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Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients

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Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. The use of a high-flux membrane, which eliminates larger molecular weight solutes with better biocompatibility, has steadily increased since the discovery of beta-2 microglobulin (β_2m) amyloidosis in 1985. The long-term effects of a dialyzer membrane on morbidity and mortality are not completely understood. To examine the membrane effect as a factor of carpal tunnel syndrome onset and mortality, multivariate Cox regression analysis with time-dependent covariate was conducted on 819 patients from March 1968 to November 1994 at a single center. Two hundred and forty-eight of the patients were either switched from the conventional to high-flux membrane or treated only with a high-flux membrane. Fifty-one patients underwent a CTS operation and 206 died. Membrane status (on high-flux or on conventional) was considered as time-dependent covariate and risk was adjusted for age, gender, type of renal disease and calendar year of dialysis initiation. The relative risk of CTS was reduced to 0.503 ($P < 0.05$) and mortality 0.613 ($P < 0.05$) by dialysis on the high-flux membrane, compared to the conventional membrane. Serial measurements of β_2m indicated significantly lower β_2m to persist in patients on the high-flux membrane. The high-flux membrane decreased the risk of morbidity and mortality substantially. Larger molecule elimination was shown important not only for preventing β_2m amyloidosis, but for prolonging survival of dialysis patients as well.

By dialysis therapy, very long-term survival of end-stage renal failure patients is possible, but frequently is attended with disabling problems associated with beta-2 microglobulin (β_2m) amyloidosis [1, 2]. Dialysis with the high-flux membrane has found increasing application in Japan since the recognition of β_2m amyloidosis as a specific complication of a chronic dialysis patient in 1985 [3]. The high-flux membrane or high-performance membrane removes larger molecular weight solutes, including β_2m, with better biocompatibility than the conventional unsubstituted cellulose membrane. These advantages should ensure a lesser incidence of β_2m-amyloidosis and better life prognosis. However, the long-term effects of the dialyzer membranes have yet to be fully determined [4–12]. Also, whether the membrane switch from conventional to high-flux membrane actually alleviates dialysis-related amyloidosis or mortality has not been confirmed [10]. This study was conducted to examine the effects of high-flux membrane for lessening the risk of the carpal tunnel syndrome (CTS), a representative manifestation of β_2m-amyloidosis, and mortality. Risk assessment was made for a large number of patients using Cox-proportional hazard model.

Key words: beta-2 microglobulin, amyloidosis, carpal tunnel syndrome, hemodialysis, high flux membrane, mortality.

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METHODS

Patients who began dialysis therapy at this hospital between January 1968 and November 1994 were studied. We excluded visiting patients. Only 819 patients participated and all had a complete dialyzer history available; this included those who had undergone hemodiafiltration or hemofiltration transiently, since the purpose of the treatment was β_2m removal. Characteristics of the patients and blood purification methods are specified in Tables 1 and 2. Mean age at hemodialysis initiation increased over the 27 years of follow-up from 35.0 to 59.9 and diabetes patients increased form 2.3 to 25.6%.

The indication for a high-flux membrane in this study was β_2m elimination with consequently less postdialysis β_2m concentration than predialysis. Accordingly, high-flux membrane materials were polymethylmethacrylate (PMMA), polyacrylonitrile (PAN/AN69), polysulfone (PS), cellulose-triacetate (CTA), and polyester-polymer-alloy (PEPA).

Before November 1984, primarily the conventional cellulosic membrane had been used. For the patients complicated with dialysis arthropathy, the high-flux membrane was used and the results are reported elsewhere [13]. Two years later when β_2m was found responsible for this type of amyloidosis, its use was started at the beginning of dialysis and continued as much as possible regardless of arthropathy. The number of patients on high-flux membrane increased steadily to 224 (58%) of 386 patients treated in 1994 (Fig. 1). No patient who had been placed on the high-flux membrane subsequently returned to the conventional membrane. Dialyzers were never reused. All patients underwent four to five hours of hemodialysis three times weekly after seven to eight hours of dialysis during 1968 to 1970.

Reverse osmosis was introduced in 1976 and was fully in use in 1981; the bicarbonate dialysate supplying system was put into use in 1984, and volumetric controllers in 1978. Endotoxin-cut ultrafilter was introduced in 1988 and a mean dialysate endotoxin at the terminal console always remained less than 20 pg/ml [1].

