Efficacy and Safety of a Very-Low-Protein Diet When Postponing Dialysis in the Elderly: A Prospective Randomized Multicenter Controlled Study

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Background: A supplemented very-low-protein diet (sVLPD) seems to be safe when postponing dialysis therapy.

Study Design: Prospective multicenter randomized controlled study designed to assess the noninferiority of diet versus dialysis in 1-year mortality assessed by using intention-to-treat and per-protocol analysis.

Setting & Participants: Italian uremic patients without diabetes older than 70 years with glomerular filtration rate of 5 to 7 mL/min (0.08 to 0.12 mL/s).

Intervention: Randomization to an sVLPD (diet group) or dialysis. The sVLPD is a vegan diet (35 kcal; proteins, 0.3 g/kg body weight daily) supplemented with keto-analogues, amino acids, and vitamins. Patients following an sVLPD started dialysis therapy in the case of malnutrition, intractable fluid overload, hyperkalemia, or appearance of uremic symptoms.

Outcomes & Measurements: Mortality, hospitalization, and metabolic markers.

Results: 56 patients were randomly assigned to each group, median follow-up was 26.5 months (interquartile range, 40), and patients in the diet group spent a median of 10.7 months (interquartile range, 11) following an sVLPD. Forty patients in the diet group started dialysis treatment because of either fluid overload or hyperkalemia. There were 31 deaths (55%) in the dialysis group and 28 deaths (50%) in the diet group. One-year observed survival rates at intention to treat were 83.7% (95% confidence interval [CI], 74.5 to 94.0) in the dialysis group versus 87.3% (95% CI, 78.9 to 96.5) in the diet group (log-rank test for noninferiority, $P < 0.001$; for superiority, $P = 0.6$): the difference in survival was -3.6% (95% CI, -17 to $+10$; $P = 0.002$). The hazard ratio for hospitalization was 1.50 for the dialysis group (95% CI, 1.11 to 2.01; $P < 0.01$).

Limitations: The unblinded nature of the study, exclusion of patients with diabetes, and incomplete enrollment.

Conclusion: An sVLPD was effective and safe when postponing dialysis treatment in elderly patients without diabetes.

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INDEX WORDS: Dialysis; low-protein diet; vegan diet; hemodialysis; mortality; morbidity; treatment outcome; elderly; peritoneal dialysis.

Editorial, p. 563

Dialysis is a well-established therapy for patients with end-stage renal disease and maintains life in as many as 1,500,000 patients

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worldwide. Nonetheless, evidence is lacking about the glomerular filtration rate (GFR) below which it is mandatory to start maintenance dialysis treatment. Current guidelines suggest a GFR less than 10 mL/min (<0.17 mL/s) per 1.73 m^2 body surface area (BSA), ie, creatinine clearance of 9 to 14 mL/min/1.73 m^2 (0.15 to 0.23 mL/s), as the threshold for starting dialysis treatment. This threshold may be decreased to a minimum value of 6 mL/min (0.10 mL/s) if nutritional status is good, hypertension is controlled, and clinical manifestations of uremia do not appear.[1-4] These suggested GFRs are higher than those used in current clinical practice; ie, 6.2 ± 2.6 mL/min (0.10 ± 0.04 mL/s)[5] or less than 5 mL/min (<0.08 mL/s) in one fourth of patients.[6] Reluctance to start dialysis treatment earlier is based on lack of evidence of better clinical outcome; less than expected dialysis benefits because of treatment complications, and the tremendous increase in cost. About 50% of incident dialysis patients are older than 65 years,[7] and they often have comorbidities that impair intradialytic cardiovascular stability and reduce the likelihood of maintaining a well-functioning dialysis vascular access, both of which increase morbidity in dialyzed patients.

A very-low-protein diet supplemented with essential amino acids and keto-analogues (sVLPD) can be well tolerated and may avoid many complications of end-stage renal disease.[8-12] Based on these studies, previous considerations, and encouraging results from our pilot study of the elderly,[13] a prospective randomized multicenter study (Diet Or Dialysis in the Elderly) was designed to define whether the sVLPD could be effective in decreasing uremic symptoms and metabolic disturbances and safe when postponing the start of dialysis treatment in elderly patients with stage 5 chronic kidney disease.[14]

METHODS

Study Protocol

The protocol of this study was published previously.[14] It is a prospective randomized controlled unblinded trial comparing mortality between 2 groups of elderly patients, the first treated with an sVLPD (diet group) and the second receiving maintenance dialysis (dialysis group), to assess at least equivalence (noninferiority) of diet in comparison to dialysis. Randomization was centralized and used closed sealed envelopes. The scheduled enrollment period lasted 18 months, and follow-up was 48 months. At the end of the study, only 112 patients were randomly assigned, instead of the 166 required by the protocol. A possible explanation for incomplete enrollment is the lack of confidence of many physicians with the sVLPD. We decided to perform statistical analysis to verify the null hypothesis of inferiority of diet versus dialysis.

The start of follow-up occurred during the hospitalization scheduled to evaluate the need for initiating dialysis therapy. At that time, the patient's relevant characteristics (age, sex, race, renal disease, and comorbid conditions), medical history, and laboratory data as previously described were recorded.[14] Clinical visits, routine laboratory tests, and charting of adverse events were done every 4 to 5 weeks in patients receiving diet therapy or undergoing long-term peritoneal dialysis (PD). Patients receiving hemodialysis (HD) came to the hospital 3 times per week for dialysis treatment and were checked each time by a physician. All data were sent to the coordinating center in Brescia, Italy, for collation and subsequent analysis.

