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Longer duration of predialysis nephrological care is associated with improved long-term survival of dialysis patients

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Abstract

Background. Late nephrological referral of chronic renal failure patients has been shown to be associated with high morbidity and short-term mortality on dialysis. However, the impact of predialysis nephrological care duration (PNCD) on the long-term survival of dialysis patients had not been evaluated.

Methods. We studied data from all 1057 consecutive patients who started dialysis treatment at the Necker Hospital from 1989 to 1998 (mean age at start of dialysis 53.8 ± 17.2 years (range 18–91 years), excluding from analysis patients who presented with acute renal failure ($n = 60$) or advanced malignancy ($n = 35$). We evaluated the effects of PNCD and clinical risk factors on all-cause mortality after long-term follow-up on dialysis.

Results. Among the 1057 patients analysed (13.2% diabetics), PNCD was <6 months in 258 patients, 6–35 months in 267 patients, 36–71 months in 227 patients and $\geqslant 72$ months in 307 patients. Cardiovascular (CV) morbidity, namely a history of myocardial or cerebral infarction, peripheral arteriopathy, and/or cardiac failure, before starting dialysis was 39.6% and 37.4%, respectively, in patients followed for <6 months or 6–35 months, compared with 24.4% in those followed for 36–71 months and 19.9% in those followed for $\geqslant 72$ months ($P < 0.001$). Five-year survival was significantly lower in patients with a PNCD of <6 months ($59 \pm 4.1\%$) than for 36–71 months or $\geqslant 72$ months (77.1 ± 3.7 and $73.3 \pm 3.6\%$, respectively, $P < 0.001$), but similar to those followed for 6–35 months ($65.3 \pm 3.9\%$, NS). By Cox proportional hazard analysis, PNCD <6 months, age, diabetes and prior CV disease were independent predictive factors of all-cause death on dialysis.

Conclusions. This study provides suggestive evidence that longer duration of regular nephrological care in the predialysis period, at least for several years prior to the start of dialysis, is associated with a better long-term survival on dialysis. Such data strongly support the argument for early referral and regular nephrological care of chronic renal failure patients.

Keywords: long-term survival of dialysis patients; predialysis nephrological care

Introduction

Treatment of end-stage renal disease (ESRD) is a major public health problem, as it consumes a considerable proportion of health care resources in all industrialized countries. Despite such financial effort, morbidity and mortality of ESRD patients remain high compared to subjects of similar age in the general population [1]. Factors involved in this high rate of mortality on dialysis are multiple, including quality of dialysis, nutritional status, comorbidity, age, ethnicity, prevalence of diabetes and, perhaps not sufficiently taken into account, duration and quality of predialysis nephrological care [2].

Optimal management of predialysis chronic renal failure (CRF) patients involves control of hypertension, prevention of fluid overload and treatment of anaemia, thus preventing or attenuating left ventricular hypertrophy and cardiac failure, together with action against tobacco smoking, dyslipidaemia and hyperhomocysteinaemia, all factors that contribute to accelerated atherosclerosis [3,4]. Thus, early referral and regular nephrological care of patients with CRF might be expected to result in improved cardiovascular and nutritional condition at the time of reaching ESRD, with a reduced prevalence of atherosclerotic arterial incidents such as myocardial or cerebrovascular infarction, and of cardiac failure [5].

However, CRF patients are often referred at an advanced stage of renal failure, only a few weeks or months prior to ESRD, and therefore do not benefit

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from long-term predialysis nephrological care. Deleterious effects of such late referral in terms of poorer clinical condition and higher morbidity have been evidenced in several recent studies [6,7]. In addition, a significantly higher mortality during the first 90 days of dialysis has been reported in late referred patients [8]. However, there is no study providing evidence that long-term survival of patients on dialysis could be favourably influenced by early nephrological referral, inasmuch as nephrological referral is not always followed by sustained nephrological care. Thus the duration of actual, regular nephrological care of patients with progressive renal failure during the predialysis phase is probably a more relevant parameter than simply the time of referral.