Carpal tunnel syndrome (CTS) was considered to be present in the case of decompression surgery. The indication for surgery was

Table 1. Patient characteristics

Number of patients	819
Sex ratio, M/F	525/294
Age at onset of dialysis	50.2 ± 17.3
Follow-up in years	5.8 ± 6.4
(range)	(0.1~27.9)
First year dialysis	
median	1982
range	1966–1994
Cause of renal failure	
Non-DM	689
CGN	458
PCK	77
Nephrosclerosis	81
Others	73
DM	130

Table 2. Method of blood purification

HD on conventional membrane	571
Switch to high-flux membrane	185[a]
HD on high-flux membrane	63
	Σ819

[a] Includes 28 cases treated temporarily by HF or HDF with high-flux membrane

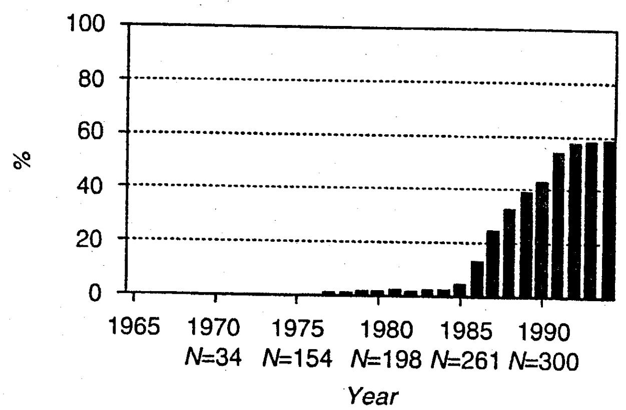

Fig. 1. Frequency of patients using high flux membrane.

made by an orthopedic physician with no knowledge of the detailed dialysis treatment, based on the intensity of clinical symptoms and electronic measurement of motor nerve conduction velocity. Patients without histological evidence of β_2m-amyloid or those without roentographycal evidence of bone cyst were excluded because of possible non-amyloidosis CTS. Two female patients operated on at four and six years of dialysis therapy were excluded.

Serum β_2m was measured serially in a subgroup of patients prior to and following the membrane switch. The membrane switch was done irrespective of residual renal function. β_2m levels were mixed with or without residual renal function in both membrane treatments. Reduction in β_2m was determined as: (Pre − Post)/Pre × 100 (%). Kt/V was calculated according to Daugirdas's formula [14], averaged and compared for sequential three years for the conventional and high-flux membranes.

Statistical analysis

The Cox proportional hazard model with a time-dependent covariate was used to assess the effects of high-flux membrane with the computer program PHREG, SAS version 6.08. Dates of the two end points, CTS surgery and death, were recorded. The time from initiation of dialysis to the end point was considered influenced by covariates of (1) patient age, (2) calendar year at dialysis initiation, (3) gender, (4) cause of renal failure, diabetes or non-diabetes and (5) membrane status. Membrane status was time-dependent because many patients initially started dialysis on conventional membrane and then switched to the high-flux membrane (**Appendix**). This approach has ever been used for analysis of heart transplant recipients [15].

Patient death, transfer to other units, switching to peritoneal dialysis or renal transplantation before CTS onset were regarded as censored information as well as continual dialysis without CTS surgery at the final observation date.

Some early cases were changed to high-flux membranes for the appearance of CTS. It could be a significant bias to include them as they were, because they would receive surgical operation very shortly. To adjust this bias, we performed three approaches with, (*a*) excluding such symptomatic cases, (*b*) including them as carryover by counting the time after switchover to operation day as conventional membrane, and (*c*) including them as censored cases at the time they changed membranes.

The contribution of covariates for explaining dependent variable was assessed by a two-tailed likelihood ratio test with *P* values less than 0.05 considered to be significant. Mann-Whitney's *U*-test and the chi-square test were used as needed. All data were expressed as mean ± SD.

Table 3. Outcomes of CTS surgery

CTS surgery		51
during conventional membrane	28	
during high-flux	23	
Censored		251
Transferred to another hospital		311
Death		196
Renal transplantation		10

Σ819, 4543 person-years

Table 4. Outcomes of death

Death		206
Cardiovascular	105	
Infection	42	
Malignancy	11	
Others	17	
Censored		289
Transferred to another hospital		314
Renal transplantation		10

Σ819, 4783 person-years

RESULTS

The summarized proportion of high-flux membrane use was PMMA 32.4%, CTA 28.6%, PAN/AN69 17.2%, PS 16.7%, PEPA 3.4% and others 1.7%. The proportion of conventional membrane use was unsubstituted cellulose membrane 77.4%, cellulose acetate 19.9% and others 2.7%.

