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This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/150750> since 2016-07-01T00:00:20Z

Published version:

DOI:10.1093/ndt/gfu251

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This is the author's final version of the contribution published as:

Bellizzi, Vincenzo; Chiodini, Paolo; Cupisti, Adamasco; Viola, Battista Fabio; Pezzotta, Mauro; De Nicola, Luca; Minutolo, Roberto; Barsotti, Giuliano; Piccoli, Giorgina Barbara; Di Iorio, Biagio. Very low-protein diet plus ketoacids in chronic kidney disease and risk of death during end-stage renal disease: an historical, cohort, controlled study.. NEPHROLOGY DIALYSIS TRANSPLANTATION. 30 (1) pp: 71-77.
DOI: 10.1093/ndt/gfu251

The publisher's version is available at:

<http://ndt.oxfordjournals.org/cgi/doi/10.1093/ndt/gfu251>

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<http://hdl.handle.net/2318/150750>

Very low-protein diet plus ketoacids in chronic kidney disease and risk of death during end-stage renal disease: a historical cohort controlled study

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Abstract

Background Very low-protein intake during chronic kidney disease (CKD) improves metabolic disorders and may delay dialysis start without compromising nutritional status, but concerns have been raised on a possible negative effect on survival during dialysis. This study aimed at evaluating whether a very low-protein diet during CKD is associated with a greater risk of death while on dialysis treatment.

Methods This is an historical, cohort, controlled study, enrolling patients at dialysis start previously treated in a tertiary nephrology clinic with a very low-protein diet supplemented with amino acids and ketoacids (s-VLPD group, $n = 184$) or without s-VLPD [tertiary nephrology care (TNC) group, $n = 334$] and unselected patients [control (CON) group, $n = 9.092$]. The major outcome was survival rate during end-stage renal disease associated to s-VLPD treatment during CKD. The propensity score methods and Cox regression model were used to match groups at the start of dialysis to perform survival analysis and estimate adjusted hazard ratio (HR).

Results In s-VLPD, TNC and CON groups, average age was 67.5, 66.0 and 66.3 years, respectively ($P = 0.521$) and male prevalence was 55, 55 and 62%, respectively ($P = 0.004$). Diabetes prevalence differed in the three groups ($P < 0.001$), being 18, 17 and 31% in s-VLPD, CON and TNC, respectively. A different prevalence of cardiovascular (CV) disease was found ($P < 0.001$), being similar in TNC and CON (31 and 25%) and higher in s-VLPD (41%). Median follow-up during renal replacement therapy (RRT) was 36, 32 and 36 months in the three groups. Adjusted HR estimated on matched propensity patients was 0.59 (0.45–0.78) for s-VLPD versus CON. Subgroup analysis showed a lower mortality risk in s-VLPD versus matched-CON in younger patients (<70 years) and those without CV disease. No significant difference in HRs was found between s-VLPD and TNC.

Conclusion s-VLPD during CKD does not increase mortality in the subsequent RRT period.

Key words CKD, CV risk, ketoacids, survival, very low-protein diet

INTRODUCTION

In patients with moderate-to-advanced chronic kidney disease (CKD) who are not on dialysis, a very low-protein diet supplemented with amino acids and ketoacids (s-VLPD) improves several metabolic abnormalities, including hyper-phosphataemia, metabolic acidosis, hyper-parathyroidism and dyslipidaemia [1–3], and contributes to the achievement of recommended therapeutic targets for proteinuria, blood pressure and haemoglobin [4–8], without serious adverse effects [9, 10]. Although this dietary treatment does not reduce the decline in glomerular filtration rate (GFR), it delays renal death sparing patients with advanced CKD from dialysis by 1–2 years [11–13]. Therefore, s-VLPD may still have a role in limiting the burden of end-stage renal disease (ESRD).

