. *J Am Soc Nephrol* 14: 3251–3263, 2003
9. Delmez JA, Yan G, Bailey J, Beck GJ, Beddhu S, Cheung AK, Kaysen GA, Levey AS, Sarnak MJ, Schwab SJ: Cerebrovascular disease in maintenance hemodialysis patients: results of the HEMO Study. *Am J Kidney Dis* 47: 131–138, 2006
10. Locatelli F, Hannedouche T, Jacobson S, La Greca G, Loureiro A, Martin-Malo A, Papadimitriou M, Vanholder R: The effect of membrane permeability on ESRD: Design of a prospective randomised multicentre trial. *J Nephrol* 12: 85–88, 1999
11. Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, Young EW: Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS. *Kidney Int* 62: 2238–2245, 2002
12. Owen WF Jr, Lew NL, Liu Y, Lowrie EG, Lazarus JM: The urea reduction ratio and serum albumin concentration as predictors of mortality in patients undergoing hemodialysis. *N Engl J Med* 329: 1001–1006, 1993
13. Locatelli F, Port FK, Pisoni RL, Martin-Malo A, Papadimitriou M, Vanholder R, Hannedouche T, Jacobson SH, Ronco C, Loureiro AC, Wizemann V: Patient and treatment characteristics in the MPO study: Validation against the DOPPS population [Abstract]. *Nephrol Dial Transplant* 18[Suppl 4]:196, 2003
14. Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, Saito A, Rayner HC, Kurokawa K, Port FK, Held PJ, Young EW: Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol* 14: 3270–3277, 2003
15. Port FK, Wolfe RA, Hulbert-Shearon TE, Daugirdas JT, Agodoa LY, Jones C, Orzol SM, Held PJ: Mortality risk by hemodialyzer reuse practice and dialyzer membrane characteristics: Results from the USRDS dialysis morbidity and mortality study. *Am J Kidney Dis* 37: 276–286, 2001
16. Chauveau P, Nguyen H, Combe C, Chene G, Azar R, Cano N, Canaud B, Fouque D, Laville M, Leverve X, Roth H, Aparicio M: Dialyzer membrane permeability and survival in hemodialysis patients. *Am J Kidney Dis* 45: 565–571, 2005
17. Krane V, Krieter DH, Olschewski M, Marz W, Mann JF, Ritz E, Wanner C: Dialyzer membrane characteristics and outcome of patients with type 2 diabetes on maintenance hemodialysis. *Am J Kidney Dis* 49: 267–275, 2007
18. van Dijk PC, Jager KJ, Stengel B, Gronhagen-Riska C, Feest TG, Briggs JD: Renal replacement therapy for diabetic end-stage renal disease: Data from 10 registries in Europe (1991–2000). *Kidney Int* 67: 1489–1499, 2005
19. Stenvinkel P: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55: 1899–1911, 1999
20. The DOPPS Report, 2004. Available at: http://www.dopps.org/pdf/dopps_report_2004.pdf. Accessed June 30, 2007
21. Cheung AK, Rocco MV, Yan G, Leypoldt JK, Levin NW, Greene T, Agodoa L, Bailey J, Beck GJ, Clark W, Levey AS, Ornt DB, Schulman G, Schwab S, Teehan B, Eknoyan G: Serum beta-2 microglobulin levels predict mortality in dialysis patients: Results of the HEMO study. *J Am Soc Nephrol* 17: 546–555, 2006

22. Cheung AK, Greene T, Leypoldt JK, Yan G, Allon M, Delmez J, Levey AS, Levin NW, Rocco MV, Schulman G, Eknoyan G: Association between serum 2-microglobulin level and infectious mortality in hemodialysis patients. *Clin J Am Soc Nephrol* 3: 69–77, 2008
23. Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. *J Am Soc Nephrol* 4: 1205–1213, 1993
24. European Best Practice Guidelines Expert Group on Hemodialysis ERA: Section IV. Dialysis Fluid Purity. *Nephrol Dial Transplant* 17[Suppl 7]: 45–62, 2002
25. Charlson ME, Pompei P, Ales KL, MacKenzie CR: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 40: 373–383, 1987
26. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML: A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med* 108: 609–613, 2000

See related editorial, "Effect of Membrane Permeability on Survival of Hemodialysis Patients," on pages 462–464.