Data for outcomes of CTS surgery and death are indicated in Tables 3 and 4 respectively. Specific causes of mortality are listed in Table 5. Cardiovascular disease and infection incidence was

Table 5. Mortality

	Cardiovascular	Infection	Malignancy	Others	
Mortality expressed as percentage of observed deaths					
Total	57.8	20.4	5.3	16.5	(%)
during low-flux	63.7	22.2	4.1	9.9	
during high-flux	60.0	20.0	11.4	8.6	
Mortality expressed as number/1000 patient-years					
Total	26.2	9.2	2.4	7.5	
during low-flux	30.2	10.5	1.9	4.7	
during high-flux	22.4	7.5	4.3	3.2	

Table 6. Relative risk for CTS calculated by three separate analyses (end point is CTS operation)

Variable	Risk ratio (*P* value)		
	Analysis A	Analysis B	Analysis C
Membrane	0.646 (0.29)	0.500 (0.05)[a]	0.311 (0.01)[a]
Female	0.727 (0.34)	0.782 (0.42)	0.917 (0.82)
Diabetes	1.046 (0.97)	0.951 (0.96)	1.351 (0.78)
Age	1.065 (0.0001)[a]	1.064 (0.0001)[a]	1.081 (0.0001)[a]
Calendar year	0.991 (0.85)	0.999 (0.97)	1.009 (0.87)

Analysis A excluded symptomatic cases with CTS, $N = 812$; analysis B dealt with them as a carryover, $N = 819$; and analysis C dealt with them as censored, $N = 819$.

[a] Statistically significant

Table 7. Relative risk of each covariate for CTS (end point was CTS operation)

	Variable	Risk ratio	95% CI[a]		*P* value chi square
			Lower	Upper	
(1)	Membrane	0.638	0.334	1.218	0.17
(2)	Membrane	0.500	0.250	0.998	0.05
	Female	0.782	0.427	1.432	0.42
	Diabetes	0.951	0.122	7.394	0.96
	Age	1.064	1.038	1.091	0.0001
	Calendar year	0.999	0.913	1.093	0.97
(3)	Membrane[b]	0.503	0.263	0.964	0.03
	Age[b]	1.062	1.039	1.086	0.0001

[a] 95% confidence intervals

[b] Significant covariates in best-fitted model

The sets of covariates included were: (1) membrane status alone, (2) all the covariates and (3) selected covariates that were statistically significant at 5%.

slightly higher during conventional membrane use but did not reach statistical significance.

Relative risks are shown in Table 6, as calculated by the proportional hazard model with three different end points for CTS surgery. The analysis (*a*) excluding symptomatic cases obviously has a strong bias in favor of the conventional membrane because established CTS needs decompression surgery very shortly. Actually, there were seven cases symptomatic of CTS who used a conventional membrane for 13.7 ± 2.0 years and underwent an operation shortly after membrane switching, at 0.27 years (3.3 months). Analysis (*b*), which dealt with this 0.27 years as carryover, was more realistic than (*c*) because it included the information of end point data (operation day). Therefore, analysis (*b*) was considered the best to adjust for such symptomatic switcher's bias, which revealed that membrane status and age at the initiation of dialysis have a significant influence on the incidence of CTS (Table 7). The high-flux membrane decreased the risk of CTS to 0.503 (Fig. 2). In the mortality analysis, membrane status, age, gender and cause of renal failure were independent prognostic factors for survival (Table 8). High-flux membrane decreased the risk of mortality to 0.613 (Fig. 3).

Changes in the mean predialysis serum β_2m and reduction rate are shown in Figures 4 and 5. In switched cases ($N = 181$), predialysis β_2m fell by 22% from 39.1 ± 11.2 mg/liter before switching to 30.5 ± 7.2 mg/liter after switching. Enhanced removal of β_2m (averaged RR 40.2 ± 21.4% after switching) continued for seven years at most (Fig. 4). In non-switched cases, predialysis β_2m was 31% less in the initially high-flux started group (26.2 ± 6.0 mg/liter, $N = 49$) than the low-flux started group (37.7 ± 9.5 mg/liter, $N = 308$; Fig. 5). Mean Kt/V slightly increased following membrane switch, 1.41 ± 0.10 to 1.48 ± 0.08 ($N = 182$, $P < 0.01$).