Recently, however, an alarming controversy on this approach has emerged; indeed, based on a *post hoc* analysis of the Modification of Diet in Renal Disease (MDRD) study-B, it has been hypothesized that prescription of s-VLPD increases mortality during the subsequent dialysis period [14]. These data contrast remarkably with previous studies. The Diet or Dialysis in Elderly (DODE) trial, a randomized controlled study designed to assess the non-inferiority of s-VLPD compared with dialysis on mortality in old patients without diabetes with ESRD, did not evidence any survival disadvantage for patients on s-VLPD in comparison with those on dialysis [13]. Similarly, an observational French study evidenced that s-VLPD treatment is not associated with any detrimental effect on the long-term outcome of younger CKD patients once renal replacement therapy (RRT) start [15]. Noteworthy, several limitations make inconclusive the findings of MDRD and of the two previous studies as well. In the MDRD study, the major drawback was discontinuation of the diet for a long period of time prior to start of dialysis as the very low-protein diet was stopped soon after the end of the original trial, thus diluting a possible effect of the treatment. In the latter two studies, selection biases (old age, no diabetes, high co-morbidities in DODE study; young age, no co-morbidities in the French study) and lack of adequate control (French study) made the study groups not representative of the general CKD population.

We designed a long-term, historical, cohort, controlled study aimed at verifying whether s-VLPD is associated with a greater mortality risk during the subsequent RRT period in comparison with the general CKD population. Additionally, we assessed survival during RRT in patients previously followed in tertiary nephrology clinics but not receiving s-VLPD in order to detect the effect of s-VLPD independently from the intensity of the nephrology care.

MATERIALS AND METHODS

Patients and groups

We selected patients with CKD Stage 5 at the start of dialysis. The s-VLPD group was constituted by a multicentre cohort of consecutive adult patients who have been prescribed an s-VLPD in tertiary CKD clinics for at least 3 months prior to dialysis start. s-VLPD consisted in a vegetarian, high energy diet, with a protein content of 0.3–0.4 g/Kg IBW/day supplemented with aminoacid and ketoacids in tablets (AlfaKappa® or Ketosteril®; Fresenius Kabi, Italia). A strict criterion for the enrolment of patients was that they had to be continuously on s-VLPD during CKD and they had to be still on diet at the start of RRT; this allows proper analysis of the effect of s-VLPD prescription on survival in the subsequent dialysis period. The enrolment time lasted from January 1995 to December 2008.

The control (CON) group was constituted by a cohort of consecutive, unselected patients starting dialysis and recruited from the Italian registry of dialysis and transplantation. These patients were included on the basis of age, that is, they had to be coeval with the s-VLPD group, the same time period of dialysis start of s-VLPD and the same geographical areas of s-VLPD. In CON patients, treatment setting prior to RRT was

unknown.

We also included, as a further control, a tertiary nephrology care (TNC) group constituted by a prospective cohort of CKD patients which took part in a multicentre Italian study [16], derived from the same regions of the s-VLPD group and had been under TNC for at least 3 months prior to RRT start without receiving s-VLPD prescription. The s-VLPD versus TNC comparison allows assessment of the isolated effect of s-VLPD, that is, independent from the other nephrology care interventions. Enrolment for this group lasted from June 2002 to December 2008.

Study design

This is an historical, cohort, controlled study conducted in patients starting chronic RRT and aimed at evaluating the effect of s-VLPD regularly prescribed during the conservative phase of CKD up to the beginning of RRT on the mortality risk during dialysis. Patients were evaluated prospectively from the time of start of RRT up to 31 December 2009. The primary end point is the time to all-cause death during RRT, comparing patients on s-VLPD versus either general, unselected ESRD population or CKD patients regularly treated in TNC but not undergoing s-VLPD. Patients receiving kidney transplantation during dialysis remained in the analysis until primary end point or end of follow-up of the study. The study was approved by the Institutional Review Board.

