Original Report: Patient-Oriented, Translational Research

American Journal of Nephrology

Am J Nephrol 2017;46:82–92
DOI: 10.1159/000478032

Received: March 22, 2017
Accepted: May 30, 2017
Published online: July 4, 2017

High-Performance Membrane Dialyzers and Mortality in Hemodialysis Patients: A 2-Year Cohort Study from the Annual Survey of the Japanese Renal Data Registry

Masanori Abe[a, b] Takayuki Hamano[a, c] Atsushi Wada[a, d] Shigeru Nakai[a, e] Ikuto Masakane[a, f]

[a]The Renal Data Registry Committee, The Japanese Society for Dialysis Therapy, and [b]Division of Nephrology, Hypertension and Endocrinology, Nihon University School of Medicine, Tokyo, [c]Department of Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine, Osaka, [d]Department of Nephrology, Kitasaito Hospital, Asahikawa, [e]Department of Clinical Engineering, Fujita Health University, Aichi, and [f]Yabuki Hospital, Yamagata, Japan

Keywords
Dialyzer · Hemodialysis · High-flux membrane · High-performance membrane

Abstract

Background: Little information is available regarding the type of dialyzer which results in good prognosis. This study is aimed at investigating the association between 7 types of dialyzers and 2-year mortality. ***Methods:*** We conducted a cohort study using data from a nationwide registry of the Japanese Society for Dialysis Therapy. Subjects were 136,676 patients on maintenance hemodialysis (HD) between 2009 and 2011 who underwent maintenance HD for at least 2 years and were treated with one of the following 7 types of high-performance membrane dialyzers: cellulose triacetate (CTA), ethylene vinyl alcohol (EVAL), polyacrylonitrile (PAN), polyester polymer alloy (PEPA), polyethersulfone (PES), polymethylmethacrylate (PMMA), and polysulfone (PS). Cox regression was used to estimate the association between baseline dialyzers and all-cause 2-year mortality, adjusting for potential confounders. ***Results:*** Data were adjusted using basic factors, with PS as a reference group, and the hazard ratio (HR) was significantly higher in CTA, PMMA, PAN, and EVAL groups. Further data adjustment for Kt/V yielded the same results as were obtained from data adjusted for basic factors. After further adjustment for nutrition- and inflammation-related factors, HR was significantly lowered for the PES and PMMA groups compared with the PS group (HR 0.88; 95% CI 0.82–0.94 and HR 0.84 95% CI 0.76–0.93, respectively). After propensity score matching, HR for the PES and PMMA groups was significantly lowered compared with the PS group. ***Conclusions:*** The use of different membrane types may affect mortality. Further long-term prospective studies are needed to clarify whether the PES and PMMA membranes can improve prognosis.

© 2017 S. Karger AG, Basel

Introduction

Global knowledge on molecular targets of uremic toxins is markedly different now from what it was in the 1980s. In 1971, uremic toxins, including neurotoxins, were reported to exist as mid-sized molecules ranging from 300 to 3,000 Da [1, 2]. In the 1980s, large molecular weight substances >5,000 Da were targeted for removal, as well as small and medium-sized toxins, while urea was

KARGER

E-Mail karger@karger.com
www.karger.com/ajn

© 2017 S. Karger AG, Basel

Masanori Abe, MD, PhD
Professor, Nephrology, Hypertension and Endocrinology
Department of Internal Medicine, Nihon University School of Medicine
Tokyo 173-8610 (Japan)
E-Mail abe.masanori@nihon-u.ac.jp

considered a surrogate marker of uremic toxins, and Kt/V for urea was used as a measure of dialysis dose [3, 4]. Now, albumin-bound toxins and low-molecular weight proteins are being targeted for removal by glomerular filtration in the normal kidney after the identification of β_2-microglobulin (β_2MG) as the amyloid precursor protein in dialysis-related amyloidosis (DRA) in 1985 [5].

Synthetic polymeric membranes were first developed in the late 1960s and are now popular. Most such membranes have high hydraulic permeability, called "high-flux" in clinical situations. Previously, higher hydraulic permeability membranes were known to have higher solute permeability for the so-called "middle molecules" that were thought to be more toxic and more difficult to remove by diffusion [1]. Simultaneously, several publications described the superiority of high-flux membranes from the perspective of biocompatibility to classical cellulosic membranes [6].

In Japan, the concept of high-performance membrane (HPM) became popular around the early 1980s. It was originally developed to eliminate middle molecular substances, which previously could not be eliminated by cellulosic membranes. Thus, the main purpose of the HPM became to eliminate uremic substances with molecular weights of 10,000–30,000 Da. The HPM concept, therefore, comprises all 3 characteristics: (1) high hydraulic permeability, (2) high solute permeability especially for "middle molecules," and (3) high biocompatibility [7]. The Japanese Society for Dialysis Therapy (JSDT) guidelines recommend the use of HPM dialyzers because they have the potential to improve patients' prognosis and reduce dialysis-related complications, and are thus considered for use in dialysis therapy [8]. There are 7 types of HPM dialyzers in Japan: cellulose triacetate (CTA), ethylene vinyl alcohol (EVAL), polyacrylonitrile (PAN), polyester polymer alloy (PEPA), polyethersulfone (PES), polymethylmethacrylate (PMMA), and polysulfone (PS) [9]. However, there is little information available regarding which type of dialyzer results in good prognosis. Therefore, we conducted a cohort study from a nationwide registry of hemodialysis (HD) patients in Japan to clarify the association between different dialyzers and mortality rate.

Methods

Database Creation

Data were obtained from the annual nationwide surveys of dialysis patients, comprising the Japanese Renal Data Registry (JRDR) system, conducted by the JSDT. Surveys were conducted by JSDT volunteers, as described previously [10, 11]. Briefly, data covered 297,126 patients undergoing HD at 4,152 facilities in the 2010 survey, and 304,592 patients at 4,205 facilities in the 2011 survey [12, 13]. The study population included patients who underwent maintenance dialysis between January 2010 and December 2011. We included patients who underwent maintenance HD 3 times a week, who had received maintenance dialysis for at least 2 years at the end of the year 2009, and who were treated with one of the 7 major dialyzers, namely, CTA, EVAL, PAN, PEPA, PES, PMMA, and PS membranes. Patients were followed for outcomes through December 31, 2011, and 2-year all-cause mortality was analyzed retrospectively. We excluded patients who had been dialyzed <3 times a week or for <2 h per session, those who had been treated with dialyzers other than the above mentioned 7 dialyzers, those who had received hemodiafiltration or peritoneal dialysis, those with a history of organ transplantation, those aged <18 years, and those whose records regarding date of birth, dialysis initiation, using dialyzers, or outcomes were incomplete.

Overall, 309,963 patients were registered at the end of 2009. After exclusions, 136,676 patients remained (Fig. 1). Demographic data and details of medical history were collected, with information on age, sex, dialysis duration, primary diseases of end-stage kidney disease, height, post-dialysis body weight, types of dialyzers, and history of vascular complications including coronary artery disease, ischemic stroke, hemorrhagic stroke, or limb amputation. The recorded dates of death were obtained from the JRDR at the end of 2011.