The hospital admission at the time of randomization was not included in the analysis of hospitalization rates in either group.

Patients

Patients older than 70 years with a GFR of 5 to 7 mL/min/1.73 m^2 BSA (0.08 to 0.12 mL/s/1.73 m^2 BSA) and cardiac ejection fraction greater than 30% were eligible for inclusion. GFR was calculated as the mean of creatinine clearance and urea clearance in a 24-hour urine collection.[4] Exclusion criteria were acute life-threatening diseases, urine protein excretion greater than 3 g/d, liver failure, human immunodeficiency virus infection, previous episodes of cardiac failure, diabetes mellitus, active malignancy other than basal cell carcinoma, chronic obstructive pulmonary disease requiring supplementary oxygen, and the presence of uremic symptoms. In 9 Italian public hospitals, 112 patients agreed to participate and were randomly assigned to the diet or dialysis group.

Supplemented Very-Low-Protein Diet

The sVLPD is a vegan diet with a calorie intake of 35 kcal/kg of body weight (BW) per day and a protein intake of 0.3 g/kg of BW supplemented for every 5 kg of BW with 1 tablet containing 607 mg of a mixture of the 5 keto-analogues of amino acids and 4 essential amino acids corresponding to 37 mg of nitrogen (Alfa-Kappa; Shire, Florence, Italy). Patients were trained by skilled dieticians to follow the sVLPD. At each visit, patients were given the pills required until the next visit; which was determined by taking into account the number of tablets still available at home, as noted on the patient's chart. Moreover, possible noncompliance with the prescribed diet should have been shown by changes in laboratory test results (eg, blood urea nitrogen [BUN] and serum phosphate levels).

The diet was supplemented every other day with folic acid (5-mg) tablets (Folina; Schwarz Pharma, Monheim, Germany) and a multivitamin tablet containing vitamins B_1 (250 mg), B_6 (250 mg), and B_{12} (500 μg; Benexol B12; Bayer, Leverkusen, Germany). Suggested sodium intake was no

more than 3 g/d. On the basis of a pilot study,[13] patients were allowed to ingest 2 free meals per week to improve their compliance with this very strict diet. Dietary protein intake was estimated from daily urea excretion according to Maroni et al.[15]

Indications for discontinuing the diet and starting dialysis therapy were the occurrence of either symptoms or signs of uremia: fluid overload (peripheral edema, pulmonary edema), uncontrollable hypertension (blood pressure $>$ 170/100 mm Hg), serum potassium level greater than 6.5 mEq/L (>6.5 mmol/L), evidence of malnutrition (serum albumin $<$ 3.0 g/dL [30 g/L], body mass index $<$ 18.5 kg/m^2), loss of appetite, nausea, and pericarditis. The decision to start dialysis treatment was made at the sole discretion of the patient's physician.

Dialysis

Of 56 patients randomly assigned to dialysis, 49 chose maintenance HD and 7 chose PD. All patients who started dialysis therapy, as well as those transferred from diet to dialysis, were trained by dieticians to ingest a diet providing 35 kcal/kg/d and 1.2 g protein/kg/d.

Dialysis dose (Kt/V urea) was calculated according to the Daugirdas second-generation formula for HD[16] and direct measurement of urea in urine and peritoneal effluent for PD. Body water volume was calculated by using Watson's formula.[17] Targets of the dialysis dose were equilibrated Kt/V urea of 1.2 or greater per treatment for HD and Kt/V urea of 2.0 or greater per week for PD according to current guidelines.[18,19]

Medicines

In both groups, antihypertensive medications and diuretics were administered to attain systolic blood pressure less than 140 mm Hg, diastolic blood pressure less than 90 mm Hg, and absence of edema. Sodium bicarbonate was administered orally to maintain venous bicarbonate concentrations at 24 to 26 mEq/L (24 to 26 mmol/L). The dose of recombinant human erythropoietin was scheduled to attain a hemoglobin level of 11 to 12 g/dL (110 to 120 g/L). Phosphate binders, calcium, and vitamin D supplements were administered, when appropriate, to prevent or treat uremic osteodystrophy.

Statistical Analysis

The primary end point is mortality. The study is designed to evaluate possible noninferiority in mortality in the diet group compared with the dialysis group. According to the approach of Blackwelder[20] to sample size calculation for a dichotomous outcome, a sample of 83 patients was needed in each group to evaluate noninferiority with 80% power and α = 10%, assuming a survival rate of 81% at 1 year in dialysis patients and noninferiority margin Δ = 15% in terms of survival difference (hazard ratio [HR], 2.1).

Noninferiority in mortality was analyzed by applying the confidence interval (CI) approach, considering where the CI lies with respect to the noninferiority margin, and using the method suggested by Com-Nougue et al[21] that evaluates noninferiority between 2 treatments by comparing survival at previously specified times (1 year in our study) or applying a modified version for noninferiority of the log-rank test. It uses estimated survivals from Kaplan-Meier[22] and/or treatment parameters estimated by means of the Cox proportional hazard model (PHM)[23] to take into account the unbalance between groups. We used 2-sided 95% CIs. Multivariate analysis was done by analyzing all predictors statistically significant at univariate analysis (log-rank test) and those unbalanced at baseline.

