Octogenarians Reaching End-Stage Renal Disease: Cohort Study of Decision-Making and Clinical Outcomes

DOMINIQUE JOLY,*† DANY ANGLICHEAU,* CORINNE ALBERTI,‡ ANH-THU NGUYEN,† MALIK TOUAM,*† JEAN-PIERRE GRÜNFELD,* and PAUL JUNGERS†

**Nephrology Unit, Necker Hospital and Université René Descartes-Paris V, Paris, France; †INSERM U5O7, Necker Hospital, Paris, France; and ‡Biostatistics, Robert Debré Hospital, Paris, France.*

Abstract. The fate of octogenarians reaching end-stage renal disease (ESRD) is poorly defined, and implicit dialysis rationing may be practiced in this age group. The main objectives of this study were to analyze the characteristics of pre-ESRD octogenarians offered dialysis or not and to identify factors influencing mortality while on dialysis, to improve prognosis assessment and decision-making. In this single-center cohort, 146 consecutive pre-ESRD octogenarians were referred to a nephrology unit over a 12-yr period (1989 to 2000). Main outcome measures were baseline characteristics of patients offered dialysis and conservative therapy and overall and 1-yr survival according to effective treatment. A therapeutic decision was made for 144 patients. Octogenarians who were not proposed dialysis ($n = 37$) differed from those who were proposed dialysis ($n = 107$) mainly in terms of social isolation (43.3% *versus* 14.7%; $P = 0.03$), late nephrologic referral (51.4% *versus* 28.9%; $P = 0.01$), Karnofsky score (55 $\pm$ 18 *versus* 63 $\pm$ 20; $P = 0.03$), and diabetic status (22.2% *versus* 6.5%, $P = 0.008$). Six patients refused the dialysis proposal. During the 12-yr observation period, 99 patients died (68.7%). Median survival was 28.9 mo (95% CI, 24 to 38) in patients undergoing dialysis, compared with 8.9 mo (95% CI, 4 to 10) in patients treated conservatively ($P < 0.0001$). In multivariable piecewise Cox analysis, independent predictors of death within 1 yr on dialysis were poor nutritional status, late referral, and functional dependence. Included in a survivor function, these covariates predict groups with low and high 1-yr mortality risk. Beyond 1 yr on dialysis, the only independent predictor of death was the presence of peripheral vascular disease. It is concluded that beside a patient's individual refusal, late referral, social isolation, low functional capacity, and diabetes may have oriented medical decision toward withholding dialysis in a significant proportion of pre-ESRD octogenarians. Although most patients on dialysis experienced a substantial prolongation of life, identification of mortality predictors in this age group should improve the process of decision-making regarding the expected benefit of renal replacement therapy.

In industrialized countries, nephrologists are currently facing an increased demand from elderly patients suffering from end-stage renal disease (ESRD). In 1997 in the United States, 22.7% of incident dialysis patients were aged 75 yr and older (1). This age segment is the most rapidly growing group among ESRD patients, with an average annual increase of 14% between 1988 and 1992 in the United States (1) and 16.3% in Canada (2). A similar trend has been observed in Europe. Particularly in our region, the proportion of patients aged 75 yr or more at the start of dialysis increased from 8.2% in 1989 to 1992 to 21.6% in 1998 (3). Among elderly ESRD patients, the "old-old" (patients aged 80+ yr) raise the most difficult problems with respect to indication and dialysis therapy management because of their frequent, multiple comorbidity and presumed short life expectancy. Despite this, studies specifically devoted to octogenarian ESRD patients are few, and their conclusions are rather discordant. Some of them report a very poor survival of octogenarians on dialysis, whereas others report more favorable outcomes. Moreover, specific predictive factors that could help in deciding whether or not dialysis would offer pre-ESRD octogenarians a substantial prolongation of life expectancy with an acceptable quality of life are lacking. In most industrialized countries, there now exists no limitation to the acceptance of patients on dialysis based on age, and the decision to initiate maintenance dialysis is based exclusively on medical considerations in the best interest of the patients (4,5). Of note, all published studies suffer an important selection bias, *i.e.*, they bear only on ESRD patients who were actually treated by dialysis, whereas nothing is known about the prevalence and outcome of other octogenarians for whom dialysis was withheld.

In an effort to comprehensively examine factors associated with the decision to propose maintenance dialysis for octogenarian patients and to identify prognosis markers for survival on dialysis, we performed a retrospective analysis of a prospectively followed cohort comprised of all consecutive patients aged 80 yr or more who were referred to our nephrology

Received July 29, 2002. Accepted December 7, 2002.
Correspondence to Dr. Dominique Joly, INSERM U 507, Necker Hospital, bâtiment Sèvres, 149 rue de Sèvres, 75015 Paris, France. Phone: 33-1-44495235; Fax: 33-1-44495450; E-mail: joly@necker.fr
1046-6673/1404-1012
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000054493.04151.80

unit for chronic renal failure from January 1989 to December 2000 and who reached ESRD during this period. Our main purpose was to better define the basis for prognosis assessment and treatment choice in this particular population.

Materials and Methods

Study Site

The Necker renal unit is based in a University hospital that provides renal services and regular dialysis for about 1.5 million people within Paris and its surroundings (Ile-de-France region). Every year, 100 to 120 new patients start dialysis at Necker hospital. Thereafter, the great majority of them continue dialysis therapy in a public or private dialysis facility closest to their home. There is no explicit rationing policy for dialysis access, whatever the patient's age, provided they are French citizens or that they benefit from full health insurance.