Statistical analysis

Continuous variables are expressed as mean and SD, and categorical variables are reported as percentages. Differences in characteristics of patients among groups were tested by means of one-way analysis of variance and Pearson χ^2 test for continuous and categorical variables, respectively. For the three groups, the crude mortality rates were calculated with 95% confidence intervals (CIs). Survival curves were estimated by the product-limit method of Kaplan–Meier and compared by the log-rank statistic. In the survival analysis, the matched propensity score method was used to compare s-VLPD versus CON group [17]. This method is useful when there is a much larger number of control subjects (CON group) than treated subjects (s-VLPD group). The propensity score was calculated using the logistic regression model with age, gender, diabetes, cardiovascular (CV) disease, renal disease and ESRD management as covariates. A 1 : 2 match without replacement was used to pair each patient in s-VLPD with at least one patient in the CON group within the designated calliper size of 0.2 [18]. The method of standardized differences was used to assess balance of covariates after matching [19]. *Cox's* proportional-hazard model was used to estimate s-VLPD versus CON hazard ratio (HR) and the corresponding 95% CI on the matched pairs with a robust sandwich estimate of the variance of the regression coefficient that accounted for the clustering within matched sets [20]. A multivariable *Cox's* proportional-hazard model was used for the s-VLPD versus TNC group comparison where the number of subjects per group was not much different. Three different models were evaluated; the first model included the same variables included into the propensity score model (age, gender, diabetes, CV disease and renal disease) except for ESRD management. The second model was further adjusted for clinical characteristics at the start of RRT (systolic blood pressure, body mass index, haemoglobin, GFR, time on CKD care), and the third model with all the previous covariates was fitted only in patients receiving haemodialysis as for ESRD treatment. Subgroups analysis comparing s-VLPD and matched-CON groups was performed by means of *Forest plot*. A two-tailed P-value of <0.05 was considered significant. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC) and STATA version 11.0 (College Station, TX).

RESULTS

The study included 9610 consecutive adult patients with CKD Stage 5; patients previously adherent to a very

low-protein diet supplemented with essential amino acids and ketoacids (s-VLPD group) were 184, unselected ESRD patients (CON group) were 9092 and patients previously treated in tertiary nephrology clinics without s-VLPD (TNC group) were 334.

Male gender and older age were prevalent (patients over 70 years: s-VLPD, 55%; TNC, 49% and CON, 49%) (Table 1). All groups showed a high CV risk profile, as testified by the high prevalence of diabetes, which was similar in s-VLPD and CON but higher in the TNC group ($P < 0.001$), as well as of a prevalent history for CV disease, which did not differ among TNC and CON but resulted higher in the s-VLPD group ($P < 0.001$) (Table 1).

Baseline characteristics of CKD-5 groups intensively treated in tertiary nephrology clinics with (s-VLPD) or without (TNC) a very low-protein diet supplemented with ketoacids and unselected subjects (CON)

At the last visit prior to dialysis start, the clinical conditions of the two groups treated in tertiary nephrology clinics were different (Table 2). Patients in the s-VLPD group were still eating a very low-protein diet (37 g/day), as compared with the low-normal protein intake in the TNC group (55 g/day), and started dialysis at a more advanced phase of renal failure and, consequently, with poorer control of blood pressure and anaemia.

Differences between CKD-5 groups intensively treated in tertiary nephrology clinics with (s-VLPD) or without (TNC) a very low-protein diet supplemented with ketoacids at the last visit prior (≤ 3 months) to dialysis start

The median follow-up time during the RRT period did not differ among groups, being 36, 32 and 36 months in s-VLPD, TNC and CON groups, respectively; during this time, the crude yearly mortality rate resulted similar in s-VLPD and TNC groups (8.0 versus 9.8%), which were both lower as compared with the CON group (13.8%) (Table 3). In the matched-CON cohort (n , 356) obtained after applying the matched propensity score method, the median follow-up was 33 months and the crude mortality was 15.2% (Table 3). The survival analysis for all-cause death, performed by the mean of Kaplan–Meier curves according to the treatment modalities during the pre-dialysis period, showed that cumulative survival by groups was similar in s-VLPD and TNC (log-rank test, $P = 0.702$), while being significantly higher in the s-VLPD group versus CON group (log-rank test, $P < 0.001$) (Figure 1). Adjusted estimate of s-VLPD versus CON comparison was calculated using the propensity score. After propensity score matching, the study population consisted of 540 patients (184 patients in the s-VLPD group and 356 patients in the matched-CON group). Before matching, significant imbalances between the two groups were observed with respect to gender, history of CV disease, renal disease and ESRD. Propensity score matching was effective in reducing the absolute standardized difference to $< 10\%$ for all considered covariates. In the *Cox* regression model fitted on matched patients, HR (95% CI) of s-VLPD versus matched-CON was 0.59 (0.45–0.78) (Table 4). In the s-VLPD versus TNC comparison, multivariable *Cox* regression models showed similar adjusted HRs (Table 4).