The proportional assumption of the PHM was tested by using Schoenfeld residuals.[24] All statistical methods were applied in both the intention-to-treat (ITT) analysis (patients were considered part of the diet group even after a switch to dialysis) and per-protocol (PP) analysis (diet group patients were censored when switched to dialysis). However, in our opinion, the PP analysis favors the diet group because of a progressive selection bias.

In a PP sensitivity analysis, we applied a PHM with diet treatment as a time-dependent covariate to evaluate the robustness of our results. For the same reason, we applied a parametric survival regression model with a log-logistic error distribution to evaluate the robustness of results with the PHM.

Possible differences in morbidity were analyzed by comparing the number of hospital admissions and duration of hospitalization. The probability of not being hospitalized was calculated by means of the Prentice-Williams-Petersen model,[25] an extension of the PHM to multivariate survival time that allows analysis of ordered multiple events (ie, hospital admissions).

Comparisons among different models or selection of prognostic variables in multivariate models were performed using the Akaike information criterion.

Continuous variables were analyzed using Student's *t*-test, Pearson test, and Wilcoxon test, when appropriate. According to their distribution pattern, variables with normal distribution are reported as mean $\pm$ SD, and when distribution is asymmetrical, as median and first and third quartile. An explorative analysis on changes over time in laboratory test results also was done. Categorical variables were analyzed using Fisher exact test. CIs reported are 95% 2-sided intervals, and P less than 0.05 is considered statistically significant.

This study conformed to the Declaration of Helsinki and was approved by the ethics committees from all hospitals involved in the clinical trial. All patients gave written informed consent. The study was supported only by the Italian public hospitals participating in the study.

RESULTS

As of July 31, 2005, a total of 56 patients had been assigned to diet, and 56 patients, to dialysis (Fig 1). No patient had uremic symptoms at randomization. Despite randomization, the 2 groups were significantly different for sex and age and marginally not significantly different for cerebral vascular disease (Table 1). Table 2 lists clinical characteristics of the 2 groups at randomization and, for the diet group, during follow-up. Indices of nutritional status (ie, body mass index

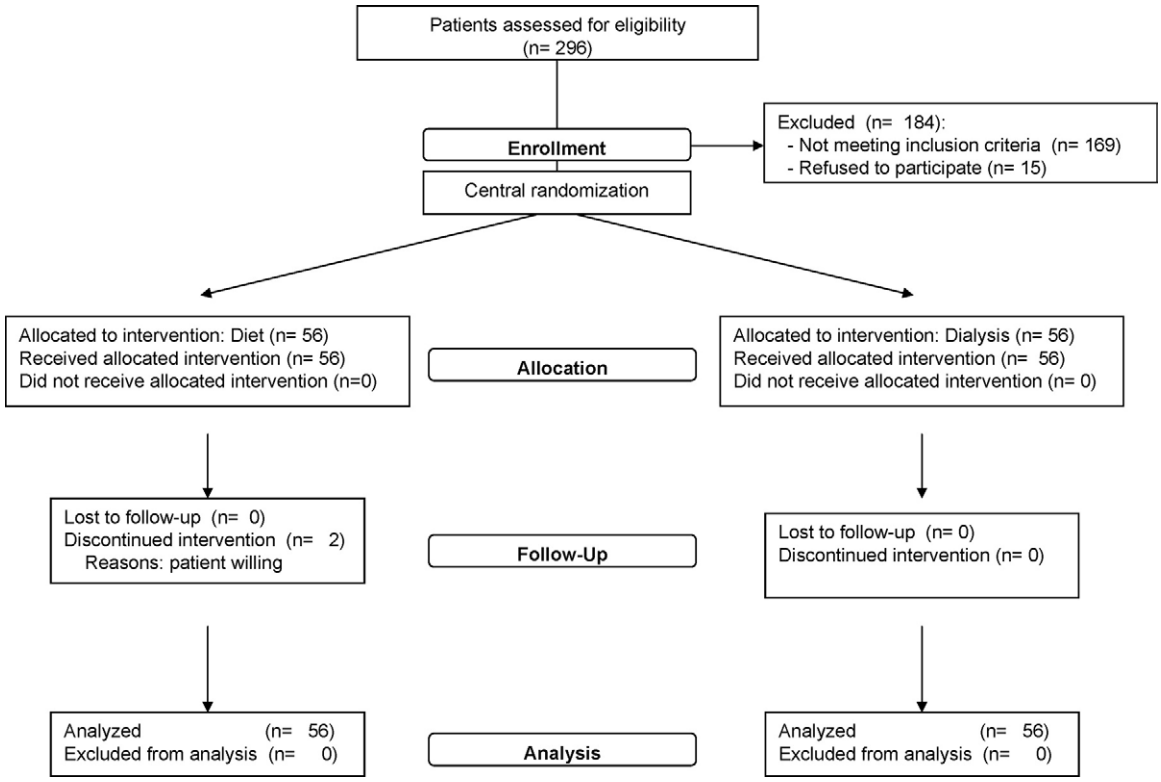

Figure 1. Consort flow chart.

and serum albumin level) did not change; serum cholesterol level decreased slightly from a statistical point of view, but without clinical relevance. Normalized protein catabolic rate and BUN levels were stable during the period following the diet. Serum potassium levels significantly increased over time, parallel to the decrease in GFR.