Patients Studied

Between January 1, 1989, and December 31, 2000, 146 consecutive patients (75 men, 71 women, 92.4% White) aged 80 yr or more with chronic renal failure and creatinine clearance below 10 ml/mn per 1.73 m^2 (according to the Cockcroft-Gault formula [6]), thus defining ESRD, and not yet on dialysis were seen in our renal unit and included in a computer-based cohort. Diagnosis of chronic renal failure was based on the patient's history, ultra-sonogram, and, when available, renal biopsy or autopsy findings. Patients with acute reversible renal failure in the absence of previous advanced chronic renal failure, patients who started dialysis somewhere else and patients who reached 80 yr of age after dialysis was started were not included. The decision whether or not to propose dialysis was formally taken in our weekly dialysis decision meeting, involving the nephrology team, a social worker, a dietitian, and a psychologist; whenever possible, the opinions of the patient, relatives, and the family doctor were taken into consideration. As no formal criteria were available, individual assessment of predictable benefits was finally used during the meeting by the nephrology consultant in charge of the patient for decision regarding dialysis recommendation. In dialyzed patients, hemodialysis prescription was adjusted to achieve a target urea reduction ratio $\geq$ 65%, adequate fluid balance, and cardiovascular stability. Most patients had thrice-weekly dialysis sessions, unless sufficient residual renal function allowed two sessions a week. All hemodialysis sessions were performed with bicarbonate buffer and high permeability membranes. Patients excluded from or refusing dialysis were maintained on conservative treatment and continued to benefit from our regular follow-up in close cooperation with the family doctor. In our institution, this continued palliative care strategy encompasses management of fluid overload (with ultrafiltration without dialysis in selected cases), relief of uremic symptoms, and pain, and also nonpharmacologic supportive measures as well as attention to psychologic, social, and spiritual concerns. To identify factors that could have influenced our therapeutic proposals, a comparison between groups was performed on the basis of the intention to propose either dialysis (group 1) or conservative treatment (group 2). Thereafter, survival analysis only took into account effective treatment (dialysis group and conservative group).

Measures, Definitions, and Data Categorization

The day of clinical and laboratory data collection and study entry (index date) was defined as the first day of dialysis treatment or the day when a written decision not to perform dialysis was consigned in the chart. Variables collected were: age, gender, ethnicity, social support, time of referral, year of referral, use of erythropoietin, Karnofsky performance status, anthropometric measures and body mass index, etiology of ESRD, presence or absence of seven major comorbid conditions associated with dialysis (neoplasia, ischemic heart disease, congestive heart failure, dysrhythmia, peripheral vascular disease, diabetes, history of stroke, or overt dementia), and several laboratory parameters. For patients on dialysis, we also recorded the type of vascular access and if dialysis was started on emergency (unplanned) or not.

Ethnicity was either defined as White or non-White. Social isolation was defined by the fact of living alone. Late referral (LR) was defined as referral to our nephrology unit less than 4 mo before index date. The Karnofsky performance score (KPS) was determined using the full ten-point scale (range, 10 to 100). For bivariate and multivariate analysis purpose, the KPS was stratified in three functional classes: $\geq$ 80 (patients with normal activity), 50 to 70 (patients requiring assistance), and $\leq$ 40 (dependent patients, or requiring institutional or hospital care). Body mass index (BMI) was defined as the ratio of weight to height squared. Diagnosis of neoplasia (actual or past) excluded basal and squamous cell carcinoma of the skin. Ischemic heart disease was defined by either (a) coronary artery disease (documented by coronary angiogram, angina pectoris associated with ischemic ECG changes, or ischemic scintigraphic changes during a stress test) or (b) myocardial infarction (documented by history, Q-waves at ECG, specific area changes at echocardiography, or myocardial scintigraphy). Congestive heart failure definition included episode(s) of pulmonary edema, echocardiographic systolic dysfunction, cardiomegaly documented by echocardiography, or chest x-ray. Peripheral vascular disease definition included claudication with absent pulses or history of amputation. Patients were classified into three groups according to their total number of comorbid conditions: no comorbidity (0), moderate comorbidity (1 to 2), heavy comorbidity ($\geq$ 3 comorbid conditions). Laboratory measurements presented in this study (hemoglobin, serum potassium, serum phosphate, serum bicarbonate) were performed in our hospital by use of automated methods. Throughout the study period, clinical and biologic data at index date were collected by two permanent investigators on a weekly basis and computed in our clinical database. Date of death or latest news were recorded once a year (in April, until April 2001) by four investigators; two investigators reviewed each death independently and assigned an underlying cause. Survival duration was measured as the number of months from index date until death or latest news.

Statistical Analyses

Results are expressed as numerical values and percentages for categorical variables and as a means ($\pm$ SD) for continuous variables. Comparisons of baseline characteristics between groups 1 and 2 were based on the χ^2 test for categorical data and *t* test for continuous data. Survival curves from date of inclusion to last news were computed using the life-table method. Because proportional hazard assumptions were not satisfied for most of the variables, a piecewise Cox model was fit to study the relationship between patient characteristics (gender, age at inclusion, Karnofsky score, body mass index, need for dialysis catheter, late referral, coronary artery disease, congestive heart failure, peripheral vascular disease) and survival. After looking at survival curves, the observation period was broken up into two periods (0 to 12 mo and more than 12 mo). Model selection used a stepwise backward-forward procedure. Results were expressed at the last step as hazard ratio (HR) and 95% confidence interval (95% CI). Predictions about survival time for particular sets of covariate values were computed and plotted on a graph. All tests were two-sided. Confidence intervals were given with a type I risk error of 5%. Statistical analysis was performed using the SAS 8.0 (SAS Inc, Cary, NC) software package for PC computer.

Results

Patients Studied and Treatment Choice

During the 12-yr observation period, 146 incident octogenarians with chronic renal failure and calculated creatinine clearance <10 ml/mn per 1.73 m^2 were followed at our unit. Two patients, who died before any therapeutic decision could be made, were not included. Demographic and medical characteristics of the remaining 144 patients included in the study are shown on Table 1 as a function of the intention to propose dialysis or not. The medical team recommended dialysis therapy in 107 cases (group 1) and not to perform dialysis but to follow conservative measures in 37 cases (group 2). We cared for an increasing number of octogenarian ESRD patients over time (1989 to 1992, $n = 34$; 1993 to 1996, $n = 48$; 1997 to 2000, $n = 62$); whereas the clinical characteristics of the patients were comparable in these three "vintages," the proportion of the patients accepted on dialysis increased with time, although not significantly (1989 to 1992, 61.8%; 1993 to 1996, 79.2%; 1997 to 2000, 77.4%; $P = 0.15$). Patients in group 2 had a slightly lower Karnofsky score (55 ± 18 *versus* 63 ± 20; $P = 0.03$) and were more likely to be socially isolated ($P = 0.03$), to have been referred late ($P = 0.014$), or to have diabetes mellitus ($P = 0.008$). Although the differences did not reach statistical significance, the female gender seemed to be overrepresented in group 2 ($P = 0.07$). Except for diabetes, the prevalence of major comorbid conditions did not differ between the two groups. The causes of ESRD were comparable in the two groups. Of note, three of the four patients with polycystic kidneys had a very low functional capacity (KPS < 40) and were not recommended dialysis. The main biologic consequences of chronic renal failure at inclusion, *i.e.*, anemia or electrolytic disorders, were not worse for patients in group 2; their calculated creatinine clearance was even slightly higher than that of patients in group 1 (7.6 ± 1 *versus* 6.5 ± 1.9 ml/mn per 1.73 m^2; $P < 0.01$).