When comparing s-VLPD and matched-CON patients, subgroup analysis showed a lower mortality risk in younger patients (< 70 years) and in those without history of CV disease (P -value of the interaction $P < 0.001$ and $P = 0.009$, respectively) (Figure 2). The estimated adjusted HR was 0.24 (0.13–0.44) in younger patients (< 70 years) and 0.43 (0.28–0.66) in those without CV disease (Figure 2). Both s-VLPD subgroups (namely younger and without history of CV disease) had a longer treatment time on s-VLPD (Table 5).

DISCUSSION

This paper provides evidence that nutritional intervention with a very low-protein diet supplemented with amino acids and ketoacids during the conservative treatment of CKD does not increase mortality risk in the subsequent dialysis period. Overall, the study may support the role of prescribing a supplemented very low-protein diet during CKD as a part of the intensive care delivered to CKD patients.

The main results are conflicting with a previous paper from the MDRD study group in which the assignment to s-VLPD in CKD patients was found to increase the risk of death after the start of dialysis [14]; such conclusion may have prevented many nephrologists from the implementation of dietary protein restriction as a part of their therapeutic strategies [21]. However, several limitations of this secondary analysis of the MDRD study may have substantially flawed the study conclusions. First, no relevant information was provided on the dietary protein intake during the follow-up; indeed, in the MDRD study, any diet was stopped at the end of the trial, which is a long time prior to the start of dialysis, and within a few months after stopping the original study no inter-group difference emerged in the actual protein intake and all patients had the same (and adequate) protein intake. In addition, after the end of the MDRD, it was evaluated the nutritional outcome and s-VLPD survivors did not show overt nutritional impairment. Hence, onset of malnutrition related to diet, which was given as an explanation to the higher death rate described in the *post hoc* analysis, may be excluded either during or even long time after the end of dietary prescription. Second, after the end of the original MDRD trial, patients were left with both no diet and no further clinical follow-up for a very long period of time. Unknown factors may have, therefore, influenced the outcome. Finally, the clinical conditions of patients at the time of dialysis start were not reported. Consequently, several potential confounders, acting during the CKD follow-up or at dialysis start, have not been considered in the survival analyses. Overall, the long period without treatment, the many confounders contributing to the dilution effect of the initial treatment and the absence of any information on patients until the occurrence of event make the study suffering of major limitations and preclude the achievement of any conclusive judgement on the safety of protein diet restriction.

In this study, dietary protein restriction was prescribed for a long time during CKD and discontinued only at the start of dialysis. Under these conditions, which allow a correct evaluation of the impact of exposure to the s-VLPD during CKD, patients on supplemented very low-protein diet had a similar mortality rate (s-VLPD, 8/100 patients/year) as compared with CKD patients receiving intensive nephrology care (TNC, 10/100 patients/year) and had lower mortality rate versus unselected CKD population (CON, 14/100 patients/year). The crude mortality is misleading and cannot be used to provide any conclusion on survival. Nonetheless, we compared the crude mortality between the s-VLPD diet group and the control subjects matched according to the propensity method; this analysis annulled the previous imbalance for the major considered risk factors for death making the groups well comparable. Consequently, the crude mortality became reliable and persisted lower as compared with the unselected, matched CKD population (matched-CON, 15/100 patients/year). These data were also confirmed by the lower hazard of risk at the adjusted *Cox's* analysis between s-VLPD and matched-CON, indicating that the risk of death during dialysis resulted reduced by 41% in s-VLPD. Therefore, the study provides evidence that the prescription of a supplemented very low-protein diet prior to ESRD is associated with a similarly lower death risk to CKD patients on intensive care in tertiary nephrology facilities, rather than enhancing the risk of death in dialysis.

Of note, we did not observe an independent effect of the s-VLPD on survival; indeed, the comparison between s-VLPD and TNC may suggest a major role of TNC on survival during RRT. Interestingly, however, at the last visit prior to the beginning of dialysis, the mean GFR was 5.4 mL/min in the s-VLPD group, which is much lower than 10.6 mL/min of TNC patients. Therefore, patients on s-VLPD regimen were able to prolong the dialysis-free period even in the presence of a more severely reduced residual renal function. This had two major clinical implications. First, the time of commencing dialysis has been preceded by at least 1-year extra time free of dialysis due to the s-VLPD, as shown previously [22]; second, though the extremely reduced renal function at start of RRT and the more advanced CKD, the survival time in dialysis resulted the same of that patients on timely dialysis start. The overall survival may, therefore, result even prolonged when considering the extra time in CKD due to the delay in dialysis initiation [23].