Outcomes

Table 3 lists mortality outcomes and causes of death. No patient was lost to follow-up. Median time following an sVLPD was 10.7 months (range, 1.0 to 58.1). At the end of the study, 50% of diet patients and 55% of dialysis patients were dead. Ten diet patients died while following an sVLPD at a mean age of 87.6 years (range, 82 to 96 years). Causes of death were cardiac in 5 patients, cerebrovascular in 3 patients, cachexia/dementia in 1 patient, and hemorrhage in 1 patient. Forty patients (71%) in the diet group started dialysis therapy after a median of 9.8 months following an sVLPD (range, 6.0 to 20.0 months); 38 patients because of hyperkalemia and/or fluid retention and 2 patients because of the patient's desire to discontinue the diet and start maintenance dialysis treatment. As of July 31, 2005, a total of 6 patients (11%) were still receiving diet treatment after a median of 16.6 months (range, 14.7 to 41.8 months).

Survival

ITT Analysis

Log-rank test for noninferiority (Com-Nouge approach) for diet was statistically significant ($P < 0.001$), and that for superiority was not ($P = 0.6$). One-year survival rates were 83.7 (95% CI, 74.5 to 94.0) and 87.3 (95% CI, 78.9 to 96.5; Fig 2) in the dialysis and diet groups, respectively.

The difference in survival was $\Delta = -3.6\%$ (95% CI, -16 to $+9$); the null hypothesis of inferiority of diet versus dialysis was refused with $P = 0.002$ assuming the noninferiority margin defined in the protocol. However, to

Table 1. Baseline Characteristics of Enrolled Patients

	Dialysis	Diet	*P*
No. of patients	56	56	
Age (y)	76.8 ± 4.3	79.3 ± 6.4	0.04*
Sex (women)	26 (46)	38 (68)	0.02†
Peripheral vasculopathy	13 (23)	14 (25)	0.1†
Cerebral vasculopathy	7 (12)	15 (27)	0.1†
Ischemic cardiopathy	14 (25)	9 (16)	0.2†
Cardiac arrhythmia	16 (29)	11 (20)	0.3†
Hypertension	48 (86)	48 (86)	1†
Urinary tract infections	8 (14)	10 (18)	0.6†
Chronic obstructive pulmonary disease	5 (9)	2 (4)	0.2†
Primary renal diseases:			0.4†
Unknown	29 (52)	34 (61)	
Ischemic nephropathy	13 (23)	11 (20)	
Obstructive nephropathy	3 (5)	2 (4)	
Interstitial nephritis	7 (12)	5 (9)	
Autosomal polycystic kidney disease	0 (0)	3 (5)	
Glomerulonephritis	4 (7)	1 (2)	

Note: Values expressed as mean ± SD or number (percent).
*Wilcoxon test.
†Pearson test.

avoid the possibility that these results were influenced by the unbalance in age and cerebral vasculopathy in favor of diet, we applied the PHM (Table 4). We then compared the adjusted HR estimated by means of the PHM with the noninferiority margin ($R = 2.1$) by means of the Coum-Nouge approach. This test showed that diet is not inferior to dialysis ($P < 0.01$). It is interesting to emphasize that parametric log-logistic survival regression showed a significant result in terms of superiority of diet versus dialysis (odds of survival, 2.21; 95% CI, 1.02 to 4.83; $P = 0.04$).

PP Analysis

Log-rank test for noninferiority (Com-Nouge approach) of diet was statistically significant ($P = 0.001$), and that for superiority was not ($P = 0.6$).

At 1 year, survival rates were 83.7 (95% CI, 74.5 to 94.0) and 83.9 (95% CI, 66.7 to 92.6) in the dialysis and diet groups, respectively (Fig 3). The difference in survival was $\Delta = -0.2\%$ (95% CI, −15 to +16). When we applied the PHM to the PP set, we obtained a significant result for diet in terms of superiority (HR, 0.30; 95% CI, 0.12 to 0.74; $P < 0.01$; Fig 4).

Diet as Time-Dependent Covariate

The PHM with diet as a time-dependent covariate and adjustment for the other prognostic factors confirmed the protective role of diet (HR, 0.045; 95% CI, 0.01 to 0.34; $P < 0.01$).

Morbidity

Number of hospitalizations and days of hospitalization per patient-year were significantly lower in the diet group ($P < 0.001$ and $P = 0.02$, respectively; Table 3). The hazard risk for hospitalization was significantly greater in the dialysis group (HR, 1.50; 95% CI, 1.11 to 2.01; $P < 0.01$). These HRs were still significantly different after adjustment for differences in age and cerebral vasculopathy. After also including for the Diet group hospitalizations for creating the first dialysis access (33 admissions and 377 days), medians became 1.0 (first and third quartile, 0.6 to 1.2) and 9.0 (first and third quartile, 4.6 to 15.5), not significantly different from those of the dialysis group ($P = 0.1$ and $P = 0.4$, respectively). No important difference was seen in causes of hospitalization except for dialysis access complications (0.31 admissions/patient-year in the dialysis group versus 0.15 for the diet group) and fluid overload (0.13 versus 0.05). In the diet group, all admissions caused by fluid overload occurred only when following an sVLPD.

DISCUSSION

To our knowledge, this is the first prospective randomized controlled study comparing mortality and morbidity of an sVLPD versus dialysis treatment. Results suggest that when renal function decreases below the level at which it is recommended that maintenance dialysis therapy be initiated,[1-4] an sVLPD is safe when postponing dialysis treatment by a median of 10.7 months (range, 1 to 58 months).