Fate of Octogenarians Treated by Dialysis or Conservative Measures

Although they were offered dialysis therapy, six patients decided not to enter the dialysis program and were submitted to conservative measures and regular follow-up similar to group 2 patients. Two patients in the conservative group received one and three ultrafiltration sessions respectively for an acute fluid overload episode but were not entered on chronic dialysis. Therefore, survival analyses based on effective treatments bear on 101 dialyzed (dialysis group) and 43 nondialyzed patients (conservative group). No patient was lost to follow-up; two patients moved to other regions, but information was obtained via communication with the regions' renal units. Figure 1 shows the unadjusted survival curves by effective treatment of renal failure. Median survival was 28.9 mo (95% CI, 24 to 38) in the dialysis group and 8.9 mo (95% CI, 4 to 10) in the conservative group ($P < 0.0001$). The 12 and 24-mo survival rates were 73.6% and 60% in patients treated by dialysis, *versus* 29% and 15% for patients treated conservatively. By the end of the study, 61 (60.4%) of 101 patients in the dialysis group and 38 (88.4%) of 43 patients in the conservative group had died. Causes of death are listed in Table 2.

Prognostic Factors Associated with Survival in Octogenarians Treated with Dialysis

Figure 2 shows the actuarial survival curves for six categorical variables in the cohort of patients treated by hemodialysis. The survival curves for the two gender groups suggested a higher female mortality during the first 2 yr of dialysis therapy and a lower mortality thereafter (Figure 2a). The difference in survival was significant ($P = 0.03$) between dependent patients (Karnofsky score ≤ 40) and patients only requiring assistance or carrying normal activity (Karnofsky score 50 to 70 or ≥ 80) (Figure 2b). Figure 2c shows survival with respect to referral. The two survival curves did not become parallel until after the first year, suggesting a short-term negative impact of late referral. Inversely, the negative effect of peripheral vascular disease on overall survival ($P = 0.055$) became obvious after 18 mo of dialysis therapy (Figure 2d). Figures 2e and 2f show that the presence of overt ischemic heart disease or chronic cardiac failure did not have a major effect on survival.

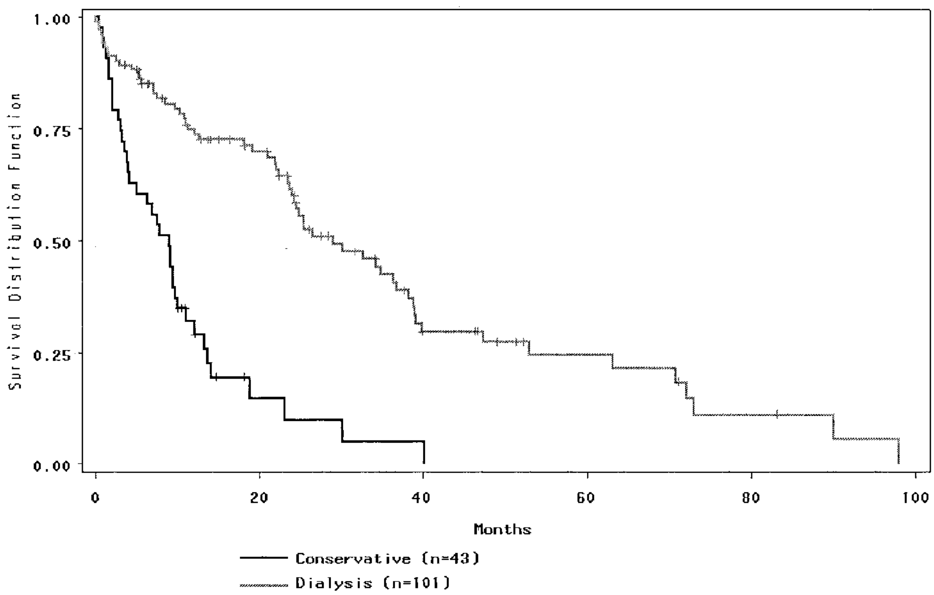
As these results suggested a non-proportionality of risks over time, we constructed a piecewise Cox proportional hazards model to identify factors predicting mortality before and after the first year of dialysis. Bivariate analysis showed a negative effect on 12-mo survival of female gender, older age, late referral, central vein catheter use, decreasing KPS or KPS < 40 (functional dependence), whereas higher BMI exerted a protective effect (all $P < 0.05$; Table 3). Of note, to fit with linearity assumption, KPS was thereafter expressed only as a 3-class nominal variable. Beyond 12 mo of dialysis therapy, survival was negatively influenced by the presence of peripheral vascular disease and by the presence of more than three comorbid conditions, whereas female gender exerted a protective effect. We found no significant effect on survival of year of referral, ischemic heart disease, cardiac failure, dysrhythmia, cerebrovascular disease, dementia, or cancer. We then evaluated the joint impact of age, gender, need for dialysis catheter, late referral, BMI, functional dependence, peripheral vascular disease, and heavy comorbidity on survival using a piecewise Cox regression multivariable analysis. Cox models tested were limited to six potential predictors. After stepwise regression, age, gender, need for dialysis catheter, and heavy comorbidity could be excluded; thus, our multivariable model was finally reduced to four independent predictors of survival in this population (Table 3). Preserved nutritional status was an important protective factor during the first year of dialysis in this model, with a hazard ratio of 0.83, suggesting a reduction of 17% in the risk of death with each BMI 1-point increase. During the same time period, the increase in mortality was 2.28 for late referral and 2.34 for functional dependence. Beyond the first year of dialysis, the increase in mortality was 5.67 for patients with peripheral vascular disease. Figure 3 shows 1-yr

Table 1. Patient characteristics by intention to propose dialysis (group 1) or conservative measures (group 2)[a]