Blood samples were drawn and assayed at each dialysis center, typically within 24 h of the sample being taken, and the most recent values, including serum albumin, hemoglobin, calcium, phosphate, C-reactive protein (CRP), β_2MG, dialysis dose, normalized protein catabolic rate (nPCR), and % creatinine generation rate (%CGR), at the time of survey were collected [14, 15]. The dialysis dose was measured by using single-pool Kt/V for urea (Kt/V) [8, 16].

Statistical Methods

Data were summarized using proportions, with mean ± SD, or median (interquartile range) as appropriate. Categorical variables were analyzed using chi-square test and continuous variables were compared using Student *t* test, as appropriate. Comparisons of the categorical data between groups were performed by using repeated-measures analysis of variance, and Tukey's significant difference test or Kruskal-Wallis test, as appropriate.

Outcome Analysis by Basic Factors, Dialysis Dose, and Nutritional Factors

Survival analyses with Cox proportional hazards regression were used to examine whether baseline basic factors including age, sex, dialysis duration, and primary kidney disease and cardiovascular comorbidity predicted survival for up to 2 years of follow up. We divided patients into 7 a priori categories based on dialysis duration (2 to <5, 5 to <10, 10 to <15, 15 to <20, 20 to <25, 25 to <30, and ≥30 years) to examine the dose-response association between dialysis duration categories and death risk. Additional analyses were performed and adjusted for dialysis dose and β_2MG. We divided patients into 8 a priori categories based on single pool Kt/V (<0.8 and ≥2.0, with intervening increments of 0.2) and on β_2MG levels (<15 and ≥40, with intervening increments of 5 mg/L) to examine the dose-response association between the categories and death risk.

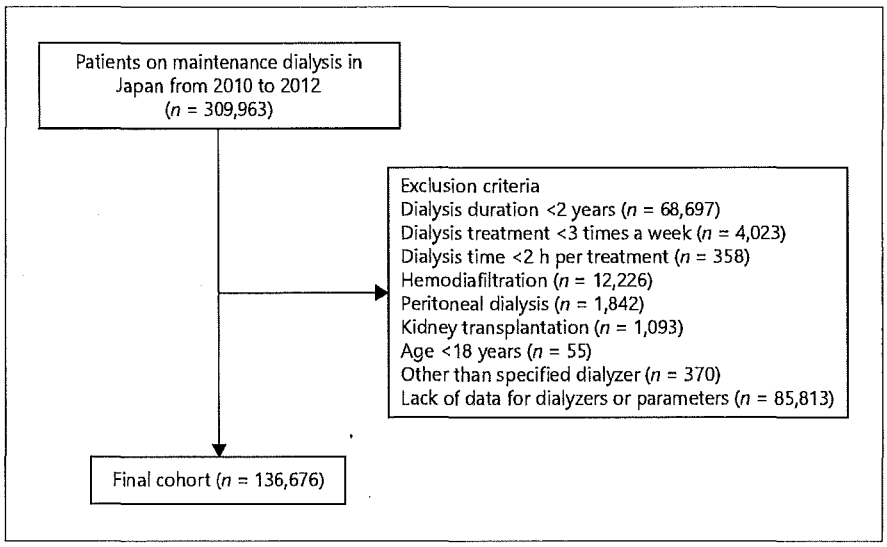

Fig. 1. Flowchart of study participants.

Additional analyses were performed with adjustment for nutrition- and inflammation-related factors, including body mass index (BMI), serum levels of CRP, hemoglobin, albumin, nPCR, and %CGR. We divided patients into 6 a priori categories based on nPCR (<0.5 and ≥1.3 g/kg/day, with intervening increments of 0.2 g/kg/day), serum albumin values (<3.0 and ≥4.5 g/dL, with intervening increments of 0.5 g/dL), BMI (<16 and ≥28 kg/m^2, with intervening increments of 2 kg/m^2), and %CGR (<60 and ≥130%, with intervening increments of 10%) to examine the dose-response association between these categories and death risk. Age, CRP levels, and hemoglobin levels were analyzed as continuous variables.

Outcome Analysis by 7 Types of Dialyzer Membranes

Survival analyses with Cox proportional hazards regression were used to examine whether different types of dialyzer membranes predicted survival for up to 2 years of follow up. The final analysis examined associations between types of dialyzer membranes and all-cause mortality. We divided patients into 7 groups based on the dialyzer membrane used. Models were analyzed when adjusted for the above mentioned basic factors, dialysis dose, and nutritional factors measured at baseline.

Subsequently, to reduce potential confounding and treatment selection bias, we adjusted the significant difference in baseline covariates with the use of propensity score matching. We calculated the propensity score for factors contributing to mortality including the above mentioned basic factors, dialysis dose, and nutritional factors, which were examined using univariate Cox proportional hazards regression analysis. The score was then used to match patients with PS membrane as a reference with the other membranes in a ratio of 1:1, resulting in 12,366, 692, 1,288, 6,267, 11,825, and 3,327 matched pairs (CTA, EVAL, PAN, PEPA, PES, and PMMA membranes, respectively). Moreover, all-cause mortality was compared for propensity score matched patients.

The protocol of this study was approved by the Ethics Committee of our hospital, and all procedures adhered to the Declaration of Helsinki. The study was registered with the University Hospital Medical Information Network (UMIN000018641). Missing covariate data were imputed by the conventional method for multivariate regression as appropriate. All analyses were conducted using JMP® version 13.0 (SAS Institute, Cary, NC, USA) and $p < 0.05$ was considered statistically significant.

Results

Study Characteristics

The baseline characteristics of patients are shown in Table 1. This cohort comprised 136,676 patients, and the average values were as follows: age 65.5 ± 12.1 years; dialysis duration, 7 (4–13) years ; female patients, 38.6%; BMI 21.2 ± 3.6; comorbidity of cardiovascular diseases (CVD), including coronary artery disease, ischemic stroke, hemorrhagic stroke, and limb amputation, 26.8%; albumin, 3.7 ± 0.4 g/dL; and hemoglobin, 10.5 ± 1.2 g/dL. Glomerulonephritis (44.9%) was most common, and diabetic nephropathy (32.7%) or nephrosclerosis (7.2%) was the cause of end-stage kidney disease. During the 2-year observation period (January 2010–December 2011), 12,053 patients (8.8%) died and 124,623 patients (91.2%) were alive at the end of the observation period.

All-Cause Mortality According to Basic Factors, Dialysis Dose, and Nutritional Factors at Enrollment

Hazard ratios (HRs) for variables evaluated as potential predictors of mortality are presented in Table 2. Male sex, increasing age, dialysis duration, presence of diabetes mellitus, and comorbid CVD were significant predictors of mortality. Higher dialysis dose, assessed by single pool Kt/V, was associated with lower mortality risk. Further-

Table 1. Demographic, clinical, and laboratory values at baseline in 136,676 HD patients