Patients enrolled in this study had GFRs of 5 to 7 mL/min/1.73 m^2 BSA (0.08 to 0.12 mL/s), which is less than the value for starting maintenance dialysis therapy suggested in several guidelines,[1-4] but not different from values reported by other investigators.[5,6,26] Guidelines suggest that maintenance dialysis be started at higher GFRs than is currently done to improve survival and decrease morbidity. This recommendation is clas-

Table 2. Clinical Characteristics of the 2 Groups at Randomization and, for the Diet Group, During Follow-Up

	At Randomization		Follow-Up in Diet Group (mo)			
	Dialysis	Diet	6	12	18	Before Dialysis
No. of patients	56	56	52	28	19	40
Body mass index (kg/cm^2)	24.3 ± 3.7	24.6 ± 3.1	24.7 ± 3.4	24.5 ± 3.4	24.2 ± 2.9	24.7 ± 2.8
		$P = 0.6$	$P = 0.5$	$P = 0.7$	$P = 0.5$	$P = 0.2$
GFR (mL/min/1.73 m^2)	6.1 ± 0.7	6.0 ± 0.7	5.1 ± 1.6	5.0 ± 1.7	4.8 ± 1.5	4.3 ± 1.1
		$P = 0.4$	$P < 0.001$	$P < 0.01$	$P = 0.001$	$P < 0.001$
BUN (mg/dL)	81.7 ± 20.8	78.4 ± 18.2	62.9 ± 31.1	63.5 ± 18.6	63.6 ± 20.4	69.9 ± 23.1
		$P = 0.4$	$P < 0.01$	$P = 0.1$	$P = 0.1$	$P = 0.1$
Normalized protein catabolic rate (g/kg BW/d)	0.55 ± 0.16	0.50 ± 0.15	0.32 ± 0.09	0.35 ± 0.10	0.37 ± 0.11	0.33 ± 0.10
		$P = 0.04$	$P < 0.001$	$P = 0.001$	$P = 0.01$	$P < 0.001$
Serum albumin (g/dL)	3.8 ± 0.6	3.9 ± 0.4	3.9 ± 0.5	4.0 ± 0.5	4.1 ± 0.4	3.9 ± 0.5
		$P = 0.1$	$P = 0.5$	$P = 0.2$	$P < 0.01$	$P = 0.8$
Hemoglobin (g/dL)	10.5 ± 1.13	10.3 ± 1.3	11.1 ± 1.2	11.4 ± 1.4	10.7 ± 1.4	10.9 ± 1.2
		$P = 0.5$	$P < 0.01$	$P < 0.01$	$P = 0.3$	$P = 0.01$
Serum cholesterol (mg/dL)	175 ± 41	183 ± 41	179 ± 38	179 ± 33	175 ± 27	172 ± 36
		$P = 0.3$	$P = 0.3$	$P = 0.8$	$P = 0.2$	$P = 0.04$
Serum potassium (mmol/L)	4.6 ± 0.4	4.6 ± 0.6	4.7 ± 0.6	4.7 ± 0.6	4.9 ± 0.5	4.9 ± 0.7
		$P = 0.7$	$P = 0.02$	$P = 0.04$	$P = 0.001$	$P = 0.001$
Serum bicarbonate (mmol/L)	24.7 ± 2.6	24.7 ± 3.2	25.6 ± 2.8	25.7 ± 2.9	25.6 ± 2.4	25.1 ± 2.7
		$P = 1$	$P = 0.1$	$P = 0.4$	$P = 0.5$	$P = 0.2$

Note: Before dialysis indicates the last value before switching from diet to dialysis. *P* in the At Randomization column refers to comparison between the diet versus dialysis group with *t* unpaired test, and during follow-up of the diet group refers to comparison versus those at randomization. To convert GFR in mL/min to mL/s, multiply by 0.01667; BUN in mg/dL to mmol/L, multiply by 0.357; albumin and hemoglobin in g/dL to g/L, multiply by 10; cholesterol in mg/dL to mmol/L, multiply by 0.02586; potassium and bicarbonate are expressed by the same digits in conventional (mEq/L) and SI (mmol/L) units.

sified as "opinion" and is not based on direct scientifically obtained evidence. It is based in part on a questionable extrapolation in predialysis patients with end-stage renal disease of data obtained from the calculation of urea kinetics in long-term PD patients.[27,28] In contrast to this guideline recommendation, of the more recent reports examining this question,[26,29,30-33] only 1

Table 3. Outcomes, Causes of Death, and Hospitalization Rates

	Dialysis	Diet			*P*
No. of patients enrolled	56	56			
Total follow-up (mo)	25.5 (15.9-55.2)	27.4 (16.2-56.0)			0.7
Time on sVLPD only (mo)		10.7 (6.6-17.6)			
Patients died	31 (55)	28 (50) (10 on diet, 18 on dialysis)			0.6
Age at death (y)	79.9 ± 4.0	82.9 ± 6.1			0.04
Causes of death					0.3
Cardiac	16 (52)	12 (43)			
Cachexia/dementia	7 (23)	2 (7)			
Hemorrhage	2 (6)	4 (14)			
Cerebrovascular	2 (6)	3 (11)			
Other	4 (13)	7 (25)			
		sVLPD	Dialysis	Total	
Follow-up (patient-y)	162	69	99	168	
No. of admissions/patient-y	1.1 (0.6-2.3)	0.5 (0-1.2)	0.6 (0-1.6)	0.6 (0.3-1.0)	0.001
Days of admission/patient-y	11.0 (3.9-22.2)	3.0 (0-14.5)	5.2 (0-16.6)	5.2 (2.4-12.2)	0.02

Note: Age reported as mean ± SD; other data expressed as median (first and third quartile). Comparisons were made versus results of the dialysis group.