Because a large proportion of patients who started dialysis at our institution over the past decade were regularly followed for many years before the start of renal replacement therapy (RRT), we were able to assess the influence of graded duration of nephrological care on the clinical status of patients at the start of dialysis and on their long-term survival on dialysis.

Patients and methods

Between January 1989 and December 1998, 1152 consecutive patients with end-stage renal failure living in the Ile-de-France district (Paris area) began maintenance dialysis at Necker Hospital. With the exception of a few patients who lived in the vicinity of Necker Hospital and who continued maintenance dialysis at our centre, all patients were subsequently managed in various dialysis facilities in the Ile-de-France area. The majority of patients (91%) were treated with haemodialysis and the other with peritoneal dialysis.

Clinical and laboratory data at start of dialysis were extracted from patients charts. For every patient, using a standardized form, we recorded: age at first dialysis, gender, ethnicity, cause of ESRD, timing of nephrological referral, clinical status, prior cardiovascular events, diabetes and malignancy. Renal function at the time of initiation of dialysis was estimated according to the Cockcroft-Gault formula. Information on the long-term course of all patients was obtained by means of an annual inquiry to all the dialysis units of the Ile-de-France area managing these patients. Thus, we were able to determine the outcome of all patients until death, kidney transplantation, departure from the Ile-de-France area, or until 1 April 1999.

Predialysis nephrological care duration (PNCD) was quantified as the time-interval between the start of regular care at our institution and the day of first dialysis. Late referral was defined as referral of the patient less than 6 months prior to start of dialysis. In most cases, referral coincided with start of regular nephrological care. This was the case in patients who received uninterrupted management by our team. However, in patients who had been referred several years earlier but who subsequently discontinued regular follow-up for more than 1 year, start of PNCD was taken as the time the patient returned to regular follow-up at our institution.

Clinical status of patients at start of maintenance dialysis was defined in two ways. We used the classification into three risk groups as proposed by Khan *et al.* [9], which combines age and comorbidity. In addition, in order to delineate more precisely the respective influence of age and comorbidity, patients were classified with respect to their cardiovascular status. Cardiovascular disease (CVD) at the time of ESRD was defined by a history of myocardial infarction (or need for coronary artery revascularization) or cerebral infarction, or presence of congestive heart failure or peripheral arteriopathy (or aortic aneurysm). Patients devoid of any of these events were classified as CVD (–) and those with at least one of these four categories of events were classified as CVD (+).

We excluded from analysis 60 patients who presented with acute or rapidly progressive renal failure because long-standing uraemia did not develop in these patients. We also excluded from analysis 35 early-referred patients with advanced malignancy which was the direct cause of death within a few months. Thus final analysis focused on 1057 patients in whom we were able to specifically analyse risk factors in relation with chronic uraemia.

Statistical analyses

Results are expressed as mean $\pm$ SD. Differences between groups were tested using Student's *t*-test, ANOVA, Chi-square test, and the log-rank method for comparing Kaplan-Meier actuarial survival plots. Clinical and laboratory parameters taken into consideration for analysis are the values obtained within 48 hours before first dialysis. PNCD was encoded into four classes according to the four quartiles for the sample (i.e. <6 months, 6–35 months, 36–71 months, and $\geqslant 72$ months). Time to death (all causes) was assessed as the study end-point during the follow-up period. Patients were censored at modality change (dialysis to transplantation), loss of follow-up, or at the end of the follow-up period. PNCD was used as dummy variable using the referral time <6 months as the reference group, and was evaluated by nested Cox proportional hazard analysis. PNCD <6 months was considered the reference group because it had been associated with the highest risk of comorbidity and short-term mortality in previous studies [3,6,8]. The results of univariate Cox proportional hazard analysis were adjusted for age, gender, diabetic status (present or not), renal diagnosis (presence or absence of hypertensive nephrosclerosis), prior cardiovascular disease (present or not), and all these prior variables. Only covariates that tended to correlate with endpoints on univariate analysis ($P<0.15$) were included in adjusted Cox analysis. Final results of adjusted Cox analysis were considered significant at $P<0.05$. Interaction between variables was tested using nested Cox proportional hazard analysis. In order to identify the effects of PNCD on all-cause mortality independently of possible influence of dialysis care, and to evaluate a possible influence of PNCD over the duration of follow-up after starting dialysis, we repeated adjusted Cox proportional hazard analysis, and restricted the study end-point to several periods of follow-up after starting dialysis (i.e. 3 months, 1 year, 2 years, 3 years and 5 years). Statistical comparisons were performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA).