Variables	Values	Variables	Values
Age, years	65.5±12.1	Albumin, g/dL	3.7±0.4
Gender, female, %	38.6	<3.0	4.7
Dialysis duration, years	7 (4–13)	≥3.0–3.5	19.3
≥2–5	28.4	≥3.5–4.0	51.9
≥5–10	33.8	≥4.0–4.5	22.7
≥10–15	17.5	≥4.0	1.4
≥15–20	9.4	Kt/V	1.46±0.29
≥20–25	5.2	<0.8	0.7
≥25–30	3.2	≥0.8–1.0	3.2
≥30	2.5	≥1.0–1.2	12.8
Comorbidity of CVD	26.8	≥1.2–1.4	27.4
Coronary artery disease	8.2	≥1.4–1.6	27.2
Ischemic stroke	15.2	≥1.6–1.8	16.7
Hemorrhagic stroke	5.2	≥1.8–2.0	7.6
Limb amputation	3.0	≥2	4.4
Primary kidney disease		nPCR, g/kg/day	0.89±0.18
Glomerulonephritis	44.9	<0.5	1.1
Diabetic nephropathy	32.7	≥0.5–0.7	12.3
Nephrosclerosis	7.2	≥0.7–0.9	40.4
Others	15.2	≥0.9–1.1	34.6
Hemoglobin, g/dL	10.5±1.2	≥1.1–1.3	10.0
Calcium, mg/dL	9.0±0.8	≥1.3	1.6
Phosphate, mg/dL	5.3±1.4	%CGR, %	100±25
Intact-PTH, pg/mL	117 (60–199)	<60	6.3
CRP, mg/dL	0.10 (0.05–0.4)	≥60–70	4.8
β_2MG, mg/L	27.9±6.5	≥70–80	8.0
BMI, kg/m^2	21.2±3.6	≥80–90	11.6
≤16	4.1	≥90–100	15.3
≥16–18	12.6	≥100–110	16.9
≥18–20	22.7	≥110–120	15.4
≥20–22	23.9	≥120–130	11.3
≥22–24	17.7	≥130	10.4
≥24–26	10.0		
≥26–28	4.8		
≥28	4.2		

Data are presented as mean ± SD, %, or median (IQR).

HD, hemodialysis; CVD, cardiovascular disease; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; CRP, C-reactive protein; β_2MG, β_2-microglobulin; BMI, body mass index; %CGR, % creatinine generation rate.

more, poorer nutritional status and increased inflammatory status, indicated by lower hemoglobin, higher CRP, lower nPCR, lower serum albumin, lower BMI, and lower %CGR were also associated with higher mortality in patients on HD.

Clinical and Demographic Characteristics According to Types of Dialyzer Membrane Materials

Patients were divided into 7 groups according to dialyzer membrane material. Table 3 shows demographics and characteristics of each group. Over half of the patients (57.0%) underwent HD with PS membrane, followed by PES (15.1%), CTA (14.3%), PEPA (7.4%), PMMA (3.8%), PAN (1.5%), and EVAL (0.9%). Characteristics of dialyzers used in this study are listed in online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000478032). Patients treated with EVAL and PAN had a higher rate of CVD comorbidity, particularly limb amputation. Furthermore, patients treated with EVAL were categorized as follows: older age, fewer males, shorter HD duration, and more than half of the patients had a BMI <20 (online suppl.

Table 2. HRs and 95% CIs for variables evaluated as potential predictors of mortality among all the patients

Factors	HR	95% CI	*p* value
Gender			
Male	1.000	Reference	Reference
Female	0.879	0.847–0.913	<0.0001
Age, years			
1 year increase	1.064	1.062–1.066	<0.0001
HD duration, years			
≥2–5	1.016	0.971–1.065	0.481
≥5–10	1.000	Reference	Reference
≥10–15	1.156	1.094–1.222	<0.0001
≥15–20	1.167	1.088–1.252	<0.0001
≥20–25	1.141	1.044–1.247	0.003
≥25–30	0.904	0.811–1.008	0.068
≥30	1.090	0.966–1.231	0.156
Presence of DM			
Non-DM	1.000	Reference	Reference
DM	1.454	1.402–1.508	<0.0001
Comorbidity of CVD			
No comorbidity of CVD	1.000	Reference	Reference
Comorbidity of CVD	2.344	2.257–2.434	<0.0001
Kt/V			
<0.8	2.904	2.551–3.305	<0.0001
≥0.8–1.0	1.861	1.707–2.031	<0.0001
≥1.0–1.2	1.278	1.205–1.356	<0.0001
≥1.2–1.4	1.000	Reference	Reference
≥1.4–1.6	0.641	0.581–0.707	<0.0001
≥1.6–1.8	0.817	0.762–0.865	<0.0001
≥1.8–2.0	0.826	0.731–0.935	<0.0001
≥2.0	0.671	0.617–0.739	<0.0001
β_2MG, mg/L			
<15	0.987	0.940–1.036	0.594
≥15–20	1.000	0.975–1.024	0.996
≥20–25	0.997	0.982–1.013	0.718
≥25–30	1.000	Reference	Reference
≥30–35	1.022	1.006–1.037	0.006
≥35–40	1.048	1.023–1.071	<0.0001
≥40	1.074	1.044–1.107	<0.0001
CRP(1 mg/dL increase)	1.206	1.199–1.213	<0.0001
Hemoglobin (1 g/dL increase)	0.761	0.750–0.772	<0.0001
nPCR, g/kg/day			
<0.5	1.536	1.325–1.782	<0.0001
≥0.5–0.7	1.163	1.098–1.232	<0.0001
≥0.7–0.9	1.000	Reference	Reference
≥0.9–1.1	0.965	0.923–1.007	0.104
≥1.1–1.3	0.966	0.904–1.033	0.326
≥1.3	0.954	0.818–1.113	0.551
Serum albumin, g/dL			
<3.0	7.674	7.305–8.064	<0.0001
≥3.0–3.5	2.627	2.511–2.748	<0.0001
≥3.5–4.0	1.000	Reference	Reference
≥4.0–4.5	0.581	0.541–0.623	<0.0001
≥4.5	0.489	0.373–0.642	<0.0001
BMI, kg/m^2			
<16.0	2.655	2.479–2.843	<0.0001
≥16–18	1.973	1.858–2.095	<0.0001
≥18–20	1.350	1.275–1.430	<0.0001
≥20–22	1.000	Reference	Reference
≥22–24	0.835	0.782–0.899	<0.0001
≥24–26	0.730	0.667–0.798	<0.0001
≥26–28	0.838	0.740–0.950	0.005
≥28	0.937	0.810–1.085	0.387
%CGR, %			
<60	4.543	4.254–4.852	<0.0001
≥60–70	2.561	2.368–2.770	<0.0001
≥70–80	1.879	1.745–1.023	<0.0001
≥80–90	1.357	1.262–1.459	0.001
≥90–100	1.000	Reference	Reference
≥100–110	0.698	0.645–0.754	<0.001
≥110–120	0.857	0.794–0.926	<0.0001
≥120–130	0.519	0.476–0.567	<0.001
≥130	0.475	0.429–0.525	<0.0001

HR, hazard ratio; DM, diabetes mellitus; HD, hemodialysis; CVD, cardiovascular disease; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; β_2MG, β_2-microglobulin; CRP, C-reactive protein; BMI, body mass index; %CGR, % creatinine generation rate.

Table 2). Conversely, PS and PES were associated with younger age, more males, lower rates of comorbid diabetes and CVD, and higher Kt/V, nPCR, and %CGR.

All-Cause Mortality According to Types of Dialyzer Membrane Materials

Unadjusted all-cause death HR for CTA, EVAL, PAN, PEPA, and PMMA groups, compared with the PS group (reference), was 1.39 (1.33–1.47), 2.52 (2.23–2.85), 2.06 (1.85–2.31), 1.11 (1.03–1.19), and 1.47 (1.36–1.61), respectively (online suppl. Table 3). Contrarily, only the PES group had significantly lower HR of 0.80 (0.75–0.85) compared with the PS group (reference).