	Group 1 (n = 107) n (%) or mean ± SD	Group 2 (n = 37) n (%) or mean ± SD	P
Inclusion period			
1989 to 1992	21 (61.8)	13 (38.2)	
1993 to 1996	38 (79.2)	10 (20.8)	.15
1997 to 2000	48 (77.4)	14 (22.6)	
Demography			
age (yr)	83.2 ± 2.9	84.1 ± 2.9	.12
male gender, %	59 (55.1)	14 (37.8)	.07
ethnic minority, %	6 (5.6)	5 (13.5)	.12
socially isolated, %	15 (14.7)	16 (43.3)	.003
Clinical			
late referral (<4 mo)	31 (28.9)	19 (51.4)	.014
EPO use before inclusion	24 (22)	8 (23.2)	.9
Karnofsky score[b]	63 ± 20	55 ± 18	.03
body mass index (kg/m^2)[c]	21.8 ± 3.3	21.3 ± 3	.5
Etiology of ESRD			
vascular disease[d]	63 (58.9)	22 (59.5)	
interstitial/obstructive nephropathy	21 (19.6)	4 (10.8)	
diabetic nephropathy	5 (4.7)	4 (10.8)	
other chronic glomerulopathy	8 (7.5)	2 (5.4)	.27
multiple myeloma	5 (4.7)	1 (2.7)	
other systemic disease	3 (2.8)	1 (2.7)	
polycystic kidney disease	1 (.9)	3 (8.1)	
nephrectomy	1 (.9)	0 (0)	
Comorbid conditions			
malignancy (actual or past)	13 (12.2)	5 (13.5)	.8
ischemic heart disease	45 (42)	18 (48.6)	.48
cardiac failure	43 (40.2)	19 (51.4)	.24
dysrhythmia	26 (24.3)	10 (27)	.74
peripheral vascular disease	23 (21.5)	8 (21.6)	.98
sequelae of stroke and/or overt dementia	13 (12.2)/6 (5.6)	8 (21.6)/3 (8.1)	.3/.6
diabetes	7 (6.5)	8 (21.6)	.008
Sum of comorbid conditions			
0	26 (24.3)	7 (18.9)	
1 to 2	59 (55.1)	18 (48.7)	.33
≥3	22 (20.6)	12 (32.4)	
Laboratory tests			
hemoglobin (g/dl)	9.7 ± 1.5	9.6 ± 1.5	.93
serum potassium (mmol/L)	4.5 ± 0.7	4.4 ± 0.7	.74
serum phosphate (mmol/L)	1.9 ± 0.5	1.6 ± 0.4	.013
serum bicarbonate (mmol/L)	22.2 ± 5.2	22.3 ± 3.1	.96

[a] EPO indicates recombinant erythropoietin; ESRD, end-stage renal disease.
[b] Data obtained for a subset of the study group (n = 135).
[c] Excluding hydration problems of ESRD.
[d] Presumptive diagnosis in most cases, in patients with a history of long-standing hypertension, bilateral small kidneys ± renal artery stenosis, mild or absent proteinuria, blank urinary sediment and no other obvious cause of nephropathy.

survival curves predicted by three significant covariates in the 12-mo multivariate model, *i.e.* BMI, time to referral, and functional dependence. According to this predictive model, 1-yr mortality probability would be 15% in a low-risk group (octogenarians referred early, with BMI = 22 and Karnofsky score > 40 at the time of dialysis initiation), and as high as 83% in a high-risk group (patients referred late, BMI = 18 and Karnofsky score ≤ 40).



Month	0	12	24	36	48	60	72	84	96
Conservative treatment									
N patients at risk	43	10	3	1	0				
N cumulated event	0	30	34	36	37				
Dialysis treatment									
N patients at risk	101	63	42	29	12	8	6	4	1
N cumulated event	0	25	35	43	54	55	57	58	60

Figure 1. Kaplan-Meier survival curves for patients undergoing dialysis or conservative treatment. Each step represents one death. Number of patients remaining in analysis at each time point are indicated. Vertical bars indicate censored data.

Table 2. Causes of death

	Dialysis	Conservative
Number of deaths (%)	61 (60.4)	38 (88.4)
Identified acute vascular event	20 (32.8)	8 (21)
Cancer	12 (19.7)	2 (5.3)
Withdrawal from dialysis or *uremia	10 (16.4)	*13 (34.2)
Cardiac failure/pulmonary edema	6 (9.8)	9 (23.7)
Sudden death	7 (11.5)	3 (7.9)
Infection	2 (3.3)	2 (5.3)
Other (suicide, bleeding, iatrogenic event)	4 (6.6)	1 (2.6)

Discussion

Very few studies specifically evaluated indications and results of maintenance dialysis in elderly patients, and their conclusions are rather discordant (2,7–17). Moreover, in all published studies, only patients who actually started dialysis were considered, whereas no indication was given about those who reached ESRD but were not referred to a nephrology unit or were withheld from maintenance therapy, although there is no formal barrier based on age for accepting older ESRD patients on a dialysis program in any Western country (7,8,13,15,18). This cohort of 146 consecutive patients, aged 80 yr or more when reaching ESRD, represents the largest single-center series of octogenarian uremic patients to date. It is unique in providing data on characteristics and outcome of contemporaneous ESRD patients who were not proposed to enter a dialysis program and who were treated conservatively. All patients, dialyzed or not, benefited from an homogeneous management policy over the entire study period, and most information was recorded prospectively, enabling a satisfactory completion of the data. At this point, we must outline several age- and location-related specific characteristics of this ESRD cohort (depicted in Table 1). The high proportion of White patients and the absence of male predominance may reflect both the specificity of patient pool in our area and some survival advantage for female patients in this age group (7,10). However, ethnicity- or gender-related differences in primary care management and access to nephrologic referral cannot be excluded. The low proportion of diabetes in this age segment (3) may reflect a survival disadvantage of diabetes over other illnesses leading to ESRD, such as hypertensive nephrosclerosis (which accounted here for nearly one half of renal diseases), or a reluctance of family physicians to refer diabetic patients with high comorbidity. Moreover, frequent nonreferral of pre-ESRD octogenarians to nephrologists has been suggested by surveys conducted in Canada and Europe (19,20). Patient se-