Results

The 1057 studied patients (95% Caucasian) were 673 males and 384 females. Their mean age at start of dialysis was 53.8 ± 17.2 years (range 18–91 years).

Of them, 140 (13.2%) were diabetics, including 120 with diabetic nephropathy and 20 with another type of nephropathy associated with diabetes mellitus; 159 (15%) had hypertensive nephrosclerosis without diabetes mellitus, and 916 (86.8%) had other non-diabetic nephropathies. By 1 April 1999, 86 had been lost to follow-up after moving out of the Paris area, 255 benefited from kidney transplantation, 261 had died and 455 were still alive on dialysis.

Referral pattern and demographics

Overall, 799 patients (75.6%) were referred at least 6 months prior to first dialysis and were regularly cared for at our institution, whereas 258 patients (24.4%) were referred later, less than 6 months prior to first dialysis. Of them, 193 (18.3%) were referred within less than 1 month (median time: 1 day) and had to start dialysis in emergency conditions. Among the 258 late-referred patients, 120 had been referred to us several years earlier but subsequently neglected or refused nephrological care and returned to our renal unit only at the advanced, symptomatic stage of CRF. The other 138 patients never received any nephrological advice before being referred to us, although renal disease was already known in 116 of them, whereas in the other 22 patients renal disease was clinically asymptomatic and therefore remained undiagnosed until the very advanced stage.

The pattern of referral remained essentially unchanged over time. The proportion of late-referred patients was 23.6% (123 of 521) during the period 1989–93, and 25.2% (135 of 536) during the period 1994–98.

Distribution of patients according to the duration of predialysis nephrological care (PNCD) is given in Table 1, together with their clinical characteristics at start of dialysis. The proportion of diabetic patients was higher in PNCD group <6 months (21.3%) and 6–35 months (17.2%) than in PNCD groups 36–71 months (9.8%, $P<0.01$) and $\geqslant 72$ months (5.5%, $P<0.001$). Similarly, the proportion of patients with vascular disease (hypertensive nephrosclerosis) was higher in PNCD groups <6 months or 6–35 months (respectively 21.7% and 17.2%) than in the other two PNCD groups (14.2% and 8.1%, $P<0.001$).

The mean age of patients at start of dialysis did not differ between the various PNCD groups. However, the mean age of diabetic patients (60.8 ± 12.2 years) and of non-diabetic patients with vascular disease (69.6 ± 12.4 years) was significantly higher than the mean age of the other non-diabetic patients without vascular disease (49.2 ± 16.4 years, $P<0.001$). Of note, the mean age of patients did not differ with respect to PNCD in any of the aetiological groups, either diabetics or non-diabetics.

Comorbidity at start of dialysis

The proportion of patients according to Khan's risk groups and to presence or absence of CVD at start of dialysis is given in Table 1. The proportion of patients in the medium and high risk groups taken together was significantly higher in patients referred <6 months (51.9%) than in those referred 36–71 months or $\geqslant 72$ months of ESRD (respectively 36.4% and 30.3%, $P<0.001$) but did not differ from the 6–35 months group (47.9%). The overall proportion of CVD (+) patients was also significantly higher among patients referred <6 months (39.6%) than in those followed for 36–71 months or $\geqslant 72$ months (respectively 24.4 and 19.9%, $P<0.001$), but did not differ from the group 6–35 months (37.4%, overall Chi-square $P<0.001$). The proportion of CVD (+) subjects was strikingly higher among diabetic and vascular patients than among other non-diabetics in all PNCD groups (data not shown).