Figure 2 shows adjusted all-cause death HRs for each group. After adjusting for basic factors, all-cause death HR for CTA, EVAL, PAN, and PMMA groups, as compared with the PS group (reference), was 1.18 (1.12–1.25), 2.06 (1.81–2.35), 1.70 (1.51–1.91), and 1.27 (1.16–1.39), respectively. However, there was no significant difference between the PEPA and PS groups. The PES group also had a significantly lower HR of 0.82 (0.77–0.87) compared with the PS group.

Table 3. Demographic, clinical, and laboratory values in 136,676 HD patients according to types of dialyzer membranes

	CTA	EVAL	PAN	PEPA	PES	PMMA	PS	*p* value
n (%)	19,507 (14.3)	1,191 (0.9)	2,063 (1.5)	10,112 (7.4)	20,693 (15.1)	5,213 (3.8)	77,897 (57.0)	
Age, years	68.1±12.2	75.1±10.6	70.0±11.6	69.2±11.9	63.2±12.1	69.1±11.8	64.5±11.8	<0.0001
Gender, female, %	40.1	56.3	45.7	41.6	33.0	44.5	38.4	<0.0001
Dialysis duration, years	6 (4–11)	5 (3–10)	7 (4–12)	6 (4–12)	8 (5–13)	7 (4–12)	8 (4–14)	<0.0001
Presence of DM, %	37.2	34.0	38.8	34.9	31.3	33.9	31.6	<0.0001
Comorbidity of CVD, %	28.2	35.7	32.4	26.6	23.2	28.9	27.0	<0.0001
Coronary artery disease	8.5	9.1	9.5	8.5	7.0	8.4	8.2	
Ischemic stroke	16.7	24.0	19.0	15.3	13.1	18.0	15.0	
Hemorrhagic stroke	5.4	7.2	4.4	5.4	4.7	5.1	5.3	
Limb amputation	3.2	4.0	5.9	2.9	2.7	3.2	3.0	
BMI, kg/m^2	21.1±3.7	19.5±3.5	20.7±3.5	21.0±3.5	21.6±3.7	20.6±3.2	21.2±3.5	<0.0001
Hemoglobin, g/dL	10.5±1.2	10.2±1.4	10.3±1.2	10.5±1.2	10.6±1.2	10.4±1.2	10.6±1.2	<0.0001
Serum albumin, g/dL	3.6±0.4	3.4±0.5	3.6±0.4	3.6±0.4	3.7±0.4	3.5±0.4	3.7±0.4	<0.0001
Calcium, mg/dL	8.9±0.8	8.8±0.9	9.0±0.8	9.0±0.8	9.0±0.8	8.9±0.8	9.0±0.8	<0.0001
Phosphate, mg/dL	5.2±1.4	5.0±1.6	5.2±1.5	5.2±1.4	5.4±1.5	5.2±1.4	5.2±1.4	<0.0001
β_2MG, mg/L	28.3±6.8	31.9±9.1	31.0±7.3	27.4±6.5	27.6±6.3	30.1±6.8	27.7±6.3	<0.0001
CRP, mg/dL	0.1 (0.05–0.4)	0.2 (0.05–0.8)	0.2 (0.05–0.6)	0.1 (0.05–0.4)	0.1 (0.05–0.3)	0.1 (0.05–0.4)	0.1 (0.05–0.4)	<0.0001
Treatment time, min	238±30	230±32	239±36	240±30	242±31	240±27	242±28	<0.0001
Kt/V	1.4±0.3	1.3±0.3	1.4±0.3	1.4±0.3	1.5±0.3	1.4±0.3	1.5±0.3	<0.0001
nPCR, g/kg/day	0.87±0.18	0.82±0.18	0.86±0.18	0.87±0.18	0.89±0.18	0.85±0.18	0.89±0.18	<0.0001
%CGR, %	98±26	82±28	94±26	99±25	103±24	96±25	102±25	<0.0001

Data are presented as mean ± SD, %, or median (IQR). HD, hemodialysis; BMI, body mass index; β_2MG, β_2-microglobulin; CRP, C-reactive protein; CTA, cellulose triacetate; CVD, cardiovascular disease; DM, diabetes mellitus; EVAL, ethylene vinyl alcohol; nPCR, normalized protein catabolic rate; PAN, polyacrylonitrile; PEPA, polyester polymer alloy; PES, polyethersulfone; PMMA, polymethylmethacrylate; PS, polysulfone, %CGR, % creatinine generation rate.

After adjusting for dialysis dose and β_2MG in addition to basic factors, HR for CTA, EVAL, PAN, and PMMA groups, as compared with the PS group (reference), was 1.11 (1.05–1.17), 1.76 (1.59–1.95), 1.59 (1.41–1.79), and 1.19 (1.09–1.31), respectively. The higher HRs for CTA, EVAL, PAN, and PEPA groups persisted. The PEPA group showed no significant difference, and the PES group had a significantly lower HR of 0.82 (0.77–0.87), compared with the PS group.

Finally, after adjusting for nutrition- and inflammation-related factors, in addition to basic factors and dialysis dose, HRs of CTA, EVAL, and PEPA groups did not differ significantly compared with the PS group. Although the lower HR for the PES group (0.88 [0.82–0.94], $p < 0.001$) persisted, HR for the PMMA group (0.84 [0.76–0.93]) became significantly lower than that for the PS group ($p < 0.001$).

Propensity Score Matching Analysis

Table 4 shows patient characteristics and baseline data in the PS and each corresponding group after propensity score matching. There were no significant differences in all variables. As shown in Figure 3, HRs of CTA, EVAL, and PEPA groups did not differ significantly compared with the PS group. The HRs for the PES group (0.90 [0.85–0.96]) and PMMA group (0.87 [0.78–0.96]) were significantly lower than that for the PS group ($p < 0.01$).

Discussion

In this study, we first confirmed the predictors for 2-year mortality in HD patients. Because survival outcome of dialysis patients might be determined by additional multiple confounding factors, dialysis-related or non-dialysis-related, investigations about the control of these factors are difficult to perform. However, we compared mortality rates between 7 HPM dialyzers adjusted for multiple predicting factors. After fully adjusting for these factors and propensity score matching, HRs for the PES and PMMA membrane groups were significantly lower than those for the PS membrane group, which was used as the reference group. This is the first study to suggest that mortality risk for HD patients might differ by the type of dialyzer used.