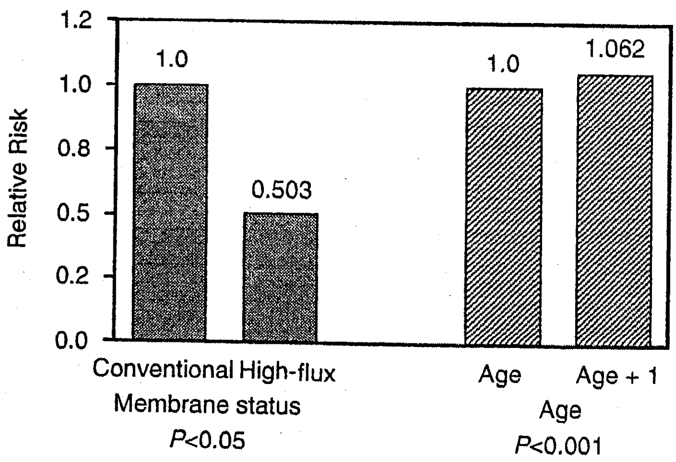

Fig. 2. Significant covariates and relative risks for carpal tunnel syndrome.

DISCUSSION

Since the late 1980s, the use of high-flux membranes has increased steadily, and recently it has been made more porous and biocompatible. Whether this membrane delays the onset of amyloid deposition and improves survival are points of the greatest concern. In spite of better permeability and biocompatibility, the results for long-term use of high-flux membrane are very few. Risk of β_2m-associated morbidity and mortality was

Table 8. Relative risk for mortality of each covariate (end point was death)

	Variable	Risk ratio	95% CI[a] Lower	95% CI[a] Upper	P value chi square
(1)	Membrane	0.794	0.528	1.194	0.27
(2)	Membrane	0.654	0.426	1.004	0.05
	Female	0.656	0.489	0.880	0.005
	Diabetes	1.977	1.403	2.786	0.0001
	Age	1.080	1.067	1.093	0.0001
	Calendar year	0.985	0.955	1.017	0.35
(3)	Membrane[b]	0.613	0.409	0.919	0.02
	Female[b]	0.652	0.486	0.874	0.004
	Diabetes[b]	1.909	1.366	2.668	0.0002
	Age[b]	1.077	1.065	1.089	0.0001

[a] 95% confidence intervals
[b] Significant covariates in best-fitted-model
The sets of covariates included were: (1) membrane status alone, (2) all the covariates, and (3) selected covariates that were statistically significant at 5%.

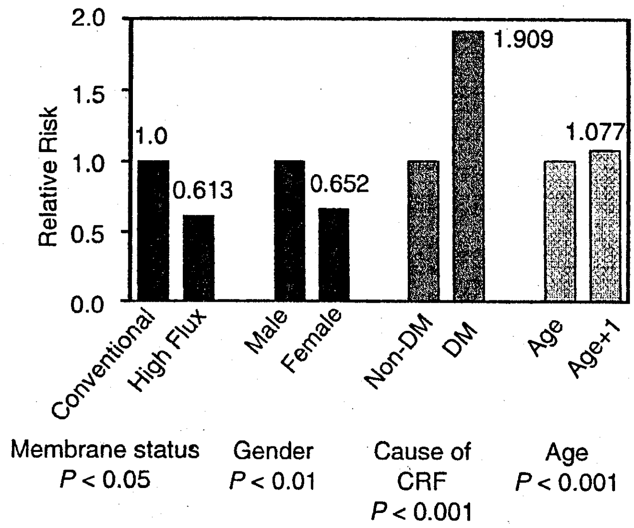

Fig. 3. Significant covariates and relative risks for mortality.

shown in this study to be influenced by use of the high-flux membranes.

Most studies deal with short-term trials or are restricted to certain membrane types such as PS, PMMA, or most often PAN [4–7, 9, 11]. Whether results with PAN/AN69 are applicable for assessment of other types of high-flux membranes is not known. In this study, attention was directed to membrane permeability, with special emphasis on β_2m elimination. Results were obtained using various types of high-flux membranes able to remove significant β_2m.

A period of at least 10 years or more is necessary to reach the primary β_2m-related end point; however, proper membrane choice for patients with disabling complications should be mandatory at present. The Cox proportional hazard model was used to exclude the effects of confounding factors. The ultrafiltration controller, medication and ultrapure dialysate are suspected determining factors, but they were not considered in the present study for it was extremely difficult to operationally define such factors. We dealt the conditions that could not be modifiable except membrane status.