Blood pressure level and laboratory parameters together with the proportion of patients who required temporary central vein access, and duration of hospitalization at start of dialysis with respect to PNCD groups are given in Table 2. Systolic and diastolic blood pressure were markedly higher in late referred patients than in patients referred at least 6 months prior to ESRD. Blood haemoglobin level, as well as serum albumin level (554 known values) was significantly lower in patients referred <6 months than in those followed for a longer time. Serum creatinine was

Table 1. Demographic characteristics and comorbidity of patients in the four quartiles of predialysis nephrological care duration (PNCD), expressed in months

	Total ($n=1057$)	<6 months ($n=258$)	6–35 months ($n=267$)	36–71 months ($n=225$)	$\geqslant 72$ months ($n=307$)	P value
Age (years)	53.8 ± 17.2	55.0 ± 17.7	54.1 ± 18.1	52.6 ± 17.1	53.0 ± 15.9	NS
Gender (M/F ratio)	1.74	2.18	1.98	1.39	1.53	0.05
Diabetics (%)	13.2	21.3	17.2	9.8	5.5	<0.001
Vascular disease (%)	15.1	21.7	17.2	14.2	8.1	<0.001
Khan's risk groups						
low (%)	58.6	48.1	52.1	63.6	69.7	<0.001
medium (%)	16.1	17.0	14.6	16.9	16.0	NS
high (%)	25.3	34.9	33.3	19.5	14.3	<0.001
CVD (+) (%)	30.1	39.6	37.4	24.4	19.9	<0.001

higher and creatinine clearance was significantly lower, as a mean, in the group of patients referred <6 months than in all other groups. Temporary central vein catheterization was used in a strikingly higher proportion of patients, and hospitalization was also markedly longer in the PNCD group <6 months than the other PNCD groups.

Relationship between PNCD, long-term survival and CV disease

Table 3 gives the 3-month, 1-year and 5-year survival rates of patients in the various PNCD groups. Short-term mortality (within 90 days of start of dialysis) was significantly higher in the PNCD group <6 months than in PNCD groups 36–71 months ($P<0.01$) and ⩾72 months ($P<0.001$). Kaplan-Meier survival curves in the four PNCD groups are given in Figure 1. The crude overall 5-year survival in the whole cohort of 1057 patients was 65%, corresponding to an average annual mortality rate of 7%. Overall 5-year survival was 57.8±4.2, 65.3±3.9, 77.1±3.7 and 77.3±3.6% in the groups followed for <6 months, 6–35 months, 36–71 months, and ⩾72 months, respectively (log-rank test, $P<0.0001$). Five-year survival did not differ between patients who received nephrological care for 36–71 months or ⩾72 months, but was significantly lower in patients followed for <6 months and also in patients referred 6–35 months before ESRD than in patients with PNCD ⩾72 months ($P<0.001$), or 36–71 months ($P<0.01$).

Five-year survival was significantly lower in CVD (+) patients taken as a whole than in CVD (−) patients (37.1±3.5 *vs* 87.1±1.8%, $P<0.0001$). However, within CVD (+) and CVD (−) aggregates, there was no significant difference in 5-year survival with respect to PNCD, with exception for patients in the PNCD group <6 months, whose survival was lower than that of all other groups irrespective of the presence or absence of CVD. Five-year survival was significantly lower