Two large randomized controlled studies, the Hemodialysis (HEMO) study [17] and the Membrane Permeability Outcome (MPO) study [18], compared low-flux HD

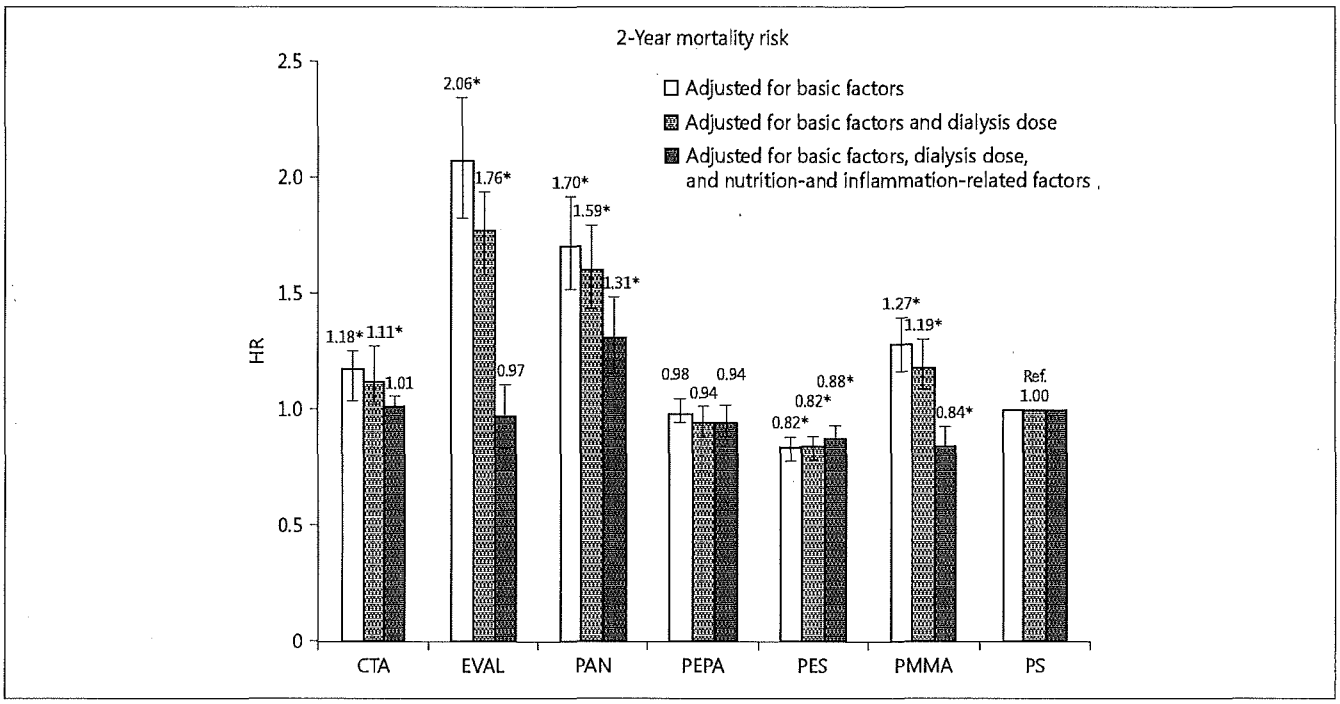

Fig. 2. HR of all-cause mortality among 7 types of dialyzer membranes in 136,676 patients undergoing maintenance hemodialysis using standard Cox proportional hazards regression. White bars are adjusted for age, sex, dialysis duration, presence or absence of diabetes, and presence or absence of cardiovascular comorbidity. Grey bars are adjusted for basic factors, dialysis dose as indicated by Kt/V, and β2-microglobulin. Dark grey bars are adjusted for basic factors, dialysis dose, and nutrition- and inflammation-related factors, including body mass index, levels of C-reactive protein, hemoglobin, and serum albumin, normalized protein catabolic rate, and % creatinine generation rate. * $p < 0.001$ vs. PS. Error bars correspond to 95% CIs. CTA, cellulose triacetate; EVAL, ethylene vinyl alcohol; HR, hazard ratio; PAN, polyacrylonitrile; PEPA, polyester polymer alloy; PES, polyethersulfone; PMMA, polymethylmethacrylate; PS, polysulfone.

with high-flux HD. During primary analysis, the HEMO study did not show any difference in mortality risk among both dialysis treatments. However, secondary analysis of patients who had been on renal replacement therapy for >3.7 years showed significantly better survival in the high-flux HD group, with a 32% reduction of the relative risk of mortality [19]. In agreement with the theoretical advantages of high-flux HD, β_2MG serum levels were found to be positively associated with mortality [20]. In the MPO study, no significant effect of high-flux HD on survival was found in the entire population. However, subgroup analysis showed significantly higher survival rates in the high-flux subgroup of patients with serum albumin <4 g/dL (relative risk 0.63) and the diabetic group. Based on these results, the European Renal Best Practice advisory board recommended that high-flux HD be used for high-risk patients [21]. Kidney Disease Outcomes Quality initiative guidelines state that the use of poorly biocompatible cellulose membranes should be discouraged [22]. In Japan, kidney transplantation has been performed in a restricted number of patients. Thus, the number of HD patients on long-term dialysis has been increasing significantly every year; there were nearly 314,180 patients at the end of 2013, and 4.2% of them had been on dialysis for over 25 years [23]. In the present study, elderly patients and those with longer dialysis durations were included. Comorbidities such as CVD, malnutrition, and DRA are common in such long-term dialysis patients, with associated physical disability and morbidity. Uremic toxicity of middle to large molecules has been implicated, especially in the pathogenesis of long-term dialysis-associated morbidities [24]. Unfortunately, no remedy for DRA has been found, although successful kidney transplant may halt disease progression. Consequently, HPM dialyzers have been the subject of major research to ameliorate comorbidities and improve patient outcomes. Unlike other countries, HPM dialyzers have been adopted in Japan, and are recommended for good outcomes in HD patients by the JSDT [8]. Japanese HD patients now undergo dialysis using high-flux membranes in an overwhelming 97% of cas-

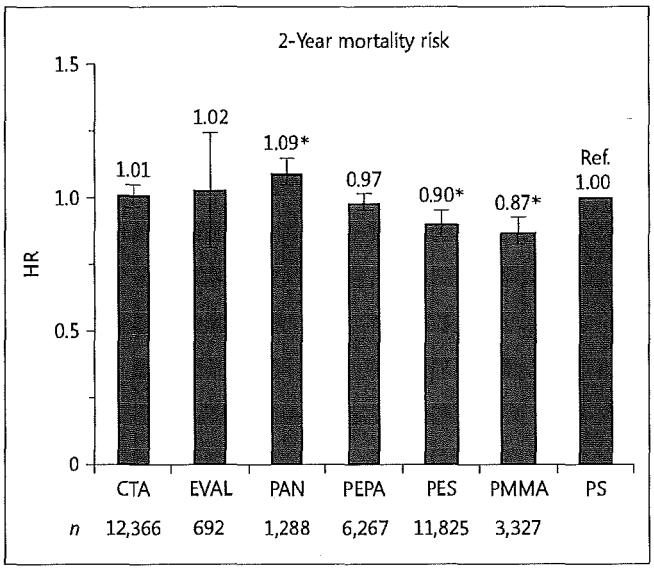

Fig. 3. HRs of all-cause mortality after propensity score matching for 6 types of dialyzer groups compared to the PS group using Cox proportional hazards regression. * $p < 0.01$ vs. PS. Error bars correspond to 95% CIs. CTA, cellulose triacetate; EVAL, ethylene vinyl alcohol; HR, hazard ratio; PAN, polyacrylonitrile; PEPA, polyester polymer alloy; PES, polyethersulfone; PMMA, polymethylmethacrylate; PS, polysulfone.

es, and 11.4% use protein-permeable membranes with β_2MG clearance >70 mL/min [25]. Therefore, our study is the first to distinguish which type among 7 HPM dialyzers results in good prognosis, not high- vs. low-flux membranes.