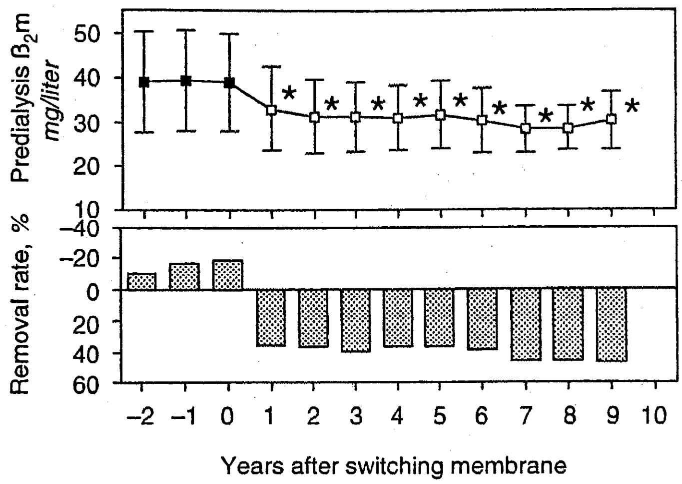

Fig. 4. Time course of predialysis β_2m and the removal rate in the membrane-switched group ($N = 181$); data are means ±SD. Symbols are: (■) conventional membrane data; (□) high-flux membrane data; (▩) upward bars (minus) indicate an increase in β_2m following the dialysis session. *$P < 0.001$ vs. 0 year.

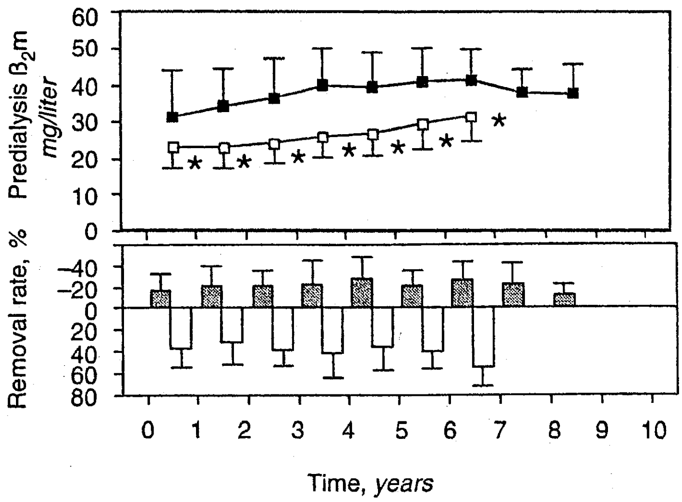

Fig. 5. Time course of predialysis β_2m and removal rate with conventional and high flux membrane groups. Data are means ± SD. Symbols in upper graph are: (■) conventional ($N = 308$) and (□) high flux ($N = 49$) membrane data; *$P < 0.001$. In the lower graph, symbols are: (▩) conventional and (□) high flux membrane data.

The membrane data from patients who changed membrane type was considered to be a time-dependent covariate in Cox's proportional hazard model [15, 16]. To accurately evaluate a time-dependent covariate, there must be no prior use of a high-flux membrane by less risky patients so that the association between membrane type and end points will not be over-rated. If we observe CTS-presenting symptomatic patients without switching to the high-flux membrane, the high-flux membrane effect would be found to be more preferable.

Only few comparisons have been made of the long-term effects of various dialysis membranes on patient morbidity and mortality. Charnard et al noted the CTS onset to be delayed in patients exclusively dialyzed on the PAN/AN69 membrane [4]. A retrospective case-control study comparing cellulosic membrane and PAN dialysis results indicated an insignificant decrease in the prevalence of arthropathy, joint pain and CTS in PAN [5]. van

Ypersele de Strihou et al observed that patients on PAN/AN69 membrane to be less likely to develop radiologically-determined bone cysts than those on the cellulosic membrane [6], but survival without CTS to be the same, which is at variance with the present results. They maintain that CTS operation is a poor marker of β_2m amyloidosis since (*1*) CTS occurs even in non-dialyzed patients and thus non-amyloid-induced CTS is possible, and (*2*) the criteria for surgery is not uniform. In the present study, however, CTS operated patients without β_2m were not included, nor were there any patients from other hospitals (no center bias). CTS operation was thus considered a significant marker for β_2m amyloidosis.