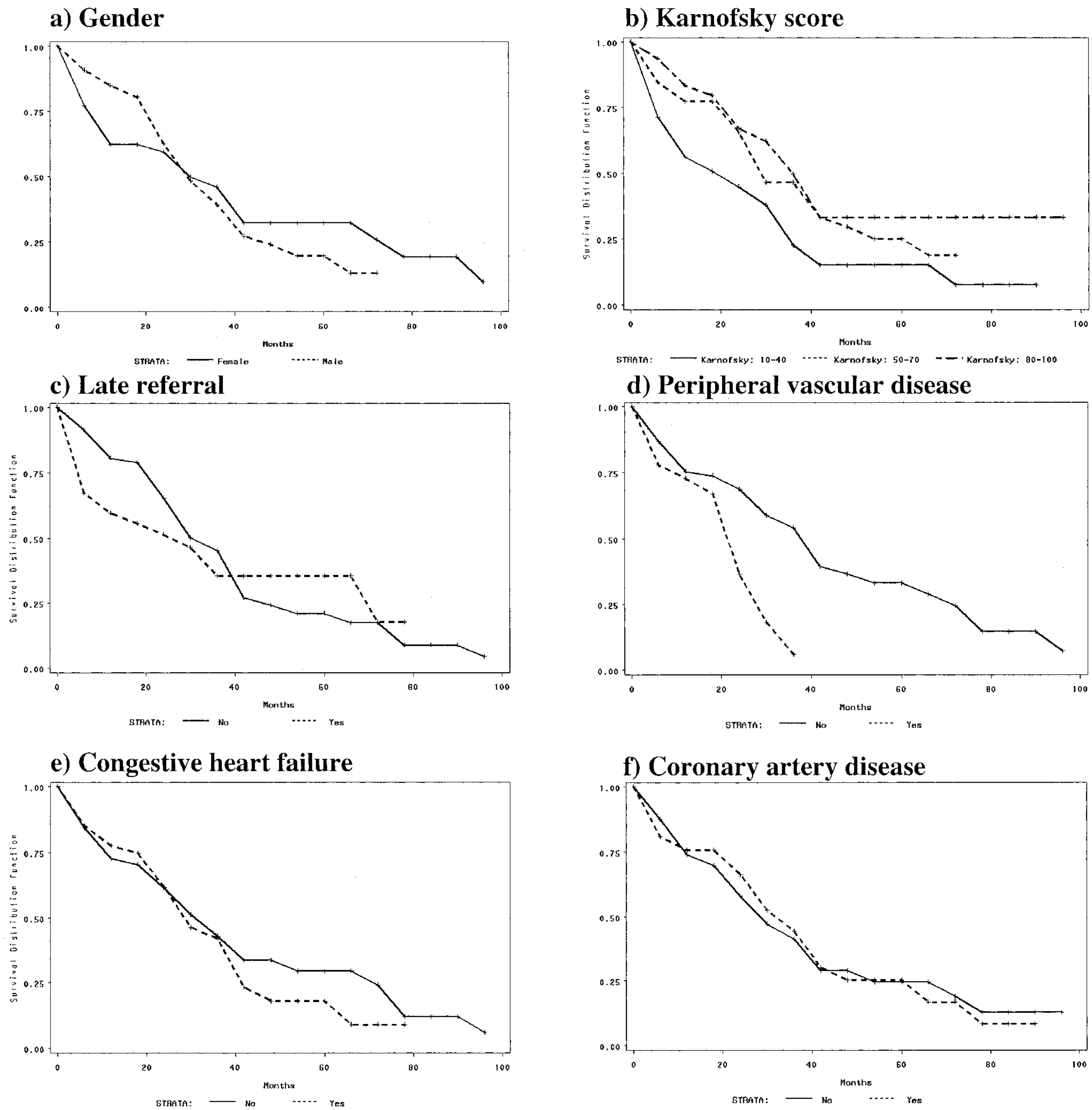


Figure 2. Actuarial survival curves in the group of hemodialyzed patients according to characteristics at inclusion. (a) Effect of gender on survival. (b) Survival in three groups defined by Karnofsky performance scale. (c) Effect of late referral. (e) Effect of peripheral vascular disease. (f) Effect of coronary artery disease. (g) Effect of cardiac failure.

lection that may have occurred at the primary care level (*i.e.*, deciding who to refer to a nephrologist) is an important limitation in generalizing the results reported in this study. Thus, our findings cannot be generalized to all pre-ESRD octogenarians and should be restricted to octogenarians referred to the nephrologist.

In the modern era, there is limited published material of withholding dialysis from ESRD patients (21). However, this practice may indeed be quite common in Western countries, despite the absence of resource rationing (22). Following the Institute of Medicine's Committee for the study of the Medicare ESRD Program recommendations (23), the Renal Physicians Association (RPA) and the American Society of Nephrology (ASN) organized a working group and recently proposed guidelines for the Shared Decision-Making in the Appropriate Initiation of and Withdrawal from Dialysis (5,24). Decision-making applied to pre-ESRD octogenarians in our center frequently led to withholding dialysis (43 [29.8%] of 144 cases). In our practical experience however, this process was more asymmetrical than shared. The decision to withhold dialysis

Table 3. Bivariable and multivariable piecewise Cox proportional hazards model for mortality predictors during the first year of dialysis or thereafter

Variable	Number at Risk or Median (range)	Bivariate Analysis		Multivariable Analysis	
		0 to 12 mo HR[a] (95% CI)	>12 mo HR[a] (95% CI)	0 to 12 mo HR[a] (95% CI)	>12 mo HR[a] (95% CI)
Gender					
male	56	1	1		
female	45	2.56 (1.13 to 5.79)[b]	0.43 (0.20 to 0.91)[b]		
Age at inclusion (yr)	83 (80 to 94)	1.13 (1.01 to 1.27)[b]	1.00 (0.88 to 1.15)		
Year of referral (1989 to 2000)	1996	0.98 (0.89 to 1.08)	0.95 (0.87 to 1.03)		
Karnofsky score (full scale)	70 (10 to 100)	0.97 (0.95 to 0.99)[c]	0.99 (0.97 to 1.01)		
Karnofsky functional class					
100 to 80 (normal activity)	32	1	1	1	1
70 to 50 (require assistance)	47	1.28 (0.47 to 3.53)	1.53 (0.66 to 3.54)	1	1
40 to 10 (dependent patients)	22	2.96 (1.05 to 8.33)[b]	1.83 (0.68 to 4.92)	2.34 (1.00 to 5.50)[b]	1.00 (0.42 to 2.36)
BMI (per kg/m^2)	21.5 (13 to 33.6)	0.84 (0.74 to 0.96)[c]	1.04 (0.95 to 1.14)	0.83 (0.73 to 0.95)[c]	1.00 (0.91 to 1.10)
Need for dialysis catheter	41	2.87 (1.29 to 6.39)[c]	0.59 (0.27 to 1.28)		
Unplanned first dialysis	35	1.96 (0.89 to 4.29)	0.74 (0.35 to 1.56)		
Late referral	28	2.45 (1.11 to 5.40)[b]	0.60 (0.25 to 1.46)	2.28 (1.02 to 5.11)[b]	0.68 (0.26 to 1.77)
Ischemic heart disease	43	0.96 (0.43 to 2.13)	1.05 (0.54 to 2.04)		
Congestive heart failure	41	0.75 (0.33 to 1.70)	1.59 (0.80 to 3.14)		
Peripheral vascular disease	23	1.15 (0.46 to 2.87)	5.91 (2.73 to 12.83)[d]	1.03 (0.40 to 2.67)	5.67 (2.45 to 13.11)[d]
Sum of comorbid conditions[e]					
0	24	1	1		
1 to 2	53	0.71 (0.27 to 1.82)	1.68 (0.70 to 4.02)		
≥3	24	1.10 (0.38 to 3.11)	3.73 (1.28 to 10.91)[b]		