Of all dialysis membranes currently used, 93% are from the parent polyarylsulfone family of which 71 and 22% are from PS and PES, respectively [26]. In the present cohort, over half of the patients were treated with PS membrane. However, most recent cases of dialysis-associated thrombocytopenia have been associated with PS membranes, especially electron beam-sterilized PS membranes [27]. Many PS membranes contain polyvinylpyrrolidone (PVP), which is incorporated into the membrane in varying amounts, both to increase hydrophilicity and affect the membrane's flux characteristics [28]. The biocompatibility of PS membranes varies according to the degree of added PVP, as well as other factors [28]. Furthermore, recent studies suggest that PS is associated with unpleasant side effects including anaphylaxis and skin lesions, supposedly caused by PVP [29–36]. Therefore, biocompatibility, no toxicity from chemical components of the dialysis membrane, and a well-balanced broad removal pattern of uremic toxins are essential basic scientific requirements for patient satisfaction.

Table 4. Baseline characteristics after propensity score matching between PS and other groups

	Matched			Matched			Matched			Matched		
	CTA	PS	*p* value	EVAL	PS	*p* value	PAN	PS	*p* value	PEPA	PS	*p* value
n	12,366	12,366	-	692	692	-	1,288	1,288	-	6,267	6,267	-
Age, years	67.8±12.1	67.8±11.8	0.783	74.5±10.8	74.1±9.1	0.462	70.0±11.6	70.0±10.3	0.809	69.0±11.7	68.8±11.6	0.085
Gender, female, %	39.3	39.1	0.754	55.6	55.2	0.871	45.9	47.1	0.527	41.9	42.1	0.814
Dialysis duration, years	6 (4–11)	6 (4–11)	0.985	5 (3–9)	5 (3–10)	0.604	7 (4–13)	7 (4–12)	0.597	7 (4–12)	7 (4–12)	0.636
Presence of DM, %	36.9	38.2	0.969	34.6	35.8	0.652	39.5	42.3	0.138	35.2	35.1	0.925
Comorbidity of CVD, %	30.0	31.0	0.537	36.4	37.2	0.738	35.7	35.9	0.837	27.8	27.8	0.990
BMI, kg/m^2	21.1±3.6	21.1±3.5	0.810	19.6±3.6	19.7±3.3	0.514	20.7±3.5	20.8±3.5	0.196	21±3.5	20.9±3.4	0.282
Hemoglobin, g/dL	10.5±1.2	10.5±1.2	0.637	10.3±1.3	10.2±1.4	0.442	10.3±1.3	10.3±1.3	0.841	10.5±1.2	10.5±1.3	0.859
Serum albumin, g/dL	3.6±0.4	3.7±0.4	0.924	3.4±0.5	3.4±0.6	0.619	3.6±0.4	3.6±0.4	0.739	3.6±0.4	3.6±0.4	0.435
β_2-MG, mg/L	27.9±6.5	27.9±6.3	0.533	32±9.3	32±9.2	0.989	31.0±7.2	31.0±7.9	0.509	27.4±6.5	27.3±6.2	0.667
CRP, mg/dL	0.1 (0.05–0.4)	0.1 (0.05–0.4)	0.270	0.2 (0.05–0.6)	0.2 (0.05–1.0)	0.521	0.2 (0.03–0.5)	0.1 (0.05–0.4)	0.548	0.1 (0.05–0.3)	0.1 (0.05–0.4)	0.083
Kt/V	1.4±0.3	1.4±0.3	0.907	1.3±0.3	1.3±0.3	0.193	1.4±0.3	1.4±0.3	0.634	1.5±0.3	1.5±0.3	0.658
nPCR, g/kg/day	0.87±0.17	0.87±0.17	0.901	0.82±0.17	0.81±0.20	0.185	0.87±0.17	0.86±0.18	0.681	0.87±0.17	0.87±0.19	0.420
%CGR, %	98±25	98±25	0.673	83±27	82±30	0.715	94±25	94±25	0.655	100±25	100±25	0.424

	Matched			Matched			Matched		
	PES	PS	*p* value	PMMA	PS	*p* value			
n	11,825	11,825	-	3,327	3,327	-			
Age, years	63.2±12.0	63.1±11.9	0.807	69.8±12	69.7±11	0.659			
Gender, female, %	33.4	33.3	0.836	43.6	43.0	0.651			
Dialysis duration, years	8 (5–14)	8 (4–14)	0.784	6 (4–11)	6 (4–11)	0.556			
Presence of DM, %	31.8	31.9	0.867	33.8	34.2	0.713			
Comorbidity of CVD, %	25.0	25.2	0.775	30.6	30.0	0.588			
BMI, kg/m^2	21.7±3.7	21.7±3.8	0.825	20.6±3.2	20.7±3.3	0.175			
Hemoglobin, g/dL	10.6±1.2	10.6±1.2	0.619	10.4±1.2	10.4±1.2	0.913			
Serum albumin, g/dL	3.7±0.4	3.7±0.4	0.422	3.5±0.4	3.5±0.5	0.686			
β_2-MG, mg/L	27.8±6.4	27.8±6.4	0.568	30.1±6.8	30±7.4	0.574			
CRP, mg/dL	0.1 (0.05–0.3)	0.1 (0.05–0.3)	0.766	0.1 (0.05–0.4)	0.1 (0.05–0.4)	0.384			
Kt/V	1.5±0.3	1.5±0.3	0.780	1.4±0.3	1.4±0.3	0.789			
nPCR, g/kg/day	0.90±0.17	0.90±0.17	0.658	0.85±0.17	0.85±0.18	0.829			
%CGR, %	103±24	103±24	0.246	97±25	97±27	0.667			

Data are presented as mean ± SD, %, or median (IQR). BMI, body mass index; β_2-MG, β_2-microglobulin; CRP, C-reactive protein; CTA, cellulose triacetate; CVD, cardiovascular disease; DM, diabetes mellitus; EVAL, ethylene vinyl alcohol; nPCR, normalized protein catabolic rate; PAN, polyacrylonitrile; PEPA, polyester polymer alloy; PES, polyethersulfone; PMMA, polymethylmethacrylate; PS, polysulfone, %CGR, % creatinine generation rate.

PMMA membranes can remove high-molecular weight pathogenic substances, such as cytokines and proteins that cannot be removed by other dialysis membranes, by adsorption [37]. Kreusser et al. [38] reported that the cumulative 5-year survival rate for dialysis patients treated with PMMA membrane is higher than that of patients treated with PS membrane (68 vs. 54%). PES membranes are a variant of PS, designed for better clearance of high-molecular weight toxins while restricting the albumin passage. Depending on the mode of modification, PES membranes may be more biocompatible than PS membranes based on the degree of leukopenia and platelet adhesion [39, 40]. The most recent generation of PES membranes exhibits the best biocompatibility characteristics and excellent low-molecular weight protein removal due to an outstanding permselectivity [41]. However, there are few reports on the superiority of PES membranes to PS with regard to patient survival. Therefore, further prospective large-scale studies are required to clarify which of these 2 dialyzers can improve the prognosis for HD patients. HD is a repetitive process usually performed over a long period, suggesting that even low-grade or minor membrane-related adverse reactions need to be avoided. Therefore, HPMs with better biocompatibility that produce weak inflammatory stimuli should be used due to their high capacity for removing uremic substances with minimum loss of essential substances from the body.