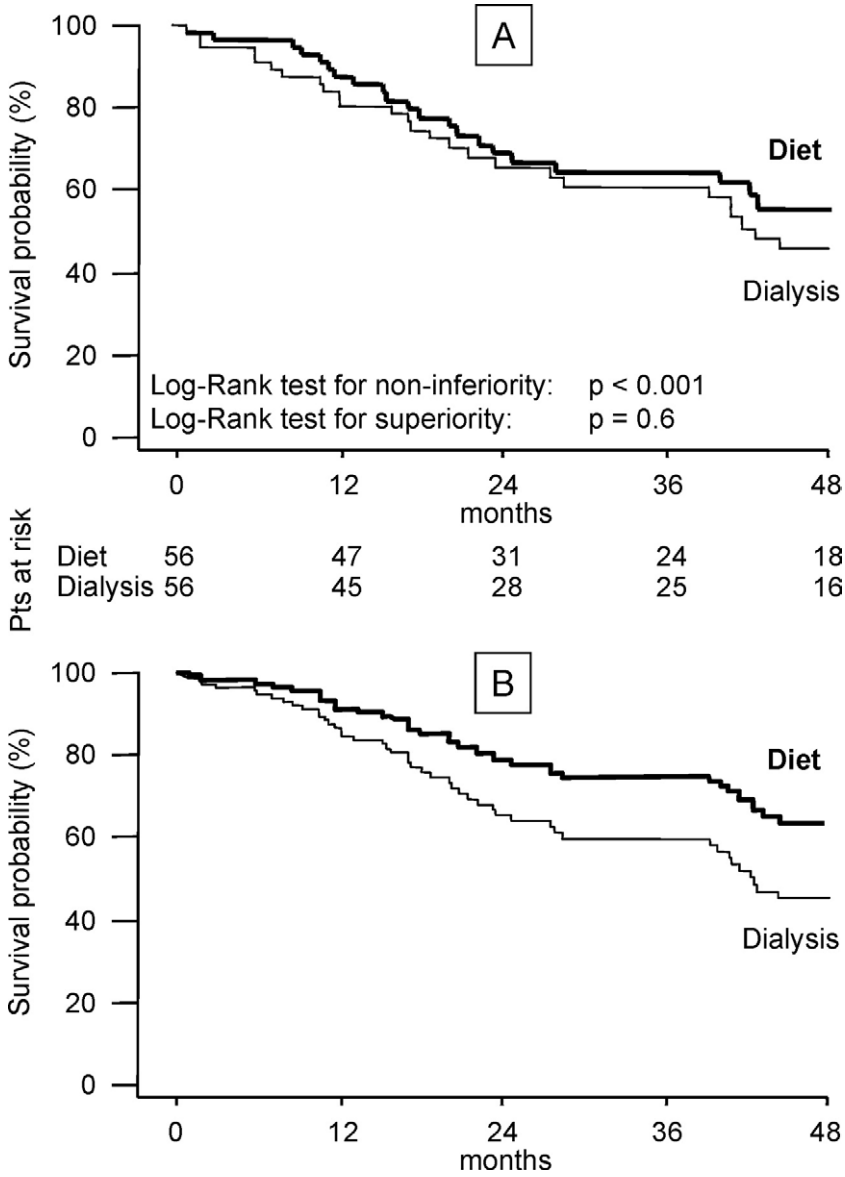

Figure 2. Survival curves as ITT analysis: (A) observed survival according to Kaplan and Meier, (B) predicted survival by Cox model after adjustment for unbalance.

study[29] found that an earlier start of dialysis treatment was marginally effective, but that apparent benefit could have depended partially on lead-time bias rather than a true improvement in survival. However, 5 retrospective studies showed that starting dialysis treatment at a higher GFR was associated with statistically significant worse survival.[26,30-33] It is noteworthy that 2 of these studies were based on very large databases, such as the US Renal Data System[32] or Medicare and Medicaid statistics.[31] Results of these studies and ours suggest that guidelines concerning the threshold for starting dialysis treatment be revised, at least for older patients and those without diabetes.

The ability of an sVLPD to reduce the progression of renal failure with no impairment in clinical and nutritional status was reported by many others.[9-11,34,35] Our study differs in that the sVLPD is used in patients with a more advanced phase of end-stage renal disease with the aim of avoiding the appearance of uremic symptoms and metabolic disturbances when postponing dialysis treatment. Baseline GFR in our patients was 6.0 mL/min (0.10 mL/s); it was 32% of the Modification of Diet in Renal Disease Study 2

Table 4. Results of Cox PHM on Patient Survival at ITT and PP Analyses

	ITT			PP		
	Relative Risk	95% CI	*P*	Relative Risk	95% CI	*P*
Diet (*v* dialysis)	0.59	0.34-1.04	0.1	0.33	0.14-0.81	0.01
Age	1.11	1.05-1.17	<0.001	1.15	1.08-1.24	<0.001
Cerebral vasculopathy	2.04	1.09-3.79	0.02	2.88	1.34-6.15	<0.01

(18.5 mL/min [0.31 mL/s]).[12] The last GFR value in the 40 diet patients who were switched to dialysis was 4.3 ± 1.1 mL/min (0.07 ± 0.02 mL/s), with a range of 2 to 7 mL/min (0.03 to 0.12 mL/s).