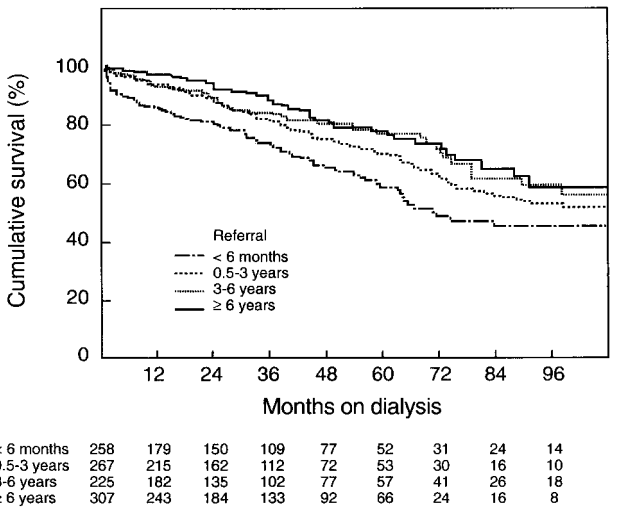

Fig. 1. Kaplan-Meier survival curves of 1057 patients with respect to predialysis nephrological care duration (PNCD, months).

Table 2. Blood pressure level and laboratory parameters, need for emergency central vein access and duration of hospitalization at start of dialysis with respect to PNCD

PNCD (months)	<6	6–35	36–71	⩾72	*P* value
SBP (mmHg)	171±23	148±17**	147±16**	141±12**	<0.0001
DBP (mmHg)	94±14	79±8**	78±7**	78±7**	<0.0001
Haemoglobin (g/dl)	8.3±1.6	9.1±1.5*	9.2±1.4*	9.5±1.9*	<0.0001
Serum albumin (g/l)	36.2±5.1	38.4±4.8*	39.3±5.4*	39.1±4.8*	<0.0001
Ccr (ml/min/1.73 m^2)	6.6±2.1	7.6±1.8*	7.6±1.7*	7.6±1.6*	<0.0001
Central vein access (%)	75.2	5.9**	4.9**	3.3**	<0.0001
Hospitalization (days)	23.8±17.1	7.5±8.9**	6.9±9.3**	5.9±5.0**	<0.0001

SBP, systolic blood pressure; DBP, diastolic blood pressure; Ccr, creatinine clearance.
PNCD <6 months *vs* each of other PNCD groups: *$P<0.01$; **$P<0.001$.

Table 3. Three-month, 1-year and 5-year survival rates (%), all-cause deaths, and CV deaths with respect to PNCD

PNCD (months)		3-month survival	1-year survival	5-year survival	All-cause deaths	CV deaths
<6	(*n* = 258)	91.7±1.7[a]	86.4±2.2[b]	57.8±4.2[c]	86	53 (62%)
6–35	(*n* = 267)	95.8±1.2	92.6±1.6	65.3±3.9	67	41 (61%)
36–71	(*n* = 225)	98.2±0.9	92.8±1.8	77.1±3.7	40	21 (52%)
⩾72	(*n* = 307)	99.3±0.6	97.5±0.9	77.3±3.6	54	29 (52%)

[a]PNCD <6 months *vs* 36–71 months: $P<0.01$; *vs* ⩾72 months: $P<0.001$.
[b]PNCD <6 months *vs* 36–71 months or ⩾72 months: $P<0.001$.
[c]PNCD <6 months *vs* 36–71 months: $p<0.01$; *vs* ⩾72 months: $P<0.001$.

in diabetics than in non-diabetics ($36.1 \pm 5.4\%$ *vs* $75.7 \pm 1.9\%$, $P < 0.0001$), and this was true of all PNCD groups. The survival benefit associated with longer PNCD was mainly apparent during the first years of follow-up on dialysis, and was less apparent in diabetic and vascular patients than in non-diabetics (data not shown).

As shown in Table 3, CVD accounted for about 60% of deaths observed in PNCD groups <6 months and 6–35 months, and nearly 50% in PNCD groups 36–71 months and $\geqslant 72$ months. Pre-existing CVD was already present at start of dialysis in virtually all patients who subsequently died from CV causes while on dialysis.