[a] HR, hazards ratio, related to 1-yr increment for age or year of referral, to 1-kg/m^2 increment for BMI (body mass index), or to 1-point increment in Karnofsky score (full scale); CI, confidence interval.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.001$.
[e] Refers to the number of comorbid conditions (listed in Table 1).

emerged from exclusive patient refusal in only rare circumstances (6 [14%] of 43). In most cases, the decision to withhold dialysis was taken by the Nephrology team (37 [86%] 43 cases); this recommendation —always exposed to and understood by patients and/or relatives — was never disputed, and there were no legal difficulties or requests for a second medical opinion. We cannot exclude that patients and/or relatives in this group had a less confrontational nature and/or different expectations regarding dialysis.

In the absence of medical octogenarian-specific, evidence-based indicators of the ability to benefit from dialysis, deciding whether or not to propose dialysis was a difficult task. Mention of terminal malignancy, cachexia, and overt dementia were extremely rare in our cohort, and reasons proposed by the Nephrology team for not offering dialysis were couched in very general terms. On the contrary, three main objective differences emerged when comparing patients who were recommended to receive dialysis with those who were offered conservative treatment, *i.e.*, Karnofsky score, social isolation, and late referral (Table 1). Such differential characteristics may have influenced part of the Nephrology team's decision to propose a conservative treatment. Mean Karnofsky score, which provides a reliable measure of global health status and physical disability, was slightly reduced in patients withheld dialysis. Some other factors frequently correlated with KPS (such as mental quality of life and cognitive status, economic and educational levels) were not formally assessed in this cohort but may well have played a role in the process of decision-making. Living alone may well have been associated with a dismal mental perception of the quality of life, with subsequent shared (medical and patient) unwillingness to extend one's lifespan; on the other hand, the presence of dedicated spouse or relatives may have oriented our decision to starting dialysis in some patients with poor prognosis. Late referral may also have oriented our choice toward a conservative treatment. The definition of late referral is arbitrary and varied among authors (1 d, 1, 3 or 4 mo). With the definition used in this study (<4 mo), many factors may have oriented our choice toward dialysis withholding, including expected greater morbidity and mortality, unplanned emergency workload, and maybe less compassion; it is also possible that decision to perform dialysis in patients referred early (>4 mo) was made and maintained despite late comorbid events or a late reduction in functional capacity. Surprisingly, the burden of most comorbid conditions was comparable in the two groups, suggesting that comorbidity *per se* was either not taken into account for decision-making or appreciated more pejoratively in the context of low functional score, late referral, or social isolation. However, these suppositions cannot justify herein the decisions that were made; our data mainly indicate that withholding dialysis in octogenarians was frequent in our center and that exclusion criteria for dialysis in the absence of formal

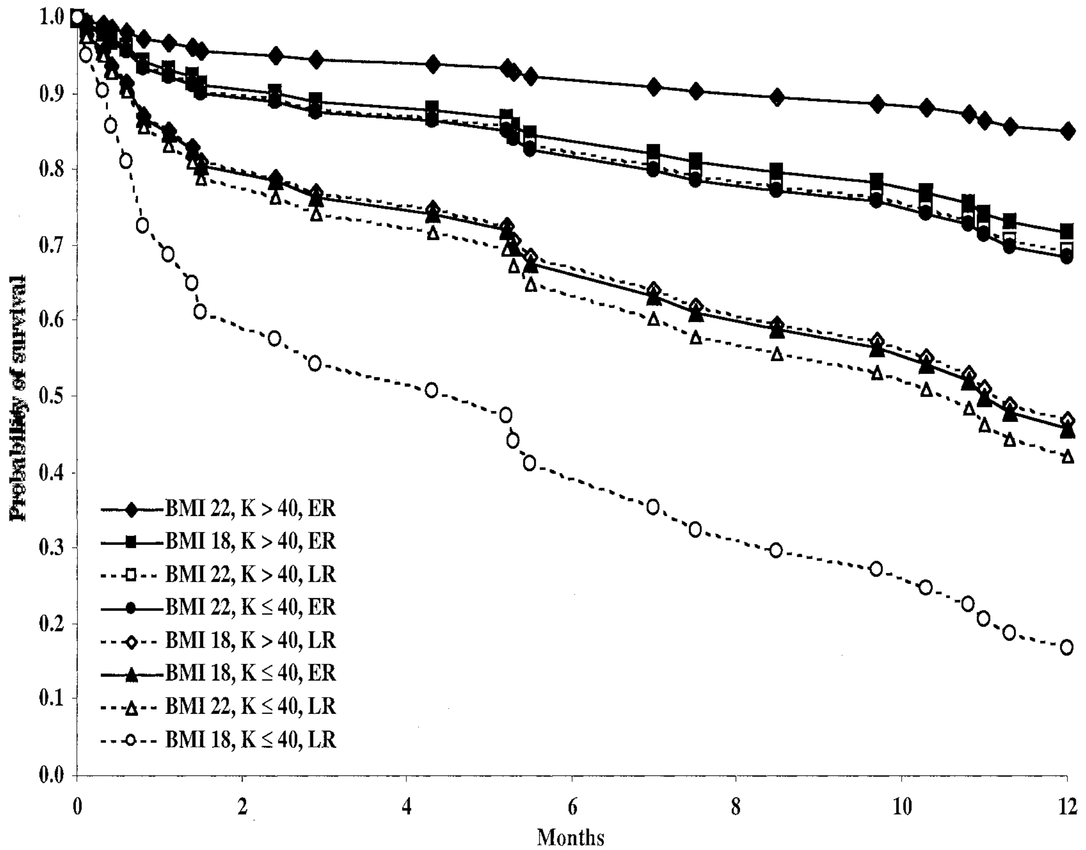


Figure 3. Survivor function estimate from month 0 to month 12 depending on covariate values. BMI, body mass index (18 or 22 kg/m^2); K, Karnofsky score; ER, early referral (>4 mo); LR, late referral (<4 mo).

guidelines remained elusive in most cases. We also realize that marked differences may exist between countries regarding the rate of elderly patients acceptance on dialysis. It is likely, for example, that the proportion of octogenarians not offered dialysis in the US is not as high as in our study. This may reflect differences in organization of health care and medical practice, but also in patient expectations. Thus, our results cannot be generalized to other countries, where acceptance rates on dialysis may be different.