This study has several limitations. First, because of the nature of any annual survey and observational cohort study, the numbers of the patients differed between the 7 groups. Information about blood pressure control, hypotensive episodes, blood flow rate, ultrafiltration rate, vascular access, and facility effects or practice patterns of the dialysis unit, which might act as potential confounders was unavailable. Therefore, mortality may vary between centers due to differences in center practice and patient population. It is known that arteriovenous fistula placement improves patient survival compared with arteriovenous graft or catheter, but the JRDR data did not include the type of vascular access for the period between 2009 and 2011. However, in 2008, it was reported that the mean blood flow rate was 200 ± 30 mL/min, and the percentage of patients who used a native vessel arteriovenous fistula was 89.7% in the JRDR [25]. Moreover, the JSDT standard for endotoxin level in dialysis fluid (<0.050 EU/mL) was achieved in 91.8% in 2010, and the JSDT standard for bacterial cell counts in dialysis fluid (<100 cfu/mL) was achieved in 98.2% in 2010 [11, 12]. Therefore, excellent water quality might be an important factor that improves the prognosis in chronic HD in Japan, and might contribute to the lower CRP levels in the present study. Second, we confirmed that all patients used the same membranes at least 1 year after inclusion, but by the end of the study we did not have information about the type of dialyzers used. Furthermore, selection bias could be present in this study. The EVAL and PAN groups had a higher number of patients with lower BMI and a higher rate of comorbidity with CVD. Therefore, prospective randomized trials are needed to compare the outcomes for each dialyzer type. Third, we had no information about the residual renal function, which could be a possible confounder. However, since the reported loss of renal function after starting dialysis was ~2.0 mL/min/year [42] and the mean estimated glomerular filtration rate at dialysis initiation was 6.52 mL/min/1.73 m^2 in 2007 throughout Japan [43], the impact of residual renal function on our cohort may be negligible because the median dialysis duration was 7 years in our cohort. Finally, patients treated with hemodiafiltration were excluded in this study to eliminate modality bias. Although the number of patients treated with hemodiafiltration was only 5.0% in Japanese dialysis population in 2010, this number has been increasing recently [13]. Hemodiafiltration, including online hemodiafiltration, is considered the most efficient technique for using high-flux membranes since it achieves higher clearance of small solutes such as urea, and a higher clearance of middle-molecular solutes, such as β_2MG, in comparison with high-flux HD [44, 45]. Therefore, additional clinical trials are required to investigate the impact of this modality on mortality in the future.

Our study suggests that the use of different membrane materials may affect mortality in HD patients. However, more long-term prospective studies are needed to clarify these findings, including whether the PES and PMMA membranes can improve prognosis.

Acknowledgements

We thank the members of the Research Subcommittee of JSDT Renal Data Registry (JRDR) for all their efforts, and the staff of all the participating dialysis facilities.

Disclosure Statements

Publication of this report was not supported by any grants. No financial support was received for this study. The authors declare that they have no other relevant financial interests.

References

1 Babb AL, Popovich RP, Christopher TG, Scribner BH: The genesis of the square meter-hour hypothesis. Trans Am Soc Artif Intern Organs 1971;7:81–86.
2 Babb AL, Farrell PC, Uvelli DA, Scribner BH: Hemodialyzer evaluation by examination of solute molecular spectra. Trans Am Soc Artif Intern Organs 1972;18:98–105, 122.
3 Lowrie EG, Laird NM, Parker TF, Sargent JA: Effect of the hemodialysis prescription of patient morbidity: report from the National Cooperative Dialysis Study. N Engl J Med 1981; 305:1176–1181.
4 Gotch F, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study. Kidney Int 1985;28:526–534.
5 Gejyo F, Yamada T, Odani S, Nakagawa Y, Arakawa M, Kunitomo T, Kataoka H, Suzuki M, Hirasawa Y, Shirahama T, et al: A new form of amyloid protein associated with chronic hemodialysis was identified as beta 2-microglobulin. Biochem Biophys Res Commun 1985;129:701–706.
6 Hakim RM, Fearon DT, Lazarus JM, Perzanowski CS: Biocompatibility of dialysis membranes: effects of chronic complement activation. Kidney Int 1984;26:194–200.
7 Yamashita AC: Mass transfer mechanisms in high-performance membrane dialyzers. Contrib Nephrol 2011;173:95–102.
8 Watanabe Y, Kawanishi H, Suzuki K, Nakai S, Tsuchida K, Tabei K, Akiba T, Masakane I, Takemoto Y, Tomo T, Itami N, Komatsu Y, Hattori M, Mineshima M, Yamashita A, Saito A, Naito H, Hirakata H, Minakuchi J; "Maintenance Hemodialysis: Hemodialysis Prescriptions" Guideline Working Group, Japanese Society for Dialysis Therapy: Japanese society for dialysis therapy clinical guideline for "maintenance hemodialysis: hemodialysis prescriptions". Ther Apher Dial 2015;19(suppl 1):67–92.
9 Sakai K, Matsuda M: Solute removal efficiency and biocompatibility of the high-performance membrane – from engineering points of view. Contrib Nephrol 2011;173:11–22.
10 Hoshino J, Yamagata K, Nishi S, Nakai S, Masakane I, Iseki K, Tsubakihara Y: Significance of the decreased risk of dialysis-related amyloidosis now proven by results from Japanese nationwide surveys in 1998 and 2010. Nephrol Dial Transplant 2016;31:595–602.
11 Masakane I, Takemoto Y, Nakai S, Tsubakihara Y, Akiba T, Watanabe Y, Iseki K: Bacteriological water quality in the central dialysis fluid delivery system from the survey of the Japanese society for dialysis therapy. Blood Purif 2009;27(suppl 1):11–16.
12 Nakai S, Iseki K, Itami N, Ogata S, Kazama JJ, Kimata N, Shigematsu T, Shinoda T, Shoji T, Suzuki K, Taniguchi M, Tsuchida K, Nakamoto H, Nishi H, Hashimoto S, Hasegawa T, Hanafusa N, Hamano T, Fujii N, Masakane I, Marubayashi S, Morita O, Yamagata K, Wakai K, Wada A, Watanabe Y, Tsubakihara Y: An overview of regular dialysis treatment in Japan (as of 31 December 2010). Ther Apher Dial 2012;16:483–521.
13 Nakai S, Watanabe Y, Masakane I, Wada A, Shoji T, Hasegawa T, Nakamoto H, Yamagata K, Kazama JJ, Fujii N, Itami N, Shinoda T, Shigematsu T, Marubayashi S, Morita O, Hashimoto S, Suzuki K, Kimata N, Hanafusa N, Wakai K, Hamano T, Ogata S, Tsuchida K, Taniguchi M, Nishi H, Iseki K, Tsubakihara Y: Overview of regular dialysis treatment in Japan (as of 31 December 2011). Ther Aphel Dial 2013;17:567–611.
14 Shinzato T, Nakai S, Fujita Y, Takai I, Morita H, Nakane K, Maeda K: Determination of Kt/V and protein catabolic rate using pre- and postdialysis blood urea nitrogen concentrations. Nephron 1994; 67: 280–290.
15 Shinzato T, Nakai S, Miwa M, Iwayama N, Takai I, Matsumoto Y, Morita H, Maeda K: New method to calculate creatinine generation rate using pre- and postdialysis creatinine concentrations. Artif Organs 1997; 21: 864–872.
16 Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol 1993; 4: 1205–1213.
17 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; Hemodialysis (HEMO) Study Group: Effect of dialysis dose and membrane flux in maintenance hemodialysis. N Engl J Med 2002; 347: 2010–2019.
18 Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, Jacobson SH, Czekalski S, Ronco C, Vanholder R: Membrane Permeability Outcome (MPO) Study Group: Effect of membrane permeability on survival of hemodialysis patients. J Am Soc Nephrol 2009; 20: 645–654.
19 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 2003; 14: 3251–3263.
20 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 2006; 17: 546–555.
21 Tattersall J, Martin-Malo A, Pedrini L, Basci A, Canaud B, Fouque D, Haage P, Konner K, Kooman J, Pizzarelli F, Tordoir J, Vennegoor M, Wanner C, ter Wee P, Vanholder R: EBPG guideline on dialysis strategies. Nephrol Dial Transplant 2007; 22:ii5–ii21.
22 National Kidney Foundation: Clinical practice guidelines for hemodialysis adequacy. Am J Kidney Dis 2006; 48(suppl 1):s12–s47.
23 Masakane I, Nakai S, Ogata S, Kimata N, Hanafusa N, Hamano T, Wakai K, Wada A, Nitta K: An overview of regular dialysis treatment in Japan (as of 31 December 2013). Ther Apher Dial 2015; 19: 540–574.
24 Vanholder RC, Glorieux G, Van Biesen W: Advantages of new hemodialysis membranes and equipment. Nephron Clin Pract 2010; 114:c165–c172.
25 Nakai S, Suzuki K, Masakane I, Wada A, Itami N, Ogata S, Kimata N, Shigematsu T, Shinoda T, Syouji T, Taniguchi M, Tsuchida K, Nakamoto H, Nishi S, Nishi H, Hashimoto S, Hasegawa T, Hanafusa N, Hamano T, Fujii N, Marubayashi S, Morita O, Yamagata K, Wakai K, Watanabe Y, Iseki K, Tsubakihara Y: Overview of regular dialysis treatment in Japan (as of 31 December 2008). Ther Apher Dial 2010; 14: 505–540.
26 Bowry SK, Gatti E, Vienken J: Contribution of polysulfone membranes to the success of convective dialysis therapies. Contrib Nephrol 2011; 173: 110–118.
27 Daugirdas JT, Bernardo AA: Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia. Kidney Int 2012; 82: 147–157.
28 Hayama M, Yamamoto K, Kohori F, Uesaka T, Ueno Y, Sugaya H, Itagaki I, Sakai K: Nanoscopic behavior of polyvinylpyrrolidone particles on polysulfone/polyvinylpyrrolidone film. Biomaterials 2004; 25: 1019–1028.
29 Masakane I: Choice of modality with the use of high-performance membrane and evaluation for clinical effects. Contrib Nephrol 2011; 173: 84–94.
30 Shu KH, Kao TW, Chiang WC, Wu VC: A case of anaphylactic shock induced by FX60 polysulfone hemodialyzer but not F6-HPS polysulfone hemodialyzer. Hemodial Int 2014; 18: 841–845.
31 Yang RC, Lindsay RM: Dialyzer reactions in a patient switching from peritoneal dialysis to hemodialysis. Hemodial Int 2005; 9: 120–126.
32 Ohashi N, Yonemura K, Goto T, Suzuki H, Fujigaki Y, Yamamoto T, Hishida A: A case of anaphylactoid shock induced by the BS polysulfone hemodialyzer but not by the F8-HPS polysulfone hemodialyzer. Clin Nephrol 2003; 60: 214–217.
33 Bigazzi R, Atti M, Baldari G: High-permeable membranes and hypersensitivity-like reactions: Role of dialysis fluid contamination. Blood Purif 1990; 8: 190–198.
34 Bacelar Marques ID, Pinheiro KF, de Freitas do Carmo LP, Costa MC, Abensur H: Anaphylactic reaction induced by a polysulfone/polyvinylpyrrolidone membrane in the 10th session of hemodialysis with the same dialyzer. Hemodial Int 2011; 15: 399–403.