A further result that emerges from this study is that in the s-VLPD group there is an interaction between

either age or previous CV disease and outcome; indeed, there was a greater reduction of death risk in younger patients and in patients without a history of CV diseases (Figure 2). Although analysis of this issue goes beyond the scope of our study, this finding is relevant and some comments can be made. Survival on dialysis is mainly determined by the CV status at initiation of dialysis since even the most innovative dialysis modalities are not capable to reverse the CV damage that has accumulated during the pre-dialysis period [24]. Hence, any therapy during CKD capable to improve the modifiable CV risks at start of dialysis represents a desirable strategy to improve survival in RRT. In the past few years, several clinical trials on the metabolic effects of the very low-protein diet supplemented with ketoacids have addressed some ‘pleiotropic’ effects of s-VLPD on the major modifiable traditional and non-traditional CV risk factors in CKD. It has been demonstrated that s-VLPD independently, or in addition to other therapies (i.e. angiotensin-converting-enzyme inhibitors), improves calcium/phosphate/PTH balance [2, 3], proteinuria [7, 25], lipid disorders [1], anaemia [5, 26], hypertension [6] and inflammation [27, 28] in patients in CKD Stages 3–5. Hence, it is conceivable that prolonged s-VLPD during CKD may have had a beneficial effect on survival during the subsequent RRT by either reducing the CV risk at the start of dialysis or preventing the onset of new CV comorbidities in younger patients. Indeed, the better survival in s-VLPD subgroups was associated with a longer duration of dietary treatment both in younger patients and patients without previous CV disease, but no survival advantage was detected in the same TNC subgroups. This study cannot be conclusive on this point, and the relation between s-VLPD, improvement of CV risk profile and survival benefit remains speculative. Of note, the propensity matching analysis allowed a homogenous distribution of the CV conditions among s-VLPD and CON groups, which at the initiation of dialysis had comparable CV risk profiles. Indeed, also the subgroup analysis showing a benefit associated with younger age and previous CV diseases was performed in these matched conditions; this makes plausible the hypothesis of such pathogenic pathway which, however, needs to be confirmed.

Therefore, the very low-protein diet supplemented with amino acids and ketoacids may have a place in the management of CKD since the early stages of disease [22, 29]. Such supplemented very low-protein diets seem more suitable for selected patients, such as younger patients and without CV diseases, but may not be suitable for all patients.

In conclusion, with the limitations inherent to the observational design, this study indicates that the prescription of a very low-protein diet during the conservative phase of CKD does not increase mortality during RRT with respect to either unselected or regularly treated CKD patients. In addition, s-VLPD is associated with longer survival in uncomplicated patients, that is, younger subjects and those free of CV disease. The role of s-VLPD in the multifactorial treatment strategy in renal clinics remains to be elucidated. This study supports the need of further randomized controlled trials on the relationship between low-protein diets and hard outcomes in the CKD population.

ACKNOWLEDGEMENTS

All authors take responsibility for the integrity of the data and the accuracy of the data analysis. V.B. drafted the paper. All authors provided critical revision of the manuscript for intellectual content and final approval. The authors thank the *Italian Registry of Dialysis and Transplantation—RIDT*, www.sin-ridt.org—for providing data for the control group of the study. The authors also thank Dr Aurelio Limido (Milan, National Past Chairman), Dr Michele Nichelatti (Milan, data manager), Dr M. Salomone (Turin, Area Piemonte Chairman), Dr A. Rosati (Florence, Area Toscana Chairman), Dr M. Postorino (Reggio Calabria, National Chairman) and Dr C. Zoccali (Reggio Calabria, Area Calabria Chairman).