Multivariate analysis

Table 4 shows the results of the Cox proportional hazard analysis for PNCD. Before adjustment, PNCD 36–71 months and $\geqslant 72$ months were associated with a significantly better survival in dialysis patients. This association persisted after adjustment for age, diabetic status, diagnosis of hypertensive nephrosclerosis, and prior cardiovascular disease in the group with PNCD $\geqslant 72$ months. Gender, haemoglobin, blood pressure and creatinine clearance were not selected on univariate analysis and were not included in the adjustment analysis. Serum albumin was selected by univariate analysis, but with limited significance ($P = 0.068$) and was no more significant in multivariate analysis. It should be noted that the values of serum albumin were known in only 554 patients, thus precluding firm conclusions. Moreover this latter association persisted even when we restricted the study end-point to shorter periods of follow-up after starting dialysis, although it appeared to be not constant over duration of follow-up. The adjusted relative risks (95% confidence interval) for PNCD $\geqslant 72$ months at 3 months, 1 year, 2 years, 3 years and 5 years were 0.13 (0.03–0.58), 0.24 (0.1–0.59), 0.44 (0.25–0.81), 0.45 (0.28–0.74) and 0.53 (0.35–0.79), respectively. These data suggest that although the presence of diabetes, prior CVD, and dialysis care could partially explain the high mortality rate observed in late referred patients, other factors could also contribute.

Discussion

Based on a large cohort of patients followed over a decade, we present here suggestive evidence that a longer duration of regular nephrological predialysis care is associated with both a significantly lower prevalence of cardiovascular morbidity at ESRD and a longer survival on maintenance dialysis. The beneficial effect of early referral was especially apparent when regular nephrological care was provided during at least the three years preceding ESRD. Cardiovascular status of patients at ESRD appears to be a major determinant of such survival, although other risk factors, particularly in patients referred within <6 months, may play an additional role.

Detrimental effects of late referral have been largely highlighted during the past decades in all countries. They include lack of adequate intervention to slow the progression of renal failure, lack of prevention of uraemic complications and of timely creation of vascular access, higher morbidity, increased duration of hospitalization, altered quality of life, untoward emotional and socio-economic consequences for the patients, and undue extra costs for the community [6,7].

Despite all efforts to inform the medical community, late referral remains frequent in all countries. We observed no decrease in the rate of late referral in the most recent years compared to the beginning of the observation period. Because there is no limitation to acceptance of patients on dialysis in France, and as all French uraemic patients benefit from 100% reimbursement for all heath expenses, the reasons for potentially avoidable late referral in our country are mostly

Table 4. Independent risk factors for death in dialysis patients

	Univariate analysis[a, b, c]			Multivariate analysis		
	RR	(95% CI)	*P* value	RR	(95% CI)	*P* value
PNCD <6 months (reference)	1.00					
PNCD 6–35 months	0.81	(0.59–1.69)	0.191	0.73	(0.53–1.01)	0.058
PNCD 36–71 months	0.55	(0.38–0.79)	0.001	0.71	(0.49–1.02)	0.066
PNCD $\geqslant 72$ months	0.45	(0.31–0.60)	0.000	0.56	(0.39–0.81)	0.002
Age (each year)	1.07	(1.06–1.08)	0.000	1.06	(1.04–1.07)	0.000
Diabetes status (yes/no)	3.39	(2.56–4.49)	0.000	1.83	(1.35–2.50)	0.000
Hypertensive nephrosclerosis (yes/no)	2.65	(2.02–3.47)	0.000	1.11	(0.81–1.49)	0.507
Prior cardiovascular disease (yes/no)	8.07	(6.12–10.58)	0.000	3.54	(2.56–4.91)	0.000

RR, Relative risk (95% confidence interval) for univariate and multivariate Cox proportional hazard models.
[a]Gender, blood pressure, hemoglobin and creatinine clearance did not predict death in dialysis patients by univariate Cox analysis and was not included in the adjustment analysis.
[b]PNCD was used as dummy variable using the referral time <6 months as the reference group.
[c]Results of univariate Cox analysis for age, diabetes, renal diagnosis and prior cardiovascular disease are expressed as adjusted variables for PNCD.

cultural, i.e. lack of awareness of the benefits of regular nephrological management by the patients and/or their physicians, including general practitioners, cardiologists and diabetologists. This was especially true of diabetic and vascular patients most of whom were referred at an advanced stage of renal disease, and already had developed CVD before being referred to us. Such late referral is all the more unfortunate because diabetic and hypertensive patients are well known to have a high risk of developing renal disease and atherosclerotic CV complications, and therefore would benefit most from early preventive measures [10].