35 Arenas MD, Gil MT, Carreton MA, Moledous A, Albiach B: [Adverse reactions to polysulphone membrane dialyzers during hemodialysis]. Nefrologia 2007; 27: 638–642.
36 Matsuda M, Sato M, Sakata H, Ogawa T, Yamamoto K, Yakushiji T, Fukuda M, Miyasaka T, Sakai K: Effects of fluid flow on elution of hydrophilic modifier from dialysis membrane surfaces. J Artif Organs 2008; 11: 148–155.
37 Sakai Y: Polymethylmethacrylate membrane with a series of serendipity. Contrib Nephrol 2011; 173: 137–147.
38 Kreusser W, Reiermann S, Vogelbusch G, Bartual J, Schulze-Lohoff E: Effect of different synthetic membranes on laboratory parameters and survival in chronic haemodialysis patients. NDT plus 2010; 3(suppl 1):i12–i19.
39 Krieter DH, Morgenroth A, Barasinski A, Lemke HD, Schuster O, von Harten B, Wanner C: Effects of a polyelectrolyte additive on the selective dialysis membrane permeability for low-molecular-weight proteins. Nephrol Dial Transplant 2007; 22: 491–499.
40 Su BH, Fu P, Li Q, Tao Y, Li Z, Zao HS, Zhao CS: Evaluation of polyethersulfone highflux hemodialysis membrane in vitro and in vivo. J Mater Sci Mater Med 2008;19:745–751.
41 Meert N, Eloot S, Schepers E, Lemke HD, Dhondt A, Glorieux G, Van Landschoot M, Waterloos MA, Vanholder R: Comparison of removal capacity of two consecutive generations of high-flux dialysers during different treatment modalities. Nephrol Dial Transplant 2011;26:2624–2630.
42 Schiffl H, Lang SM, Fischer R: Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. Nephrol Dial Transplant 2002;17:1814–1818.
43 Watanabe Y, Yamagata K, Nishi S, Hirakata H, Hanafusa N, Saito C, Hattori M, Itami N, Komatsu Y, Kawaguchi Y, Tsuruya K, Tsubakihara Y, Suzuki K, Sakai K, Kawanishi H, Inaguma D, Yamamoto H, Takemoto Y, Mori N, Okada K, Hataya H, Akiba T, Iseki K, Tomo T, Masakane I, Akizawa T, Minakuchi J; "Hemodialysis Initiation for Maintenance Hemodialysis" Guideline Working Group, Japanese Society for Dialysis Therapy: Japanese society for dialysis therapy clinical guideline for "hemodialysis initiation for maintenance hemodialysis". Ther Aphel Dial 2015;19(suppl 1):93–107.
44 Penne EL, van der Weerd NC, Blankestijn PJ, van den Dorpel MA, Grooteman MP, Nubé MJ, Ter Wee PM, Lévesque R, Bots ML; CONTRAST Investigators: Role of residual kidney function and convective volume on change in beta2-microglobulin levels in hemodiafiltration patients. Clin J Am Soc Nephrol 2010;5:80–86.
45 Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol JM, Martinez-Castelao A; ESHOL Study Group: High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. J Am Soc Nephrol 2013;24:487–497.