The present study confirms a lesser risk of mortality by the high-flux membrane, as also noted by Hornberger et al [16]. Follow-up time in the latter was rather short, but the relative risk of mortality decreased to 0.24 with the high-flux membrane, and the annual mortality was substantially less, that is, 7% compared to 20% by the conventional cellulosic membrane. Chandran, Liggett and Kirkpatrick observed a lower mortality rate in patients on PAN/AN69 than would be expected from the U.S. Renal Data System mortality project [8]. More recently, Hakim et al clearly demonstrated that the relative risks of mortality with modified cellulose or synthetic membranes are 20 to 25% lower than with unsubstituted cellulose membrane, adjusting Kt/V and regional effects in a large number of patients [10].

In contrast to these results, there is a pessimistic view of membrane effect. Bonomini et al specified membranes as cellulosic or synthetic [17] and could found no significant difference in long-term effects between them. Membrane classification and maintenance predialysis β_2m were in contrast to the present study. The capacity for β_2m elimination, not membrane material, was the basis for membrane classification in the current study. Thus, our patients on high-flux membrane clearly showed lower predialysis β_2m than on the conventional membrane.

Predialysis β_2m in some studies has been shown to remain unchanged after a mid-term of high-flux dialysis, but the present study indicated that a sustained decrease (22%) was basically the same as that of Mrowka and Schiffl, who reported reduced β_2m 20 to 35% for over six years with the PS membrane [18]. Locatelli et al also demonstrated 16 to 23% decrease in predialysis β_2m in high-flux membrane hemodialysis or hemodiafiltration for 24 months [12]. β_2m amyloidosis may possibly be caused by retention of β_2m over many years. β_2m synthesis in dialysis patients takes place essentially to the same extent as in normal control subjects [19]. Sufficient β_2m removal to counterbalance its generation should thus avoid its further retention that would pose risk factor. β_2m itself expresses biological activity that is particularly strong on becoming an advanced glycation end product [20]. β_2m should thus be removed and maintained at low level. Even moderate reduction (22 to 31%) in maintenance predialysis β_2m compared to conventional membrane is suggested by the present study to reduce the risk of β_2m-associated morbidity.

Nutritional improvement [21], less frequent infection, less nephrotoxic effect, plasma lipoprotein profile improvement [22], and less acute intradialytic deleterious effects compared to bioincompatible membranes may be possible explanations for the present results [23]. However, the specific reasons for these results cannot be ascertained from this study. The cause for mortality with either membrane appeared to be essentially the same. Kt/V is a very important indicator of the adequacy of dialysis that is related to morbidity and mortality [24]. In this study, Kt/V increased with the high-flux membrane, but only slightly. Desirably high Kt/V was achieved prior to use, possibly due to the considerable clearance of small molecules by either membrane and unchanged time of dialysis. Kt/V increment would thus have contributed less to the present result.

As this is a retrospective and uncontrolled study, caution is needed in interpreting the results. The results, however, were obtained in a single center, so the data collection and treatment policy are uniform and without "center effect"; there are very long term-follow-ups and serial β_2m measurements. It is important to underline the fact that the beneficial effect was at least associated with continually reduced β_2m due mainly to flux and some extent to by biocompatibility [25]. The elimination of larger toxins such as β_2m should also be considered not only for preventing β_2m amyloidosis, but also prolonging the dialysis patient survival. The results should provide a motivation to prospectively test the importance of flux as well as the biocompatibility of dialyzer membranes.

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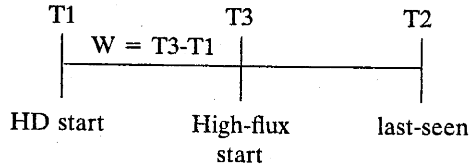
APPENDIX

Abbreviations

Abbreviations used in this paper include: CTS, carpal tunnel syndrome; β_2m, β-2 microglobulin; PMMA, polymethylmethacrylate; PAN/AN69, polyacrylonitrile; PS, polysulfone; CTA, cellulose-triacetate; PEPA, polyester-polymer-alloy.

Time dependent covariate

There are certain situations in which the proportional hazard assumption do not hold in the Cox model. That means that hazard ratios or the value of covariate change across time. In this study, membrane status (Z), was treated as a segmented time-dependent covariate as shown below.



In this model, T1 is the time of hemodialysis initiation, T2, the time of the end point or censored time and T3, the time of change to the high-flux membrane. W represents the term on conventional membrane. Z can be defined as 0 if time is less than W or 1 if time equal to or greater than W. Accordingly, Z is a time-dependent covariate.

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