Normalized protein catabolic rate, calculated without subtracting nitrogen intake from keto-analogues and amino acid supplementation (7.4 mg/kg BW), significantly decreased after start-

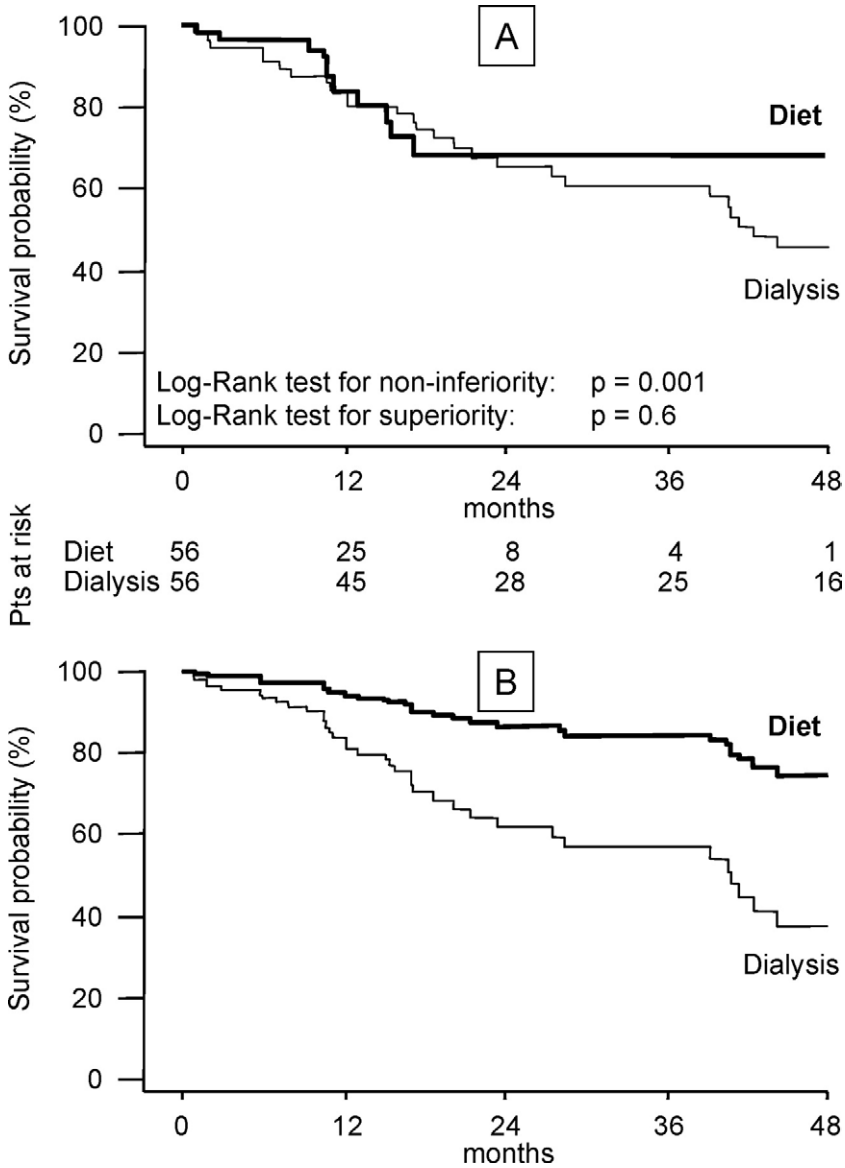

Figure 3. Survival curves as PP analysis: (A) observed survival according to Kaplan and Meier, (B) predicted survival by Cox model after adjustment for unbalance.