Several studies compared the long-term survival of patients on dialysis with respect to the pattern of predialysis nephrological care. Campbell *et al.* [11] reported a 1-year mortality rate of 39% in patients referred within less than 1 month of dialysis, 19% in those referred within 1–4 months and only 6% in those who had been referred at least 4 months prior to start of dialysis. Eadington *et al.* [7] reported a 2-year death rate of 69% in patients referred within less than 4 months of dialysis, compared to 56% in those referred earlier. Khan *et al.* [12] observed a 2-year mortality of 75% among patients referred within less than one month of dialysis, compared to 41% in those referred earlier. Ellis *et al.* [13] reported a 1-year death rate of 40% in patients referred within 3 months of start of RRT, compared to 27% in those referred within more than 3 months. At variance with other groups, Roubicek *et al.* [14] observed only a slight, not significant difference between late (<4 months) and early referred ESRD patients with death rates, respectively, of 31% *vs* 24% at 3 years, and 48% *vs* 44% at 5 years.

However, all of these studies used variable definitions of late referral (ranging from 1 month to 4 or 6 months before starting dialysis), and they compared early to late referral groups taken as a whole, but none analysed survival with respect to the duration of predialysis nephrological care. As a large proportion of our patients received regular nephrological care for many years prior to ESRD (in our series, the median nephrological follow-up duration was as high as 4.2 years in patients referred at least 6 months prior to ESRD), we were able to analyse the influence of graded durations of nephrological care on survival of patients and prevalence of CVD at ESRD.

We excluded from analysis of long-term survival those patients who presented with acute or rapidly progressive renal failure, in whom irreversible renal failure developed within some weeks or months and therefore had no potential to develop long-term complications of chronic uraemia. We also excluded patients with advanced malignancy acting as the direct cause of death within a few months and therefore it was not possible to analyse the effect of uraemia *per se*. We observed a nearly twofold higher prevalence of CVD at start of dialysis in patients who had been referred late, and therefore had not received optimal management during the years preceding ESRD, than in those who benefited from long, regular nephrological care during the predialysis period. As a matter of fact, hypertension and anaemia were markedly more severe and serum albumin level was lower in late- than in early-referred patients. Indeed, metabolic and clinical complications of chronic uraemia mainly develop at the advanced stage of CRF, when creatinine clearance declines under 30–40 ml/min/1.73 m^2 [15]. According to the type of chronic renal disease, it may take 3–10 years, on average, to progress from this GFR level to ESRD [16]. Thus, optimal nephrological care is critical during the last predialysis years to prevent or limit complications of chronic uraemia.

The overall 5-year survival observed in our patients favourably compares with the survival reported in other studies. The rather low mortality rate (7% per year on the average) is much less than that recently reported in the USA [17], but similar to the mortality rate recorded in most European countries. As an example, the overall 5-year survival recorded in Italy among 6444 patients, whose mean age was 56.4 years at start of dialysis, was 69.9% [18]. The favourable survival observed in our series may be also explained by the rather young age of our patients at start of dialysis (53.8 years on the average) and by exclusion from analysis of patients with acute irreversible renal failure, who most often suffered from severe diseases, and of patients with advanced malignancy.