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Table 1. Baseline characteristics of CKD-5 groups intensively treated in tertiary nephrology clinics with (s-VLPD) or without (TNC) a very low protein diet supplemented with ketoacids and unselected subjects (CON)

	s-VLPD (n = 184)	TNC (n = 334)	CON (n = 9,092)	P-value
Age (years)	67.5 ± 17.3	66.0 ± 14.1	66.3 ± 14.5	0.521
Male gender (%)	55	55	62	0.004
Diabetes (%)	18	31	17	<0.001
History of CVD (%)	41	31	25	<0.001
Renal disease				
Diabetic nephropathy (%)	12	16	17	0.005
Vascular/hypertension (%)	18	19	21	
Glomerulonephritis (%)	19	15	12	
Tubulointerstitial nephritis (%)	10	11	9	
PKD (%)	9	9	6	
Others (%)	7	8	10	
Unknown (%)	24	22	25	
ESRD management				
Haemodialysis (%)	88	100	82	<0.001
Peritoneal dialysis (%)	11	0	17	
Renal transplantation (%)	1	0	1	
CKD care (months) [IQR]	19 [11–40]	24 [14–37]	–	–
LPD (% yes/no/unknown)	100/0/0	35/14/51	–	–

CVD, cardiovascular disease; PKD, polycystic kidney disease; LPD, low-protein diet prescription.

Table 2. Differences between CKD-5 groups intensively treated in tertiary nephrology clinics with (s-VLPD) or without (TNC) a very low-protein diet supplemented with ketoacids at the last visit prior (≤3 months) to dialysis start

	s-VLPD (n = 184)	TNC (n = 334)	P-value
GFR (mL/min)	5.4 ± 2.3	10.6 ± 3.8	<0.001
Weight (kg)	65.9 ± 13.1	70.7 ± 14.1	0.001
BMI (kg/m ²)	24.3 ± 3.5	26.4 ± 4.6	<0.001
SBP (mmHg)	149 ± 20	140 ± 19	<0.001
DBP (mmHg)	81 ± 11	81 ± 10	0.601
Haemoglobin (g/dL)	10.9 ± 1.1	11.5 ± 1.8	0.001
Protein intake (g/kg/die)	0.58 ± 0.18	0.83 ± 0.27	<0.001

GFR, glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 3. Crude mortality during RRT in CKD-5 groups intensively treated in tertiary nephrology clinics with (s-VLPD) or without (TNC) a very low-protein diet supplemented with ketoacids, unselected subjects (CON) and matched unselected controls (Matched-CON)

	s-VLPD (n = 184)	TNC (n = 334)	CON (n = 9,092)	Matched-CON* (n = 356)
Death (n/100 patients/year) [95% CI]	8.0 [6.0–9.9]	9.8 [7.7–11.8]	13.8 [13.4–14.2]	15.2 [13.0–17.4]
Events, (n of deaths/samples)	63/184	88/334	4437/9092	182/356
Follow-up RRT (months) [IQR]	36 [17–92]	32 [19–46]	36 [17–62]	33 [16–57]

RRT, renal replacement therapy.

*Matched-CON cohorts obtained after applying matched propensity score method (see statistical methods).

Table 4. Risk of all-cause death during RRT in CKD-5 patients; Cox regression model

	HR (95% CI)	P-value
s-VLPD versus matched-CON ^a	0.59 (0.45–0.78)	<0.001
s-VLPD versus TNC ^b	0.82 (0.56–1.19)	0.300
s-VLPD versus TNC ^c	0.84 (0.51–1.39)	0.496
s-VLPD versus TNC ^d	0.76 (0.45–1.28)	0.305

s-VLPD, group intensively treated in tertiary nephrology clinics with very low-protein diet supplemented with ketoacids; matched-CON, matched unselected controls (reference group); TNC, group intensively treated without s-VLPD.

^aResults of matched propensity score (see statistical methods).

^bHR adjusted for age, sex, diabetes, previous CVD and renal disease.

^cHR adjusted for the previous covariates and for SBP, BMI, haemoglobin, GFR and time on CKD care.

^dHR adjusted for all the previous covariates from model and fitted only in haemodialysis patients.