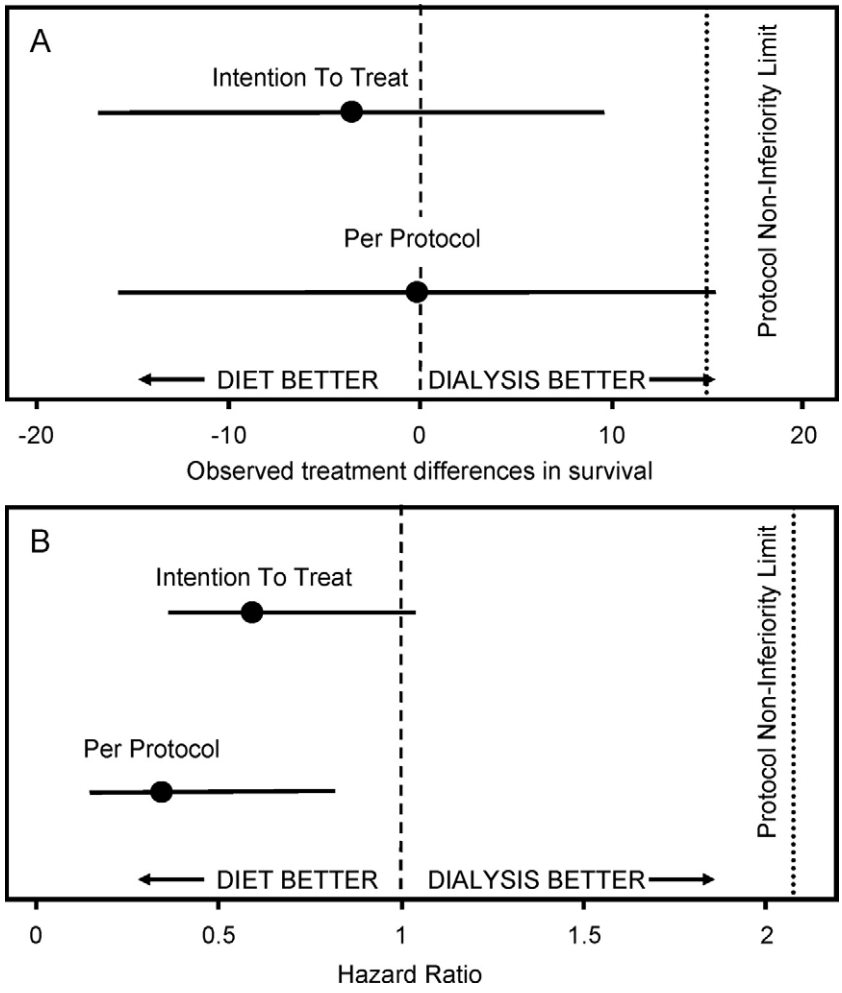

Figure 4. (A) Observed treatment differences in survival (percent survival) in PP and ITT analyses (2-sided 95% CI) and (B) HRs for survival at PP and ITT analyses after adjustment for unbalance (2-sided 95% CI).

ing the sVLPD, but afterward, it remained stable at values supporting good compliance with the prescribed diet (Table 2). In addition, the stability of BUN levels supports good compliance with the diet. The sVLPD had no negative effect on nutritional status, supported by the stability in body mass index and serum albumin values. It is noteworthy that the progressive increase in serum potassium levels was concurrent with a decrease in GFR. The vegetable diet necessarily has a high potassium content, and the severely failing kidney is unable to completely excrete it. Stability of serum bicarbonate and hemoglobin levels is affected by changes in erythropoietin and bicarbonate administration. Only 2 of our patients (5%) did not tolerate the sVLPD and preferred to initiate dialysis therapy.

Patient survival was not significantly different between the diet and dialysis groups (Fig 2), even without taking into account baseline differences (age and cerebral vasculopathy) that were disadvantageous to diet patients. After correction for these prognostic differences (Table 4), a marginally not significant difference ($P = 0.1$) by means of Cox analysis was found in the ITT analysis. These results indicate that an sVLPD compared with maintenance dialysis treatment is not less effective for preserving life for a time in older patients who are willing to accept an sVLPD. The best results achieved by diet at the PP and time-dependent analyses could be the consequence of a selection bias in favor of diet.

Median dialysis-free time gained by diet is a little less than 1 year, similar to that observed in a nonrandomized study of patients following an sVLPD with a mean age of 52 years and baseline GFR higher than in our patients.[35]

During the entire follow-up period, admission rates and days of hospitalization were lower in the diet group; 57% and 66% of those of the dialysis group, respectively. This difference was caused mainly by dialysis access–related complications. The diet enables delaying placement of vascular access; in this way, the related complications are reduced. The incidence of admissions caused by fluid overload was not different between diet patients while following an sVLPD and dialysis patients, but no admission occurred for this cause in the diet group after they were transferred to dialysis treatment. It seems that patients following an sVLPD may learn over time to limit salt and fluid intake and self-check for signs of overhydration. This practice may have increased their compliance in this regard.

The lower hospitalization rate in the diet group was not caused by more frequent clinic visits. Conversely, clinic visits were scheduled every 30 to 35 days for diet patients, whereas HD patients were visited by a physician at every dialysis treatment; ie, 13 to 15 times in the 30- to 35-day period. Fewer accesses to the hospital is 1 more point in favor of diet because it decreased both family and psychosocial burdens and had a less detrimental effect on quality of life.

Limitations of this study are incompleteness of the enrollment as defined by the protocol, which reduces the power of statistics, and its unblinded nature. Exclusion of patients with diabetes limits the generalizability of results, but the safety of an sVLPD in patients with diabetes, because of its high carbohydrate content, is unknown. Incompleteness of enrollment was the cause of some imbalance between the 2 groups; the incompleteness could have occurred because Italian nephrologists are used to prescribing a low-protein diet (0.6 g of protein/kg BW) to uremic patients, but few are confident with the sVLPD proposed by our protocol.

In summary, this study does not suggest that the start of maintenance dialysis treatment can or should be postponed by diet for all elderly patients. Rather, for patients satisfying the selection criteria of this study and willing to follow an sVLPD, the start of dialysis treatment can be delayed for about 1 year without increasing their risk of either death or hospitalization.

In late-referral patients, when dialysis is not urgent, the diet could allow time to plan the creation of a vascular access and wait until a venipuncture can be done safely. In this way, it is possible to avoid the use of central venous catheters, which often are complicated by infection or thrombosis.[36]

Postponing dialysis treatment should be cost saving in countries where the number of elderly and very sick patients with chronic kidney disease stage 5 is continuously growing and causing enormous treatment costs. Possibly, the sVLPD could be helpful in 2 other settings: developing countries, where dialysis treatment is not available,[37,38] and western countries, where some patients with chronic kidney disease stage 5 refuse dialysis and prefer to be managed conservatively in palliative care programs.[39-41]

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