As expected, the survival of patients treated conservatively was markedly shorter than survival of patients accepted on the dialysis program (Figure 1). Of note, nearly 60% of deaths in the conservative group were attributed to uremia or pulmonary edema (Table 2), suggesting that dialysis therapy, if initiated, would have prolonged life to some unpredictable extent. In octogenarian patients accepted on the dialysis program, median survival was 28.9 mo (95% CI, 24 to 38), which favorably compares with the results recently reported in several cohorts of elderly patients treated with hemodialysis (7–10) or peritoneal dialysis (2,11,12). Such outcomes are much more encouraging than those recorded in other reports (13–17). The reasons for such discrepancy remain unclear, but, at least in Europe, an independent "center effect" may account for significant differences in survival among dialysis patients (25). However, it must be kept in mind that differences between countries regarding primary care referral policy and acceptance rate on dialysis, almost never reported, may account for part of the observed survival differences. Finally, the 2.4-yr life expectancy offered to our dialyzed octogenarians represents about one quarter to one third of the life expectancy in the general population over 80 yr of age reported by the French National Institute of Statistics and Economic Studies INSEE (26). As in other reported series, causes of death in our patients were mainly cardiovascular in origin, but were also frequently due to malignancy or dialysis withdrawal (7,14).

According to RPA/ASN guidelines, pre-ESRD patients, and/or their families should receive full information about their vital prognosis before entering the process of sharing in the decision as whether to begin dialysis or not (24). However, these guidelines do not provide specific reliable means for making an overall prognosis estimate in octogenarians (5). Among our octogenarian patients, the negative impact of increasing age (+13% increase per year in 1-yr mortality) was outweighed by other identified prognostic factors, further indicating that age by itself should not be a barrier to nephrologic referral or dialysis therapy (15). In this cohort, we found that the prognostic factors influencing short-term and long-term survival were not the same (Table 3), suggesting nonproportionality of risks over time. We found that KPS, BMI, and time to nephrologic referral at index date were major predictors of 1-yr survival in octogenarians on dialysis, a conclusion reached by other authors in cohort studies composed mainly of younger patients (13,15,27,28). These factors' impact on survival was limited to the first year on dialysis and was not maintained thereafter. However, KPS and/or BMI changes after dialysis initiation were not measured in our cohort; the impact of these additional time-dependent covariates on >1 yr survival should be addressed by future studies. Surprisingly, neither individual comorbidities (including diabetes) nor a simple comorbidity score influenced 1-yr survival. Using a different assessment of comorbidity (*i.e.*, taking severity and not just number of comorbid conditions into account) may have yielded different results. Of note, by using a different definition of late referral (1 mo) in this cohort, this variable was no more statistically predictive of 1-yr survival. This variation may reflect either a loss of statistical power due to the diminution of at-risk patients ($n = 19$) or a real difference between being referred >1 or >4 mo before dialysis initiation. This question will be ideally resolved by future studies, comprising larger cohorts.

Our simple comorbidity assessment did not mask the strong negative prognostic influence of peripheral vascular disease (PVD) and high comorbidity score on long-term survival (more than year on dialysis). Interestingly, PVD alone accounted for 50% of the variance of the comorbidity score, and being more closely related than the latest to >1-yr survival, was kept in the final multivariate model (Table 3). The strong impact of PVD on survival has been outlined by other studies in younger dialysis patients as well as in the general population (15,29,30). It is also possible that other comorbid conditions (mostly cardiovascular and neoplastic) progressively worsened after dialysis initiation, resulting ultimately in delayed mortality.

Finally, our opinion is that the most convenient way to provide prognosis information to patients and/or families when discussing inclusion or exclusion for dialysis is risk classification related to 1-yr survival. However, the two main available risk categorization protocols for dialysis patients were not specifically designed for octogenarians (13,31). Application of the criteria proposed by Khan *et al.* (31) to our cohort, for example, would lead to inclusion of all patients in a high-risk group, *i.e.*, a 1-yr survival rate of 73.6%. Our predictive model (Figure 3), based on three simple covariates (BMI, time to referral, Karnofsky score), delineates several groups, including a low-risk group (1-yr survival probability, 85%) and a high-risk group (1-yr survival probability, 18%). We currently use the above risk classification curves related to 1-yr survival for individual assessment of survival probability on dialysis among pre-ESRD octogenarians, with adjustment when the patient's calculated BMI is different from 18 or 22. Our opinion is not to systematically withhold dialysis in all high-risk patients, whose benefit would be debatable because expected financial savings would be minimal, and such an attitude would sacrifice some long-term survivors (13). Rather, we hope that a precise estimation of the expected prolongation of life will help physicians and patients make the appropriate decisions. In addition to life duration, most elderly patients, and their families and physicians as well, wish to consider the predictable quality of life before expressing their decision regarding dialysis. Our study does not provide data on this issue, but a formal assessment of the quality of life using the SF 36 questionnaire was used in a prospective cohort study in ESRD patients aged ≥70 yr on dialysis in the London area (15). Surprisingly, the scores of mental quality of life in incident and prevalent elderly patients on dialysis were not significantly different from those of elderly people in the general UK or US populations, whereas scores of physical quality of life were significantly lower. However, specific data on octogenarians and criteria predicting an improved or reduced quality of life after dialysis initiation are not available at the moment and will require further investigation. When undecided patients pose this question, we feel that a time-limited dialysis trial should be proposed.

Identification of social isolation and late referral as baseline characteristics of patients who were not offered dialysis suggest that, besides physicians and patients, an involvement of social workers and primary healthcare professionals may optimize the decision-making process in elderly ERSD patients. Interventions by social workers to minimize the consequences of social isolation could help physicians and patients consider prolongation of life differently. The education of primary healthcare professionals regarding the importance of early referral of elderly patients with renal disease could, as suggested by our data, both influence decision-making toward offering dialysis and positively influence outcome after dialysis initiation. We also hope that encouraging median survival reported in this study will minimize non-referral of pre-ESRD octogenarians to nephrologists.