Table 5. Demographic and clinical characteristics of s-VLPD patients (intensive renal care plus very low-protein diet with ketoacids) stratified for the age of >70 years or history of CVD

	Age >70		P-value	Previous CVD events		P-value
	No (n = 82)	Yes (n = 102)		No (n = 109)	Yes (n = 75)	
Age (years)	51.4 ± 13.0	80.4 ± 5.6	–	63.1 ± 19.1	73.9 ± 11.7	<0.001
Male gender (%)	54	57	0.664	51	61	0.182
Diabetes (%)	12	23	0.069	11	28	0.003
CVD (%)	27	52	0.001	–	–	–
GFR (mL/min)	5.7 ± 2.3	5.2 ± 2.5	0.180	5.2 ± 2.2	5.6 ± 2.6	0.387
SBP (mmHg)	145 ± 20	152 ± 21	0.060	150 ± 20	147 ± 21	0.354
DBP (mmHg)	86 ± 8	78 ± 11	<0.001	83 ± 12	79 ± 10	0.059
Hb (g/dL)	10.8 ± 1.1	10.6 ± 1.8	0.664	10.6 ± 1.8	10.7 ± 1.3	0.728
BMI (kg/m ²)	24.5 ± 3.3	24.0 ± 4.5	0.452	24.0 ± 4.5	24.5 ± 3.2	0.434
Time on KA (months) [IQR]	30 [13–60]	14 [9–24]	<0.001	24 [13–51]	14 [7–30]	0.002

CVD, cardiovascular disease; GFR, glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, haemoglobin; BMI, body mass index; KA, ketoacids

FIGURE 1 : Survival of adult CKD-5 patients during RRT according to nephrology care characteristics during the previous CKD-4/5 period. Patients intensively treated in the tertiary nephrology clinic with (-----s-VLPD, n = 184) and without (.....TNC, n = 334) very low-protein diet and ketoacids; unselected subjects (____CON, n = 9.092).

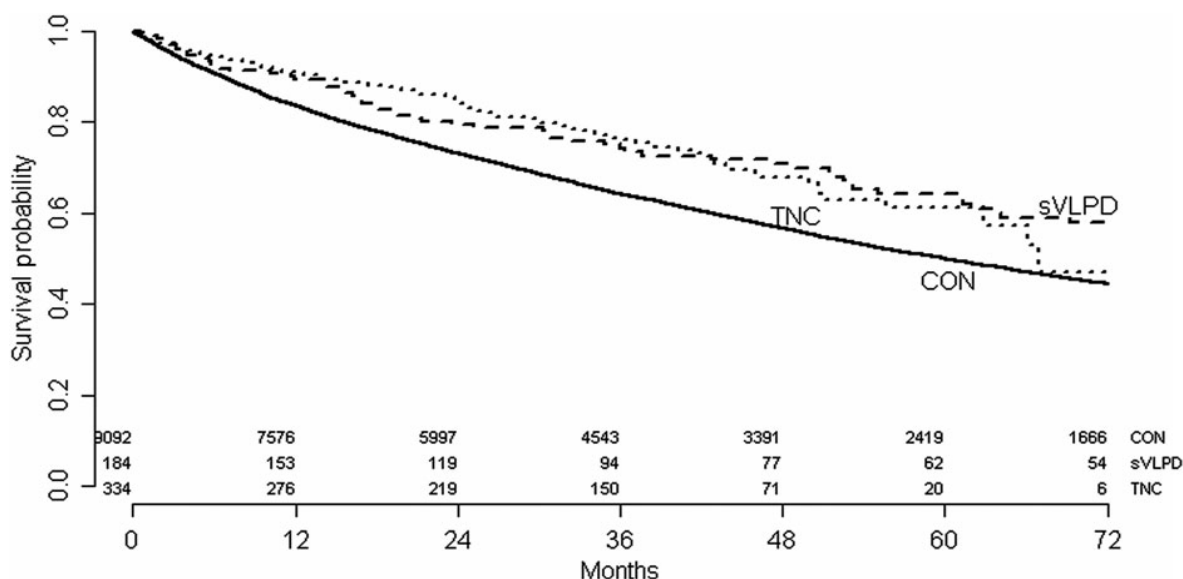


FIGURE 2: Subgroups analysis of risk of death during RRT in CKD-5 patients prescribed a very low-protein diet plus ketoacids compared with unselected control subjects matched by means of propensity score (reference group): *Forest plot* analysis. CVD, cardiovascular disease. *P < 0.05 for heterogeneity of HR's within subgroups.