Optimal management involves prevention of all amendable clinical and biochemical complications associated with loss of renal function, namely hypertension, calcium phosphate disorders, acidosis, anaemia, malnutrition and factors of accelerated atherosclerosis such as dyslipidaemia, smoking and hyperhomocysteinaemia [1,5,19]. Thus, one may rightfully expect that CRF patients regularly managed for many years should exhibit a lesser incidence of left ventricular hypertrophy, cardiac failure and coronary or cerebrovascular accidents when reaching ESRD. In this respect, the most salient finding of our study is to suggest that a sufficiently long duration of regular predialysis nephrological care is needed to influence subsequent long-term survival of patients, as only regular nephrological care for several years before start of dialysis was associated with a significantly lower prevalence of CVD at ESRD, at least in non-diabetic patients. This observation was possible because a large proportion of our patients were regularly followed at our institution for more than 3 years. This may explain why previous studies, where most patients had a limited duration of predialysis nephrological care, did not reach such a conclusion.

There are, however, several limitations in our retrospective, observational study. First, the aetiological distribution of our cohort of patients may have influenced survival [20]. In our series, 13% of patients were diabetic, i.e. a proportion much lower than what is observed in the USA and in Northern Europe, but similar to that observed in other European countries. The Dialysis Outcomes and Practice Patterns Study (DOPPS) based on 327 haemodialysis centres throughout the world, which started in 1996, records diabetes

mellitus as the cause of ESRD in 40.9% of patients in the USA compared to 25% in Germany, 10.7% in Italy and 10.4% in France [21]. Second, we cannot exclude that in some cases physicians were reluctant to refer patients with severe CV comorbidity, in whom CVD was indeed the cause of late referral rather than its consequence. Third, we did not record the exact time of occurrence of CV events during the predialysis period in our patients. However, in diabetic and vascular patients, CV events most often antedated nephrological referral, especially in late referred patients, so that intervention of the nephrologist could not prevent the occurrence of such events. Fourth, we could not assess the quality of dialysis delivered to individual patients among the various centres. However, an homogeneous policy is followed by all centres and all patients were expected to have a Kt/V of no less than 1.2. As a matter of fact, a recent cohort study in France over the period of January 1996 to July 1998 recorded a mean weekly dialysis time of 12.2 ± 1.7 h and a mean Kt/V of 1.34 ± 0.34 [22]. Thus, large discrepancies in dialysis adequacy between centres are not likely to have occurred and to have influenced survival on dialysis. Moreover the association between PNCD and all-cause mortality was present even after the restriction of study end-point to short periods of follow-up after start in dialysis.

The major role of CVD in the mortality of dialysis patients is well established. Half of deaths observed in dialysis patients are due to CV complications [23], and this was also observed in our patients. Moreover, virtually all of our patients who died from such complications already had CV comorbidity at start of dialysis. Evidence has been provided that the CV status of patients at start of dialysis is the most important predictive factor of survival while on maintenance dialysis [24,25]. Silberberg *et al.* first pointed out the impact of left ventricular hypertrophy on survival of dialysis patients [26], and the adverse influence of hypertension and anaemia, through left ventricular hypertrophy and congestive heart failure was stressed by Foley and coworkers [27]. Such cardiac complications are already present at start of dialysis in most patients, but they are in part preventable. In particular, optimal blood pressure control, prevention of fluid overload and partial correction of anaemia in predialysis patients may limit the development of left ventricular hypertrophy [1,5].

Finally, our results support the concept that early, regular predialysis nephrological care may help to limit the development of CV disease in chronic renal failure patients. This, in turn, results in reduced subsequent CV mortality and improved long-term survival of ESRD patients. Thus, preservation of the CV status appears to be an important intermediate factor related to long-term survival. Because risk factors for atherosclerosis and CVD are present early in the course of CRF, early implementation of preventive measures should be advisable to improve cardiovascular status, quality of life and life expectancy of uraemic patients.

In conclusion, our data, based on a large, homogeneous cohort of patients strongly suggest that regular predialysis nephrological care for several years prior to ESRD is associated with better preserved CV condition of patients and improved long-term survival on dialysis. The finding that early nephrological care not only reduces morbidity, short-term mortality and costs, but also improves long-term survival of patients on dialysis is a strong argument to encourage early referral and regular nephrological care of renal patients.

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