References

1. Wright LF: Survival in patients with end-stage renal disease. *Am J Kidney Dis* 17: 25–28, 1991
2. Dimkovic N, Oreopoulos DG: Chronic peritoneal dialysis in the elderly: A review. *Perit Dial Int* 20: 276–283, 2000
3. Jungers P, Choukroun G, Robino C, Massy ZA, Taupin P, Labrunie M, Man NK, Landais P: Epidemiology of end-stage renal disease in the Ile-de-France area: A prospective study in 1998. *Nephrol Dial Transplant* 15: 2000–2006, 2000
4. Stack AG, Messana JM: Renal replacement therapy in the elderly: Medical, ethical, and psychosocial considerations. *Adv Ren Replace Ther* 7: 52–62, 2000
5. Moss AH: Shared decision-making in dialysis: The new RPA/ASN guideline on appropriate initiation and withdrawal of treatment. *Am J Kidney Dis* 37: 1081–1091, 2001
6. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
7. Peri UN, Fenves AZ, Middleton JP: Improving survival of octogenarian patients selected for haemodialysis. *Nephrol Dial Transplant* 16: 2201–2206, 2001
8. Schaefer K, Rohrich B: The dilemma of renal replacement therapy in patients over 80 years of age. Dialysis should not be withheld. *Nephrol Dial Transplant* 14: 35–36, 1999
9. Vandelli L, Medici G, Perrone S, Lusvarghi E: Haemodialysis therapy in the elderly. *Nephrol Dial Transplant* 11: 89–94, 1996
10. Neves PL, Sousa A, Bernardo I, Anunciada AI, Pinto I, Bexiga I, Aniceto J, Amorim JP: Chronic haemodialysis for very old patients. *Age Ageing* 23: 356–359, 1994
11. Issad B, Benevent D, Allouache M, Durand PY, Aguilera D, Milongo R, Dubot P, Lavaud S, Gary J: 213 elderly uremic patients over 75 years of age treated with long-term peritoneal dialysis: A French multicenter study. *Perit Dial Int* 16: S414–S418, 1996

12. Vrtovsnik F, Porcher R, Michel C, Hufnagel G, Queffeulou G, Mentre F, Mignon F: Survival of elderly patients on peritoneal dialysis: Retrospective study of 292 patients, from 1982 to 1999. *Perit Dial Int* 22: 73–81, 2002
13. Chandna SM, Schulz J, Lawrence C, Greenwood RN, Farrington K: Is there a rationale for rationing chronic dialysis? A hospital based cohort study of factors affecting survival and morbidity. *Bmj* 318: 217–223, 1999
14. Munshi SK, Vijayakumar N, Taub NA, Bhullar H, Lo TC, Warwick G: Outcome of renal replacement therapy in the very elderly. *Nephrol Dial Transplant* 16: 128–133, 2001
15. Lamping DL, Constantinovici N, Roderick P, Normand C, Henderson L, Harris S, Brown E, Gruen R, Victor C: Clinical outcomes, quality of life, and costs in the North Thames Dialysis Study of elderly people on dialysis: A prospective cohort study. *Lancet* 356: 1543–1550, 2000
16. V: Patient mortality and survival in ESRD. *Am J Kidney Dis* 34: S74–S86, 1999
17. Byrne C, Vernon P, Cohen JJ: Effect of age and diagnosis on survival of older patients beginning chronic dialysis. *Jama* 271: 34–36, 1994
18. Mallick N, El Marasi A: Dialysis in the elderly, to treat or not to treat? *Nephrol Dial Transplant* 14: 37–39, 1999
19. Mendelssohn DC, Kua BT, Singer PA: Referral for dialysis in Ontario. *Arch Intern Med* 155: 2473–2478, 1995
20. Parry RG, Crowe A, Stevens JM, Mason JC, Roderick P: Referral of elderly patients with severe renal failure: Questionnaire survey of physicians. *BMJ* 313: 466, 1996
21. Hirsch DJ, West ML, Cohen AD, Jindal KK: Experience with not offering dialysis to patients with a poor prognosis. *Am J Kidney Dis* 23: 463–466, 1994
22. Lowance DC: Factors and guidelines to be considered in offering treatment to patients with end-stage renal disease: A personal opinion. *Am J Kidney Dis* 21: 679–683, 1993
23. Cassel CK, Moss AH, Retting RA, Lewinski NG: Ethical issues, in *Kidney Failure and the Federal Government*, edited by Retting RA, Lewinski NG, Washington, National Academy Press, 1991, pp 51–61
24. Nephrology RPAaASo. Shared Decision Making in the Appropriate Initiation of and Withdrawal from Dialysis. Clinical Practice Guideline Number 2, Rockville, Renal Physician Association, 2000
25. Khan IH, Campbell MK, Cantarovich D, Catto GR, Delcroix C, Edward N, Fontenaille C, Fleming LW, Gerlag PG, van Hamersvelt HW, Henderson IS, Koene RA, Papadimitriou M, Ritz E, Russell IT, Stier E, Tsakiris D, MacLeod AM: Survival on renal replacement therapy in Europe: is there a 'centre effect'? *Nephrol Dial Transplant* 11: 300–307, 1996
26. Institut National d'Etudes Demographiques (INED). Life tables 1996–1998, INSEE source. Available at http://www.ined.fr/englishversion/figures/france/index.html
27. Chauveau P, Combe C, Laville M, Fouque D, Azar R, Cano N, Canaud B, Roth H, Leverve X, Aparicio M: Factors influencing survival in hemodialysis patients aged older than 75 years: 2.5-year outcome study. *Am J Kidney Dis* 37: 997–1003, 2001
28. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag MJ, Levey AS, Powe NR: The timing of specialist evaluation in chronic kidney disease and mortality. *Ann Intern Med* 137: 479–486, 2002
29. Johnson JG, Gore SM, Firth J: The effect of age, diabetes, and other comorbidity on the survival of patients on dialysis: a systematic quantitative overview of the literature. *Nephrol Dial Transplant* 14: 2156–2164, 1999
30. Leng GC, Lee AJ, Fowkes FG, Whiteman M, Dunbar J, Housley E, Ruckley CV: Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 25: 1172–1181, 1996
31. Khan IH, Catto GR, Edward N, Fleming LW, Henderson IS, MacLeod AM: Influence of coexisting disease on survival on renal-replacement therapy. *Lancet* 341: 415–418, 1993

See related editorial, "Geriatric Nephrology Is Coming of Age," on pages 1099–1101.